

Immune Deficiency Foundation

# Patient & Family Handbook

for Primary Immunodeficiency  
Diseases



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.

FIFTH EDITION

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Immune Deficiency Foundation

# Patient & Family Handbook

for Primary Immunodeficiency  
Diseases

*5th Edition*

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through a generous grant from

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# Preface

The Mission Statement of the Immune Deficiency Foundation (IDF) pledges that, as the national patient organization for primary immunodeficiency, it is dedicated to improving the diagnosis, treatment and quality of life of persons with primary immunodeficiency diseases through advocacy, education and research. Since its founding in 1980, one of the ways IDF has tried to achieve this goal is by the publication of pamphlets, booklets and more extensive publications such as this IDF Patient and Family Handbook to provide a reliable source of information about these often unfamiliar diseases to patients, 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 seven different languages.

The first edition was composed of nine chapters covering five primary immunodeficiency diseases. By the time the 4th edition was published in 2007, it contained 22 chapters and covered about 60 disorders. This new 5th edition expands the content of the Handbook by another 50% to 33 chapters with descriptions of nearly 100 different primary immunodeficiencies. 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 18 chapters covering the specific details of many of the individual primary immunodeficiency diseases themselves. There are additional chapters with general information relevant to the inheritance, laboratory diagnosis, general care and specific medical treatments of primary immunodeficiencies as well as chapters on life management issues for patients of different ages.

Important new chapters have been added on subjects such as autoimmunity, allergies and infections-topics of critical interest to many in our community. There are also new chapters on *Stem Cell and Gene Therapy*, *Innate Immune Defects* and an enlarged section on phagocytic cell disorders within the Chronic Granulomatous Disease chapter. In addition to the new chapters, 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, we plan to develop an online supplement that will provide more detailed reports about some of these disorders as well as breaking research news of new insights or treatment successes. This will keep our community informed of advances between publication of new print editions of the Handbook.

It is important to recognize that a regular dialogue between the patient, the family and the 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 patient's 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 patient and family and healthcare providers is critically important for success in the management of life-long challenges like those presented by primary immunodeficiency diseases.

*The Editors*  
*Baltimore 2013*

## Letter from the President & Founder

Years ago, my son's immunologist told me about a saying that many doctors are taught in medical school, "when you hear hoof beats, think horses, not zebras." However, immunologists are taught to look for zebras, not horses. Rather than focus on the likeliest possibilities when making a diagnosis, they look for the unusual ones.

At IDF, we believe that patients with primary immunodeficiency diseases are the zebras of the medical world, and that more physicians need to think about the unique diagnosis, not the horse, but a zebra. Zebras in a herd might all look alike, but their stripe patterns are as distinctive as fingerprints—no two are the same. And no two members of our patient community are the same either!

Since IDF was founded in 1980, we have strived to develop and provide innovative resources to meet the individual needs of patients and families living with primary immunodeficiency diseases. Our first edition of the *IDF Patient & Family Handbook* represented the first information in the world on primary immunodeficiency developed specifically for patients. We continue that effort as we introduce this fifth edition of the *IDF Patient & Family Handbook for Primary Immunodeficiency Diseases*. We are incredibly proud of this publication! Written and edited by leading immunologists, nurses and life management specialists, it focuses on what is important to our community—sharing information to advance diagnosis and treatment, as well as quality healthcare and life management skills that can make a positive difference in daily life.

We hope that you will benefit from this expanded and updated version of the Handbook and that you will continue to connect with IDF's vital network of resources. Our programs offer a wealth of valuable education, information and support when you need it. We welcome you to stay in touch, online or by phone. Rest assured you can rely on IDF!

As the national patient organization dedicated to persons living with primary immunodeficiency diseases, IDF encourages you to THINK ZEBRA! and live a fulfilling life with your primary immunodeficiency!

### **Marcia Boyle**

*President & Founder*

*Immune Deficiency Foundation*



Efforts have been made to ensure that the material presented in this Handbook is accurate, reliable and in accordance with current standards at the time of publication. However, as research and experience expands, recommendations for care, treatment and management may change. Please visit [www.primaryimmune.org](http://www.primaryimmune.org) for updated information.

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## Primary Immunodeficiency Disease Search List

Please use this search list to locate the chapter that contains information on the particular disease in which you are interested. With more than 250 primary immunodeficiency diseases recognized by the World Health Organization, it was not possible to include them all in this Handbook. However, there is information about many of the disorders, including those that are less common.

Over the years, the names of some disorders have changed. Those alternative names are listed. Sometimes a chapter discusses several different primary immunodeficiency diseases. In that case this list directs you to the chapter subsection where you can find information about that disease.

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# The Immune System and Primary Immunodeficiency Diseases



## Chapter 1

*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.*

## 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*). 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 bone marrow and thymus represent training grounds for two cells of the 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 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 transplant. It is related to embryonic stem cells, but is a distinct cell type. In most cases, development of one cell type is independent of the other cell types.

Primary immunodeficiencies can affect only a single component of the immune system or multiple cells and proteins. To better understand the immune deficiencies discussed later, this section will describe the organization and maturation of the immune system.

Although all components of the immune system interact with each other, 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 termed 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 not to attack our own cells. The advantages of the adaptive responses are their long-lived memory and the ability to adapt to new germs.

Central to both categories of immune responses is the ability to distinguish foreign invaders (things that need to be attacked) from 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 from their mother but do not make their own antibodies for several weeks.

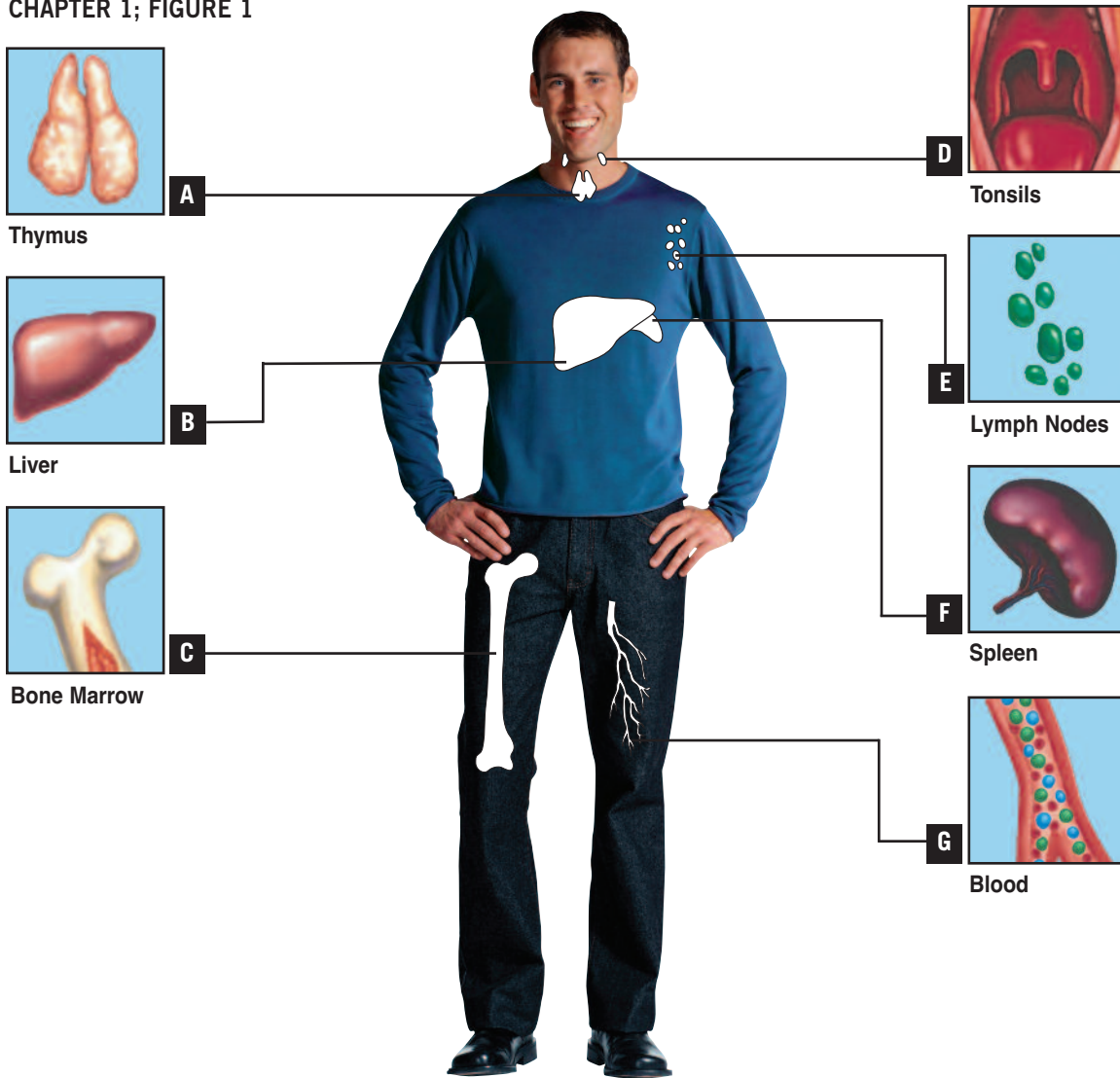
The adaptive immune system is functional at birth, but it has not gained the experience necessary for optimal memory responses. Although this formation of memory occurs throughout life, the most rapid gain in immunologic experience is between birth and three years of age. Each infectious exposure leads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

Over the first few years of life, most children catch a wide variety of infections and produce antibodies directed at those specific infections. The cells producing the antibody “remember” the infection and provide long-lasting

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## Major Organs of the Immune System

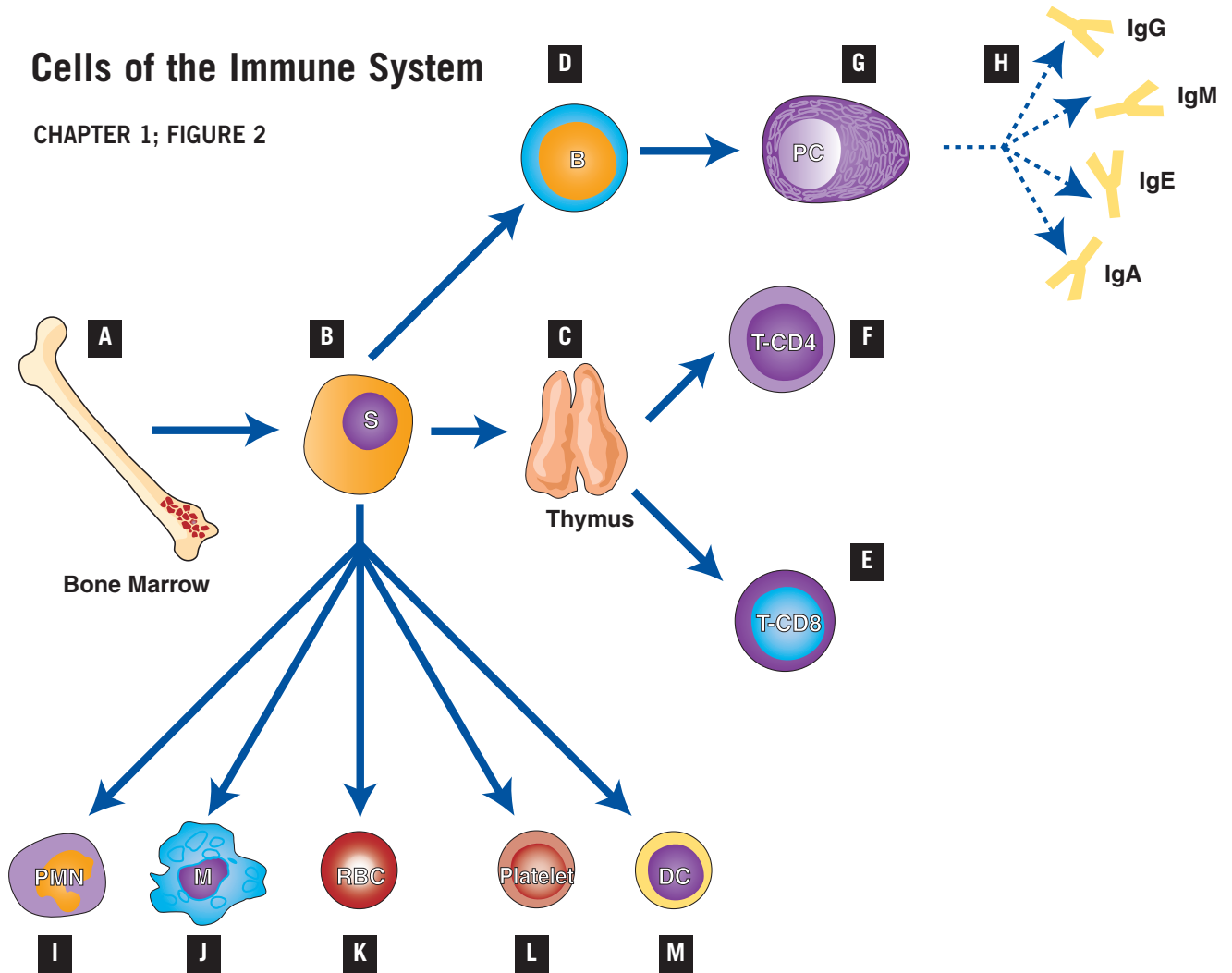
CHAPTER 1; FIGURE 1



- A. Thymus:** The thymus is an organ located in the upper chest. Immature lymphocytes leave the bone marrow and find their way to the thymus where they are “educated” to become mature T-lymphocytes.
- B. Liver:** The liver is the major organ responsible for synthesizing proteins of the complement system. In addition, it contains large numbers of phagocytic cells which 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 primitive stem cells.
- D. Tonsils:** Tonsils are collections of lymphocytes in the throat.
- E. Lymph Nodes:** Lymph nodes are collections of B-lymphocytes and T-lymphocytes throughout the body. Cells congregate in lymph nodes to communicate with each other.
- F. Spleen:** The spleen is a collection of T-lymphocytes, B-lymphocytes and monocytes. It serves to filter the blood and provides a site for organisms and cells of the immune system to interact.
- G. Blood:** Blood is 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

CHAPTER 1; FIGURE 2



- A. Bone marrow:** The site in the body where most of the cells of the immune system are produced as immature or stem cells.
- B. Stem cells:** These cells have the potential to differentiate 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-lymphocytes.
- 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 infected cells.
- 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 for the serum and the secretions.

- 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 all possible microorganisms in our environment.
- I. Neutrophils (Polymorphonuclear PMN Cell):** A type of cell found in the blood stream that rapidly ingests microorganisms and kills them.
- J. Monocytes:** A type of phagocytic cell found in the blood stream which develops into a macrophage when it migrates to tissues.
- K. Red Blood Cells:** The cells in the blood stream which carry oxygen from the lungs to the tissues.
- L. Platelets:** Small cells in the blood stream which are important in blood clotting.
- M. Dendritic Cells:** Important cells in presenting antigen to immune system cells.

## (Organization and Development of the Immune System continued)

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 below. Immune deficiencies can affect a single component or multiple components. The manifestations of immune deficiencies can be a single type of infection or a more global susceptibility to infection. Because of the many interactions between the cells and proteins of the immune system, some immune deficiencies can be associated with a very limited range of infections. For these immune deficiencies, there are other elements that “take up the slack” and can compensate at least partly for the missing piece. In

other cases, the ability to defend against infection is very weak over all and the person may have significant problems with infections.

The 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 signaling proteins (often called cytokines), antibodies, 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 called immunoglobulins or gamma-globulins). B-cells develop in the bone marrow from hematopoietic stem cells. As part of their 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 material (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. Antibodies, the major product of plasma cells, find their way into the bloodstream, tissues, respiratory secretions, intestinal secretions, and even tears. Antibodies are highly specialized serum protein molecules.

For every foreign antigen, there are antibody molecules specifically designed to fit that antigen, like a lock and key. For example, there are antibody molecules that physically fit the poliovirus, others that fit diphtheria, and still others that fit the measles virus. The variety of different antibody molecules is extensive so that B-cells have the ability to produce them against virtually all



## (Lymphocytes of the Immune System continued)

microbes in our environment. However, each plasma cell produces only one kind of antibody.

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 germ. 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 (*Figure 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, 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.

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 or viruses.

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. T-cells directly attack cells infected with viruses, and they also 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. Mature T-cells leave the thymus and populate other organs of the immune system, such as the spleen, lymph nodes, bone marrow and blood.

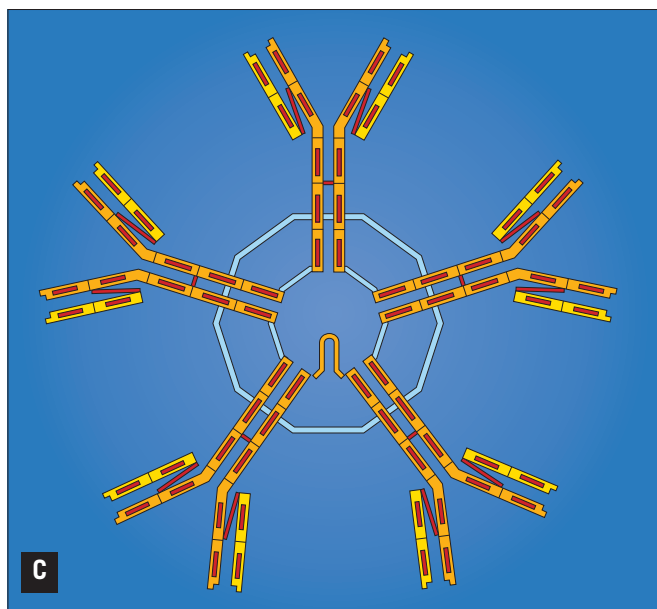
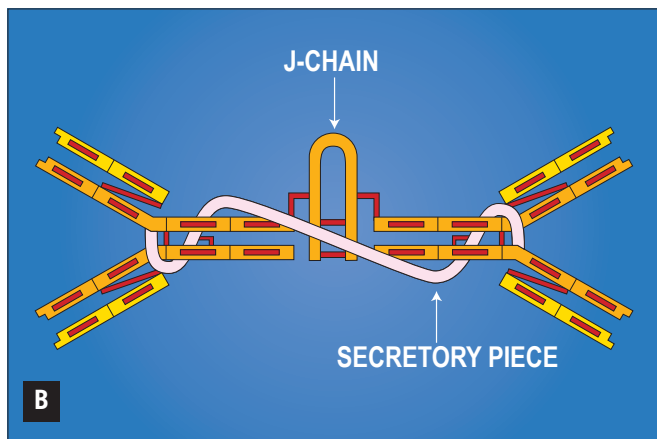
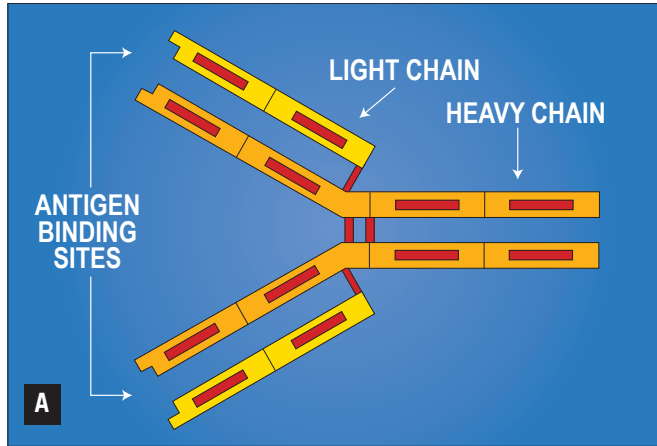
Each T-cell reacts with a specific antigen, just as each antibody molecule reacts with a specific antigen. In fact, T-cells have molecules on their surfaces that are similar to antibodies. The variety of different T-cells is so extensive that the body has T-cells that can react against virtually any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

*continued on page 8*

## Immunoglobulin Structure

CHAPTER 1; FIGURE 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.
- 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, intestinal juices 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.

## (Lymphocytes of the Immune System continued)

Killer, or cytotoxic, T-cells perform the actual destruction of infected cells. 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. Killer T-cells also respond to foreign tissues in the body, such as a transplanted kidney. The killer cell must migrate to the site of infection and directly bind to its target to ensure its destruction.

Helper T-cells assist B-cells to produce antibodies and assist killer T-cells in their attack on foreign substances.

Regulatory T-cells suppress or turn off other T-lymphocytes. Without regulatory cells, the immune system would keep working even after an infection has been cured. 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.

### 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 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 it with a killer potion of chemicals. 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) and the varicella virus (the cause of chickenpox).

### Neutrophils

Neutrophils or polymorphonuclear leukocytes (polys or PMN's) 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 (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 packets of cell membrane that then fuse with other parts of the neutrophil that contain toxic chemicals that kill the microorganisms. They 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 5-10 percent of the white blood cells. They also line the walls of blood vessels in organs like the liver and spleen. Here they capture microorganisms in the blood as the microorganisms 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 hormones for the immune system. They are produced in response to a threat and

## (Lymphocytes of the Immune System continued)

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 germs 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 infection. 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 4*).

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

## 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.

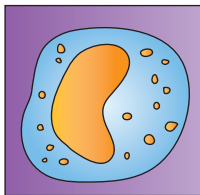
Circulating T-cells and NK cells become alerted to a viral invasion and migrate to the site where they kill the particular cells that are harboring the virus. This is a very destructive mechanism to kill the virus because many of our own cells can be sacrificed in the process. Nevertheless, it is an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

At the same time the T-lymphocytes are killing the virus, they are also instructing the B-lymphocytes 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.

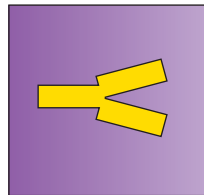
## Normal Anti-Bacterial Action

CHAPTER 1; FIGURE 4

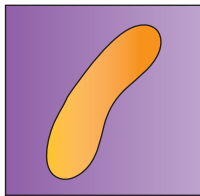
### Key



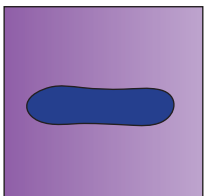
Neutrophil



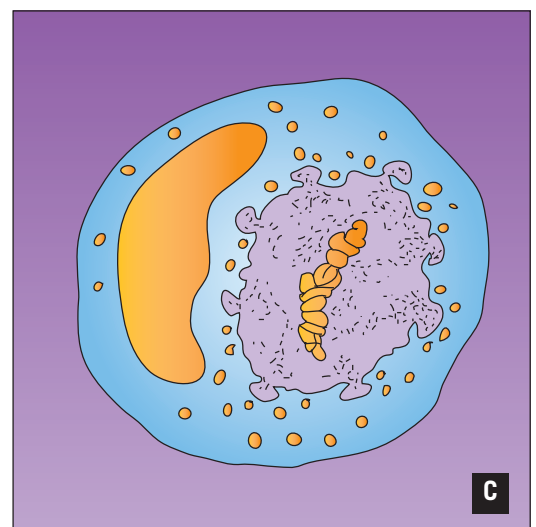
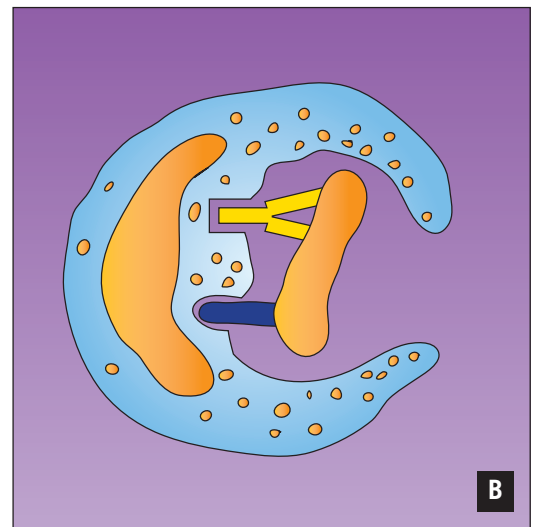
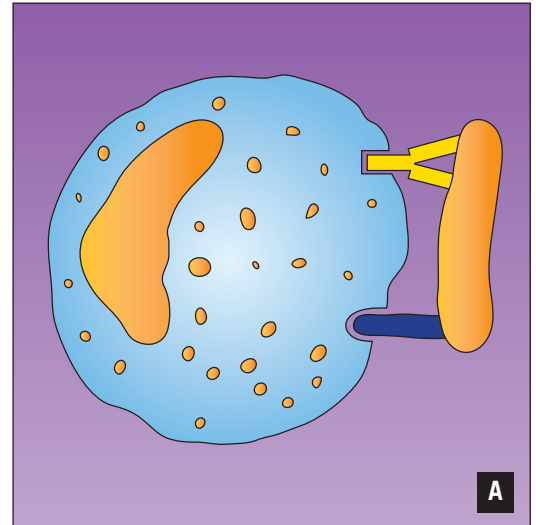
Antibody



Bacteria



Complement



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

- A. Neutrophil (Phagocytic Cell) Engages Bacteria (Microbe):** The microbe is coated with specific antibody and complement. The phagocytic cell then begins its attack on the microbe by attaching to the antibody and complement molecules.
- B. Phagocytosis of the Microbe:** After attaching to the microbe, the phagocytic cell begins to ingest the microbe by extending itself around the microbe and engulfing it.
- C. Destruction of the Microbe:** Once the microbe is ingested, bags of enzymes or chemicals are discharged into the vacuole where they kill the microbe.

## The Immune System and Primary Immunodeficiency Diseases

Immune deficiencies are categorized as primary immune deficiencies or secondary immune deficiencies. Primary immune deficiencies are “primary” because the immune system is the primary cause and most are genetic defects that may be inherited. Secondary immune deficiencies are so called because they have been caused by other conditions.

Secondary immune deficiencies are common and can occur as part of another disease or as a consequence of certain medications. The most common secondary immune deficiencies are caused by aging, malnutrition, certain medications and some infections, such as HIV.

The most common medications associated with secondary immune deficiencies are chemotherapy agents and immune suppressive medications, cancer, transplanted organ rejection or autoimmune diseases. Other secondary immune deficiencies include protein losses in the intestines or the kidneys. When proteins are lost, antibodies are also lost, leading to low immune globulins 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 immune deficiency and provision of immunologic support can be helpful. The types of support offered are comparable to what is used for primary immune deficiencies.

The primary immunodeficiency diseases are a group of disorders caused by basic defects in immune function that are intrinsic to, or inherent in, the cells and proteins of the immune system. There are more than 250 primary immunodeficiency diseases. 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 primary immunodeficiency diseases 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 Severe Combined Immune Deficiency (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 primary immunodeficiency diseases have an increased susceptibility to infection. This may include too many infections, infections that are difficult to cure, 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 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 primary immunodeficiencies 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 primary immunodeficiencies 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

(The Immune System and Primary Immunodeficiency Diseases continued)

lymphoproliferative syndrome (ALPS) and IPEX (an X-linked syndrome of immunodeficiency, polyendocrinopathy and enteropathy).

Primary immunodeficiency diseases can occur in individuals of any age. The original descriptions of these diseases were in children. However, as medical experience has grown, many adolescents and adults have been diagnosed with primary immunodeficiency diseases. This is partly due to the fact that some of the disorders, such as CVID and Selective IgA Deficiency,

may have their initial clinical presentation in adult life. Effective therapy exists for several of the primary immunodeficiencies, and many people with these disorders can live relatively normal lives.

Primary immunodeficiency diseases were initially felt to be very rare. However, recent research has indicated that as a group they are more common than originally thought. It is estimated that as many as 1 in every 1,200–2,000 people may have some form of primary immunodeficiency.

# Agammaglobulinemia: X-Linked and Autosomal Recessive



## Chapter 2



*The basic defect in both X-Linked Agammaglobulinemia and autosomal recessive agammaglobulinemia is a failure of B-lymphocyte precursors to mature into B-lymphocytes and ultimately plasma cells. Since they lack the cells that are responsible for producing immunoglobulins, these patients have severe deficiencies of all types of immunoglobulins.*

## Definition of X-Linked Agammaglobulinemia (XLA) and Autosomal Recessive Agammaglobulinemia (ARA)

X-Linked Agammaglobulinemia (XLA) was first described in 1952 by Dr. Ogden Bruton. This disease, sometimes called Bruton's Agammaglobulinemia or Congenital Agammaglobulinemia, was one of the first immunodeficiency diseases to be identified. XLA is an inherited immunodeficiency disease in which patients lack the ability to produce antibodies, the proteins that make up the gamma globulin or immunoglobulin fraction of blood plasma.

Antibodies are an integral part of the body's defense mechanism against certain types of microorganisms or germs, like bacteria or viruses. Antibodies are important in the recovery from infections and protect against getting certain infections more than once. There are antibodies specifically designed to combine with each and every microbe—much like a lock and key.

When a germ, such as bacteria, lands on a mucus membrane or enters the body, antibody molecules that recognize it stick to its surface. Antibody bound to the surface of a microorganism 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 antibody prevents the germs from “sticking” to the cells.

Antibody on the surface of some microbes 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 which

are not coated with antibody. All of these actions prevent germs from invading body tissues where they may cause serious infections. (See chapter titled “*The Immune System and Primary Immunodeficiency Diseases.*”)

The basic defect in XLA is an inability of the patient to produce antibodies. Antibodies are produced by specialized cells in the body, called plasma cells. Plasma cells develop in an orderly sequence of steps beginning with stem cells located in the bone marrow. The stem cells give rise to immature lymphocytes, called pro-B-lymphocytes. Pro-B-lymphocytes next develop into pre-B-cells, which then give rise to B-lymphocytes. Each B-lymphocyte bears on its cell surface a small amount of the immunoglobulin that it is able to produce. This cell surface immunoglobulin can bind foreign substances, (an antigen). When the B-lymphocyte comes into contact with its specific antigen, like pneumococcus or tetanus, it is triggered to mature into a plasma cell which is specialized in making and secreting large amounts of that specific antibody. Each B-cell makes a slightly different antibody, or immunoglobulin, to allow the body to respond to millions of different foreign substances.

Most patients with XLA have normal numbers of B-lymphocyte precursors, but very few of these go on to become B-lymphocytes. This is the underlying defect in XLA, a failure of B-lymphocyte precursors to mature into B-cells. Patients with XLA have mutations in a gene that is necessary for the normal development of

## (Definition of X-Linked Agammaglobulinemia and Autosomal Recessive Agammaglobulinemia continued)

B-lymphocytes. This gene, discovered in 1993, is named Bruton's Tyrosine Kinase (BTK) in honor of the discoverer of the disorder, Colonel Ogden Bruton, MD. As the name of the disorder suggests, the BTK gene is located on the X chromosome.

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. Since XLA is an x-linked disorder, only boys are affected; however, it had been known for several years that there were girls who had an immunodeficiency that looked just like XLA and immunologists had suggested that there were forms of agammaglobulinemia with autosomal recessive inheritance (ARA).

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

- $\mu$  heavy chain (*IGHM*)
- $\lambda 5$  (*IPLL1*)
- Ig $\alpha$  (*CD79A*)
- Ig $\beta$  (*CD79B*)
- BLNK (*BLNK*)

All of these genes code for proteins that work with BTK to support the maturation of pro-B-cells into pre-B-cells. Patients with mutations in any of these genes have clinical and laboratory findings that are very similar to those seen in patients with mutations in BTK.

## Clinical Presentation of X-Linked Agammaglobulinemia and Autosomal Recessive Agammaglobulinemia

Patients with either XLA or ARA are prone to develop infections because they lack antibodies. The infections frequently occur at or near the surfaces of mucus membranes, such as the middle ear (otitis), sinuses (sinusitis) and lungs (pneumonia or bronchitis), but in some instances infections can involve the bloodstream or internal organs as well.

Gastrointestinal infections can also be a problem, especially those caused by the parasite, *Giardia*. *Giardia* may cause abdominal pain, diarrhea, poor growth or loss of serum proteins like gamma globulin. Some patients with agammaglobulinemia also have problems with skin infections.

In patients without antibodies, any of these infections may invade the bloodstream and spread to other organs deep within the body, such as the bones, joints or brain. Infections in XLA and ARA patients are usually caused by microorganisms that are killed or inactivated very

effectively by antibodies in normal people. The most common bacteria that cause infections are the pneumococcus, the streptococcus, the staphylococcus and *Hemophilus influenzae*. Some specific kinds of viruses may also cause serious infections in these patients.

The defect in B-cells is present at birth, and infections may begin at any age. However, infections often do not occur with unusual frequency until sometime between 6-18 months of age because, until then, infants are protected by antibodies acquired from the mother during the pregnancy.

On physical examination, most patients with agammaglobulinemia have very small tonsils and lymph nodes (the glands in your neck). This is because most of the bulk of tonsils and lymph nodes is made up of B-lymphocytes. In the absence of B-lymphocytes, these tissues are reduced in size.

## Diagnosis of X-Linked Agammaglobulinemia and Autosomal Recessive Agammaglobulinemia

The diagnosis of agammaglobulinemia should be considered in any child with recurrent or severe bacterial infections, particularly if the patient has small or absent tonsils and lymph nodes.

The first screening test should be an evaluation of serum immunoglobulins. In most patients with agammaglobulinemia, all of the immunoglobulins (IgG, IgM and IgA) are markedly reduced or absent. However, there are exceptions; some patients with XLA make some IgM or IgG. In addition, normal babies make only small quantities of immunoglobulins in the first few months of life, making it difficult to distinguish a normal baby with a normal delay in immunoglobulin production from a baby with true immunodeficiency.

If the serum immunoglobulins are low or if the physician strongly suspects the diagnosis of agammaglobulinemia, the number of B-cells in the peripheral blood should be

measured. A low percentage of B-cells (nearly absent) in the blood is the most characteristic and reliable laboratory finding in patients with either XLA or ARA.

If a newborn baby has a brother, sister, maternal cousin or maternal uncle with agammaglobulinemia, the baby is at risk to have a similar immunodeficiency and the family and physicians 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; however, members of the same family usually have the same mutation. The specific gene that causes ARA can be identified by DNA analysis.

## Inheritance of X-Linked Agammaglobulinemia and Autosomal Recessive Agammaglobulinemia

XLA and ARA are 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.

Now that the precise gene that causes XLA has been identified, it is possible to test the female siblings (sisters) of a patient with XLA, and other female relatives such as the child's maternal aunts, to determine if they

are carriers of the disease. Carriers of XLA have no symptoms, but they have a 50% chance of transmitting the disease to each of their sons.

In some instances, it is also possible to determine if a fetus of a carrier female will be born with XLA. Currently, these genetic tests are being performed in only a few laboratories. (*See the chapter titled "Inheritance."*)

## Treatment of X-Linked Agammaglobulinemia and Autosomal Recessive Agammaglobulinemia

At this time, there is no way to cure patients who have agammaglobulinemia. The defective genes cannot be repaired or replaced, nor can the maturation of B-lymphocyte precursors to B-lymphocytes and plasma cells be induced. However, patients with agammaglobulinemia can be given some of the antibodies that they are lacking. The antibodies are supplied in the form of immunoglobulins (or gamma globulins) and can be given directly into the blood stream (intravenously) or under the skin (subcutaneously). (See chapter titled “Immunoglobulin Therapy and Other Medical Therapies for Antibody Deficiencies.”)

Immunoglobulin preparations contain antibodies that substitute for the antibodies that the patients with agammaglobulinemia cannot make themselves. These

products contain antibodies to a wide variety of microorganisms. Immunoglobulin is particularly effective in preventing the spread of infections into the bloodstream and to deep body tissues or organs. Some patients may also benefit from the use of daily oral antibiotics to protect them from infection or to treat chronic sinusitis or chronic bronchitis.

Patients with either XLA or ARA should not receive any live viral vaccines, such as live polio, the measles, mumps, rubella (MMR) vaccine, the chicken pox vaccine (Varivax) or the rotavirus vaccine (Rota-teq). Although uncommon, it is possible that live vaccines, particularly the oral polio vaccine, in patients with agammaglobulinemia can transmit the diseases that they were designed to prevent.

## Expectations for Patients with X-Linked Agammaglobulinemia and Autosomal Recessive Agammaglobulinemia

Most patients with XLA or ARA who receive immunoglobulin on a regular basis will be able to lead relatively normal lives. They do not need to be isolated or limited in their activities. Active participation in team sports should be encouraged. Infections may require some extra attention from time to time, but children with

agammaglobulinemia can participate in all regular school and extracurricular activities, and when they become adults can have productive careers and families. A full active lifestyle is to be encouraged and expected.

# Common Variable Immune Deficiency



## Chapter 3

*Common Variable Immune Deficiency (CVID) is a frequently diagnosed immunodeficiency, especially in adults, characterized by low levels of serum immunoglobulins and antibodies, which causes an increased susceptibility to infection. While CVID is thought to be due to genetic defects, the exact cause of the disorder is unknown in the large majority of cases.*

## Overview of Common Variable Immune Deficiency

Compared to other human immune defects, 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 patient to patient, hence, the word “variable.” In some patients, there is a decrease in both IgG and IgA; in others, all three major types of immunoglobulins (IgG, IgA and IgM) are decreased. In still others there are defects of the T-cells, and this may also contribute to increased susceptibility to infections as well as autoimmunity, granulomata and tumors.

To be sure that CVID is the correct diagnosis, there must be evidence of a lack of functional antibodies and other possible causes of these immunologic abnormalities must be excluded. Frequent and/or unusual infections may first occur during early childhood, adolescence or adult life. Patients with CVID

also have an increased incidence of autoimmune or inflammatory manifestations, granulomata 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.

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 AIDS virus (HIV) and should not be used for individuals with CVID, as these disorders are very different.

## Clinical Features of Common Variable Immune Deficiency

Both males and females may have CVID. In the majority, the diagnosis is not made until the third or fourth decade of life. However, about 20% of patients have symptoms of the disease or are found to be immunodeficient in childhood. Because the 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, nasal 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 bronchial tree, a condition termed bronchiectasis, may develop.

## (Clinical Features of Common Variable Immune Deficiency continued)

The organisms commonly found in these sinopulmonary infections are bacteria that are widespread in the population and that often cause pneumonia (*Hemophilus influenzae*, pneumococci, and staphylococci) even in people who do not have CVID. The purpose of treatment of lung infections is to prevent their recurrence and the accompanying chronic and progressive damage to lung tissue. A regular cough in the morning and the production of yellow or green sputum may suggest the presence of chronic bronchitis or bronchiectasis.

Patients with CVID may also develop enlarged lymph nodes in the neck, the chest or abdomen. The specific cause is unknown, but 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 granulomas, can be found in lungs, lymph nodes, liver, skin or other organs. These are largely composed of cells called monocytes and macrophages. They may be a response to an infection, but the cause is not really known.

Although patients with CVID have depressed antibody responses and low levels of immunoglobulins in their blood, some of the antibodies that are produced by these patients 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 defect is a finding of very low platelets in the blood or severe anemia due to destruction of red cells. Autoantibodies may also cause other diseases such as arthritis or endocrine disorders, like thyroid disease.

Gastrointestinal complaints such as abdominal pain, bloating, nausea, vomiting, diarrhea and weight loss are not uncommon in CVID. Careful evaluation of the digestive organs may reveal malabsorption of fat and certain sugars or inflammatory bowel disease. If a small sample (biopsy) of the bowel mucosa is obtained, characteristic changes may be seen. These changes are helpful in diagnosing the problem and treating it. In some patients with digestive problems, a small parasite called *Giardia lamblia* has been identified in the biopsies and in the stool samples. Eradication of these parasites by medication may eliminate the gastrointestinal symptoms.

Some patients with CVID who may not be receiving optimal immunoglobulin 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 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 rarely affected. Symptoms of joint inflammation usually disappear with adequate immunoglobulin therapy and appropriate antibiotics. In some patients, however, arthritis may occur even when the patient is receiving adequate immunoglobulin replacement.

Finally, patients with CVID may have an increased risk of cancer, especially cancer of the lymphoid system or gastrointestinal tract.

## Diagnosis of Common Variable Immune Deficiency

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, against vaccine antigens such as tetanus or diphtheria, measles, mumps, or rubella, hemophilus or pneumococcal polysaccharide. Patients 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 physician decide if the patient will benefit from immunoglobulin replacement therapy and can be key in obtaining insurance authorization for this therapy. The number of B- and T-lymphocytes may also be determined and their function tested in tissue cultures.

## Genetics and Inheritance of Common Variable Immune Deficiency

Patients with CVID usually have normal numbers of the cells that produce antibody (B-lymphocytes), 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 a small group of genes in a few patients. These include inducible co-stimulatory (ICOS) and a few other proteins on B-cells. These appear to be causes of autosomal recessive CVID. Mutations in a cell receptor (TACI)

needed for normal growth and regulation of B-cells have also been found in about 8% of patients with CVID. However, a causative role of TACI mutations in this immune defect is not yet clear, since some of these mutations can be found in people with normal immunoglobulins. As these are very rare gene defects for the most part, genetic testing is not yet required or indicated for the diagnosis of CVID.



## Treatment of Common Variable Immune Deficiency

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, immunoglobulin 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 chapter titled “Immunoglobulin Therapy and Other Medical Therapies for Antibody Deficiencies.”)*

Patients 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 toilet 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.

Patients with gastrointestinal symptoms and malabsorption should be evaluated for the presence of *Giardia lamblia*, rotavirus and a variety of other gastrointestinal infections. In some cases inflammatory bowel disease is found, and this is treated by the medications normally prescribed for patients who are non-immunodeficient. Maintaining a balance between the immunosuppression used to control the autoimmune process while avoiding compounding the defects of the underlying primary immunodeficiency requires close cooperation between the patient and the various specialists involved in their care. *(See chapter titled “Autoimmunity in Primary Immunodeficiency.”)*

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. However when patients with CVID have these complications, there is a tendency for them to be less responsive to therapy. Regular checkups including lung function are recommended.

## Expectations for Patients with Common Variable Immune Deficiency

Immunoglobulin replacement therapy combined with antibiotic therapy has greatly improved the outlook of patients with CVID. The aim of the treatment is to keep the patient free of infections and to prevent the development of chronic inflammatory changes in tissues. The outlook for patients with CVID depends on how much damage has occurred to their lungs or other

organs before the diagnosis is made and treatment with immunoglobulin 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, granulomata or malignancy can have a significant impact on the quality of life and response to treatment.

# Selective IgA Deficiency



## Chapter 4

*Individuals with Selective IgA Deficiency lack IgA, but usually have normal amounts of the other types of immunoglobulins. Selective IgA Deficiency is relatively common in Caucasians. Many affected people have no illness as a result. Others may develop a variety of significant clinical problems.*

## Definition of Selective IgA Deficiency

Selective IgA Deficiency is defined as a primary immunodeficiency characterized by an undetectable level of immunoglobulin A (IgA) in the blood and secretions but no other immunoglobulin deficiencies.

There are five types (classes) of immunoglobulins or antibodies in the blood: IgG, IgA, IgM, IgD and IgE. IgG is present in the largest amount, followed by IgM and IgA. IgD is much lower, and IgE is present in only minute amounts. IgM and IgG mainly protect us from infections inside our 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, colostrum, genital, respiratory and gastrointestinal secretions.

The IgA antibodies in the secretions play a major role in protecting us from infections in these areas. IgG and IgM are also found in secretions but not in nearly the same amount as IgA. IgA present in these secretions is also termed secretory IgA. If human mucosal surfaces were spread out flat, they would cover an area equal to

one and a half tennis courts, so the importance of IgA in protecting mucosal surfaces cannot be overstated.

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 chapter titled “*The Immune System and Primary Immunodeficiency Diseases.*”) In order for this unit to be secreted, it must also be 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.

Although individuals with Selective IgA Deficiency do not produce IgA (or produce only extremely small amounts), they do make all the other immunoglobulin classes; hence the term Selective IgA Deficiency. Furthermore, the functions of their T-lymphocytes, phagocytic cells and complement systems are all normal.

## Clinical Features of Selective IgA Deficiency

Selective IgA Deficiency is one of the most common primary immunodeficiency diseases. Studies have indicated that as many as one in every 500 Caucasian people has Selective IgA Deficiency. The rate of occurrence may be different in other ethnic groups.

Many of these individuals appear healthy, or have relatively mild illnesses, and are generally not sick enough to be seen by a doctor and may never be discovered to have IgA deficiency. On the other hand, there are individuals with Selective IgA Deficiency who

(Clinical Features of Selective IgA Deficiency continued)

have significant illnesses. Currently, it is not understood why some individuals with IgA deficiency have almost no illness while others are very sick.

Also, it is not known precisely what percent of individuals with IgA deficiency will eventually develop complications; estimates range from 25% to 50%. Some patients with IgA deficiency also have very low levels of certain IgG subclasses (usually IgG2 and/or IgG4). That may be part of the explanation of why some patients with IgA deficiency are more susceptible to infection than others, but this is not the case for all patients with IgA deficiency who develop complications or for those who have low IgG2 and/or IgG4 in addition to absent IgA.

A common problem in Selective IgA Deficiency is susceptibility to infections. This is seen in about half of the patients with IgA deficiency that come to medical attention. Recurrent ear infections, sinusitis, bronchitis and pneumonia are the most common infections seen in patients with Selective IgA Deficiency. Some patients also have gastrointestinal infections and chronic diarrhea. The occurrence of these kinds of infections is easy to understand since IgA protects mucosal surfaces. These infections may become chronic. Furthermore, the infection may not completely clear with treatment, and patients may have to remain on antibiotics for longer than usual. Sometimes long-term antibiotic prophylaxis is needed to keep them free from infections.

A second major problem in IgA deficiency is the occurrence of autoimmune diseases. These are found in about 25% to 33% of patients who seek medical help. In autoimmune diseases, individuals produce antibodies or T-lymphocytes, which react with their own tissues

with resulting inflammation and damage. Some of the more frequent autoimmune diseases associated with IgA deficiency are: rheumatoid arthritis, systemic lupus erythematosus and immune thrombocytopenic purpura. Other kinds of autoimmune disease may affect the endocrine system and/or the gastrointestinal system.

Allergies may also be more common among individuals with Selective IgA Deficiency than among the general population. These occur in about 10-15% of these patients. The types of allergies vary. Asthma is one of the common allergic diseases that occurs with Selective IgA Deficiency. It has been suggested that asthma may be more severe, and less responsive to therapy, in individuals with IgA deficiency than it is in people with normal IgA. Food allergy may also be associated with IgA deficiency. It is not certain whether there is an increased incidence of allergic rhinitis (hay fever) or eczema in Selective IgA Deficiency.

The causes of Selective IgA Deficiency are unknown. It is likely that there are a variety of causes, and this explains why the symptoms or health problems may vary from individual to individual.

Low but detectable serum IgA (sometimes called partial IgA deficiency), like undetectable serum IgA, is also relatively common. Similarly, most people with low serum IgA have no apparent illness. Some people with low serum IgA have a clinical course very similar to people with Common Variable Immune Deficiency (CVID). (*See chapter titled "Common Variable Immune Deficiency."*)

## Diagnosis of Selective IgA Deficiency

The diagnosis of Selective IgA Deficiency is usually suspected because of chronic or recurrent infections, autoimmune diseases, chronic diarrhea or some combination of these problems. Other patients are identified when immunoglobulins are ordered for some non-immunologic problem. The diagnosis is established when blood tests demonstrate undetectable levels of IgA (reported usually as < 5-7 mg/dL), with normal levels of the other major classes of immunoglobulins (IgG and IgM).

Occasionally, some patients with IgA deficiency may also have low levels of IgG2 and/or IgG4 and associated

antibody deficiency. B-cell numbers and the numbers and functions of T-lymphocytes are normal. (See chapters titled “Specific Antibody Deficiency” and “IgG Subclass Deficiency.”)

Several other tests that may be important include a complete blood count, measurement of lung function and urinalysis. Other tests that may be obtained include measures of thyroid function, kidney function, nutrient absorption in the GI tract and antibodies directed against the body’s own tissues (autoantibodies).

## Inheritance of Selective IgA Deficiency

Familial inheritance of Selective IgA Deficiency occurs in approximately 20% of cases and, within families, Selective IgA Deficiency, CVID and Transient Hypogammaglobulinemia of Infancy may be associated.

If family members are suspected of having immune problems, immunoglobulin levels may be obtained to determine a familial pattern of disease.

## Treatment of Selective IgA Deficiency

It is not currently possible to replace IgA in patients with IgA deficiency, although research toward purification of human IgA is ongoing. However, it remains to be seen if replacement of IgA by any route (IV, oral or topical) will be beneficial for humans with IgA deficiency, in part because IgA in the serum, unlike IgG, does not remain in the circulation for very long.

Treatment of the complications associated with Selective IgA Deficiency should be directed toward the particular problem. For example, patients with chronic or recurrent infections need appropriate antibiotics. Ideally, antibiotic therapy should be targeted at the specific organism causing the infection. Unfortunately, it is not always

possible to identify these organisms and their antibiotic sensitivities precisely, and the use of broad-spectrum antibiotics may be necessary.

Certain patients who have chronic sinusitis or chronic bronchitis may need to stay on long-term preventive antibiotic therapy (antibiotic prophylaxis). It is important that the doctor and the patient communicate closely so that appropriate decisions can be made regarding therapy.

As mentioned above, some patients with IgA deficiency also have IgG2 and/or IgG4 subclass deficiency and/or a deficiency of antibody production. However, these

## (Treatment of Selective IgA Deficiency continued)

laboratory findings do not always predict a greater frequency or severity of infections. If a patient has many infections, poor vaccine antibody responses and fails other preventive treatment (for example, antibiotic prophylaxis) a trial of immunoglobulin replacement therapy may be considered. (See chapter titled *“Immunoglobulin Therapy and Other Medical Therapies for Antibody Deficiencies.”*)

Patients with Selective IgA Deficiency are often considered to be at increased risk of life-threatening allergic reactions, or anaphylaxis when they receive blood products, including intravenous immunoglobulin (IVIG), that contain some IgA. This is thought to be due to IgG (or possibly IgE) anti-IgA antibodies, which may be found in some IgA-deficient individuals. However, most patients with IgA deficiency do not have adverse reactions to blood products or IVIG.

There is no consensus among experts in this field regarding the exact magnitude of the risk of these types of reactions in patients with IgA deficiency, or the need for caution or measurement of anti-IgA antibodies before administration of blood or IVIG. However, these reactions are very rare overall. Furthermore, anaphylaxis

has not been reported in patients with IgA deficiency receiving subcutaneous immunoglobulin infusions.

There are a variety of therapies for the treatment of autoimmune diseases. Anti-inflammatory drugs, such as aspirin, ibuprofen or naproxen, are used in many diseases that cause joint inflammation. Steroids may also be helpful in a variety of autoimmune diseases. Many biological drugs (monoclonal antibodies) have also been developed to treat inflammatory and autoimmune diseases. If autoimmune disease results in an abnormality of the endocrine system, replacement therapy with hormones may be necessary.

Treatment of the allergies associated with IgA deficiency is similar to treatment of allergies in general. It is not known whether immunotherapy (allergy shots) is helpful in the allergies associated with Selective IgA Deficiency; although there is no evidence of any increased risk associated with this therapy in these patients.

The most important aspect of therapy in IgA deficiency is close communication between the patient (and/or the patient’s family) and the physician so that problems can be recognized and treated as soon as they arise.

## Expectations for Patients with Selective IgA Deficiency

Although Selective IgA Deficiency is usually one of the milder forms of immunodeficiency, it may result in severe disease in some people. Therefore, it is difficult to predict the long-term outcome in an individual patient with Selective IgA Deficiency.

In general, the prognosis in Selective IgA Deficiency depends on the prognosis of the associated diseases. It is important for physicians to continually assess and reevaluate patients with Selective IgA Deficiency for the

existence of associated diseases and the development of more extensive immunodeficiency. For example, rarely, IgA deficiency will progress to become CVID with its associated deficiencies of IgG and/or IgM.

The physician should be notified of anything unusual, especially fever, productive cough, skin rash or sore joints. The importance of good communication with the physician and the initiation of therapy as soon as disease processes are recognized cannot be overstated.

# IgG Subclass Deficiency



## Chapter 5

*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 IgG 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. Although this deficiency may occasionally explain a patient's problems with infections, IgG subclass deficiency is a controversial diagnosis and experts disagree about the importance of this finding as a cause of repeated infections.*

*The misdiagnosis of IgG subclass deficiency as a cause of presumed immunodeficiency is common, often leading to the unnecessary long-term use of Ig replacement therapy. A subclass deficiency needs to be considered and looked for only under special circumstances discussed in this chapter.*

## Definition of IgG Subclass Deficiency

Antibodies are also called immunoglobulins. There are five types or classes of immunoglobulin: IgG, IgA, IgM, IgD and IgE. (See chapter titled *"The Immune System and Primary Immunodeficiency Diseases."*) Most of the antibodies in the blood and the fluid that surround the tissues and cells of the body are of the IgG class. The IgG class of antibodies is composed of four different subtypes of IgG molecules called the IgG subclasses. These are designated IgG1, IgG2, IgG3 and IgG4.

Patients with persistently low levels of one or two IgG subclasses and a normal total IgG level have a selective IgG subclass deficiency.

While all the IgG subclasses contain antibodies to components of many disease-causing bacteria and viruses, each subclass serves a slightly different function in protecting the body against infection. For example, IgG1 and IgG3 subclasses are rich in antibodies against

proteins such as the toxins produced by the diphtheria and tetanus bacteria, as well as antibodies against viral proteins. In contrast, IgG2 antibodies are predominantly against the polysaccharide (complex sugar) coating (capsule) of certain disease-producing bacteria (such as, *Streptococcus pneumoniae* and *Haemophilus influenzae*).

The IgG in the bloodstream is 60-70% IgG1, 20-30% IgG2, 5-8% IgG3 and 1-3% IgG4. The amount of the different IgG subclasses present in the bloodstream varies with age. For example, IgG1 and IgG3 reach normal adult levels by 5-7 years of age while IgG2 and IgG4 levels rise more slowly, reaching adult levels at about 10 years of age. In young children, the ability to make IgG2 antibodies to the polysaccharide coatings of bacteria develops more slowly than the ability to make antibodies to proteins.



## (Definition of IgG Subclass Deficiency continued)

IgG subclass deficiencies affect only IgG subclasses (usually IgG2 or IgG3), with normal total IgG and IgM immunoglobulins and other components of the immune system being at normal levels. These deficiencies can affect only one subclass or involve an association of two subclasses, such as IgG2 and IgG4.

IgG2 or IgG3 deficiencies are the most common IgG subclass deficiencies. Since IgG1 comprises 60% of the total IgG level, deficiency of IgG1 usually drops the total IgG level below the normal range, resulting in hypogammaglobulinemia.

IgG4 is present in very low levels in children younger than 10 years of age, so IgG4 deficiencies are not usually diagnosed before age 10. IgG4 may be undetectable in the serum of many “normal” adult individuals, and therefore low IgG4 alone is insufficient evidence of an antibody deficiency disorder requiring Ig replacement.

All patients with IgG subclass deficiency require more extensive diagnostic evaluation including the

demonstration of a poor antibody response to vaccine challenge before the patient is diagnosed with a clinically significant IgG subclass deficiency necessitating specific treatment that may include Ig replacement therapy.

IgG subclass deficiencies may be associated with other immunoglobulin abnormalities. One common pattern is IgG2 and IgG4 subclass deficiency associated with IgA deficiency. IgG subclass deficiencies are also an integral component of other well-known primary immunodeficiency diseases, such as Wiskott-Aldrich Syndrome and Ataxia-Telangiectasia.

IgG subclass deficiencies are sometimes associated with poor or partial responses to pneumococcal polysaccharides, specifically IgG2 deficiency with or without IgG4 deficiency. Recently, a number of inflammatory diseases, including some forms of pancreatitis, were found to be associated with an elevated IgG4 level. The causes for this elevation are not clear at this point.

## Clinical Presentations of IgG Subclass Deficiency

Patients with any form of IgG subclass deficiency occasionally suffer from recurrent respiratory infections similar to the ones seen in other antibody deficiency syndromes, chiefly infections with encapsulated bacteria like *Streptococcus pneumoniae* and *Haemophilus influenzae*. An increased frequency of viral upper respiratory infections may not be an indication of antibody deficiency. Therefore, it is critical to distinguish between infections caused by respiratory viruses from those due to bacterial pathogens.

Often a child with IgG subclass deficiency will first come to a healthcare provider’s attention because of recurrent ear and/or sinus infections, but bronchitis and

pneumonia may also have occurred. The infections in patients with selective IgG subclass deficiency may not be as severe as infections in patients with more significant antibody and immunoglobulin deficiencies, such as Agammaglobulinemia or Common Variable Immune Deficiency (CVID).

However, a few patients with IgG subclass deficiency may appear very similar to patients with severe immunoglobulin deficiencies. Rarely, IgG subclass deficient patients may have recurrent episodes of bacterial meningitis or infections of the bloodstream (sepsis).

## Diagnosis of IgG Subclass Deficiency

Measurement of IgG subclass levels is not universally recommended as part of the evaluation of antibody mediated immunity in patients with recurrent or severe infections. Assessing IgG subclasses adds cost and is not always reliable so that all abnormal values need to be repeated at least once in a separate blood sample. When subclasses are measured, all four subclasses should be determined at the same time.

It is important to consider that IgG subclass levels vary up or down over time, and the normal ranges used in different laboratories also vary. The “normal range” values are usually defined as those values found in 95% of normal individuals of that person’s age. Unfortunately, some physicians and patients forget when using this range that 2.5% of normal individuals will then have values that fall below that “normal” range and 2.5% of normal individuals will have values above that range. (See chapter titled “Laboratory Tests.”) Therefore test values below the “normal range” may not necessarily indicate an abnormally low value, particularly if the value is only a small distance below the stated range.

The finding of an IgG subclass deficiency should prompt reevaluation over a period of months before determining

that the patient is truly immunodeficient. Subclass deficiencies need to be carefully interpreted taking into account the clinical status of the patient as well as the person’s ability to produce specific antibodies in response to vaccines.

Measurement of IgG subclasses can be recommended in the presence of known associated abnormalities, particularly if recurrent infections are also present.

These circumstances include:

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

Another indication for evaluation could be confirmation of a prior diagnosis of IgG subclass deficiency made at another lab or clinic.

## Inheritance of IgG Subclass Deficiency

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 IgA deficiency or CVID. A partial gene deletion has been found in a few patients with IgG subclass deficiency.

## Treatment of IgG Subclass Deficiency

Recurrent or chronic infections of the ears, sinuses and lungs need comprehensive treatment to prevent permanent damage that might result in hearing loss or chronic lung disease. It is also important to encourage patients to continue normal activities of daily living, such as school or work.

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.

Ig therapy is an option for selected symptomatic patients that have persistent IgG subclass deficiencies, documented poor responses to polysaccharide vaccines and who fail prophylactic antibiotic therapy. (*See chapter titled “Immunoglobulin Therapy and Other Medical Therapies for Antibody Deficiencies.”*) The decision to begin Ig replacement therapy needs to be carefully discussed with the healthcare provider, and most insurers will require documentation that more conservative treatment has failed. In addition to lab studies showing persistently low IgG subclass levels and deficient antibody responses to vaccines, this may also include culture

evidence of bacterial infection, X-ray studies consistent with active infection and documentation that antibiotic treatment was unsuccessful in controlling the infections.

Since many young children appear to outgrow their IgG subclass deficiencies, as they get older, it is important to reevaluate the patient to determine if the subclass deficiency is still present. Reevaluation requires discontinuation of Ig replacement therapy (usually in the summer months when infections are less frequent) and at least four to six months of observation before IgG levels are re-tested. If the subclass deficiency has resolved, Ig replacement therapy may no longer be needed. If infections recur, Ig therapy may be reinstated. In teenagers and adults, the subclass deficiency is less likely to be outgrown or resolve.

Patients with frequent infections and persistent IgG subclass deficiencies with normal anti-polysaccharide antibodies should also be treated using adequate prevention, vaccine and antibiotic therapy, perhaps even considering the use of Ig replacement if other treatment fails. However some insurers may not cover the costs of Ig replacement in such cases and the costs associated usually run to many thousands of dollars yearly.

## Expectations for Patients with IgG Subclass Deficiency

The natural history of patients with selective 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 patients with a persistent deficiency, the use of 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. However, IgG subclass deficiencies may persist in some children and adults. In some instances, a selective IgG subclass deficiency may develop into a more serious antibody deficiency, such as CVID. (*See chapter titled “Common Variable Immune Deficiency.”*) At this time, it is not possible to determine which patients will have the transient type of subclass deficiency and which patients may later develop 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



## Chapter 6

*Among the five classes of immunoglobulins: IgG, IgA, IgM, IgD, and IgE, IgG has the predominant role in protection against infection. Some patients have normal levels of immunoglobulins and all forms of IgG, but do not produce sufficient specific IgG antibodies that protect us from some viruses and bacteria. Patients who otherwise produce normal immunoglobulin levels but who lack the ability to produce protective IgG molecules 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 of Specific Antibody Deficiency

The previous chapters described forms of hypogammaglobulinemia and IgG subclass deficiencies in which patients may have recurrent infections due to a lack or low level of these IgG molecules. 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. They 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. Normally, most children begin to make stronger immune responses to these bacteria around 2 years of age, and can 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 have 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 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 patients 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 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 of Specific Antibody Deficiency

Recurrent ear infections, sinusitis, bronchitis and pneumonia are the most frequently observed illnesses in patients with SAD. Some patients will show an increased frequency of infection beginning in the first years of life. In other patients, the onset of infections may occur later. Often a child with SAD will first come to the physician's attention because of recurrent ear or other respiratory infections. At any age, recurrent or chronic sinusitis, bronchitis and/or pneumonia may develop. In general,

the infections suffered by patients with SAD are not as severe as those suffered by patients who have combined deficiencies of IgG, IgA and IgM, like X-linked Agammaglobulinemia (XLA) or Common Variable Immune Deficiency. However, patients may present with a single severe pneumonia or other infection at the time of diagnosis.

## Diagnosis of Specific Antibody Deficiency

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, IgG subclasses and antibody titers to specific bacteria such as tetanus, diphtheria, and/or *Streptococcus pneumoniae*. When total immunoglobulins or IgG subclasses are low, a more profound immunodeficiency is usually present. Some patients have low antibody titers to *Streptococcus pneumoniae* during the initial evaluation, and this finding usually requires vaccination and additional testing. Patients 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 titers to 23 strains (serotypes) of these bacteria. Antibody titers are measured again four to six weeks later to determine if adequate protective antibody titers were produced. It is felt that normal individuals respond to a majority of the

serotypes in these vaccines and retain those protective titers for years after receiving it. Antibody responses may not last as long in young children. For therapy, it is also possible to reimmunize with Pevnar 13, a different type of pneumococcal vaccine, which, for most patients, may be more immunogenic than Pneumovax. However, this vaccine cannot be used to diagnose SAD.

The criteria for the diagnosis of SAD have been somewhat controversial. However, most immunologists now agree that several patterns of response are seen after receiving the vaccine. Patients may fail to respond to any of the serotypes included in the vaccine and have a more severe form of SAD. 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. An additional subset of patients appears to respond normally initially then lose protective levels within months.

## Inheritance of Specific Antibody Deficiency

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

## Natural History of Specific Antibody Deficiency

The natural history of patients with SAD is not completely understood. SAD seems to occur more often in children, probably due to 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. Both IgG subclass deficiencies and SAD may evolve into CVID. (*See chapter titled “Common Variable Immune Deficiency.”*) At the

present time, it is not possible to determine which patients will have the transient type of deficiency and in which patients 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 titers is necessary.

## Treatment of Specific Antibody Deficiency

Patients with SAD frequently suffer 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 patients 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 (like prophylaxis) of infections.

For immunodeficiency diseases in which patients are unable to produce adequate levels of the major immunoglobulin classes (IgG, IgA and IgM) and fail to make antibodies against proteins or polysaccharide antigens, like XLA and CVID, immunoglobulin (Ig) replacement therapy is clearly needed. (*See chapter titled “Immunoglobulin Therapy and Other Medical Therapies for Antibody Deficiencies.”*)

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 patients with SAD in whom infections and symptoms can be controlled with antibiotics, Ig replacement therapy is usually not necessary. However, for patients 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 the patient to determine if the deficiency is still present. If replacement therapy has been initiated, reevaluation requires discontinuation of Ig therapy and at least four to six months of observation before immunity is re-evaluated. Measurement of antibody levels and consideration of re-immunization with pneumococcal vaccines is done at this time. If the response to vaccination is adequate, Ig therapy may be discontinued and the patient 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 for Patients with Specific Antibody Deficiency

The outlook for patients with SAD is generally good. Many children appear to outgrow their deficiency as they get older, usually by age 6. For those patients for whom the deficiency persists, the use of 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.

# Transient Hypogammaglobulinemia of Infancy



## Chapter 7



*An unborn baby makes no IgG (antibody) and only slowly starts producing it after birth. However, starting at about the sixth month of pregnancy, the fetus starts to receive maternal IgG antibody through the placenta. This increases during the last trimester of pregnancy until at term birth the baby has a level of IgG, the main class of antibody in the circulation, equivalent to that of the mother.*

## Transient Hypogammaglobulinemia of Infancy

The baby does not get any maternal IgM, IgA or IgE as they do not cross the placenta, so if IgM is found it may suggest the baby has encountered an infection in utero. If the baby is born prematurely, the IgG level is lower than that of a term infant, in proportion to the degree of prematurity. The IgG from the mother protects the baby from many infections in the first months of life.

The newborn baby may get additional antibody via breast feeding, but this antibody does not get absorbed from the baby's gastrointestinal tract. However its presence in the baby's pharynx and intestinal tract protects the baby from diarrheal diseases, and to some extent from respiratory disease.

The transplacental IgG slowly disappears from the infant's circulation and is essentially all gone by about 6 months of age. The baby, however, starts to make its own IgG starting at birth and this increases gradually

throughout the first months of life. Between 3 and 6 months all infants have low levels of IgG as a result of the maternal IgG falling and the infant's IgG just starting to be made. This low level is termed physiologic hypogammaglobulinemia of infancy and is usually not clinically significant. It is more pronounced in premature infants because the amount of IgG from the mother is decreased.

In addition to lower levels of IgG and other immunoglobulins, the newborn's immune system is immature and does not respond as well to vaccines or infections, so it is more vulnerable to many infectious diseases.

In some infants the period of hypogammaglobulinemia is more severe or prolonged beyond 6 months of age. This is termed transient hypogammaglobulinemia of infancy (THI) and is the subject of this chapter.

## Definition of Transient Hypogammaglobulinemia of Infancy

THI is defined in infants over 6 months of age whose IgG is significantly lower (less than 2 standard deviations) than 97% of infants at the same age. This most commonly is corrected by 24 months of age but may persist for a few more years. Typically the IgG level is less than 400 mg/dl and IgA and IgM antibodies may

also be lower. However the ability of these infants to make antibodies is frequently near normal and most of the patients are not unusually susceptible to infection.

The frequency of THI is unknown. It has been described in all parts of the world and is believed to be

### (Definition of THI continued)

significantly underdiagnosed. There is a male predominance (2:1), and approximately 60% of patients are discovered by age 1 and the remaining 40% thereafter, often times not until age 5 or 6. In one survey of 17 immunodeficiency centers within the U.S., THI was found to represent about 2% of immunodeficient patients.

Most children with THI are diagnosed because they have recurrent infections. Others are diagnosed because another family member was diagnosed with immunodeficiency. Immune globulin levels are not routinely measured in normal infants so that the actual incidence of asymptomatic THI may be considerably higher.

## Cause of Transient Hypogammaglobulinemia of Infancy

Proposed causes for THI include: (1) suppressive maternal antibodies (IgG) which cross the placenta and suppress fetal immunoglobulin production; (2) genetic variation in certain families with a propensity to immunodeficiency; (3) abnormal T-lymphocytes that fail

to stimulate antibody production by B-cells; (4) unbalanced cytokine production; (5) abnormal or immature B-cells, not unlike patients with Common Variable Immune Deficiency (CVID).

## Clinical Features of Transient Hypogammaglobulinemia of Infancy

The usual clinical features include upper respiratory tract infections (in about two-thirds of patients), lower respiratory tract infections (approximately a third of patients), allergic manifestations (one-half of patients) and gastrointestinal difficulties (in 10% of patients). Typically, children have a combination of these symptoms. Ear and sinus infections are most common. Nasal and throat infections as well as swollen glands are also seen. Bronchitis, bronchiolitis or pneumonia are less common. Occasionally, severe chickenpox, persistent thrush (candida on the mucous membranes of the mouth) and urinary tract infections are reported. Severe infections from live viral vaccines have not been reported. Severe life-threatening infections are rare but have included severe pneumonia, opportunistic infections

caused by fungi or staphylococcus, gastrointestinal problems or bloodstream infections.

As in many disorders with immune dysregulation or immaturity, allergic diseases may be present including asthma (25%), eczema (15%) and food allergy (12%). Gastrointestinal symptoms may include chronic diarrhea, persistent vomiting, food allergy and/or intolerance. Neutropenia (low white blood cells) is not uncommon.

Most infants with THI appear normal with none of the classic findings present in other primary immunodeficiency diseases, although the tonsils and lymph nodes may be small. The chest x-ray is usually normal, and the thymus is typically normal in size.

## Diagnosis of Transient Hypogammaglobulinemia of Infancy

By definition, the IgG level is lower than two standard deviations below the mean for age. More than one-half of children with THI have IgG levels as low as 200 mg/dl. Levels less than 100 mg/dl and/or pan-hypogammaglobulinemia (very low IgM and IgA as well as IgG) may suggest a permanent immunodeficiency.

Most children with THI produce normal antibodies to vaccines including tetanus, diphtheria, conjugated Haemophilus influenzae, hepatitis A and B vaccines as well as to measles, mumps and rubella vaccines. In the U.S. most infants receive the conjugated pneumococcal vaccine (Pevnar 13) and will respond adequately. Tetanus antigen is a potent vaccine and lack of response suggests a more serious defect and should prompt a more comprehensive evaluation.

If the child lacks protective antibodies against a prior vaccine, a booster shot can be given and the antibody

response checked four to six weeks later. If the antibody response is poor, repeat titers may be done in six months. If the young child continues to have frequent or severe infections, additional studies and referral/consultation with an immunologist might be required.

A complete blood count with differential may suggest a primary immunodeficiency. B- and T-cell enumeration is indicated if there is lymphopenia, persistent or severe fungal infections, failure to thrive, chronic diarrhea, and infections with opportunistic microorganisms or severe skin disease.

Chest or sinus X-ray or CT scans may be helpful in the child with chronic respiratory tract infection.

## Treatment of Transient Hypogammaglobulinemia of Infancy

For asymptomatic infants and young children, no treatment is required. Clinical observation and supportive counseling may be all that is required. IgG levels should be repeated every four to six months.

For infants with recurrent or persistent infections, common sense measures such as reducing exposure to infections (e.g. choosing a smaller day care center, judicious restriction of exposure to other children) and prompt and appropriate treatment of respiratory infections is warranted. Inactivated (killed) vaccines (diphtheria, tetanus, pertussis, Haemophilus influenzae and pneumococcal vaccines, killed influenza vaccine, killed polio vaccine, inactivated Hepatitis A and B vaccines) should be given as scheduled.

Live viral vaccines (measles, mumps, rubella, Varicella, Rotavirus) should be postponed. (*See chapter titled*

*“General Care.”*) Occasionally, prophylactic antibiotic therapy during the respiratory infection season may be prescribed. Monitoring immunoglobulin levels and vaccine antibody levels are done at four to six month intervals.

Immunoglobulin (Ig) replacement therapy is not usually necessary except in rare instances when infections are severe and the child is not thriving. Ig administration will mask or even delay the recovery of these patients. If the child is doing well on Ig for several months, a trial off of Ig therapy is indicated. Generally in cases such as this, Ig treatment is discontinued in the spring or summer when respiratory infections are not as prevalent and the child is retested when the child has been off of Ig for four to five months.

## Expectations for Patients with Transient Hypogammaglobulinemia of Infancy

Most children with THI develop age appropriate levels of IgG by age 3. Another 40% attain normal levels by age 5, but 10% may persist beyond this age. In those children with protracted hypogammaglobulinemia, some may develop normal IgG levels but have persistent selective antibody deficiency (impaired response to polysaccharide antigen). Some may have selective IgG subclass deficiency, have persistent infections and may require prolonged antibiotic therapy.

Some children, whose hypogammaglobulinemia persists beyond 5 years of age, may have adequate antibody responses and do not experience serious infections. Why this occurs, is subject to debate. Occasionally, some patients with THI develop serious infections, have persistently low IgG levels and functional antibody defects and may have a CVID-like disease that persists for several years or permanently.

# Other Antibody Deficiency Disorders



## Chapter 8

*In addition to the more common immunodeficiencies described in other chapters, there are several other rare, but nevertheless well-described, antibody deficiency disorders. Similar to the patients described in the chapters on X-Linked Agammaglobulinemia (XLA), Hyper IgM Syndrome, Selective IgA Deficiency, Common Variable Immune Deficiency (CVID) and Specific Antibody Deficiency (SAD), individuals with less common antibody deficiencies usually present with upper respiratory infections or infections of the sinuses or lungs, typically with organisms like streptococcus pneumonia and hemophilus influenzae. Laboratory studies show low immunoglobulins and/or deficient specific antibody production. Many of these disorders also include abnormalities in the cells responsible for generating or maintaining an antibody response. The patients often improve with antibiotics but get sick again when these are discontinued. The cornerstone of therapy for antibody deficiency disorders is immunoglobulin (Ig) replacement.*

### **Antibody Deficiency with Normal or Elevated Immunoglobulins**

These patients have severe infections similar to patients with CVID, but their immunoglobulin levels are normal or elevated. They have decreased antibody levels to most vaccine antigens, both protein and polysaccharide, which differentiates them from patients with selective antibody deficiency.

### **Selective IgM Deficiency**

These patients have low IgM (less than 30 mg/dl in adults, less than 20 mg/dl in children) with recurrent infections that are often severe. There are variable antibody responses. Some patients are asymptomatic. This disease may be clinically similar to CVID though it should not be referred to by that name. It is important to note that IgM deficiency is also seen commonly in DOCK8 deficiency, typically in association with normal IgG and elevated IgE.

### **Immunodeficiency with Thymoma (Good's Syndrome)**

This primary immunodeficiency is characterized by low immunoglobulins together with a thymic tumor (thymoma). Good's Syndrome is usually first suspected when a thymic tumor is seen on a chest X-ray although in about half the cases the history of recurrent infections precedes the detection of the thymoma. Most patients are adults. Removal of the thymoma does not cure the immunodeficiency although it may help other symptoms. Eosinophils may be very low or undetectable in these patients.

### **Transcobalamin II Deficiency**

Transcobalamin 2 is a protein that transports vitamin B12 to the tissues from the gastrointestinal tract. A hereditary deficiency is associated with anemia, failure to thrive, low white cell counts and hypogammaglobulinemia. It can be treated with B12 injections.

(Other Antibody Deficiency Disorders continued)

## Warts, Hypogammaglobulinemia, Infection, Myelokathexis (WHIM) Syndrome

WHIM is an autosomal recessive disorder with severe warts, recurrent bacterial and viral infections, low but not absent immunoglobulins and neutropenia (low granulocytes). (See chapter titled “Inheritance.”) The neutropenia is due to failure of the bone marrow to release granulocytes into the blood stream (myelokathexis). WHIM is caused by a defective gene for CXCR4, a chemokine receptor protein that regulates leukocyte movement. In addition to Ig replacement, treatment includes granulocyte growth factor (G-CSF).

## Drug-Induced Antibody Deficiency

Technically this is not considered a primary immunodeficiency disease but must be ruled-out as a cause for antibody deficiency during the evaluation of any patient presenting with defective antibody production. Several medications may depress immunoglobulin and antibody levels, and this may result in recurrent infections. The chief drugs implicated include high-dose steroids (particularly when given intravenously), anticonvulsant drugs (Dilantin and others), anti-inflammatory drugs used for arthritis, and the monoclonal antibody, Rituximab (Rituxan). Rituximab specifically targets B cells, the precursors of the antibody-producing plasma cells. In some instances, severe and permanent agammaglobulinemia can occur with drug therapy, but usually the hypogammaglobulinemia reverses when the drug is discontinued. If antibody deficiency and insufficient response to vaccine challenge persists when the drug is stopped, Ig replacement may be needed.

## Kappa Chain Deficiency

This Ig light chain deficiency is inherited from both parents (autosomal recessive). Susceptibility to infection may be due to reduced activation of B-cells to make antibody and to a reduced variety of antibodies. However, some patients may be asymptomatic.

## Heavy Chain Deficiencies

In rare individuals, multiple genes that code for different immunoglobulins (IgA, IgG1, IgG2, etc.) may be missing (deleted). These people can only make one or a few types of immunoglobulin (for example, only IgM and IgG3). These individuals may exhibit susceptibility to respiratory and other infections, but they are also often asymptomatic.

## Post-Meiotic Segregation (PMS2) Disorder

*PMS2* gene mutation leads to defective Ig class switching from IgM to IgG and IgA. It is a very rare primary immunodeficiency resulting in low serum IgG and IgA with elevated serum IgM. This disorder results in café-au-lait spots on the skin, and patients have a predisposition to several types of malignancies.

## Unspecified Hypogammaglobulinemia

This diagnosis applies to all forms of low concentrations of serum immunoglobulins, like IgG, IgA, IgM deficiency. In general, these patients are not found to have impaired ability to produce adequate levels of vaccine antibody. It is somewhat of an older term to describe a patient with one or more deficiencies of these serum immunoglobulins. In some patients, unspecified hypogammaglobulinemia may simply be a physiologic variant without any clinical significance. However, it may indicate a developing immunodeficiency and should be monitored, particularly if the patient begins to develop frequent and/or severe infections.

# Severe Combined Immune Deficiency and Combined Immune Deficiency



## Chapter 9



*Severe Combined Immune Deficiency (SCID, pronounced "skid") is a potentially fatal primary immunodeficiency in which there is combined absence of T-lymphocyte and B-lymphocyte function. 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 the most serious of the primary immunodeficiencies. Fortunately, effective treatments, such as stem cell transplantation, exist that can cure the disorder. The future holds the promise of gene therapy for several more types of SCID.*

## Definition of Severe Combined Immune Deficiency

SCID is a rare, potentially 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, or NK, lymphocyte function). The different genetic causes of SCID vary with respect to laboratory findings and patterns of inheritance.

### Deficiency of the Common Gamma Chain of the T-Cell Receptor (X-SCID)

The most common form of SCID, affecting nearly 45% of all cases, is due to a mutation in a gene on the X chromosome that encodes a component (or chain) shared by the T-cell growth factor receptor and other growth factor receptors. This component is referred to as  $\gamma_c$ , for common gamma chain. Mutations in this gene result in very low T-lymphocyte and NK-lymphocyte counts, but the B-lymphocyte count is high (a so-called T-, B+, NK- phenotype). Despite the high number of B-lymphocytes, there is no B-lymphocyte function since the B-cells have abnormal receptors for growth factors on their cell surfaces. (See chapter titled "The Immune System and Primary Immunodeficiency Diseases.")

This deficiency is inherited as an X-linked recessive trait. (See chapter titled "Inheritance.") 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.

### Adenosine Deaminase Deficiency

Another 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 15% of cases. Babies with this type of SCID have the lowest total lymphocyte counts of all, and T, B and NK-lymphocyte counts are all very low. This form of SCID is inherited as an autosomal recessive trait. (See chapter titled "Inheritance.") Both boys and girls can be affected. Lack of the ADA enzyme also leads to neurological problems such as cognitive impairment, hearing and visual impairment, low muscle tone and movement disorders. The neurological problems are not fully curable by bone marrow transplantation.

### Deficiency of the Alpha Chain of the IL-7 Receptor

Another form of SCID is due to mutations in a gene that encodes another growth factor receptor component, the alpha chain of the IL-7 receptor (IL-7R $\alpha$ ). When T, B and NK-cell counts are done, infants with this type have B- and NK-cells, but no T-cells. However, the B-cells do not work because of the lack of T-cells. IL-7R $\alpha$  deficiency is

## (Definition of Severe Combined Immune Deficiency continued)

the third most common cause of SCID accounting for 11% of SCID cases. It is inherited as an autosomal recessive trait. (See chapter titled "Inheritance.") Both boys and girls can be affected.

### Deficiency of Janus Kinase 3

Another type of SCID is caused by a mutation in a gene that encodes an enzyme found in lymphocytes called Janus kinase 3 (Jak3). This enzyme is necessary for function of the above-mentioned  $\gamma$ c. Thus, when T, B and NK-lymphocyte counts are done, infants with this type look very similar to those with X-linked SCID, they are T-, B+, NK-. Since this form of SCID is inherited as an autosomal recessive trait both boys and girls can be affected. (See chapter titled "Inheritance.") 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 a group of molecules on the surface of T-lymphocytes, the T-cell receptor complex, CD3. These SCID-causing gene mutations result in deficiencies of CD3 $\delta$ ,  $\epsilon$  or  $\zeta$  chains. These deficiencies are also inherited as autosomal recessive traits.

### Deficiency of CD45

Another type of SCID is due to mutations in the gene encoding CD45, a protein found on the surface of all white cells that is necessary for T-cell function. This deficiency is also inherited as an autosomal recessive trait.

### Other Causes of SCID

Five more types of SCID for which the molecular cause is known are those due to mutations in genes that encode proteins necessary for the development of the immune recognition receptors on T- and B-lymphocytes. These are: recombinae activating genes 1 and 2 (RAG1 and RAG2) deficiency (in some instances mutations in these genes also cause Omenn's Syndrome), Artemis deficiency, Cernunnos deficiency, and Ligase 4 deficiency. Infants with these types of SCID lack T- and B-lymphocytes but have NK-lymphocytes, that is they have a T-B-NK+ phenotype. These deficiencies are all inherited as autosomal recessive traits. (See chapter titled "Inheritance.")

Finally, there are probably other SCID-causing mutations that have not yet been identified.

## Less Severe Combined Immunodeficiencies

There is another group of rare genetic disorders of the immune system that results in combined immunodeficiencies that usually do not reach the level of clinical severity that would qualify them as severe combined immunodeficiency. Unfortunately, this distinction and thus the prognosis is not always easy to determine at the level of the individual child. This becomes important when considering the relative potential risks vs. the potential benefits of a particular

treatment strategy. Fortunately, the success rate of stem cell transplantation, particularly for patients 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.

A list of several of these disorders follows, although there may be additional syndromes that qualify for

## (Less Severe Combined Immunodeficiencies continued)

inclusion as combined immunodeficiency (CID) that are not listed. These disorders include Bare Lymphocyte syndrome (MHC class-II deficiency); purine nucleoside phosphorylase (PNP) deficiency; ZAP70 deficiency; CD25 deficiency; Cartilage-Hair Hypoplasia; Coronin 1A deficiency and MHC class I deficiency. Sometimes a

child with clinical CID is found to have a mutation in a gene (listed previously under Other Causes of SCID) 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.

## Clinical Presentation of Severe Combined Immune Deficiency

Severe infection is the most common presenting symptom of patients with SCID. These infections are not usually the same infections that normal children have. The infections of the patient with SCID can be much more serious and even life threatening, and may include pneumonia, meningitis 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 patient must have a high index of suspicion in order to detect this condition.

Children with SCID may develop infections caused by organisms or vaccines, which are usually not harmful in children who have normal immunity. Among the most dangerous is an organism called *Pneumocystis jiroveci*, which can cause a rapidly fatal pneumonia (PCP) if not diagnosed and treated promptly.

Another dangerous organism is the chicken pox virus (varicella). Although chicken pox is annoying and causes much discomfort in healthy children, its effects are usually limited to the skin and mucous membranes and the disease resolves in a matter of days. In the patient with SCID, chicken pox can be fatal because it does not resolve and can progress to cause infection in the lungs, liver and brain. Cytomegalovirus (CMV), which nearly all people carry in their salivary glands, may cause fatal pneumonia in patients with SCID.

Other dangerous viruses for patients with SCID are the cold sore virus (Herpes simplex), adenovirus,

parainfluenza 3, Epstein-Barr virus (EBV, the infectious mononucleosis virus), polioviruses, measles virus (rubeola) and rotavirus.

Since vaccines for chicken pox, measles, mumps, rubella and rotavirus are live virus vaccines, children with SCID can contract infections from those vaccine viruses if they receive these immunizations. If 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 it has been determined that the new infant does not have SCID. This is especially a problem with the rotavirus vaccine, which is routinely given when babies are 6-8 weeks old. The baby with SCID may not have been diagnosed by this time unless the disease has been discovered in the infant’s newborn screening. Note that newborn screening for SCID is not yet universal in the United States although the number of states that screen is increasing each year. (*See chapter titled “Newborn Screening.”*)

Fungal (yeast) infections in patients with SCID may be very difficult to treat. As an example, candida fungal infections of the mouth (thrush) are common in most babies but usually disappear spontaneously or with simple oral medication. In contrast, in the child with SCID, oral thrush does not spontaneously resolve. When antifungal medicines are given it may improve, but it does not go completely away and usually recurs as soon as the medication is stopped. The diaper area may also

## (Clinical Presentation of Severe Combined Immune Deficiency continued)

be an area where candidal infections can occur. Occasionally, candida pneumonia, abscesses, esophageal infection or even meningitis may develop in patients with SCID.

Persistent diarrhea, resulting in growth failure or malabsorption, is a common problem in children with SCID. The diarrhea may be caused by the same bacteria, viruses or parasites, which affect normal children. However, in the case of patients with SCID, the organisms are difficult to get rid of once established. Often, the intestines in patients with SCID function poorly even in the absence of infection.

The skin may also be involved in children with SCID. The skin may become chronically infected with the same fungus (candida) that causes thrush. Patients with SCID may also have a rash that is mistakenly diagnosed as eczema, but 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). Sometimes a small number of T-cells develop in the infant and attack the GI tract (causing diarrhea) and the skin causing a similar rash. This is called Omenn's syndrome.

## Diagnosis of Severe Combined Immune Deficiency

The diagnosis of SCID is usually first suspected in children because of the clinical features discussed previously. However, in some instances, there has been a previous child with SCID in the family, and this positive family history may prompt diagnostic screening for SCID before the child develops any symptoms. In some states, screening for SCID is done on every newborn via routine newborn screening. (*See chapter titled "Newborn Screening."*)

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 healthcare provider 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 lymphocyte count for patients with all types of SCID is 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 and counted. 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 of T-cell function. The most definitive test to examine the function of the T-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

## (Diagnosis of Severe Combined Immune Deficiency continued)

undergoing cell division. In contrast, lymphocytes from patients with SCID usually do not react to these stimuli.

Immunoglobulin levels are usually very low in SCID. Most commonly (but not always), all immunoglobulin classes are depressed (IgG, IgA, IgM and IgE). Since IgG from the mother passes into the baby's blood through the placenta, it is often present in the newborn's and young infant's blood at nearly normal levels. Therefore, IgG deficiency may not be present in babies with SCID until the transferred maternal IgG is metabolized away. This may take a few months.

The diagnosis of SCID can also be made before the baby is born if there has been a previously affected infant in the family and if the gene defect has been identified. If genetic analysis had been completed on the previously affected infant, a diagnosis can be determined during subsequent pregnancies. This can be done by molecular testing of cells from a chorionic villous sampling (CVS) or from an amniocentesis, where a small amount of amniotic fluid (which 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 fetus is a female, she would not be affected.

In a majority of cases, unless termination of the pregnancy is a consideration if the fetus is affected, the diagnosis is best made at birth on cord blood lymphocytes, since there is some risk to the fetus by the above procedures or if blood is collected for lymphocyte studies while the baby is in utero.

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 months of life have a 94% success rate. In fact, screening newborns to detect SCID soon after birth has been made possible because of recent scientific advances. Approximately half of the babies born in the U.S. are now being screened for SCID. If routine screening were extended to infants born in all states, nearly every infant with SCID could be diagnosed within days of birth. The search for a donor could then begin, and most of these babies that do not require "conditioning" should be able to undergo stem cell transplantation or gene therapy within the three month window of time after birth that has the highest chance for a successful outcome.

## Inheritance of Severe Combined Immune Deficiency

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 where both parents carry a defective gene. (*See chapter on "Inheritance."*)

Parents of children with SCID should seek genetic counseling so that they are aware of the risks of future

pregnancies and can make informed decisions about childbearing.

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 of Severe Combined Immune Deficiency

Children with this life-threatening condition need all the support and love that parents can provide. 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 a patient 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. If the stress of the child's illness and treatment destroys the family structure, a successful therapeutic outcome for the patient is a hollow victory. In addition to medical care, patients and families will require psychosocial support and care.

Until definitive treatment such as stem cell transplantation, the infant with SCID needs to be isolated from children outside the family, especially from young children. If there are siblings who attend daycare, religious school, kindergarten or grade school, the possibility of bringing infectious illnesses into the home represents the greatest danger.

Nevertheless, the parents need to alert the school authorities as to this danger, so that they can be notified, particularly if and when chickenpox is in the school. If the siblings have been vaccinated or have had chickenpox, there is no danger. If the siblings have a close exposure and they have not been vaccinated nor had chickenpox themselves, they should live in another house during the incubation period (11-21 days). Examples of close contacts for the sibling would be sitting at the same reading table, eating together or playing with a child who breaks out in the "pox" anytime within 72 hours of that exposure.

If the sibling breaks out with pox at home and exposes the patient, the patient should receive varicella immunoglobulin or immunoglobulin replacement therapy immediately. If, despite this, the infant with SCID breaks out with pox, the infant should be given intravenous acyclovir in the hospital for 5-7 days.

Usually the child with SCID should not be taken to public places (day care nurseries, church nurseries, 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 chapter titled "General Care.")

Death from infection with *Pneumocystis jiroveci*, a widespread organism which rarely causes infection in normal individuals, but causes pneumonia in patients with SCID, is a common occurrence in this syndrome. Pneumonia from this organism can be prevented by 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 doctor suspect that your child has a serious immunodeficiency, you should not allow rotavirus, chicken pox, mumps, rubella, measles, live virus polio or BCG vaccinations to be given to your child until their immune status has been evaluated. As mentioned above, the patient's siblings should not receive the new rotavirus vaccine. There is usually not a problem if the patients' siblings receive the other live viral vaccines. The exception to this could be the chickenpox vaccine. If the sibling develops a rash with blisters, chicken pox could be transmitted to the child with SCID.

### (General Treatment of Severe Combined Immune Deficiency continued)

If your baby with SCID needs to have a blood or platelet transfusion, the product should be irradiated (to kill T-lymphocytes in the blood that could attack the infant), it should test negative for the CMV virus (to prevent

possible infection with this virus) and it should be depleted of leukocytes (white blood cells), in order to prevent possible interference with future bone marrow transplant.

## Specific Therapy of Severe Combined Immune Deficiency

Immunoglobulin therapy should be given to all infants with SCID. Although immunoglobulin 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 of benefit.

For patients with SCID due to ADA deficiency, replacement therapy with a modified form of the enzyme (from a cow, called PEG-ADA) has been used with some success. The immune reconstitution with PEG-ADA is not as good as with a transplant and is not a permanent cure; it requires two intramuscular injections weekly for the rest of the child's life. Simultaneous PEG-ADA treatment is not recommended if the patient has the opportunity for a stem cell transplant or gene therapy because it may interfere with engraftment of the donor or gene-corrected cells. In this case, the PEG-ADA treatment can be stopped for a few days before those treatments so as to not interfere with their success.

The most successful therapy for SCID is immune reconstitution via stem cell transplantation. Stem cell transplantation for SCID is best performed at medical centers that have had experience with SCID and where there are pediatric immunologists overseeing the transplant. Stem cells for the transplant can be obtained from the bone marrow, peripheral blood or even from cord blood from related or unrelated donors that at least partially match the tissue type of the patient.

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

three decades that permit good success with matched unrelated donors and even 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 60-70%. However, the outcomes are better if the donor is a matched sibling (>85% success rate) and if the transplant can be performed soon after birth or at less than 3.5 months of life (>96% survival even if only half-matched). HLA-matched bone marrow or cord blood transplantation from unrelated donors has also been used successfully to treat SCID, and the immune reconstitution after these types of transplants is often better than when a half-matched parent is a donor.

There does not appear to be any advantage to in utero marrow stem cell transplantation over transplantation performed immediately after birth. For in utero transplantation, the mother would probably not be able to be used as the donor since anesthesia required for the bone marrow harvesting procedure would cause some risk to the fetus. In addition to potential risk for the mother and baby, there is no way to detect GVHD in the infant who has undergone an in utero transplant.

Finally, another type of treatment that has been explored over the past two decades is gene therapy. Gene therapy has been used successfully in patients with both X-linked and ADA SCID and research in this area is ongoing. One cannot perform gene therapy unless the abnormal gene is known, hence the importance of making a molecular diagnosis.

## Expectations for Patients with Severe Combined Immune Deficiency

SCID is generally considered to be the most serious of the primary immunodeficiencies. Without a successful stem cell transplant, enzyme replacement therapy or gene therapy, the patient is at constant risk for severe or fatal infections. With a successful transplant, the patient's own defective immune system is replaced with a normal immune system, and normal T-lymphocyte

function is restored. Usually, but not always, there is correction of the B-cell defect so the transplanted infant makes their own immune globulin and no longer needs immunoglobulin replacement therapy. The first bone marrow transplantation for SCID was performed in 1968. That patient is alive and well today.



# Wiskott-Aldrich Syndrome



## Chapter 10

*Wiskott-Aldrich syndrome (WAS) is unique among primary immunodeficiency diseases because, in addition to being susceptible to infections, patients have problems with abnormal bleeding. The bleeding problems are the result of unusually small, dysfunctional platelets (blood cells that play an important role in the formation of blood clots). For patients with WAS, this leads to unique health challenges that are not typically seen in other immunodeficiency disorders. 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 of Wiskott-Aldrich Syndrome

Wiskott-Aldrich syndrome was first described in 1937 by Dr. Alfred Wiskott, a German pediatrician who identified three brothers with low platelet counts (thrombocytopenia), bloody diarrhea, skin rash (eczema) and recurrent ear infections. All three subsequently 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 patients 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 chapter titled “Inheritance.”) In 1994, the gene that is defective in patients with WAS was discovered and this subsequently led to the understanding that milder forms of disease exist that have mutations in the same gene.

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

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

In addition to this basic triad of symptoms, patients with WAS also have an increased risk of developing severe autoimmune disease and have an increased incidence of malignancy (cancer), particularly lymphoma or leukemia. (See chapter titled “Autoimmunity in Primary Immunodeficiency.”)

### Bleeding Tendency

Thrombocytopenia (a reduced number of platelets) is a common feature of patients with WAS. In addition to being decreased in number, the platelets themselves are small and dysfunctional, less than half the size of normal platelets. As a result, patients 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 physicians recommend that toddlers with very low platelet counts (<15,000) wear a helmet to protect them from head injuries until treatment is able to raise their platelet count. Since WAS is the only disorder where small platelets are found, their presence is a useful diagnostic test for the disease.

## (Clinical Presentation of Wiskott-Aldrich Syndrome continued)

**Infections**

The immunodeficiency associated with WAS causes the function of both B- and T-lymphocytes to be significantly abnormal. As a result, infections are common in the classic form of WAS and may involve all classes of microorganisms. These infections may include upper and lower respiratory infections such as ear infections, sinus infections and pneumonia. More severe infections such as sepsis (bloodstream infection or “blood poisoning”), meningitis and severe viral infections are less frequent but can occur. Occasionally, patients with the classic form of WAS may develop pneumonia caused by the fungus (*pneumocystis jiroveci carinii*). The skin may become infected with bacteria such as Staphylococcus in areas where patients have scratched their eczema. In addition, a viral skin infection called molluscum contagiosum is also commonly seen in WAS. Vaccination to prevent infections is often not effective in WAS since patients do not make normal protective antibody responses to vaccines.

**Eczema**

An eczema rash is common in patients with classic WAS. In infants, the eczema may occur on the face or scalp and can resemble “cradle cap.” It can also have the appearance of a severe diaper rash, or 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 around the wrist. Since eczema is extremely itchy, patients often scratch themselves until they bleed, even while asleep. These areas where the skin barrier is broken can then 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 and attacks specific cells or organs of the body. Clinical problems caused by autoimmunity are commonplace in WAS, affecting almost half of all patients. Among the most

common autoimmune manifestations observed is the destruction of red blood cells or platelets by auto-reactive antibodies generated inappropriately by the immune system. Red blood cell destruction is called hemolytic anemia and platelet destruction is called idiopathic thrombocytopenic purpura (ITP). ITP can worsen an already low platelet count.

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 muscles, heart, brain or other internal organs, which can cause a range of symptoms. Some patients have a more generalized 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. Each of these autoimmune features may last only a few days or may occur in waves over a period of many years and may be difficult to treat.

**Malignancies**

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

**Milder Forms of Disease**

The clinical presentation of WAS varies from patient to patient. Some patients have all three classic manifestations, including low platelets, 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, patients with XLT

## (Clinical Presentation of Wiskott-Aldrich Syndrome continued)

do not have significant immunodeficiency but they do have an increased risk of malignancy although the risk is not as high as in WAS. Another very rare disorder

associated with a mutation in the WAS gene causes a form of neutropenia called XLN.

## Diagnosis of Wiskott-Aldrich Syndrome

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

The immune problems typically begin to manifest themselves in toddlers and older children when patients begin to develop frequent infections. Evaluation of the

immune system typically shows that patients 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 T-lymphocyte function is often abnormal.

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

## Inheritance of Wiskott-Aldrich Syndrome

WAS is caused by mutations (or alterations) in the WAS gene which produces the Wiskott-Aldrich Syndrome Protein (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 chapter titled "Inheritance."*) This means that boys develop the disease, but their mothers or sisters who may carry one copy of the disease gene, do not have symptoms. Because of the X-linked recessive inheritance, boys with WAS may also have brothers or maternal uncles (mom's brothers) who have the disease. It is estimated that

approximately one-third of newly diagnosed patients with WAS have no identifiable family history and instead, are the result of new gene mutations that occur at the time of conception. Identification of the precise gene mutation of a patient 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 patient 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.

## (Inheritance of Wiskott-Aldrich Syndrome continued)

Identification of the mutation that causes WAS in a particular family not only allows the diagnosis of WAS in a specific patient but also makes it possible to identify females in the family that may carry a mutant copy of

the gene and to perform prenatal DNA diagnosis for any male pregnancies using cells obtained by amniocentesis or chorionic villus sampling.

## Treatment of Wiskott-Aldrich Syndrome

### Vaccines

Because patients with WAS have abnormal T- and B-lymphocyte 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 prevented by early treatment following exposure with antiviral drugs, high dose immunoglobulin replacement therapy or Varicella Zoster Immune Globulin (VZIG). Other “non-live” vaccinations can be given safely to patients with WAS but may not generate protective levels of antibody.

### Infections

Since patients with WAS have abnormal antibody responses to vaccines and to invading microorganisms, most are treated prophylactically with immunoglobulin infusions to prevent infections. Because of the bleeding tendency in WAS, most physicians prescribe intravenous immunoglobulin (IVIG) therapy instead of subcutaneous immunoglobulin (SCIG) injections because of concern that SCIG injections may cause bleeding. Patients who have had a splenectomy are particularly susceptible to rapid, severe bacterial blood stream infections, so immunoglobulin 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

Platelet transfusions are typically not used prophylactically in WAS to increase the platelet count in an attempt to prevent bleeding episodes. In cases of active bleeding or injury however, they may be required to stabilize the patient and prevent organ damage. For example, if serious bleeding cannot be stopped by usual measures, platelet transfusions are indicated. Hemorrhages into the brain usually require immediate platelet transfusions to try and stop the bleeding. Due to increased blood loss, iron deficiency anemia is common among patients 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 in autoantibodies are often trapped by the spleen so they can be destroyed. For patients with WAS, this may become a significant problem. Surgical removal of the spleen (splenectomy) has been performed in these patients in an attempt to correct thrombocytopenia and in many cases, does improve platelet counts. It also improves the ability of high dose immunoglobulin replacement therapy to raise the platelet count. Since the spleen also filters bacteria out of the blood stream, splenectomy significantly increases the susceptibility of patients 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

(Treatment of Wiskott-Aldrich Syndrome continued)

spleen, these infections can be rapidly fatal so it is imperative that the patients receive regular prophylactic antibiotics and immunoglobulin replacement therapy for the remainder of their lives. Splenectomy does not cure the other features of WAS and should only be used to control particularly severe thrombocytopenia.

## Eczema

The eczema in WAS can be severe and persistent, requiring constant care. If known food allergies exist and certain foods make the eczema worse, attempts should be made to remove these items from the diet. Excessive bathing may dry the skin further and worsen the eczema. Application of a good moisturizing cream after bathing and several times a day to areas of dry skin/eczema will make a significant difference. Lotions that contain alcohol should be avoided. Steroid ointments can be applied to control inflammation in areas that are more significantly affected, but they may thin the skin with chronic use so should be used sparingly. Stronger fluorinated steroid ointments should never be used on the face because of the risk of skin thinning.

## Autoimmune Disease

Autoimmune complications may require treatment with drugs that further suppress the patient's immune system. Systemic steroids (such as prednisone) are often the first immunosuppressant medication used to treat autoimmune disease and are often helpful in patients 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. High dose immunoglobulin replacement therapy may also be beneficial in treating autoimmune disease in some cases.

## Bone Marrow/Stem Cell Transplantation

Until recently, the only permanent cure for WAS was transplantation of stem cells from bone marrow, peripheral blood or cord blood. (*See chapter titled "Immunoglobulin Therapy and Other Medical Therapies for Antibody Deficiencies" and "Stem Cell Therapy and Gene Therapy."*) Patients with WAS have some residual T-lymphocyte and NK cell function despite having an immune deficiency and this has the potential to cause rejection of transplanted donor cells. To prevent this, patients must undergo some "conditioning," or treatment with chemotherapy drugs and/or total body irradiation to destroy their own immune cells, before the donor stem cells are infused. There are four potential donor types for any transplant: matched sibling donor, matched unrelated donor, haploidentical donor (half-matched, typically a parent), and cord blood donor. In general, the risks of transplant rejection and Graft Versus Host Disease (GVHD) are decreased, the more closely the HLA-types match between the donor and recipient. In WAS, the outcomes using an HLA-identical sibling donor bone marrow are excellent with an overall success (cure) rate approaching 90% 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. In contrast, transplant with cells from a haploidentical (half-matched) donor is successful in only approximately 50% of cases. After transplant, most patients remain on immunosuppressant medications for a period of time in order to decrease the risk of GVHD.

(Treatment of Wiskott-Aldrich Syndrome continued)

## Gene Therapy

Gene therapy is an approach whereby a normal copy of the WAS gene is delivered into the patient's own bone marrow cells using a virus so the blood cells coming from the bone marrow are then able to make normal WASp protein. Since the patient's own cells are being modified, there is no risk for graft versus host disease like that observed after bone marrow transplantation. The major risk of gene therapy is that the virus may insert a copy of its DNA into one of the patient's chromosomes and cause abnormal production of one or more proteins that can cause cancer. Recently, gene

therapy was used to successfully treat a small number of patients with WAS, correcting their bleeding problems and immune deficiency. Unfortunately, at least one patient developed leukemia as a result of the gene therapy virus inserting its DNA into a sensitive region of the patient's chromosomes. Studies are currently underway to test new gene therapy viruses that are potentially safer and to develop alternative non-viral gene therapy methods. The initial success of gene therapy in WAS is very encouraging, but a number of problems remain to be solved before it becomes more broadly applicable.

## Expectations for Patients with Wiskott-Aldrich Syndrome

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, improvements in immunoglobulin supplementation, antibiotics, and other supportive care have improved quality of life and significantly prolonged the survival of patients. In addition, improvements in bone marrow transplant protocols, the development of

additional drugs to treat infectious complications, and experience have substantially improved the outcomes of bone marrow transplantation. Indeed, follow-up of the earliest WAS bone marrow transplant recipients for more than 30 years has demonstrated that this therapy is curative. The recent success of gene therapy for WAS holds promise for being the treatment of choice for this disease in the future if the serious side effects observed in some patients can be prevented.

# Hyper IgM Syndromes



## Chapter 11



*Patients with Hyper-IgM (HIGM) syndrome are susceptible to recurrent and severe infections and in some types of HIGM syndrome opportunistic infections and an increased risk of cancer as well. The disease is characterized by decreased levels of immunoglobulin G (IgG) in the blood and normal or elevated levels of IgM. A number of different genetic defects can cause HIGM syndrome. The most common form is inherited as an X-chromosome linked. Most of the other forms are inherited as autosomal recessive traits and therefore can affect both boys and girls.*

## Definition of Hyper IgM Syndromes

Patients with HIGM syndrome 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, patients with this disease have decreased levels of IgG and IgA 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. Normally, B-lymphocytes can produce IgM antibodies on their own, but they require interactive help from T-lymphocytes in order to switch from IgM to IgG, IgA or IgE. HIGM results from a variety of genetic defects that affect this interaction between T-lymphocytes and B-lymphocytes.

The most common form of HIGM syndrome results from a defect or deficiency of a protein that is found on the surface of activated T-lymphocytes. The affected protein is called CD40 ligand because it binds, or ligates, to a protein on B-lymphocytes called CD40. CD40 ligand is made by a gene on the X-chromosome. Therefore, this primary immunodeficiency disease is inherited as an X-linked recessive trait.

As a consequence of the deficiency in CD40 ligand, the T-lymphocytes in patients with X-linked Hyper IgM (XHIGM) are unable to instruct B-lymphocytes to switch their production of immunoglobulins from IgM to IgG, IgA and IgE. CD40 ligand is also important for other functions carried out by T-lymphocytes, so patients with X-linked hyper IgM syndrome (XHIM) have defective cellular

immunity and are also susceptible to all kinds of infections, particularly opportunistic infections and to some types of cancer.

Other forms of HIGM syndrome are inherited as autosomal recessive traits and have been observed in both girls and boys. (See chapter titled “Inheritance.”) 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 syndrome result from defects in genes that are involved in the CD40 signaling pathway (they are abbreviated AID and UNG). The function of these genes is limited to antibody switching, so the other T-lymphocyte functions of CD40 ligand are not affected, and these patients are less likely to have opportunistic infections or cancer.

Finally, a defect in another X-linked gene (NEMO) that is necessary for the activation of the signaling molecule NF- $\kappa$ B has been identified in a form of HIGM syndrome that is associated with a skin condition called ectodermal dysplasia. (See chapter titled “NEMO Deficiency Syndrome.”) These patients have immunodeficiency with sparse hair and conical teeth among other abnormalities. NF- $\kappa$ B is activated by CD40 and is necessary for the signaling pathway that results in antibody switching. NF- $\kappa$ B is also activated by other signaling pathways that are important in fighting infections. Therefore, these affected boys are susceptible to a variety of serious infections.

## Clinical Presentation of Hyper IgM Syndromes

Most patients with HIGM syndrome develop clinical symptoms during their first or second year of life. The most common problem in all forms of HIGM syndrome 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 patients 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 the child has HIGM syndrome. Viruses such as Cytomegalovirus and fungi such as *Cryptococcus* may also cause lung infections.

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 patients 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 patients respond to treatment with colony stimulating factor, G-CSF. Severe neutropenia is often associated with oral ulcers, proctitis (inflammation and ulceration of the rectum) and skin infections.

Autoimmune disorders may also occur in patients with XHIGM syndrome or CD40 defects. Their manifestations may include chronic arthritis, low platelet counts (thrombocytopenia), hemolytic anemia, hypothyroidism and kidney disease.

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

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

## Diagnosis of Hyper IgM Syndromes

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.

Failure to express CD40 ligand on activated T-cells is a characteristic finding. However, there are some patients with other forms of immunodeficiency who may have a markedly depressed expression of CD40 ligand while their CD40 ligand gene is perfectly normal; these patients do not have HIGM. The exact diagnosis of XHIM syndrome depends on the identification of a mutation affecting the CD40 ligand gene. This DNA analysis can be done in specialized laboratories.

The autosomal recessive forms of HIGM can be suspected if a patient has the characteristics of XHIGM but is either a female and/or has a normal CD40 ligand gene with normal expression on activated T-lymphocytes. NEMO can be suspected in a patient who has features of ectodermal dysplasia (such as sparse hair and conical teeth) and recurrent infections, normal or elevated IgM and low IgG, IgA and IgE as well as normal CD40 ligand expression on activated T-lymphocytes.

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 of Hyper IgM Syndromes

X-linked Hyper IgM (XHIGM) and NEMO with immunodeficiency are inherited as X-linked recessive disorders, and only boys are affected.

Since the autosomal recessive forms of HIGM require that the gene on both chromosomes be affected, 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 of the HIGM syndromes will allow initiation of treatment prior to the development of long-term consequences of serious infections.

## Treatment of Hyper IgM Syndromes

Since patients with all forms of HIGM syndrome have a severe IgG deficiency, they require immunoglobulin replacement therapy. (See chapter titled *“Immunoglobulin Therapy and Other Medical Therapies for Antibody Deficiencies.”*) The immunoglobulin replaces the missing IgG and often results in a reduction or normalization of the serum IgM level.

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

When present, neutropenia may also improve during IgG replacement. Patients 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. However, G-CSF treatment is only necessary in selected patients and long-term treatment with G-CSF is usually not recommended.

Patients 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*.

Patients with XHIGM or CD40 deficiency have defects in T-lymphocyte function in addition to their antibody deficiency, and treatment with immunoglobulin replacement may not fully protect these patients against all infections. Hematopoietic stem cell transplantation (bone marrow or cord blood stem cell) has been performed successfully in many patients with XHIM. (See chapter titled *“Stem Cell Therapy and Gene Therapy.”*) While a permanent cure is anticipated after successful stem cell transplantation, the long-term prognosis for these patients is not yet known.

Since patients 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.

## Expectations for Patients with Hyper IgM Syndromes

There is a broad range of severity seen amongst patients with different genetic forms of HIGM. Those with defects primarily involving antibody class switching can be effectively treated by immunoglobulin replacement and can live long and productive lives. Those HIGM patients 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 autoimmune disorders and cancer as further challenges. The experience with hematopoietic stem cell transplantation is encouraging for those with more severe disease, and further studies to evaluate long-term outcomes are underway.

# Ataxia-Telangiectasia



## Chapter 12

*Ataxia-Telangiectasia (A-T) is an inherited disease that affects several body systems, including the immune system. People with A-T have an unsteady, wobbly gait (ataxia) that gets worse as they get older; dilated, corkscrew-shaped blood vessels (telangiectasia) on the whites of the eyes and on sun-exposed areas of skin; immunodeficiency involving both humoral (B-lymphocytes) and cellular (T-lymphocytes) immunity; and a high rate of cancer.*

*Not all features of the syndrome are present in all people with A-T, and the severity of each symptom also varies a great deal from person to person. For example, some patients with A-T may have a severe humoral immunodeficiency preventing them from making antibodies and requiring immunoglobulin replacement therapy. Others with A-T may be able to mount completely normal antibody responses to vaccines and infections, and have no evidence of immunodeficiency.*

## Clinical Features of Ataxia-Telangiectasia

The first presenting symptom of A-T is generally ataxia. Children with A-T usually have a delayed onset of walking and when they do, they sway, stagger and wobble. They are usually unstable when sitting unsupported or when trying to stand in one place (for example, when standing in front of a sink to brush their hair or teeth). The ataxia is caused by abnormalities in the cerebellum, a part of the brain that controls balance and movement. As toddlers, most children with A-T are thought to have a neurologic disorder such as cerebral palsy or an unspecified movement disorder. The diagnosis of A-T is often difficult to make when ataxia is the only symptom present.

A-T causes progressive decline of motor neurologic function, which may not be apparent until age 4 or 5 years. It is the deterioration that most often leads to the

correct diagnosis, as neurologic deterioration does not happen to people with cerebral palsy. With increasing age, children with A-T develop abnormalities in eye movements (delayed initiation of eye movement, jerky eye movements and difficulty with eye/head coordination when tracking moving objects or following a single line of print in a book), and fine motor control (writing or feeding themselves). They have more and more difficulty walking and usually need to use a wheelchair for at least part of the day by the age of 10-12 years. They develop an intention tremor, and difficulties with speaking (dysarthria) and swallowing (dysphagia). While the neurologic symptoms progress in all children, the rate of progression and the relative severity of each neurologic problem vary widely from individual to individual.

## (Clinical Features of Ataxia-Telangiectasia continued)

Dilated and corkscrew-shaped blood vessels (telangiectasias) cause the whites of the eyes to look bloodshot or as if there is pink eye (conjunctivitis) or an allergy. Telangiectasias eventually occur in most patients with A-T but do not occur in all patients with A-T and are only rarely present in infants and very young children, another reason that the diagnosis of A-T may be delayed until school age. Telangiectasias may also be seen on sun-exposed areas of skin such as the ears, neck and extremities.

Patients with A-T have an increased susceptibility to infection. Infections most commonly affect the lungs and/or sinuses and can be caused by bacteria and viruses. Part of the explanation for these infections is immunodeficiency, particularly related to low immunoglobulin levels and problems making antibody. About two thirds of people with A-T have low levels or complete deficiency of IgA, the antibody that protects us from infections on mucosal surfaces (such as the inside of the cheek and lining of the airways, nose and intestines). Many patients have problems making antibody responses to vaccines and infections. There is a particular problem making antibody to the large sugar molecules (polysaccharides) found on the outside of some of the bacteria that are frequent causes of sinusitis, bronchitis and pneumonia. These deficient antibody responses may be associated with low levels of IgG, IgA, IgM and/or IgG subclasses.

The immunodeficiency of A-T generally remains stable over time but gets worse with age in about 15% of patients. A thorough evaluation by an immunologist is necessary for every patient with A-T to determine if there is a deficiency of humoral immunity that is severe enough to require immunoglobulin replacement or other therapy. The usual indication for immunoglobulin is a problem making antibody, not just a low level of one or more immunoglobulin classes.

Most patients with A-T have reduced numbers of T- and B-lymphocytes, an abnormality that can be easily measured by a blood test. They may have problems with warts and a skin infection called molluscum, but they do not usually get opportunistic infections. However, if they are treated with steroids (such as prednisone) at high doses or for long periods of time, or if they need chemotherapy to treat cancer, the T-lymphocyte counts may become low enough that they become susceptible to opportunistic infections such as pneumocystis pneumonia.

Immunodeficiency is not the only explanation for lung infections in patients with A-T. Problems with swallowing (dysphagia) can cause aspiration. This occurs when solid foods or liquids go down the windpipe (trachea) and into the lungs instead of going down the esophagus into the stomach. Patients with A-T also have an ineffective cough, so they have difficulty clearing aspirated material and mucus from the airways. Chronic lung infections are sometimes managed by using prophylactic (preventive) antibiotics, and wearing special vibrating vests several times a day to help clear mucus. A gastrostomy tube may be inserted to provide calories directly into the stomach, providing nutrition and decreasing the amount of food and liquid that needs to be taken by mouth.

Patients with A-T are at an increased risk for developing all types of cancers, but particularly cancers of the immune system (lymphomas or leukemias). Cancer occurs in about 1/4 of all patients with A-T. It can occur at any age, and the risk cannot be predicted by the severity of immunodeficiency or any other feature of the disease.

## Diagnosis of Ataxia-Telangiectasia

The diagnosis of A-T is usually based on common clinical features (ataxia, telangiectasia, abnormal eye movement and speech) and supported by laboratory tests (see list at right). When all of the clinical signs and symptoms are observed (usually in older children and adults), the diagnosis is made relatively easily. In young children, the diagnosis is much harder to make. Often the only presenting symptom is ataxia. Telangiectasias do not usually occur until after the age of 5 years, and do not occur at all in some patients. Eye movements are almost always normal in young patients. A history of recurrent upper and lower respiratory tract infections may be another clue to the diagnosis.

One of the most important lab tests used in the diagnosis of A-T is the measurement of the alpha

fetoprotein level in the blood, as about 95% of patients with A-T have elevated levels of alpha fetoprotein after age 18-24 months. Other confirmatory laboratory tests include:

- Elevated level of the blood protein CA125
- Increased cell death or chromosomal breakage after exposure of blood cells to x-rays in the laboratory
- Absence of the ATM protein on a Western blot
- Abnormal DNA sequence (mutation) of the A-T gene (ATM)

## Inheritance of Ataxia-Telangiectasia

A-T is inherited as an autosomal recessive disorder. (See chapter titled "Inheritance.") The ATM gene is found on the long arm of chromosome 11. This gene controls the production of the ATM protein, an essential enzyme involved in cellular responses to DNA damage and other forms of stress in every cell of the body. For example, if there is a break in the double strand structure of the DNA, ATM signals the cell to stop

growing and dividing (cell cycle arrest), and ATM signals the DNA repair machinery of the cell to start working. The identification of the gene responsible for A-T has made carrier detection and prenatal diagnosis possible. Unfortunately, the sequencing test required to identify the mutation in the ATM gene is expensive and available in only a few laboratories.

## General Treatment of Ataxia-Telangiectasia

There is no cure for any of the problems associated with A-T. Treatment is supportive but should be proactive. There are many parts of this disease, and a team approach, including the patient and family, primary care provider, immunologist, pulmonologist and neurologist is essential. A nutritionist as well as physical, occupational

and speech therapists, will have important contributions to make for specific problems that patients encounter. An example of the utility of the team approach is to monitor for and manage swallowing problems. Dysphagia and tremor can make meals last a long time and be very fatiguing, can interfere with nutritional



## (General Treatment of Ataxia-Telangiectasia continued)

intake, and can lead to aspiration. Once recognized, early placement of a gastrostomy tube (G-tube, a tube that goes through the skin of the abdomen directly into the stomach) can provide supplemental nutrition that allows growth, improves stamina and decreases the risk of lung damage from aspiration.

All suspected infections should be properly evaluated and treated. Infection prevention efforts are important. This includes hand washing and making sure that those people with whom the patient comes in contact do not have acute respiratory tract infections. All household members should receive an influenza vaccination every fall. Patients with A-T who do not need immunoglobulin should receive all standard immunizations, as well as yearly influenza vaccine and a pneumococcal (pneumonia) vaccine every five to ten years.

Respiratory problems can be serious for patients with A-T. Often they have problems taking deep breaths and effectively coughing to clear mucus from their airways. They may benefit from daily chest physiotherapy and/or the use of a therapy vest. A regular program of respiratory care should be established before serious, irreversible lung problems develop. If chronic lung disease develops, patients may benefit from antibiotic prophylaxis, inhaled corticosteroids to decrease airway inflammation, and/or supplemental oxygen therapy. Patients who are having problems with aspiration (food and liquids going down the trachea into the lungs) may improve when thin liquids are eliminated from the diet.

On occasion, it is safest for most food and liquid to be delivered directly into the stomach with a G-tube instead of being swallowed.

Diagnostic x-rays should be limited as A-T is a chromosomal breakage disorder, and there is the theoretical risk that x-rays could cause chromosomal damage. In general, x-rays should be performed only if the results will influence treatment and management, and the information cannot be obtained in any other manner.

Children with A-T should be able to attend school, but most of them will eventually require full time aides to assist with activities of daily living while at school. Academic difficulties occur because progressively impaired eye movements make reading difficult and because the delay in initiation of speech and impaired ability to write or use a computer limit the ability of patients with A-T to demonstrate what they have learned. Cognitive function and hearing is not impaired. It is often helpful to introduce books-on-tape at an early age to foster the development of listening skills, which will become increasingly important as visual problems progress. Computers can also be particularly helpful as they can be adapted to the particular needs of people who have problems with eye and hand coordination. Counseling for the patient and the family is almost always helpful.

## Specific Therapy for Ataxia-Telangiectasia

There is neither a cure for A-T nor is there a specific therapy for the neurological problems associated with the disease. Nobody has yet shown in a convincing way that physical therapy or specific nutritional supplements (as opposed to general good nutrition) have helped, though there are many proponents of these approaches.

Management of immunodeficiency and general nutrition, prevention of pneumonia, and providing some exercise will improve the quality and length of life. Neither bone marrow transplantation nor injection of neural stem cells into the brain is considered safe at this time.

## Expectations for Patients with Ataxia-Telangiectasia

A-T is a progressive disease, but the timetable for this progression is not predictable in an individual patient. Not all patients with A-T are the same. Even within the same family, where the specific genetic defect is the same, there is great variability in the severity and types of problems experienced by each affected person. Being aware of potential problems may affect progression. For example:

- A chronic cough may indicate a lung or sinus infection
- Choking when drinking may indicate aspiration
- Failure to grow or a child falling off of their growth curve may indicate nutritional issues
- Infections that recur or do not get better when appropriate antibiotics are used may indicate an immunodeficiency

These and other concerns should be communicated to the healthcare team as soon as possible, rather than assuming that they are an inevitable part of the disease and that nothing can be done about them. The earlier a problem is addressed, the greater the chance for successful management of that problem.

Even if complications are promptly addressed, the reality is that there will be neurological deterioration. It is realistic to assume that all patients with A-T will, eventually, be unable to ambulate safely and will require a wheel chair and other adaptive devices. Usually, this occurs by the time the patient is a teenager. Similarly, some degree of lung disease can be expected, even if lung infections are aggressively and promptly treated. If cancer is diagnosed, it can be treated but modification of the treatment regimen may be necessary. For example, patients with A-T should never be treated with radiation therapy because of the potential of the radiation causing chromosomal breakage.

It is important to remember that as research and knowledge about A-T increase so does the hope for changing the course of the disease. In the past, children with A-T seldom lived to adulthood. At present, a few patients with A-T are part-time students at community colleges and have been able to live independently. Some have lived into their fifties. The goal of ongoing research is to make this the norm for patients with A-T, rather than the exception.

# DiGeorge Syndrome



## Chapter 13

*DiGeorge Syndrome is a primary immunodeficiency disease caused by abnormal migration and development of certain cells and tissues during fetal development. As part of the developmental defect, the thymus gland may be affected and T-lymphocyte production may be impaired, resulting in low T-lymphocyte numbers and frequent infections.*

## Definition of DiGeorge Syndrome

DiGeorge Syndrome (DGS) is a primary immunodeficiency, often but not always, characterized by cellular (T-cell) deficiency, characteristic facies, congenital heart disease and hypocalcemia. DGS is caused by abnormal formation of certain tissues during fetal development. During fetal development, various tissues and organs often arise from a single group of embryonic cells. Although the tissues and organs that ultimately develop from this group of embryonic cells may appear to be unrelated in the fully formed child, they do have a similar origin.

Approximately 90% of patients with DGS have a small deletion in chromosome number 22 at position 22q11.2. Thus another name for this syndrome is the 22q11.2 deletion syndrome. Other names include velocardiofacial syndrome and conotruncal anomaly face syndrome.

While the genetic defect is the same in the majority of patients with DGS, they all do not present in the same way. For example, some patients with DGS have severe cardiac anomalies; some have none at all. Some have major learning disabilities; others have none. This is called phenotypic variability. There is wide phenotypic variability in patients with DGS.

Patients with DGS may have any or all of the following:

Unusual facial appearance - Features may include an underdeveloped chin, eyes with heavy eyelids, ears that are rotated back and small upper portions of their ear

lobes. These facial characteristics vary greatly from person to person and may not be prominent in many patients.

Heart defects - These include a variety of heart (or cardiac) defects. The defects usually involve the aorta and the part of the heart from which the aorta develops. In some patients, heart defects may be very mild or absent.

Thymus gland abnormalities - The thymus is crucial in the development of the cellular (T-cell) immune system. It is normally located in the upper area of the front of the chest behind the breastbone. The thymus begins its development high in the neck during the first three months of fetal development. As the thymus matures and gets bigger, it drops down into the chest to its ultimate location under the breastbone and in front of the heart.

The thymus controls the development and maturation of one kind of lymphocyte, the T-lymphocyte, "T" for "Thymus." (See chapter titled *"The Immune System and Primary Immune Deficiency Diseases."*) The size of the thymus affects the number of T-lymphocytes that can develop. Patients with a small thymus produce fewer T-lymphocytes than those with a normally sized thymus. T-lymphocytes are essential for protection against infections. Some T-lymphocytes, the cytotoxic T-lymphocytes, directly kill viruses. T-lymphocytes also help B-lymphocytes to develop into

## (Definition of DiGeorge Syndrome continued)

antibody producing plasma cells. Patients with DGS may have poor T-cell production compared to their peers, and as a result, have an increased susceptibility to viral, fungal and bacterial infections.

As with the other defects in DGS, the T-lymphocyte defect varies from patient to patient. In a very small number of patients with DGS the thymus is completely absent, so the number of T-cells is severely low. These patients require prompt medical attention since they are severely immunocompromised. The majority of patients with DGS have less severe or mild deficiencies.

Autoimmunity - Patients with DGS develop autoimmune disease at a rate that is higher than in the general population. Autoimmune disease occurs when the immune system inappropriately attacks its own body. (*See chapter titled "Autoimmunity in Primary Immunodeficiency."*) It is not known why this happens in people with T-lymphocyte problems. The most common autoimmune diseases in DGS are idiopathic thrombocytopenia purpura (antibodies against platelets), autoimmune hemolytic anemia (antibodies against red blood cells), autoimmune arthritis, and autoimmune disease of the thyroid gland.

Parathyroid gland abnormalities - These glands may be underdeveloped in patients with DGS, causing hypoparathyroidism. The parathyroids are small glands found in the front of the neck near the thyroid gland, hence the name "parathyroid." They function to control the normal metabolism and blood levels of calcium. People with DGS may have trouble maintaining normal levels of calcium, and this may cause seizures (convulsions). In some cases, the parathyroid abnormality is not present at all, relatively mild or only a problem during times of stress such as severe illness or surgery. The parathyroid defect often becomes less severe over time.

Miscellaneous clinical features - Patients with DGS may have a variety of other developmental abnormalities including cleft palate, poor function of the palate, delayed acquisition of speech and difficulty in feeding and swallowing. In addition, some patients have learning disabilities, behavioral problems, psychiatric disorders and hyperactivity. For example schizophrenia occurs at a higher rate in patients with DGS compared to the rate in the general population.

## Diagnosis of DiGeorge Syndrome

The diagnosis of DGS is made on the basis of signs and symptoms that are present at birth, or develop soon after birth, along with confirmatory genetic testing. Some infants may have facial features that are characteristic of DGS. Affected infants may also show signs of low blood calcium levels as a result of hypoparathyroidism. This may show up as low blood calcium on a routine blood test, or the infant may be "jittery" or have seizures as a result of the low calcium.

Affected infants may also show signs and symptoms of a heart defect. These may include a heart murmur that is detected on a routine physical exam. They may show signs of heart failure, or they may have low oxygen content of their arterial blood and appear "blue" or cyanotic. Affected infants may also develop infection because of their low T-lymphocyte levels.

In some children, all of the classical features are present and the diagnosis of DGS is made very early. In

## (Diagnosis of DiGeorge Syndrome continued)

other people, all of the different organs and tissues may not be affected, and the organs and tissues that are involved may be impaired to different degrees so that the presentation is more subtle and the diagnosis is not made until later on in life when a speech delay, feeding problems or autoimmune disease are noted.

In the past, the diagnosis of DGS was usually made when all the characteristic findings described above were present without obtaining a confirmatory genetic test. Unfortunately, this caused many mild cases to be missed. In recent years, the genetic test has been more widely used.

Approximately 90% of patients with the clinical diagnosis of DGS have a small deletion of a specific portion of chromosome number 22 at position 22q11.2, called a microdeletion. This is usually identified by a

blood test called a FISH analysis (for Fluorescent In Situ Hybridization). The FISH test has made the diagnosis of DGS more precise and more common.

Approximately 90% of 22q11.2 deletions occur spontaneously and have not been passed on from the mother or father of the child. But once the diagnosis has been made, genetic counseling is critically important and testing should be offered to parents and other family members.

DGS is the most common microdeletion syndrome. The rate of occurrence is estimated at approximately 1 in 4,000 people. For patients who do not have the 22q11 microdeletion, a DGS diagnosis can still be made on the basis of the characteristic combination of clinical features and by excluding a diagnosis of other syndromes.

## Therapy for DiGeorge Syndrome

Therapy for DGS is aimed at correcting the defects in the affected organs or tissues. Therefore, therapy depends on the nature of the different defects and their severity. In general, patients with DGS have the same response rates to therapies as do the general population.

Treatment of the low calcium and hypoparathyroidism may involve calcium supplementation and replacement of the missing parathyroid hormone.

A heart (or cardiac) defect may require medications or corrective surgery to improve the function of the heart. Surgery can be performed before any immune defects are corrected. If there is a problem with the T-cells, precautions must be taken as with other children with congenital T-cell immunodeficiencies. These include

irradiating all blood products to prevent graft vs. host disease and ensuring the blood products are free of potentially harmful viruses. (*See discussion of General Treatment in the chapter titled "Severe Combined Immune Deficiency and Combined Immune Deficiency."*)

The need for therapy of the T-lymphocyte defect varies. Most people with DGS have normal T-lymphocyte function and do not require therapy for immunodeficiency. Other children initially have mild defects in T-lymphocyte function that improve, as they grow older. In these cases the small amount of thymus tissue present provides adequate T-lymphocyte function.

## Management of DiGeorge Syndrome

Immunologic care for patients with DGS includes monitoring the overall immune system including the numbers and function of T-lymphocytes. Patients who have initially been deemed immunocompetent but then develop frequent, severe or unusual infections should have their immune system reevaluated.

Between 1-2% of patients with DGS completely lack T-cells. This is a serious, potentially fatal, condition that is similar to Severe Combined Immune Deficiency (See chapter “Severe Combined Immune Deficiency and Combined Immune Deficiency.”) This is sometimes called “complete” DiGeorge syndrome and is usually associated with severe low blood calcium causing seizures. In this situation, T-cells must be

reconstituted for the infant to survive. This can be achieved with a thymus transplant (available only on a research basis) or by stem cell transplantation.

In some patients with DGS, the T-lymphocyte defect is significant enough to cause the B-lymphocytes to fail to make sufficient antibodies. This occurs because antibodies are produced by B-lymphocytes under the direction of a specific subset of T-lymphocytes. (See chapter titled “The Immune System and Primary Immunodeficiency.”) When the B-cells are affected, the result is simply a delay in the production of antibodies. Immunoglobulin replacement therapy is sometimes required.

## Expectations for Patients with DiGeorge Syndrome

The outlook for people with DGS depends on the function of each affected organ system. The severity of heart disease is usually the most important determining factor. With the improvements made in cardiac surgery and management of immunodeficiency, the infant

mortality rate in DGS is estimated to be relatively low at approximately 4%. Early diagnosis is important and optimal management of patients with DGS requires a multidisciplinary approach including an immunologist as part of the team of specialists.

# Other Primary Cellular Immunodeficiencies



## Chapter 14



*Cellular immunodeficiencies (T-cell deficiency) discussed in previous chapters included Severe Combined Immune Deficiency (SCID), Ataxia-Telangiectasia, Wiskott-Aldrich Syndrome and DiGeorge Syndrome. Some patients with less common cellular immunodeficiencies may have severe immunodeficiency with early onset and significant morbidity and mortality while others have only mild problems. Patients with these types of deficiencies have some defect of their T-cell (cellular) immune system resulting in a different spectrum of infection problems than those individuals with typical antibody deficiency. These include deep-seated bacterial infections, viral and fungal infections, tuberculosis and other mycobacterial infections. Cellular immunodeficiencies are usually more difficult to treat and may need cellular reconstitution via hematopoietic stem cell transplantation or eventually perhaps gene therapy.*

### **Chronic Mucocutaneous Candidiasis (CMC)**

CMC is characterized by persistent *Candida* (fungus) infections of the mucous membranes, scalp, skin and nails. Rarely, the infection may spread to the blood stream or internal organs. CMC is usually hereditary and presents soon after birth with persistent oral *Candida* infections (thrush). Later, the nails and skin become chronically infected. These infections respond to anti-*Candida* treatment but recur when the treatment stops.

CMC is associated with a selective T-cell deficiency to *Candida* and a few related fungi. Except for this T-cell deficiency, patients with CMC have a normally functioning immune system. The most common abnormal laboratory finding is a negative delayed hypersensitivity skin test to *Candida* antigen despite widespread *Candida* infection.

One hereditary form of CMC is the APECED Syndrome (autoimmune polyendocrinopathy-candidiasis-ectodermal dysplasia) associated with multiple endocrine problems (for example, hypothyroidism,

diabetes or Addison disease) due to an AIRE gene defect on chromosome 21. However, the CMC in this disease is also partly due to autoantibodies directed against critical *Candida* fighting molecules made by the disordered immune system. Several other forms of CMC are due to mutations in the gene signal transducer and activator of transcription 1 (STAT1). Other causes of CMC are associated with autoantibodies to critical *Candida* fighting molecules and with mutations in very uncommon genes such as interleukin 17. Treatment requires life-long antifungal medicines.

### **Cartilage Hair Hypoplasia (CHH)**

CHH is an autosomal recessive immunodeficiency associated with dwarfism and other medical problems. It is particularly common among the Amish because of family intermarriage. Most patients have very fine brittle hair and an unusual susceptibility to viral infections. The degree of immunodeficiency is variable and usually involves both antibody and cellular immunity. Some patients have been treated by bone marrow transplantation, but this will not correct their hereditary short stature.

(Other Primary Cellular Immunodeficiencies continued)

## **X-linked Lymphoproliferative (XLP) Syndromes 1 and 2**

XLP is characterized by life-long vulnerability to Epstein-Barr virus (EBV) infection, which can lead to severe and fatal infectious mononucleosis, lymph node cancers (lymphomas), combined immunodeficiency and, less commonly, aplastic anemia (inability to produce red blood cells) or vasculitis (inflammation in the blood vessels). XLP is associated with a defect on the X chromosome termed SH2DIA. As it is X-linked, this defect only affects males. (*See chapter titled "Inheritance."*) Most patients with XLP do well until they are exposed to EBV. Then, they become seriously ill with fever, swollen lymph nodes, enlarged liver and spleen, and hepatitis. This infection triggers a condition called "hemophagocytic syndrome," which also occurs in other immune deficiencies and can be fatal. If patients recover, they go on to develop one of the above-named problems.

Some patients are initially misdiagnosed with Common Variable Immune Deficiency (CVID). Early recognition is crucial since the disease can be cured by bone marrow or cord blood transplantation. Early screening of infant boys in families known to have had children with XLP is also critically important so that they can be transplanted before contracting an EBV infection. There are two forms of this disorder: XLP1 due to defects in the SH2DIA gene, and XLP2 due to defects in the XIAP gene.

## **X-linked Immune Dysregulation with Polyendocrinopathy (IPEX) Syndrome**

IPEX is characterized by multiple autoimmune endocrine diseases (particularly diabetes and thyroid problems), chronic diarrhea and a rash resembling eczema. It is an x-linked disease so only boys are affected. (*See chapter titled "Inheritance."*) IPEX is caused by abnormalities of a gene on the X chromosome termed FOXP3. These boys have activated T-cells, which stimulate autoimmune problems. Immunosuppressive medications followed by bone marrow transplantation are commonly used as treatments.

## **Veno-occlusive Disease (VODI)**

Hepatic veno-occlusive disease is an extremely rare form of immunodeficiency inherited in autosomal recessive fashion with impairment of both T-cells and B-cells. Patients with VODI have a predisposition to leaving the patient subject to fungal infections such as *Pneumocystis jiroveci* infection. Patients may also have thrombocytopenia (low platelet counts) and enlarged livers. Intravenous immunoglobulin (IVIG) and *Pneumocystis jiroveci* prophylaxis as soon as the diagnosis of VODI is established is important. Liver transplantation is sometimes considered, but the rate of complications may be high.

## **Hoyeraal-Hreidarsson Syndrome (Dyskeratosis Congenita)**

This syndrome has X-linked inheritance, and patients have poor growth inside the womb, microcephaly (small head), pancytopenia (low numbers of all blood cells), and especially decreased natural killer cells. Patients experience a progressive loss of cellular and humoral immunity and are thus susceptible to infections by virtually any pathogen. Accurate diagnosis of Dyskeratosis Congenita is critical to ensure proper clinical management, because patients who have DC and bone marrow failure do not respond to immunosuppressive therapy and may have increased morbidity and mortality associated with hematopoietic stem cell transplantation.

## **Immunodeficiency with Centromeric Instability and Facial Anomalies (ICF)**

ICF syndrome is a very rare disorder inherited from both parents due to defects in the DNA methyl transferable gene DNMT3B. Abnormal facial features are prominent such as macroglossia (large tongues). T-cell and B-cell numbers and serum immunoglobulins are all low and patients are susceptible to bacterial and opportunistic infections. Early diagnosis of ICF is important since early introduction of immunoglobulin supplementation can

## (Other Primary Cellular Immunodeficiencies continued)

improve the course of the disease. Allogeneic stem cell transplantation should be considered as a therapeutic option in patients with severe infections or failure to thrive.

### Schimke Syndrome

Schimke Syndrome is a very rare primary immunodeficiency with autosomal recessive inheritance that results in decreased circulating T-cells but normal levels of B-cells and serum immunoglobulins. Features associated with this syndrome are short stature, intrauterine growth retardation, kidney disease, bone marrow failure and problems fighting all types of infections. It is caused by a mutation in the gene responsible for chromatin remodeling (SMARCA1). Additional features include ischemic cerebral attacks, migraine-like headaches, hematologic abnormalities of leucopenia, anemia and thrombocytopenia, enteropathy, hyper-pigmented skin macules, unusual hair and small teeth. The course of the disease varies from severe with intrauterine or early childhood onset and death in childhood to milder disease with survival into adulthood. For both severe and mild disease, the therapy is mainly symptomatic.

### Comel-Netherton Syndrome

This is a very rare disorder with an autosomal recessive inheritance pattern. Patients have normal T-cell numbers but reduced numbers of B-cells. Patients exhibit increased IgE and IgA levels with variable-specific antibody function. Newborns exhibit ichthyosis (scaly skin), bamboo type hair (thin, tubular and fragile), an increased incidence of bacterial infections and growth failure. If antibody deficiency can be confirmed by vaccine challenge, immunoglobulin replacement could be tried.

In the neonatal period, 20% of the babies suffer from dehydration, electrolyte imbalances, perturbed thermoregulation, failure to thrive and recurrent infections which may result in early death. The hallmark of C-NS is trichorrhexis invaginata (bamboo hair), but other abnormalities, including pili torti (twisted hair) and trichorrhexis nodosa (hair of varying diameter) have been observed. Markedly elevated IgE levels, allergic reactions to food and common antigens, malnutrition, and increased susceptibility to skin, respiratory tract or systemic infections are also characteristic.

# Chronic Granulomatous Disease and Other Phagocytic Cell Disorders



## Chapter 15

*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 hydrogen peroxide and other chemicals needed to kill certain bacteria and molds. As a result of this defect, patients with CGD get more infections, and they also get too many immune cells forming "knots" called granulomas, hence the name of the disease. Another problem in CGD is that patients can get excessive inflammation even when there is not an infection, and that inflammation can cause diarrhea, and bladder and kidney problems.*

## Definition of Chronic Granulomatous Disease

Phagocytes (from the Greek, phagein, "to eat") are white blood cells that can surround and ingest microorganisms into tiny compartments in the cell. These compartments, called phagosomes, are filled with chemicals that help kill bacteria and fungi. These chemicals include hydrogen peroxide and bleach, which are made in these compartments and reach high levels there. There are two main types of phagocytes, neutrophils and monocytes. They crawl out of blood vessels and head directly for where there is infection. When they get to the infection site, they seek out the bacteria or fungus and ingest it into the phagosomes. Then the normal phagocyte pumps hydrogen peroxide, bleach and other toxins into the compartment to kill the infecting organism.

CGD phagocytes go normally to sites of infection, where they ingest infecting microbes. However, they cannot make the hydrogen peroxide and bleach that

normal cells do because they are missing key proteins that help generate the bleach. It is very remarkable that the phagocytes of patients with CGD can defend against most infections, but not all. Patients with CGD have normal immunity to most viruses and some bacteria and fungi, which is why they are not infected all the time. They may go months to years without infections and then have a severe one. Patients with CGD make normal antibodies, so unlike patients with lymphocyte problems, patients with CGD are not particularly susceptible to viruses.

In summary, CGD phagocytes fail to make hydrogen peroxide and bleach, leading to infections with only a few bacteria and fungi including *Staphylococcus aureus*, *Burkholderia cepacia complex*, *Serratia marcescens*, *Nocardia* and *Aspergillus*. Much of the rest of their immune system is normal.

## Clinical Presentation of Chronic Granulomatous Disease

Children with CGD are usually healthy at birth. The most common CGD infection in infancy is a skin or bone infection with the bacteria *Serratia marcescens*, and any infant with an infection with this particular organism 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 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 very quickly with fever and cough. *Nocardia* in particular, causes high fevers and lung abscesses that can destroy parts of the lung. It is important to identify infections and the causative pathogen early and treat the infection completely, usually for a long period of time, so it is critical to seek medical attention early. Chest X-rays and computerized tomography (CT) scans of the chest are very helpful. However, if pneumonia is seen, it is very important to figure out exactly which microbe is causing it, 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 patients with CGD. An abscess can present as fever and fatigue, but it may also cause mild pain over the right upper

abdomen. Some sort of scan is required for diagnosis (magnetic resonance imaging or MRI, CT scan, ultrasound), and needle biopsy are necessary to determine the specific cause of the infection.

*Staphylococcus aureus* causes most liver abscesses in patients with CGD. Often the liver abscesses are hard to drain and may need surgery. Sometimes abscesses can be treated with antibiotics and steroids, which reduce the inflammation and let the antibiotics work better.

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

There are new antibiotics and antifungals becoming available, many very active by mouth. Rates of cure for infections in patients with CGD are very high and are greatly improved by early diagnosis and therapy.

One of the most difficult aspects of CGD is the bowel problems. About 40-50% of patients with CGD develop inflammation in the intestine that is not clearly due to a specific infection. This inflammation can be mistakenly diagnosed as Crohn's disease, and it does look a lot like it. It also responds to most of the same treatments (antibiotics, steroids, other immune suppression drugs). However, injectable drugs that block the inflammatory molecule tumor necrosis factor alpha (TNF $\alpha$ ), which are very effective in Crohn's disease, lead to severe infections in patients with CGD and should be avoided. Similar problems can occur in the bladder or ureters, causing problems with urination.

## Diagnosis of Chronic Granulomatous Disease

There are five different genetic kinds of CGD. The most common form is called X-linked, because it is on the X chromosome (70% of cases in the U.S) and affects almost only boys. However, the other four types are located on other chromosomes and have autosomal recessive inheritance. These forms affect boys and girls equally, so around 15% of cases are in girls. For the X-linked form, boys get disease while girls are relatively asymptomatic carriers. (*See chapter titled "Inheritance."*)

The severity of CGD can partly be determined from the specific mutation in the gene. Usually infections begin in childhood leading to the diagnosis. However, some patients with CGD may not have infections until late adolescence or adulthood. Pediatricians and internists cannot ignore the possibility of CGD in an adult with pneumonia with a characteristic CGD organism.

Therefore, any patient of any age with a CGD type infection (*Staphylococcus aureus*, *Burkholderia cepacia* complex, *Serratia marcescens*, *Nocardia* and *Aspergillus*) should be tested for CGD unless there is a good reason not to.

The most accurate test for CGD measures hydrogen peroxide in phagocytes using a chemical called dihydrorhodamine. The test is called dihydrorhodamine reduction or DHR. There are other types of tests still used to diagnose CGD, such as the Nitroblue Tetrazolium (NBT) slide test. The NBT test is still valuable but more prone to incorrect reading.

Once the diagnosis of CGD is made, it is useful to confirm the genetic sub-type of CGD for genetic counseling and because some types of CGD need bone marrow transplantation more than others.

## Treatment of Chronic Granulomatous Disease

Early diagnosis of infection and prompt, aggressive use of appropriate antibiotics is the best way to treat CGD infections. Initial therapy with antibiotics aimed at the usual suspects makes sense while waiting for results of cultures, 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.

All patients with CGD should receive antibiotic prophylaxis (prevention), usually with trimethoprim/sulfamethoxazole (*cotrimoxazole*, *Bactrim* or *Sepra*) and itraconazole. These reduce infections by almost 70%. Since the infections that are important in CGD are in the environment and not carried in our bodies normally, the effect of prophylaxis is to build a wall around the patient: it can still be jumped over, but

prophylaxis makes it harder for infections to get in. This also means that the organisms that are an issue are not usually seeing the antibiotics, so they do not develop resistance.

Daily doses of the oral antifungal drug itraconazole reduce fungal infections in CGD. Maximum infection prophylaxis for CGD involves treatment with twice-daily oral doses of cotrimoxazole and once daily itraconazole, plus three times weekly injections of gamma interferon. With these prophylactic treatments, the average incidence of severe infections in CGD is less than once every four years. Of course, individual factors will influence this frequency as well.

Interferon gamma is made normally by the body, but it can also be given by injection to boost immunity. Patients with CGD who receive interferon gamma (under the skin three times a week) have 70% fewer infections, and

## (Treatment of Chronic Granulomatous Disease continued)

when infections do occur, they may be less serious. Interferon gamma is not a cure for CGD. It may cause fever, fatigue and depression. Acetaminophen (Tylenol) taken before the injection may help. Some patients choose not to take interferon gamma because they do not like injections, because of the cost or because of the side effects. Even doses lower than the standard recommendation may provide some protection against infection. Side effects are usually related to the dose and may be decreased by lowering the dose or how often it is given.

CGD can be cured by bone marrow transplantation, but this is complex and not yet widely available. Patients may lack a fully matched normal sibling or may be doing well enough with normal treatment that they do not want a transplant. However, some patients with CGD have good transplant options and may want to explore this. With the right donor and a healthy patient, bone marrow transplantation can be highly effective. Gene therapy is not yet an option to cure CGD. However, some laboratories are working on this new therapy, and gene therapy might be an option in the future.

Many physicians suggest that swimming should be confined to well-chlorinated pools. Brackish water in particular may expose patients to organisms that are specifically dangerous in CGD (*Francisella philomiragia*, *Chromobacterium violaceum*). Aspergillus is present in many samples of marijuana, so patients with CGD should avoid it.

A major risk to patients with CGD is the handling of garden mulch (shredded moldy tree bark) or potting soil. This type of exposure can cause a severe life-threatening pneumonia due to inhalation of the fungus Aspergillus, which likes to live in decaying plant matter. Patients 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 patients with CGD. Patients should 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. Patients should see their doctors about even minor infections.

## Expectations for Patients with Chronic Granulomatous Disease

The quality of life and longevity for patients with CGD has improved dramatically over the last 50 years. The great majority of children with CGD can expect to live well into adulthood, and many adult patients with CGD have jobs, get married and have children. However, patients with CGD remain at significant risk for infection throughout life. They must take their prophylaxis, remain cautious, and get early diagnosis and treatment for possible infections.

Hospitalizations may be required for patients 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 patients reach adulthood, when serious infections tend to occur less frequently.



## Other Phagocytic Cell Disorders

The chief phagocytic white blood cell is the polymorphonuclear granulocyte (PMN, also known as neutrophil). To be effective, the neutrophil must move to a site of infection, ingest the organism and then kill the organism. (See chapter titled “*The Immune System and Primary Immunodeficiency Diseases.*”)

### Neutropenias

Neutropenias are disorders characterized by low numbers of granulocytes, usually defined as a neutrophil count of less than 500 cells/ul (normal is more than 2,000 cells/ul). Depending on its severity and duration, neutropenia can lead to serious and fatal infection or intermittent infection of the skin, mucus membranes, bones, lymph nodes, liver, spleen or blood stream (sepsis).

Neutropenia can occur at birth and can be life-long. One form, termed severe congenital neutropenia (Kostmann syndrome), is an autosomal recessive disorder. This disorder is associated with a gene abnormality of a gene called *HAX1*. These infants require treatment with granulocyte colony stimulating factor (G-CSF) and may be candidates for bone marrow transplantation.

Another form of neutropenia is cyclic neutropenia, which is an autosomal dominant disorder in which the neutropenia occurs every two to four weeks and lasts about a week. It is associated with a gene defect termed *ELA2*.

A third form, benign chronic neutropenia, has low, but not life threatening, neutropenia and is often asymptomatic. A final form is immune neutropenia, usually present at birth but sometimes presents later. In this condition, there is an antibody to the neutrophils that causes their destruction. Treatment for all of these disorders may include antibiotics for infections, prophylactic antibiotics, intravenous immunoglobulin, G-CSF injections or bone marrow transplantation.

Several primary immunodeficiencies may have an associated neutropenia. These immunodeficiencies include X-linked hyper-IgM syndrome (CD40 ligand deficiency), Common Variable Immune Deficiency (CVID), X-linked Agammaglobulinemia (XLA), WHIM syndrome, Wiskott-Aldrich Syndrome and GATA2 deficiency. Some of these patients acquire an autoimmune antibody to their own neutrophils. This antibody causes autoimmune neutropenia due to accelerated destruction of the neutrophils. All of these diseases are discussed in more detail in other chapters in this Handbook.

### Phagocyte Killing Defects

Several rare phagocyte defects involve an inability to kill organisms similar to patients with CGD. They should be suspected in patients who seem to have CGD, but tests for that disorder are normal. These include enzyme defects or deficiencies of glucose-6-phosphate dehydrogenase, myeloperoxidase, glutathione reductase and glutathione synthetase.

### Leukocyte Adhesion Deficiencies

For neutrophils to go into the tissue and remove invaders, they must be able to exit blood vessels and enter tissues. This process is complex and there are several specific defects that impair it. Leukocyte adhesion deficiency type I (LAD1) is the result of mutations in a gene called CD18. LAD1 is by far the most common cause of leukocyte adhesion deficiency and it is usually corrected by bone marrow transplantation. However, milder forms of LAD1 can sometimes be managed with antibiotics alone. Leukocyte adhesion deficiency type II (LAD2) is due to mutations in an enzyme that attaches fucose (a type of sugar) to proteins. These patients can be treated by eating large amounts of fucose. Leukocyte adhesion deficiency type III (LAD3) is caused by mutations in a gene called *FERMT3*.

(Other Phagocytic Cell Disorders continued)

## Specific Granule Deficiency

Specific granule deficiency is extremely rare and is associated with killing defects and decreased granules within the neutrophils. Patients are at risk for bacterial and fungal infections.

## Glycogen Storage Disease Type Ib

Glycogen storage disease type Ib is a disorder with neutropenia, poor granulocyte killing, 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.

## $\beta$ -actin Deficiency

$\beta$ -actin Deficiency is associated with poor granulocyte movement (chemotaxis) and recurrent infection.  $\beta$ -actin is a structural protein that allows cell movement. Some patients with chemotactic disorders have severe periodontitis and early tooth loss. Three of these syndromes are termed Papillon-Lefebvre syndrome, prepubertal periodontitis and juvenile periodontitis.

## Chediak Higashi

Chediak-Higashi syndrome (CHS) is a rare autosomal recessive disorder that arises from a microtubule polymerization defect. CHS is a disease causing impaired bacterial killing due to failure of phagolysosome formation. There is impaired lysosome degranulation within phagosomes, so phagocytosed bacteria are not destroyed by the lysosome's enzymes. Giant granules within the neutrophils are characteristic. In addition, secretion of lytic secretory granules by cytotoxic T-cells is affected. People with CHS have partial albinism (light skin and silvery hair) and have problems with sun sensitivity and photophobia. Other signs and symptoms vary considerably, but frequent infections and neuropathy are common. The infections involve mucous

membranes, skin and the respiratory tract. Affected children are susceptible to infection by Gram-positive and Gram-negative bacteria and fungi, with *Staphylococcus aureus* being prominent. Most children with CHS ultimately reach a stage known as the accelerated phase, also known as the lymphoma-like-syndrome. This severe phase of the disease may be triggered by a viral infection, usually the Epstein-Barr virus (EBV). In the accelerated phase, defective white blood cells divide uncontrollably and invade many of the body's organs. The accelerated phase is associated with fever, episodes of abnormal bleeding, overwhelming infections and organ failure. These medical problems are usually life threatening in childhood. There is no specific treatment for CHS. Bone marrow transplants appear to have been successful in several patients. Infections are treated with antibiotics and abscesses are surgically drained when appropriate.

## Griscelli Syndrome

Griscelli syndrome (GS) is a rare autosomal recessive disorder that results in pigmentary dilution of the skin and hair, the presence of large clumps of pigment in hair shafts, and an accumulation of melanosomes in melanocytes. There are three different forms of GS, each caused by a different gene defect, and only GS type 2 (caused by mutation in the RAB27A gene) is a primary immunodeficiency disease. Griscelli described children with a disorder resembling CHS. Features were partial albinism, frequent pyogenic infections, and acute episodes of fever, neutropenia, and thrombocytopenia. Despite an adequate number of T- and B-lymphocytes, the patients were hypogammaglobulinemic, deficient in antibody production, and incapable of delayed skin hypersensitivity and skin graft rejection. Differences from CHS were morphologic normality of polymorphonuclear leukocytes; the giant granules of CHS were not found. The morphologic characteristics

## (Other Phagocytic Cell Disorders continued)

of the hypopigmentation also distinguished the disorder from CHS, as well as from other pigmentary anomalies of man. Another difference was normal leukocyte specific protease activity, which is very low in CHS. GS with partial albinism and immune impairment (now called GS type 2) is a serious immunodeficiency disorder with many patients developing a hemophagocytic syndrome potentially leading to death in the absence of bone marrow transplantation. Because the prognosis is poor, early bone marrow transplantation is strongly recommended for GS-2.

The three forms are Griscelli syndrome type 1 (GS1) which represents hypomelanosis with a primary neurologic deficit but without immunologic impairment or manifestations of hemophagocytic syndrome (associated with a defect in the MYO5A gene). Griscelli syndrome with immune impairment, or Griscelli syndrome type 2, is caused by mutation in the RAB27A gene. Griscelli syndrome type 3, characterized by hypomelanosis with no immunologic or neurologic manifestations, is caused by mutation in the melanophilin (MLPH gene).

# Complement Deficiencies



## Chapter 16

*Complement is the term used to describe a group of serum proteins that are critically important in our defense against infection. There are deficiencies of each of the individual components of complement. Patients with complement deficiencies encounter clinical problems that depend on the role of the specific complement protein in normal function.*

## Description of the Complement System and Its Pathways

The complement system consists of more than 30 proteins, present in blood and tissues, as well as other proteins anchored on the surfaces of cells. The primary functions of the complement system are to protect from infection, to remove particulate substances, (like damaged or dying cells, microbes or immune complexes) and to help modulate adaptive immune responses. As part of the innate immune system, complement acts immediately to start the process of removal and resolution of the problem. Complement works with the inflammatory cells of the innate immune

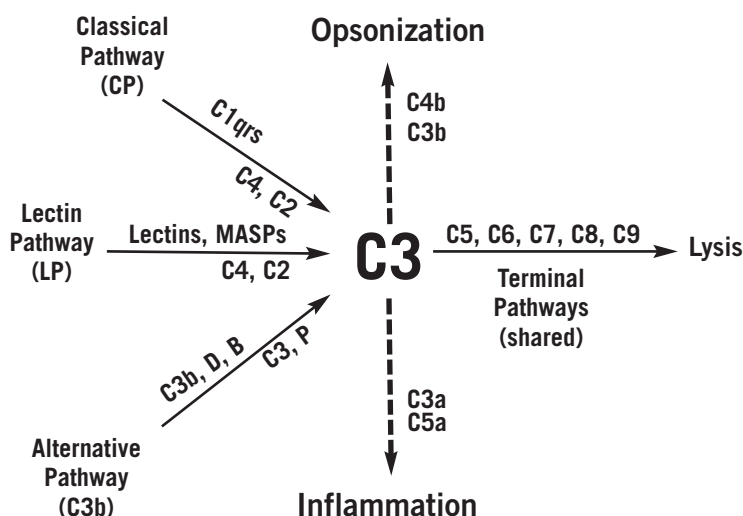
system and those of adaptive or acquired immunity. It also interacts with proteins of the coagulation and kinin generating systems along with others.

Complement activation is tightly regulated and designed to kill invading microbes while producing minimal “collateral damage” that could result in the destruction of host tissues. Complement proteins in the circulation are not activated until triggered by an encounter with a bacterial cell, a virus, an immune complex, damaged tissue or other substance not usually present in the body.

Complement activation is a cascading event like the falling of a row of dominoes. It must follow a specific order if the end result is to be achieved. The circulating proteins have been grouped into three activation pathways, based on the types of substances and proteins that initiate the activation. If you visualize a trident, the three tines represent the different initiation routes, while the handle represents the lytic mechanism by which this cascade ultimately destroys the threat, no matter which activation pathway started the response. The diagram in *Figure 1* depicts the activation pathways.

**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

CHAPTER 16; FIGURE 1



## (Description of the Complement System and Its Pathways continued)

cell membrane surfaces or other tissues. Aggregates of immunoglobulins such as cryoglobulins also activate the CP. 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 Collectin can initiate the LP.

Associated with these are enzymes referred to as MASPs (MBL-Associated Serine Proteases). C2 and C4 also participate in the LP. The LP is thought to be the most evolutionarily primitive of the complement pathways and the first to react before the adaptive immune response occurs.

**The Alternative Pathway (AP)** is initiated by fragments of the complement component C3. 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 alternative pathway to set up a very efficient mechanism for putting lots of C3b onto the surface of the activating cells, protein complexes or particles in the immediate vicinity of the activation site. Because the ability of the C3b to bind to these surfaces decays rapidly, the activation is limited to just the region around the C3 cleavage site. This time-limitation is another control mechanism for the complement pathway.

**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 or MAC) that kills susceptible bacteria or other cells that activate complement on their surfaces. The TP is

dependent upon at least one of the other pathways to initiate the process that it then completes. The components of the TP are C3, C5, C6, C7, C8 and C9. A fluid phase form of the MAC, called the Terminal Complement Complex (TCC) can be found in the circulation after complement activation occurs and makes a useful laboratory marker for complement activation.

Control mechanisms to prevent unregulated activity (and tissue damage) are present in each pathway. C1-esterase inhibitor (C1-inh) is a serine protease inhibitor (SERPIN) that 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 CP, and the MASPs in the LP along with several enzymes in the coagulation system.

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 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, with the danger met and the situation returned rapidly to normal. The diseases that accompany uncontrolled activation or inadequate performance of complement's functions are often the result of inherited deficiency or subtle impairment of one or more of the components.

## Complement Deficiencies and Their Diagnosis

Clinical indications for possible complement deficiencies include recurrent mild or serious bacterial infections, autoimmune disease, or episodes of angioedema (a painless, but often dramatic, swelling under the skin, or swelling in the intestines, which can be extremely painful). Very rarely angioedema in the brain can be fatal. This swelling does not respond to antihistamines or epinephrine. The list of potential complement-related 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, most of which are inherited as autosomal co-dominant conditions. All genes, except for those in the Male sex chromosome Y, come in pairs, one inherited from mom and one from dad.

Co-dominance occurs when the contributions of both alleles are visible in the phenotype. In the ABO blood group example, the A and B allele classes are co-dominant in producing the AB blood group phenotype, in which both A-type and B-type antigens are made. By contrast, with traditional dominant–recessive gene combination like eye color, a single brown allele is dominant and if the other parent contributed a blue color allele, the eyes will be brown rather than a mix of brown and blue. In this context it means both the normal and mutant complement proteins are produced in the affected individuals. There is an exception in the

case of Properdin, the gene for which is on the X chromosome and is inherited as an x-linked disease. (See chapter titled “Inheritance.”)

The initial tests done to evaluate a patient’s complement system are critical because they can often identify an inherited defect and indicate what further testing must be done to make the diagnosis. The aim of the evaluation process is to clearly define the complement component deficiency with as few tests as possible, while ruling out acquired causes of low complement values. Several screening tests are available that make it easier to find the answers. 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 genetic counseling for inherited deficiencies.

Therapeutics 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 several drugs available. For uncontrolled complement activation as in PNH or due to dysfunctional FH, there are a few drugs available to treat acute episodes or to prevent recurrence. Therapeutics for complement-derived diseases is in its infancy at this time, but more treatments should become available in the near future.

## Deficiencies in the Classical Pathway: C1q, C1r, C1s, C4, C2, C1-Inh

Rapid clearance of immune complexes, dying cells and debris from damaged tissues is a job that is performed efficiently by a normal CP. Primary deficiency of C1q, C1r, C1s or C4 is closely linked to development of systemic lupus erythematosus (SLE) or rheumatoid arthritis (RA), thought to be due in part to the inability of complement to clear immune complexes and dying

cells. Small complexes are cleared from the circulation when they bind to complement receptors on macrophages in the spleen and liver.

Without complement, the complexes can grow too large to be easily cleared. The resulting aggregates can activate the alternative pathway, allowing C3 to be

## (Deficiencies in the Classical Pathway: C1q, C1r, C1s, C4, C2, C1-Inh continued)

deposited into the matrix, with re-solubilized complexes that can be dealt with by the clearance through the liver and spleen. Failing this, these large complexes are no longer soluble, and form deposits in the tissues and become a site of inflammation. Dying cells, if not cleared by non-inflammatory CP activity, may serve as sources of altered self-antigens with the potential for inducing autoantibodies.

**C2 deficiency** is the most common complement deficiency in Caucasian populations, with frequency estimates between 1 in 10,000 to 1 in 20,000 for homozygous C2-deficient patients. C2 deficiency is found in a slightly higher proportion of SLE patients compared to healthy controls. In primary immunodeficiency, C2 deficiency is found in young children who have recurrent infections, primarily upper respiratory infections with *Streptococcus pneumoniae* or similar organisms. These children often have frequent ear infections and colds.

**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 swelling in the

extremities, face, lips, larynx or GI tract. The patients describe a sensation of fullness but not pain or itching in the affected area except for those with abdominal swellings who often experience acute abdominal pain. The latter two presentations are of the most concern because suffocation can occur if the airways are obstructed, and the acute swelling of the abdominal region produces intense pain often resulting in exploratory surgery.

The mechanism for production of the swelling involves not the complement enzymes, but the kinin-generating pathway. It is the production of Bradykinin through this pathway that is responsible for the tissue permeability changes that cause the swelling. Acute treatments include C1 inhibitor, a replacement therapy (both plasma derived and recombinant products are available); ecallantide, a kallikrein inhibitor; and icatibant, a bradykinin-2 receptor antagonist. Prophylactic treatments include attenuated androgens and C1 inhibitor.

## Deficiencies of the Lectin Pathway Components

### MBL, M-ficolin, L-ficolin, H-ficolin, CL-11, MASPs

MBL deficiency is fairly common, affecting approximately 5-30% of individuals. There is some controversy over the importance of the lectins to overall immunity, but most authors agree that the early months of a baby's life are dependent on the ability of the lectin

pathway to fight bacterial infections during the period when maternal antibodies decrease and the child's own antibody production is not fully functional. Other studies have shown increased susceptibility to herpes simplex virus-2, influenza A, *Pseudomonas aeruginosa* and *Staphylococcus aureus*.



## Deficiencies of the Alternative Pathway

### Factors D, B and Properdin

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. Factor B is an acute phase protein and increases during inflammation. There is only one unconfirmed report of this deficiency in humans.

Properdin is the only complement protein that is X-linked. The protein is synthesized by monocytes, granulocytic cells and T-cells. Several mutant forms of the protein have been identified that result in decreased AP function. Properdin deficiency increases the susceptibility to bacterial infections of the *Neisseria* family of organisms. The most prominent in the group is *N. Meningitis*, the cause of a serious form of meningitis. Typical family histories include male relatives who have had or died from *Neisserial* infections.

### Alternative Pathway Control Proteins

Deficiencies of factor H are linked with a wide variety of symptoms. Complete deficiency of H leads to uncontrolled activation of the AP and depletion of C3 occurs. This form of factor H deficiency is similar in presentation to the late component deficiencies due to the low or absent levels of C3. 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 and the resulting dysregulation of the AP is associated with various forms of kidney disease including atypical Hemolytic Uremic Syndrome (aHUS), as well as age-related macular degeneration (AMD). These diseases are examples of control processes gone awry on the surfaces of the organs affected.

## Treatment of Complement Deficiencies

Deficiencies of the early classical and lectin pathway components are primarily accompanied by upper respiratory infections, otitis media, along with lupus-like symptoms. Any complement deficiency should be treated as an immune deficiency, and the patient should be immunized against the likely candidate microbes for their deficiency. Antibody responses should be checked after vaccination, since the inability to activate complement impairs the immune response to some extent. Currently, there are no specific treatments for complement deficiencies. Infection prevention and appropriate treatment of infections (usually with antibiotics), when they do occur is key in the care of patients with these deficiencies. Fresh frozen plasma has been tried in some cases, but carries the risk that the patient may make antibody to the missing complement component, so

prolonged use is not advised. Prophylactic antibiotics can be used if the patient experiences repeated infections, and increased vigilance with rapid treatment of problems is another option. Most of these patients eventually make antibodies against the offending bacteria and do not get sick as often.

Boys with Properdin deficiency (X-linked) should be immunized against *Neisseria meningitidis*, in addition to the usual vaccinations of childhood. Often there is a family history of an uncle or other relative who died from *Neisserial* infection at an early age. Deficiencies of the other alternative pathway components and the terminal pathway proteins are also susceptible to *Neisseria meningitidis* and should be immunized. The vaccine titers should be verified in these individuals as well.

# Hyper IgE Syndrome



## Chapter 17

*Hyper IgE Syndrome (HIES) is a rare primary immunodeficiency disease characterized by eczema, recurrent staphylococcal skin abscesses, recurrent lung infections, eosinophilia (a high number of eosinophils in the blood) and high serum levels of IgE. Most cases of HIES are sporadic, but some familial cases of HIES have been reported, with either an autosomal dominant (AD) or autosomal recessive (AR) mode of inheritance.*

## Definition of Hyper IgE Syndrome

HIES is a rare primary immunodeficiency characterized by recurrent eczema, skin abscesses, lung infections, eosinophilia and high serum levels of IgE. Two forms of HIES have been described, including an autosomal dominant (AD, or type 1) and an autosomal recessive

(AR, or type 2) form. These two forms share overlapping clinical and laboratory features including eczema, recurrent infections, skin abscesses, high IgE level and increased eosinophil number. However, they also exhibit distinct clinical manifestations, courses and outcomes.

## History of Hyper IgE Syndrome

HIES was described first as “Job syndrome” by Davis and colleagues in 1966, in two girls with many episodes of pneumonia, eczema-like rashes and recurrent skin boils remarkable for their lack of surrounding warmth, redness or tenderness (so-called “cold abscesses”). In 1972, the syndrome was refined and clarified by Buckley and colleagues who noted similar infectious problems in two boys who also had 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 (type 1)-HIES. In 2009 mutations and deletions in the DOCK8 gene were found to underlie the majority of cases with AR (type 2)-HIES.

## Clinical Presentation of Hyper IgE Syndrome

AD-HIES, associated with heterozygous mutations in the transcription factor STAT3, is the more common form of HIES in the U.S. It commonly presents with respiratory infections and skin findings including newborn rash, eczema, recurrent skin abscesses and ear, sinus and lung infections resulting in formation of cavitory lesions in the lungs (pneumatocoles). Other frequent findings of

STAT3 deficiency include mucocutaneous candidiasis (candida fungus on mucous membranes and/or skin), manifesting typically as thrush, vaginal candidiasis or candida nail infection (onychomycosis). Additional findings include connective tissue and skeletal abnormalities such as a typical facial appearance characteristic of patients with this syndrome, hyper-

## (Clinical Presentation of Hyper IgE Syndrome continued)

extensibility of their joints, retained primary teeth and recurrent bone fractures secondary to even minimal trauma.

AR-HIES with DOCK8 deficiency is particularly common in areas of the world with high consanguinity rates (intermarriage among close relatives), where its occurrence may exceed that of AD-HIES. AR-HIES similarly presents with eczema, skin abscesses, recurrent respiratory infections, candidiasis and other fungal infections. However, patients with AR-HIES are distinguished from those with AD-HIES by the occurrence of severe, recurrent viral infections caused by pathogens

such as *Herpes simplex*, *Herpes zoster* and *Molluscum contagiosum*. They are also susceptible to allergic and autoimmune manifestations, including food allergy, hemolytic anemia (due to red blood cell destruction by antibodies) and vasculitis (inflammation within blood vessels). Patients with AR-HIES also have a high frequency of neurologic complications, including encephalitis (brain inflammation) and vascular brain lesions. The mechanisms of those complications may include viral infections of the central nervous system and autoimmunity. Finally, unlike their AD-HIES counterparts, those with AR-HIES do not manifest connective tissue or skeletal abnormalities.

## Skin Affected by Hyper IgE Syndrome

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*.

DOCK8 deficient patients also have severe eczema-like rashes, starting early in life, although not necessarily in the newborn period. They also suffer from recurrent skin abscesses, usually associated with *Staphylococcus aureus* infection. Severe recurrent or persistent skin viral infections with *Herpes simplex*, *Herpes zoster* and *Molluscum contagiosum* can also be features of DOCK8 deficiency. These infections can be persistent and are frequently difficult to treat.

Skin and nail infections with candida are common to both AD- and AR-HIES.

## Lungs Affected by Hyper IgE Syndrome

Recurrent bacterial pneumonias are often encountered in patients with AD-HIES. Pneumonias typically start in childhood, and the most frequent bacterial isolates are *Staphylococcus aureus*, *Streptococcus pneumoniae*,

and *Haemophilus influenzae*. Fungal lung infections, especially with *Aspergillus fumigatus*, are also common. Similar to the occurrence of cold skin abscesses, these pneumonias may present with fewer symptoms than

## (Lungs Affected by Hyper IgE Syndrome continued)

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. However, the severity of lung tissue damage and the subsequent emergence of chronic lung disease are higher in patients with AD-HIES as compared to those with AR-HIES. 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 with STAT3 mutations.

Recurrent lung infections with both gram-positive and negative bacteria are common in patients with AR-HIES with DOCK8 deficiency, and they may also lead to chronic lung disease with damage to the airways (bronchiectasis) and lung tissues.

## Skeletal and Connective Tissues Affected by Hyper IgE Syndrome

Involvement of both the connective and skeletal tissues is an important feature of AD-HIES with STAT3 mutations. 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. Patients with AD-HIES exhibit hyperextensibility 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. Fused skull bones (craniosynostosis) and extra or abnormally formed ribs or vertebrae are also found more often in patients with AD-HIES than in the general population. None of these skeletal abnormalities are seen in DOCK8 deficient patients.

## Teeth Affected by Hyper IgE Syndrome

Abnormalities affecting dentition is another common feature of AD-HIES with STAT3 mutations. Retention of primary (or baby) teeth even after the permanent teeth have erupted is a consistent finding. Reduced resorption of primary tooth roots leads to failure to shed primary teeth, which in turn prevents the appropriate eruption of permanent teeth. 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 necessary for healthy dentition in this disorder. Children who have had their retained primary teeth extracted have had normal eruption of their permanent teeth. In contrast to AD-HIES patients, those with AR-HIES due to DOCK8 deficiency patients do not manifest abnormalities in their dentition.

## Other Clinical Findings of Hyper IgE Syndrome

Deep tissue abscesses are commonly encountered in patients with AD-HIES, most frequently caused by staphylococcal infections.

Both AD- and AR-HIES patients are at increased risk for malignancies, especially lymphomas. Other cancers described in STAT3 deficiency include leukemia and cancers of the vulva, liver and lung. Patients with DOCK8 deficiency are susceptible to papilloma virus-induced squamous cell carcinoma and to lymphomas. Autoimmune diseases have also been associated with both types of HIES, but it is most often seen in DOCK8 deficiency.

DOCK8 deficient patients have more symptomatic neurologic disease than those who have STAT3 deficiency. Neurologic manifestations may range from limited involvement such as in facial paralysis to more severe manifestations such as hemiplegia (one side of the body paralyzed) and encephalitis. The causes of the neurologic complications are not clear but fungal, viral agents and vasculitis may be responsible. Central nervous system involvement is responsible for a significant number of fatalities in this disorder.

## Laboratory Findings of Hyper IgE Syndrome

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. Total white blood cell counts are typically high in patients with AD-HIES and STAT3 mutations but may not increase appropriately during acute infection. Neutropenia (low blood numbers of white blood cells called neutrophils) has been reported but is uncommon. Serum IgG, IgA,

and IgM typically are normal, although some individuals with AD-HIES have deficiencies in one or more of these immunoglobulin subtypes.

Patients with AR-HIES and DOCK8 deficiency typically exhibit very high eosinophil numbers in the peripheral blood in the face of severely low numbers of T-cells. They manifest low serum IgM levels and fail to sustain specific antibody responses upon vaccination.

## Diagnosis of Hyper IgE Syndrome

The diagnosis of HIES can be made based on a combination of clinical and laboratory findings for both types of HIES. An elevated level of serum IgE is a virtually universal finding in these patients. However, it is not sufficient on its own to make the diagnosis as patients with other conditions such as severe eczema may exhibit IgE levels in the HIES range. Certain features, such as pneumatocele formation in the context

of other findings of HIES, are strongly supportive of the diagnosis of type 1 HIES.

An HIES scoring system has been previously developed at the National Institutes of Health (NIH) that can help with the diagnosis of type 1 HIES. In this system, patients are evaluated for the existence and severity of the following clinical and laboratory features: newborn rash, eczema, skin abscesses, recurrent upper

## (Diagnosis of Hyper IgE Syndrome continued)

respiratory infections, pneumonia, lung changes (cavities), candidiasis, other severe infections, fatal infections, characteristic facial appearance, increased nasal width, high palate, retained primary dentition, joint hyperextensibility, fractures with minor trauma, scoliosis, midline anatomic abnormalities, lymphoma, high serum IgE level, and eosinophilia. The score correlates with the severity of the disease (scores of 0 to 15 unaffected, 16 to 39 possibly affected, 40 to 59 probably affected, and 60 or more definitively affected). The scoring system is a particularly useful tool for the diagnosis of AD-HIES but less so for AR-HIES. Definitive diagnosis can be

established with genetic analysis of the STAT3 and/or DOCK8 genes.

Decreased serum IgM concentrations and peripheral blood T-cell counts are important laboratory findings of DOCK8 deficiency. Absent DOCK8 protein in blood cells is encountered in more than 95% of patients with DOCK8 deficiency and as such can be useful in confirming the diagnosis in suspected patients but not in excluding it if DOCK8 protein expression is normal. The diagnosis in the latter individuals would have to be established by DNA sequencing methods.

## Inheritance of Hyper IgE Syndrome

Autosomal dominant HIES (with STAT3 mutations) - AD-HIES occurs in both males and females of all ethnic groups with apparently equal frequency. In families with more than one affected person, disease transmission is consistent with autosomal dominant inheritance. In most patients, the disease occurs sporadically. STAT3 mutations cause most, if not all, cases of autosomal dominant HIES. Mutational analysis of the STAT3 gene would enable definitive diagnosis and genetic counseling.

Autosomal recessive HIES (DOCK8 deficiency) - Most, but not all, of the patients with AR-HIES are from consanguineous families. Deletions and mutations in the DOCK8 gene on chromosome 9 account for most of the cases, although a few patients with AR-HIES have normal DOCK8 gene. Mutational analysis of the DOCK8 gene is important for diagnosis and genetic counseling.

## Treatment of Hyper IgE Syndrome

Therapy of HIES remains largely supportive. Antibiotic prophylaxis with trimethoprim-sulfamethoxazole is a frequently used as prophylaxis against recurrent respiratory infections. Treatment for these infections, when they occur, should be started promptly. Given that patients with HIES suffer from significant eczema and skin infections and that the compromised skin offers a

portal of entry to pathogens to cause deep seated infections, skin care and prompt treatment of skin infections is an important component of HIES management. When the eczema is severe, topical moisturizing creams and limited use of topical steroids can help achieve healing. Antiseptic treatments of the skin greatly reduce the bacterial burden in the skin

## (Treatment of Hyper IgE Syndrome continued)

without leading to emergence of antibiotic resistant bacteria.

Skin abscesses may require incision and drainage but can largely be prevented with prophylactic oral antibiotics. The role of prophylactic antibiotics has not been rigorously investigated, but there is general consensus in favor of use of antibiotics against *Staphylococcus aureus* in both HIES groups. Lung and other deep tissue abscesses may require drainage or resection. Following the resolution of acute pneumonias, pulmonary cysts or cavities form places for colonization with *Pseudomonas aeruginosa*, *Aspergillus* and other fungal species. These super infections can be a difficult aspect of HIES. Potential management strategies include continuous treatment with antifungal drugs and/or, aerosolized antibiotics.

Candidiasis of the fingernails, mouth or vagina in HIES rarely spreads to deeper tissues and responds well to oral antifungals. Although the over-use of antibiotics and antifungals is discouraged in general with “normal” patients due to concerns about selection for resistant organisms, the under-use of antibiotics in HIES patients leaves this group at risk for infections that are debilitating and dangerous.

A remarkable feature of HIES is how well the patients 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, a HIES patient may deny feeling sick and may not see the need for invasive diagnostic testing or prolonged therapy. Moreover, doctors unfamiliar with HIES are hesitant to believe that patients who do not appear very ill and appear about the same as usual can really be quite ill.

Poor antibody responses to vaccination in both AD- and AR-HIES lend support to the use of immunoglobulin replacement therapy in those patients. The role of interferon-gamma, granulocyte-colony stimulating factor or other immune modulators in HIES is, however, unproven. Bone marrow transplantation is curative for AR-HIES with DOCK8 deficiency and is recommended given the severity of the disease and the life-long risk of developing fatal complications, including infections, autoimmunity and malignancies. In contrast, AD-HIES patients generally do well with intensive therapy and supportive care, and bone marrow transplantation is not recommended for those individuals.

## Expectations for Patients with Hyper IgE Syndrome

Patients 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 patients with AD-HIES do fairly well. The more severe nature of AR-HIES should prompt early

consideration of bone marrow transplantation, which is curative. Genetic counseling is advised for families with HIES children and is especially important for those families where consanguinity is involved.



# Innate Immune Defects



## Chapter 18

*Primary immunodeficiency diseases are disorders in which part of the body's immune system is missing or does not function properly. These disorders can be divided into two groups:*

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

*This chapter focuses only on the following innate immune disorders: Toll-like receptor (TLR), natural killer (NK) and interferon- $\gamma$ /interleukin 12 (IFN- $\gamma$ /IL-12) defects.*

## **Innate Versus Adaptive Immunity**

The mechanisms by which the innate and adaptive (acquired) immune systems function are different: 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 cells, basophils and mast cells and complement proteins. Innate responses to infection occur rapidly and reliably. Even small infants have excellent innate immune responses. The innate immune system recognizes microbes through a class of proteins found on cells termed pattern recognition receptors (PRRs), which bind to unique proteins of various microorganisms. A major class of PRRs are called toll-like receptors (TLRs), molecules found on the surface and within cells.

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 not to attack our own cells and to become more efficient for eliminating invading germs. In contrast to the innate immune system, adaptive immune responses recognize microbes by specific receptors found on T- and B-cells. The advantages of the adaptive responses are their long-lived memory and the ability to adapt to new germs. Each T- and B-lymphocyte acquires a unique receptor during development that can respond to a specific microbe. As a group, these cells are capable of recognizing virtually all microbial or other antigens found in nature.

## Toll-like Receptors

There are ten human TLRs termed TLR1 to TLR10. The TLRs recognize microbes by forming pairs with each other. After recognizing a molecule on the microbe, the TLRs begin a series of chemical reactions that allow signals to enter the innate immune cell and allow it to function in the killing of the microbe. If one or more of these chemical molecules are defective, the innate immune cell cannot kill the microbe and patients with these defects present with recurrent infections.

The pairing of TLR1/2 or TLR2/6 recognizes bacteria such as those that cause tuberculosis. The TLR3 recognizes certain viruses; TLR4 recognizes certain molecules on bacteria found in the gastrointestinal tract such as *E. coli*; TLR5 recognizes whip-like structures on bacteria called flagella; TLR7, 8 and 9 recognize certain viruses such as influenza and human immunodeficiency virus I (HIV-I). The function of TLR10 is not yet known. In recent years several deficiencies of TLRs have been identified in patients who present with recurrent infections. The knowledge of the function of these TLRs has provided an important basis for the diagnosis and treatment of these disorders.

### Toll-like Receptor (TLR) Deficiencies

As described previously, TLRs are proteins present on the surface of many types of white blood cells that react with proteins present on many microbes. Upon contact with these microbes TLRs send internal messages to the nucleus of the cell to secrete cytokines, which stimulate the immune system to combat invading microorganisms.

Cytokines are important proteins in the body that serve as hormones 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. There are

several families of cytokines and two of these are called interleukins (ILs) that number 1 through 37 and a family of interferons, originally described by their ability to interfere with viral replication, and which include interferon-alpha (IFN- $\alpha$ ), interferon-beta (IFN- $\beta$ ) and interferon-gamma (IFN- $\gamma$ ).

Several TLR immunodeficiencies have been described in which cellular proteins that should transmit the message from the TLRs to the nucleus are abnormal. These signaling defects result in a failure of cytokines to be produced in response to bacterial infection. Two of these are disorders termed MyD88 deficiency and IRAK-4 deficiency. Other disorders of this type include UNC93B deficiency and TLR3 mutations and ectodermal dysplasia with immunodeficiency (EDA-ID), an X-linked disorder associated with a defect of a gene termed NEMO. (See chapter titled “Nemo Deficiency Syndrome.”)

### Clinical Presentation of TLR Deficiencies

The typical presentation of TLR deficiencies is susceptibility to infection with either bacteria or viruses. The innate immune system defects also play a major role in allergy and asthma, atherosclerosis and human immunodeficiency virus (HIV) infection.

### MyD88 Deficiency

All TLRs except TLR3 use a signaling protein called MyD88 (myeloid differentiation primary response protein 88), a protein that allows the innate immune cell to function normally. MyD88 deficiency was initially described in nine children suffering from recurrent and severe pus-forming or pyogenic bacterial infections. These children were susceptible to invasive infections with *S. pneumoniae*, *S. aureus*, and *P. aeruginosa*, but had normal resistance to other common bacteria, viruses, fungi, and parasites. Susceptibility to infection improved with age in affected patients, although MyD88 levels did not change, indicating that the function of

## (Toll-like Receptors continued)

MyD88 can be replaced by other systems as the immune system matures. The defect in the children with this disorder displayed autosomal recessive inheritance.

### IRAK4 Deficiency

Another signaling defect with a similar clinical pattern similar to MyD88 deficiency is called IRAK 4 deficiency. Patients with IRAK4 deficiency have recurrent severe infections (cellulitis, arthritis, meningitis, osteomyelitis, organ abscesses and sepsis) mainly caused by *S. aureus*, *S. pneumoniae* (*pneumococcus*) and *Pseudomonas aeruginosa*. One report described recurrent bacterial infections, mostly localized to the upper respiratory tract and skin. No patients had severe viral, fungal or parasitic infections. Invasive pneumococcal infections caused the most disease and were the cause of death in 33 percent of affected

patients. Initial invasive infections occurred before the age of two years in 88 percent. The clinical status of patients with IRAK-4 deficiency seems to also improve with age, regardless of therapy, similar to patients with MyD88 defects.

### UNC93B Deficiency and TLR3 Mutations

UNC93B1 is another signaling molecule involved in the production of interferon important in the killing of viruses. Signaling through TLRs 3, 7, 8, and 9 normally induces production of interferons following their binding to viral RNA. Deficiency of UNC93B1 or TLR3 leads to susceptibility to encephalitis caused by herpes simplex (HSV-1) (the virus that causes cold sores) due to decreased production of interferons in the central nervous system.

## Human Natural Killer Cell Deficiencies

Natural killer (NK) cells are innate immune cells important in the killing of viral-infected or malignant cells. NK cells are so named because they kill cells without the presensitization needed for cytotoxic T-cells (part of adaptive immunity). NK cells are present in relatively low numbers in the bloodstream and in tissues.

NK cells kill virus-infected cells by inserting toxic proteins into their membranes. They are particularly important in the defense against herpes viruses. This family of viruses includes Herpes simplex virus (that causes cold sores and genital herpes), Epstein-Barr virus (that causes infectious mononucleosis) and varicella virus (that causes chicken pox and shingles).

Human NK cell deficiencies have been divided into two categories:

1. Quantitative defects: with decreased numbers of NK cells in the peripheral blood
2. Qualitative defects: with normal numbers of NK cells with abnormal function

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

Two genetic causes of NK cell deficiency have been identified including an autosomal recessive CD16 functional defect and an autosomal dominant GATA2 mutation causing classic NK deficiency.

## Defects in Interferon- $\gamma$ (IFN- $\gamma$ ) and Interleukin-12 (IL-12) Signaling

A major way the cells of the innate immune system can kill microbes that are found within cells, such as the tuberculosis bacteria, is to cooperate with the T-cells of the adaptive system to stimulate interferon- $\gamma$  (IFN- $\gamma$ ) production. IFN- $\gamma$ /IL-12 pathway deficiencies are rare genetic disorders characterized by susceptibility to mycobacteria (the family of bacteria which cause

tuberculosis and related infections) and salmonella infections. Many of the affected infants become ill after receiving a live BCG tuberculosis vaccination, given routinely at birth in many countries, although not the U.S. Other patients have skin infections, swollen lymph nodes or blood stream infections with an enlarged liver and spleen.

## Diagnosis of Innate Immune Defects

Most of patients with innate immune system defects have intact adaptive immune systems with normal immunoglobulins, antibodies and T-cells. A type of white blood cell called an eosinophil may be increased in the blood; elevated IgE immunoglobulin levels may also be present. The diagnosis is usually made by measuring cytokine production by white blood cells, activated by

microbial products that stimulate the cells. Testing of TLR function is becoming available through commercial reference laboratories. Abnormal tests need to be confirmed by repeat testing. Persistently abnormal tests may be followed up by specific genetic tests.

## Treatment of Innate Immune Defects

The usual treatment for these defects is antibiotic therapy to treat acute infection. Prophylactic antibiotic therapy is also used. Some providers have also prescribed immunoglobulin therapy as infection prophylaxis.

New treatments of innate immune system defects have included new TLR-BASED THERAPIES. There are several new therapies in use or development that utilize emerging knowledge of TLR biology.

TLR7 agonists are drugs that activate TLR7 and have been found to slow the growth of malignancies and

inhibit viral replication. Imiquimod is a synthetic agonist of TLR7 that is effective topically on basal cell carcinoma and genital warts. Isatoribine is another TLR7 agonist used in the treatment of hepatitis C.

TLR9 agonists include CpG DNA — pieces of DNA that stimulate TLR9 activation to fight viruses. When added to hepatitis B vaccine (Engerix-B), they may boost the response to the vaccine. They may also be of value in augmenting cancer therapy.

## Expectations for Patients with Innate Immune Defects

Patients with the defects of the innate immune system are being recognized with increasing frequency. Since these illnesses are rare and only recently identified, the long-term outlook has not yet been established. There is

considerable variability in the severity of their disease, and all the complications that may occur have not yet been identified. It is best to consult an immunologist who has specific expertise in this area.

# NEMO Deficiency Syndrome



## Chapter 19

*The NEMO deficiency syndrome is a complex disease caused by genetic mutations in the X-linked NEMO gene (also known as IKK gamma or IKKG). It can involve many different parts of the body and often manifests in different ways in different individuals. The most common symptoms are skin disease and susceptibility to certain bacterial infections that can be severe and affect virtually any part of the body.*

## Definition of NEMO Deficiency Syndrome

The NEMO syndrome was originally described as an association between ectodermal dysplasia (ED) and susceptibility to infections. Patients with ED have thickened skin, conical teeth, absence of sweat glands, and thin, sparse hair. In addition to the dry, flaky skin of ectodermal dysplasia, patients with NEMO deficiency have a range of infections with pus-inducing (pyogenic) organisms (Pneumococcus and Staph) being the most common. Infections may be found virtually anywhere in the body, including the lungs, skin, central nervous system, liver, abdomen, urinary tract, bones and gastrointestinal tract. Almost all cases of NEMO occur in boys.

The early description of these patients indicated a wide range of disease severity and infections. Many patients had humoral immunity problems with a complete lack of antibody response against bacteria such as Pneumococcus. Other patients exhibited defects in other arms of the immune system that caused increased susceptibility to mycobacteria and skin infections.

In 1999, the genetic defect responsible for the large majority of these cases was discovered. The disease was

named the NEMO syndrome to reflect the genetic mutation. NEMO stands for the “NF-kappa B Essential Modulator” and is also known as the Inhibitor of Kappa B Kinase gamma (IKK gamma). The protein is required for the activation of the NF-kappa B family of transcription factors, which regulate gene expression and the development of a number of organ systems, including the immune system. The complete absence of NEMO activity is not compatible with life.

In the NEMO syndrome, the NEMO protein retains partial activity. An embryo develops, but many organ systems fail to develop normally, including the immune system. In the NEMO syndrome, B-cells, T-cells, neutrophils, macrophages and dendritic cells all respond poorly to bacterial and fungal invasion. This leads to problems in the function of the innate immune system and problems with the formation of protective antibodies against microbes, as well.

There is at least one additional genetic cause of a NEMO-like syndrome with defects in a similar pathway. While this form can affect both males and females, it is extremely rare.



## Clinical Presentation of NEMO Deficiency Syndrome

The NEMO syndrome can be difficult to diagnose because of the wide range of possible symptoms. Three typical presentations are: 1) susceptibility to pyogenic infections, 2) ED and 3) susceptibility to mycobacterial infection. Patients tend to present with susceptibility to pyogenic infections. Most commonly, patients tend to present with severe pneumococcal infections despite vaccination. Meningitis during the first year of life is also a common presentation. Patients can also have deep tissue infections with *Staphylococcus Aureus* in the skin, liver, abdomen, bones and lungs.

ED is difficult to recognize early in life. Many infants often have eczematous rashes and thin, sparse hair, so infants with true ED may go undetected. The eruption of conical teeth, however, is an important sign that should be examined closely.

In developing countries, particularly those that use the Bacillus Calmette-Guérin (BCG) live vaccine against tuberculosis, patients with NEMO may develop disseminated infection with the vaccine strain of the BCG mycobacteria. This organism often invades several organ systems.

While meningitis or other deep tissue infections raises the immediate concern for a primary immunodeficiency, the presentation of the NEMO syndrome can be much more subtle with patients having a history of recurrent skin infections or an infectious history similar to the presentation of Common Variable Immune Deficiency. Fungal infections have also been noted in patients with NEMO.

## Diagnosis of NEMO Deficiency Syndrome

Once NEMO is suspected, a patient must have a thorough immunologic screen to evaluate the NEMO syndrome although genetic testing is the only means to conclusively make the diagnosis. Patients with NEMO can have varied results of immunologic tests.

Patients with NEMO syndrome may have an elevated IgM or IgA, but not both. The IgM is not usually as high as is seen in classic hyper IgM syndrome. Patients also tend to have low IgG and IgE. However, it is important to note that patients may also have normal levels of all immunoglobulins early in life. Patients may also have normal to high total white blood cell counts. Lymphocyte subsets are often normal and common clinical tests of T-cell function are normal or only subtly diminished.

One key (and nearly universal) feature of the NEMO syndrome is absence the development of

anti-pneumococcal responses following pneumococcal vaccination with either the conjugated (Pneumovax) or polysaccharide pneumonia vaccine (Pneumovax). This lack of response is notable even in patients with normal total serum immunoglobulin levels.

Innate immune cells from patients with the NEMO syndrome also demonstrate poor responses after stimulation with molecules derived from microbes. Though such findings do not make a definite diagnosis of NEMO syndrome, these tests offer valuable insights into host defense defects.

Genetic testing for the NEMO gene (IKK gamma) is commercially available. As noted above, the NEMO syndrome almost always follows an X-linked inheritance pattern.

## Therapy for NEMO Deficiency Syndrome

Therapy for the NEMO syndrome is aimed at preventing infections and complications stemming from infection. Patients receive immunoglobulin replacement for the antibody immunodeficiency. While this is a cornerstone of therapy, it is insufficient to control infections given the broad-based immune defects in these patients. Therefore, patients also receive a series of prophylactic antibiotics as part of their preventive regimen. These antibiotics are aimed at protecting the patients against *Pneumococcus*, *Staph*, and mycobacterial infections.

Patients with the NEMO syndrome should see their primary care physician and immunologist regularly as problems and complications can be frequent. Patients with the NEMO syndrome should also be monitored for bone health, as patients with NEMO syndrome may be less able to make strong bones, though recurrent fractures are not very common in these patients.

## Expectations for Patients with NEMO Deficiency Syndrome

Patients with NEMO syndrome have a number of issues that make prediction of their clinical course difficult. First, the relatively recent recognition of the disease and its rarity mean that little data exist to give clear guidance with regard to long-term outcomes. Second, there is wide variability in the severity of the immune deficiency. While some patients can expect relatively normal life expectancy, many patients have severe forms of the disease with both infectious and non-infectious

complications. These non-infectious complications have been particularly difficult to understand as these often mimic infections during presentation.

Further research is needed to fully understand the immune defects observed in patients with NEMO. Bone marrow transplantation has been used for some patients with NEMO with varying outcomes.

# Inheritance



## Chapter 20

*Many diseases have a genetic origin and are passed on in families. Most primary immunodeficiency diseases are 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 primary immunodeficiency disease and may be useful to identify a particular pattern of inheritance.*

## **Inheritance of Primary Immunodeficiency Diseases**

Most of our physical characteristics are passed along from parents to children. Examples of these include the color of our eyes and hair, and the proteins that determine our blood type. In the same manner, many primary immunodeficiency diseases are inherited, or passed on, in families. The DNA in our cells contains about 30,000 genes that are responsible for the characteristics that make an individual unique. These genes are packaged on long, string-like structures called chromosomes. Every cell in the body contains all the chromosomes and consequently, all of the genes necessary for life.

Each of our cells contains 23 pairs of chromosomes, hence, 23 sets of genes. One of each pair of chromosomes is inherited from our mother while the other is inherited from our father. Since genes are on these chromosomes, we also inherit one gene (or message) for a certain characteristic (such as eye color) from our biological mother and one gene for the same characteristic from our biological father.

During egg and sperm production, the total number of 46 parental chromosomes (23 pairs) is divided in half. One chromosome of each pair, and only one, is normally passed on in each egg or sperm. When fertilization of the

egg occurs, the 23 chromosomes contained in the egg combine with the 23 chromosomes in the sperm to restore the total number to 46. In this way each parent contributes half of their genetic information to each offspring.

All of the chromosomes except the sex chromosomes are called autosomes and are numbered from 1-22 according to size. One additional pair of chromosomes determines the sex of the individual. These are called the sex chromosomes and are of two types, X and Y chromosomes. As shown in *Figure 1*, females have two X chromosomes, and males have an X and a Y chromosome. As a result of having two X chromosomes, females can only produce eggs that have an X chromosome. In contrast, since men have both an X and Y chromosome, half of the sperm produced will contain an X chromosome and half will carry a Y chromosome. The sex of the baby is determined by which type of sperm fertilizes the egg. If the sperm that fertilizes (or combines with) the egg carries an X chromosome, the child that results will be a female. If the sperm carries a Y chromosome, the child that results will be a male.

## Types of Inheritance

Many diseases are genetic in origin and are passed on in families. Most of the primary immunodeficiency diseases are inherited in one of two different modes of inheritance: X-linked recessive or autosomal recessive; rarely, the inheritance is autosomal dominant.

Laboratory studies can be helpful in establishing the possible role of genes or chromosomes in a particular primary immunodeficiency disease. In addition, family history information may help to identify a particular pattern of inheritance, as can comparisons to other families with similar problems.

Consult the appropriate handbook chapter or your physician to learn whether a particular primary immunodeficiency disease is genetic, and if so, what form of inheritance is involved.

### X-linked Recessive Inheritance

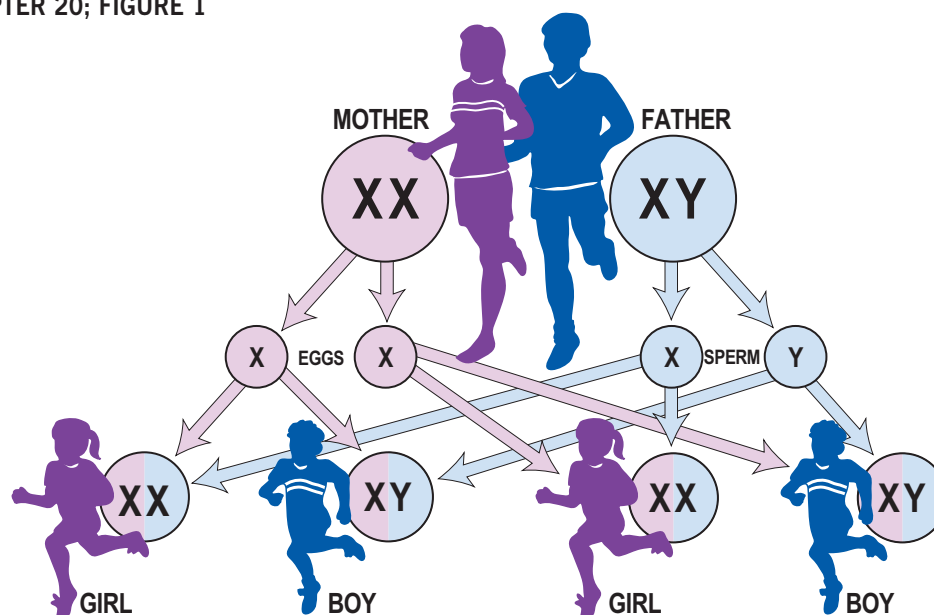
Since women have two X chromosomes, they usually do not have problems when a gene on one X chromosome does not work properly. This is because the second

X chromosome usually carries a normal gene and compensates for the abnormal gene on the affected X chromosome. Men have only one X chromosome, which is paired with their male-determining Y chromosome. The Y chromosome does not carry much active genetic information. Therefore, if there is an abnormal gene on the X chromosome, the paired Y chromosome has no normal gene to compensate for the abnormal gene on the affected X chromosome, and the boy (man) has the disorder. This special type of inheritance is called X-linked recessive.

In this type of inheritance, a family history of several affected males may be found. The disease is passed on from females (mothers) to males (sons). While the males are affected with the disease, the carrier females are generally asymptomatic and healthy even though they carry the gene for the disease because they carry a normal gene on the other X chromosome. The diagram in *Figure 2* illustrates how this kind of inheritance operates in the usual situation.

## The Sex Chromosomes

CHAPTER 20; FIGURE 1



(Types of Inheritance continued)

X-Linked Agammaglobulinemia (XLA) is used as the specific example. Parents in the situation shown in *Figure 2* can have four different types of children with respect to XLA.

The X chromosome is diagrammed as an “X.” An X chromosome that carries the gene for agammaglobulinemia is represented by an “AX.” A normal X chromosome is represented by an “NX.” A “Y” represents a Y chromosome.

The mother, who is a carrier, can produce two kinds of eggs—one containing an X chromosome carrying the agammaglobulinemia gene (AX) and one containing an X chromosome with a normal gene (NX). The father, who is unaffected, can produce two kinds of sperm—one containing a normal X chromosome (NX), and one containing a Y chromosome.

If the egg containing the agammaglobulinemia X chromosome (AX) combines with (or is fertilized by) the sperm containing the normal X chromosome, then a

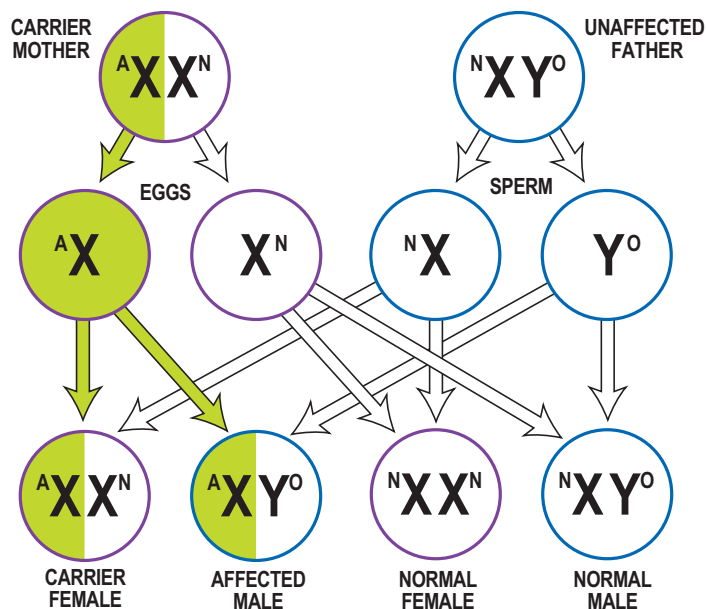
daughter who is a carrier (AX/NX) is produced. The gene for agammaglobulinemia is balanced out by the normal gene on the other X chromosome.

If the egg containing the agammaglobulinemia X chromosome (AX) combines with the sperm containing the Y chromosome (Y), then a male who is affected with agammaglobulinemia (AX/Y) is produced. In this case, there is no gene on the Y chromosome that corresponds to the gene that can cause agammaglobulinemia, and only the agammaglobulinemia gene is active in the child.

If the egg containing the normal X chromosome (NX) combines with the sperm containing the normal X chromosome (NX), then a normal female (NX/NX) is produced. In this case the child does not carry the agammaglobulinemia gene. Finally, if the egg containing the normal X chromosome (NX) combines with the sperm containing the Y chromosome (Y), then a normal male (NX/Y) results.

## X-linked Recessive Inheritance - Carrier Mother

CHAPTER 20; FIGURE 2



## (Types of Inheritance continued)

Examples of Primary Immunodeficiency Diseases with X-Linked Recessive Inheritance:

- X-Linked Agammaglobulinemia (XLA)
- Wiskott-Aldrich Syndrome
- Severe Combined Immune Deficiency (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

The chances for a given egg combining with a given sperm are completely random. According to the laws of probability, the chance for any given pregnancy of a carrier female to result in each of these outcomes is as follows:

- Carrier female: 1 in 4 chance or 25%
- Agammaglobulinemia male: 1 in 4 chance or 25%
- Normal female: 1 in 4 chance or 25%
- Normal male: 1 in 4 chance or 25%

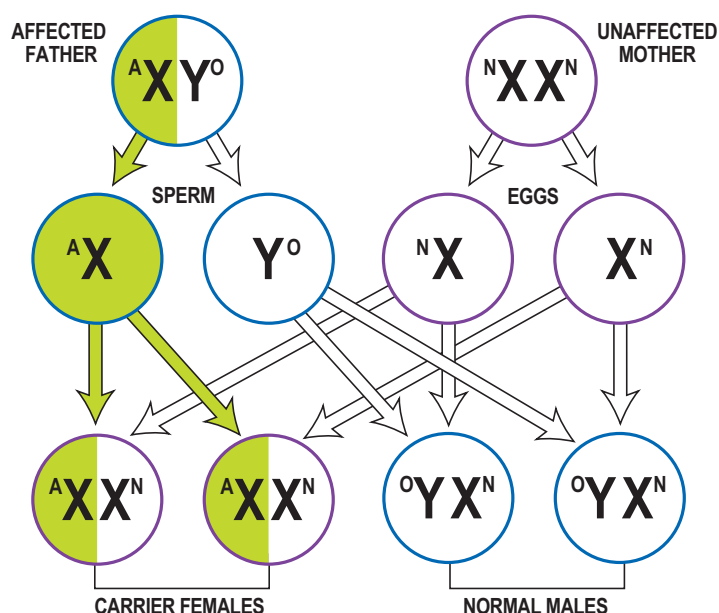
It should be noted that the outcome of one pregnancy is not influenced by the outcome of a previous pregnancy. Just as in coin flipping, the fact that you get a “heads” on your first toss does not mean you will get a “tails” on the next. Similarly, if you have a son with agammaglobulinemia with your first pregnancy, you are not guaranteed to have an unaffected child with your second pregnancy; your chances of having a son with agammaglobulinemia are still 1 in 4 (25%) with each pregnancy.

In several of the X-linked primary immunodeficiency diseases, carrier females can be identified by laboratory tests. If the gene mutation in a given family has been determined, genetic testing can identify carriers for any disease. Consult with your physician or genetic counselor to learn if carrier detection is available in your specific situation.

With earlier diagnosis and improved therapy, many young men with X-linked disorders, such as agammaglobulinemia, are reaching adulthood and having children of their own. *Figure 3* illustrates the

## X-linked Recessive Inheritance - Affected Father

CHAPTER 20; FIGURE 3



(Types of Inheritance continued)

kind of children that a man with XLA would have if he married a woman who did not carry the gene for agammaglobulinemia. As can be seen in *Figure 3*, all of the daughters of an affected male would be carrier females and none of the sons would be affected.

**Autosomal Recessive Inheritance**

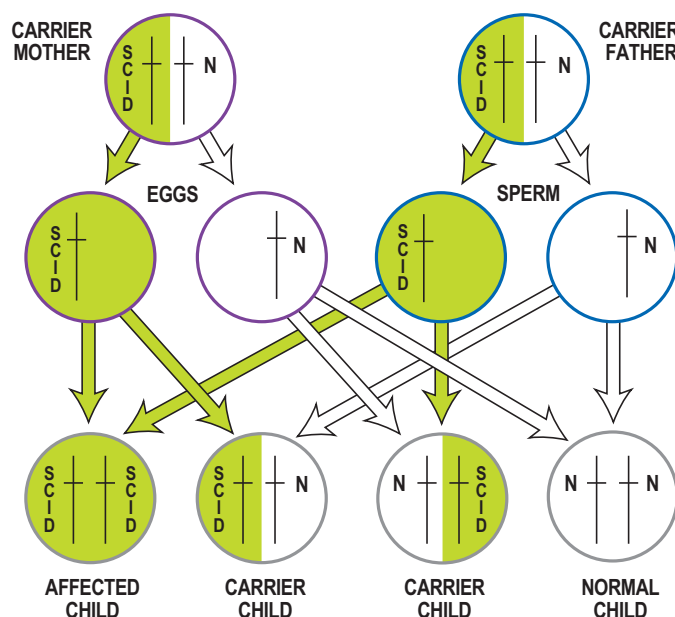
If a primary immunodeficiency disease can only occur if two abnormal genes (one from each parent) are present in the offspring, then the disorder is inherited as an autosomal recessive disorder. If an individual inherits only one gene for the disorder, then he or she carries the gene for the disorder but does not have the disorder itself.

In this form of inheritance, males and females are affected with equal frequency. Both parents carry the gene for the disease although they themselves are healthy. *Figure 4* illustrates how this kind of inheritance operates in the usual situation. ADA-SCID is used as the specific example.

As illustrated in *Figure 4*, these parents, each of whom is a carrier, can have three different types of children with respect to SCID. The chromosome carrying the gene for SCID is diagrammed as a vertical line with the initials SCID next to it. The normal chromosome is diagrammed as a vertical line with the initial “N” next to it. The mother can produce two kinds of eggs—one containing the chromosome carrying the SCID gene and one containing a chromosome carrying the normal gene. Similarly, the father can produce two kinds of sperm—one kind containing the chromosome carrying the SCID gene and the other containing the chromosome carrying the normal gene. If an egg containing the SCID chromosome combines with a sperm containing the SCID chromosome, then a child with SCID is produced; in this case the child has two genes for SCID and no normal genes to counteract the SCID genes. If an egg containing the chromosome carrying the SCID gene combines with a sperm containing a normal chromosome then a carrier child results; in this case the

**Autosomal Recessive Inheritance - SCID Example**

CHAPTER 20; FIGURE 4





## (Types of Inheritance continued)

gene for SCID is balanced by a normal gene and the child is well, but still carries the gene for SCID. Similarly, if an egg containing the normal chromosome combines with a sperm containing the chromosome carrying the SCID gene, a carrier child is produced.

Finally, if an egg containing the normal chromosome combines with a sperm containing the normal chromosome, a normal child who is not a carrier is produced.

The chances for a given egg to combine with a given sperm are completely random. According to the laws of probability, the chance for any pregnancy of carrier parents to result in each of the following outcomes is as follows:

- Affected child: 1 in 4 chance or 25%
- Carrier child: 2 in 4 chance or 50%
- Normal child: 1 in 4 chance or 25%

Again, it should be noted that the outcome of one pregnancy is not influenced by the outcome of a previous pregnancy. Just as in coin flipping, the fact that you get a “heads” on your first toss does not mean you will get a “tails” on your next. Similarly, if you have a child with SCID with your first pregnancy you are not guaranteed an unaffected child or a carrier child with your second pregnancy; your chances of having a child with SCID are still 25% or 1 in 4 with each pregnancy.

Examples of Autosomal Recessive Inheritance:

- Severe Combined Immune Deficiency, several forms
- Chronic Granulomatous Disease, several forms
- Ataxia-Telangiectasia

## Autosomal Dominant Inheritance

In rare situations, a normal gene in the presence of a mutated gene cannot compensate for the defective gene; in this situation, the abnormal gene is said to exert a “dominant negative effect.”

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) (WHIM syndrome)
- DiGeorge Syndrome
- Some rare forms of defects in the IFN- $\gamma$ /IL-12 pathway

As illustrated in *Figure 5*, if one parent is affected with autosomal dominant Hyper IgE Syndrome, or Job’s syndrome, due to a mutation in only one of the two genes for STAT3 (causing Job’s syndrome), and the other parent has two normal STAT3 genes, only two types of children are possible.

The chromosome carrying the gene for Job’s is diagrammed as a vertical line with the initials “JOBS” next to it. The normal chromosome is indicated as a vertical line with the initial “N”.

In this situation, the father is affected, but since both his parents are normal, a “de novo” mutation had to have happened during the development of either the sperm or egg that formed the father. De novo refers to a “new” mutation causing an altered gene that was not present in either parent. De novo mutations occur regularly in the human genome, but since such a small fraction of the inherited DNA actually codes for functional genes, most de novo mutations go unnoticed. Only when such a mutation occurs in a critical gene does its presence become apparent in later generations. It has been estimated that for some rare X-linked diseases, as many as a third of newly diagnosed affected boys resulted from a de novo mutation that was not present in the genomic DNA of the mother.

The affected father produces two kinds of sperm, those containing the chromosome carrying the HIES (Job’s) gene with the STAT3 mutation and those containing the chromosome carrying the normal gene. The unaffected

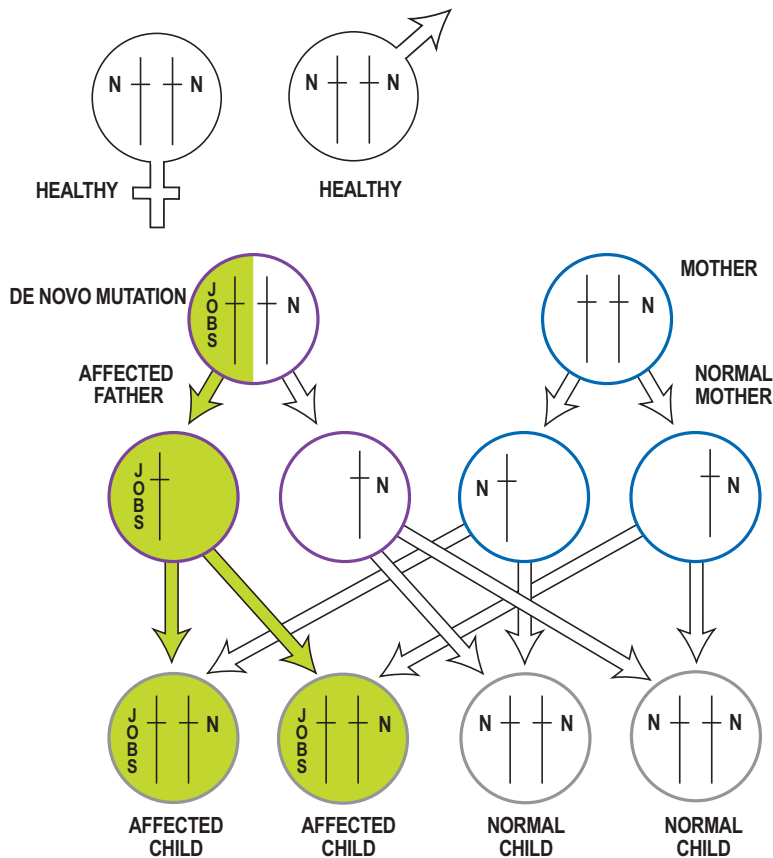
(Types of Inheritance continued)

mother, however, produces only eggs containing the chromosome with the normal gene. If such an egg combines with a sperm containing the chromosome with the HIES gene, the offspring (male or female) is affected. If the egg is fertilized by sperm containing the chromosome with the normal STAT3 gene, the offspring is unaffected.

Because the chances that a given egg combines with a given sperm (normal or with the HIES gene mutation) are completely random, the chance to have an affected child in this situation is 50% (2 in 4 possible outcomes). Again, the “coin flipping rule” applies: each pregnancy has a 50% chance of resulting in an affected child.

## Autosomal Dominant Inheritance – Jobs Syndrome Example

CHAPTER 20; FIGURE 5



## Carrier Testing

In many primary immunodeficiency diseases, carrier parents can be identified by laboratory tests. Consult with your physician or genetic counselor to learn if carrier detection is available in your specific situation.

## Reproductive Options

After the birth of a child with a special problem, many families face complicated decisions about future pregnancies. The risk of recurrence and the burden of the disorder are two important factors in those decisions. For instance, if a problem is unlikely to occur again, the couple may proceed with another pregnancy even if the first child's problem is serious. Or if the risk of recurrence is high, but good treatment is available, the couple may be willing to try again. On the other hand, when both the risk and the burden are high, the circumstances may seem unfavorable to some families. It should be emphasized that these decisions are personal. Although important information can be gained from speaking to a pediatrician, immunologist, obstetrician and/or genetic counselor, ultimately the parents must decide which option to choose.

There are options available regarding family planning for families with members who have genetically determined (inherited) primary immunodeficiency diseases. In some situations, prenatal testing of a fetus in the uterus can determine whether the infant will be affected.

Chorionic villus sampling (CVS) or amniocentesis 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 16-17 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.

Chromosome studies can be performed on cells from CVS or amniocentesis. In addition to determining the

chromosome number and structure, this study will identify the sex of the fetus. For conditions that are X-linked, identification of the sex will help determine whether the fetus could be affected by the disease (if male) or could be a possible carrier (if female). The fetal sample can also be used to provide DNA (deoxyribonucleic acid) for gene testing. There are two main types of DNA studies: direct and indirect. For some of the primary immunodeficiency diseases, specific gene changes, or mutations, can be identified in affected individuals. If the specific change, or mutation, is known in the affected family member who has the disorder, the mutation can then be tested for in the DNA from a fetal sample obtained during a subsequent pregnancy. This direct testing of the DNA for a specific mutation is the most accurate form of DNA testing. If a specific mutation has not been identified, or cannot be identified, a family linkage study may be possible to follow the mutated gene's transmission through the family. Normal DNA variations near the gene in question, called polymorphisms or markers, can be identified in some families. The inheritance of these markers near the gene of concern can be used to determine whether the gene has been passed on to the fetus.

In certain situations, other prenatal testing techniques may provide information about the risk of an affected fetus. For some conditions, biochemical measurement of a particular enzyme or protein in the fetal cells may provide an alternative method of testing for the disorder. Absence or severe deficiency of the enzyme produced by the gene mutation would indicate the presence of the disorder. A detailed sonogram at 16-18 weeks of pregnancy can often identify the sex of the fetus. This

## (Reproductive Options continued)

information can be helpful to families deciding whether to undergo amniocentesis for an X-linked disorder. For some families, testing chorionic villus or amniotic fluid cells will not provide the proper information about the fetus's status, but testing of the fetus's blood will provide the proper information. This procedure can be performed after 18 weeks of pregnancy and involves the insertion of a needle into the fetus's umbilical cord or liver vein to withdraw a small amount of blood for testing.

If an affected fetus is identified through prenatal testing, the couple can then decide whether they wish to continue the pregnancy. Some couples at risk for autosomal recessive disorders elect to use donor sperm through a process called artificial insemination. Alternatively, in both autosomal recessive and X-linked recessive disorders, donor eggs can be used. The risk for an affected child is reduced substantially by using an unrelated donor, as the donor would be unlikely to be a carrier of the same condition. Finally, for certain conditions, testing of the early embryo may be possible after in vitro fertilization (conception outside the womb).

This process, called pre-implantation diagnosis, allows for those embryos unaffected with the genetic condition to be transferred to the woman's uterus. Afterwards the child is carried like any other until birth. Although this type of procedure is not yet readily available for the majority of the primary immunodeficiency diseases, it may be more accessible in the future.

Finally, the option of maintaining the current family size may seem best to some couples. This may be because the possibility of having an affected child is unacceptable or because the demands of the current family are high. Expansion of the family just may not be desired. Careful consideration of these options is important before decisions can be reached. In addition, periodic consultation with the medical staff can be helpful in keeping current with recent medical advances that could potentially provide more information for your family. Once again, it should be emphasized that these decisions are personal. Although important information can be gained from speaking to your pediatrician, immunologist, obstetrician and/or genetic counselor, the parents ultimately decide which option they choose.

# Laboratory Tests



## Chapter 21

*Laboratory studies are necessary to determine the presence of a primary immunodeficiency disease. 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 patient's medical history and physical exam direct the appropriate choice of laboratory tests.*

## Normal vs. Abnormal Laboratory Values

An important aspect in the proper interpretation of any laboratory value is what values are considered normal or abnormal. To determine what is normal, samples are obtained from 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 normal results. Another statistical test often used is to calculate the mean (the average) and the standard deviation of the mean. One standard deviation above and below the mean includes 65% of the values and 2 SDs encompass 95% of the values. Thus, values that deviate more than 2 SDs represent 2.5% that are unusually high or 2.5% that are unusually low. It is important to note that when the definition of the normal range is set as a 95% confidence interval, the 5% of the selected normal population outside the 95% will fall in the abnormal range, 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 little 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.

Another important issue is the group that was used to determine the normal range. This is crucial since the immune system undergoes substantial development during infancy and childhood. The range of test values that are normal in infancy will probably 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 laboratory tests used to evaluate immune disorders are used to identify antibody deficiencies, cellular (T-cell) defects, neutrophil disorders and complement deficiencies. These four major categories of tests for immune deficiencies are described on following pages.

## Laboratory Evaluation for Antibody Deficiency, or Humoral Immunity

The standard screening tests for antibody deficiency starts with measurement of immunoglobulin levels in the blood serum. These consist of IgG, IgA and IgM 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 responds to vaccines. In this approach, the patient is immunized with common vaccines, including those that have protein antigens (such as tetanus toxoid, diphtheria toxoid) and those with carbohydrate antigens (such as Pneumovax, HiB vaccine). Blood samples are obtained immediately prior to and approximately four weeks after the immunization to evaluate how well the patient forms specific antibodies.

In some instances, the patient 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 patient may have little or no specific antibody prior to the immunization. The use of different types of vaccines is necessary because certain patients 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.

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. The interpretation of vaccine responses is best done by a physician who deals with patients with primary immunodeficiency diseases on a regular basis.

The ability to evaluate the antibody response in a patient already receiving immunoglobulin replacement therapy is more difficult. This is because immunoglobulin 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 immunoglobulin

treatment and any that might have been made by the patient. 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 immunoglobulin preparations. Uncommon vaccines, such as typhoid or rabies vaccine, can serve this purpose.

It is important to note that in a patient with a previously confirmed defect in antibody production, stopping therapy to recheck for antibody levels and immunization response is unnecessary and may place the patient at risk of acquiring an infection during the period when the replacement therapy is stopped. However, in a patient whose diagnosis of a humoral immunodeficiency is unclear, it may be necessary to stop replacement therapy for a period of four to six months so that the patient's humoral immunity can be adequately assessed.

Additional studies used to evaluate patients with antibody deficiencies include measuring the different types of lymphocytes in the blood by marking those cells with molecules that can identify the different types. A commonly used test is called flow cytometry that can identify B-cells (and other kinds of lymphocytes) present in the circulation. The B-cell is the lymphocyte that has the ability to produce antibody. B-cells may be absent in certain immune disorders associated with antibody (such as X-linked Agammaglobulinemia [XLA]).

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 immunoglobulin production by cultured lymphocytes in response to a variety of different kinds of stimuli.

## Evaluation of 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 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 access for diminished T-cell numbers, since normally about three-quarters of the circulating lymphocytes are T-cells and a reduction in T-lymphocytes will usually cause a reduction in the total number of lymphocytes, or total lymphocyte count. This 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 phytohemagglutinin [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 chemicals 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 immune deficiencies are associated with specific genetic defects. This is particularly true of Severe Combined Immune Deficiency (SCID) where more than 12 different genetic causes for SCID 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.

## Evaluation of 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 a patient 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. An elevated IgE level may also suggest the diagnosis of Job's Syndrome (Hyper IgE Syndrome) along with other clinical features

that are associated with this syndrome. If these initial screening tests of neutrophil numbers were normal, testing would then focus on two possible primary immune disorders: 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 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 including a simple dye reduction test called the Nitroblue



## (Evaluation of Neutrophil Function continued)

Tetrazolium (NBT) test. A more recently developed 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 15 years, and it is extremely sensitive in making the diagnosis. As a result of its excellent performance, this test has become the standard in most laboratories supporting clinics that see patients with CGD regularly. The best confirmation of the specific type of CGD is suggested by the results of the DHR test, but 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 Evaluation of Complement

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 (the “alternate”) complement 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 mannan-binding pathway and there are some patients with a deficiency in mannan binding lectin.

## Laboratory Tests of 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.

## Looking to the Future

Newborn screening for severe T-cell immunodeficiency is now recommended by the Secretary of the Department of Health and Human Services and has become a reality in more than 10 states, at time of publication, with more to follow. Newborn screening should make the successful cure 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 immune reconstitution using bone marrow (hematopoietic stem cell) transplantation, can be readily undertaken. (See chapter titled “Newborn Screening.”)

Genetic testing (mutation analysis) is likely to undergo significant changes in the near future based on the newer technologies. This enables genetic evaluation of large parts of or the entire genetic code for an individual at relatively low cost. These types of approaches are referred to in discussions of personalized medicine based on an individual's unique genetic code, but when this will become reality at a clinical level remains to be defined.

## Summary of Laboratory Tests

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.

It is the direct link between the clinical findings and laboratory testing that has extended our understanding of primary immunodeficiency diseases. 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 primary immunodeficiencies.

# Infections



## Chapter 22

*Infections are the hallmark of a primary immunodeficiency. For many patients, a primary immunodeficiency diagnosis is suspected and made only after the patient has had recurrent infections or infections that are uncommon or unusually severe. This section discusses common infections.*

## Infections in the Patient with Primary Immunodeficiency

Anyone can get an infection, and everyone does. But an infection in a person with a primary immunodeficiency may require different treatment than a similar infection in a person with a normal immune system. For example, the person with a primary immunodeficiency may require a longer course or higher dose of antibiotics than someone who does not have a primary immunodeficiency.

Your primary care provider should be the first point of contact when you are ill. The provider may then want to confer with your immunologist about the management and treatment of a particular infection. Your immunologist needs to know about the infections that you are having, as this knowledge may affect your treatment. For example, antibody deficient individuals who receive immunoglobulin (Ig) 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 patient, family 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 follows. Many other infections including skin infections, deep abscesses, bone infections, meningitis and encephalitis are not covered in this chapter, but these may occur in patients with primary immunodeficiency.

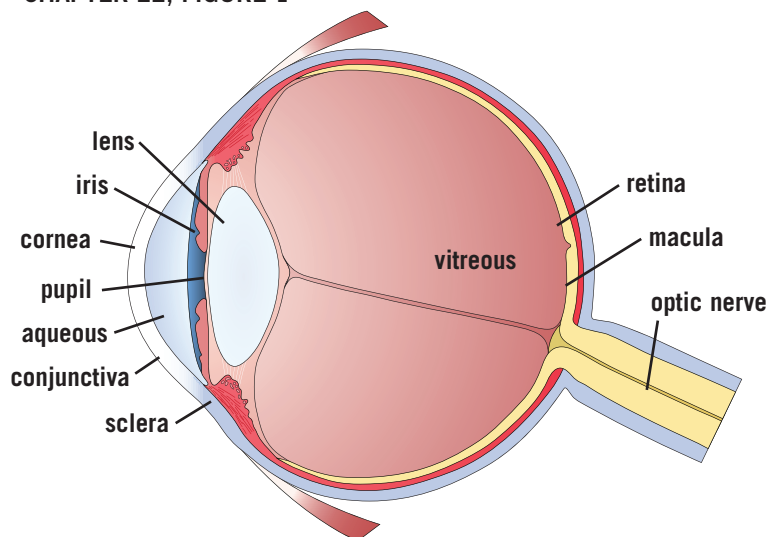
Remember that the suffix “itis” means an inflammation of a particular body part, like tonsillitis or appendicitis. The inflammation is usually caused by an infection, but not always.

### Eye Infections

**Conjunctivitis** – 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 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

## The Eye

CHAPTER 22; FIGURE 1



## (Infections in the Patient with Primary Immunodeficiency continued)

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.

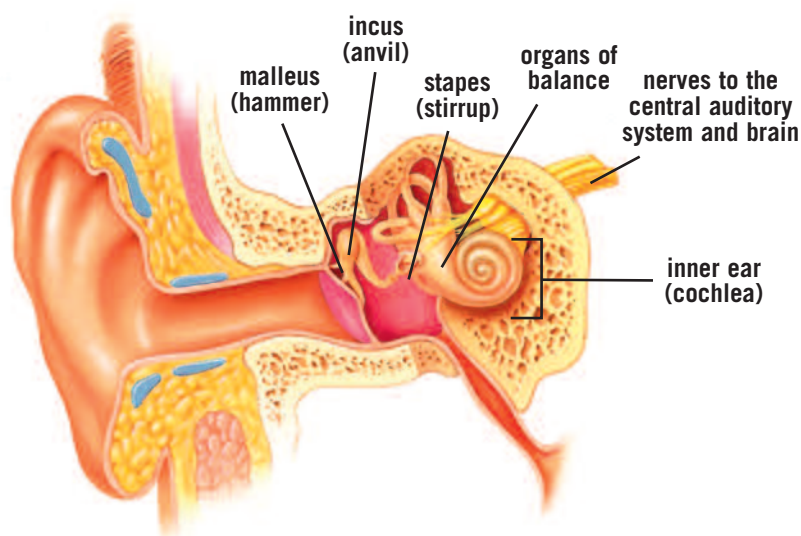
## Ear Infections

**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

## The Ear

### CHAPTER 22; FIGURE 2



(Infections in the Patient with Primary Immunodeficiency continued)

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 cure 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.

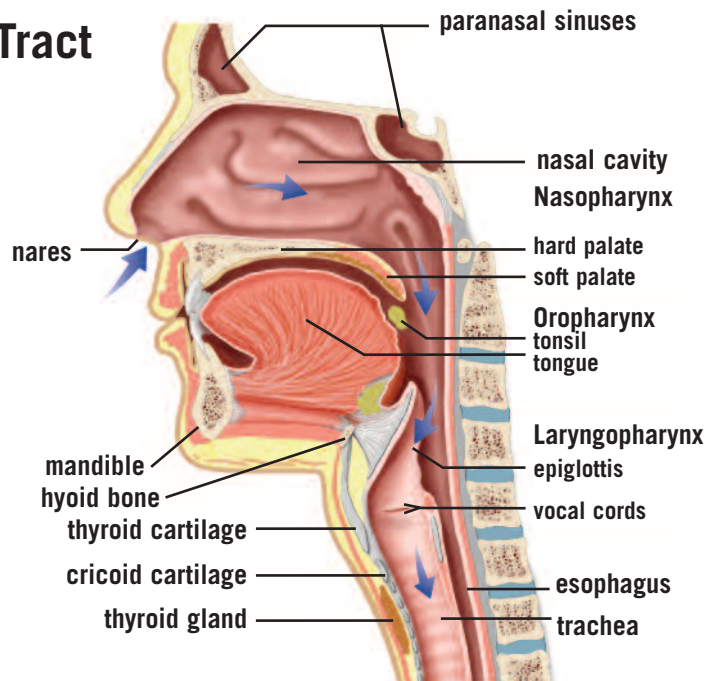
## Upper Respiratory (Sinus and Throat) Infections

**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 nasal discharge is a sign of acute infection, but this may not always be the case.

**Acute Sinusitis** – 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 is characteristic symptoms. In addition, there may

## Upper Respiratory Tract

CHAPTER 22; FIGURE 3



## (Infections in the Patient with Primary Immunodeficiency continued)

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 the patient with a primary immunodeficiency and may require a longer course of antibiotics than would be usually prescribed. Many patients get benefit from the use of daily sinus rinses to keep the sinuses free of accumulating secretions. 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 a rhinovirus. Symptomatic treatment may bring some relief, but there is no antibiotic currently available that will kill or inactivate a rhinovirus. Taking an antibiotic will not cure a cold any quicker. A cold generally lasts about a week. There is some validity to that old joke that a cold with treatment lasts about seven days and without treatment, a week.

But if your “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 you should see your primary care provider.

**Influenza** – Influenza, or “Flu” (a short form of the word “influenza”), is a term that is often used generically to describe the fever, aches, cough, congestion, etc. that

we associate with many common respiratory viruses. However, true influenza is caused only by an influenza virus and 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 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 a primary immunodeficiency and medical attention should always be sought.

**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* (strep throat) can cause other diseases such as rheumatic fever or kidney inflammation if they are not treated. If you have a sore throat, you should seek medical attention as a quick test or culture to determine if it is a Strep infection is usually indicated.

**Tonsillitis** – Tonsillitis is an inflammation of the tonsils. Some people have chronic tonsillar infections, and it may be recommended that the tonsils be removed (sometimes along with the adenoids).

## (Infections in the Patient with Primary Immunodeficiency continued)

**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.

## 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

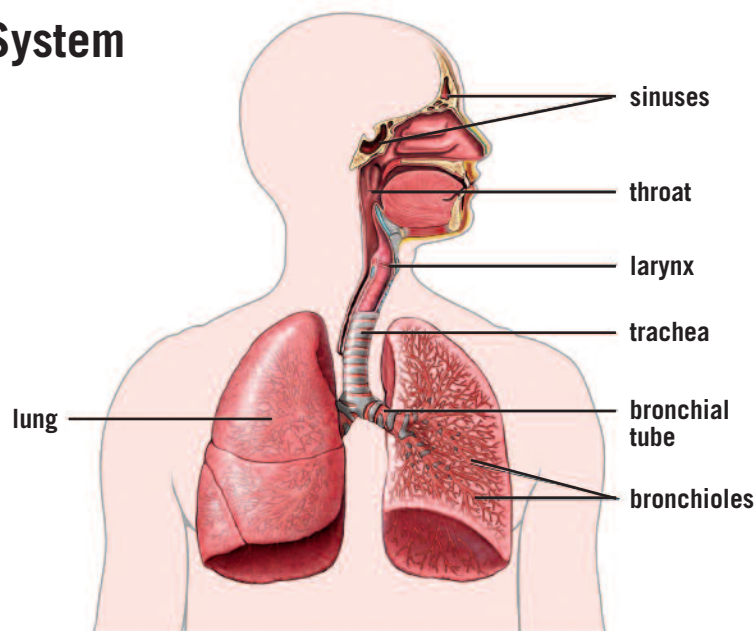
anxiety may increase the severity of the symptoms. It is important for the parents to remain as calm and as reassuring as possible. Urgent medical attention may be needed. Depending on the severity of symptoms, advice may be sought from the primary care on call provider, and sometimes an emergency room 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.

**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 primary immunodeficiency, 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.

## The Respiratory System

CHAPTER 22; FIGURE 4





## 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 cure infections that are caused by bacteria. Expectorants may be prescribed to liquify (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 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 (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. Frequent hand washing is critical to prevent the spread of the infection. 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

## (Gastrointestinal (GI) Infections continued)

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 membranes
- 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, including weak tea, sports drinks, bouillon and “flattened” (without carbonation) soft drinks. 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

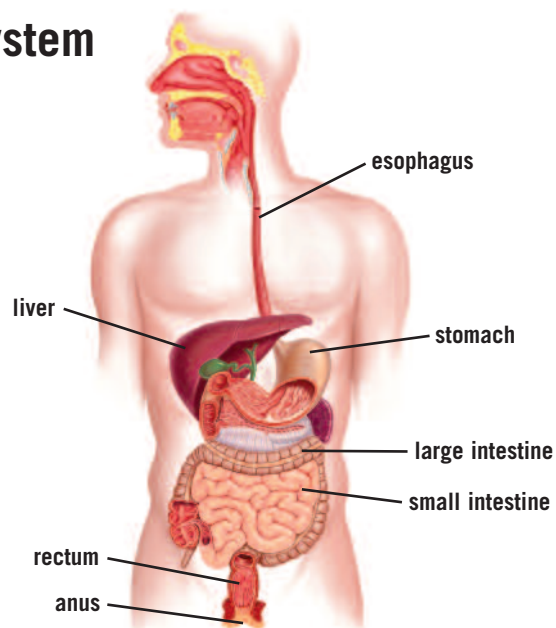
the skin and reduce irritation from frequent diarrheal stools. Soiled diapers and clothing should also be changed immediately. The older child and adult may be encouraged to rinse his or her mouth with water regularly. This helps to relieve mouth dryness and “bad taste” associated with illness and is 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 is essential for everyone.

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 Crohns disease, etc., and additional testing may be required to determine its cause.

## The Gastrointestinal (GI) System

CHAPTER 22; FIGURE 5



## 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, 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 those that affect individuals with defects in T-cells or B-cell/antibody production. For example, children with Chronic Granulomatous Disease (CGD) 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 primary immunodeficiency diseases 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 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 patients with CGD. It 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.

## 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. An infection can only be cured if it is treated with the right drug. 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 immunodeficiencies. 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 disorders 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 primary immunodeficiency.

Sometimes prophylactic (or preventive) antibiotics may be prescribed for patients with some immunodeficiencies. 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 primary immunodeficiencies. 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 your immunologist can determine if prophylactic antibiotics are appropriate for you.

It is always important to try and determine the cause of a particular infection in someone with a primary immunodeficiency. In order to determine what the “right” drug is, it may be necessary to get a culture. For example, if you have 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. 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.

## Summary of Infections

While infections of all kinds (acute, chronic, frequent or recurrent) are always going to be problematic for people with primary immunodeficiencies, 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. However, once symptoms of an infection are present, seeking medical care in a timely manner is critical so that infections can be diagnosed early and treated appropriately, thereby preventing complications.

# General Care



## Chapter 23

*The diagnosis of a primary immunodeficiency disease means different things to different people. For most, it represents both an end and a beginning. It is the end of a quest for answers to the questions: Why am I always sick? Why do I have more infections than anyone else does? Why is my child sicker than his brothers, sisters and friends? Sometimes this quest can take a very long time, involve many care providers and lengthy diagnostic testing.*

*Nevertheless, once the 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 the diagnosis of a primary immunodeficiency disease, but some modifications may be needed. Remember that most people with primary immunodeficiency diseases are able to live full and (relatively) normal lives. Adopting a healthy life style is the key to insuring that this is the case.*

## General Health Measures

### Nutrition

A healthy diet provides nutrients essential for normal growth and development, body repair and maintenance. While good dietary habits are important for everyone, they are especially important for an individual with primary immunodeficiency disease. A lack of adequate nutrition can lead to many illnesses, including infections for which the individual with primary immunodeficiency disease is already at risk. Dietary guidelines for Americans encourage eating a variety of foods, maintaining an ideal body weight, consuming adequate starch and fiber and limiting the intake of fat, cholesterol, sugar, salt and alcohol. (See *Figure 1.*) The primary healthcare provider is an excellent resource for direction and advice regarding a healthy diet.

### Special Diets

Unless the individual with primary immunodeficiency disease has another condition, like diabetes, gluten sensitivity or congestive heart failure, there is usually no need for a special diet. However, in times of acute illness, there may need to be some modification of the regular diet. For example, when the patient has an intestinal infection, like a “GI bug,” a diet of clear liquids while the patient is having nausea, vomiting and/or diarrhea may be recommended. The primary healthcare provider will give recommendations, direction and instructions when these modifications are necessary.

(General Health Measures continued)

### Special Dietary Interventions

In some circumstances, if patients are not able to eat or drink normally, or if they can eat but are unable to absorb nutrients adequately from their stomach and intestines, there are ways to assist them in maintaining adequate nutrition.

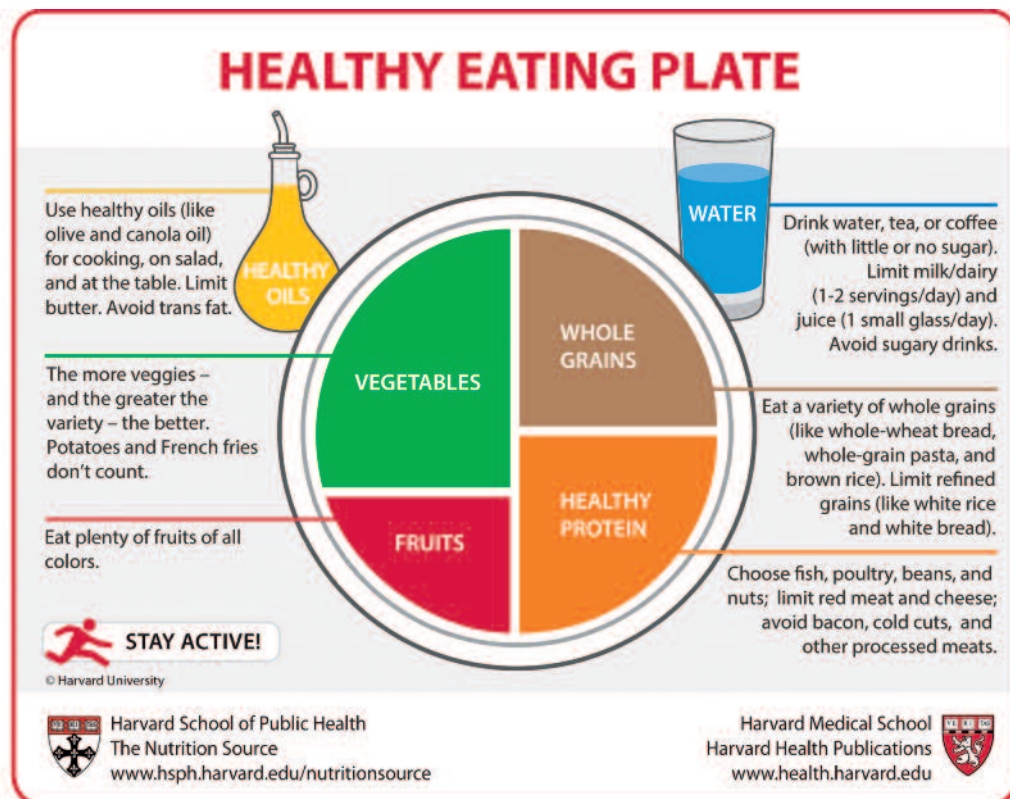
Enteral nutrition, feeding directly into the stomach or intestine with a special tube, may be recommended for patients who are unable to eat enough calories to insure adequate nutrition or drink enough to maintain adequate hydration. This method of feeding may also be suggested for patients who have swallowing difficulties, such as those patients with Ataxia-Telangiectasia. (See chapter titled "Ataxia-Telangiectasia.")

Two common methods of providing enteral nutrition are with the use of a nasogastric (NG) tube or a gastrostomy tube (G-tube). A nasogastric tube involves placement of

a small, flexible plastic tube through the nose, down into the esophagus and then to the stomach. A gastrostomy tube involves the surgical placement of a feeding tube through the skin of the abdomen directly into the stomach. It is also possible to place a tube directly into the duodenum or jejunum, which are the upper two sections of the small intestine, bypassing the stomach. A prescribed amount of liquid feeding is administered through the tube continuously or at regular intervals. Various commercial formulations are available to provide balanced amounts of calories, fats, proteins and carbohydrates, as well as other necessary minerals and vitamins.

Total parenteral nutrition (TPN) and hyperalimentation are the terms for nutrition administered intravenously. Solutions containing all essential nutrients, fluids and calories are delivered directly into the blood stream, bypassing the stomach and intestines. TPN is used to

CHAPTER 23; FIGURE 1



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## (General Health Measures continued)

maintain the nutritional status of an individual who is very ill, malnourished or who is not able to absorb nutrients from their digestive tracts. The TPN solution usually contains protein, carbohydrates, electrolytes, vitamins, water and essential trace minerals. Fats may be supplied in a separate solution. Various types of intravenous catheters are used to administer these solutions. Nutrition via TPN is usually a short-term solution to meet the patient's immediate nutritional needs.

### Nutritional Supplements

There are thousands of nutritional supplements available on the open market. These include vitamins, herbal supplements, botanicals, probiotics and naturopathic products. In some cultures, use of herbal supplements is especially common. Many of these products are aggressively marketed and make claims to improve health by “boosting the immune system.” These products are not considered “drugs” by the United States Food and Drug Administration (FDA) so are not FDA regulated. The claims of improving health or strengthening the immune system are not based on scientific data, and virtually anything can be claimed or put into these products.

There is no scientific evidence that any product will boost the immune system or make it stronger. Extreme caution should be used when considering taking any of these products. Some of these supplements can be harmful or interact adversely with prescription medicines the individual is already taking. The healthcare provider's opinion should always be sought before taking any of these products. Sometimes the provider will recommend vitamins, electrolyte supplementation or probiotics for certain patients but remember that supplements are no substitute for a healthy, balanced diet.

### Hygiene

General principles of good hygiene are essential for patients with primary immunodeficiency diseases and their families. This includes regular bathing or showering and the use of soap. For some patients, the use of special germ-killing soaps may be prescribed. Regular hand washing should become routine—before and after meals, after using the bathroom, after blowing the nose, coughing—any time there is a concern that excess germs have gotten onto one's hands. It is essential to remember that to be truly effective, hands must be washed vigorously with soap and water for at least 15 seconds, which is generally longer than most people think. It usually takes 15 seconds to sing “Happy Birthday” once or the “Alphabet Song” twice.

When hands are not visually dirty, alcohol-based hand sanitizers can be an effective alternative. These have the advantage of being able to neutralize germs, are portable and can be applied rapidly. The regular use of hand gels has been shown to reduce the occurrence of colds and other viral infections. Individually wrapped and disposable hand wipes are another alternative to soap and water and are excellent for school lunches and for outings.

Some individuals with a primary immunodeficiency are prone to tooth decay and to infections that stem from having decayed teeth. Regular visits to the dentist, proper brushing and flossing should be a key part of the regular health regimen.

A common sense approach to infection prevention is generally the best policy to follow. Individuals with a primary immunodeficiency should avoid exposure to people who have signs of an obvious infection, like people who are coughing, have a fever or have vomiting and/or diarrhea. During periods of influenza outbreaks, it might be wise to avoid crowded areas such as shopping centers and movie theatres. Many patients with primary immunodeficiency disease people have questions about flying or other travel. When in doubt, ask the immunologist or primary healthcare provider for advice.



## (General Health Measures continued)

**Day Care**

Families with young children who have a primary immunodeficiency may need to use day care just like everyone else. Unfortunately, children in day care are exposed to many infections that are easily transmitted. While most of these infections are not serious, of course they reduce quality of life and impact parents' education, work and stress. Exposure to infections tends to be greater in large institutional day care settings. Depending on the degree of immune compromise and the effectiveness of therapy, parents may want to consider options with smaller numbers of children or in home day care, if these are available.

**Exercise**

A healthy life style always includes exercise. Physical activity should be encouraged for all people, immunocompetent or immunodeficient. Not only are these activities good for the body, they are good for the mind, as well. Regular exercise 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 are physically fit and participate in regular exercise are known to get sick less than people who do not exercise. Organized sports may be an excellent outlet for children who are struggling with coping with their illness. Playing on a team with immunocompetent children may help the child with an immunodeficiency feel that he or she is not so different and is "just a regular kid" like everyone else.

Some kinds of exercise may be contraindicated for people with specific immunodeficiencies. For example, a boy with Wiskott-Aldrich Syndrome who is known to have a low platelet count should not engage in contact sports. People with Chronic Granulomatous Disease (CGD) should never swim in the ocean or fresh water. The immunologist can recommend appropriate types of exercise for their patients.

**Sleep**

Getting an adequate amount of sleep is an essential requirement for good health. Most scientists recommend a consistent number of hours of sleep per night and consistent bed times and waking times, as well. While "sleeping in" on a Saturday may seem like a special treat, it may not be the best thing to do to insure good health. Erratic sleep patterns have been shown to have negative effects on the immune system. Some helpful sleep guidelines include:

- Go to sleep and wake up at roughly the same time each day.
- Avoid late nights.
- Avoid consumption of caffeine (such as caffeinated coffee, sodas or tea) or alcohol in the evening.
- Avoid eating heavy meals in the evening or snacking right before bedtime.
- Minimize potential disturbances during the night.
- Avoid long naps during the day that could interfere with the regular sleep schedule.
- Plan the schedule around a night that will include an age-appropriate amount of sleep.

Adequate amounts of sleep are essential for children. Children age 3 and younger require naps during the day in addition to their nighttime sleep. (See Table 1.)

**Age Appropriate Nightly Sleep****CHAPTER 23; TABLE 1**

Age	Average Nighttime Sleep Duration (Hours)	Average Daytime Sleep Duration (Hours)
6 mos	11	3 1/2
1 yr	12	2
2 yrs	11 1/2	2
3 yrs	11	2
4 yrs	11	1
6 yrs	11	Ø
8 yrs	10 1/2	Ø
10 yrs	10	Ø
13 yrs	9	Ø
16 yrs and up	8	Ø

(Adapted From *Pediatrics*. 2003. Vol 111, Page 302-307.)

(General Health Measures continued)

## Stress

The notion that people get sick more often when they are under increased stress is supported by scientific data. Chronic illness, itself, is known to be a major life stressor. Some studies suggest that stress negatively affects the functioning of the immune system. There are also scientific studies that suggest reducing stress can improve immune function. Many stress reducers are easy to incorporate into one's daily life. These include massage therapy, biofeedback, meditation and hobbies.

The importance of physical activity and adequate sleep in helping to reduce stress has already been discussed.

If you find that you are unable to deal with the stresses in your life, you should absolutely discuss these concerns with your primary care provider. They can assist you or refer you to someone who can help you to minimize and effectively deal with stress. You should never feel that there is nothing that can be done for the stress that you feel is overwhelming and keeps you from living and enjoying your life.

## Primary Care

Regularly seeing the primary care provider for health maintenance screening is important for everyone, but even more so for the individual with a primary immunodeficiency. Some types of immunodeficiencies are associated with other illnesses. For example, it is known that some patients with Common Variable Immune Deficiency are at a higher risk for developing autoimmune diseases or leukemias and/or lymphomas than those in the general population. Children especially should have annual physicals. Sometimes failure to grow or develop properly may be the first signal that there is a problem in a child.

As discussed in this Handbook, our immune systems consist of two major categories of defense: the innate immune system and the adaptive immune system. The innate system is the first line of defense with its various components ready-to-go immediately when they encounter a microbe threatening our bodies. This is a critically important defense mechanism, but the innate system is not pre-programmed against every potential threat. It is the adaptive immune system that has the capacity to ramp-up a protective response to new threats. It does this by the generation of specific immune T-cells and B-cells, and the production of antibodies that are specifically designed to combat the new threat. The adaptive immune system takes several days before it reaches full power, but once it is fully activated, it remains on duty for a long time. If the body encounters the same threat again sometime in the future, this system has memory and is therefore able to respond much faster.

## Immunization

Perhaps the greatest advances to improve general health over the past two centuries have been the introduction of vaccines that effectively protect individuals from many of the worst microbial threats in our environment. Since primary immunodeficiency diseases interfere with the ability of the body's immune system to respond appropriately, does it make any sense or do any good to give vaccines to patients with primary immunodeficiency diseases? Like so many things in life, it depends.

Vaccines are designed to activate the adaptive immune system to respond to specific microbes that innate immunity alone is not capable of controlling. We are familiar with the usual "childhood vaccines" that have greatly reduced the incidence of serious infectious diseases that in earlier generations sickened or killed

## (Primary Care continued)

millions of people. Polio, measles, whooping cough, mumps, Rubella, HPV, chickenpox, HiB, tetanus, meningococcus, diphtheria, rotavirus and influenza are the vaccines most commonly given today, and most communities require that children be up-to-date on their immunizations before being able to attend public school. So, what about people with primary immunodeficiency diseases?

First, it is important to recognize that many types of primary immunodeficiency diseases are fully capable of making a normal response to vaccines. Those with innate system defects like CGD and other phagocytic cell defects, individuals with complement deficiency, and even some with significant adaptive system deficiencies can produce antibodies to many vaccines and thus benefit from immunization. However, there are many others with primary immunodeficiency diseases that will be unable to develop protective immunity following vaccination, and in some cases the vaccine itself may represent a threat to the recipient.

Since vaccines for chicken pox, measles, mumps, smallpox, rubella, rotavirus, BCG, yellow fever, oral polio and the influenza nasal spray are live attenuated vaccines, individuals with primary immunodeficiency diseases could potentially contract infections if they receive these immunizations. In practice, infants with Severe Combined Immune Deficiency (SCID) are at greatest risk and it is the general recommendation that others with defects in adaptive immunity also avoid receiving any live agent vaccines. (*See chapter titled "Severe Combined Immune Deficiency and Combined Immune Deficiency."*) Since some of these live vaccine viruses (oral polio, rotavirus) can be found in the some body fluids and stools for up to two weeks following vaccination, it may be necessary to limit contact between any recently immunized individual and infants with SCID until the period of viral shedding has passed. For children and adults with primary immunodeficiency diseases who are receiving immunoglobulin (Ig) replacement treatment, the infused antibodies should give them adequate protection from any secondary spread of vaccine virus.

The usefulness of vaccination during treatment with intravenous or subcutaneous Ig therapy is not fully understood, in part due to complexity of the range of underlying immune defects treated with Ig therapy. Assessing patients' antibody responses to vaccine is confounded by antibody in infused Ig. Vaccines can also stimulate T-cell responses, which may have antibody-independent (such as cellular immune) protective effects, but those are harder to measure and even less well understood with respect to their role in protection independent of immune globulins.

Some patients with milder forms of immunodeficiency (such as selective IgA deficiency, mild hypogammaglobulinemia, partial DiGeorge syndrome) can receive live virus vaccines at the discretion of their doctor.

Purified protein, polysaccharide or non-viable whole-agent vaccines pose no infectious risk to patients. However, for most vaccines, the patient's antibody response is likely to be inferior to what is provided by Ig therapy. New vaccine agents may be exceptions to this general rule. For example, antibody to new strains of influenza may not be found yet in therapeutic Ig, and consideration should be given to administering such a vaccine to patients receiving Ig treatment. Although there may be theoretical benefit to inducing T-cell responses in patients on Ig, clinical benefit is unproven, and this practice may not be cost-effective, particularly for expensive vaccines such as HPV.

For families with a member who has a primary immunodeficiency disease, we recommend that all members of the family group, including the patient, should keep their immunizations up-to-date. This is particularly important for readily communicable diseases like influenza with many different strains circulating that change from year to year. Why do we recommend that everyone be immunized to influenza? First, some patients with a primary immunodeficiency may respond and benefit directly from the influenza vaccine. Even if they do not, there is little down side to receiving the killed vaccine. Family members who are able to respond to a vaccine will be protected. Even if the patient with a

### (Primary Care continued)

primary immunodeficiency disease does not respond to the immunization, they will benefit from having everyone else in the home protected from infection and thus not susceptible to bringing the virus home with them. This is particularly important if there are other school-aged

children in the home. We want to create a “protective cocoon” of immunized persons surrounding patients with primary immunodeficiency diseases so that they have less chance of being exposed to a potentially serious infection like influenza.

## General Care during Times of Acute Illness

Even after a diagnosis of primary immunodeficiency disease has been made and appropriate treatment initiated, people with primary immunodeficiency diseases are still going to get sick. Hopefully these illnesses will be reduced in number and intensity, but it is unrealistic to think that because one is being treated for one’s primary immunodeficiency disease that they will not be sick any more. When acutely ill, people with primary immunodeficiency diseases should:

- Seek medical advice. Do not ignore symptoms such as fever or a productive cough and think they will “just go away.”

- Never self treat. Taking leftover antibiotics or those prescribed for another family member is not a good idea.
- Follow the healthcare provider’s advice. If 14 days of antibiotics are prescribed, take 14 days. Do not stop after a week because you feel better. If there is a recommendation to stay home from work or school for several days, then stay home.

Undertreating or trying to ignore an illness may seem okay for the short term, but it can absolutely have long term negative consequences.

## Summary of General Care

The diagnosis of a primary immunodeficiency disease is a life-changing event, but it can be viewed in a positive rather than a negative way. The diagnosis and initiation of 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 recommendations and advice of the healthcare team for treatment of the primary immunodeficiency diseases can maximize the potential for a full and normal life.

# Immunoglobulin Therapy and Other Medical Therapies for Antibody Deficiencies



## Chapter 24

*There are several specific medical therapies available for patients with primary immunodeficiency diseases involving the humoral immune system. These illnesses include X-Linked Agammaglobulinemia (XLA) and Common Variable Immune Deficiency (CVID), among others, and are characterized by a lack of and/or impaired antibody function. Effective therapies for these disorders are a reality for most patients, and optimize their health, improve their quality of life and allow them to become productive members of society. In this chapter, therapy for antibody disorders will be discussed. For all of these therapies, individual risk/benefit ratios should be discussed with your healthcare provider.*

## Immunoglobulin Therapy

The term “immunoglobulin” refers to the fraction of blood plasma that contains immunoglobulins, or antibodies. These immunoglobulins (Ig) in the serum or plasma are IgG, IgM, IgA, IgD and IgE. Individuals who are unable to produce adequate amounts of Ig or antibodies, such as patients with XLA, CVID, Hyper-IgM Syndromes, Wiskott Aldrich Syndrome or other forms of antibody deficiency may benefit from replacement therapy with Ig. Only the IgG is purified from the plasma to produce commercial Ig products, so Ig used for treatment contains very little of any of the other Ig types.

As explained in other chapters of this handbook, B-lymphocytes mature into plasma cells, which manufacture antibodies and release them into the bloodstream. (See chapter titled “The Immune System and Primary Immunodeficiency Disease.”) There are literally millions of different antibodies in every normal person, but because there are so many different germs, no one person has made antibodies to every germ. The best way to ensure that the Ig will contain a wide variety of antibodies is to combine or “pool” the plasma from many individuals.

Ig was first used to prevent infectious diseases in World War II and first given for primary immunodeficiency diseases in 1952. Until the early 1980’s, the only form that was available was usually given by deep injection into muscle (intramuscular or IM), although it was also given by subcutaneous infusion rarely in the U.S. but more commonly in other parts of the world (for example, Scandinavia). Ig products for intramuscular injection continue to be used to give normal individuals a boost of antibodies after exposure to some specific diseases such as measles or hepatitis, or before they travel to areas where those diseases are prevalent. In these instances, the amount of Ig needed to prevent diseases is small, generally 5-10 cc (1-2 teaspoons).

### What is Ig Replacement Therapy?

Ig is prepared from the plasma collected from a large number of normal individuals, usually between 10,000-50,000, who have been carefully screened to make sure they are healthy and do not harbor certain infectious diseases. The plasma contains a broad range of specific antibodies to many different types of bacteria and viruses. Each plasma donor must be acceptable as a

## (Immunoglobulin Therapy continued)

blood donor according to the strict rules enforced by the American Association of Blood Banks and the U.S. Food and Drug Administration (FDA). Donors are screened for travel or behavior that might increase the risk of acquiring an infectious disease. Only the IgG is purified from the pooled plasma. To commercially prepare the Ig for patients with primary immunodeficiency diseases, the immunoglobulin must first be purified (extracted) from the plasma. All Ig licensed in the U.S. is made from plasma collected in the U.S.

The blood, or plasma, from each donor is carefully tested for evidence of transmissible diseases, such as AIDS or hepatitis, and any plasma sample that is even suspected of having one of those viruses is discarded. The first step in Ig production is to remove all the red and white blood cells. This is frequently done right as it comes out of the donor's arm by a process called plasmapheresis, which collects the plasma and then returns the red and white cells directly back to the donor. Plasmapheresis is done at centers specifically designated for this purpose. Then, the immunoglobulins are chemically purified from the plasma in a series of steps. This process results in the purification of antibodies of the IgG class; only trace amounts of IgA and IgM, and other plasma proteins remain in the final product.

In the early 1980's, new manufacturing processes were developed to make Ig preparations that could be safely injected intravenously, that is directly into the vein. Now multiple Ig preparations are licensed in the U.S. for intravenous use. Products developed for intravenous use have also been used successfully subcutaneously, which is administered under the skin, and in recent years products for subcutaneous use have been licensed. For the most part, the products are equivalent in antibody activity. However, there are some differences which may make one particular preparation more suitable than another for a given individual. Most products contain some type of sugar or amino acid that help preserve the IgG molecules and prevent them from sticking together to form aggregates. If aggregates were

present, they could cause severe side effects. Although these sugar and protein additives are harmless for most people, some of them may cause problems for specific individuals. Your prescriber is your best source of information about which product is best for you.

Purified Ig has been used for more than 50 years and has an excellent safety record. During the purification process and with the final product, there are several steps that destroy or remove many types of viruses, including HIV, to ensure that the final Ig product cannot transmit any known infectious diseases to the patient. Thus, the final Ig product contains highly purified plasma IgG that has a broad range of specific antibodies to many types of bacteria and viruses. It is also effective in helping the white cells in the body kill bacteria, viruses and other germs that may be in the tissues or blood of the patient being treated, and is safe to administer.

## Administration of Ig Replacement Therapy

It is important to understand that the Ig that is given partly replaces what the body should be making, but it does not stimulate the patient's own immune system to make more Ig. Since Ig only replaces the missing end product, but does not correct the patient's defect in antibody production, Ig replacement is usually necessary for the patient's lifetime. In addition, the Ig only provides temporary protection. Most antibodies, whether produced by the patient's 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 is generally administered either intravenously (abbreviated IVIG), or subcutaneously (abbreviated SCIG). IVIG infusions are usually given every three or four weeks. SCIG infusions may be given as often as daily, weekly, or as infrequently as every

## (Immunoglobulin Therapy continued)

three to four weeks (similar to IVIG), depending on the specific SCIG product that is being prescribed, the patient's age and the preferences of the patient and the prescriber.

Since IVIG infusions are usually given once every three or four weeks directly into a vein, there is a very high “peak” IgG level in the blood right after the dose is given and a lower IgG level in the blood at the “trough” just before the next dose is due.

SCIG is injected relatively slowly, directly under the skin. Because small amounts of Ig are given (often) more frequently and because the Ig is absorbed more slowly, the peak and trough associated with IVIG are very blunted or eliminated when giving SCIG. Patients who have side effects from high peaks of IgG or feel “washed out” or weak before their next IVIG dose is due may prefer SCIG.

SCIG therapy may be an alternative for those patients who have difficulty getting venous access and/or who have systemic adverse reactions to IVIG. Collaborating with their healthcare provider, patients have the flexibility to develop a dosing regime that is tailored to their lifestyle. The number of infusions per week or month, when the infusions are done, the number of needles used, using an infusion pump or manually pushing the drug, and the rate of infusion are all variables that can be considered to design an individual patient's SCIG regimen. Patients must be committed to this therapy and should not “skip” doses or change their regimen without consulting their provider.

### Side Effects from Ig Replacement Therapy

Most patients tolerate Ig very well. Infusions can be administered either in an outpatient clinic or, after tolerability and safety is demonstrated in a controlled setting, in the patient's own home. A typical IVIG infusion will take two to four hours from start to finish. Some patients may tolerate more rapid infusion while others may require longer times. Use of intravenous products allows physicians to give larger doses of Ig at one time

than could be given subcutaneously. In fact, doses can be given that are large enough to keep the IgG levels in the patient's serum in the protective range, even just before the next infusion when the level would be lowest.

There is a potential for some side effects associated with IVIG. These can include low-grade fever, aching muscles or joints or post-infusion headaches occur. These symptoms can usually be alleviated or eliminated by infusing the immunoglobulin at a slower rate and/or by giving acetaminophen, non-steroidal anti-inflammatory drugs like ibuprofen, or even small amounts of short-acting systemic steroids. Sometimes saline infusions may be given before IVIG, and/or infusions may be run more slowly to help minimize side effects. Less often, patients experience hives, chest tightness or wheezing. These symptoms usually respond to antihistamines such as diphenhydramine (Benadryl™) and/or asthma medications like albuterol.

Headaches associated with Ig are not uncommon and may occasionally be severe, especially in patients with a history of migraine headaches. These headaches may occur during the infusion or as long as three days later. Some patients with severe and persistent headaches have been found to have an increase in the number of white blood cells in the cerebral-spinal fluid. This condition is known as aseptic meningitis. The cause of this apparent inflammation is not known, but it is not an infection and patients have not had permanent injury. It is important to note that every patient who develops a post-infusion headache does not necessarily have aseptic meningitis. You should notify your prescriber if you experience headaches that do not respond to standard medications such as acetaminophen or non-steroidal anti-inflammatory drugs like ibuprofen.

It may take several infusions to develop a tolerable specific IVIG regimen for each patient. Variables include the product used, the rate of infusion, and the need for any pre-medications. Once a regimen that is well tolerated has been found, it should be followed with EVERY infusion. While all Ig products provide necessary antibody replacement, each has subtle differences and



## (Immunoglobulin Therapy continued)

thus are NOT interchangeable. Switching from one brand to another is one of most common causes for side effects. Patients need to know what their product is, the dose, and their specific infusion protocol. IDF ePHR is a good place to keep this information ([www.idfephr.org](http://www.idfephr.org)).

Patients who experience significant side effects from IVIG infusions may benefit from changing to SCIG. Because the doses given at any one time are usually (not always) smaller, and because the Ig is slowly absorbed, there are fewer systemic side effects associated with SCIG. Side effects associated with SCIG tend to be localized skin reactions that tend to decrease over time. Changes to the individual infusion regimen, including the number of sites used, the length of the subcutaneous needle(s) used, the amount of drug given into each site and the rate of infusion are all things that can be modified to decrease the incidence of localized reactions to SCIG.

### Qualifying for Ig Replacement Therapy and Appropriate Dosage

Before starting Ig replacement therapy, it is important that your provider completes all the immune studies to demonstrate that your immunoglobulins are not only low but that you do not make specific antibodies normally following natural infections or immunization with vaccines. An exception to this rule is those patients that have extremely low serum immunoglobulins, like a serum IgG of 200 mg/dl or less. Immunologists generally use tetanus toxoid and pneumococcal vaccines (Pneumovax) to test the ability of the patient 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 you follow through with this second blood draw to determine your response to vaccines within this four to six week timeframe. Insurance companies often review this information before approving Ig therapy.

The dose of Ig varies from patient to patient. In part, the dose is determined by the patient's condition and weight.

The dose by the intravenous route generally starts at 400-600 mg/kg per month, and 100-175 mg/kg/week by the SC route. However, some patients require higher doses, especially those with chronic lung disease. Recent studies have shown that an optimal trough level (if given by the intravenous route) or steady state IgG plasma level (if given by the subcutaneous route) is approximately 850 mg/dL to insure adequate prophylaxis (infection protection). Your prescriber will measure your Ig levels and monitor your clinical status (such as how you are feeling, if you are having infections) to insure that you are receiving an adequate dose of replacement therapy.

### Choice of Route

The choice of route of administration of Ig therapy (IVIG or SCIG) should be a decision based on discussions between the patient and provider. This decision is usually based on a number of factors including the clinical characteristics of each patient, the patient's preferences for therapy, appropriate site of care (home, hospital, infusion center), and sometimes, even insurance coverage.

Some patients with chronic sinusitis and chronic lung diseases, such as bronchitis, do better when given higher doses of Ig. Some patients, who lose IgG molecules from their digestive tracts or kidneys, may require more frequent doses and/or higher doses.

Remember that although our current Ig products are very good, they do not duplicate exactly what nature normally provides. The manufactured Ig is almost pure IgG, so no IgA or IgM is transferred to the patient. The specific protective functions of these immunoglobulins are therefore not replaced. The IgA on the mucosal surfaces of the respiratory tract is not being replaced, which may be part of the reason that antibody deficient patients remain somewhat more susceptible to respiratory infections, even though they are receiving enough immunoglobulin to maintain normal or near-normal blood levels of IgG.

## Prophylactic Antibiotic Therapy

Some providers may prescribe prophylactic antibiotics for patients with a history of sinus or pulmonary disease in order to cover against bacterial infections of the sinuses and lungs. Prophylactic doses of antibiotics are low dose antibiotics generally given at about half the daily full dose. Common prophylactic antibiotics are amoxicillin, Bactrim/Septa (trimethoprim/sulfamethoxazole) or azithromycin.

Generally, antibiotics used for treatment of active infection are not used as prophylaxis. Some providers rotate prophylactic antibiotics with the goal of reducing the development of bacterial resistance, although there is no true evidence that this approach is necessary. Some prefer to treat with a single drug. Depending on the specific circumstances of the individual case and

the type of antibiotic and the microbe needing prophylaxis, the prophylactic antibiotic may be stopped temporarily during the treatment of an active infection with a different antibiotic and resumed after the resolution of the infection and completion of the new treatment. There is no true evidence that this approach is necessary. Some prefer to treat with a single drug. There is some controversy regarding the use of prophylactic antibiotics, as some providers believe that the potential for developing drug resistant pathogens is a risk that outweighs the benefit. The decision needs to be discussed with a specialist. In patients with sinus infections the provider may also recommend a topical nasal steroid and/or saline nasal washes.

## Summary of Immunoglobulin Therapy and Other Medical Therapies for Antibody Deficiencies

The goal of Ig therapy for antibody disorders is to provide protection from infection. Patient compliance with 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:

- Not all infections can be prevented. After starting Ig therapy, you may still get infections. However, it is hoped that 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 regimen must be developed for each patient and modified as necessary to achieve treatment goals and the needs of each person.
- Once a diagnosis has been made, therapy will probably be needed life long. In some instances, reevaluation of the diagnosis may be undertaken. This will be done by taking the patient off of therapy and reevaluating humoral immunity.

# Stem Cell Therapy and Gene Therapy



## Chapter 25

*Hematopoietic stem cell transplantation (HSCT) represents the mainstay of treatment for several severe forms of primary immunodeficiency diseases. Progress in cell manipulation, donor selection, the use of chemotherapeutic agents, and prevention and management of transplant-related complications has resulted in significant improvement in survival and quality of life after HSCT. In some forms of severe primary immunodeficiency diseases, gene therapy may represent a valid alternative for patients who lack acceptable stem cell donors.*

## Hematopoietic Stem Cell Transplantation

A “stem cell” is a type of cell that can divide over and over and produce more stem cells as well as descendant cells that turn into different types of cells. Embryonic stem cells, for instance, can make descendants that turn into any tissue in the body, like skin cells, brain cells, heart cells etc. For each organ in the mature body, there are specific stem cells that can make all the different kinds of cells in that organ. For example, in the blood system, hematopoietic (“blood-forming”) stem cells (HSC) give rise to each of the different types of blood cells such as red blood cells (RBC), white blood cells (WBC) and platelets.

Traditionally, HSCs were obtained from the bone marrow. This process was called “bone marrow transplantation.” However, new methods now obtain HSC from peripheral blood, or blood taken from the placenta at birth (“cord blood”). Cord blood, in particular, provides an excellent alternative source of HSC for the immune and blood systems. The process of taking HSCs from one person and transfusing them into another is called hematopoietic stem cell transplantation, or HSCT. Unlike transplantation of a solid organ (such as a kidney or liver), HSCT does not involve surgery. It is more similar to a blood transfusion. But instead of just blood, the fluid transfused contains HSCs.

The primary immunodeficiency diseases for which HSCT is most commonly performed include Severe Combined Immune Deficiency (SCID), Wiskott-Aldrich Syndrome (WAS), IPEX Syndrome, Hemophagocytic Lymphohistiocytosis (HLH) and X-linked Lymphoproliferative Disease (XLP). It can also be used in the treatment of Chronic Granulomatous Disease (CGD) and many other severe primary immunodeficiency diseases. The transplantation of HSCs from a “normal” individual to an individual with a primary immunodeficiency disease has the potential to replace the deficient immune system of the patient with a normal immune system and, thereby, affect a cure.

There are two potential obstacles that must be overcome for HSCT to be successful. The first obstacle is that the patient (known as the recipient or host) may have enough immune function remaining after the transplant to recognize the transplanted stem cells as something foreign. The immune system is programmed to react against things perceived as foreign and tries to reject them. This is called graft rejection. In order to prevent rejection, most patients require chemotherapy and/or radiation therapy to weaken their own residual immune system enough to prevent it from rejecting the transplanted HSCs. This is called “conditioning” before transplantation. Many patients with SCID have so little

## (Hematopoietic Stem Cell Transplantation continued)

immune function that they are incapable of rejecting a graft and do not require conditioning before HSCT.

A similar situation occurs when the recipient's bone marrow is full of its own, defective stem cells and the HSC cannot find anyplace to establish themselves. This is called "failure of engraftment." To prevent this, chemotherapy may be given to reduce the number of defective HSC in the recipient's bone marrow in order to "make room" for the new HSC to engraft.

Although the chemotherapy treatment prevents the host from rejecting the transplanted HSCs, it may cause serious side effects. These include transient loss of all of the cells of the bone marrow so the patient is very susceptible infections, anemia (low RBC) and bleeding problems due to low platelets. Chemotherapy also may cause severe blistering of the mouth or other mucous

membranes that makes getting adequate hydration and nutrition very difficult. It is because of these serious complications that HSCT is reserved for those patients with the most severe immune defects.

The second obstacle that must be overcome for the transplant to be successful is Graft versus Host Disease (GVHD). This occurs when the mature T-cells from the donor or which develop after the transplant, perceive the host's tissues as foreign and attack these tissues. To prevent GVHD, medications to suppress inflammation and T-cell activation are used. These medications may include steroids, cyclosporine and other drugs.

In order to prevent some of these potential obstacles, it is important to try to identify a "matched" donor. A matched donor is one whose Human Leukocyte Antigens (HLA) are the same as those of the recipient.

## Selecting a Donor

HLA are tissue types. Each of us has our own collection of HLA antigens on our cells including the cells of our immune system and bone marrow, as well as on cells in most other tissues and organs. The exact structure of these HLA antigens is determined by a series of genes clustered on the sixth (6th) human chromosome. Compatibility of HLA is very important to determine the chance of successful engraftment while keeping the risk of GVHD low.

There are many different variants for each of these HLA genes in humans. The combination of HLA alleles of each individual is relatively unique. However, since the HLA genes are closely clustered on chromosome 6, they are usually inherited as a single unit. Therefore, the chance that an individual's brother or sister shares the same HLA alleles is relatively high.

There is a 1 in 4 chance that any sibling could be a perfect match for the patient. Unfortunately, due to the laws of probability and the fact that most families have a limited number of children, fewer than 25% of patients have a sibling who is a "match." Therefore, there has been a major effort to develop alternative methods to offer the possibility of a transplant to patients who do not have a matched donor in their own family.

One alternative is to try to find a suitable matched donor through one of the worldwide computer-based registries of individuals who have volunteered to serve as bone marrow donors. The National Marrow Donor Program in the U.S. has listings of hundreds of thousands of individuals who have provided a blood sample to have their HLA type measured. Similar registries are present in many countries around the world.

## (Selecting a Donor continued)

Information on the combination of HLA alleles of more than 19 million volunteer donors is collected in Bone Marrow Donors Worldwide (BMDW). This database can be easily accessed by authorized healthcare professionals to explore the possibility that there is a matched unrelated donor (MUD) available for a patient who needs HSCT and does not have an HLA-matched donor in the family.

Successful transplants for patients with a primary immunodeficiency disease using donors found through this worldwide registry have saved the lives of many patients over the past 20 years. Results of transplantation using fully matched unrelated donors for some diseases now approaches the success rate for transplants using sibling matches.

Another source of HSC used for transplantation in patients with primary immunodeficiency diseases is umbilical cord blood. In the growing fetus, HSC frequently leave the marrow and are found circulating in high numbers in the blood. At the time of birth, the placenta can be recovered, the blood that is remaining removed and the HSC isolated and banked. These cord blood HSC may then be HLA typed and used for transplantation. Since cord blood contains fewer mature T-lymphocytes than the marrow or blood of adult donors, sometimes cord blood transplants have been successful even though the degree of match between donor and patient was not very good. One limitation of cord blood HSC transplantation is that because of the limited volume of umbilical cord blood, there may not be a sufficient numbers of HSC to treat a larger child or adult.

If a perfect match cannot be identified, it is sometimes possible to use one of the parents as a donor. Either parent has half of the same alleles as the patient; the parent is said to be “haploidentical” to the patient. There are some problems that can occur with this type of transplant. The mature T-lymphocytes contained in

the bone marrow of the haploidentical parent would be able to recognize the HLA alleles that are unique to the patient, and would thus cause GVHD.

In order to prevent this complication, it is essential to remove the mature T-lymphocytes (called T-cell depletion) from the bone marrow before infusing the stem cells into the patient. This is done with a preparative regimen before the transplant. After the mature T-cells are removed from the HSC, the risk of GVHD is markedly reduced.

T-lymphocytes of donor origin that develop from the transplanted HSC and reconstitute the patient’s T-lymphocyte immunity will remain haploidentical to the rest of the cells of the patient. However, the risk of GVHD from these T-lymphocytes is low because these cells develop inside the new host from immature precursor cells in the grafted marrow. Like a person’s own T-cells, they are “educated” during their maturation to ignore or “tolerate” the cells and tissues of the host.

It may take as long as six to eight months for the stem cells to reconstitute T-lymphocytes and for these newly generated T-cells to mature and learn to work with other cells in the host. Therefore, restoration of immune function after T-cell depleted HSCT takes longer than after fully matched HSCT (where mature T-lymphocytes contained in the graft may immediately provide some immune function).

Sometimes, complete immunologic reconstitution may not occur after HSCT. In some cases after haploidentical T-cell depleted HSCT, more than one transplant has to be performed to achieve T-cell reconstitution. Full immune reconstitution (including antibody production) is achieved less often than after fully matched transplantation.

Some centers use T-cell depleted HSCT for treatment of babies with SCID who do not have a matched family donor, while other centers believe that the search for a

## (Selecting a Donor continued)

matched unrelated donor is the best first choice option.

The best choice depends on many factors including:

- The type of SCID or primary immunodeficiency disease
- How much immune function remains
- The degree of matching of potential donors
- The types of HSCT available (cord blood vs. bone marrow)
- The age of the patient
- How sick they are and what types of complications they have had

## Procedures

HSC are “harvested” from the donor by removing bone marrow from the pelvic bones. Bone marrow is removed by drawing the marrow up through a needle that is about 1/8 of an inch in diameter. Only two teaspoons are taken from each puncture site because, if more is taken, the sample is diluted with the blood that flows through the bone marrow space. Bringing blood with the bone marrow increases the risk of the sample carrying the mature T-cells that have the potential to cause GVHD.

Usually, two teaspoons are taken for each two pounds of the recipient’s body weight. The average donor might have only a few punctures performed to get enough stem cells for a baby, but more than 100 punctures may be required to get enough stem cells for a teen or full sized adult. The procedure may be performed under general anesthesia or under spinal anesthesia. The discomfort after the procedure varies from donor to donor.

Almost all donors will require some type of pain control medication for two to three days after the procedure, but most donors are not required to stay in the hospital overnight and are able to return to full activity shortly afterwards. The donor’s immune system is not compromised because HSC and marrow quickly regenerate.

Once it has been harvested, the bone marrow is passed through a fine sieve to remove any small particles of bone and processed further, if necessary, to remove incompatible red blood cells, or to remove T-cells. It is then placed into a sterile plastic bag and infused into the host intravenously just like a blood transfusion.

As an alternative to bone marrow harvesting, HSC can be obtained from peripheral blood and then purified via a process known as apheresis. The donor’s blood is collected from an arm vein, using a needle that is connected with a machine that removes the white blood cells. After white blood cells are removed from the blood, the remaining red blood cells are then returned to the donor via a vein in the opposite arm. The HSC are then purified from the other white blood cells. Typically, in order to enrich the amount of HSC in peripheral blood, the donor receives subcutaneous injections of granulocyte-colony stimulating factor (G-CSF) or of plerixafor in the days that precede the blood collection. Both G-CSF and plerixafor mobilize the HSC from the bone marrow, transferring them into peripheral blood, so that a large number of HSC are present in the peripheral blood before the apheresis procedure.

## Results of HSCT

HSCT between HLA matched siblings has been successfully employed in the treatment of primary immunodeficiency diseases since 1968. The first child to receive a transplant (a patient with X-SCID) is still alive, healthy and has a family of his own. This case suggests that, as best as can be determined, the graft is very long lasting and appears to be permanent.

In the case of infants with SCID, HSCT involving a matched marrow has minimal graft versus host disease risk and is associated with an overall success rate of as high as 90%. Results of HSCT from unrelated donors from a haploidentical parent are not as good, yet approximately 60-80% of the infants survive and demonstrate robust T-cell reconstitution.

The chance of survival depends on the health of the patient at the time of the transplant. If the patient is in relatively good health, free from infection at the time of the transplantation and does not have lung damage from previous infections, the outlook is very good. Because of this, survival is very good (>90%) in infants with SCID who receive HSCT within 3-4 months of age, even when the donor is not a family match. This emphasizes the importance of early recognition of SCID, and the benefit of newborn screening for this disease, that is BEFORE the patient has a serious infection.

While reconstitution of the number and function of T-lymphocytes is the rule after HSCT for SCID, normalization of antibody production occurs in some, but not all, patients. Reconstitution of antibody production after HSCT for SCID depends on the specific form of SCID, on the type of donor (matched vs. haploidentical) and on the use of chemotherapy as part of the preparative regimen before the HSCT. If antibody production is not reconstituted after HSCT, patients will require Ig replacement therapy indefinitely to help protect them from infection. Even if replacement therapy is required, these patients usually enjoy a good quality of life after transplant.

HSCT is also an effective form of treatment for other forms of primary immunodeficiency diseases, including WAS, IPEX, HLH), XLP, X-linked hyper-IgM (also known as CD40 ligand deficiency), CGD and other primary immunodeficiency diseases.

In most of these conditions, conditioning with chemotherapy is required before the transplant to allow engraftment of donor-derived stem cells, even when the donor is a matched sibling. The success rate after HSCT from an unrelated donor in these cases is nearly as good (70-80% survival) as using a matched sibling for the donor. Here again, the initial health of the patient is extremely important and the best survival rates are in children who are transplanted under the age of 5, who are relatively free of infections and who do not have pre-existing lung or liver damage.

Mixed chimerism (that is persistence of the patient's immune cells along with donor-derived white blood cells) after HSCT is sufficient to cure the disease in many of these disorders (IPEX, HLH, XLP, X-linked hyper-IgM, CGD), and this may allow doctors to use less intense chemotherapy, thus also reducing the risk of related toxicity. In boys with WAS, mixed chimerism is associated with a higher risk of complications (autoimmunity, persistence of low platelets) and more intense chemotherapy regimens are typically used for this disease.

HSCT is not always indicated in patients with CD40 ligand deficiency and CGD, as many of these patients do well on medical management. The risks and benefits of the procedure must always be carefully weighed.

It must be noted that HSCT from a haploidentical parent is not as successful in primary immunodeficiency diseases other than SCID and is typically reserved to very severe cases that cannot be safely managed otherwise. Again the risks and benefits must be carefully addressed.



## Gene Therapy

Most primary immunodeficiency diseases are caused by errors (mutations) in specific genes. It has long been the hope that one day it would be possible to cure these diseases by fixing the mutation that causes the disease and thus affect a cure. As a result of the human genome project and similar efforts to map all of the genes present in human beings, we now know the identities of the specific genes involved in many diseases, including the vast majority of primary immunodeficiency diseases. More genes are being identified nearly every week. We have finally reached the stage where that long held hope is becoming a reality.

Not every genetic disorder, including some primary immunodeficiency diseases, will eventually be correctable by gene therapy. However primary immunodeficiency diseases, as a general rule, may be better suited for this therapy than almost any other class of genetic disease. Transplantation of HSC taken from a normal donor has been successful in curing many of these disorders, so it should theoretically also be possible to take the patient's own HSC and correct the genetic defect in those cells by adding a normal copy of the gene that is causing the disease.

To introduce the gene, we take advantage of the ability of some viruses (retroviruses) to penetrate into cells and to insert their genome into the patient's own DNA. For the purpose of gene therapy, viruses have been modified so that their own genes have been largely removed and replaced with the normal copy of the defective human gene that is causing the primary immunodeficiency diseases.

To perform gene therapy, the patient's HSCs are first isolated from the bone marrow or from peripheral blood, and they are then cultured in the laboratory with the virus containing the gene of interest. Various growth factors are added to the culture to make HSC proliferate and to facilitate infection with the virus. After two to four days, the cultured cells are washed to remove any free

virus, and then they are transfused into the patient. The cells that have incorporated the gene of interest into their chromosomes will pass it to all cells that will be generated when these cells divide. Because the gene has been inserted into HSC, the normal copy of the gene will be passed to all blood cell types, but not to other cells of the body. Because primary immunodeficiency diseases are caused by gene defects that affect blood cells, this can be sufficient to cure the disease.

Gene therapy represents a life-saving alternative for those patients with severe forms of primary immunodeficiency diseases, who do not have a matched sibling donor. In these cases, performing an HSCT from a haploidentical parent or even from a MUD would carry some significant risks of GVHD. In contrast, GVHD is not a problem after gene therapy, because in this case the normal copy of the gene is inserted into the patient's own HSC, negating the need for a HSC donor.

Until now, gene therapy has been used to treat patients with SCID secondary to adenosine deaminase (ADA) deficiency, X-linked SCID, CGD and 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 deficiency. 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 cure children with ADA-SCID by targeting HSC for gene correction. The results have been spectacular with most of the more than two dozen ADA-SCID patients attaining a significant long lasting increase of the T- and B-lymphocyte count

(Gene Therapy continued)

and a remarkable improvement of immune function. Importantly, no episodes of serious adverse reactions or cases of leukemia have occurred in the patients with ADA deficiency treated by gene therapy.

The next primary immunodeficiency disease to be treated by gene therapy was X-linked SCID. This trial 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 have been 20 X-SCID babies around the world that have been treated with gene therapy. In these infants, gene therapy was performed without any need for chemotherapy prior to the transfusion of HSC that had been cultured with the virus. Eighteen of these patients are currently alive, and in 17 of these 18 children gene therapy alone was sufficient to restore development of T-lymphocytes and immune function and no other treatment was needed.

Unfortunately, while the SCID was cured, five of these patients developed leukemia. Four of the children's leukemia was cured, but one child died.

Gene therapy trials are ongoing with patients with other primary immunodeficiency diseases. Overall, the experience with gene therapy in primary immunodeficiency diseases has demonstrated that it is possible to cure the disease by inserting a normal copy of the gene into the patient's HSC. However, there are some risks that need to be overcome and safer vectors need to be developed. Various laboratories around the world are working at modifications of the viral vectors in order to improve their safety. Nevertheless, gene therapy must still be regarded as an experimental therapy. It is likely that the inherent problems will be worked out in the coming years and that a larger number of primary immunodeficiency diseases will be cured by gene therapy.

# Newborn Screening



## Chapter 26

*Severe Combined Immune Deficiency (SCID) leads to life-threatening infections unless the immune system can be restored through a bone marrow transplant, enzyme replacement or gene therapy. Infants with SCID who lack a family history have been diagnosed in the past only after developing serious infections. Early identification of SCID through screening of all newborns can make possible life-saving intervention before infections occur. Currently, several states have adopted the T-cell receptor excision circle (TREC) assay as part of their routine newborn screening programs. TREC screening has identified infants with most forms of SCID and also some infants with very low T-lymphocytes due to other conditions.*

## Why Screen for SCID?

The absence of T-cell and antibody immunity causes severe infections, diarrhea and failure to thrive. These are the problems that bring infants with SCID to medical attention. The infections experienced by the child with SCID are often caused by weakly pathogenic, opportunistic organisms, organisms that which would not make a child with an intact immune system ill. Prior to 1968, when the first successful bone marrow transplant was performed, SCID was always fatal. Now it can be treated by transplantation of bone marrow stem cells from a healthy donor, or by enzyme replacement or even gene therapy.

Knowing how SCID is inherited has permitted some families, often following tragic loss of an affected infant due to infection, to make the diagnosis in subsequent affected children at birth, or even before birth. In these circumstances, early treatment of infants with SCID who have avoided infections has led to a very high likelihood of survival free of complications. Population based newborn screening for SCID is based on the recognition that pre-symptomatic identification and treatment would improve survival for all infants born with SCID, not just those with a known affected relative.

## Screening Test for SCID: T-cell Receptor Excision Circles (TREC)

Population based newborn screening is different from testing undertaken by immunologists confronted with a known or suspected case of immunodeficiency in their practice. Screening tests are performed on a large scale in centralized state public health laboratories that use blood from a heel stick that is spotted onto filter paper and dried, as first developed in 1963 by Robert Guthrie

for population based testing of newborns for phenylketonuria. Dried blood spots (DBS) can be handled by automated testing and tracking methods, enabling state laboratories to run thousands of samples at a time. The typical newborn screening test is done on a 1/8" disc that is punched out of the DBS.

## (Screening Test for SCID continued)

Unlike individual clinical tests done because of suspicion for a disease by either genetic or clinical information, a screening test looks for a rare, but serious condition in all infants, the vast majority of whom will not have the condition. Therefore, false negative results, or the failure to identify true cases, must be kept to an absolute minimum. On the other hand, false positive results produce anxiety and make follow up testing necessary that also needs to be minimized.

The first suggestion that all newborns be screened for SCID grew from recognizing that the majority of cases could be identified by a complete blood count and differential to determine the absolute number of lymphocytes. T-cells are approximately 70% of lymphocytes in healthy infants, and absence of T-cells causes the total lymphocyte count of most infants with SCID to be low. However, some forms of SCID are

associated with the presence of B-lymphocytes, and maternal T-cells are also sometimes found in the blood of infants with SCID. Therefore lymphocyte counts, though simple to perform but require a venipuncture, would not capture all SCID cases. Moreover, T-cell counts cannot be measured in DBS.

Therefore, the TREC test was developed. TREC are circular DNA molecules formed within T-cells developing in the thymus. TREC DNA circles are measured by a technique called polymerase chain reaction (PCR). Normal infant blood samples have one TREC per 10 T-cells, reflecting the high rate of new T-cell generation early in life. Infants with SCID lack TREC altogether.

Occasionally, DBS fail to show TREC DNA for technical reasons; such samples need to have repeat determinations, sometimes requiring a new blood spot

## Conditions Found by Screening for Low or Absent TREC

### CHAPTER 26; TABLE 1

Typical SCID, due to defects that include <i>IL2RG</i> (X-linked), <i>ADA</i> , <i>IL7R</i> , <i>JAK3</i> , <i>RAG1</i> , <i>RAG2</i> , <i>DCLRE1C</i> ( <i>Artemis</i> ), <i>TCRD</i> , <i>TCRE</i> , <i>TCRZ</i> , and <i>CD45</i>
Leaky SCID or Omenn syndrome, due to mutations in typical SCID genes that do not completely abolish gene function
Variant SCID, with persistently low T-cells but no defect in a known SCID gene
Syndromes with variably affected cellular immunity that may be severe, including: <ul style="list-style-type: none"> <li>• Complete DiGeorge syndrome or partial DiGeorge syndrome with low T-cells</li> <li>• CHARGE syndrome</li> <li>• Jacobsen syndrome</li> <li>• Trisomy 21</li> <li>• <i>RAC2</i> dominant interfering mutation</li> <li>• <i>DOCK8</i> deficient hyper-IgE syndrome</li> <li>• Cartilage hair hypoplasia</li> </ul>
Low T-cells as a consequence of other conditions, including: <ul style="list-style-type: none"> <li>• Neonatal cardiac surgery</li> <li>• Neonatal leukemia</li> <li>• Gastrointestinal malformations</li> <li>• Extreme prematurity (resolves to normal with time)</li> <li>• Intrauterine growth retardation</li> </ul>

### (Screening Test for SCID continued)

from the infant. Repeated unsatisfactory tests where PCR fails as well as tests indicating low or absent TRECs need to be followed up with a liquid blood sample from the infant that is tested for total lymphocyte numbers and subsets of T, B and natural killer (NK) cells as well as naïve and memory T-cells by flow cytometry. Infants with abnormally low numbers of T-cells should be seen promptly by a pediatric immunologist to determine whether the infant has SCID.

In addition to SCID, other conditions in which T-cell numbers are low can be flagged by TREC testing, as listed in *Table 1*.

The TREC method was first adapted to statewide testing in Wisconsin, followed by Massachusetts, California and New York. Now many other states are conducting TREC screening for SCID, and still more are in the planning stages of offering this testing. These programs have successfully identified SCID and related conditions, allowing infants to receive prompt treatment without the burden of devastating infections. In California alone, at time of publication, 11 cases of SCID, three cases of leaky SCID and Omenn syndrome, four cases of variant SCID, and 15 cases of low T-cells in association with other syndromes have been found. To see if your state screens for SCID, visit [www.primaryimmune.org/SCID](http://www.primaryimmune.org/SCID).

## TREC Testing - Good, but Not Perfect

TREC newborn screening followed by lymphocyte subset measurement has now been proven to have clinical utility in several states. Many infants with otherwise unsuspected SCID or related T-cell disorders have been referred for prompt evaluation and treatment, and reports of successful outcomes are emerging. As more experience accumulates and more states add newborn TREC screening, it will be important to document outcomes of the current programs. Not only the total incidence but also the severity spectrum and relative incidence of these rare conditions in different population subgroups remain to be defined.

The Newborn Screening Translational Research Network (NBSTRN) has established a program for tracking and

reporting cases found by prospective screening so that diagnoses and screening test performance can be compared and analyzed between states and in the country as a whole.

Not all T-cell deficiency diseases are detected by the TREC test. Diseases in which T-cells develop in the thymus to the point of production of the DNA circles but have impaired function are missed. For example, newborns with Zap70 deficiency, MHC Class II deficiency and NF-kappa-b essential modulator (NEMO) deficiency have had normal TRECs, as has one patient with late-onset adenosine deaminase (ADA) deficiency.

## Future Issues for Newborn Screening for Immune Disorders

Now that TREC screening has become available and its effectiveness has been shown, spreading its implementation to all states is important. As screening becomes widespread, the true incidence and proportions of each type of SCID can be determined.

Immediate measures can be put in place for all patients—immunoglobulin replacement therapy and prophylactic antibiotics, avoidance of live vaccines, protection from exposure to infections—while the best type of definitive treatment is planned. Optimal transplant protocols for very young infants with SCID remain controversial, but with newborn screening these protocols can be established by multicenter studies.

All primary immunodeficiency diseases, not just SCID, stand to benefit from early diagnosis. Continued

advances in molecular and genomic technology may soon allow screening for lack of B-cells, with testing for B-cell kappa chain excision circles, or KRECs.

Moreover, it is possible that future newborns will have extensive testing for DNA mutations or sequencing of their entire genome, from which a blueprint of risks for a great variety of conditions affecting health can be ascertained. Even predisposition to the more common multifactorial immune disorders with later onset may become possible through deep sequence analysis of DNA from newborns. However, since the mere presence of a mutation does not fully predict phenotype for these conditions, much more needs to be learned about the true predictive value of each proposed type of screening.

# Primary Immunodeficiency Diseases and Allergies



## Chapter 27



*Allergic diseases and symptoms occur because of an active immune system that reacts to things that are usually harmless, such as pollens, pet dander or foods. For that reason, it can be puzzling that people with immune deficiencies would have allergies. In fact, taken as a whole, people with immune deficiencies probably have a far greater disease burden of allergy than the general population, although perhaps not in the same patterns. It is generally true that people with immunodeficiencies do not have problems with allergies as often as those who are immunocompetent. However, specific changes to the immune system in some immune deficiency diseases may increase the risk of the developing allergies.*

## Definition of Primary Immunodeficiency Diseases and Allergies

Allergies manifest in a number of very specific ways, including nasal and eye symptoms, allergic asthma, eczema, hives and anaphylaxis. It is common for a person to have more than one allergic disease. The immune system in people with allergies reacts in a specific way to allergens. Allergens are those things that trigger allergic symptoms. Common allergens include materials and particles in the air and environment such as dust mites, molds, pet dander, tree pollen, grasses and weeds, foods, drugs and stinging insect venoms.

Generally, an allergic reaction occurs when a person develops “allergic” antibodies, called IgE, which are specific for an allergen. The IgE antibodies bind tightly to allergic cells, called mast cells or basophils, in the skin, airways, gastrointestinal tract and around blood vessels. The allergic cells get activated when the bound IgE recognizes an allergen, and these cells then release histamine, a chemical that can cause hives, runny nose, sneezing and itching. Depending

upon where in the body the reaction between the IgE and the allergen happens, different symptoms can occur.

### Hay Fever

Hay fever, or allergic rhinitis, causes itchy, stuffy, and runny noses and sneezing when the affected person breathes in certain allergens. Watery, red and itchy eyes (allergic conjunctivitis) can also occur. The timing and severity of symptoms depends upon exposure to the allergens to which the person reacts; for example, symptoms are prominent in the spring for patients with tree pollen allergy but occur in the fall for patients with ragweed allergy. When the stuffiness gets very bad, it can lead to rhinosinusitis where fluid and pressure accumulates in the sinuses, leading to discomfort and risk of infection. This is particularly a problem in people with immune deficiencies, as it can be difficult to determine whether sinus problems are due to infection, allergy or, as is often the case, a combination of the two.

(Definition of Primary Immunodeficiency Diseases and Allergies continued)

**Managing hay fever can include:**

- Avoidance of allergens when possible, such as dust mites, mold or pet dander.
- Oral ‘non-sedating’ antihistamines, such as Zyrtec (cetirizine), Allegra (fexafenidine) or Claritin (loratidine); Benadryl (diphenhydramine) or Atarax (hydroxyzine) are anti-histamines that are sometimes used, but these usually cause drowsiness, so should be used with caution.
- Nasal steroids for more severe symptoms, particularly with nasal congestion.
- Allergy shots (immunotherapy).

**Allergic Asthma**

Allergic asthma is a chronic allergic condition of the lungs. In people with allergic asthma, breathing difficulties such as wheezing, chest tightness and coughing can be triggered after inhaling something to which they are allergic, like tree pollen or mold. Changes in temperature, smoke, strong smells and other non-allergens can trigger symptoms as well. Asthma is usually diagnosed based on symptoms and by using pulmonary function tests where a computer measures airway function. Asthma is a chronic disorder that requires ongoing management. Treatment of asthma includes therapy, such as albuterol, to dilate constricted airways for immediate relief of symptoms. For many patients, depending on the severity and frequency of symptoms, daily inhaled steroids and other medications are also used to prevent symptoms and control the disease.

Of special relevance to people with known or suspected immune deficiencies, asthma attacks, especially those, which occur when the affected person has a fever, can often be confused with pneumonia. It is important to differentiate between an asthma attack and pneumonia as the treatment for the two problems is very different.

**Food Allergies**

Food allergies result from the development of specific immune responses to foods. Symptoms of food allergy usually occur within minutes to a few hours of eating a food to which a person is allergic. Symptoms of food allergy can include hives (which look like mosquito bites), flushing and itching of the skin, vomiting, diarrhea or abdominal cramping. In severe cases, difficulty breathing, a feeling of throat closure. Significant decrease in blood pressure and unconsciousness can occur. Food allergies are treated by carefully avoiding the offending foods. In cases of an anaphylactic reaction, an injection of epinephrine is used.

**Food Intolerances**

Food intolerances do not involve the immune system, and they are not usually life threatening. An example of food intolerance is lactose intolerance in which the lack of an enzyme to break down milk sugars results in abdominal cramping and diarrhea, when dairy products are consumed. Celiac disease, in which affected people experience gastrointestinal symptoms after eating gluten-containing products, like wheat, is an immune disease directed at wheat and not a “true” food allergy.

**Eczema**

Eczema, or atopic dermatitis, is chronic skin inflammation that is sometimes made worse by exposure to foods or environmental allergens, particularly in children. The main problem with eczema is usually a breakdown of the skin barrier and activation of the immune system in the skin, leading to inflammation with severe itchiness. The skin barrier functions to keep water in the skin and to keep other things (such as bacteria and allergens) out. Loss of this barrier leads to skin dryness and increased risk of infection. Interactions between genetic susceptibility and environmental exposures early in life are likely to play a major role in the development of eczema. Several immune deficiencies are associated with the

## (Definition of Primary Immunodeficiency Diseases and Allergies continued)

development of eczema, including Wiskott-Aldrich Syndrome, the autosomal dominant hyper-IgE syndrome and IPEX, but the underlying genetic causes are quite different.

Treating eczema requires ensuring that the skin barrier stays intact by frequently bathing to soak the skin, applying emollients to lock in moisture and lock out unwanted exposures, and adding topical steroids or

other drugs that can calm down the immune response (inflammation) in the skin. In some patients with primary immunodeficiency, skin bacteria can worsen the symptoms, and so oral and topical antibiotics are often used. In addition, many patients also respond well to bleach baths (or swimming in chlorinated pools) as another way of killing the bad skin bacteria.

## Drug Allergies and Intolerances

Drug allergies and intolerances are more common in people with immune deficiencies largely because they are exposed to more drugs. In general, the more types of drugs and exposures to drugs people have had, the greater the chances to develop drug allergies or intolerances. Having reactions to drugs does not necessarily mean that the person is an “allergic” person, but of course, much care must be taken to avoid serious reactions.

As with food allergies, many reactions to drugs are not true “allergies” caused by IgE; however, these reactions still can be severe and must be taken very seriously. A

thorough evaluation of previous reactions is critical to ensuring that the use of potentially dangerous medications is avoided, while not restricting medications unnecessarily. In some patients with allergic reactions to drugs, particularly antibiotics, allergists can temporarily “desensitize” patients so that they can receive these medications in life-threatening situations.

## Diagnosis of Primary Immunodeficiency Diseases and Allergies

Diagnosing allergies can be tricky, especially in the context of an immune deficiency. The most common tests used are skin prick testing and a blood test for IgE specific for allergens (sometimes referred to as a RAST test, Cap RAST or ImmunoCap). Skin prick testing involves taking a drop of allergen and poking the surface of the skin. Positive reactions lead to what looks like a hive. Blood tests can be sent to see if the person has IgE that reacts to specific allergens. The validity of the results varies depending on which allergen is being tested (food allergens tend to be the most accurate). However, especially in settings when the IgE is high, and when people have immune deficiencies, it is sometimes difficult to interpret these results. Allergy testing in patients with primary immunodeficiency should never be interpreted without the help of someone who regularly cares for patients with primary immunodeficiency diseases and allergies.

Some primary immunodeficiencies are more commonly associated with allergic issues. These include Hyper-IgE syndromes (HIES) and IPEX.

**Omenn's Syndrome** is caused by the same genetic mutations that lead to Severe Combined Immune Deficiency (SCID). However, for reasons we do not fully understand, a few T- and B-cells "leak out" as it were and lead to swelling of the lymph nodes, spleen and liver, and lead to a head to toe rash that looks like terrible eczema. Patients have very high IgE levels and many eosinophils. However, they do not really have allergies to specific foods or anything else because the T-and B-cells they make are unable make a specific response.

**Hyper IgE Syndromes (HIES)** are a series of immune deficiencies, which are characterized by extraordinarily high levels of IgE. These patients are prone to serious infections. The most wellknown and best-characterized HIES are the autosomal dominant hyper-IgE syndrome (AD-HIES), which is due to STAT3 mutations, and autosomal recessive HIES cause by DOCK8 deficiency. Not everyone with a high level of IgE has a HIES. Many people with bad eczema or allergies can have high IgE (thousands to tens of thousands), and no other symptoms at all. People with AD-HIES have a specific set of symptoms that includes Staph abscesses, pneumonias, fungal infections of the skin, easily broken bones, very flexible joints and retained childhood teeth. People with DOCK8 deficiency not only have bacterial infections but also have severe viral infections, especially of the skin, very bad eczema, allergies to foods and an increased risk of a number of cancers. *(See chapter titled "Hyper IgE Syndrome.")*

**IPEX** is a syndrome of immunodeficiency, endocrine, gastrointestinal and skin disease, which has an X-linked pattern of inheritance. Boys with IPEX have severe eczema, high levels of IgE and allergies.

# Autoimmunity in Primary Immunodeficiency



## Chapter 28

*The immune system is a complex set of organs, cells, proteins and other substances that function to prevent infection. Primary immunodeficiency diseases are characterized by abnormalities in specific components of the immune system that lead to an increased susceptibility to infection. Many times, abnormalities in the immune system that lead to primary immunodeficiency diseases also result in immune dysregulation, which is an immune response that is not properly controlled or restrained. This can lead to autoimmunity, one form of immune dysregulation in which the immune response is directed against normal parts of the body such as cells, tissues or organs (called auto-antigens). Put another way, it is when the immune system attacks the body in which it resides.*

## Definition of Autoimmunity in Primary Immunodeficiency

A normal immune system makes proteins known as antibodies that recognize and prevent foreign organisms (bacteria, viruses) from causing infection. One common type of autoimmunity is when the immune system makes antibodies against normal cells and/or tissues of the body which are known as “autoantibodies.” Sometimes people with primary immunodeficiency diseases cannot make “good” antibodies to protect against infection but only make “bad” autoantibodies, which then cause autoimmune disease. Sometimes these antibodies themselves are harmless but suggest the presence of an autoimmune disease. In other autoimmune diseases, the cellular immune system may also react against a body’s auto-antigens.

One of the ironies of this situation is that the treatment for autoimmune conditions is the use of immune suppression to shut down the inappropriate immune response that is causing the problem. Obviously, using immunosuppressive treatment in a patient already afflicted with immunodeficiency involves a complex balancing act to avoid unwanted infections and other serious side effects while still using sufficient immunosuppressive treatment to control the autoimmune process. It is recommended to use a team approach when

using immunosuppressive treatment, joining the skills of the immunologist with those of a specialist in treating the organ system involved, be it gastroenterology, rheumatology, pulmonology, endocrinology, nephrology, dermatology or hematology.

Autoimmune complications have been reported in a wide range of primary immunodeficiency diseases. However, certain primary immunodeficiency diseases have autoimmune disease as their primary problem. These include Autoimmune Polyendocrinopathy; Candidiasis; Ectodermal Dysplasia (APECED or APS-1); Autoimmune Lymphoproliferative Syndrome (ALPS); and Immune dysregulation; Polyendocrinopathy, Enteropathy, and X-linked (IPEX) syndrome.

Certain other immune disorders are frequently associated with autoimmune complications. These include Common Variable Immune Deficiency (CVID), Wiskott-Aldrich Syndrome (WAS), IgA deficiency, Good Syndrome, Hyper IgM Syndrome, Idiopathic T-cell Lymphopenia (ICL) and Complement disorders. Most of these diseases are discussed in greater detail in other chapters. The focus of this chapter is to provide an overview of the types of immune dysregulation and autoimmunity that can occur in various primary immunodeficiency diseases.

## Autoimmune Cytopenias

The development of autoantibodies that bind to and destroy blood cells is the most common autoimmune disease seen in primary immunodeficiency diseases. The blood cells affected are the red blood cells (RBCs), platelets and white blood cells (WBCs).

### Red Blood Cells

The RBCs carry oxygen to the body's tissues. Oxygen is necessary for the body's tissues to perform their function. Anemia is the term used to describe a low number of RBCs. Autoantibodies against the RBCs can cause destruction of these cells and is called autoimmune hemolytic anemia (AIHA).

Symptoms associated with AIHA include fatigue, headache, dizziness, fainting and poor exercise tolerance. 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. Patients 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 tarry, 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.

The most significant symptom associated with AIN is fever, as this may indicate a serious infection. Other signs of infection such as cough, 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. Patients 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 simple blood count is the blood test performed to establish the presence of a cytopenia. Additional blood tests can determine whether an autoantibody is present. A specialist such as a clinical immunologist, hematologist or oncologist typically evaluates patients for these disorders. Sometimes a bone marrow sample needs to be obtained to determine whether 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), steroids, chemotherapy drugs and drugs such as anti-CD20, which is used to specifically deplete B-cells that produce antibodies. The therapy that is best for a

### (Autoimmune Cytopenias continued)

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. Patients rarely require blood transfusions except in extreme circumstances. In all cases, patients with cytopenias require close follow-up by their specialist.

Most patients can be treated successfully and have no major restrictions on their daily activities. However patients with chronically low platelet counts 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 patients with primary immunodeficiency diseases, 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. This is called interstitial lung disease and interferes with the ability of oxygen to be absorbed into the bloodstream.

Some patients with certain types of primary immunodeficiency diseases develop aggregates of immune cells called granulomas in the lung. 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 primary immunodeficiency diseases. Two primary immunodeficiency diseases that often have granulomas in the lung are Chronic Granulomatous Disease (CGD) and CVID. Patients with CVID sometimes develop both interstitial lung disease and granulomas in the lung. This disease is called Granulomatous Lymphocytic Interstitial Lung Disease (GLILD). Occasionally, patients with Ataxia-Telangiectasia and APECED also develop interstitial lung disease. At times, the inflammation

caused by granulomas and/or the accumulation of white blood cells in the interstitium of the lung can be so severe and persistent that fibrosis, or scarring, develops in the lung.

### Symptoms

In most cases, the symptoms of interstitial lung disease develop slowly over time. Patients with CGD will usually have a more acute onset as they have a persistent infection causing the lung inflammation. Patients may notice a decrease in their endurance with everyday 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 itself. Patients often complain of a cough, which is usually non-productive. Enlargement and rounding of the toenails and fingernails can be seen and is termed clubbing. Clubbing is not specific to primary immunodeficiency diseases or to lung damage but is a clue that the lungs should be evaluated. In some cases, the lung damage can lead to a severe lowering of blood oxygen causing patients to have a bluish tint to their skin or mucous membranes 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



## (Autoimmune Lung Disease continued)

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 primary immunodeficiency diseases.

### Diagnosis of Pulmonary Complications

Radiology tests can be helpful in identifying lung problems. Chest X-rays are useful for diagnosing infections (pneumonia). However, a chest X-ray can sometimes be normal, even when there is still significant lung disease present. A chest CT scan can frequently pick up abnormalities not seen on a routine chest X-ray. In patients with CVID and GLILD, changes on the chest CT scan will often appear before the patient exhibits symptoms.

Breathing tests, called pulmonary function tests (PFTs), can indicate the degree of lung impairment. There are changes in PFTs that can be found in interstitial lung disease and other types of lung disease. However, patients often must lose a significant amount of lung function to demonstrate symptoms that prompt 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 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 (for example, cancer, infection, interstitial lung disease, granuloma).

### Treatment

Patients with malignancies are referred to an oncologist (cancer doctor) for continuing care. Patients with infections are treated with antibiotics. Inflammatory changes in the lung are usually treated with immunosuppressant drugs that suppress or alter the immune system. The most common medicine used is corticosteroids (like prednisone), which can be given by inhalation, orally or intravenously (IV). Steroids can be effective, but sometimes may not provide long-term improvement. Prolonged oral or IV steroid use is associated with significant side effects such as high blood pressure, high blood sugar, osteopenia (weak bones), hyperlipidemia (high cholesterol), and stress on the kidney and eyes. 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 can sometimes improve the inflammation in the lungs in addition to other drugs.

Without treatment, interstitial lung disease can progress and cause permanent lung damage. Fibrosis (scarring), which is the end result of chronic untreated inflammation, cannot be reversed. It is very important that your doctor has the correct diagnosis of your specific lung disease and expertise in treating the specific disorder in order to insure the best outcome.

## Autoimmune Skin Disease

Skin conditions due to autoimmunity or immune dysregulation are not unique to people with primary immunodeficiency diseases. Common skin conditions like eczema or psoriasis are seen in people with normal immune systems as well. Sometimes, skin disease is one of the earliest symptoms of a primary immunodeficiency disease and can lead to further clinical or laboratory evaluation to identify immune deficiency. In addition to skin disorders that are autoimmune or inflammatory in nature, other abnormal skin manifestations, such as dry, sparse hair, abnormally formed teeth and fingernails, and absent sweat glands, can be seen in certain primary immunodeficiency diseases but are not due to autoimmunity, and 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 primary immunodeficiency diseases. Often referred to as “the itch that rashes,” eczema typically begins as patches of dry, itchy skin which worsen and erupt into rash as they are scratched. It is not unusual for patients with primary immunodeficiency diseases who have other autoimmune manifestations to also have eczema. Some primary immunodeficiency diseases are, however, associated with more severe eczema. These include WAS, Hyper-IgE Syndrome (HIES), IPEX syndrome, and certain forms of Severe Combined Immune Deficiency (SCID). In these disorders, the eczema may be quite resistant to typical therapies.

### Psoriasis

Psoriasis is another type of autoimmune skin disease that is more severe than eczema. Psoriasis plaques are typically red, raised, itchy and painful. They are characterized by the presence of 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. It occurs most frequently in patients with CVID but can also be seen in IPEX and occasionally in other primary immunodeficiency diseases.

### Hair and Skin Pigmentation Changes

Multiple primary immunodeficiency diseases can have autoimmunity that affects the hair and skin pigment. Some patients 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 patients 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 T-cell disorders such as 22q11 deletion (Di George) syndrome although they can develop in a wide range of primary immunodeficiency diseases.

### 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 what type of rash it is. Biopsies are typically taken from the area where the rash is most evident using a sharp “punch” that cuts and removes a small circular core of skin tissue that can be evaluated microscopically by a pathologist to determine what type of rash it is. This is typically a very minor procedure that can be done in the office with local numbing of the skin.

### Treatment

While not typically life threatening, autoimmune and inflammatory disorders of the skin can lead to significant emotional consequences and in rare situations can lead to permanent disfigurement. Because the skin plays an important role as a barrier to bacteria and other organisms from the environment, severe rashes like eczema may serve as an entry point to the bloodstream for bacteria from the skin.

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

### (Autoimmune Skin Disease continued)

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, ointments containing more potent steroids or other

immunosuppressant medications can be applied. In rare cases, oral or IV immunosuppressant medications may be needed to treat severe disease.

## Autoimmune Gastrointestinal Disease

Autoimmune gastrointestinal diseases are common among patients with primary immunodeficiency diseases, particularly patients 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 bathed in bacteria, bacterial products and food, which all have the potential to cause irritation of the intestinal lining (the mucosa). As a result, the immune system plays a particularly important role in maintaining the barrier function of the intestines and in protecting the body from invasion by the bacteria present in the bowel.

### Mucosal Changes

Autoimmune or inflammatory diseases of the gastrointestinal tract can disrupt 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 patients with primary immunodeficiency diseases who have bowel infections with organisms such as *Giardia*, *Cryptosporidium* or *Clostridium difficile*. Because both autoimmune and infectious complications can lead to serious problems in patients with primary immunodeficiency diseases, it is important that new

gastrointestinal symptoms be evaluated (*see next page*) when they arise. In rare cases, ongoing gastrointestinal symptoms can be a sign of cancer in the bowel, which is more common in some types of primary immunodeficiency diseases 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 are: the metabolism of nutrients absorbed from the intestines, the production of important blood proteins such as clotting factors, the metabolism of drugs and other toxic molecules present in the blood, and the removal of waste products from the blood and excretion of these into the bile.

Autoimmune or inflammatory disease of the liver, which can occur in primary immunodeficiency diseases, can cause temporary or permanent damage that can disrupt 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 primary immunodeficiency diseases 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. Since infections by certain viruses, including Hepatitis (A, B, or C), Cytomegalovirus (CMV), Epstein Barr virus (EBV), and others, can also cause severe liver inflammation and

(Autoimmune Gastrointestinal Disease continued)

damage, these are typically excluded as the cause of disease before autoimmunity can be confirmed.

## Diagnosis of Gastrointestinal Disease

The diagnosis of gastrointestinal disorders in primary immunodeficiency diseases often requires a combination of approaches that include a physical exam, laboratory tests on blood and stool, radiology tests, and endoscopy with biopsies of the intestinal mucosa. Common physical exam findings include oral or anal ulcers, abdominal tenderness, fluid in the abdomen (ascites), enlargement or tenderness of the liver, cracks or fissures around the anus, etc.

Laboratory tests that are often recommended on the blood include a complete blood count to determine whether the patient may be losing blood in the inflamed bowel, measures of inflammation including 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 exclude the possibility of a bowel infection, stool is often collected and cultured to identify bacteria or viruses. Samples of stool are also stained and evaluated under the microscope for the presence of specific bacteria or parasitic 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 definitive diagnosis of either bowel or liver inflammation

is to obtain a fragment of tissue that can be evaluated under the microscope by a pathologist. In the bowel, this is done by passing an endoscope into the bowel to both look at the mucosa and to obtain small pinch biopsies of mucosal tissue from the inside surface of the intestine. In the liver, this is done by obtaining a small piece of liver tissue with a biopsy needle inserted into the liver through the skin. 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 patients with primary immunodeficiency diseases. This process is very individualized requiring flexible treatment plans to balance the severity and risks of the autoimmune process with the severity and risks of the immune deficiency and immunosuppressive therapy. In some cases, including the bowel disease associated with CVID or CGD, steroids are often the first line of therapy, and in many cases, may be sufficient to control symptoms. In contrast, the severe bowel disease associated with IPEX syndrome or Omenn syndrome typically requires more aggressive immunosuppression with stronger medications. For patients with primary immunodeficiency diseases who have significant gastrointestinal symptoms, it is essential to have a gastroenterologist involved to assist with diagnostic testing and with 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 most common form of autoimmune kidney disease in primary immunodeficiency diseases is called glomerulonephritis; inflammation and destruction of the glomeruli caused

either by direct attack or by deposition of immune complexes (aggregates containing autoantibodies and the proteins they are bound to). Destruction of the glomeruli leads to progressive loss of filtering capacity and decreased kidney function.

## (Autoimmune Kidney Disease continued)

Glomerulonephritis is a common feature of patients with complement deficiencies, particularly those affecting complement components C1, C2, C3, or C4.

Autoimmune kidney disease can also be seen less commonly in other primary immunodeficiency diseases including CVID and APECED.

### Symptoms

In many cases, the first sign of autoimmune kidney disease is elevated blood pressure. This is often accompanied by the appearance of blood or protein in the urine. In the setting of active glomerulonephritis, blood in the urine may not appear pink, but instead 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 readily available test strips that are frequently called urine “dipsticks.” If there is substantial 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 just how dysfunctional the kidneys may have become. Evaluation of the urine for the presence of blood, protein, inflammatory cells and electrolytes is also typically very informative. 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 core of tissue, which is usually sufficient to make the diagnosis. The biopsy is evaluated by a pathologist, who performs a variety of tests on the kidney tissue including a microscopic examination.

### Treatment

Patients 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 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). The endocrine organs secrete important hormones that play essential roles in maintaining basic bodily functions. Autoimmunity directed against endocrine organs can therefore cause significant health problems. Patients who have endocrine autoimmunity are often referred to an endocrine specialist (endocrinologist) for evaluation and management.

### Thyroiditis

The thyroid gland secretes thyroid hormone, which plays an important role in maintaining the metabolic rate of the

body. Patients 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, patients 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 with an incidence of approximately 1 in 200. In certain primary immunodeficiency diseases, including CVID and IPEX syndrome, the incidence is even higher.

## (Autoimmune Endocrine Disease continued)

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 or radiation or other drugs. This is always done under the direction of an endocrinologist.

### Diabetes

Diabetes (abnormally elevated blood sugar levels) results from either not being able to produce enough insulin (Type I diabetes) or as a result of the cells of the body becoming resistant to the effects of insulin (Type II diabetes). Type I diabetes (T1D) is the form caused by autoimmune attack on 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 below a particular threshold, patients develop diabetes. T1D is very common in some primary immunodeficiency diseases, such as IPEX syndrome where it occurs in approximately 70% of patients. Incidence is also higher in other primary immunodeficiency diseases, including CVID, APECED syndrome and others.

T1D is typically diagnosed by screening for the presence of glucose (sugar) in the urine and by measuring blood 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 toward proteins in the pancreas (anti-islet cell antibodies) can help confirm that the process is autoimmune.

Treatment of T1D typically involves the administration of insulin either via shots or via an

insulin pump. Even though T1D is autoimmune mediated, it is not yet clear whether the use of potent immunosuppressive drugs early in the course of disease will change the need for insulin treatment or not, but there are a number of therapeutic trials have been designed to address this question.

### Other Autoimmune Endocrine Disorders

Insufficient parathyroid function leading to problems with regulation of calcium levels is a feature of DiGeorge syndrome and CHARGE syndrome, but in these cases the defect is caused by abnormal development of the glands, not by autoimmunity. Parathyroid autoimmunity does, however, occur as one of the main features of APECED syndrome, often in association with autoimmunity to adrenal glands and gonads.

### Diagnosis of Endocrine Complications

As discussed above, 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 critically important hormones that are supposed to be made by the targeted 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 malady 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 patients with primary immunodeficiency diseases but some primary immunodeficiency diseases 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 patients with XLA develop arthritis at some point, although it is often not terribly inflammatory and frequently resolves when immunoglobulin replacement therapy (IVIG or SCIG) is optimized. In contrast, patients with CVID can develop severe 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 primary immunodeficiency diseases with one exception, which is a dermatomyositis syndrome that occurs in patients with XLA who become infected with a particular type of bacteria called *Helicobacter*. In these cases, the inflammation is not treated with immunosuppressant medications but instead with antibiotics to treat the bacterial infection.

### Symptoms

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 worst after not moving the joint, like in the morning after sleep or after resting, and often

improves somewhat with activity. When the arthritis is active and flaring, patients 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. Patients 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 extremely informative in making a firm 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

Treatment of arthritis typically 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 patient with primary immunodeficiency diseases 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

Significant autoimmune or inflammatory disease is common among patients with primary immunodeficiency diseases. Early recognition and treatment of these symptoms is critical for optimizing quality of life and decreasing complications associated with primary immunodeficiency diseases. This requires that patients and their care 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 primary immunodeficiency requires close cooperation between the patient and the various specialists involved in their care. Treatment may require frequent dosage adjustments or changes in overall approach to reach the desired balance.



# Infants and Children Living with Primary Immunodeficiency Diseases



## Chapter 29

*When a child is diagnosed with a primary immunodeficiency disease, each member of the family begins an unexpected and challenging journey. The whole family must come to terms with the illness and perhaps make major changes in schedules and priorities. As a result, it is a journey that may have unforeseeable turns but also many joys and rewards—a journey that can be meaningful.*

## Helping Your Child Understand

Children's understanding of their primary immunodeficiency disease 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 you can help your child better understand:

**Infants and Toddlers (ages 0-2)** are just beginning to develop trust and security, and they usually do not have an understanding of their primary immunodeficiency disease. They may experience challenges to their development of trust and security when they experience pain, restriction of motion and separation from parents. You can help by staying with your child for medical procedures and hospitalizations as well as holding, comforting and interacting with your child as much as possible. Bringing a favorite stuffed animal, pacifier or blanket along to treatments may be helpful as well.

**Preschool Children (ages 3-4)** 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. You can help by

being firm and consistent with things your 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. Praising your child for making positive choices about their health is also important.

**Early School Age Children (ages 5-10)** 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, by hitting their sibling or by not following rules at home. At this stage, children are also beginning to notice that they may seem different from their peers. You can help by making sure your child knows that their primary immunodeficiency disease 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

(Helping Your Child Understand continued)

control. Parents can also 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. You 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

better. They may not feel as though they need it any longer. While they are better able to understand their primary immunodeficiency disease and its treatment, they should not be expected to react as adults do. You can help by explaining to your child how important medications can be in the management of primary immunodeficiency, even when they begin to feel better. With the approval of your child's healthcare provider, your child should participate in school or other activities whenever possible. Be sure to include your child in discussions with their medical team when possible. This will help children feel included and give them a greater sense of control over the situation. Listening to your child is always essential and it may be helpful to encourage your child to express these emotions through play, art, drawing, music or reading. *(See the chapter titled "Adolescents Living with Primary Immunodeficiency Diseases.")*

## Normalizing Your Child's Life

Parents of a child living with a primary immunodeficiency disease are often faced with many challenges, difficulties and decisions that other parents will never have to face. This may be overwhelming, however, there are ways to support your child and help your family cope.

### Medical

**Explain the diagnosis to your child.** One of the most important things parents can do for children with primary immunodeficiencies is to provide accurate age-appropriate information and encourage the 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 also important to let children know that the diagnosis is not their fault and that it is not a punishment. Make sure your child knows that you are there to answer any questions they may have. Having open and honest communication with your child helps build trust and a sense of security, and it helps your child cope better.

**Become informed about special medical issues affecting your child.** These may include:

- Infection precautions, including co-sleeping, school, sleep overs, camps and airline travel
- Use of antibiotics if they get sick or following known exposures
- Vaccines for your child and family
- Avoidance (if necessary) of swimming, gardening, playing in the leaves, etc.

## (Normalizing Your Child's Life continued)

- Precautions about school sports if necessary
- Nutrition
- Dental hygiene
- Medical alert badge
- Dental and medical procedure pre-medications
- Genetic counseling of parents
- Insurance issues

**Prepare your child for medical procedures.** Children need to know what to expect in their lives. Explain, in an age-appropriate way, the reasons why the procedure is 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 critically important to give consistent and accurate information. For example, do not tell your child that something will not be painful or uncomfortable when you know that 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 your child deal with feelings about the diagnosis.**

Try to understand the many emotions that children experience regarding their primary immunodeficiency disease. You can help your child cope with difficult emotions by talking openly about how everyone in the family may be experiencing something similar. Providing routine and predictable times to check in with your child gives them opportunities to talk and to share, and it gives you opportunities to reassure them that their feelings are normal and acceptable. You can ask questions in a way to get your child talking by using open-ended questions. “What kind of questions do you have?” is very different than “Do you have any questions?” You 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 your child

get rid of unhappy feelings. Some examples include using play or art to express feelings.

**Give your child some choices.** Many children living with primary immunodeficiencies 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 your child for the reactions of others.** Children with primary immunodeficiency diseases 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. You can help by teaching your child a simple and short explanation of the diagnosis. Make sure your child is comfortable explaining what is necessary to keep well. It may help for you and your child 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 primary immunodeficiency disorders 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, including family retreat weekends, patient education meetings and a national conference held every other year. You can share and ask questions on IDF's social network, *IDF Friends*, [www.idffriends.org](http://www.idffriends.org). You can ask IDF to connect you with a trained peer support volunteer that

### (Normalizing Your Child's Life continued)

has experience living with a child who has a primary immunodeficiency disease. Children often benefit from having contact with others who have the same illness. IDF can connect your child with other children living with a primary immunodeficiency disease.

**Coordinate with your child's school.** Living with a primary immunodeficiency disease may disrupt a child's schooling. It is important for parents to meet with teachers, counselors, nurses and administrators to explain their child's primary immunodeficiency disease

and the potential impact on school (such as frequent absences, fatigue, activity restrictions). You should talk about what parents and other children in the class should be told about your child's primary immunodeficiency disease. A plan should be developed to help your child keep up with schoolwork when they cannot attend school. A good resource to help you coordinate with your child's school is the *IDF School Guide*, available to order or download at [www.primaryimmune.org](http://www.primaryimmune.org).

## Family Life with Infants and Children Living with Primary Immunodeficiency Diseases

A child living with a chronic illness 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 your family in many ways. You may experience increased worry, stress and 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 healing process for you and your family. Parents 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 illness. Financial worries may also increase.

Siblings may experience a wide range of emotions when their brother or sister is living with a primary immunodeficiency disease. 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 children 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 your child lead as normal a life as possible.**

To whatever extent possible, you should try to treat your child with a primary immunodeficiency disease just like any other child. At the same time, you need to take into consideration your child's health and any special needs that they may have. This can be quite a balancing act, but it is important for parents to encourage their child's participation in activities that involve other children of the same age.

## (Family Life Continued)

**Maintain family routines.** You should, 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 primary immunodeficiency. 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 regular routines and schedules for all family members.

**Help your other children cope.** A child living with a primary immunodeficiency disease demands a lot of parental attention. It is no wonder that brothers and sisters often feel jealous, angry and lonely and worry about their sibling and sometimes about their parents. They also might worry that they might get the disease. You should explain the disease to your other children. Try to get them to ask questions and to express their concerns. Parents need to keep open lines of communication 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 your child with a primary immunodeficiency disease 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 primary immunodeficiency 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 and even for one-on-one parent-child dates, as mentioned earlier—each parent spending individual time with each child.

## Coordinating Your Child's Healthcare

When your child is diagnosed with a primary immunodeficiency disease, you become part of your child's healthcare team and their main advocate. Your role in monitoring your child's symptoms, responses to treatments and communicating your observations and concerns is vital to the medical team's assessment and treatment of your child. In many cases, more than one provider will be involved in caring for your child; therefore, coordinating communication and keeping

comprehensive and accurate records of your child's medical course is essential. Many parents suggest that a journal is an invaluable tool to document events affecting your child's medical care. IDF ePHR, an online personal health record designed for the primary immunodeficiency community, is another tool to help record your child's medical information:  
[www.idfephr.org](http://www.idfephr.org).

(Coordinating Your Child’s Healthcare continued)

**Recommended information to record:**

- Brief history leading to the diagnosis, written by you or your child’s healthcare provider
- Copies of laboratory evaluations confirming the diagnosis
- Current list of providers caring for your 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 your child’s current medications
- Allergies to medications
- Immunization record
- Current insurance information
- Explanation of benefits records 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, and a journal or IDF ePHR will be useful if your 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 issue 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 you can be extremely helpful for those times when others care for your 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 patient’s medical routine.

- **Plan ahead:** Be prepared for a change in plans or long office visits. Sometimes you and your child will go for tests immediately after the visit or the visit could be extended for other reasons. If this is the case, you may need to make arrangements for your other children.
- **Communicate directly with the child:** Encourage the medical professional to communicate directly with your child when possible. Although your 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, as well as give you written instructions to be placed in your journal or scanned and saved into the ePHR.
- **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 because you do not want to go home with more germs. You can also prepare age-appropriate activities to engage them
  - *Books:* Take along favorite books or a new book to help your 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:* You 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 Your Child's Advocate

As a parent, you are your child's best advocate. It is important to communicate with your child's providers the concerns and questions you or your child may have. Using a journal or IDF ePHR will help you remember what to discuss with your child's provider at various visits.

### How you can advocate for your child:

- Ask questions about your child's diagnosis, treatment and plan. If you do not understand, ask again.
- Inquire about what can be done to improve your child's health such as diet, physical activity, sleep and social activities.
- Maintain consistent communication with the school as your child may miss school days.
- Know your insurance policy and communicate if there are any changes to your provider.
- If your child receives immunoglobulin (Ig) therapy, make notes of how it is going and/or any side effects.
- Build positive relationships with your 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](http://www.primaryimmune.org) or 800-296-4433.

## Transitioning Responsibility to Your Child

As children develop, they begin to form their own thoughts and opinions of their care. Again, when it is appropriate, offer choices to your child. This helps your child build confidence because they have some control over decision-making and prepares your child to

participate and eventually take care of themselves 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 primary immunodeficiency disease 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 of family 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. It is also important to support the needs of the entire family. Counseling services can be a valuable part of your 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 primary immunodeficiency diseases. 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 or fear, sadness and depression, hopelessness, irritation, anger, disinterest or lack of pleasure in activities formerly of interest, emptiness, guilt, and frequent worrying
- **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 acting out by not listening, fighting, or even hitting
- **School:** academic problems, change in school performance, and difficulty with concentration
- **Social issues:** isolation from peers, feeling disconnected from people, lack of interest in things they previously enjoyed, and fights with friends
- **Self-esteem issues:** sense of being different, low self-confidence, and negative self-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 ignoring other family members
- **Parent issues:** time-management difficulties, financial worries, marital stress, guilt, self-blame and/or blame of others, grief, and discipline problems
- **Physical issues:** changes in eating, sleep disturbances, stomachaches or headaches, tiredness, and 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. You 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 Your Needs

Parents should remember to take care of themselves. Addressing your own needs will allow you to provide better care for your child.

**Educate yourself about your child's diagnosis.** Being knowledgeable allows parents 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.

**Take care of yourself.** This may seem like a difficult task for many parents. Nevertheless, it is vital for parents to take care of themselves. Otherwise, you 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 primary

immunodeficiency disease. Allow others to help by giving you a break and be sure to carve out time to do something you enjoy. Find someone to listen to your worries and make it a priority to spend quality time with your partner on a regular basis. Learn to deal positively with your stress by eating right, exercising, keeping a journal and spending quality time with your children.

**Be hopeful.** Coping with a primary immunodeficiency disease can be discouraging and scary. It is incredibly important to stay positive and hopeful. Do not ignore or dwell on your worries or negative feelings. Instead, recognize and address them in a positive manner. If you try to find the positive side of things, you will be teaching your child a valuable lesson as well as maintaining your own peace of mind.

# Adolescents Living with Primary Immunodeficiency Diseases



## Chapter 30

*Adolescents diagnosed with a primary immunodeficiency disease and their families face not only the day-to-day challenges of any family, but they also face learning how to manage the effects of a rare and chronic disease while nurturing growth towards adulthood. Adolescence is a time of great transition cognitively, developmentally and emotionally. When adolescents are diagnosed, they face some unique difficulties, and it is important to help them manage the impact of a primary immunodeficiency disease while striving to achieve the developmental tasks of a teenager.*

*Although typical adolescent trials may be more stressful and confusing for those living with primary immunodeficiency disease, you and your adolescent can work together to overcome challenges, enjoy this time and prepare for the transition into adulthood.*

## Normalizing Your Adolescent's Life

As adolescents grow, they develop the maturity needed to establish and maintain family and social relationships as well as continuing an educational path toward an occupation. They typically go through a series of steps in this maturing process, commonly having both successes and setbacks in navigating 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, primary immunodeficiency diseases manifest differently in each patient; therefore families must make choices that best suit the adolescent's physical and mental health, as well as abilities.

You can help your adolescent through this time by teaching them coping skills needed to manage day-to-day issues associated with the primary immunodeficiency

disease while helping them live the normal life of a teenager.

**Begin a dialogue with your adolescent**, so that they can become a part of the 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, and there will be times when you learn that their viewpoint and concerns may be very close to the concerns that you may have.

**Help your adolescent maintain a balanced life.** Teens who best manage their disease are those who find a balanced approach to the disease and to life. It is understandable that adolescents would often want a break from focusing on the disease, yet neglect of symptoms or treatment routines can lead to a serious health setback. An emphasis should be placed on both managing the disease (the signs, symptoms and treatments) and maintaining overall

## (Normalizing Your Adolescent's Life continued)

health itself (the activities and relationships that promote a healthy lifestyle). Contact the Immune Deficiency Foundation (IDF) about getting your child involved with the IDF Teen Program to help them learn about living with the disease and to connect with others living with primary immunodeficiency: [www.primaryimmune.org](http://www.primaryimmune.org) or 800-296-4433.

**Coordinate with your adolescent's school.** Living with a primary immunodeficiency disease may disrupt schooling, and as previously mentioned, school is an integral part of an adolescent's life. You should meet with teachers, counselors, nurses and administration to explain your teen's primary immunodeficiency disease and the potential impact on school, such as frequent absences, fatigue and illness. Work with them to develop a plan to help your adolescent keep up with schoolwork when they cannot attend school. 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](http://www.primaryimmune.org).

**Encourage your adolescent to explore their talents and interests,** and help them make appropriate modifications when necessary. Set realistic expectations based upon their individual capabilities and medical needs, but focus on all that they can do. Encourage participation in athletics, music, dance and 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 adolescent to participate in school and social activities** to help them feel 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 primary immunodeficiency disease can be very difficult for them. Acknowledge such disappointments while balancing their health. Your adolescent should participate in events whenever possible. There is always a chance that patients can become ill since germs exist everywhere, but preventing your teen

from participating in group events can create feelings of anxiety and depression. Making simple modifications, such as using hand sanitizer, avoid sharing beverages, and staying away from actively coughing individuals, can allow them to participate.

There are certain restrictions that some patients with primary immunodeficiency diseases must follow. For example, those with thrombocytopenia should avoid contact sports. Football or soccer is risky for patients with Chronic Granulomatous Disease (CGD) because of exposure to dust or grass with potential pneumonia. These should be explored with your healthcare provider.

**Help your adolescent develop strategies to educate peers** and to explain their condition, including the appropriate terms for diagnosis and treatment. Teenagers already struggle with identity issues and confidence, and feeling different can further complicate this matter. Because primary immunodeficiency diseases are rare, your adolescent may not know many other children 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.

**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 talking to your adolescent about how to talk about their primary immunodeficiency disease 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 primary immunodeficiency disease, that person is not the right person for them. It is important to let your adolescent know their value and that people with primary immunodeficiency diseases date, marry, have children and lead full lives.

## Family Life with Adolescents Living with Primary Immunodeficiency Diseases

Adolescents and their families who best cope with an ongoing health problem typically follow a pattern during the maturing process. In early adolescence, parents are more involved in directing learning and serving as role models. Later, parents encourage increased involvement of the adolescent in management of their disease, with parents monitoring their increasing responsibility of self-care. Finally, as the adolescent moves toward adulthood, parents encourage them to take main responsibility for managing the disease, with family members as more distant supporters.

Families may struggle to find a balanced approach to maintaining their family life and addressing the health issues of their adolescent. Time, activities and family decisions may require daily modifications. In addition adolescents with primary immunodeficiency diseases often feel guilty that they are burdening their parents with the additional pressures of their illness. Be sure to let your adolescent know all the wonderful things that they add to your life to let them know how valued they are.

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 their brother or sister with a primary immunodeficiency disease. Acknowledging the impact of the disease upon the non-patient sibling is important. Praising the sibling for their patience and acknowledging the challenges of having a sibling with a chronic illness can help decrease resentment and validate the sibling's experience. Encourage sibling input on family decision-making, so that the non-patient sibling feels that their needs are just as important as the patient's.

When two children in the family have primary immunodeficiency diseases, 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 disease. It is important to individualize each child's needs and not to generalize their experiences.

## Preparing for Tough Questions from Adolescents Living with Primary Immunodeficiency Diseases

**Common questions that you may hear from your adolescent:**

*I hate being treated differently! Why can't I be just like everybody else?*

Adolescents will vary in 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 primary immunodeficiency diseases?*

This may be related to the question about being treated differently. It also involves learning relationship skills of trust building and sharing. Your adolescent 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

## (Preparing for Tough Questions continued)

sharing. Encourage them to take advantage of the IDF Teen Program and IDF Common Ground to learn more about their disease and to connect with other teens.

*How do I handle this at school?*

When your adolescent asks this, it might be more about the friendship aspect of school. They may also 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 realistic expectations for balancing health and school performance. Consult the *IDF School Guide*, which can be ordered or downloaded at [www.primaryimmune.org](http://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 the child was younger can be changed or modified to meet the needs of the older child. 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 a primary immunodeficiency disease. Schedule an appointment with your adolescent's immunologist 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 primary immunodeficiency disease 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 disease, 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!*

This is a very tough question. It is one often asked by parents as well as adolescents. This may be a question about their particular disease 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." Reach out to the people and resources that you currently seek out to find meaning in life.

## Resources and Professional Assistance

Many adolescents with primary immunodeficiency diseases often feel misunderstood. As much as family and friends may attempt to understand the impact of these diseases, only patients can really understand what this disease feels like. Encourage your adolescent to connect with peers with primary immunodeficiency diseases through the IDF Teen Program. Having other adolescents to relate to is invaluable in providing support. Not only can it foster supportive friendships, but their involvement with others with primary immunodeficiency diseases can also help them feel that they are neither alone nor different from others. IDF Common Ground is a social networking site designed specifically for adolescents, where they can connect with other young people who understand what it is like to live with a primary immunodeficiency disease: [www.idfcommonground.org](http://www.idfcommonground.org). IDF Teen Escape weekends, which are held a few times 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 primary immunodeficiency disease. IDF holds

biennial National Conferences and Retreats, during which there are programs for teens. For more information about programs and resources for teens, contact IDF: [www.primaryimmune.org](http://www.primaryimmune.org) or 800-296-4433. Teens may not feel they need to attend such programs, but those who do attend have extremely positive experiences.

Seek professional assistance if your adolescent displays 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 Primary Immunodeficiency Diseases

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 support. Having a place to vent about how difficult this challenge can be is important and receiving support from friends, family and partners is necessary. But just as it is imperative that your adolescent is connected to the primary immunodeficiency disease community, you should be

too. Having the connection to another parent who understands your experience can be emotionally healing. Parents of patients may understand your experience more than friends and family who may find it difficult to relate to the daily pressures of primary immunodeficiency diseases. IDF offers a variety of resources and programs to connect you with other parents. Taking care of your emotional well-being can make it easier for you to manage caring for your adolescent.



## Coordinating Your Adolescent's Healthcare

Managing the healthcare of your adolescent calls for a high level of communication and teamwork among healthcare providers, family members and the adolescent. Knowing what local resources are available and creating positive relationships with healthcare providers, teachers, and others involved with your teen increases the chance that your child's healthcare needs can be effectively met.

Adolescents are more likely to make positive choices in the future if they feel they have some say in the decision-making process now. Find providers who are willing to work with you and your adolescent, and allow for private time between the child and providers. They 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 listened to and develop a good relationship with healthcare providers.

Planning appointments around your adolescent's school and social activities allows them to maintain social relationships, which is 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 adolescent and healthcare providers, develop a personalized list of successful approaches to managing their health:

- What health and wellness habits have been most successful in keeping your adolescent 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 teens's primary immunodeficiency disease, 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 for their adolescents 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, your adolescent can develop lifetime habits of positive coping skills for health challenges.

## Being Your Adolescent's Healthcare Advocate

As your child's patient advocate, you work to make sure the needs of your teen are being met by the healthcare team. With younger children, the parent is the chief patient 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 the child matures 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 you build positive relationships with healthcare providers.

### **Recommended information to record and keep readily available in a journal or in IDF ePHR ([www.idfephr.org](http://www.idfephr.org)):**

- 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 adolescent 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 adolescent's current medications
- 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

### **How you can advocate for your adolescent:**

- Ask questions about the diagnosis, treatment and plan. If you do not understand, ask again.
- Inquire about what can be done to improve your adolescent's 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 your adolescent receives Ig therapy, make note of how it is going and/or any side effects.
- Build positive relationships with your adolescent's providers, teachers and therapists. Know who 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](http://www.primaryimmune.org) or 800-296-4433.

## Plan for Life After High School

Having this disease should not impede your adolescent from pursuing post-secondary education and/or living independently, but it will influence the decision in terms of obtaining healthcare and living conditions. Some patients 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. Contact student support services at their colleges of choice to discuss the child's diagnosis and possible resources and accommodations. If your adolescent secures a part-time or full-time job, make sure it suits their interests and abilities.

When researching new providers and facilities, you need to understand your adolescent's insurance benefits and what providers and facilities are covered. Be sure to choose healthcare providers who best suit your adolescent's needs. 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 in that area. Your current providers may be helpful in making recommendations. Many immunologists are associated with universities that can support their research, so you could consider those universities and cities. If they 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. You and your adolescent

should establish care, if possible, before moving day to give the healthcare provider time to get to know your adolescent and time to request authorization for treatment from the insurance plan.

If your adolescent receives Ig therapy and is relocating 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. Also, inquire about their policy for administering intravenous medications in university housing.

If your adolescent receives 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 an adolescent turns 18, they are legally considered an adult. At that point, parents need the patient's written permission to access healthcare records and to speak with the healthcare team. 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 your adolescent build confidence because they have some control over decision-making and 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 immunologist 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 adolescent become independent with current healthcare providers.

*On the following pages are checklists to be completed by your adolescent to help them prepare for the transition to adulthood.*

## Transition Skills Checklist

*Ages 12-14*

<b>General Information</b>	<b>Yes</b>	<b>Almost</b>	<b>No</b>
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, such as IDF ePHR.			
My parents and I carry a medical summary, such as the in case of emergency (ICE) report from IDF ePHR.			
<b>Medications and Treatment</b>			
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.			
<b>Medical Appointments</b>			
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.			
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.			
<b>Understanding the Healthcare System</b>			
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.			
<b>Healthcare Transition</b>			
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 (Transition Skills to be added to the 12–14 Checklist)*

General Information	Yes	Almost	No
My parents and I keep a personal health record, such as IDF ePHR.			
I carry a medical summary, such as the ICE report from IDF ePHR.			
<b>Medications and Treatment</b>			
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.			
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.			
<b>Medical Appointments</b>			
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.			
<b>Understanding the Healthcare System</b>			
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).			
<b>Healthcare Transition</b>			
I know if any of my healthcare providers will only treat me until I am 21.			
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*

General Information	Yes	Almost	No
I keep a personal health record, such as IDF ePHR.			
I carry a medical summary, such as the ICE report from IDF ePHR.			
<b>Medications and Treatment</b>			
I understand and/or arrange payment for my medications, equipment and treatments.			
<b>Medical Appointments</b>			
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.			
I locate and share healthcare information with my providers and in making decisions about my care.			
I sign medical consent forms.			
<b>Understanding the Healthcare System</b>			
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).			
<b>Healthcare Transition</b>			
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.			

# Young Adults Living with Primary Immunodeficiency Diseases



## Chapter 31



*Young adulthood is a time of independence and self-exploration when individuals separate from their parents and make life choices about education, career, lifestyle, living environment and peer relationships. Although the physical signs of primary immunodeficiency diseases often get the most attention, emotional health is just as important. The transition to adulthood is a challenging time for most people, but the potential ramifications of primary immunodeficiency diseases often require some unique life adjustments.*

*It is important that you, the patient, have the emotional support and skill set required to cope. Everyone experiences the disease differently, and your individual needs and strengths should be taken into consideration. With the support of family and friends, an effective healthcare team and necessary coping skills, you can lead a fulfilling and productive life.*

## Normalizing Your Life

Having a primary immunodeficiency disease can affect your daily life and your life choices, but you can make decisions that will help you have a normal, healthy life.

**Maintain a balanced life.** Those who best manage their disease are those who find a balanced approach to the disease and to life. It is understandable that you would often want a break from focusing on the disease, yet neglect of symptoms or treatment routines can lead to serious health setbacks. It is critically important to manage your disease, including your symptoms and your necessary treatments, while maintaining all the activities and relationships that promote a healthy lifestyle.

**Make positive lifestyle choices.** The lifestyle choices that you make affect your health. Young adults, especially those living on their own and/or

attending college, may experience living in cramped quarters, late night studying, peer pressures of drugs and alcohol, and dating. However, incorporating good care into your life is realistic. If you attend college, take a manageable course load. If you have a part-time or full-time job, make sure it suits your interests and abilities. Generally maintain good hygiene and enjoy healthy recreational activities. Know your limits.

**Participate in recreational activities.** Managing a chronic illness can be demanding, especially as you assume the role of healthcare manager and the responsibilities that come with adulthood. However, you should take an emotional break from the disease and form an identity outside of the disease. Make time for recreational activities that you enjoy.

(Normalizing Your Life continued)

**Maintain an ongoing dialogue with your parents.**

Specifically, have conversations about your changing roles and the transition of managing care. If you were diagnosed as a child, your parents probably play a large role in your healthcare. It can be a big shift for you since your parents have been managing your healthcare and school demands, and it may be difficult for your parents to let go, fearing that you may not make the best choices. It is essential that you are able to manage your healthcare on your own and at your own pace, but keeping open lines of communication and relying on your parents for support and guidance as needed can be beneficial as you navigate adulthood.

**Build a support system of family and friends.**

Your relationship with your family and friends will evolve as a young adult. You will need to learn to take care of yourself independently of your family and under different living conditions. This may mean depending upon friends and significant others for help while you are ill. Learning to ask for support when you need further assistance can be difficult, but you should assess which role your family members and friends are best suited to fill. Some may be helpful with logistics, like picking up medications when necessary or dropping you off at a procedure or appointment. Others may be supportive in an emotional sense, like listening to your frustrations and helping you to make sensible decisions.

## Talking with Others About Your Diagnosis

Because primary immunodeficiency diseases are rare, most people are unaware of the diseases and about the ways they affect patients. You should develop strategies to respond to questions and misconceptions. Although not ill intended, people often do not understand how their comments, minimization of the illness or lack of understanding can really undermine your sense of self-worth and leave you feeling misunderstood or alone. You may encounter people in school or work settings who have never met someone with primary immunodeficiency disease before. Pressures regarding performance and attendance can be difficult. You may face resistance from fellow students and co-workers who think that you are faking it or always sick.

A very common phrase heard among patients with primary immunodeficiency diseases is, “Well, you don’t look sick.” Although not usually intended in a negative

way, non-patients do not understand how hurtful such statements can be. When you are made to feel you are making up an illness, it can leave you with the sense that you are not trusted or that you are lazy or unproductive. This experience can be incredibly devastating, especially when other well-known, recognizable chronic illnesses are not treated in the same way.

It is important that you find a comfortable way to communicate with others and deal with ignorant commentary. Such statements may become opportunities to educate others and empower yourself by owning your diagnosis and experience. You should consider sharing some information about your primary immunodeficiency disease so that people may be less judgmental and fearful.

## Dating and Partner Choices for Young Adults Living with Primary Immunodeficiency Diseases

Young adulthood is a time when peer and romantic relationships are a top priority. It is important that you make positive choices in terms of maintaining your physical and emotional health. Physically, you should conduct safe sexual practices and communicate with a long-term partner about any potential health risks from infections. Emotionally, you should carefully consider revealing and discussing your disorder with your romantic partner, which can be difficult for you because of fears of rejection and lack of understanding. You must make sure that your partner is accepting and supportive of your medical condition.

Deciding when to tell a romantic partner about the disease is a personal choice, but it is best not to tell the person too early or too late. Disclosing too early without knowing a partner can lead to early rejection, and waiting too long may make the other person feel that they were not trusted. When you know that the person is someone whom you may potentially want to have a long-term relationship with, carefully consider finding the right time to have a discussion.

As you begin to develop romantic relationships, you must first be comfortable in your own acceptance of the illness. You should be prepared to answer personal questions in a sincere manner, yet be aware of what you would like to share. Questions posed by potential romantic partners may include the following:

- Can you have children?
- Is this contagious?
- Will your children inherit this disorder?

Other questions about the illness may follow. Knowing the answers to these types of questions and what you would like to share in advance can decrease anxiety and feelings of vulnerability. Consult your immunologist about how to answer such questions. Contact IDF to connect with someone who has had similar experiences through peer support: [www.primaryimmune.org](http://www.primaryimmune.org) or 800-296-4433. Role-playing these types of discussions with family or friends can be helpful in reducing anxiety and make you feel more relaxed when these questions arise. Finding the right partner can be a very satisfying experience. Many patients with primary immunodeficiency diseases choose to marry and have children. Whatever you choose for yourself, primary immunodeficiency disease does not have to be an obstacle to leading a full life.

## Post-Secondary Education for Young Adults Living with Primary Immunodeficiency Diseases

Many young adults with primary immunodeficiency diseases continue their education in post-secondary schools, including vocational and career schools, two- and four-year colleges and universities. Students should become knowledgeable about their rights and responsibilities as well as the responsibilities that post-secondary schools have toward the student.

Having this disease should not impede you from pursuing continuing education and/or living independently, but it will influence your decision in terms of obtaining healthcare, living conditions and caring for yourself. Some patients may choose to attend a local college or university and live at home. Others choose to go away to college, sometimes far

from home. Contact student support services at your colleges of choice to discuss your diagnosis and possible resources and accommodations.

Students requesting accommodations at the post-secondary level will want to work with the admissions office to identify the contact person at the school that can provide information on how to provide accommodations. Additional information regarding post-secondary education is available in this handbook. (See chapter titled “Adolescents Living with Primary Immunodeficiency Diseases.”) You can also consult the *Immune Deficiency Foundation (IDF) School Guide*, which can be ordered or downloaded at [www.primaryimmune.org](http://www.primaryimmune.org).

## Employment Decisions for Young Adults Living with Primary Immunodeficiency Diseases

When making employment decisions, you should consider your individual strengths while making adaptable changes that will address your limitations. Although some individuals may experience anxiety around making a career choice and having a primary immunodeficiency disease, it is important to remember that everyone has limitations in terms of their abilities. You can make good choices based on your own interests, abilities and health needs, which will lead to a successful career and a positive life experience. Because of the disease, however, you must understand your rights and benefits and how to best communicate with your employer. Insurance coverage is a critical consideration in choosing a job and or career—you will likely have to make career choices based on access to good health insurance.

(See chapter titled “Health Insurance.”) To learn more about choosing health insurance, visit the IDF Patient Insurance Center: [www.primaryimmune.org/patient-insurance-center](http://www.primaryimmune.org/patient-insurance-center).

For more information about your rights, contact these government agencies:

- U.S. Department of Justice Civil Rights Division, Office of ADA: [www.usdoj.gov](http://www.usdoj.gov)
- U.S. Department of Labor, Employment Standards Administration, Wage and Hour Division: [www.dol.gov](http://www.dol.gov)
- U.S. Equal Employment Opportunity Commission (EEOC): [www.eeoc.gov](http://www.eeoc.gov)

## Managing Stress

Learning how to cope with the emotional stress of living with a primary immunodeficiency disease is extremely important, and it can vary from individual to individual. Managing pain, dealing with the unpredictability of infection, and missing out on recreational, social and family activities can predispose you to feelings of sadness, isolation and anger. You may benefit from processing your feelings with close friends and family members. It is also essential that you connect with the primary immunodeficiency community. The value of having others who “get it” and understand the complications that are unique to these diseases can be very powerful. IDF ([www.primaryimmune.org](http://www.primaryimmune.org)) offers many programs to make those interpersonal connections. You can participate in the Young Adult Forum on IDF Friends ([www.idffriends.org](http://www.idffriends.org)), an online community specifically for patients and families living with primary immunodeficiency diseases. You can contact IDF and

connect directly with another young adult through peer support. You can also attend an in-person event, like the IDF National Conference, Retreat or a local patient meeting—they are all opportunities to connect with others. You may form invaluable relationships that can be both rewarding and supportive.

You may require further assistance to cope with the challenges and stress of living with a primary immunodeficiency disease. Changes in your overall outlook, feelings of hopelessness, sadness, irritability and isolation may indicate that you may be experiencing clinical depression. Consider seeking professional assistance if symptoms persist. Talking to a therapist cannot only be a helpful experience, but it also may be necessary if such symptoms begin to disrupt your daily life.

## Coordinating Your Healthcare and Being Your Own Healthcare Advocate

If you choose to move away from home or you need or want to change your primary care or other doctor, you will need to create a new healthcare team. If you were diagnosed as a child, your parents had the responsibility of making all healthcare decisions. Once you turn 18, you are legally considered an adult. At that point, your parents need your written permission to access healthcare records and to speak with your healthcare team. So, it is important that you and your parents work together with your healthcare providers

to help you take on the responsibility as your own healthcare manager.

Transitioning care from a pediatric setting to an adult setting whether home or away is a big step for parents and young adults alike. Whether transitioning to a completely new area or staying within the same care facility but assuming responsibility for your own care, you need to be your own best advocate. Therefore, it’s important for you to become familiar with all aspects of your care.

(Coordinating Your Healthcare and Being Your Own Healthcare Advocate continued)

**Recommended information to record and keep readily available in a journal or in IDF ePHR**

([www.idfephr.org](http://www.idfephr.org)):

- 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 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

**How you can advocate 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](http://www.primaryimmune.org) or 800-296-4433.

## Understanding the Importance of Treatment for Young Adults Living with Primary Immunodeficiency Diseases

As a young adult, you make decisions of your own. 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

patients, treatment is life-saving as well as life-long. Consult your immunologist about the vital role of your treatment in regards to your overall, long-term health.

## Searching for New Healthcare Providers for Young Adults Living with Primary Immunodeficiency Diseases

When researching new providers and facilities, you should fully understand your insurance benefits and what providers and facilities are covered. Be sure to choose healthcare providers who best suit your needs. The location of the potential healthcare providers may influence where you choose to live or attend school. If you are relocating or attending college away from home, you should research immunologists in that area. Consult your current providers for recommendations, or contact IDF to locate a specialist. Many immunologists are associated with universities that can support their research, so you could consider those universities and cities. If you are moving out of state, it is also important to remember that hospitals and clinics may not be able to accept the orders from a previous physician. You should establish care, if possible, before moving day, giving the new healthcare provider time to get to know you and time to request authorization for treatment from the insurance plan.

### Infusion Providers for Patients Receiving Immunoglobulin Therapy

It may not always be necessary to change infusion providers if you are relocating or if you are going away to college. If you are receiving infusions through a specialty pharmacy in a home care setting, you may be able to continue with the same provider. To find out if this could be the case, check with your current infusion provider several months before moving. Additionally, if a change in providers is required, the current provider should participate in coordinating the care and transition to the new provider.

If you are receiving infusions in a clinic or outpatient hospital setting, it will be important to coordinate the care in advance with as much notice as possible. For example, some colleges or universities may not allow infusions to be given 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 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 or delays in therapy which could impact your health.

## Summary of Young Adults Living with Primary Immunodeficiency Diseases

As a young adult, you make choices that impact your overall health. You can take control of your healthcare by taking steps to stay healthy, making informed decisions and keeping good records. Take advantage of resources from IDF that can help you through this transition. To balance your life, build strong

relationships with family and friends, pursue a career that suits your interests and abilities, and make time for recreation. These will help you find and build the courage and strength to manage your primary immunodeficiency disease.

# Adults Living with Primary Immunodeficiency Diseases



## Chapter 32



*Many adults with primary immunodeficiency diseases live full lives. The well-informed patient working with an attentive healthcare team can often pursue a career and live an active, productive life.*

## Introduction to Adults Living with Primary Immunodeficiency Diseases

Although the first primary immunodeficiency diseases were identified in children, there has been a growing awareness that adults also can have a primary immunodeficiency disease. Advances in medicine as well as earlier diagnosis and treatment of the childhood immunodeficiency diseases have allowed many patients born with a primary immunodeficiency disease to grow into adulthood. In other cases, many children born with apparently normal immune systems go on to develop a primary immunodeficiency disease later in adolescence or adulthood. Unfortunately, the Immune Deficiency Foundation (IDF) survey research has shown that adults with an undiagnosed primary immunodeficiency disease

will, on average, experience symptoms of their immunodeficiency for more than nine years before a diagnosis is made.

No matter how old you were when you were diagnosed, it is important for you 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 primary immunodeficiency diseases.

## Normalizing Your Life

Primary immunodeficiency diseases affect people in different ways, but, like everyone else, individuals with primary immunodeficiency diseases 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 that interfere with their level of

## (Normalizing Your Life continued)

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 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 primary immunodeficiency diseases 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.

**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 primary immunodeficiency diseases and make sure that you feel comfortable with that person. They should welcome and encourage your questions and input. Patients 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 patients who are curious, willing to learn about their health issues and treatments, and want to collaborate in their care. IDF can help you locate a specialist in your area, go to [www.primaryimmune.org](http://www.primaryimmune.org) or call 800-296-4433.

**Take advantage of resources.** 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](http://www.primaryimmune.org), and to continue asking questions of your healthcare providers.

**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 primary immunodeficiency diseases, often feel isolated and that they are struggling 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 another patient 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 Primary Immunodeficiency Diseases

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 be no longer 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 patients 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.

If you and your partner consider growing your family, it is important to understand the genetic implications of primary immunodeficiency diseases. Your immunologist or a genetic counselor can address these questions and concerns. (*See chapter titled "Inheritance."*)

## Managing Stress

Not everyone with the same disease is affected in the same way. It is typical for patients 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 patients feel and the ways they cope vary greatly from patient to patient. 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.

### (Managing Stress continued)

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 and Health Insurance for Adults Living with Primary Immunodeficiency Diseases

Adult patients, in choosing a job or career, 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.

Patients with primary immunodeficiency diseases work in all kinds of jobs. For many patients, 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.

## (Employment and Health Insurance for Adults Living with Primary Immunodeficiency Diseases continued)

Health insurance is a concern that all people with a primary immunodeficiency diseases 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 chapter titled “Health Insurance.”*)

## Coordinating Your Healthcare and Being Your Own Healthcare Advocate

It is essential for you learn how to coordinate your healthcare and become your own healthcare advocate by establishing a relationship with your healthcare providers. You have to learn to understand each other. Communication is the key, and the secret to effective communication is in your grasp.

Communication is how we share information. 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. Communication does not just use words; it also uses tone of voice, body language, emotion and touch. Noise interferes with communication. We live in a noisy world. “Noise” can come from our environment, our culture, our psyche, and our choice of words and how any of those affect how our words are understood.

To improve your care, it is important to pay careful attention to the communication with your healthcare team and the noise affecting it. Your healthcare team includes anyone who helps you get the care that you need. The members of your healthcare team 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.** When you first meet your provider, remember it may be the start of a long-term relationship, so smile, introduce yourself, shake hands, make eye contact and pay attention. 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. Do your best to keep the environmental noise down, such as silencing 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.

(Coordinating Your Healthcare and Being Your Own Healthcare Advocate continued)

**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 IDF ePHR, an online personal health record ([www.idfephr.org](http://www.idfephr.org)). 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 receive immunoglobulin (Ig) replacement therapy
- An 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

**Prepare your questions.** If you have been searching the Internet for information about your condition or treatment, do not bring in a stack of printouts. Instead, bring a list of the most important questions that you have. Do not expect that you are going to find a miracle cure for a chronic disease. Search reputable sources like [www.primaryimmune.org](http://www.primaryimmune.org) or [www.nlm.nih.gov](http://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.

**Feel comfortable asking questions.** 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. Remember, communication is a two-way process, and it is neither effective nor complete until the message is understood.

**At your initial visit, ask questions like:**

- What is the best way to get a message to you?
- 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, right after you say your hello; it will help them focus on what you need. Ask questions, but be concise. Ask your questions early, not at the end of your visit. Give the provider a chance to think and carefully consider your questions.

**Forget your stereotypes about your providers.** With their white coats and degrees on the wall, they seem like authority figures. 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. They are your partners in your healthcare.

## (Coordinating Your Healthcare and Being Your Own Healthcare Advocate continued)

Our attitudes or inhibitions can hamper communication by creating psychological noise. 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?

**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.

**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. How you can advocate for yourself:

- 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 your 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 when.
- Ask about resources for further information at the local, state and national level.
- Connect with IDF for additional resources: [www.primaryimmune.org](http://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. Identify and silence as much of the noise around your communication as you can. Apply the aforementioned principles. 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.

# Health Insurance



## Chapter 33



## Introduction to Health Insurance

Great progress has been made in the treatment of primary immunodeficiency diseases. However, these treatments often come at a significant financial burden to the patient or family living with these diseases. The majority of patients 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 frustrate patients and caregivers. Even individuals who have adequate insurance coverage often face expensive insurance premiums or high co-payments or co-insurance. Patients may be confused about their insurance

options. Others simply lack affordable health insurance and feel forced to stop treatment.

This chapter provides information regarding health insurance. While not designed to solve each and every problem, the information will help prepare you to be your own best advocate. It is essential to understand your family's current utilization of healthcare and learn to evaluate and compare medical insurance plans available in your area. The selection of an appropriate insurance plan can affect the health and finances of both the patient with primary immunodeficiency disease and family members. When it comes to your healthcare insurance coverage, never hesitate to ask questions and search for as many resources as possible.

## Group Health Insurance

Group health insurance coverage is a policy that is purchased by an employer and is offered to eligible employees of the company (and often to the employees' family members) as a benefit of working for that company. The majority of Americans have group health insurance coverage through their employer or the employer of a family member. Many people do not realize that health insurance is issued differently for different types of employers, and that, because insurance is regulated at the state level of government, the laws regarding health insurance offered by the different types of employers can vary significantly from state to state. Millions of Americans work for small employers, which for health insurance purposes are generally those with 50 employees or less.

Millions of other Americans get their health insurance coverage through large employers. Generally, those are business with more than 50 employees. The laws about how coverage can be issued to large groups are different than those for small groups, and premium rates are also determined differently. Federal law mandates that no matter what pre-existing health conditions small employer group members may have, no small employer or an individual employee can be turned down by an insurance company for group coverage. This requirement is known in the insurance industry as "guaranteed issue."

## COBRA

If you lose your job or resign, you are usually able to continue your group health insurance benefits via federal law called the Consolidated Omnibus Budget Reconciliation Act of 1985 (COBRA). However, COBRA does not apply to all employers; so many states have developed other continuation-of-coverage options for people who are not covered by COBRA. Also, many people leaving group insurance to buy individual health insurance privately have portability benefits required by another federal law.

You are responsible for paying the premium, which is usually kept at 102% of what your employer was paying on your behalf. (The 2% is for administrative fees). For job termination or a reduction in hours, COBRA's duration is normally 18 months. In the case of a divorce, separation or death of a spouse, COBRA may be available for up to 36 months. In the case of a dependent child ceasing to be a dependent child under the parent's employer plan, coverage may be extended up to 36 months. If you are deemed disabled by Social Security within 60 days of your

termination of employment or reduction in hours of employment, you are able to extend the COBRA continuation period from 18 months to 29 months. The extended period of time offered is designed to protect you until you become eligible for Medicare, since there is a 29 month waiting period before you can receive Medicare benefits.

When these situations, known as "qualifying events" occur, it is your responsibility, as the employee, to notify the human resources department of your employer (that person or group responsible for medical insurance) within 60 days or you lose the option.

For further information on COBRA coverage and your rights under COBRA law, you should contact the human resource department or the benefits manager within your organization or call your local Department of Labor.

## Individual Health Insurance

Individual health insurance is coverage that a person buys independently. It can be for an individual, a parent and dependent children, or a family. The majority of Americans get their health insurance coverage through an employer or through a government program, and some of the population purchases private health coverage on an individual basis. Each state separately regulates how individual policies may be marketed and sold.

Individual health insurance is very different than group health insurance, which is the type of insurance that is offered through an employer. Benefits in individual

plans are generally less extensive than what most people would receive through the group coverage they have through their employer. Individual consumers may be surprised to learn that some benefits that may be considered standard in a group policy may not be included in an individual plan.

Individual health insurance companies are much more limited than group insurance companies in their ability to "spread risk" among a large group of people, so the laws concerning individual health insurance are different in most states. This means that applicants for individual insurance will need to complete a medical

## (Individual Health Insurance continued)

questionnaire when applying for benefits and, unlike a group insurance policy, in most states a company can decide not to cover people with very serious medical conditions, like primary immunodeficiency diseases, deeming them uninsurable.

The Affordable Care Act (ACA) of 2010, commonly known as healthcare reform, has mandated the creation of state exchanges for all states. An exchange is a marketplace where individuals and small

employers will be able to shop for insurance coverage. They must be set up by October 1, 2013 and policies go into effect on January 1, 2014. Plans offered through the exchanges will be subject to the same restrictions against excluding coverage for those with pre-existing conditions as other health insurance plans. More information about state exchanges can be found under the Affordable Care Act section.

## Medicare

Medicare is a federal health insurance program that provides coverage for people over the age of 65, blind, disabled individuals, and people with permanent kidney failure or end-stage renal disease. The Medicare program is administered by the Centers for Medicare and Medicaid Services (CMS) and pays only for medical services and procedures that have been determined as “reasonable and necessary.” Medicare is divided into four parts—Parts A, B, C and D.

**Part A** covers inpatient hospital services and certain follow-up care. This includes the cost of lab tests, x-rays, nursing services, meals, semi-private rooms, medical supplies, medications, necessary appliances, and operating and recovery rooms.

**Part B** covers physician’s services and other medical expenses. Medicare Part B will cover both the intravenous immunoglobulin (IVIG) product and administration when provided in a physician’s office or in the hospital outpatient setting. The coverage determination for immunoglobulin (Ig) therapy is reviewed by each Medicare regional carrier through their medical policy department. Each carrier will issue

their own local coverage determination, which outlines the specific coverage guidelines for the use of Ig therapy. The Medicare Modernization Act created a home infusion coverage provision only for patients with primary immunodeficiency diseases.

While the law was written to only include coverage and reimbursement for the Ig product itself and to exclude coverage for items and services related to the infusion, the Medicare IVIG Access Act was signed into law in January 2013, creating a three-year demonstration project allowing for the payment of home infusion services for Medicare patients with primary immunodeficiency diseases to be implemented within one year of its signing. The demonstration project should prove the cost effectiveness of allowing Medicare patients with primary immunodeficiency diseases access to home infusions of IVIG, thus paving the way for a permanent fix to this issue.

Subcutaneous immunoglobulin (SCIG) therapy in the home setting is processed through the Medicare Part B DME (durable medical equipment) benefit. Beneficiaries must pay a monthly premium and a

## (Medicare continued)

small deductible each year for all approved services covered under Part B.

**Part C** (Medicare Advantage) plans allow you to choose to receive all of your healthcare services through a provider organization. These plans may help lower your costs of receiving medical services, or you may get extra benefits for an additional monthly fee, such as hearing, vision and dental benefits. You must have both Parts A and B to enroll in Part C. You should check with individual plans for how they cover Ig therapy, as like private insurance, the benefits will differ from plan to plan.

**Part D** the Medicare Prescription Coverage program (Medicare Part D) went into effect on January 1, 2006. Anyone who has Medicare coverage can choose the prescription coverage benefit. The prescription benefit coverage was passed by Congress to give Medicare beneficiaries more options for prescription drug coverage that had never before been covered under the Medicare program. As it relates to coverage of IVIG, Medicare Part D program does not cover Ig in the home setting for those who have a primary immunodeficiency disease. However, Medicare Part D

may cover Ig in the home for other disease states. CMS administers the Part D program through contracts with commercial and private payers referred to as Medicare Prescription Drug Plans (PDPs). To learn more about the prescription drug coverage go to [www.medicare.gov](http://www.medicare.gov), or call 800-MEDICARE (800-633-4227).

For most of these services, Medicare pays 80% of the bill, and the beneficiary pays the 20% coinsurance. You must first have Part A before receiving Part B. If you apply for Social Security disability, you will receive Medicare benefits after being on disability for two years.

Individuals may also consider purchasing a Medigap (supplemental insurance) policy, which differ from state to state. Medigap policies help pay some of the healthcare costs that your original Medicare plan will not cover. Some of these plans will help pay for the 20% coinsurance under the Medicare Part B program. To learn more about the various plans and coverage guidelines go to [www.medicare.gov/medigap](http://www.medicare.gov/medigap), or call 800-MEDICARE (800-633-4227).

## Medicaid

Medicaid, jointly funded by the federal and state governments, serves as in the U.S. primary source of health insurance coverage for low-income populations, as well as certain health categories, including persons who are blind, aged, disabled or pregnant.

Medicaid enrollment criteria also vary from state to state, but coverage is usually available only to those who are not eligible for any other type of health insurance and meet poverty guidelines. Each state has a pre-determined income level that an individual or

family must meet to qualify for Medicaid benefits. The local office of the State Department of Social Services is responsible for reviewing applications and managing eligibility requirements. Some states require Medicaid beneficiaries to join managed care plans. Medicaid programs may require prior authorization for certain forms of treatment or prescription drugs. This means that your physician must contact Medicaid to obtain approval for reimbursement of the treatment before you receive it.

## State Assistance Programs

Your state may have a special assistance program for people with particular chronic conditions. Most of these programs are funded by state and local budgets and are designed to meet the needs of adults and/or children who are not eligible for any other medical coverage. They may also serve as a secondary or supplemental coverage to Medicaid. The level of coverage available will change according to such variables as state needs and available funding. These programs may be identified under such names as Children with Special Health Care Needs, Crippled Children's Services or Children's Medical Services.

Coverage for children with a primary immunodeficiency disease may be severely restricted or not available at all. It is best to check with your local sources of information for eligibility information before considering this as a coverage option. Supplemental Security Income (SSI) makes monthly payments to aged, disabled and blind people with limited income and resources. Children, as well as adults, may qualify for SSI payments. Eligibility and benefits vary by state, but more information can be obtained by contacting your local Social Security Office.

## State Children's Health Insurance Program (SCHIP)

As part of the Balanced Budget Act of 1997, Title XXI or State Children's Health Insurance Program (SCHIP) of the Social Security Act was passed in late 1997. SCHIP gives grants to states to provide health insurance coverage to uninsured children up to 200% of the federal poverty level (FPL). States may provide this coverage by expanding Medicaid or by expanding and creating a separate state children's health insurance program. The program's primary purpose is to help children in working families with incomes too high to qualify for Medicaid but too low to afford private family coverage. Although benefits vary from state to state, children generally are eligible for regular check-ups, immunizations, eyeglasses, doctor visits, prescription drug coverage, and hospital care. Based on income levels, states can impose premiums, deductibles, or fees for some services. Since coverage and benefits do vary, it is important that families investigate the options available in their respective state.

## Understanding Health Plans

Most health insurance companies offer several types of programs with many variations in deductibles, copayments and covered services. Review the details of any specific plan very carefully before purchasing to ensure it will meet the specific needs of you and your family. Below is a description of the different types of plans offered through insurance companies, starting with the most restrictive and typically least expensive plan.

**HMO** is a Health Maintenance Organization. As a member of an HMO, you select a primary care physician from a list of doctors in that HMO's network. Your primary care physician will be the first medical provider you call or see for a medical condition. They will make any needed referrals to a medical specialist. Typically, these specialists will be part of the HMO network. If you obtain care without your primary care physician's referral or obtain care from a non-network member, you will be responsible for paying the entire bill (with exceptions for emergency care). Normally HMOs have a copayment for the visit or service. This is the most restrictive type of plan.

**POS** is a Point-of-Service Plan. It is a type of managed care plan that is an HMO with an out-of-network option. You can decide whether to go to a network provider and pay a flat dollar amount or to an out-of-network provider and pay a deductible and/or a coinsurance charge.

**PPO** is a Preferred Provider Organization. As a member of a PPO, you can use the doctors and hospitals within the PPO network or go outside of the network for care. You do not need a referral to see a specialist. If you obtain care from a medical provider outside of the PPO network, you will pay more for the service. For example, a PPO might pay 80-90% of the cost for a visit with an in-network doctor, but only 60-70% of the cost for a visit to a non-network doctor. You will typically pay a copayment for each office visit. You will usually be responsible for paying an annual deductible.

**Indemnity** plans are commonly known as a fee for service or traditional plans. If you select an Indemnity plan, you have the freedom to visit any medical provider. You do not need referrals or authorizations; however, some plans may require you to pre-certify for certain procedures. Most indemnity plans require you to pay a deductible. After you have paid your deductible, indemnity policies typically pay a percentage of "usual and customary" charges for covered services; often the insurance company pays 80% and you pay 20%. Most plans have an annual out-of-pocket maximum, and once you have reached this they will pay 100% of all "usual and customary" charges for covered services. Many health insurance companies have moved away from indemnity plans. This is the least restrictive, therefore typically the most expensive type of health plan.

**FSA and HSA** - Flexible Spending Accounts (FSA) are accounts offered and administered by employers that allow employees to set aside, out of their paycheck, pretax dollars to pay for the employee's share of insurance premiums or medical expenses not covered by the employer's health plan. The employer may also make contributions to a FSA. Typically, benefits or cash must be used within the given benefit year or the employee loses the money. FSAs can also be provided to cover childcare expenses, but those accounts must be established separately from medical FSAs.

**Health Savings Accounts (HSA)** are medical savings accounts available to taxpayers who are enrolled in insurance plans that meets federal rules. The funds contributed to the account are not subject to federal income tax at the time of deposit. Funds must be used to pay for qualified medical expenses. Unlike a FSA, funds roll over year to year if you do not spend them.

For further information about FSA and HSA, you should contact the human resource department or the benefits manager within your organization.

## Health Insurance Portability and Accountability Act of 1996 (HIPAA)

We all are susceptible to a variety of events in life that may affect health insurance coverage. Situations such as the onset of a chronic illness or disabling disease, changing jobs or a business closing can have adverse consequences when locating or attempting to keep your health insurance coverage. HIPAA protects health insurance coverage for workers' families when they change or lose their jobs. Due to the fact that the HIPAA law is very complex and contains many more provisions than indicated in this writing, we recommend that you contact your employer's benefits administrator or your State Insurance Commissioner's office for further information about how HIPAA can affect you and/or your family.

### Key Provisions of HIPAA

**Group Health Insurance** - Employees can credit time spent under their previous employer's plan satisfying a pre-existing exclusion towards the new employer's plan, as long as they do not have more than a 63 day break between coverage.

### Moving from Group Health to an Individual

**Health Plan** - If you are no longer eligible for group coverage, you are able to obtain coverage with an individual health plan if:

- You have an aggregate 18 months or more of previous coverage under a group health, government or church plan.
- You have had no lapse in coverage longer than 63 days.
- You are not eligible under another group plan, Medicare or Medicaid.
- You do not have any other health insurance coverage.
- You have exhausted any eligible COBRA coverage.
- You were not terminated from your most recent prior coverage due to non-payment of premiums or fraud.

Be aware that your state law may provide for greater protection than HIPAA, but not less than the minimum requirement mandated by the HIPAA law.

## The Affordable Care Act

The Affordable Care Act (ACA) of 2010, also known as healthcare reform, puts in place strong consumer protections, provides new coverage options and gives you the tools you need to make informed choices about your health. In this section, learn about how the law affects you and the primary immunodeficiency disease community as it relates to private health insurance. For more information related to the ACA, visit [www.healthcare.gov](http://www.healthcare.gov). As the law is implemented, IDF will

provide updated information in the IDF Patient Insurance Center: [www.primaryimmune.org/patient-insurance-center](http://www.primaryimmune.org/patient-insurance-center).

### Young Adult Coverage

insurance policy until they turn 26 years old. Before the ACA, insurance companies could remove enrolled children usually at age 19, sometimes older for full-time students. Now, most health plans that cover children

## (The Affordable Care Act continued)

must make coverage available to children up to age 26. By allowing children to stay on a parent's plan, the law makes it easier and more affordable for young adults to get health insurance coverage. Your children can join or remain on your plan even if they are married, not living with you, attending school, not financially dependent on you or eligible to enroll in their employer's plan. There is one temporary exception: *Until 2014, "grandfathered" group plans do not have to offer dependent coverage up to age 26 if a young adult is eligible for group coverage outside their parent's plan. Your insurer was required to provide you notice of its decision to remain a grandfathered plan. If you are unsure about your plan's status, ask your employer or insurer.*

### Lifetime and Annual Limits

The ACA prohibits health plans from putting a lifetime dollar limit on most benefits you receive. The law also restricts and phases out the annual dollar limits a health plan can place on most of your benefits and does away with these limits entirely in 2014. Before the healthcare law, many health plans set an annual limit, which was a dollar limit on their yearly spending for your covered benefits. Many plans also set a lifetime limit, which was

a dollar limit on what they would spend for your covered benefits during the entire time you were enrolled in that plan. You were required to pay the cost of all care exceeding those limits.

### Affordable Insurance Exchanges

Affordable Insurance Exchanges are designed to make buying health coverage easier and more affordable. Starting in 2014, exchanges will allow individuals and small businesses to compare health plans, get answers to questions, find out if they are eligible for tax credits for private insurance or health programs like the Children's Health Insurance Program (CHIP), and enroll in a health plan that meets their needs. An exchange can help you look for and compare private health plans, get answers to questions about your health coverage options, find out if you are eligible for health programs or tax credits that make coverage more affordable, and enroll in a health plan that meets your needs. For individuals and families, the exchange is a single place where you can enroll in private or public health insurance coverage.

## Comparing Plans

It is important to consider specific issues when deciding on a health insurance policy. It cannot be emphasized enough that it is critical for you to be your own best advocate when dealing with your health plan

- **You should compare:** the cost of premium, coinsurance, copayments, deductibles, and the prescription coverage.
- **Ask such questions as:** How are chronic conditions like primary immunodeficiency diseases covered

within the plan? What about referrals to specialists? What are the procedures? Do they have restrictions on prescription drugs?

- **Read your policy** and then ask your personnel department, IDF and any other resource you can find lots of questions. Try to keep current with information concerning the new rules affecting your policy.
- **Review your medical bills** to check for mistakes; billing errors occur more often than you might think.



## (Comparing Plans continued)

- **Keep important information** such as your policy number, your ID number, insurer's address and phone number as well as you doctors' contact information in one place to refer to whenever you communicate with your insurer. Use IDF ePHR to keep this and all of your medical information in one place: [www.idfephr.org](http://www.idfephr.org).
- **Many employers offer open enrollment** once a year when you may change your coverage to another plan offered by your employer. Ask your employer if and when an open enrollment period is offered. If you have difficulty getting benefits through your employer, consider coverage through associations, schools, professional groups, farm groups, or local chambers of commerce. You may qualify for individual or group benefits.
- **Document each time you contact your insurer.** Get the full name and title of each person you talk with whenever you contact your insurer. This information will be important if you experience difficulties with your coverage and need to document your situation in writing.

If your problem becomes more complicated, there are other courses of action. You, and/or your physician, may appeal to the medical director of the insurance company and may need to work with the provider to submit additional justification of your claim. Often, in the case of primary immunodeficiency diseases, insurers need to be educated as to what the condition is and what the approved forms of treatment are. Most of the manufacturers of Ig offer reimbursement support services for their products and can be an excellent source of information.

There may come a time when an insurance company terminates your policy. If it does so for any other reason than bankruptcy, they are required by state and federal law to find you new coverage. Enforcing this law is up to the State Insurance Commissioner. Arbitrary cancellation is illegal.

## Summary

Some patients are fortunate to never have to experience health insurance issues. Others may spend many hours in a seemingly endless search for insurance coverage or adequate reimbursement. Never hesitate to seek assistance from resources. Health insurance remains a complex issue in America today. It is important for all individuals to be educated about their health insurance, as it directly impacts the well-being of the individual and their family.

Every effort was made to assure that the information provided in this chapter was accurate at the time of

publication. However, because matters regarding health insurance change frequently, scan the QR code to the right to visit the IDF Patient Insurance Center for updated information.



## Healthcare and Insurance Related Acronyms

ACA:	Affordable Care Act	HSA:	Health Savings Account
ACO:	Accountable Care Organization	MAP:	Medicare Advantage Plan
CAP:	Consumer Assistance Program	MLR:	Medical Loss Ratio
CHIP:	Children’s Health Insurance Program	OEP:	Open Enrollment Period
COB:	Coordination of Benefits	OON:	Out-of-Network
COBRA:	Consolidated Omnibus Budget Reconciliation Act	OOP:	Out-of-Pocket
DME:	Durable Medical Equipment	PBM:	Pharmacy Benefit Manager
EOB:	Explanation of Benefits	PCP:	Primary Care Physician
EPO:	Exclusive Provider Organization	PDP:	Prescription Drug Plan
FMLA:	Family and Medical Leave Act	PFTs:	Pulmonary Function Tests
FPL:	Federal Poverty Level	POS:	Point-of-Service Plan
FSA:	Flexible Spending Account	PPO:	Preferred Provider Organization
GEP:	General Enrollment Period	SEP:	Special Enrollment Period
HDHP:	High Deductible Health Plan	SNF:	Skilled Nursing Facility
HHS:	Health and Human Services	TPA:	Third Party Administrator
HIPAA:	Health Insurance Portability and Accountability Act	UCR:	Usual, Customary and Reasonable
HMO:	Health Maintenance Organization		
HRA:	Health Reimbursement Arrangement		

## Healthcare Plans and Systems

**Catastrophic Plan:** A healthcare plan that only covers certain types of expensive care, like hospitalizations. It may also include plans that have a high deductible, so that your plan begins to pay only after you have first paid up to a certain amount for covered services.

**Children’s Health Insurance Program (CHIP):** Insurance program jointly funded by state and federal government that provides health insurance to low-income children and, in some states, pregnant women in families who earn too much income to qualify for Medicaid but cannot afford to purchase private health insurance coverage.

**Durable Medical Equipment (DME):** Specialized equipment that is prescribed by a healthcare provider and furnished by a supplier, which is to be used in a patient’s home or institutions constituting a home. DME may include but are not limited to items such as standard oxygen delivery systems, hospital bed, wheelchair, walker, traction apparatus, intermittent positive pressure breathing machine, brace, crutch or any other items that are determined Medically Necessary.

## (Healthcare Plans and Systems continued)

**Exclusive Provider Organization (EPO) Plan:** A managed care plan in which services are covered only if you go to doctors, specialists, or hospitals in the plan's network (except in an emergency).

**Flexible Spending Account (FSA):** Accounts offered and administered by employers that allow employees to set aside, out of their paycheck, pretax dollars to pay for the employee's share of insurance premiums or medical expenses not covered by the employer's health plan. The employer may also make contributions to a FSA. Typically, benefits or cash must be used within the given benefit year or the employee loses the money. Flexible spending accounts can also be provided to cover childcare expenses, but those accounts must be established separately from medical FSAs.

**Health Maintenance Organization (HMO):** An insurance plan that usually limits coverage to care from doctors who work for or contract with the HMO. Generally the plan will not cover out-of-network care except in an emergency, and may require you to live or work in its service area to be eligible for coverage. HMOs often provide integrated care and focus on prevention and wellness.

**Health Reimbursement Arrangement (HRA):** A medical savings account to which employers contribute funds that can cover an employee's costs not covered by the plan. The employer can choose whether or not to allow unused funds to rollover to the following year.

**Health Savings Account (HSA):** A medical savings account available to taxpayers who are enrolled in a High Deductible Health Plan (HDHP) that meets federal rules. In 2013, to qualify for use with an HSA, an HDHP plan must have a minimum deductible of \$1,250 for an individual plan and \$2,500 for a family plan, and an out-of-pocket maximum of \$6,250 for an individual plan and \$12,500 for a family plan (these

number are adjusted annually). The funds contributed to the account are not subject to federal income tax at the time of deposit. Funds must be used to pay for qualified medical expenses. Unlike a Flexible Spending Account (FSA), funds roll over year to year if you do not spend them.

**High Deductible Health Plan (HDHP):** A plan that features higher deductibles than traditional insurance plans. HDHPs can be combined with a health savings account (under certain circumstances) or a health reimbursement arrangement to allow you to pay for qualified out-of-pocket medical expenses on a pre-tax basis. (*See Health Savings Account [HSA].*)

**Managed Care Plan:** A plan that generally provides comprehensive health services to its' members, and offers financial incentives for patients to use the providers who belong to the plan. Examples include: health maintenance organizations (HMOs), preferred provider organizations (PPOs), exclusive provider organizations (EPOs), and point of service plans (POs).

**Medicaid:** A state-administered health insurance program for low-income families and children, pregnant women, the elderly, people with disabilities, and in some states, other adults. The federal government provides a portion of the funding and sets guidelines. States also have choices in how they design their program, so Medicaid programs and eligibility vary state by state and may have a different name in your state.

**Medicare:** A federal health insurance program for people who are age 65 or older and certain younger people with disabilities. It also covers people with End-Stage Renal Disease.

**Medicare Part A:** Hospital insurance that helps cover inpatient care in hospitals, skilled nursing facility, hospice and home care.

(Healthcare Plans and Systems continued)

**Medicare Part B:** Medical coverage that helps to cover medically-necessary services like doctors' services, outpatient care, home health services, other medical services and preventive services.

**Medicare Advantage (Medicare Part C):** A type of Medicare health plan offered by a private company that contract with Medicare to provide Medicare Part A and Part B benefits.

**Medicare Part D:** A program that helps pay for prescription drugs for people with Medicare who join a plan that includes Medicare prescription drug coverage.

**Point-of-Service Plan (POS) Plan:** A type of plan in which you pay less if you use doctors, hospitals, and other healthcare providers that belong to the plan's network. POS plans may also require you to get a referral from your primary care doctor in order to see a specialist.

**Preferred Provider Organization (PPO) Plan:** A type of healthcare plan that contracts with medical providers, such as hospitals and doctors, to create a

network of participating providers. You pay less if you use providers that belong to the plan's network. You can use doctors, hospitals and providers outside of the network for an additional cost.

**Pharmacy Benefit Manager (PBM):** A third party administrator of prescription drug programs. They are primarily responsible for processing and paying prescription drug claims. They also are responsible for developing and maintaining the formulary, contracting with pharmacies, and negotiating discounts and rebates with drug manufacturers.

**Primary Care Physician (PCP):** A physician who usually is the first health professional to examine a patient and who recommends secondary care physicians, medical or surgical specialists with expertise in the patient's specific health problem, if further treatment is needed. Formerly known as the family doctor.

## Health Insurance and Reform

**Accountable Care Organization (ACO):** A group of healthcare providers who give coordinated care, chronic disease management, and thereby improve the quality of patient care. The organization's payment is tied to achieving healthcare quality goals and outcomes that result in cost savings. ACOs can include various types of doctors – primary care, specialists, etc. – as well as other medical providers (nurses, physician's assistants, etc.) and institutions (hospitals, multi-physician practices).

**Affordable Care Act (ACA):** The comprehensive healthcare reform law enacted in March 2010. The law was enacted in two parts: The Patient Protection and Affordable Care Act was signed into law on March 23, 2010 and was amended by the Healthcare and Education Reconciliation Act on March 30, 2010. Affordable Care Act refers to the final, amended version of the law.

## (Health Insurance and Reform continued)

**Allowed Charge:** Discounted fees that insurers will recognize and pay for covered services. Insurers negotiate these discounts with providers in their health plan network, and network providers agree to accept the allowed charge as payment in full. Each insurer has its own schedule of allowed charges.

**Annual Limit:** A cap on the benefits your insurance company will pay in a year while you are enrolled in a health insurance plan. Annual caps are sometimes placed on particular services such as prescriptions or hospitalizations. Annual limits may be placed on the dollar amount of covered services or on the number of visits for a particular service. After the annual limit is reached, you must pay all associated healthcare costs for the rest of the year. Under the Affordable Care Act, all group health plans (existing and new) and all new individual policies (issued after 3/23/2010) must phase out annual limits. Plan or policy years starting after 9/23/2011 but before 9/23/2012 cannot have an annual limit lower than \$1.25 million. For the following year, plans cannot have an annual limit lower than \$2 million. No annual dollar limits are allowed on “essential” services in 2014.

**Balance Billing:** The practice of billing a patient for charges not paid by his/her insurance plan because the charges are in excess of covered amounts. Balance billing amounts will often be charges that are above the usual and customary rates.

**Benefits:** The healthcare items or services covered under a health insurance plan. Covered benefits and excluded services are defined in the health insurance plan’s coverage documents. In Medicaid or CHIP, covered benefits and excluded services are defined in state program rules.

**Biosimilar Biological Products:** The generic version of more complicated medications. Technically, they are reproductions of biotechnologically manufactured biopharmaceuticals that partially mimic proteins naturally present in the body.

**Care Coordination:** The process of organizing your treatment across several healthcare providers. Medical homes and accountable care organizations are two common ways to coordinate care.

**Chronic Disease Management:** An integrated care approach to managing illness – typically using multiple healthcare providers including various physicians, nurses, and others – which includes screenings, check-ups, monitoring and coordinating treatment, and patient education. It can improve quality of life while reducing healthcare costs if you have a chronic disease, by preventing or minimizing the effects of a disease.

**Claim:** A request for payment that you or your healthcare provider submits to your health insurer when you get items or services you think are covered.

**COBRA (Consolidated Omnibus Budget Reconciliation Act):** A federal law that may allow you to temporarily keep health coverage if your employment ends, you lose coverage as a dependent of the covered employee, or if there is another qualifying event. COBRA requires you pay 100% of the premiums, including the share the employer used to pay, plus a small administrative fee.

**Co-insurance:** A form of medical cost sharing in a health insurance plan that requires an insured person to pay a stated percentage of medical expenses after the deductible amount, if any, was paid. Once any deductible amount and coinsurance are paid, the insurer is responsible for the rest of the reimbursement for covered benefits up to allowed charges: the individual could also be responsible for any charges in excess of what the insurer determines to be ‘usual, customary and reasonable.’

**Co-payment:** A flat dollar amount you must pay for a covered program. Example: you may have to pay a \$15 copayment for each covered visit to a primary care doctor.

(Health Insurance and Reform continued)

**Cost Sharing:** The share of costs covered by your insurance that you pay out-of-pocket. Generally includes deductibles, coinsurance and copayments, or similar charges, but it does not include premiums, balance billing amounts for non-network providers, or the cost of non-covered services. Cost sharing in Medicaid and CHIP also includes premiums.

**Creditable Coverage:** Health insurance coverage under any of the following: a group health plan; individual health insurance; student health insurance; Medicare; Medicaid; CHAMPUS and TRICARE; Veterans Administration (VA) coverage; the Federal Employees Health Benefits Program; Indian Health Service; the Peace Corps; Public Health Plan (any plan established or maintained by a State, the U.S. government, a foreign country), including the new federal high risk pool (PCIP, or the Pre-Existing Condition Insurance Program); Children's Health Insurance Program (CHIP) or a state health insurance high risk pool. If you have prior creditable coverage, it will reduce the length of a pre-existing condition exclusion period under new job-based coverage..

Depending on state law, this may also apply to other types of coverage, such as state high risk pools, in your state.

**Deductible:** The amount you must pay for covered care before your health insurance begins to pay. Insurers apply and structure deductibles differently. Example: under one plan, a comprehensive deductible might apply to all services while another plan might have separate deductibles for benefits such as prescription drug coverage. Some plans may also cover some services before the deductible is met, such as annual exams.

**Dependent Coverage:** Insurance coverage for family members of the policyholder, such as spouses, children, or partners. Under the Affordable Care Act, plans must cover children up to age 26 on their parent's policy.

**Disability:** A limit in a range of major life activities. This includes activities like seeing, hearing, walking and tasks like thinking and working. Different state, federal or private programs may have different disability standards. A legal definition of disability can be found at: [www.ada.gov/pubs/ada.htm](http://www.ada.gov/pubs/ada.htm)

**Donut Hole, Medicare Prescription Drug:** Most plans with Medicare prescription drug coverage (Part D) have a coverage gap, called a donut hole. This means that after you and your drug plan have spent a certain amount of money for covered drugs you have to pay all costs out-of-pocket for your prescriptions up to a yearly limit. Once you have spent up to the yearly limit, your coverage gap ends and your drug plan helps pay for covered drugs again.

**Emergency Room Services:** Evaluation and treatment of an illness, injury or condition that needs immediate medical attention in an emergency room.

**Essential Health Benefits:** A set of healthcare service categories that must be covered by certain plans, starting in 2014. The Affordable Care Act defines essential health benefits to "include at least the following general categories and the items and services covered within the categories: ambulatory patient services; emergency services; hospitalization; maternity and newborn care; mental health and substance use disorder services, including behavioral health treatment; prescription drugs; rehabilitative and habilitative services and devices; laboratory services; preventive and wellness services and chronic disease management; and pediatric services, including oral and vision care."

All new plans sold to individuals and small businesses, including those offered in Exchanges, and all Medicaid state plans must cover these services by 2014.

Starting with plan years or policy years that began on or after September 23, 2010, health plans can no longer impose a lifetime dollar limit on spending for

## (Health Insurance and Reform continued)

these services. All plans, except grandfathered individual health insurance policies, must begin phasing out annual dollar spending limits for these services starting with plan/policy years that began on or after September 23, 2010. For the majority of health insurance plans, annual dollar limits on essential health benefits will be completely phased out by 2014.

The Department of Health and Human Services has issued guidance outlining a process for selecting EHBs in each state, based on existing coverage options in the small group and other employer plans. Learn more about this process at [www.healthcare.gov](http://www.healthcare.gov).

**Exchange:** New state-based organizations that will be set up to create a more organized and competitive market place for individuals and small businesses to buy health insurance. Exchanges will offer a choice of different health plans, which meet certain benefits and cost standards, and provide information to help consumers better understand their options.

**Exclusions:** Items or services that are not covered under a contract for insurance and which an insurance company won't pay. Example: your policy may not cover certain therapies or medications.

**Explanation of Benefits (EOB):** A form or document sent by the insurance company to both enrollees and providers. The document provides necessary information about claim payments and patient responsibility amounts of healthcare services however it is not a bill. It should include data on what was paid or is in process of being reviewed for payment by the insurance company. Your EOBs may help you track your healthcare expenditures and serve as a reminder of the medical services you received during the past several years.

**Family and Medical Leave Act (FMLA):** A federal law that guarantees up to 12 weeks of job protected leave for certain employees when they need to take time off due to serious illness or disability, to have or adopt a child or to care for another family member. When on leave under FMLA, you can continue coverage under your job-based plan. Learn more about FMLA at: <http://www.dol.gov/whd/fmla>.

**Federal Poverty Level (FPL):** A measure of income level issued annually by the Department of Health and Human Services. FPL is used to determine eligibility for certain programs and benefits. For more information on FPL please visit: <http://aspe.hhs.gov/poverty/12poverty>.

**Fee for Service:** A reimbursement plan in which doctors and other healthcare providers are paid for each service performed, such as for tests and office visits.

**Flexible Benefits Plan:** Offers employees a choice between various benefits including cash, life insurance, health insurance, vacations, retirement plans, and child care. Although a common core of benefits may be required, you can choose how your remaining benefit dollars are to be allocated for each type of benefit from the total amount promised by the employer. Sometimes you can contribute more for additional coverage. Also known as a Cafeteria plan or IRS 125 Plan.

**Formulary:** A list of drugs your insurance plan covers. May include how much you pay for each drug. If the plan categorizes drugs into different groups requiring different co-pays, also known as tiers, then the formulary may list drugs by these tiers. Formularies may include both generic drugs and brand-name drugs.

(Health Insurance and Reform continued)

**Fully Insured Job-based Plan:** A plan in which the employer contracts with an insurer to assume financial responsibility for the enrollees' medical claims and for all incurred administrative costs.

**General Enrollment Period:** Medicare beneficiaries who did not enroll in Part B when they first became eligible for Medicare may elect Part B coverage during the General Enrollment Period, which extends from January 1 through March 31 each year. Enrollment becomes effective on July 1 of the same year.

**Grandfathered Health Plan:** As defined in the Affordable Care Act, a group health plan that was created—or an individual health insurance policy that was purchased—on or before March 23, 2010. Grandfathered plans are exempt from many changes required under the Affordable Care Act. Plans or policies may lose their grandfathered status if they make certain significant changes that reduce benefits or increase costs to consumers. A health plan must disclose in its plan materials whether it considers itself to be a grandfathered plan and must also advise consumers how to contact the U.S. Department of Labor or the U.S. Department of Health and Human Services with questions. (*See New Plan.*)

**Guaranteed Issue:** A requirement that health plans must permit you to enroll regardless of health status, age, gender or other factors that might predict the use of health services. Except in some states, guaranteed issue does not limit how much you can be charged if you enroll.

**Guaranteed Renewal:** A requirement that your health insurance issuer must offer to renew your policy as long as you continue to pay premiums. Except in some states, guaranteed renewal does not limit how much you can be charged if you renew your coverage.

**Healthcare Workforce Development:** The use of incentives and recruiting to encourage people to enter into healthcare professions such as primary care and to encourage providers to practice in underserved areas.

**Health Insurance Portability and Accountability Act (HIPAA):** A 1996 federal act that eliminated discrimination by health insurers for those with preexisting medical conditions. Example: when leaving a group policy, patients cannot be denied coverage in other group policies based on a pre-existing medical condition. In order to qualify for HIPAA, you must meet the following two conditions: (1) you have had 18 months of consecutive, continuous prior health coverage, and (2) you must get new coverage with another group medical plan within 63 days. Many insurance plans offer open-enrollment periods when anyone can join, regardless of pre-existing conditions.

**Health Status:** Refers to your medical conditions (both physical and mental health), claims experience, receipt of healthcare, medical history, genetic information, evidence of insurability and disability.

**HIPAA Eligible Individual:** Your status once you have had 18 months of continuous creditable health coverage. To be HIPAA eligible, at least the last day of your creditable coverage must have been under a group health plan: you also must have used up any COBRA or state continuation coverage for which you are eligible; you must not be eligible for Medicare or Medicaid; you must not have other health insurance; and you must apply for individual health insurance within 63 days of losing your prior creditable coverage. When you are buying individual health insurance, HIPAA eligibility gives you greater protections than you would otherwise have under state law.



## (Health Insurance and Reform continued)

**Home Healthcare:** Healthcare services and supplies in your home that a doctor approves under a plan of care established by your doctor.

**Individual Health Insurance Policy:** Policies for people who are not connected to job-based coverage. Individual health insurance policies are regulated under state law. Note that the phrase “individual policies” when used in this way, policies that are unconnected to employment, can be used for policies that cover a single person or multiple people (families, mother and dependent child, husband and wife, etc.).

**Individual Responsibility:** Under the Affordable Care Act, starting in 2014, you must be enrolled in a health insurance plan that meets basic minimum standards. If you aren't, you may be required to pay a penalty. Exempt from this are people with very low income for whom coverage is unaffordable based in their household income, or for other reasons, including religious beliefs.

**In Network Provider:** A physician, certified nurse midwife, hospital, skilled nursing facility, home healthcare agency, or any other duly licensed or certified institution or health professional under contract with your insurance provider.

**Insurance Co-Op:** A non-profit entity in which the same people who own the company are insured by the company. Cooperatives can be formed at a national, state or local level, and can include doctors, hospitals and businesses as member-owners.

**Job-based Health Plan:** Coverage that is offered to an employee (and often his or her family) by an employer.

**Lifetime Limit:** A cap on the total lifetime benefits you may get from your insurance policy. An insurance company may impose a total lifetime dollar limit on benefits (like \$1 million) or limit specific benefits (like a \$200,000 lifetime cap on organ transplants or one gastric bypass per lifetime) or a combination of the two. After a lifetime limit is reached, the insurance plan will no longer pay for covered services. By September 23, 2011, the majority of policies should not have lifetime dollar limits on essential health benefits.

**Long-Term Care:** Medical and non-medical services provided to people who are unable to perform basic activities of daily living such as dressing or bathing. Long-term supports and services can be provided at home, in the community, in assisted living or in nursing homes. Individuals may need long-term supports and services at any age. Medicare and most health insurance plans do not pay for long-term care.

**Managed care provisions:** Features within health plans that provide insurers with a way to manage the cost, use and quality of healthcare services received by group members. Examples of managed care provisions include:

- **Preadmission certification** - Authorization for hospital admission given by a healthcare provider to a group member prior to hospitalization. Failure to obtain a preadmission certification in non-emergency situations reduces or eliminates the healthcare provider's obligation to pay for services rendered.
- **Utilization review** - The process of reviewing the appropriateness and quality of care provided to patients. Utilization review may take place before, during, or after the services are rendered.

(Health Insurance and Reform continued)

- **Preadmission testing** - Requirement designed to encourage patients to obtain necessary diagnostic services on an outpatient basis prior to non-emergency hospital admission. The testing is designed to reduce the length of a hospital stay.
- **Non-emergency weekend admission restriction** - A requirement that imposes limits on reimbursement to patients for non-emergency weekend hospital admissions.
- **Second surgical opinion** - A cost-management strategy that encourages or requires patients to obtain the opinion of another doctor after a physician has recommended that a non-emergency or elective surgery be performed. Programs may be voluntary or mandatory in that reimbursement is reduced or denied if the participant does not obtain the second opinion. Plans usually require that such opinions be obtained from board-certified specialists with no personal or financial interest in the outcome.

**Medical Loss Ratio (MLR):** A financial measurement used in the Affordable Care Act to encourage health plans to provide value to enrollees. Example: If an insurer uses 80 cents of every premium dollar to pay its customers' medical claims and activities that improve the quality of care, the company has a medical loss ratio of 80%. This indicates that the insurer is using the remaining 20 cents of each premium dollar to pay overhead expenses, including salaries, administrative costs, and agent commissions. The Affordable Care Act sets minimum medical loss ratios for different markets, as do some state laws. Insurers who do not meet the minimum MLR must issue rebates to policy holders beginning in 2012.

**Medically Necessary:** Services or supplies that are needed for the diagnosis or treatment of your health condition and meet accepted standards of medical practice. Definitions of medical necessity vary by plan.

**Medical Underwriting:** A process used by insurance companies that uses your health status when you are applying for health insurance coverage to determine whether to offer you coverage, at what price and with what exclusions or limits.

**Minimum Essential Coverage:** The type of coverage an individual needs to have to meet the individual responsibility requirement under the Affordable Care Act. This includes individual market policies, job-based coverage, Medicare, Medicaid, CHIP, TRICARE and certain other coverage.

**New Plan:** As referenced in the Affordable Care Act, a health plan that is not grandfathered and therefore subject to all of the reforms in the Affordable Care Act. In the individual health insurance market, a plan that your family is purchasing for the first time. In the group health insurance market, a plan that your employer is offering for the first time. New employees and new family members may be added to existing grandfathered group plans – so a plan that is new to you and your family may still be a grandfathered plan.

In both the individual and group markets, a plan that loses its grandfathered status will be considered a new plan. This happens when it makes significant changes to the plan, such as reducing benefits or increasing cost-sharing for enrollees. Also see “Grandfathered Plan” above.

**Nondiscrimination:** A requirement that job-based insurance not discriminate based on health status by denying or restricting health coverage, or charging more. Job-based plans can restrict coverage based on other factors such as part-time employment that are not related to health status.

**Open Enrollment Period (OEP):** The period of time set up to allow you to choose from available plans, usually once a year.

## (Health Insurance and Reform continued)

**Out-of-Network (OON) Providers:** A duly licensed or certified institution or health professional not under contract with your insurance provider.

**Out-of-Pocket Costs:** Your expenses for medical care that are not reimbursed by insurance. Out-of-pocket costs include deductibles, coinsurance and copayments for covered services plus all costs for services that are not covered.

**Out-of-Pocket Limit (OOP):** The maximum amount you will be required to pay for covered services in a year. Generally, this includes the deductible, coinsurance, and copayments (varies from plan to plan). Example: In some plans the out-of-pocket limit does not include cost sharing for all services, such as prescription drugs. Plans may have different out-of-pocket limits for different services. In Medicaid and CHIP, the limit includes premiums. Additionally, many plans do not have out-of-pocket limits.

**Plan Year:** A 12-month period of benefits coverage under a group health plan. This 12-month period might be different than the calendar year.

**Policy Year:** A 12-month period of benefits coverage under an individual health insurance plan. This 12-month period might be different than the calendar year.

**Pre-authorization:** A pre-authorization requirement means that the insurance company will not pay for a service unless the provider gets permission to provide the service. This permission is to ensure that a patient has benefit dollars remaining and that a particular kind of service is eligible for payment under the patient's contract. Authorization could be granted retroactively after receiving emergency care; generally a patient or hospital may have a 24-hour window to notify a payer.

**Pre-certification:** A pre-certification requirement means that a payer must review the medical necessity of a proposed service and provide a certification number before a claim will be paid. This is often true with augmentation therapy as well as other elective procedures. A physician or nurse with the payer must review a physician's order and the medical record to agree that a proposed procedure is medically appropriate. (Many insurers have adopted strict guidelines in regards to coverage for augmentation therapy.)

**Premium:** A monthly payment you make to your insurer to get and keep insurance coverage. Premiums can be paid by employers, unions, employees or individuals or shared among different payers.

**Preventive Services:** Routine healthcare that includes screenings, check-ups, and patient counseling to prevent illnesses, disease, or other health problems.

**Primary Care:** Health services that cover a range of prevention, wellness and treatment for common illnesses. Primary care providers include doctors, nurses, nurse practitioners and physician assistants. They often maintain long-term relationships with you, and they advise and treat you on a range of health-related issues. They may also coordinate your care with specialists.

**Qualified Health Plan:** Under the Affordable Care Act, starting in 2014, an insurance plan that is certified by an Exchange, provides essential health benefits, follows established limits on cost-sharing (like deductibles, copayments, and out-of-pocket maximum amounts), and meets other requirements. A qualified health plan will have a certification by each Exchange in which it is sold.

(Health Insurance and Reform continued)

**Qualifying Event:** Any event or occurrence such as death, termination of employment, divorce or a terminal illness that changes an employee's eligibility status and permits an acceleration or continuation of benefits or coverage under a group health plan. The term is most frequently used in reference to COBRA eligibility

**Rate Review:** A process that allows state insurance departments to review rate increases before insurance companies can apply them to you. Under the Affordable Care Act, insurers that submit rate increases of 10% or more are considered "unreasonable" and are subject to additional review.

**Reinsurance:** A reimbursement system that protects insurers from very high claims. It usually involves a third party paying part of an insurance company's claims once they pass a certain amount. Reinsurance is a way to stabilize an insurance market and make coverage more available and affordable.

**Rescission:** The retroactive cancellation of a health insurance policy. Insurance companies will sometimes retroactively cancel your entire policy if you made a mistake on your initial application when you buy an individual market insurance policy. Under the Affordable Care Act, rescission is illegal except in cases of fraud or intentional misrepresentation of material fact as prohibited by the terms of the plan or coverage.

**Rider (exclusionary rider):** An amendment to an insurance policy. Some riders add coverage while other riders exclude coverage (known as exclusionary rider). Example: You buy a maternity rider to add coverage for pregnancy to your policy. An exclusionary rider is an amendment permitted in individual policies that permanently excludes coverage for a health condition, body part or body system (such as a certain disease state or disability). Beginning in September 2010, exclusionary riders cannot be applied to coverage for children. Starting in 2014, no exclusionary riders will be permitted in any health insurance.

**Risk Adjustment:** A statistical process that takes into account the underlying health status and health spending of the enrollees in an insurance plan when looking at their healthcare outcomes or healthcare costs.

**Self-Insured Plan:** Type of plan usually present in larger companies where the employer itself collects premiums from enrollees and takes on the responsibility of paying employees' and dependents' medical claims. These employers can contract for insurance services such as enrollment, claims processing, and provider networks with a third party administrator, or they can be self-administered.

**Skilled Nursing Facility (SNF) Care:** Skilled nursing care and rehabilitation services provided on a continuous, daily basis, in a skilled nursing facility. Example: Physical therapy or intravenous injections that can only be given by a registered nurse or doctor.

**Special Enrollment Period:** A time outside of the open enrollment period during which you and your family have a right to sign up for job-based health coverage. Job-based plans must provide a special enrollment period of 30 days following certain life events that involve a change in family status (such as marriage or birth of a child) or loss of other job-based health coverage.

**Special Healthcare Need:** The healthcare and related needs of children who have chronic physical, developmental, behavioral or emotional conditions. Such needs are of a type or amount beyond that required by children generally.

## (Health Insurance and Reform continued)

**State Continuation Coverage (“Mini-COBRA”):** A state-based requirement similar to COBRA that applies to group health insurance policies of employers with fewer than 20 employees. In some states, state continuation coverage rules also apply to larger group insurance policies and add to COBRA protections. Example: in some states, older workers (generally 55 or older) leaving a job-based plan may be allowed to continue COBRA coverage until they reach the age of Medicare eligibility.

**Third Party Administrator (TPA):** An individual or firm hired by an employer to handle claims processing, pay providers, and manage other functions related to the operation of health insurance. The TPA is not the policyholder or the insurer. The TPA may often be a company you associate with health insurance, such as Aetna or Blue Cross, but in this role they are not the actual insurer but are simply managing the plan on behalf of the employer.

**Uncompensated Care:** Healthcare or services provided by hospitals or healthcare providers that do not get reimbursed. Often uncompensated care arises when people do not have insurance and cannot afford to pay the cost of care.

**Usual, Customary, and Reasonable (UCR)**

**Charges:** A healthcare provider’s usual fee for a service that does not exceed the customary fee in that geographic area and is reasonable based on the circumstances. Instead of UCR charges, PPO plans often operate based on a negotiated (fixed) schedule of fees that recognize charges for covered services up to a negotiated fixed dollar amount. Conventional indemnity plans typically operate based on UCR charges.

**Waiting Period (Job-based coverage):** The time that must pass before coverage can become effective for an employee or dependent, who is otherwise eligible for coverage under a job-based health plan. It applies to all new employees and is not based on health status. This is different than a pre-existing condition exclusion period, which is applied to individual employees and is based on health status.

**Well-baby/Well-child Visits:** Routine doctor visits for comprehensive preventive health services that occur when a baby is young and annual visits until a child reaches age 21. Services include physical exam and measurements, vision and hearing screening and oral health risk assessments.

**Wellness Programs:** A program intended to improve and promote health and fitness that’s usually offered through the work place, although insurance plans can offer them directly to their enrollees. The program allows your employer or plan to offer you premium discounts, cash rewards, gym memberships, and other incentives to participate. Programs that tie financial incentives to achieving certain outcomes (like set goals such as BMI, glucose levels or blood pressure) must meet certain federal rules. Examples of some wellness programs: programs to help you stop smoking, diabetes management programs, weight loss programs, and preventative health screenings.

*Source: [www.healthcare.gov/glossary/04262011a.pdf](http://www.healthcare.gov/glossary/04262011a.pdf)*

*The BLS National Compensation Survey*

# Glossary

- Acquired immune deficiency syndrome (AIDS):** A secondary immunodeficiency caused by the HIV virus.
- Acute:** A descriptive term used to describe 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.
- Agammaglobulinemia:** An almost total lack of immunoglobulin or antibodies.
- Amniocentesis:** The withdrawing of amniotic fluid surrounding a fetus in order to perform prenatal genetic testing.
- Anaphylaxis:** A life-threatening type of 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 cells (B-lymphocytes, plasma cells) 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 kind of fungus which is particularly a problem for individuals with CGD 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 caused by neurological abnormalities.
- Autoantibody:** An antibody produced by the body in reaction to any of its own cells or cell products.
- Autoimmune disease:** A disease that results when the body's immune system reacts against the person's own tissue.
- Autosomal recessive inheritance:** A form of inheritance where the characteristic, or disease, is inherited from both parents.
- Autosomes:** Any chromosome other than the sex chromosome.
- 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 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 peptide 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):** Involves the 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 cells are inadequate or lacking.
- 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 (CBC):** A blood test that includes separate counts for red and white blood cells.
- Congenital:** Present at birth.
- Consanguineous:** Descended from the same family or ancestors.
- Cord blood:** Blood obtained from the 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 inflammatory responses. Interleukins and interferons are cytokines.
- DNA (deoxyribonucleic acid):** Found in the cell nucleus, DNA carries genetic information.
- Eczema:** Skin inflammation with redness, itching, encrustations and scaling.
- Endocrine system:** A series of glands in the body that produce hormones.
- Eosinophilia:** An increase in the number of granular white blood cells that stain with the dye eosin, which occurs with some allergies and parasitic diseases.
- Febrile illness:** An illness accompanied by fever.
- Ficolins:** Ficolins are humoral molecules of the innate immune system, which recognize carbohydrate molecules on pathogens, apoptotic and necrotic cells.
- Fungus:** Member of a class of relatively primitive microorganisms including mushrooms, yeast and molds.
- Gamma globulin:** The protein fraction of blood that contains immunoglobulins or antibodies.
- Gamma interferon:** A cytokine primarily produced by T-lymphocytes that improves bacterial killing by phagocytes; used in the treatment for Chronic Granulomatous Disease (CGD).
- 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:** Treatment of genetic diseases by providing the correct or normal form of the abnormal gene which is causing the disease.
- Graft-versus-host disease:** A reaction in which transplanted immunocompetent cells attack the tissue of the recipient.
- Graft rejection:** The immunologic response of the recipient to the transplanted organ or tissue resulting in rejection of the transplanted organ or tissue.
- Granulocyte:** A white cell of the immune system characterized by the ability to ingest (phagocytize) foreign material; neutrophils, eosinophils and basophils are examples of granulocytes.
- Granuloma:** A mass of granulation tissue typically produced in response to infection, inflammation, or the presence of a foreign substance.
- Haplotype:** a set of genetic determinants located on a single chromosome, often used to describe the series of genes clustered on the sixth human chromosome that determines the major histocompatibility complex (MHC), the tissue antigens involved in the “tissue types” important in transplantation of organs and bone marrow.
- Helper lymphocytes (Helper T-cells):** A subset of T-lymphocytes that help B-lymphocytes and T-lymphocytes to function more optimally.

## Glossary

**Heterozygous Mutation:** Each diploid cell has two copies of every gene. 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:** Chemicals 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 for our tissue type.

**Homozygous Mutation:** Each diploid cell has two copies of every gene. Any given gene may contain a mutation. If both copies of the gene contain the 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 and secreted into tears, saliva and on the mucous membranes of respiratory and intestinal tracks.

**IgD:** An immunoglobulin whose function is poorly understood at this time.

**IgE:** An immunoglobulin found in trace amounts in the blood and responsible for allergic reactions.

**IgG:** The most abundant and common of the immunoglobulins. IgG functions mainly against bacteria and some viruses. It is the only antibody that can cross the placenta from the mother to the developing fetus.

**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 foreign substances.

**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.

**Immunoglobulin replacement therapy:** The intravenous, intramuscular or subcutaneous injection of immunoglobulin to provide antibodies that the immunodeficient person cannot make themselves.

**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.

**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 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):** 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 or bacteria are used in some vaccines; live vaccines (particularly oral polio) can transmit the disease they were designed to prevent when given to seriously immunocompromised individuals.
- Lymph:** Fluid made up of various components of the immune system that flows throughout tissues of the body via the lymph nodes and lymphatic vessels.
- 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 and macrophages.
- Lymphocytes:** Small white cells, normally present in the blood and in lymphoid tissue, 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:** Type of cancer of the lymphocytes.
- Macrophages:** A phagocytic tissue cell of the immune system that functions in the destruction of foreign antigens (as bacteria and viruses) and serves as an antigen-presenting cell.
- Major histocompatibility complex:** A series of genes on chromosome 6 that direct the synthesis of the chemicals 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 living material.
- Microorganisms:** Minute living organisms, usually one-cell organisms, which include bacteria, protozoa, and fungi.
- Molecules:** The smallest unit of matter of an element or 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 mucus 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.

## Glossary

**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 includes the bacterium that causes 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.

**Nystagmus:** Involuntary, usually rapid movement of the eyeballs.

**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 control the normal metabolism and blood levels of calcium.

**Petechiae:** Pinhead-sized red spots resulting from bleeding into the skin.

**Phagocyte:** A general class of white blood cells that ingest microbes and other cells and foreign particles; monocytes, macrophages and neutrophils are types of phagocytes.

**Phagosomes:** A cellular compartment in which pathogenic microorganisms can be killed and digested.

**Phenotypic Variability:** The range of differences seen from individual to individual in the effect that any particular single gene may produce. Often used to describe differences in disease severity amongst family members who all have inherited the same mutant gene.

**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-producing cells descended from B-lymphocytes.

**Plasmapheresis:** A process in which blood taken from a patient is treated to extract the cells and corpuscles, which are then added to another fluid and then returned to the patient's body.

**Platelets:** Smallest and most fragile of the blood cells; 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 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:** Infections, such as otitis, sinusitis, pneumonia, deep-seated abscess, osteomyelitis, bacteremia or meningitis that occur repeatedly.

**Secondary immunodeficiency:** 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 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.

**Staphylococcal:** Staph is short for *Staphylococcus*, a type of bacteria. There are over 30 types, but *Staphylococcus aureus* causes most staph infections.

**Stem cells:** Cells from which all blood cells and immune cells are derived, bone marrow is rich in stem cells.

**Subcutaneous immunoglobulin (SCIG) infusion:** Administration of immunoglobulin directly under the skin.

**Telangiectasia:** Dilation of the blood vessels.

**Thrombocytopenia:** Low platelet count.

**Thrush:** A fungal disease on mucous membranes of the mouth caused by *Candida* infections.

**Thymus gland:** A lymphoid organ located behind the upper portion of the sternum (breastbone). The thymus is the chief 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 amount of some antibodies found in a patient's blood.

**T-lymphocytes (or T-cells):** Lymphocytes that are processed in the thymus; they are responsible in part for carrying out the immune response.

**Unusual infectious agents:** These are normally non-pathogenic agents or those not generally found in humans, which can cause serious disease in immunocompromised patients.

**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 in the cytoplasm of a cell containing fluid.

**Vectors:** Modified viruses containing normal genes; 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).

# Immune Deficiency Foundation Resources

[www.primaryimmune.org](http://www.primaryimmune.org), 800-296-4433, [idf@primaryimmune.org](mailto:idf@primaryimmune.org)

## For Patients and Families

- **Ask IDF:** Contact IDF with questions about living with primary immunodeficiency diseases through the IDF web site: [www.primaryimmune.org/ask-idf](http://www.primaryimmune.org/ask-idf). IDF has a vast reserve of innovative resources and individualized assistance to help with the unique aspects of living with a primary immunodeficiency. From learning more about the diseases, to understanding insurance coverage, to lifestyle issues and more, be sure to Ask IDF.
- **Locate a Physician:** Contact IDF to find a physician in your area who is an expert on primary immunodeficiency diseases.
- **Peer Support:** Connecting people and patients who share similar relationships to primary immunodeficiency diseases.
- **Patient Assistance Resources:** Individualized assistance is available for patients experiencing problems with insurance denials for treatment, reimbursement issues, concerns with Medicare or Medicaid, disability, and accessing copayment and premium assistance. Resources and tools are available to help tackle insurance challenges.
- **Information about Patient Rights:** Patients can contact IDF to learn about their rights concerning product choice and treatment options, employment and school issues, as well as fair treatment, privacy or other rights.
- **IDF ePHR:** An electronic personal health record designed for the primary immunodeficiency community to help organize health information in one place.
- **PI CONNECT:** The IDF Patient-Powered Research Network brings together the information patients enter in IDF ePHR with the United States Immunodeficiency Network (USIDNET) patient-consented registry, which contains clinical data on several thousand patients with primary immunodeficiency. PI CONNECT gives patients access to an exclusive research forum to discuss research related to primary immunodeficiency.
- **Local Patient Meetings:** Education programs featuring local experts and networking opportunities.
- **IDF Retreats:** Weekend events for all ages that feature medical and life management sessions.

- **IDF Youth Programs:** Designed for children diagnosed with a primary immunodeficiency or have a family member with this condition.
- **IDF Teen Escape:** Weekend program developed to acquaint teens diagnosed with primary immunodeficiency diseases.
- **IDF National Conference:** The world's largest gathering of individuals and families affected by primary immunodeficiency diseases.
- **Volunteer:** Network of volunteers who provide peer support, create awareness, help host educational meetings, advocate for public policy, visit plasma centers and organize fundraising events throughout the country.
- **IDF Plasma Partners Program:** Awareness and fundraising initiatives within plasma centers across the country arranged by IDF that highlights the work of plasma center staff members, plasma donors and IDF volunteers.

## For Healthcare Professionals

[www.primaryimmune.org/healthcare-professionals](http://www.primaryimmune.org/healthcare-professionals)

**IDF Consulting Immunologist Program:** A free service for physicians which provides the opportunity to consult with expert clinical immunologists about patient specific questions and obtain valuable diagnostic, treatment and disease management information regarding primary immunodeficiency.

**IDF & USIDNET LeBien Visiting Professor Program:** Promotes improved knowledge by providing faculty at teaching hospitals with a Visiting Professor with expertise in primary immunodeficiency and offers Grand Rounds and clinical presentations at medical institutions throughout the U.S.

**IDF Online Continuing Education Course for Nurses (English) - Primary Immunodeficiency Diseases and Immunoglobulin Therapy:** A free, 5-hour, U.S. accredited course for nurses that provides an update on primary immunodeficiency, immunoglobulin therapies and the nurse's role with these therapies. Video Translations for Nurses in French, German, and Spanish are also available. Go to: [www.primaryimmune.org/healthcare-professionals/continuing-education-course-for-nurses](http://www.primaryimmune.org/healthcare-professionals/continuing-education-course-for-nurses).

## (immune Deficiency Foundation Resources continued)

**United States Immunodeficiency Network (USIDNET):**

USIDNET is a research consortium established to advance research in the field of primary immunodeficiency by maintaining a patient registry, and providing education and mentoring for young investigators. USIDNET, a program of the Immune Deficiency Foundation (IDF), is funded in part by the National Institute of Allergy and Infectious Diseases (NIAID) and the National Institutes of Health (NIH) an agency of the Department of Health & Human Services.

**IDF Medical Advisory Committee:** Comprised of prominent immunologists to support the mission of IDF.

**IDF Nurse Advisory Committee:** Comprised of exceptional nurses to support the mission of IDF. Available as a resource for nurses administering immunoglobulin therapy or treating patients with primary immunodeficiency.

**Publications**

All publications are available at no cost, and they can either be ordered, or downloaded and printed.

[www.primaryimmune.org/idf-publications](http://www.primaryimmune.org/idf-publications)

**For Patients and Families**

- *IDF Patient & Family Handbook for Primary Immunodeficiency Diseases 5th Edition*
- *Our Immune System* (Children's Book)
- *A Zebra Tale from the Immune Deficiency Foundation* (Children's Book)
- *Immune Deficiency Foundation School Guide for Students with Primary Immunodeficiency Diseases Students with Primary 3rd Edition*
- *IDF Presents: In Tune with your Immune System, Battle of the Bands* (Comic Book)

**For Healthcare Professionals**

All publications are available at no cost, and they can either be ordered, or downloaded and printed.

[www.primaryimmune.org/idf-publications](http://www.primaryimmune.org/idf-publications)

- *IDF Diagnostic & Clinical Care Guidelines for Primary Immunodeficiency Diseases 3rd Edition*
- *IDF Guide for Nurses on Immunoglobulin Therapy for Primary Immunodeficiency Diseases 3rd Edition*

• *IDF Clinical Focus on Primary Immunodeficiencies:*

- "Diagnostic Approaches to Antibody Deficiencies"
- "Subcutaneous Immunoglobulin Replacement"
- "Chronic Granulomatous Disease"
- "Clinical Update in Immunoglobulin Therapy for Primary Immunodeficiency Diseases"
- "Subcutaneous IgG Therapy in Immune Deficiency Diseases"
- "Primary Humoral Immunodeficiency Optimizing IgG Replacement Therapy"
- "The Clinical Presentation of Primary Immunodeficiency Diseases"
- "Treatment and Prevention of Viral Infections in Patients with Primary Immunodeficiency Diseases"
- "IgG Subclass Deficiency"
- "Immunization Of The Immunocompromised Host"

**Communications**

- *IDF ADVOCATE:* Newsletter, published three times per year.
- *Primary Immune Tribune:* E-newsletter, published monthly.
- *IDF Friends*, [www.idffriends.org](http://www.idffriends.org): A social network exclusively for the primary immunodeficiency community.
- *IDF Common Ground*, [www.idfcommonground.org](http://www.idfcommonground.org): An online community for teens with primary immunodeficiency diseases.
- *IDF Videos*, [www.primaryimmune.org/idf-videos](http://www.primaryimmune.org/idf-videos): IDF Videos is the hub to access all of IDF's video channels. The majority of the content is generated by individuals with primary immunodeficiency.
- *IDF Arcade*, [www.primaryimmune.org/idf-arcade](http://www.primaryimmune.org/idf-arcade): Games designed for children ages 4 to 12 that are a great way to have fun, while learning about the immune system.
- *IDF Reel Stories*, [www.primaryimmune.org/idf-reelstories](http://www.primaryimmune.org/idf-reelstories): IDF Reel Stories is a patient-generated video community designed to encourage and empower fellow patients and their loved ones.

(IDF Resources continued)

- *IDF Blog*, [www.primaryimmune.org/blog](http://www.primaryimmune.org/blog): Includes updates on IDF programs and services as well as important issues. Users can comment, submit news, and share posts about awareness activities, advocacy initiatives, fundraising events and more.
- *IDF SCID Newborn Screening Blog*, [www.idfscidnewbornscreening.org](http://www.idfscidnewbornscreening.org): Documents the fight to establish Severe Combined Immune Deficiency (SCID) newborn screening programs in all 50 states.

### Public Policy Initiatives

[www.primaryimmune.org/idf-advocacy-center](http://www.primaryimmune.org/idf-advocacy-center)

- IDF maintains a robust advocacy program focused on national, state, and local healthcare issues that ensure the PI community has access to all treatments, all sites of care, and specialists needed to live a healthy life. Access to quality care is IDF's top advocacy initiative, and members of the PI community are encouraged to take action using IDF's comprehensive advocacy resources.

- IDF's grassroots advocacy program mobilizes members of the PI community by having advocates take meaningful action by making phone calls to their government representatives, testifying at hearings, and sending letters of support to promote healthcare legislation that will positively affect the community.
- IDF Advocacy Center utilizes an Action Alert System that allows user to receive legislative updates about issues affecting their healthcare and easily voice their concerns to lawmakers.
- Advocacy Channel features patient and caregiver stories that demonstrate how the patient voice can effectively enact change while providing guidance on how to overcome barriers to care.

## Information about Primary Immunodeficiencies

### Immune Deficiency Foundation

[www.primaryimmune.org](http://www.primaryimmune.org)  
800-296-4433

The Immune Deficiency Foundation, founded in 1980, is the national non-profit patient organization dedicated to improving the diagnosis and treatment of patients with primary immunodeficiency diseases through research, education and advocacy.

### International Patient Organization for Primary Immunodeficiencies

[www.ipopi.org](http://www.ipopi.org)

International Patient Organization for Primary Immunodeficiencies (IPOPI) is an international organization whose members are national patient organizations for primary immune deficiencies. The website provides general information on primary immunodeficiency disease and resource contacts for patients and professionals worldwide.

### The Jeffrey Modell Foundation

[www.jmfworld.org](http://www.jmfworld.org)  
866-INFO-4-PI (866-463-6474)

The Jeffrey Modell Foundation is dedicated to early and precise diagnosis, meaningful treatments, and ultimately cures of primary immunodeficiencies.

### Disease Specific Patient Groups and Organizations

#### A-T Children's Project

[www.atcp.org](http://www.atcp.org)

The A-T Children's Project is a non-profit organization that raises funds to support and coordinate biomedical research projects, scientific conferences and a clinical center aimed at finding a cure for Ataxia-Telangiectasia, a lethal genetic disease that attacks children, causing progressive loss of muscle control, cancer and immune system problems.

## (Information about Primary Immunodeficiencies continued)

**Chronic Granulomatous Disease Association**

[www.cgdassociation.org](http://www.cgdassociation.org)

The Chronic Granulomatous Disease Association (CGDA), founded in 1982, is a non-profit international support group for persons with chronic granulomatous disease (CGD), their families and physicians. The organization networks patients with similar CGD-related illnesses or infecting organisms. It provides research grants aimed at finding a cure for CGD.

**Hereditary Angioedema Association, Inc.**

[www.haea.org](http://www.haea.org)

Founded and staffed by HAE patients and HAE patient caregivers, U.S. Hereditary Angioedema Association, Inc. (US HAEA) is a non-profit patient advocacy organization dedicated to serving persons with angioedema. The Association provides HAE patients and their families with a support network and a wide range of services including physician referrals, and individualized patient support.

**Severe Combined Immune Deficiency**

[www.scid.net](http://www.scid.net)

This site contains information about Severe Combined Immune Deficiency (SCID) with links to journal articles, latest research developments and patient support.

**SCID Angels for Life**

[www.scidangelsforlife.com](http://www.scidangelsforlife.com)

SCID Angels for Life is a non-profit organization that increases awareness, benefits research and provides parent and family education for those affected by Severe Combined Immune Deficiency (SCID).

**Understanding XLP**

[www.xlp.ca](http://www.xlp.ca)

This site provides families and patients with X-linked Lymphoproliferative Disorder (XLP) a means of communication.

**Wiskott-Aldrich Foundation**

[www.wiskott.org](http://www.wiskott.org)

This site provides information about Wiskott-Aldrich Syndrome (WAS). The links on this site include information for patients and families, the latest research related to WAS and financial support.

**XLP Research Trust**

[www.xlpresearchtrust.org](http://www.xlpresearchtrust.org)

This organization promotes and funds research into the cause, management, symptoms and cure for X-linked Lymphoproliferative (XLP) disease; raises awareness of the disease; and is a point of contact and support for families affected by XLP.

## National Organizations

**American Academy of Allergy,  
Asthma, and Immunology**

[www.aaaai.org](http://www.aaaai.org)

313-371-8600

Physician Referral Service: 800-822-2762

The American Academy of Allergy, Asthma, and Immunology (AAAAI) is a professional organization for physicians who treat patients with allergies, asthma and immunologic disorders. The organization provides a worldwide referral system for physicians in various geographical regions.

**American Academy of Pediatrics**

[www.aap.org](http://www.aap.org)

847-434-4000

The American Academy of Pediatrics (AAP) is a professional organization for pediatricians. It is committed to the attainment of optimal physical, mental, and social health and well-being for all infants, children, adolescents, and young adults.

(National Organizations continued)

**Clinical Immunology Society**

www.clinimmsoc.org  
414-224-8095

The mission of the Clinical Immunology Society (CIS) is to facilitate education, translational research and novel approaches to therapy in clinical immunology to promote excellence in the care of patients with immunologic/inflammatory disorders.

**Federation of Clinical Immunology Societies**

www.focisnet.org

The Federation of Clinical Immunology Societies (FOCIS) exists to improve human health through immunology by fostering interdisciplinary approaches to both understand and treat immune-based diseases.

**Immunoglobulin National Society**

www.ig-ns.org

Immunoglobulin National Society (IgNS) is a professional organization dedicated to nursing professionals in education, management, practice and research in the field of immunoglobulin (Ig) therapy.

**Infusion Nurses Society**

www.ins1.org

The Infusion Nurses Society (INS) is dedicated to exceeding the public's expectations of excellence by setting the standard for infusion care.

**National Marrow Donor Program**

www.marrow.org  
800-627-7692

The National Marrow Donor Program (NMDP) is a non-profit organization that facilitates unrelated marrow and blood stem cell transplants for patients with life-threatening diseases who do not have matching donors in their families.

## International Organizations

**European Society for Immunodeficiencies (ESID)**

www.esid.org

The European Society for Immunodeficiencies (ESID) is a non-profit medical organization. The purpose of ESID is to foster excellence in research and medical practice and to promote interaction with nurses and patient associations, so as to increase exchange of information among patients, parents of patients, nurses, doctors and researchers.

**International Nursing Group for Immunodeficiencies (INGID)**

www.ingid.org

The purpose of the International Nursing Group for Immunodeficiencies (INGID) is to improve and extend the quality of nursing care of patients with primary immunodeficiencies, and to increase the awareness and understanding of primary immunodeficiencies amongst nurses.

**International Patient Organization for Primary Immunodeficiencies (IPOPI)**

www.ipopi.org

The International Patient Organization for Primary Immunodeficiencies (IPOPI) is an international organization whose members are national patient organizations for primary immunodeficiencies. The site provides general information on primary immunodeficiency and resource contacts for patients and professionals worldwide. The following is a list of Member Organizations and International Support Groups:

Argentina: [www.aapidp.com.ar](http://www.aapidp.com.ar)

Australia: [www.idfaustralia.org](http://www.idfaustralia.org)

Austria: [www.oespid.at](http://www.oespid.at)

Belarus: [Andron116@yandex.ru](mailto:Andron116@yandex.ru)

Canada: [www.cipo.ca](http://www.cipo.ca)



## (International Organizations continued)

Chile: vidaporlavirus@gmail.com  
 Colombia: www.fundacionfip.org.co  
 Cyprus: Maria.g.charalambous@cyta.com.cy  
 Denmark: www.idf.dk  
 Estonia: janne.rimmel@mail.ee  
 Finland: anna-riitta.satama@luukku.com  
 France: www.associationiris.org  
 Germany: www.dsai.de  
 Greece: www.paed-anosia.gr  
 Hungary: hzs86@gmail.com  
 Iceland: onaemisgalli@onaemisgallar.is  
 India: www.ipspiindia.org  
 Iran: www.ipidr.tums.ac.ir  
 Ireland: ipiasecretary@gmail.com  
 Italy: www.aip-it.org  
 Japan: www.npo-pidtsubasa.org  
 Mexico: www.fumenip.org.mx  
 Morocco: www.hajar.org.ma  
 The Netherlands:  
 www.stichtingvoorafweerstoornissen.nl  
 New Zealand: www.idfnz.org.nz  
 Norway: evabrox@online.no  
 Poland: www.immunoprotect.pl  
 Portugal: mjmousinho@gmail.com

Romania: www.arpid.ro  
 Russia: anton\_emelin@hotmail.com  
 Serbia: www.pospid.org  
 South Africa: www.pinsa.org.za  
 Spain: www.aedip.com  
 Sweden: www.pio.nu  
 Switzerland: www.svai.ch  
 Turkey: www.imyed.org.tr  
 United Kingdom: david@ipopi.org  
 United States: www.primaryimmune.org,  
 www.info4pi.org  
 Venezuela: idpvenezuela@gmail.com

**Latin American Society for Primary Immunodeficiencies (LASID)**

www.lasid.org

The Latin American Society for Primary Immunodeficiencies (LASID) is a professional organization comprised of physicians from various Latino countries who are dedicated to promoting the awareness, diagnosis and treatment of primary immunodeficiency diseases in these countries.

**Federal Organizations****Centers for Disease Control and Prevention, National Immunization Program**

www.cdc.gov/vaccines  
 800-CDC-INFO (800-232-4636)

This division of the CDC provides information on general vaccinations and specific precautions for individuals affected with primary immunodeficiencies.

**Center for Biologics Evaluation and Research, FDA**

www.fda.gov/BiologicsBloodVaccines  
 800-835-4709

A division of the Food and Drug Administration (FDA) whose mission is to protect and enhance public health through regulation of biological products to ensure their safety, effectiveness and timely delivery to patients. This agency provides information on biological products, such as blood and plasma, including new product approvals, adverse events, product recalls and withdrawals.

(Federal Organizations continued)

**Centers for Medicare and Medicaid Services**

www.cms.gov  
800-633-4227

The Centers for Medicare and Medicaid Services (CMS) provides information for individuals receiving services from Medicare, Medicaid or SCHIP.

**National Institutes of Health**

U.S. Department of Health And Human Services:  
National Institutes of Health  
www.nih.gov  
301-496-4000

The National Institutes of Health (NIH) provides information on advances in health, science and medical issues. The following are divisions of NIH:

**National Cancer Institute**

www.cancer.gov  
800-422-6237

National Cancer Institute (NCI) provides the following information about cancer: topics, trials, statistics and research.

**National Heart, Lung and Blood Institute**

www.nhlbi.nih.gov  
301-592-8573

The National Heart, Lung and Blood Institute (NHLBI) provides leadership for a national program in diseases of the heart, blood vessels, lung, and blood; blood resources; and sleep disorders.

**National Human Genome Research Institute**

www.genome.gov  
301-402-0911

The National Human Genome Research Institute (NHGRI) applies genome technologies to the study of specific diseases and the genetic components of complex disorders.

**National Institute of Allergy and Infectious Diseases**

www.niaid.nih.gov  
Office of Communications: 301-496-5717

The National Institute of Allergy and Infectious Diseases (NIAID) provides information on allergy and infectious diseases, as well as primary immunodeficiencies.

**National Institute of Child Health and Human Development**

www.nichd.nih.gov  
800-370-2943

The National Institute of Child Health and Human Development (NICHD) provides general information on children's health issues, including an in-depth booklet on primary immunodeficiencies.

**NIH Clinical Trials**

www.clinicaltrials.gov  
800-411-1222

The NIH Clinical Trials site contains current information on clinical trials being conducted, some of which may be pertinent to primary immunodeficiencies.

**NIH Health Information**

www.health.nih.gov

This is an A-Z index of NIH health resources, clinical trials, MedlinePlus and health hotlines.

**NIH Office of Rare Diseases**

www.rarediseases.info.nih.gov  
301-402-4336

The NIH Office of Rare Diseases (ORD) coordinates research on rare diseases and supports research to respond to the needs of patients who have any one of the more than 6,000 rare diseases known today.

**NIH Research Training and Scientific References**

www.nih.gov/science

This site contains information about intramural research, Human Embryonic Stem Cell Registry, scientific interest groups, library catalogs, journals, training, labs, scientific computing and more.

**National Library of Medicine**

www.nlm.nih.gov  
888-346-3656

The National Library of Medicine (NLM) is the world's largest medical library. The library collects materials and provides information and research services in all areas of biomedicine and healthcare.

## (Federal Organizations continued)

**National Office of Public Health Genomics**

[www.cdc.gov/genomics](http://www.cdc.gov/genomics)  
770-488-8510

This site provides updated information on how human genomic discoveries can be used to improve health and prevent disease. It also provides links to Centers for Disease Control and Prevention (CDC) activities in public health genomics.

**U.S. Department of Education**

[www.ed.gov/parents/landing.jhtml](http://www.ed.gov/parents/landing.jhtml)

This site contains information for parents about education for children of all ages and abilities.

**U.S. Department of Health and Human Services**

[www.hhs.gov](http://www.hhs.gov)  
877-696-6775

The U.S. Department of Health and Human Services (HHS) is the U.S. government's principal agency for protecting the health of all Americans and providing essential human services. The site contains information on the department's numerous federal programs.

**U.S. Department of Labor: Continuation of Health Coverage (COBRA)**

[www.dol.gov/dol/topic/health-plans/cobra.htm](http://www.dol.gov/dol/topic/health-plans/cobra.htm)

COBRA gives workers and their families who lose their health benefits the right to choose to continue group health benefits provided by their group health plan for limited periods of time under certain circumstances such as voluntary or involuntary job loss, reduction in the hours worked, transition between jobs, death, divorce and other life events.

**U.S. Department of Labor, Employment Standards Administration, Wage and Hour Division**

[www.dol.gov](http://www.dol.gov)  
866-4USA-DOL (866-487-2365)

Administers and enforces the Family and Medical Leave Act (FMLA) for all private, state and local government employees, and some federal employees. FMLA entitles eligible employees to take up to 12 weeks of unpaid, job-protected leave in a 12-month period for specified family and medical reasons.

**U.S. Equal Employment Opportunity Commission**

[www.eeoc.gov](http://www.eeoc.gov)  
800-669-4000

Individuals can find information about the Equal Employment Opportunity Commission (EEOC), its current activities and legislative documents such as The Americans with Disabilities Act (ADA), which protects civil rights in the areas of employment, public accommodation, transportation and telecommunications for people with disabilities, including developmental disabilities.

**U.S. Social Security Administration**

[www.ssa.gov](http://www.ssa.gov)

This website contains complete information about Social Security.

## Government Support and Assistance Programs

### **GovBenefits.gov**

[www.benefits.gov](http://www.benefits.gov)

This site includes program descriptions and contact information about federal and state assistance programs.

### **Healthfinder**

[www.healthfinder.gov](http://www.healthfinder.gov)

Healthfinder.gov is a Federal website for consumers, developed by the U.S. Department of Health and Human Services together with other Federal agencies. It is a key resource for finding government and nonprofit health and human services information on the Internet.

### **Health References and Services Administration**

[www.findahealthcenter.hrsa.gov](http://www.findahealthcenter.hrsa.gov)

The Health References and Services Administration (HRSA) provides information about federally funded healthcare centers that provide free or low cost care.

### **Hill-Burton Free and Reduced Cost Health Care**

[www.hrsa.gov/gethealthcare/affordable/hillburton](http://www.hrsa.gov/gethealthcare/affordable/hillburton)

In 1946, Congress passed a law that gave hospitals, nursing homes and other health facilities grants and loans for construction and modernization. In return, they agreed to provide a reasonable volume of services to persons unable to

pay and to make their services available to all persons residing in the facility's area. The program stopped providing funds in 1997, but about 300 healthcare facilities nationwide are still obligated to provide free or reduced-cost care.

### **State Health Insurance Assistance Program**

[www.seniorsresourceguide.com/directories/National/SHIP/index.html](http://www.seniorsresourceguide.com/directories/National/SHIP/index.html)

[www.medicare.gov/contacts/organization-search-criteria.asp](http://www.medicare.gov/contacts/organization-search-criteria.asp)

State Health Insurance Assistance Program (SHIP) provides counseling services to Medicare beneficiaries. They help assist patients in making educated, informed decisions on their healthcare benefits.

### **State Programs for Children with Special Needs**

[http://wdcrobcop01.ed.gov/Programs/EROD/org\\_list.cfm?category\\_ID=SCH](http://wdcrobcop01.ed.gov/Programs/EROD/org_list.cfm?category_ID=SCH)

States offer individual programs which provide medical assistance for children with special needs. These may offer assistance in covering medical expenses, help with finding a diagnosis, and other services depending on the state.

## Patient Advocacy and Support Organizations

### **BenefitsCheckUp**

[www.benefitscheckup.org](http://www.benefitscheckup.org)

Many older people need help paying for prescription drugs, healthcare, utilities and other basic needs. Ironically, millions of older Americans—especially those with limited incomes—are eligible for but not receiving benefits from existing federal, state and local programs. Ranging from heating and energy assistance to prescription savings programs to income supplements, there are many public programs available to seniors in need if they only knew about them and how to apply for them.

### **Caregiver Action Network**

[www.nfcacares.org](http://www.nfcacares.org)

800-896-3650

The Caregiver Action Network (CAN) is a family caregiver organization working to improve the quality of life for those who care for loved ones with chronic conditions, disabilities, disease or the frailties of old age.

## (Patient Advocacy and Support Organizations continued)

**Children's Defense Fund**

[www.childrensdefense.org](http://www.childrensdefense.org)  
800-233-1200

The Children's Defense Fund is a non-profit organization devoted to children's issues, including the Children's Health Insurance Program.

**Families USA**

[www.familiesusa.org](http://www.familiesusa.org)  
202-628-3030

Families USA is a non-profit organization dedicated to the achievement of high-quality, affordable health and long-term care for all Americans. The website contains state and national resources.

**Family Voices**

[www.familyvoices.org](http://www.familyvoices.org)  
888-835-5669

Family Voices is a national organization that provides information and education concerning the healthcare of children with special health needs.

**Health Insurance Resource Center**

[www.healthinsurance.org](http://www.healthinsurance.org)

A resource for families, individuals and the self-employed, the Health Insurance Resource Center provides the tools to become a better-informed health insurance consumer.

**Insure Kids Now**

[www.insurekidsnow.gov](http://www.insurekidsnow.gov)

This site provides links to state child and adolescent health insurance programs.

**Invisible Disabilities Association**

[www.invisibledisabilities.org](http://www.invisibledisabilities.org)

The Invisible Disabilities Association (IDA) helps those living with various conditions, as well as their loved ones, through their website, articles, literature, projects and seminars.

**The Medicine Program**

[www.themedicineprogram.com](http://www.themedicineprogram.com)

The Medicine Program is a patient advocacy organization helping individuals and families all across America get access to up to 2,500 prescription medications available today for free or nearly free of charge through Patient Assistance Programs.

**National Committee for Quality Assurance**

[www.ncqa.org](http://www.ncqa.org)

The National Committee for Quality Assurance (NCQA) is a private, not-for-profit organization dedicated to assessing and reporting on the quality of managed care plans.

**National Disabilities Rights Network**

[www.ndrn.org](http://www.ndrn.org)

The National Disabilities Rights Network (NDRN) is a non-profit membership organization for the federally mandated Protection and Advocacy (P&A) Systems and Client Assistance Programs (CAP) for individuals with disabilities.

**National Organization for Rare Disorders**

[www.rarediseases.org](http://www.rarediseases.org)  
800-999-NORD

The National Organization for Rare Disorders (NORD) is a non-profit organization which provides information, programs and services for thousands of rare medical conditions, including primary immunodeficiencies.

**National Patient Travel Center**

[www.patienttravel.org](http://www.patienttravel.org)  
800-296-3797

The National Patient Travel Center is a non-profit organization that provides a variety of services to individuals and families seeking ways to travel long-distances for specialized medical evaluation, diagnosis and treatment.

(Patient Advocacy and Support Organizations continued)

**NeedyMeds**

[www.needymeds.org](http://www.needymeds.org)

NeedyMeds provides information on programs that help people facing problems paying for medications and healthcare; assists those in need in applying to programs; and provides health-related education using innovative methods.

**Partnership for Prescription Assistance**

[www.pparx.org](http://www.pparx.org)

888-4PPA-NOW (888-477-2669)

The Partnership for Prescription Assistance brings together America's pharmaceutical companies, doctors, other healthcare providers, patient advocacy organizations and community groups to help qualifying patients who lack prescription coverage get the medicines they need through the public or private program that's right for them.

**Patient Advocate Foundation**

[www.patientadvocate.org](http://www.patientadvocate.org)

800-846-4066

The Patient Advocate Foundation is a national non-profit organization that seeks to safeguard patients through effective mediation assuring access to care, maintenance of employment and preservation of their financial stability.

**Patient Notification System**

[www.patientnotificationsystem.org](http://www.patientnotificationsystem.org)

888-UPDATE-U (888-873-2838)

The Patient Notification System is a program developed by the Plasma Protein Therapeutics Association (PPTA) to notify patients who receive plasma products, such as intravenous immunoglobulin (IVIG), about product recalls.

**Patient Services Incorporated (PSI)**

[www.patientservicesinc.org](http://www.patientservicesinc.org)

800-366-7741

Patient Services Incorporated (PSI) is a non-profit charitable organization dedicated to subsidizing the high cost of health insurance premiums and co-payments for persons with specific chronic illnesses, including primary immunodeficiencies.

**RxAssist**

[www.rxassist.org](http://www.rxassist.org)

Patient assistance programs are run by pharmaceutical companies to provide free medications to people who cannot afford to buy their medicine. RxAssist offers a comprehensive database of these patient assistance programs, as well as practical tools, news, and articles so that healthcare professionals and patients can find the information they need.

**Save Babies Through Screening Foundation**

[www.savebabies.org](http://www.savebabies.org)

888-454-3383

Save Babies Through Screening Foundation educates parents, pediatric healthcare providers, and policy makers about available comprehensive newborn screening.

**SKIP: Sick Kids Need Involved People**

[www.skipofny.org](http://www.skipofny.org)

212-268-5999

This is an advocacy group which helps families in the state of New York receive financial aid, nursing services and government medical services that they may be entitled to for their chronically ill child.

## Education Resources

### HEATH Resource Center

[www.heath.gwu.edu](http://www.heath.gwu.edu)  
800-544-3284

The HEATH Resource Center is the national clearinghouse on postsecondary education for individuals with disabilities. It provides information about educational support services, policies, procedures, adaptations and opportunities at American campuses, vocational-technical schools and other postsecondary training sites.

### National Information Center for Handicapped Children and Youth

[www.nichcy.org](http://www.nichcy.org)  
800-695-0285

National Information Center for Handicapped Children and Youth (NICHY) is a national information and referral center that provides information on disabilities and disability-related issues for families, educators and other professionals. Specific information on early intervention programs, special education, individualized education programs, education rights and transition to adult life can be found through this organization.

## Manufacturing Companies and Product Related Organizations

Manufacturing companies' websites offer a wealth of valuable information and may provide information about the companies, their products, general information about primary immunodeficiency diseases and reimbursement assistance.

### Baxalta Incorporated

[www.myigsource.com](http://www.myigsource.com)  
MylgSource: 855-250-5111

Baxalta Incorporated manufactures Gammagard Liquid, Gammagard S/D and HyQvia.

### Bio Products Laboratory

[www.bpl.co.uk](http://www.bpl.co.uk)  
+44 (0) 20 8957 2342

Bio Products Laboratory manufactures Gammplex.

### Biotest Pharmaceuticals Corporation

[www.biotestpharma.com](http://www.biotestpharma.com)  
800-458-4244  
Bivigam Cares Program: 855-248-4426 (BIVIGAM)

Biotest Pharmaceuticals manufacturers Bivigam.

### CSL Behring

[www.cslbehring.com](http://www.cslbehring.com)  
Care Coordination Center: 800-676-4266, option 5  
IgIQ Resource Hotline: 877-355-IgIQ (877-355-4447)

CSL Behring manufactures Hizentra, Carimune and Privigen.

### Grifols

[www.grifols.com](http://www.grifols.com)  
Grifols USA Customer Service: 800-243-4153 and 888-325-8579, option 3  
Patient Assistance for Flebogamma: 888.GRIFOLS (888-474-3657)  
Gamunex Connexions Program (comprehensive support program): 888-694-2686

Grifols manufactures Flebogamma DIF and Gamunex-C.

### Horizon Pharma

[www.horizonpharma.com](http://www.horizonpharma.com)  
Comprehensive Personalized Patient Prescription Advocacy and Support Services (COMPASS) Program: 877-305-7704

Horizon Pharma manufactures Actimmune.

(Manufacturing Companies and Product Related Organizations continued)

**Kedrion Biopharma**

[www.kedrion.usa](http://www.kedrion.usa)

Medical Inquiries, Reimbursement & Customer Service:  
855-353-7466

Kedrion manufactures Gammaked.

**Octapharma**

[www.octapharma.com](http://www.octapharma.com)

Customer Service: 866-766-4860

Reimbursement: 800-554-4440

Octapharma manufactures Octagam.

**Plasma Protein Therapeutics Association**

[www.plasmatherapeutics.org](http://www.plasmatherapeutics.org)

410-263-8296

The Plasma Protein Therapeutics Association (PPTA) is the primary advocate for the leading producers of plasma-based and related recombinant biological therapeutics. The website provides specific information on the quality, safety and efficacy of plasma products.

**Sigma Tau Pharmaceuticals**

[www.sigmatau.com](http://www.sigmatau.com)

Product Information: 866-634-2765

Coverage Assistance and Patient Access Program:  
866-352-3229

Sigma-Tau Pharmaceuticals manufactures Adagen.

## Genetic Issues

**DNA from the Beginning**

[www.dnaftb.org](http://www.dnaftb.org)

DNA from the Beginning is an animated primer on the basics of DNA, genes and heredity, organized around key concepts. The science behind each concept is explained by: animation, image gallery, video interviews, problem, biographies and links.

**Genetic Alliance**

[www.geneticalliance.org](http://www.geneticalliance.org)

800-336-GENE

The Genetic Alliance is an international coalition of families, health professionals, and genetic support organizations that provide information, support and advocacy to those affected by genetic conditions, including primary immunodeficiencies.

**Gene Tests**

[www.ncbi.nlm.nih.gov](http://www.ncbi.nlm.nih.gov)

At this site one can enter a diagnosis and pull up scholarly articles about many primary immunodeficiency diseases.

**Human Genome Project: Ethical, Legal, and Social Issues (ELSI)**

[www.ornl.gov/hgmis/elsi/elsi.html](http://www.ornl.gov/hgmis/elsi/elsi.html)

The ELSI division of the Human Genome Project is the world's largest bioethics program devoted to studying these issues related to the availability of genetic information. The website contains information on genetic testing with regard to privacy and legislation, gene patenting, gene therapy and genetics used in the courtroom.

**Immunodeficiency Resource**

<http://bioinf.uta.fi/idr/index.shtml>

Immunodeficiency Resource (IDR) is a compendium of information on the immunodeficiencies available online, including data for clinical, biochemical, genetic, structural and computational analyses. IDR includes also articles, instructional resources, analysis and visualization tools as well as advanced search routines.







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