Your Immune System

An educational tool for patients, healthcare providers and managed care practitioners

IMMUNOe
HEALTH CENTERS
excellence in immune health

Introducing your immune system

THE GOAL OF THIS MATERIAL IS TO:

- Increase your understanding of the immune system
- Gain understanding of the role the immune system plays in primary and secondary immune deficiency
- Expand your understanding of how the immune system links to other disease states
- Explain how intravenous immunoglobulins (IGIV) can replace missing components of the immune system or modulate a dysregulated immune system

To begin, we need to have an overview of the different components of the immune system and where IGIV can replace or correct a dysregulated immune system.

What are immune deficiencies?

It is possible for any number of disorders and diseases to affect the immune system and cause immune system diseases. Some of these disorders are characterized by the failure of the body's immune system to recognize or react against a host of foreign materials or infectious particles, including bacteria or viruses.

PRIMARY IMMUNE DEFICIENCY (PID)

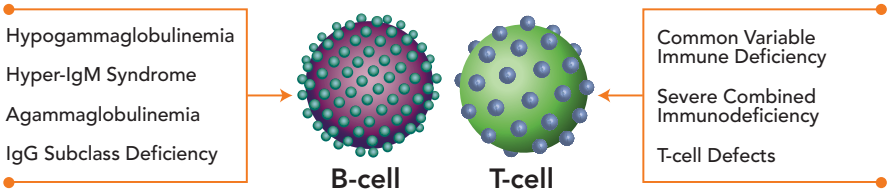
'Primary immune deficiency', or PID, is a term used to describe diseases in which the failure of the immune system occurs as the result of an intrinsic congenital defect within the immune system itself. Although most PID diseases are present in infancy and childhood, many patients do not display significant symptoms until they become adults.

Primary immune deficiency diseases have been divided into B-cell and T-cell defects: these disorders occur when either genetic inheritance or genetic mutation causes a defect within the immune system.

Primary immune deficiency syndrome goes undiagnosed in one of every 500 Americans. On average, it takes 10 years to diagnose PID.

MECHANISM OF DISEASE

B-cells and T-cells are the main players in immune deficiency.



10 warning signs of PID:

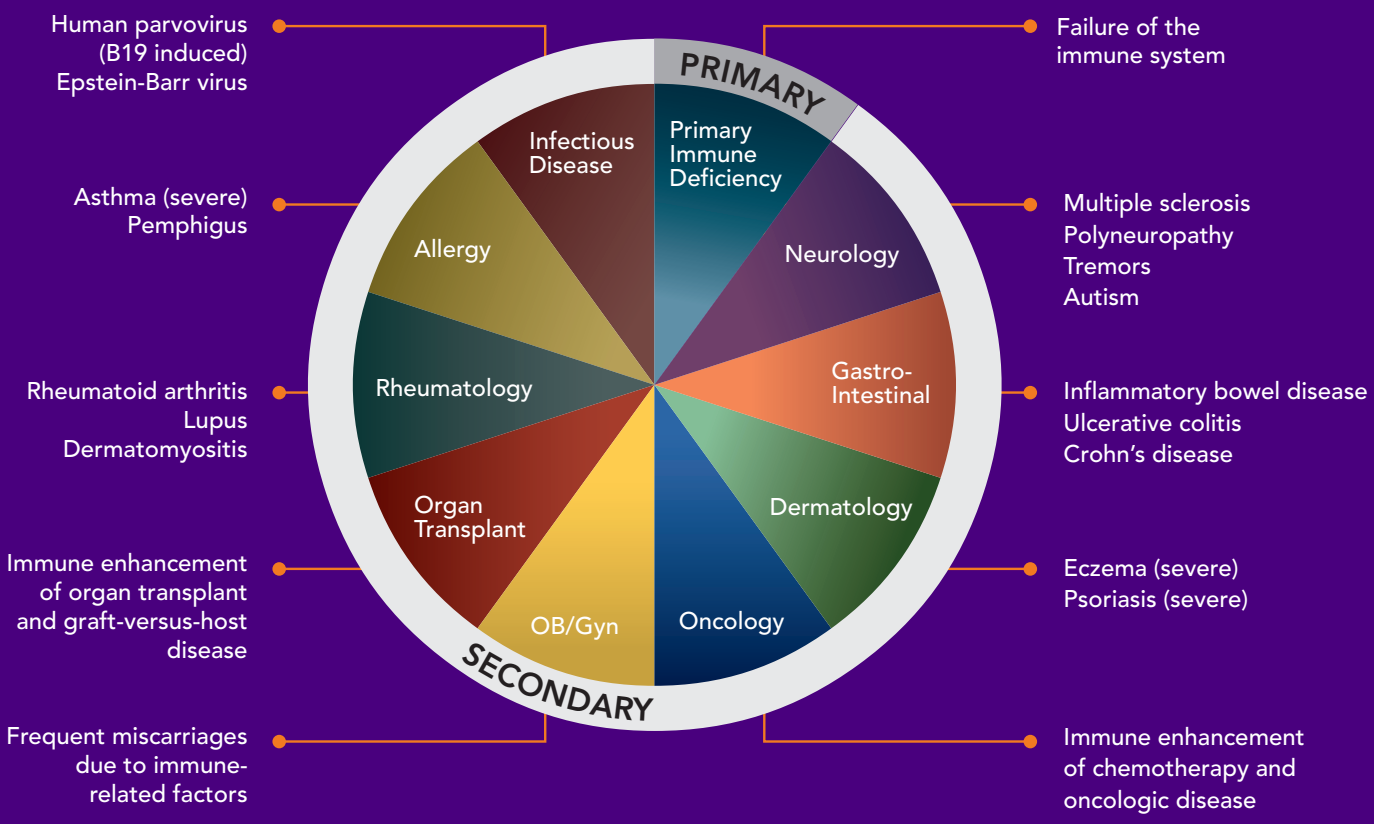
1. Eight or more new ear infections within one year
2. Two or more serious sinus infections within one year
3. Two or more months on antibiotics with little effect
4. Two or more cases of pneumonia within one year
5. Failure of an infant to gain weight or grow normally
6. Recurrent deep skin or organ abscesses
7. Persistent thrush in the mouth or else-where on skin after one year
8. Need for IV antibiotics to clear infections
9. Two or more deep-seated infections in one year
10. A family history of primary immune deficiency

SECONDARY IMMUNE DEFICIENCY

Secondary immune deficiencies occur when an environmental factor damages the immune system. While there are many potential causes of secondary immune deficiencies, bacterial and viral infections, radiation and chemotherapy are the primary contributors.

Since every person's genetic make-up and environmental profiles are different and unique, symptoms of a dysregulated immune system can vary widely from patient to patient. An immunologist trained to understand the links in symptoms will be able to determine the underlying cause.

PRIMARY AND SECONDARY IMMUNE DEFICIENCIES



Your immune system

THE SYMPHONY OF THE IMMUNE SYSTEM

The immune system can be likened to a 'symphony'. In order for beautiful music to be made, many different players must function in harmony. The same is true for a healthy immune response. In order for this extremely complex interaction to function properly, all individual members must 'play' their part in order.

INNATE VERSUS ADAPTIVE IMMUNE SYSTEM

Both innate and adaptive immunity have humoral (fluid) and cellular components.

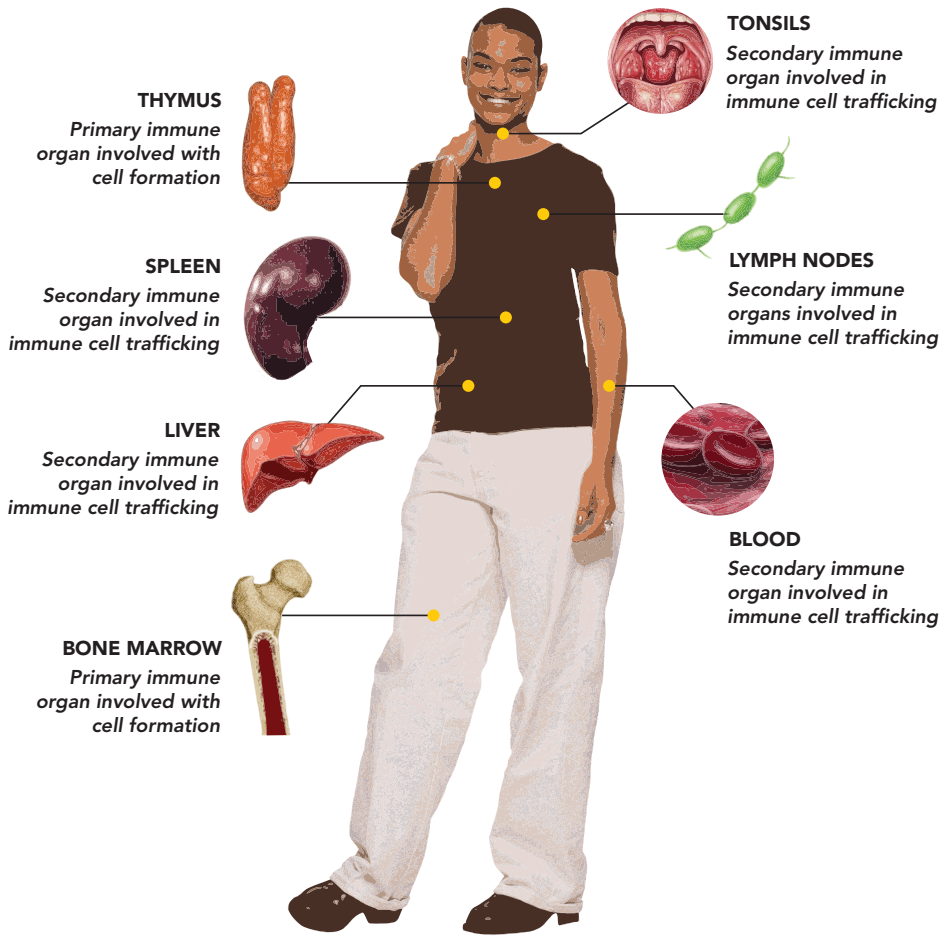
Cellular Component—All immune system cells originate in the marrow from either myeloid or lymphoid stem cells. Myeloid stem cells differentiate to form platelets, red blood cells, neutrophils, monocytes/macrophages and dendritic cells, while lymphoid stem cells form B-lymphocytes (B-cells), T-lymphocytes (T-cells) and natural killer cells (NK). T-cells express different peptides on their membranes and are designated by those peptides. For example, CD4+ T-cells express CD4 on the cell membrane and are thusly designated.

Humoral Component—The humoral component is derived from secretory proteins released from immune cells that are directed against specific antigens or stimulatory proteins.

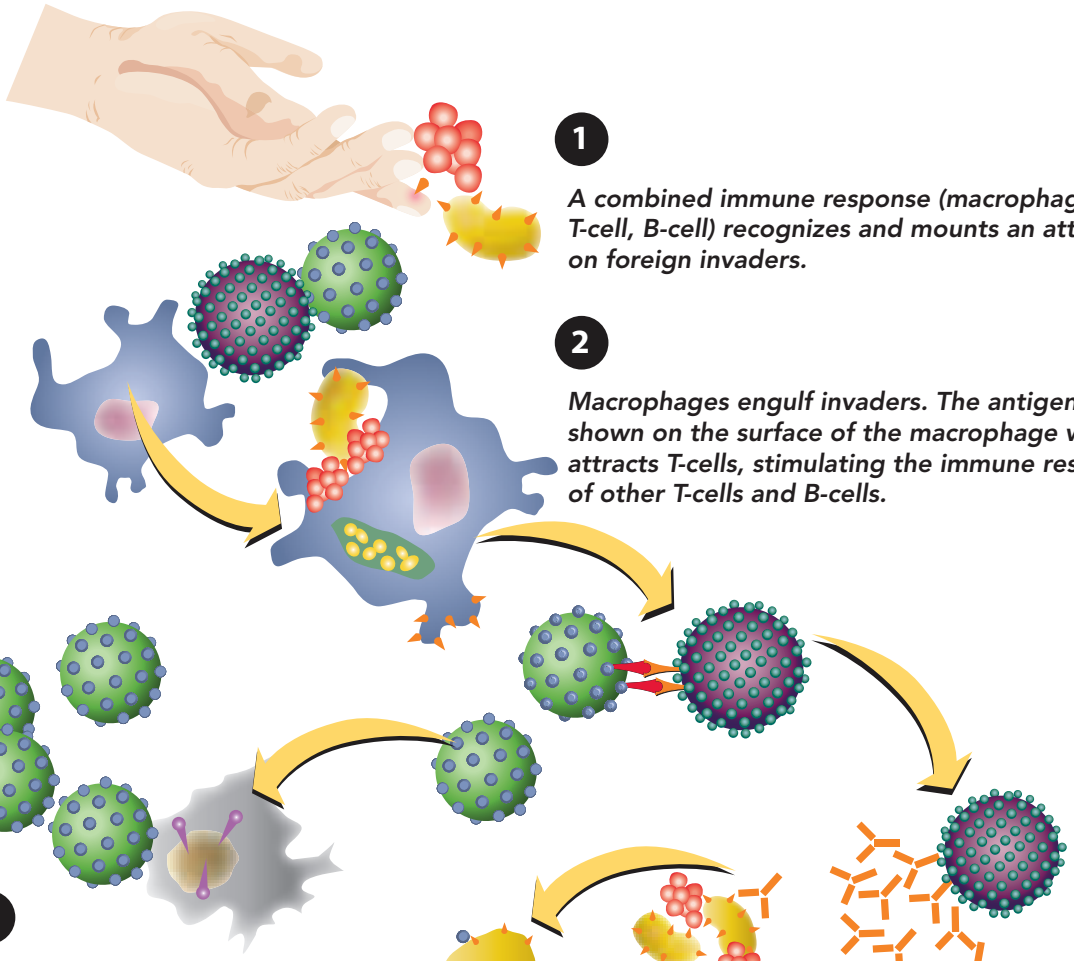
Adaptive Immune Response—The adaptive immune response, lymphocyte activation, requires antigen presentation plus the presence of cytokines to become activated. 'Lymphocyte activation' is defined as an increase in proliferation and the functional differentiation of the various lymphocyte lineages.

Immune Response—It is the combined fighting capabilities of the innate and adaptive system that orchestrate the immune response.

OVERVIEW OF THE IMMUNE SYSTEM



IMMUNE SYSTEM RESPONSE



1

A combined immune response (macrophage, T-cell, B-cell) recognizes and mounts an attack on foreign invaders.

2

Macrophages engulf invaders. The antigen is shown on the surface of the macrophage which attracts T-cells, stimulating the immune response of other T-cells and B-cells.

3

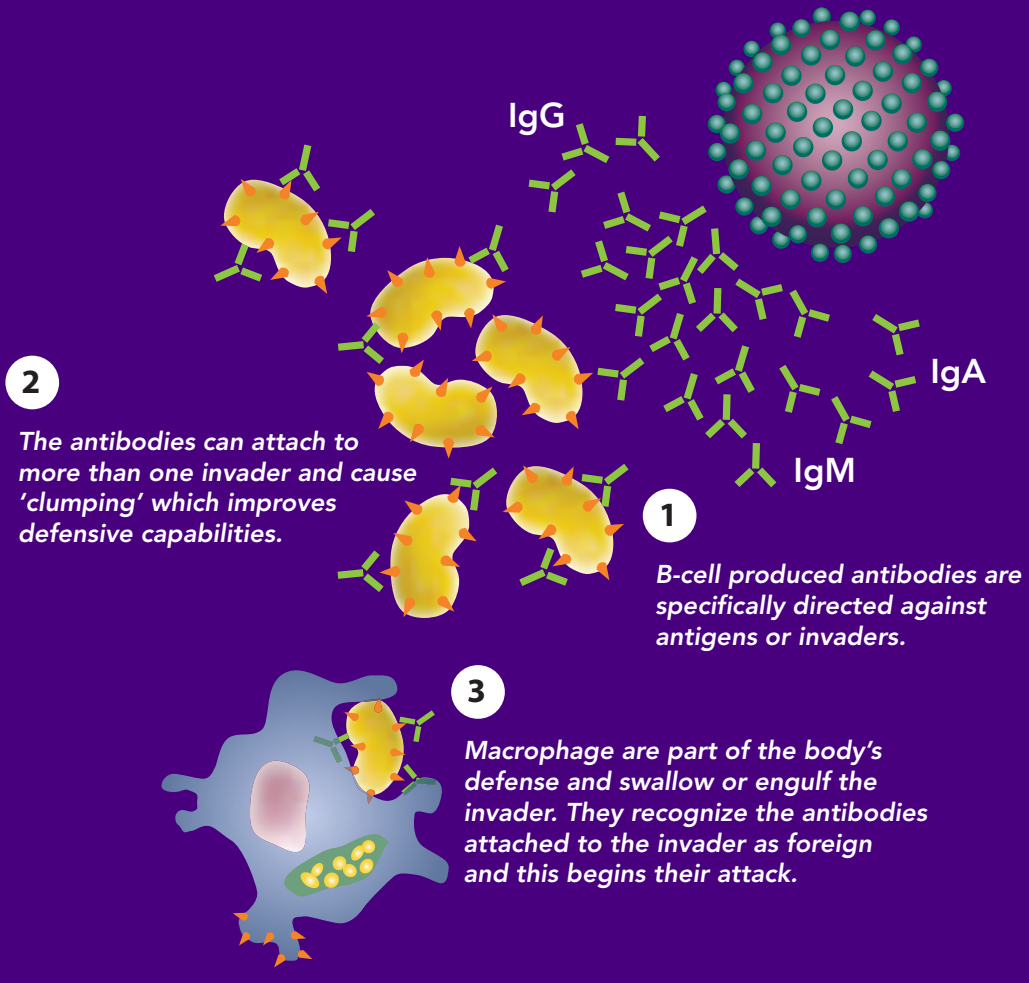
Specialized T-cells (killer T-cells) formed in response to the helper T-cell stimulation attack macrophages which engulf viruses.

4

Antibodies continue to bind to the bacterial invaders until all are destroyed.

HUMORAL

Humoral immunity is mediated through either cytokine release or by antibodies secreted from B-cells that are specific to antigens. These antibodies are formed and secreted by B-cells after a previous encounter with antigens. Antibodies, it should be noted, bind to antigens on the surface of the invading organism.



CELLULAR T-CELLS

T-cells originate from lymphoid stem cells; some migrate to the thymus to differentiate and become CD4+ T-helper cells or CD8+ pre-cytotoxic T-cells. The T-helper cells can express as 1) TH1, which help the CD8+ T-cells differentiate into cytotoxic or suppressor T-cells or 2) TH2, which help the B-cells differentiate into plasma cells which secrete antibodies. The ratio between CD4/CD8 cells is a noteworthy measurement of activation or inflammation. The T-cells that do not migrate to the thymus become NK cells.

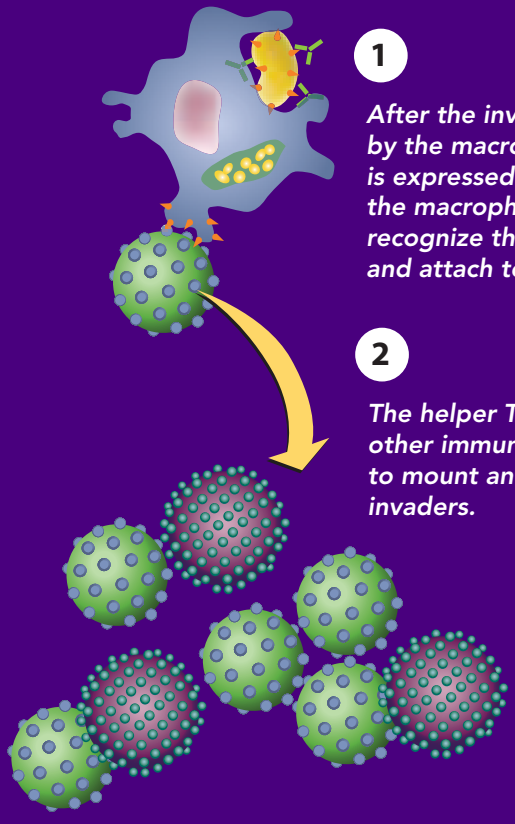
Both T-cell formation and function are extremely complex and specialized. Various T-cell levels play important roles in a healthy immune system as dysregulated or unbalanced numbers within the body can lead to numerous disorders.

T-REGULATORY CELLS

Regulatory T-cells, also known as suppressor T-cells, are CD8+ T-cells. Needed to maintain balance within the immune system, they are a critical 'self-check mechanism' and are responsible for suppressing the activated immune system: they prevent the immune system from over-reacting. Regulatory T-cells help shut down the immune response after attacking an invader and prevent an over- reactive immune system from attacking 'self'. They are key to understanding and measuring autoimmune diseases.

T-CELL FUNCTION

Even if the number of T-cells is within the normal range, their function may not be normal. For unknown reasons T-cells may not be active or give the proper reaction. T-cell function needs to be tested by stimulation to see if a response can be mounted.



1

After the invader is engulfed by the macrophage, the antigen is expressed on the outside of the macrophage. Helper T-cells recognize the antigen as foreign and attach to it.

2

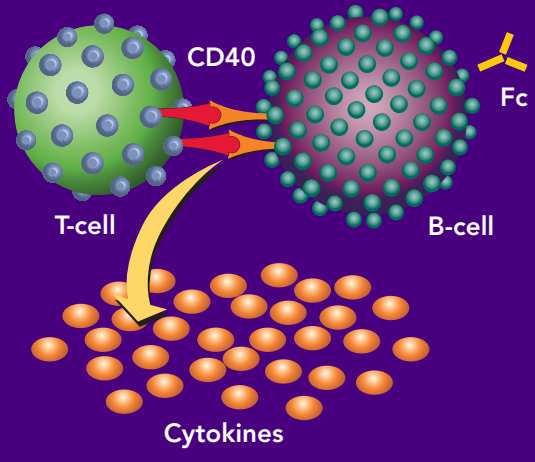
The helper T-cell then stimulates other immune cells and T-cells to mount an attack against the invaders.

ROLE OF CYTOKINES IN IMMUNE DISEASE

Cytokines are small peptides that are produced in multiple cell types. Depending on the type of cells from which they originate, as well as their target cells, they may have more than one function. Cytokines can affect distant target cells by traveling through the blood stream (endocrine); they can also impact cells that are nearby (paracrine) or those that are within the cell that produces it (autocrine). Cytokine levels and expression are crucial to a well-balanced immune system and can be used to monitor various disorders. Some well-known cytokines are the interferons and interleukins.

LINKAGE BETWEEN HUMORAL AND CELLULAR

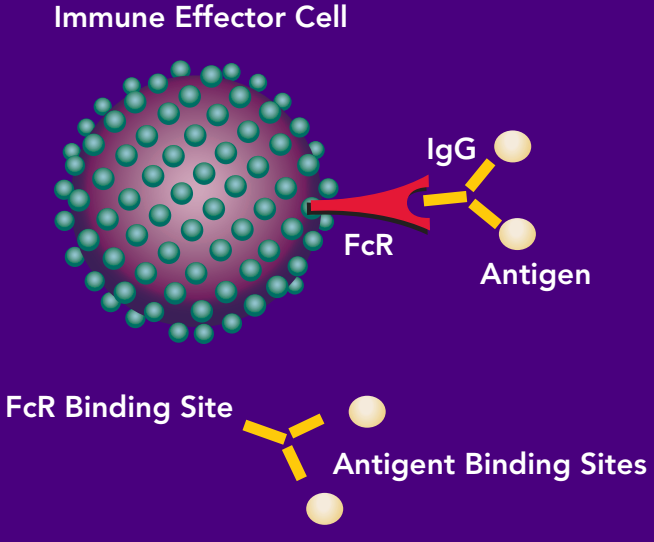
The role of CD40 ligand—The interaction between the antigen-presenting B-cell and the antigen-specific responding T-cell is critical for the initiation of the immune response. The T-cell response coupling is followed by the engagement of accessory molecules that stabilize the interaction and regulate subsequent cellular responses. One important interaction is that of the B-cell CD40 molecule with the T-cell CD40 ligand (molecule). Interactions such as this are necessary to promote the efficient activation of both cell types.



FCγ RECEPTOR MEDIATES IGG FUNCTION

Fcγ receptors are found on monocytes, B cells, macrophages, NK cells, neutrophils, eosinophils, mast cells and platelets.

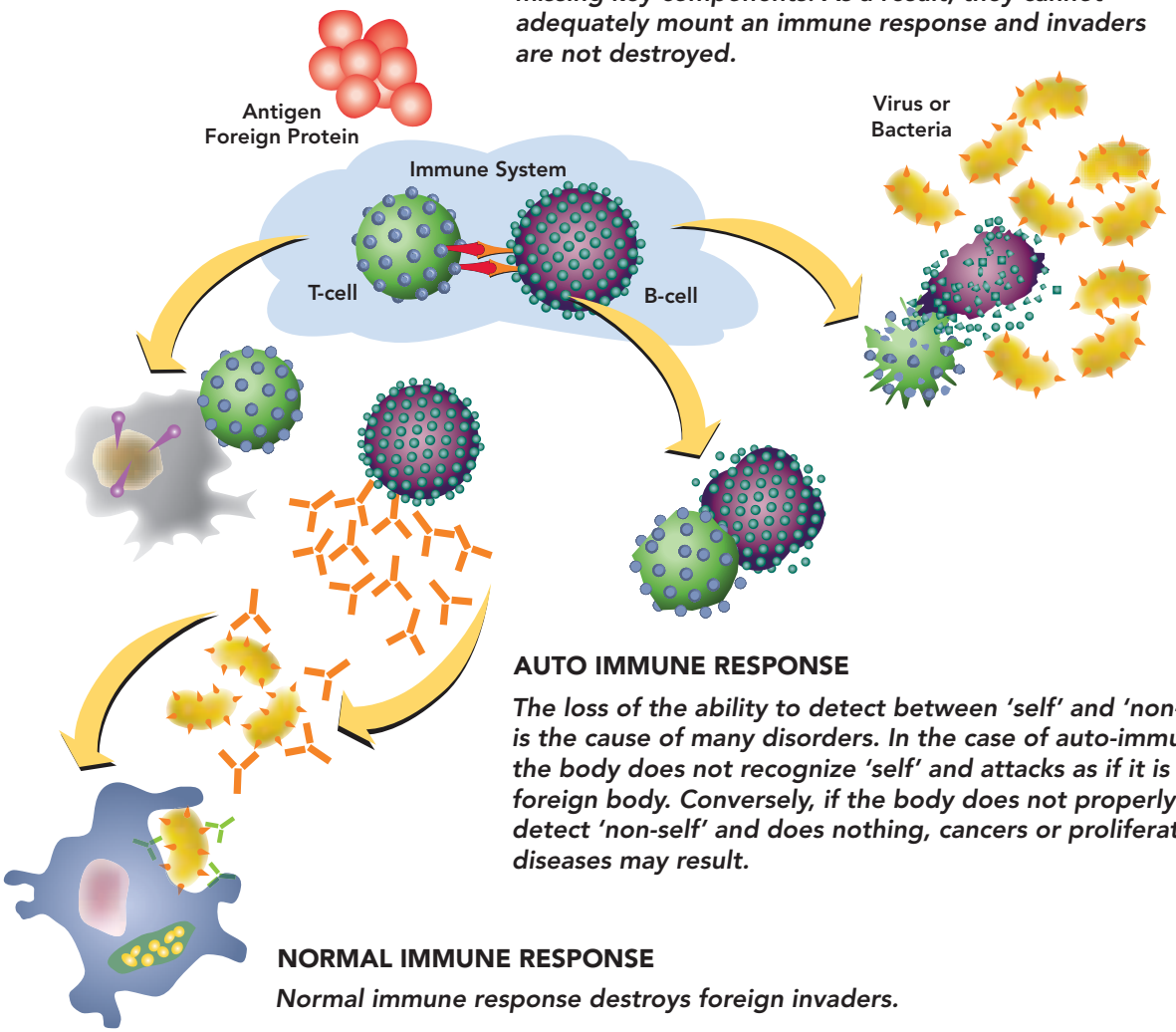
FcR binding site on IgG molecule binds to Fcγ receptor to mediate antibody function.



WHEN THE IMMUNE SYSTEM MALFUNCTIONS

WEAK OR NO IMMUNE RESPONSE (PID)

B-cells or T-cells either do not function properly or are missing key components. As a result, they cannot adequately mount an immune response and invaders are not destroyed.



AUTO IMMUNE RESPONSE

The loss of the ability to detect between 'self' and 'non-self' is the cause of many disorders. In the case of auto-immunity, the body does not recognize 'self' and attacks as if it is a foreign body. Conversely, if the body does not properly detect 'non-self' and does nothing, cancers or proliferative diseases may result.

NORMAL IMMUNE RESPONSE

Normal immune response destroys foreign invaders.

Who is a candidate for IGIV therapy?

When diagnosing an immune deficiency, many factors must be taken into consideration:

- Medical history
- Infection history
- Autoimmune history
- Laboratory support of immune deficiency
- Imaging (sinus CT or chest CT)

CANDIDATES FOR IGIV THERAPY CHECKLIST

- Frequently exhibit recurring illnesses without explanation
- Suffer from chronic sinus, viral, bronchial or respiratory infections
- Have recurring infections that are more severe when they return, requiring more time for recovery
- Often require antibiotics
- Often experience body aches, feel fatigued, listless or lethargic

GUIDELINES FOR IGG REPLACEMENT AUGMENTATION

- IgG < 200 mg/dL: all patients
- IgG 200 – 500 mg/dL: when a specific antibody deficiency is identified and frequent infections are documented.
- IgG > 500: When a specific antibody deficiency is identified and severe/recurrent infections are documented.

Treatment for immune deficiency

IMMUNE REPLACEMENT FOR IMMUNE DEFICIENCY

In cases of primary immune deficiencies (PID), where components of the immune system are missing, IGIV is used as replacement therapy. In such cases, IGIV helps to improve a patient's overall quality of life by reducing both the number of infections and the deleterious side effects caused by the disorder.

IMMUNE MODULATION FOR IMMUNE-RELATED DISEASES

In the case of secondary immune deficiency, studies have shown that IGIV can be used to restore balance to a dysregulated immune system. Often, a series of seemingly unrelated symptoms are really the result of such a dysregulated system. In these instances, correction by immune modulation is prescribed.

INDICATIONS FOR USE

Even if the number of T-cells is within the normal range, their function may not be normal. For unknown reasons T-cells may not be active or give the proper reaction. T-cell function needs to be tested by stimulation to see if a response can be mounted.

FDA approved

Allogeneic bone marrow transplant

Chronic lymphocytic leukemia

Idiopathic thrombocytopenic purpura

Pediatric HIV

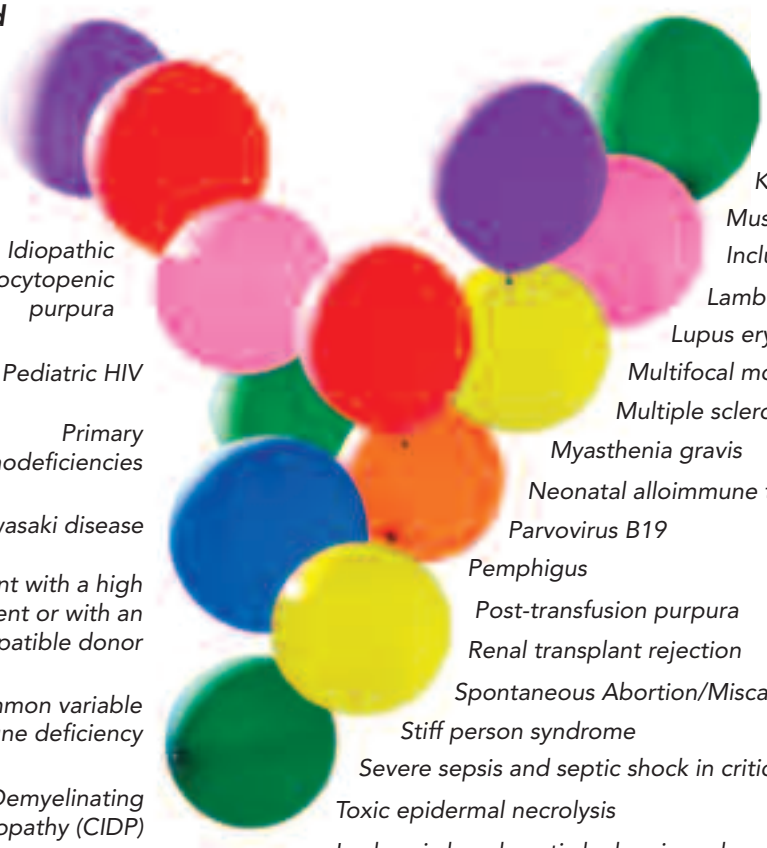
Primary immunodeficiencies

Kawasaki disease

Kidney transplant with a high antibody recipient or with an ABO incompatible donor

Common variable immune deficiency

Chronic Idiopathic Demyelinating Polyneuropathy (CIDP)



Common off-label approved

Dermatomyositis and polymyositis

Graves' ophthalmopathy

Guillain-Barré syndrome

Kawasaki disease

Muscular Dystrophy

Inclusion body myositis

Lambert-Eaton syndrome

Lupus erythematosus

Multifocal motor neuropathy

Multiple sclerosis

Myasthenia gravis

Neonatal alloimmune thrombocytopenia

Parvovirus B19

Pemphigus

Post-transfusion purpura

Renal transplant rejection

Spontaneous Abortion/Miscarriage

Stiff person syndrome

Severe sepsis and septic shock in critically ill adults

Toxic epidermal necrolysis

In chronic lymphocytic leukemia and multiple myeloma, as well as various rare deficiencies of immunoglobulin synthesis (e.g. X-linked agammaglobulinemia, hypogammaglobulinemia), IVIG is administered to maintain adequate immunoglobulin levels to prevent infections.

Immunoglobulin replacement therapy

WHO CAN BENEFIT FROM IG REPLACEMENT THERAPY OTHER THAN IMMUNE DEFICIENCY?

In certain patients, antibody deficiency can be transient. Among individuals for whom this is true may be adults undergoing cytotoxic chemotherapy as part of their cancer treatment and all patients receiving bone marrow transplants.

Many patients who do not have antibody deficiency diseases are prescribed IGIV because of its immuno-modulatory and/or anti-inflammatory properties. In the pediatric population, the most common such condition for which IGIV is prescribed is Kawasaki Syndrome. IGIV is also used in the treatment of Idiopathic thrombocytopenic purpura (ITP) and Guillain-Barre Syndrome. Recently, neuro-immune indications were expanded to include chronic idiopathic demyelinating (CIPD), as well as other autoimmune diseases.

A FEW FACTS ABOUT IMMUNOGLOBULIN

- Without question, immunoglobulin (Ig) replacement yields impressive benefits in the treatment of primary antibody deficiencies. In fact, no other therapy has proven to be as successful in reducing the number and severity of infections.
- The optimal dose of IGIV needed to achieve reduction goals is still a matter for investigation. Typically, the dose can be between 400 – 800 mg/kg body weight. While the average half-life of IgG is 21 days, IgG metabolism shows significant variation among individuals.
- Active infection, endocrine disorders and autoimmunity have all been associated with increased IgG catabolism.
- Residual serum IgG, also called trough levels, should be monitored every two months until 'steady state' has been reached, and every six months after that.

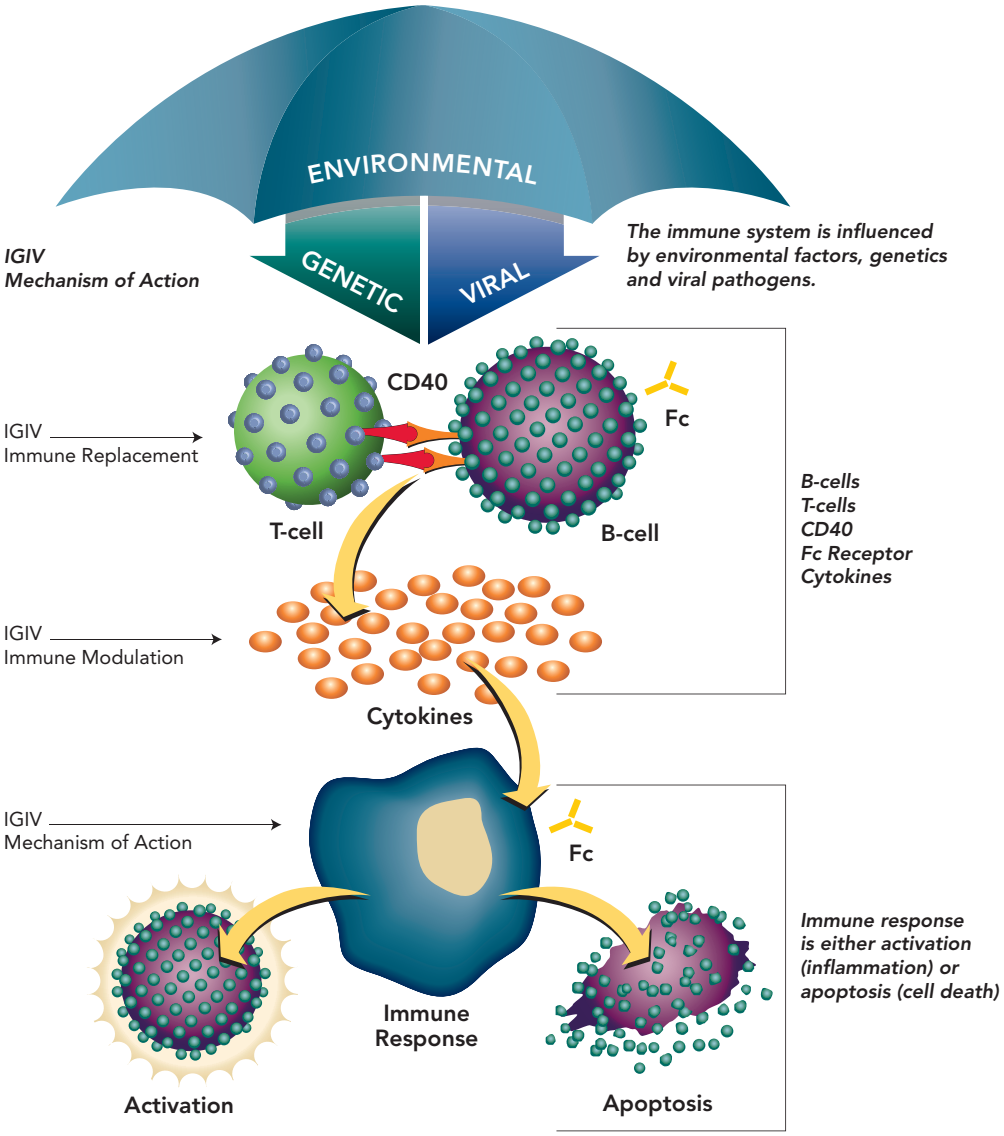
PRODUCT

All commercial IGIV products are produced from large pools of human plasma. Donors are screened for antibodies to syphilis, HIV-1, HIV-2 and HCV, and for HBV and HIV antigens. Extremely sensitive tests for HCV, HIV-1, HBV and Parvovirus B-19 nucleic acids have recently been introduced and are now being used to further elimi-nate window period donation.

To separate out IgG, plasma is fractionated via cold ethanol fractionation. Most viral components are removed during the fractionation, with further cleaning by viral inactivation and nano-filtration.

SIDE EFFECTS

- Side effects are also referred to as adverse drug reactions.
- Mild or moderate side effects typically occur due to the manner in which the treatment is administered; these side effects can be managed.
- Serious side effects are rare and can be reduced by screening the patient for factors that predispose them to complications.
- Anaphylactic and anaphylactoid reactions to IGIV therapy can occur in any patient at any time.
- Nearly all side effects can be safely controlled; often, they can be eliminated altogether.



POTENTIAL TARGETS FOR IGIV

Often times, when the immune system malfunctions, it ceases to provide people with all the protectors they need or with the ability to fight off diseases. In such cases, infection can develop. If infections are persistent, resist treatment or recur, a physician may prescribe IGIV to replace the immunoglobulins that help the body destroy the germs that cause the infection(s).

Patients' most commonly asked questions

HOW DO I GET INSURANCE AUTHORIZATION?

Once a diagnosis is confirmed, a case summary will be submitted to your insurance company; included in the summary will be your physician's request for authorization for IGIV therapy. Although you and your physician function as a team, it is vital that you take an active role in advocating for yourself (or for a family member) with your insurance company--experience has shown that YOU are your own best champion. Whenever possible, we recommend that you request that a patient care coordinator, who will serve as your main point of contact, be appointed by your insurance company. This will not only make it easier to address any questions which may arise, but will speed the process along and allow you to stay informed about the status of your infusion billing, as well.

It's important to know that it can take several months to gather and prepare all of the necessary medical history and summary reports for submission to your insurance company. That is why it is critical that you work to ensure that all medical records requested by your physician arrive in a timely manner. Please remember that this is a process... and, frequently, a lengthy one at that.

After you receive insurance authorization, you will be scheduled for either a telephone conference or pre-infusion visit (this will be determined by your physician's orders). During that conversation, you will be able to discuss what you should expect and what you need to do to prepare for your first infusion.

HOW OFTEN WILL I RECEIVE IGIV?

IGIV infusions may be scheduled every 21 – 28 days, depending on your diagnosis and your physician's recommendation. You will need to select a day of the week that best fits both your schedule and that of the infusion center.

WHAT SHOULD I DO TO GET READY FOR MY INFUSION?

It is extremely important that you be rested and well hydrated throughout your treatment regimen. Beginning the day before, and continuing throughout your infusion and for two days afterwards, you will need to drink large amounts of fluids. We highly recommend that the fluids contain electrolytes (e.g., Gatorade or Smart Water), as IGIV is a concentrated solution of immune proteins. By doing this one simple thing, you may be able to significantly reduce the possibility of experiencing any side effects.

It should be noted that some physicians recommend 'pre-medication' for IGIV infusions and others do not. Pre-medications are frequently used to reduce possible side effects; they can include antihistamines (taken several days pre- and post-infusion), or short-acting steroids given intravenously just before the infusion itself. Your physician will discuss these options with you.

WHAT DO I DO IF I'M SICK?

If you are not feeling well, or are sick the day before your infusion, it is imperative that you call and talk to the nurse. It may be that you will need to delay your infusion until you are well. You may also receive a call the day before your scheduled infusion to confirm your appointment. If you are sick the day of your infusion, you must call the center as soon as possible to insure that they do not prepare your product: IGIV is extremely valuable and doing so will avoid waste and expense. (Other centers may wait until you arrive to prepare your product.)

WHAT SHOULD I EXPECT THE DAY OF INFUSION…AND HOW SHOULD I PREPARE?

Prior to your visit, your immunologist will calculate the amount of IGIV, in grams, that will be infused. The dosage, which is based on your weight and diagnosis, will determine the length of the infusion process. You may want to inquire about approximately how long your infusion will last before you come to the center so that you can plan accordingly. As IGIV infusions can last from 2 to 6 hours, you will want to be prepared—you may wish to bring something to drink or eat; you may also want to bring a book or a laptop to keep up with work or homework. Some infusion centers offer TVs, DVDs, internet access and gaming centers for children but each are different so it's best to ask about what amenities are provided prior to your appointment.

We recommend that you wear comfortable clothing the day of your infusion. You may also want to bring something that makes you feel 'comfy' or 'cozy', such as blankets, pillows, stuffed animals, etc. This is especially important with young patients—be sure to bring something that will ease their fears, calm their nerves or make the infusion experience be as positive as possible. There have been a number of books written to educate young children about the infusion process. You may want to ask the staff at your infusion center if they have these books available to read ahead of time so that your child...and you...will have a good understanding of what will be happening.

When you arrive at the center, the infusion nurse will insert a catheter to start your IV; the arms and hands are the most common insertion sites. An IV bag that contains your IGIV product will then be attached to the catheter. At first, the rate of infusion will be low. If you easily tolerate the procedure (your vital signs will be closely monitored throughout), your nurse will begin, using prescribed increments, to increase the rate until the highest allowed rate is achieved. The rate of increase will most likely be slower during your first visit; during subsequent sessions, it may be faster, as indicated by your ability to tolerate the infusion. As mentioned before, the length of your infusion will be determined by rate and dosage.

Remember to drink plenty of fluids, eat (as needed) and relax as much as possible during your infusion.

WHAT SHOULD I EXPECT AFTER MY INFUSION?

You may feel tired or lethargic after your infusion. This is very normal, so rest as much as possible. Be sure to continue to drink lots of fluid for the next 48 hours.

It's possible that you may experience some side effects from your infusion (although some patients do not). The most common adverse reactions are:

- Eczema
- Nausea
- Asthma symptoms
- Tiredness
- Skin Rashes
- Vomiting
- Achiness
- Loss of appetite
- Headache
- Fever
- Eye pain
- Joint pain

Side effects generally last for only a few days. If they continue longer, you need to talk to your nurse so that she or he can relay this information to your physician. Pre-medications or other methods may be prescribed to reduce your side effects. We know that it can be difficult to remember details between infusion visits, so we recommend that you keep a diary so that you pass on all information—negative and positive--to your infusion nurse.

Remember--the more you take care of yourself by resting, eating right and drinking large amounts of the appropriate fluids, the fewer side effects you may have.

WILL I FEEL BETTER…AND WHEN?

We encourage you to start watching for positive changes in your health and well being after your initial infusion. Although it may take several months to begin to feel improvement in your quality of life, some patients report noticing progress almost immediately.

- Among the improvements that patients, depending on their diagnosis, routinely begin to notice are:
- Fewer infections--and a reduction in the use of antibiotics
- Increased energy--and less fatigue
- Reduction in pain and pain medication (used for either joint discomfort or neuropathy)
- Fewer days missed from work or school
- Improved cognition
- Overall improvement in the quality of life

Many patients also report improvement in symptoms that they did not associate with their diagnosis. That is because a healthier immune system can positively impact other systems within the body, as well.

We cannot stress strongly enough how important it is that you maintain a consistent infusion cycle and keep regular appointments with your immunologist. When you do, you ensure that your condition--and your progress—is being managed in a way that enables you to achieve the highest level of improvement possible. The better your adherence, the better your outcome!

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