The image features three vertical DNA double helix structures on the left side of the page. Each helix is composed of two dark blue ribbons representing the sugar-phosphate backbone, twisted around each other. Between the ribbons are horizontal lines representing base pairs, colored in red, yellow, and blue. The background is a light blue gradient.

Immune Deficiency Foundation
**Diagnostic & Clinical
Care Guidelines**

for Primary Immunodeficiency Diseases

Readers may redistribute this article to other individuals for non-commercial use, provided the text, html codes, and this notice remain intact and unaltered in any way. The Immune Deficiency Foundation Diagnostic and Clinical Care Guidelines for Primary Immunodeficiency Diseases may not be resold, reprinted or redistributed for compensation of any kind without prior written permission from the Immune Deficiency Foundation.

SECOND EDITION

Copyrights 2008, 2009 the Immune Deficiency Foundation



Immune Deficiency Foundation

Diagnostic & Clinical Care Guidelines

for Primary Immunodeficiency Diseases

The Immune Deficiency Foundation, in partnership with expert immunologists, developed these diagnostic and clinical care guidelines to enhance earlier diagnosis, improve health outcomes and increase access to specialized health care and optimal treatment for patients with primary immunodeficiency diseases. The development and revision of the guidelines was funded by an unrestricted educational grant from Talecris Biotherapeutics.

The Immune Deficiency Foundation is the national patient organization dedicated to improving the diagnosis, treatment and quality of life of persons with primary immunodeficiency diseases through advocacy, education and research.

Table of Contents

| | |
|--|----|
| Primary Immunodeficiency Diseases | 3 |
| Introduction | 4 |
| Antibody Production Defects | 5 |
| Cellular or Combined Defects | 11 |
| Phagocytic Cell Immune Defects | 15 |
| Complement Defects | 19 |
| Practical Aspects of Genetic Counseling: General Considerations | 22 |
| Life Management Considerations | 24 |
| Health Insurance | 25 |
| Sample Physician Insurance Appeal Letter | 27 |
| Glossary | 28 |

EDITOR

Rebecca H. Buckley, MD

Duke University School of Medicine

CONTRIBUTORS

Mark Ballow, MD

Women and Children's Hospital of Buffalo
Division of Allergy and Immunology

Melvin Berger, MD, PhD

Case Western Reserve University

R. Michael Blaese, MD

Medical Director
Immune Deficiency Foundation

Francisco A. Bonilla, MD, PhD

Children's Hospital, Boston

Mary Ellen Conley, MD

University of Tennessee College of Medicine
St. Jude Children's Research Hospital

Charlotte Cunningham-Rundles, MD, PhD

Mt. Sinai School of Medicine

Alexandra H. Filipovich, MD

Cincinnati Children's Hospital

Thomas A. Fleisher, MD

Department of Laboratory Medicine, CC
National Institutes of Health, DHHS

Ramsey Fuleihan, MD

Children's Memorial Hospital, Chicago

Erwin W. Gelfand, MD

National Jewish Medical and Research Center

Steven M. Holland, MD

Laboratory of Clinical Infectious Diseases - NIAID
National Institutes of Health

Richard Hong, MD

University of Vermont School of Medicine
Department of Pediatrics

Richard B. Johnston, Jr., MD

University of Colorado School of Medicine
National Jewish Medical and Research Center

Roger Kobayashi, MD

Allergy, Asthma and Immunology Associates
UCLA School of Medicine

Howard Lederman, MD, PhD

Johns Hopkins Hospital

David Lewis, MD

Stanford University School of Medicine

Harry L. Malech, MD

Genetic Immunotherapy Section
Laboratory of Host Defenses - NIAID
National Institutes of Health

Bruce Mazer, MD

McGill University Health Center
Montreal Children's Hospital

Stephen Miles, MD

All Seasons Allergy, Asthma and Immunology

Hans D. Ochs, MD

Department of Pediatrics
University of Washington School of Medicine

Jordan Orange, MD, PhD

The Children's Hospital of Philadelphia

Jennifer Puck, MD

Department of Pediatrics
University of California San Francisco

William T. Shearer, MD, PhD

Texas Children's Hospital

E. Richard Stiehm, MD

Mattel Children's Hospital at UCLA
UCLA Medical Center

Kathleen Sullivan, MD, PhD

The Children's Hospital of Philadelphia

Jerry A. Winkelstein, MD

Johns Hopkins University School of Medicine

PRIMARY IMMUNODEFICIENCY DISEASES

ANTIBODY PRODUCTION DEFECTS

| DISEASE | COMMON NAME | ICD 9 CODE |
|--|--|------------|
| X-Linked Agammaglobulinemia (Bruton's) | Agammaglobulinemia, XLA | 279.04 |
| Common Variable Immunodeficiency (CVID) | Late Onset Hypo- or Agammaglobulinemia, CVID | 279.06 |
| X-Linked or Autosomal Hyper IgM Syndrome | Hyper IgM | 279.05 |
| Selective IgA Deficiency | IgA Deficiency | 279.01 |

CELLULAR OR COMBINED DEFECTS

| DISEASE | COMMON NAME | ICD 9 CODE |
|---|----------------------------|------------|
| Severe Combined Immunodeficiency | "Bubble Boy" Disease, SCID | 279.2 |
| DiGeorge Syndrome also known as 22q11 Deletion Syndrome | Thymic Aplasia | 279.11 |
| Ataxia Telangiectasia | AT | 334.8 |
| Wiskott-Aldrich Syndrome | WAS | 279.12 |

PHAGOCYtic CELL IMMUNE DEFECTS

| DISEASE | COMMON NAME | ICD 9 CODE |
|---------------------------------------|-------------|------------|
| Leukocyte Adhesion Defect | LAD | 288.9 |
| Chronic Granulomatous Disease | CGD | 288.1 |
| Chediak Higashi Syndrome | CHS | 288.2 |
| Cyclic Neutropenia Kostman Disease | Neutropenia | 288.0 |

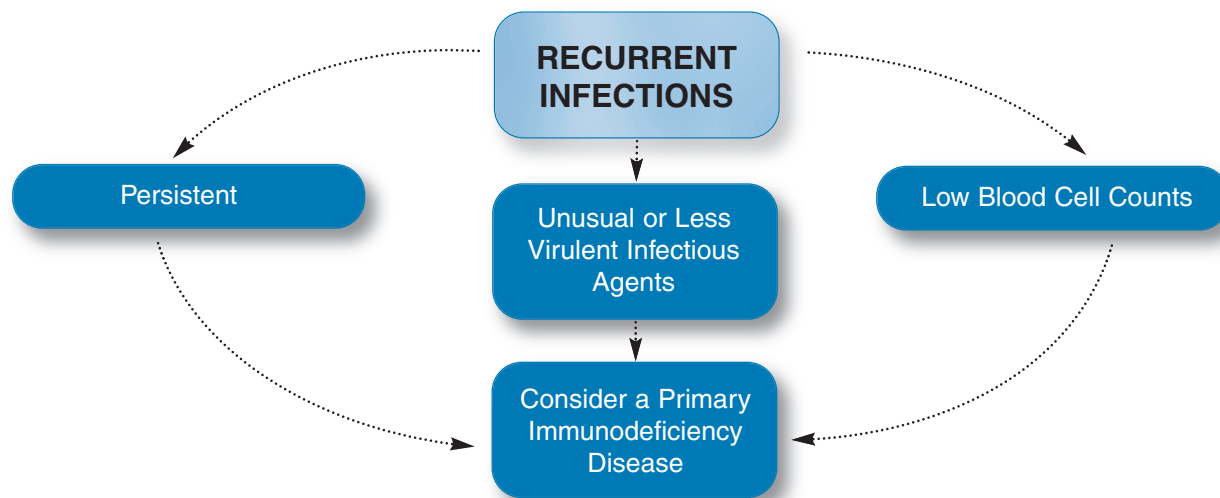
COMPLEMENT DEFECTS

| DISEASE | COMMON NAME | ICD 9 CODE |
|---|-----------------------|------------|
| C1 Esterase Inhibitor Deficiency | Hereditary Angioedema | 277.6 |
| Complement Component Deficiencies (e.g. C1, C2, C3, C4, C5, C6, C7, etc.) | Complement Deficiency | 279.8 |

INTRODUCTION

The hallmarks of primary immunodeficiency are recurrent or unusual infections. Some of the infections may be persistent and some may be due to unusual microorganisms that rarely cause problems in healthy people. The primary immunodeficiency diseases are a group of more than 150 genetically determined conditions that have an identified or to be determined molecular basis. Because most of these are lifelong conditions, it is very important to perform a detailed diagnostic evaluation before initiating therapies that will be continued in an open-ended fashion. The guidelines that follow

are intended to provide practical information for patients and health care providers who are concerned about whether or not an individual's immune system is functioning normally. Currently, no screening is performed for these defects at birth, during childhood or in adulthood. Therefore, primary immunodeficiency diseases are usually detected only after the individual has experienced recurrent infections that may or may not have caused permanent organ damage. There is obviously a great need for the early detection of these defects.



Suspect a primary immunodeficiency if:

- » There are recurrent infections or there is an unusual or persistent infection
- » A usually mild childhood disease takes a turn for the worse (may become life-threatening)
- » Blood cell counts are low or persistently high

KEY CONCEPTS

| SITE OF INFECTIONS | POSSIBLE CAUSE | SCREENING DIAGNOSTIC TESTS |
|--|--|---|
| Upper Respiratory Tract | Antibody or Complement Deficiency | Serum immunoglobulin levels, antibody titers to protein and polysaccharide vaccines; isohemagglutinins; CH50 |
| Lower Respiratory Tract | Antibody or Complement Deficiency; T Cell Deficiency; Phagocytic Cell Defect | Serum immunoglobulin levels, antibody titers to protein and polysaccharide vaccines; isohemagglutinins; CH50; WBC with manual differential to count neutrophils, lymphocytes and platelets; Respiratory Burst Assay |
| Skin, internal organs | Phagocytic Cell Defect | Respiratory Burst Assay/CD11/CD18 Assay |
| Blood or Central Nervous System (meninges) | Antibody or Complement Deficiency | Serum immunoglobulin levels, antibody titers to protein and polysaccharide vaccines; CH50 |

ANTIBODY PRODUCTION DEFECTS

Part A: Recognition and Assessment

An infection recurring in a single site is generally not indicative of a primary immunodeficiency disease. Rather it suggests an anatomic abnormality. On the other hand, several types of infections affecting various organ systems may be indicative of an underlying immunologic deficiency.

These infections and conditions include:

- ❖ Recurrent sinopulmonary infections
 - » Pneumonia with fever
 - » Sinusitis documented by X-ray or Computerized tomography (C-T) scan
 - » Otitis media (Although frequent ear infections are seen in normal children, an evaluation may still be indicated for individuals on a case by case basis.)
- ❖ Meningitis and/or sepsis (blood stream infection)
- ❖ Gastrointestinal infections
- ❖ Cutaneous (skin) infections

The occurrence of infections with unusual organisms also suggests the presence of a primary immunodeficiency disease. This is how some patients are diagnosed. Examples are atypical mycobacteria, which would suggest an IFN- γ R defect, or *Pneumocystis jiroveci*, which would suggest Severe Combined Immunodeficiency (SCID) or Hyper IgM syndrome.

In addition, certain types of autoimmune and allergic conditions may be associated with some types of primary immunodeficiency, including antibody deficiency disorders. Examples of autoimmune disorders include autoimmune endocrine disorders, rheumatic conditions, and autoimmune hemolytic anemia, neutropenia or thrombocytopenia (low platelet count). These autoimmune disorders are seen especially in patients with IgA deficiency, Common Variable Immunodeficiency (CVID), chronic mucocutaneous moniliasis (CMC or APCED), X-linked immune dysregulation, polyendocrinopathy and enteropathy (IPEX), autoimmune lymphoproliferative syndrome (ALPS) and Wiskott-Aldrich syndrome. Allergic disorders with elevated serum IgE can also be seen in IgA deficiency, Wiskott-Aldrich syndrome, the Hyper IgE syndrome, IPEX and Omenn syndrome.

Useful Physical Examination Findings

- ❖ Absence or reduced size of tonsils and lymph nodes in X-linked agammaglobulinemia and in X-linked Hyper IgM syndrome
- ❖ Enlarged lymph nodes and splenomegaly in CVID and autosomal recessive Hyper IgM syndrome

- ❖ Scarred tympanic membranes
- ❖ Unusual skin changes such as, complete absence of eyebrows and hair, severe eczema resistant to treatment, mouth thrush resistant to treatment after 4 months of age, candida skin infections, petechiae, vitiligo, recurrent or persistent warts or severe molluscum contagiosum
- ❖ Rales and rhonchi in lungs, clubbing of the fingers

Useful Diagnostic Screening Tests

- ❖ Complete blood count and manual differential
 - » These tests are of great clinical importance because they allow the physician to know whether the lymphocyte, neutrophil and platelet counts are normal. Many immune defects can be ruled out by these simple tests. In the setting of immunodeficiency disorders, the manual differential is more reliable than an automated differential.
- ❖ Quantitative serum immunoglobulin (IgG, IgA, IgM and IgE) levels
 - » Quantitation of immunoglobulin levels can be performed at any CLIA (Clinical Laboratories Improvement Act) approved laboratory. However, the assay results should be evaluated in the context of the tested patient's age and clinical findings. An important problem exists for IgA levels, which may be reported as the value at the lower limit of sensitivity of the method but may actually be zero. Most commercially available assays for IgA are not sensitive enough to distinguish between very low and absent levels. Results of all immunoglobulin measurements must be compared with age-adjusted normal values to evaluate their significance. IgG subclass measurements are rarely helpful.
- ❖ Measurement of specific antibodies to vaccines
 - » These tests are of crucial importance in determining whether there is truly an antibody deficiency disorder when the serum immunoglobulins are not very low or even if they are low. It is important to test for antibodies to both protein (i.e. tetanus or diphtheria) and polysaccharide (i.e. pneumococcal polysaccharides) antigens. Isohemagglutinins (antibodies to red blood cells) are natural anti-polysaccharide antibodies; if they are missing this also suggests an antibody deficiency disorder.

When these screening tests are not conclusive and the clinical suspicion of an immunodeficiency is strong, the patient should be referred to an immunologist for further evaluation before beginning immune globulin (IG) replacement therapy. This is particularly true

ANTIBODY PRODUCTION DEFECTS

| DISEASE | COMMON NAME | ICD 9 CODE |
|--|--|------------|
| X-Linked Agammaglobulinemia (Bruton's) | Agammaglobulinemia, XLA | 279.04 |
| Common Variable Immunodeficiency (CVID) | Late Onset Hypo- or Agammaglobulinemia, CVID | 279.06 |
| X-Linked or Autosomal Hyper IgM Syndrome | Hyper IgM | 279.05 |
| Selective IgA Deficiency | IgA Deficiency | 279.01 |

ANTIBODY PRODUCTION DEFECTS

for those who have been diagnosed with IgG subclass deficiency or “polysaccharide antibody deficiency.” The latter diagnoses are often based on the results of measurements of serum IgG subclass levels or tests of pneumococcal antibody titers. The results of such tests are highly variable from laboratory to laboratory and sometimes misinterpreted. If IG therapy is started before referral to an immunologist, it would seriously confound the ability of the immunologist to perform further immunologic testing. Therefore, it is very important that all of the tests listed in this section be done before IG replacement is started.

Part B: Management, Expectations, Complications and Long Term Monitoring

With the exceptions of selective IgA deficiency and transient hypogammaglobulinemia of infancy, patients with an identified antibody deficiency disorder are generally treated on at regular intervals throughout life with replacement IG, either intravenously or subcutaneously. IG therapeutic products are comprised of numerous IgG antibodies purified from blood or plasma donations from approximately 60,000 donors per batch. The half-life of these IgG antibodies is 19-21 days and the amounts of the other classes of immunoglobulins are extremely low, so they do not affect the patient's blood level of these proteins. The intervals between IG doses are generally 2 to 4 weeks for the intravenous route of administration and more frequently (1 to 14 days) for the subcutaneous route. An immunologist should participate in the determination of the proper dose and interval for IG therapy in each patient. Typical total monthly doses are in the range of 400 to 600 mg/kg body weight. Trough (pre-dose) blood levels of IgG can be evaluated more frequently initially and at least once a year after that to determine if there has been a change in the pharmacokinetics and resultant blood levels of IgG in a specific individual. IG dose adjustments are obviously necessary during childhood related to normal growth or during pregnancy. However, once an IG dose has been established for an adult, it is not usually necessary to routinely measure trough IgG levels unless the patient is not doing well clinically. The trough level should be at least at or above the lower range of normal for IgG levels or >500 mg/dl. This may vary depending on the judgment of an immunologist as to the patient's clinical condition. For example, in one study, when IgG trough levels in patients with agammaglobulinemia were maintained above 800 mg/dl, serious bacterial illness and enteroviral meningoencephalitis were prevented. Higher trough levels (>800 mg/dl) may also have the potential to improve pulmonary outcomes. It is important to recognize that, for virtually all confirmed antibody deficiencies, lifelong IG replacement is required.

IG replacement is preventive therapy, and the regular dose should not be considered adequate to treat infections. Many patients with antibody production disorders also benefit from the use of prophylactic antibiotics or adjunctive therapy with full dose antibiotics rotating on a monthly schedule. This is because IG

therapy only replaces IgG and there is no way to replace IgA in the patient's serum or external secretions. Patients with antibody deficiencies are at risk for developing chronic sinus and lung disease; therefore, it is best to obtain an annual assessment of pulmonary function and sinus or chest x-rays or perhaps high resolution C-T scans. Families should expect that their affected relative will have decreased absences from school and/or work with proper therapy. However, while sepsis and meningitis attacks will stop with IG treatment, sinopulmonary and gastrointestinal infections may continue to occur, although with less frequency.

If there is evidence of bronchiectasis in an individual with an antibody deficiency disorder, a high-resolution C-T scan of the lungs should be obtained and repeated as needed or if therapy is altered to monitor progression. Excessive scanning should be avoided.

Spirometry (lung breathing tests) should also be performed annually or at 6-month intervals if the disease appears to be progressing adversely at a more rapid rate. Complete pulmonary function testing should also be done periodically in CVID patients who have interstitial lung disease in order to measure their diffusion capacities. Liver and renal function blood tests should be checked prior to beginning IG therapy and at least once a year thereafter.

In the face of any abnormal neurologic or developmental findings, a baseline lumbar puncture (spinal tap) for the examination of spinal fluid may be helpful in detecting an insidious meningoencephalitis (brain) infection due to enterovirus, particularly in patients with X linked (Bruton's) agammaglobulinemia. Developmental assessments of such children should also be obtained annually or at 6-month intervals if the disease appears to be progressing adversely at a more rapid rate.

From a prognostic point of view, antibody deficient patients determined to have B cells by flow cytometry (e.g. likely to have CVID) are also at risk for autoimmune disease complications.

Granulomatous lesions in the skin, liver, spleen and lungs in patients with CVID may be misdiagnosed as sarcoid and their occurrence also diminishes the prognosis.

Patients with CVID, Bruton's agammaglobulinemia or X-linked Hyper IgM may present with chronic diarrhea and have malabsorption due to infection with parasites, e.g. *Giardia lamblia* or *Cryptosporidium*, or from overgrowth in the small intestines with certain types of gram negative bacteria, e.g. *C. difficile*.

IG Therapy When Diagnosis is Uncertain

When there is uncertainty of the diagnosis, and IG replacement has already been started, it is useful to reassess the need for IG treatment. This is particularly true if the patient's serum contains IgA, IgM and IgE, which are not present in significant amounts in IG preparations. If these classes of immunoglobulin are present in the patient's serum, this means that the patient is producing them. However, the serum IgG level and antibody titers to vaccine antigens could all be from the IG therapy. To further evaluate whether the patient can produce IgG antibodies normally, the patient can be challenged with a neoantigen (e.g. a vaccine not routinely administered, such bacteriophage phi X174) for which

ANTIBODY PRODUCTION DEFECTS

there is no specific antibody in IG preparations. While bacteriophage immunizations are useful because it is not necessary to discontinue IG replacement when they are given, the vaccine and testing are available at only a few research institutions under an IND application. Alternately, only under the advisement of an immunologist, IG treatment can be stopped in the spring or summer when infection risks are less. After three months the patient can be reimmunized with standard killed vaccines and the antibody titers to these vaccines tested two to three weeks later. If the patient's serum immunoglobulins and antibody titers to bacteriophage phiX174 and/or to vaccine antigens are found to be in the normal range, then IG replacement is not necessary. Skin testing for allergies is also useful; individuals who have positive allergy skin tests are producing IgE antibodies to the allergens and are not likely to need IG replacement.

Monitoring IG Therapy in Antibody Deficient Patients

Frequency of testing for trough levels

- ❖ Monitor IgG levels at least once a year (more often if the patient is having infections) just before the next infusion. Be aware that gastrointestinal tract infection with the parasite *Giardia lamblia* or other enteropathies can cause enteric loss of IgG leading to unexpectedly low IgG levels. Generally, once the optimal dose of immune globulin has been established in a patient, monthly monitoring of the IgG level is not indicated unless there is protein loss through the GI or urinary tracts.

Long-term follow up of patients on IG therapy

- ❖ Evaluations regarding hepatitis A, B, and C by PCR (polymerase chain reaction) screening may be indicated. Yearly PCR screening for hepatitis C is the standard of care in European Union countries.

Adverse event monitoring on IG therapy

- ❖ Every 6-12 months creatinine level and liver function tests are useful.

Other Screenings

Cancer screening may be indicated on a periodic basis, as it is for individuals with intact immune systems. Some subgroups of those with a primary immunodeficiency disease, such as patients with CVID, particularly those with chronic lymphadenopathy may merit baseline complete pulmonary function studies, CT, MRI and/or PET scans and more intensive screening. Lymphoma evaluation is the same as for those without hypogammaglobulinemia. Useful diagnostic screening tests for malignancy include determination of uric acid, LDH (lactic dehydrogenase) and ESR (erythrocyte sedimentation rate).

Vaccinations

Patients receiving regular infusions of IG possess passive antibodies to the agents normally given in vaccines. Thus, while a patient is receiving IG, there is no need for immunizations. Some immunologists recommend influenza vaccination, but the patient is unlikely to respond to it with antibody production. However, all household contacts should receive regular immunizations with killed vaccines, particularly annual influenza immunizations. Live virus

vaccines, even if attenuated, pose a substantial risk to certain individuals with primary immunodeficiency diseases. These vaccines include the the new rotavirus vaccines (Rototek® or Rotorix®), oral polio vaccine, mumps, measles and German measles (rubella) vaccine (MMR®), yellow fever vaccine, and the chickenpox vaccine (Varivax®). In addition, FluMist®, an intranasal, attenuated live influenza vaccine could potentially be a risk for those with primary immunodeficiency, although adverse events from this have not yet been reported. Agents used to counteract bioterrorism such as vaccinia vaccine to provide immunity to smallpox may also be harmful to a person with associated T cell defects.

Part C: Practical Aspects of Genetic Counseling

The genetic bases of many of the common antibody production defects are currently unknown. This is especially true for most patients with Common Variable Immunodeficiency and Selective IgA deficiency where the underlying molecular defect has been identified in less than 10% of patients. For this reason, genetic counseling can be complicated in families affected by these disorders. The inheritance pattern and recurrence risk to family members is difficult to predict without a molecular diagnosis, but an accurate family history may be helpful in this aspect. It should be noted, however, that these disorders can also occur sporadically and the family history in those cases would be negative. Even though the inheritance pattern for some disorders may not be clearly understood, research has shown that family members of patients with CVID and Selective IgA deficiency also have an increased risk of antibody deficiencies and autoimmune disorders. It is also important to note that, when the gene defect has not been identified for a specific disorder, prenatal diagnosis is not an option.

The genetic bases of other antibody production defects are known and these disorders include patients with absent B cells and agammaglobulinemia and most cases of the Hyper IgM syndrome. These disorders can follow either an X-linked recessive or an autosomal recessive inheritance pattern. Please see the general genetic counseling section for a more detailed explanation of inheritance. Because mutations in a variety of different genes can cause these conditions, molecular testing is important to determine the specific gene involved and its mutation. This can help predict the clinical manifestation of the disorder in the affected individual. The gene identification along with an accurate family history will also help determine the pattern of inheritance in the family, risks for family members that could be affected, as well as identification of at-risk carrier females of X-linked disorders. Genetic testing is currently available in specialized labs for diagnostic confirmation, carrier testing and prenatal diagnosis of some of these diseases. For a current list of these laboratories, consult your immunologist or contact the Immune Deficiency Foundation.

ANTIBODY PRODUCTION DEFECTS

Part D: Frequently Asked Question about Antibody Deficiency Disorders

1. Will the patient outgrow the disease?

While it is unlikely that a patient will outgrow a primary immunodeficiency disease, identifying changes in the patient's medical condition and their management is best performed by your immunologist.

2. What is IG?

IG stands for immune globulin, a family of plasma proteins that help fight infections. Commercially available preparations of these globulins are comprised of numerous IgG antibodies purified from blood or plasma donations from approximately 60,000 donors per batch. The name IVIG refers to the intravenous (in the vein) form of IG and SCIG is IG, which is given subcutaneously under the skin.

3. Is there a need for extra IG during infections, such as pneumonia, and during surgery?

During an infection, the antibodies to that infectious agent are rapidly used up, so there may be a need for additional amounts of IG during that illness. IG may also provide broad protection against infections that may occur during invasive surgery. Appropriate antibiotic coverage should also be considered during surgery.

4. Can IG be given orally and is there any place for this as a treatment?

While IG has been given by mouth to some patients, trying to mimic the situation in very young animals where the infant animal receives protective antibodies in mother's milk, there are no research trials that confirm its usefulness in people.

5. Is there protection in IG from West Nile Virus?

At the present time, this is unknown. However, there is no risk of transmitting the virus by IG.

6. What is the safety of IG?

There is a remote or theoretical possibility of blood borne disease transmission. However, laboratory screening methods are very good and can identify infected donors as well as those developing infection. In addition, the manufacturing of IG separates and may inactivate potentially contaminating viruses. To date, there has been no evidence of prion (the agent of Mad Cow Disease) or HIV transmission by IG.

7. Why is it important to record the brand, infusion rate and lot numbers of IG that is infused?

On rare occasions, a problem is identified in a specific lot of IG from a specific manufacturer. With good record keeping, you can know if the potential problem affects you or you can avoid infusing the specific lot. The best way to learn about these types of problems when they happen is to sign up for the Patient Notification System, by calling 1-888-UPDATE-U (1-888-873-2838).

8. Is it appropriate to have a central vascular line (Infusaport, Broviac or Hickman) implanted to receive IVIG treatments?

While surgically implanted central lines may make infusions easier, they carry real risks of serious infection and blood clotting that could greatly complicate the care of a person with a primary immunodeficiency disease. Therefore, central lines are not recommended if only to be used for this purpose. When "standard" venipunctures are made to start IV lines for the infusion of IVIG, it is helpful in younger patients to apply a topical anesthetic cream like EMLA 30 to 60 minutes before the "stick."

9. Can IG be given in any way besides by vein?

There have been a number of studies that demonstrate that IG can be infused subcutaneously (SC), under the skin in restricted volumes, with good clinical results. Use of SCIG may be a good choice for those with poor vascular access, very young children and those with numerous reactions to the intravenous infusions. Immunology specialists will be familiar with this technique and can advise you whether it is appropriate for you. One IG preparation for subcutaneous administration has been licensed in the United States and it is anticipated that there will be others in the near future.

10. What are some types of reactions to IG?

Reactions are common during the first infusions of IVIG after the diagnosis has been established. They are of several different types. True allergic reactions are rare, occur early during the time of the infusion and are characterized by hives, chest tightening, difficulty in swallowing or breathing, feeling faint, abdominal discomfort and blood pressure or pulse changes. The first response should be to stop the infusion. Your medical provider may then take additional steps if the symptoms do not rapidly subside.

Lot-to-lot and product-to-product reactions may include headache, flushing, lightheadedness, nausea, vomiting, back or hip pain and fatigue. These side effects are more common and are usually rate related, occurring generally at the higher infusion rates.

Headaches may be a significant complication and most often occur within 24 hours of an IVIG infusion. Some headaches can be managed with milder analgesic agents like acetaminophen (Tylenol®), aspirin or ibuprofen. However, some headaches represent the syndrome of aseptic meningitis. Severe headaches occur most frequently in individuals with a prior history of migraine headaches.

For specific information about less common but serious reactions, you should refer to the specific IVIG package insert.

ANTIBODY PRODUCTION DEFECTS

Part D: Frequently Asked Question about Antibody Deficiency Disorders

Patients experiencing reactions should NOT be treated at home. Newly diagnosed patients or patients using a new product should receive their first infusion in a medical setting.

11. How is IG reimbursed?

Ask your provider for an itemized bill to help clarify billing questions, or ask your insurance company for an Explanation of Benefits (EOB). Reimbursement for IG may vary from year to year and from insurance plan to insurance plan. It is very important to understand your plan and its coverages.

12. As more patients receive their IG infusions in the home, what is the recommendation for follow up with an immunology specialist?

An immunologist should follow up most patients every 6 to 12 months, but patients with secondary complications, such as chronic lung or gastrointestinal disease may need more frequent follow-up and/or more than one specialist.

13. What expectations should the patient with antibody deficiencies have once he or she is on immune globulin therapy?

IG therapy should protect the patient from sepsis (blood stream infection), meningitis (infection of the coverings of the brain) and other serious bacterial infections. In addition, school/work absences will decline. However, do not expect all infections to stop. There may still be a need for the use of antibiotics. Children in general fare better than adults do. Quality of life should be greatly improved on immune globulin therapy.

14. What is the role of antibiotics in antibody deficiency diseases?

Antibiotics may be used chronically if there is evidence of chronic infection or permanent damage to the lungs (bronchiectasis) or sinuses. The antibiotics should be given in full treatment doses. Often, different antibiotics will be prescribed on a rotating schedule on a monthly basis. Prophylactic antibiotic therapy may be useful for some patients with Selective IgA deficiency, as IG therapy is not indicated for that condition.

15. What is the role of over-the-counter immune stimulants?

There is no evidence that these stimulants have any helpful effects.

16. Is it OK to exercise and play sports?

Yes. Physical activity and sports may help improve patients' sense of well-being and enable them to participate in some of life's enjoyable activities.

17. Is it OK to have pets?

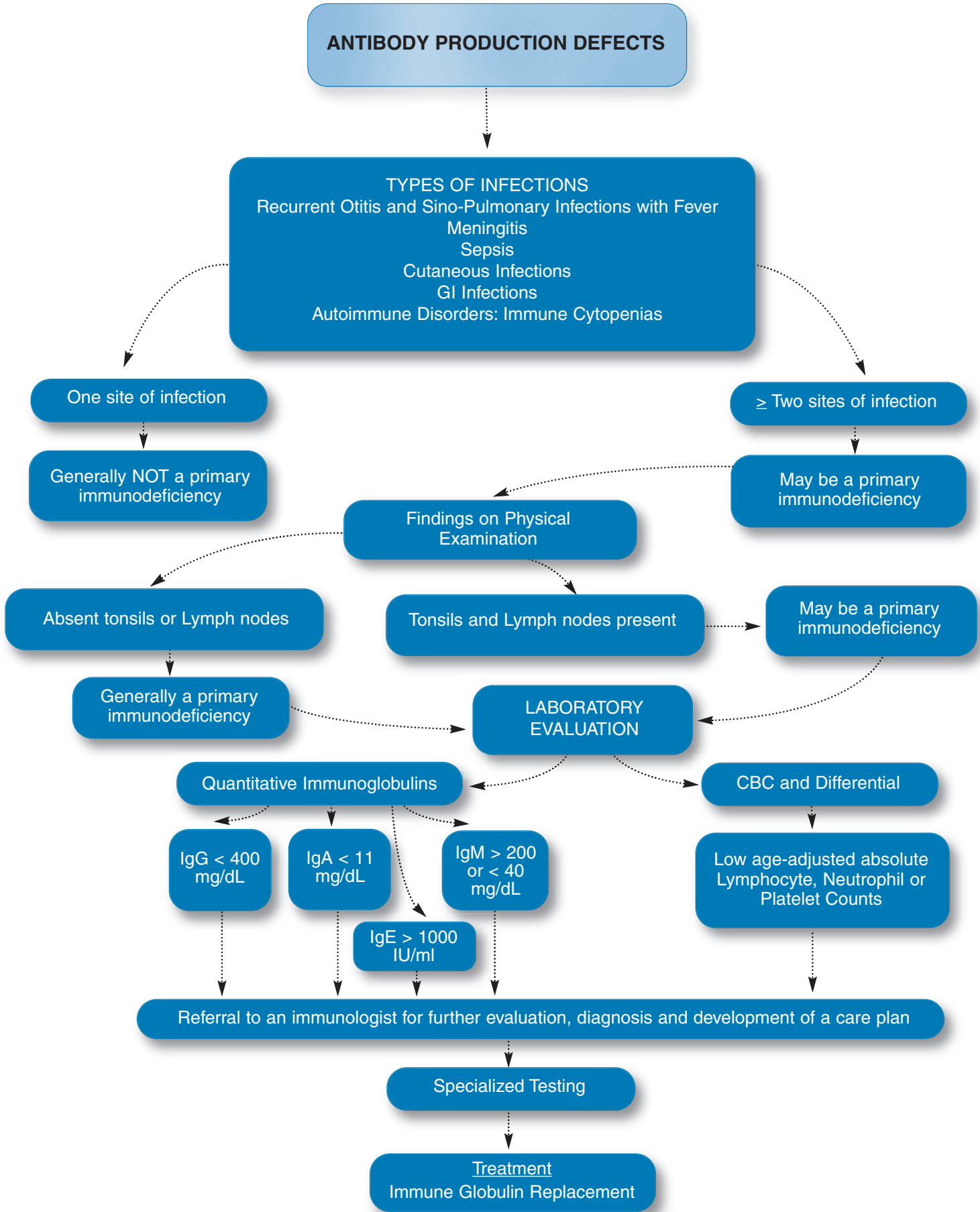
Yes, but be aware that animals may carry infections such as streptococcal infections that can be transmitted to humans. In addition, live vaccines may be given to domestic pets and could potentially pose a risk to the person with primary immunodeficiency.

18. Can IG be given during pregnancy?

Yes and it should be given as when not pregnant.

For additional information on the use of IVIG, see:

Orange JS, Hossny EM, Weiler CR, Ballou M, Berger M, Bonilla FA, Buckley RH et al. Use of intravenous immunoglobulin in human disease: a review of evidence by members of the Primary Immunodeficiency Committee of the American Academy of Allergy, Asthma and Immunology. *J Allergy Clin Immunol* 117: S525-S553, 2006.



CELLULAR OR COMBINED DEFECTS

Part A: Recognition and Assessment

These individuals have abnormal T cell function and, as a consequence, also have problems with antibody production. Affected individuals have both common and unusual infections. Typically, the patient is an infant or a young child and would not survive without early medical diagnosis and intervention(s). Some affected individuals present clinically in the nursery, such as those with severe or complete DiGeorge syndrome or some with the Wiskott-Aldrich syndrome. However, most other infants with severe T cell defects have no outward signs to alert anyone to their problem until infections begin. Those with the most severe forms of cellular or combined defects represent a true pediatric emergency and should receive prompt referral to an immunologist so that plans can be made for treatment — often a transplant to achieve immune reconstitution. Early diagnosis can avoid infections and make survival more likely. Patients may:

- ❖ Appear ill
- ❖ Have facial dysmorphism (DiGeorge syndrome) or ectodermal dysplasia (NEMO)
- ❖ Fail to thrive
 - » Weight is a more important determinant than length
- ❖ Have congenital heart disease (heart murmur at birth, cyanosis, DiGeorge syndrome)
- ❖ Have skin changes
 - » Severe diaper rash or oral candidiasis (thrush)
 - » Eczema as in Wiskott-Aldrich syndrome or Graft versus Host Disease (GVHD)
 - » Red rash as in GVHD, Omenn's syndrome or atypical complete DiGeorge syndrome
 - » Telangiectasia (prominent blood vessels)
 - » Petechiae in Wiskott-Aldrich syndrome
 - » Absence of nails, hair or sweating (NEMO)
- ❖ Have chronic intractable diarrhea
- ❖ Develop intractable viral infections due to Respiratory syncytial virus (RSV), parainfluenza, cytomegalovirus (CMV), Epstein Barr Virus (EBV), or adenovirus
- ❖ Have infections not accompanied by lymphadenopathy except in the Wiskott-Aldrich syndrome

- ❖ Have adverse reactions after live vaccines such as Varivax, given to prevent chicken pox
- ❖ Have neurological findings such as ataxia or tetany of the newborn (DiGeorge syndrome)
- ❖ Have X-linked immune dysregulation and polyendocrinopathy (IPEX), or chronic mucocutaneous candidiasis (CMC,APCED)
- ❖ Need to have a diagnosis of Human Immunodeficiency Virus (HIV) infection excluded

Some combined defects, though ultimately fatal without treatment, are not initially as severe so do not present as early as SCID. Examples are zeta-associated protein (ZAP) 70 deficiency, purine nucleoside phosphorylase (PNP) syndrome, Wiskott-Aldrich syndrome or nuclear factor of kappa B essential modulator (NEMO) deficiency. The clinical recognition of Ataxia Telangiectasia may also be delayed, as signs develop progressively during the first several years of life.

Laboratory Testing

A white blood cell count with a manual differential should be obtained to determine whether the patient has a low absolute lymphocyte count (i.e. is lymphopenic). Age-appropriate normal values must be considered.

DEFINITION OF LYMPHOPENIA

| | |
|-------------------------|-----------|
| Birth | ≤ 2500/μL |
| 5–6 Months up to 1 year | ≤ 4000/μL |
| Adult | ≤ 1000/μL |

These tests would also reveal whether the patient has too low a neutrophil count (i.e. is neutropenic) or has an elevated neutrophil count, as is seen in leukocyte adhesion deficiency (LAD). Platelet counts and platelet size measurements may also be useful to rule out Wiskott-Aldrich syndrome. Referral to an immunologist should be made for more detailed lymphocyte analysis by flow cytometry. T cell functional testing is of greatest importance. Quantitative immunoglobulin measurement and antibody testing should be performed. Genetic testing is complicated by the fact that there are at least twelve different molecular causes of SCID. If a diagnosis of SCID is suspected, the infant should be kept away from other small children and those with infections and immediately referred to an immunologist for definitive treatment as this is a pediatric emergency.

CELLULAR OR COMBINED DEFECTS

| DISEASE | COMMON NAME | ICD 9 CODE |
|---|----------------------------|------------|
| Severe Combined Immunodeficiency | “Bubble Boy” Disease, SCID | 279.2 |
| DiGeorge Syndrome also known as 22q11 Deletion Syndrome | Thymic Aplasia | 279.11 |
| Ataxia Telangiectasia | AT | 334.8 |
| Wiskott-Aldrich Syndrome | WAS | 279.12 |

CELLULAR OR COMBINED DEFECTS

Part B: Management, Expectations, Complications and Long Term Monitoring

Only irradiated (5000 RADS), CMV-negative, leukocyte-depleted blood products should be used in managing the patient with SCID or other suspected T cell deficiencies. No live virus vaccines should be administered to any member of the household, including the patient. This includes no rotavirus (Rotateq® or Rotarix®), oral polio, MMR®, FluMIST® or Varivax® vaccines and no BCG in countries where these practices are recommended. However, all household contacts should receive regular immunizations with killed vaccines, particularly annual influenza immunizations. Typical serious, often overwhelming or fatal infections in SCID are PJP (Pneumocystis jiroveci pneumonia), candida, RSV, parainfluenza 3, CMV, EBV and adenovirus. If an infant is suspected of having SCID, he or she should be placed on PJP prophylaxis with trimethoprim/sulfamethoxazole. If there is a family history of an early death due to infection, a diagnosis or exclusion of SCID in a subsequent birth can be done by performing a white blood cell count and a manual differential on the cord blood to look for a low lymphocyte count. If the count is low, flow cytometry, a specialized laboratory test, should be performed to see if T cells are present.

Immune reconstitution in SCID generally requires bone marrow transplantation early in life. No pre-transplant chemotherapy nor post-transplant GVHD prophylaxis is needed for true SCID infants because they do not have T cells. Gene therapy has

been tried with notable success, but there have been serious adverse events. SCID patients who have received successful bone marrow transplants require at least annual follow up by an immunologist at a specialized center. There may be unanticipated complications and patients should also have the opportunity to benefit from new therapeutic developments.

Patients with combined immune deficiencies (CID) who have low but not absent T cell function may additionally fail to make antibodies normally despite normal or elevated immune globulin levels. They also require IG replacement therapy. For example, although Wiskott-Aldrich patients may have normal serum immunoglobulin levels, they are usually treated with IG because their ability to make antibodies is abnormal. In the complete form of DiGeorge syndrome, there is no T cell function and thymic transplantation is the recommended treatment. The long-term outcome for partial DiGeorge syndrome is generally satisfactory from an immunologic perspective, however, susceptibility to other complications such as developmental delay, seizure, severe autoimmune disease or EBV induced lymphoma remains. AT (Ataxia Telangiectasia) patients and patients with SCID due to Artemis gene mutations should minimize their exposure to ionizing irradiation, as they have an increased risk for chromosomal breakage and its complications.

Part C: Practical Aspects of Genetic Counseling

The genetic basis is known for many of the cellular or combined immune defects. Several of these disorders follow X-linked inheritance; many others follow autosomal recessive inheritance. Please refer to the general genetic counseling section for an explanation of inheritance patterns. A special consideration for genetic counseling of families affected by these disorders is the fact that there are several different genes that, when mutated, result in the same clinical disorder. For example, it is currently known that mutations in one of at least eleven genes can cause SCID. The most common form of SCID follows X-linked inheritance; all other forms of SCID follow autosomal recessive inheritance. It is therefore crucial that genetic testing be done to determine the specific gene involved in these disorders to provide accurate estimates of risks for family members being affected. However, genetic testing should not delay initiation of appropriate treatment. Genetic testing for many of the cellular or combined

immunodeficiency disorders is only available in specialized laboratories in the U.S. and abroad. For more specific information refer to the general section on genetic counseling.

DiGeorge syndrome is one of the few primary immunodeficiency diseases that may follow autosomal dominant inheritance, however most cases are sporadic. It is caused by a deleted portion of a region on chromosome 22 in more than half of the cases, by mutations in a gene on chromosome 10 in another 10% and is of unknown cause in the other cases; it affects both males and females. While many of these cases occur as new mutations in the genes responsible on chromosome 22, it is also important to do molecular testing of the parents of a child with this condition because there can be clinical variability and an affected parent may have previously gone undiagnosed. Whether or not the chromosome defect is inherited or due to a new mutation has significant impact on recurrence risk for a family. Genetic testing for chromosome 22 deletions is widely available in laboratories across the United States.

CELLULAR OR COMBINED DEFECTS

Part D: Frequently Asked Questions

1. What happens if my child is exposed to chickenpox?

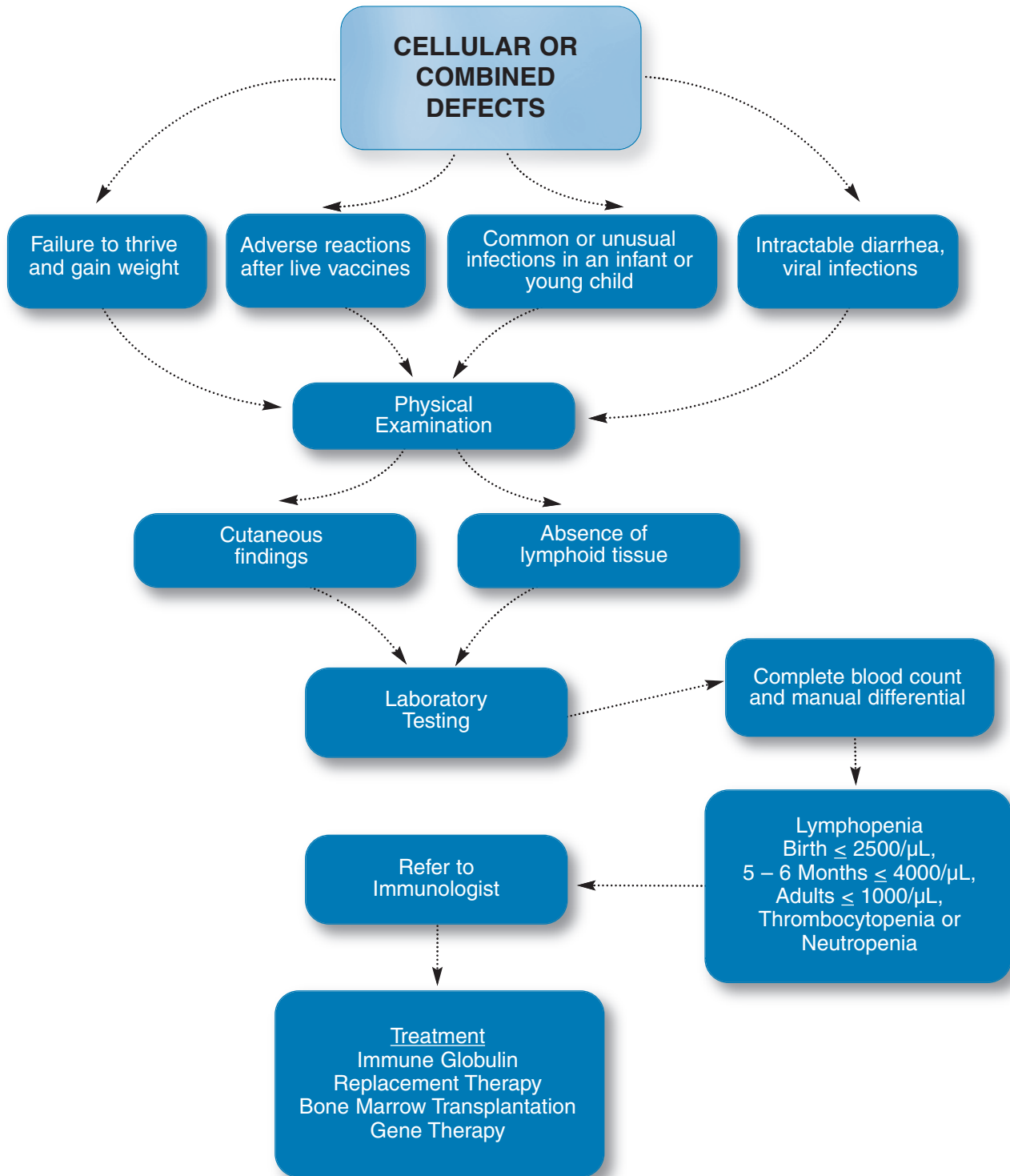
You need to let your physician know immediately so he or she can receive VariZIG (Varicella IG), an investigational hyperimmune globulin, within 48 hours of exposure. IG replacement therapy in the usual doses can also provide antibodies against the chickenpox virus. The incubation period of varicella is 11 to 21 days. If your child already has a vesicular rash, which looks like small blisters, he or she will need to be treated with acyclovir, an antiviral agent. Intravenous (IV) acyclovir is superior to oral.

2. What is the risk to those with primary immunodeficiency diseases if attacks of bioterrorism occur?

Individuals with T cell defects are at serious risk if widespread smallpox immunization programs are initiated. Anti-vaccinia antibodies in immune globulin therapy may offer some protection. Research is being conducted to find additional treatments, and vaccinia hyper-immune globulin is being developed.

3. What kind of vaccines can my child receive?

All of the killed vaccines are safe, but he or she should not receive any live vaccines such as rotavirus (Rotateq® or Rotarix®), oral polio, measles, mumps, rubella (MMR®), varicella (Varivax®), or intra nasal influenza vaccine (FLuMist®). Antibodies in IG may give protection against some or all of these viruses. In general, immunodeficient patients who are receiving IG replacement should not be given vaccines, although some immunologists give influenza immunizations. If the patient is immune deficient enough to need IG replacement, he or she probably would not be able to respond with antibody production. It is uncertain whether there would be a T cell response that could be helpful. However, the antibodies in the IG replacement therapy would neutralize most vaccines and they would be ineffective.



PHAGOCYtic CELL IMMUNE DEFECTS

Part A: Recognition and Assessment

Signs of defects in the phagocytic cells are manifest in many organ systems. The onset of symptoms is usually in infancy or early childhood.

- **Skin**—abscesses (boils) (seen in CGD and the Hyper IgE syndrome) and/or cellulitis (inflammation of the skin) (seen in LAD)
- **Lymph nodes**—may be swollen and contain pus in CGD patients
- In **LAD** there may be delayed shedding of the umbilical cord or infection of the cord base (omphalitis) and cellulitis but no abscesses.
- **Osteomyelitis**—an infection of bone seen frequently in patients with chronic granulomatous disease (CGD).
- **Hepatic Abscess**—liver abscesses may also be seen in CGD
- **Lungs**—Aspergillus (mold) lung disease is insidious and common in patients with CGD. Abscesses and other infections may occur in these patients due to pathogens that do not result in abscesses in normal hosts.
- **Gastrointestinal tract outlet** and/or **urinary tract obstruction** resulting in abdominal or back pain is often seen in CGD, as is constipation
- **Mouth** (gingivitis)—gum inflammation, mouth ulcers
- **Unexplained fever** without identifiable cause
- **Malaise** and **fatigue**
- **Albinism** may be seen in Chediak Higashi syndrome

Laboratory Tests

Defects in phagocytic cells can be due to an insufficient number of such cells, an inability of the cells to get to an infected area, or to an inability to kill ingested bacteria or fungi normally.

- A complete blood count and differential are needed to determine whether phagocytic cells (neutrophils) are present in normal number. In the case of cyclic neutropenia, the test (absolute neutrophil count or ANC) has to be repeated sequentially (e.g. 2 times per week for 1 month).
- A test for CD11/CD18 expression on white cells is needed to exclude LAD.
- A Respiratory Burst Assay (the replacement for the NBT assay) should be performed to determine if phagocytic cells can produce oxygen radicals needed to kill bacteria and fungi. Neutrophils from patients with CGD do not produce these oxygen radicals.
 - « As is the case in CGD, patients with the Hyper IgE syndrome also present with abscesses (boils) although they have a normal number of neutrophils and a normal Respiratory Burst Assay result. Thus, a serum IgE level should be measured in patients with recurrent abscesses to make certain that the Hyper IgE syndrome is not the underlying cause.

PHAGOCYtic CELL IMMUNE DEFECTS

| DISEASE | COMMON NAME | ICD 9 CODE |
|---------------------------------------|-------------|------------|
| Leukocyte Adhesion Defect | LAD | 288.9 |
| Chronic Granulomatous Disease | CGD | 288.1 |
| Chediak Higashi Syndrome | CHS | 288.2 |
| Cyclic Neutropenia Kostman Disease | Neutropenia | 288.0 |

PHAGOCYTIC CELL IMMUNE DEFECTS

Part B: Management, Expectations, Complications and Long Term Monitoring

In general, neutropenia (reduced numbers of phagocytes) is most commonly secondary to a drug or an infection and the patient should be referred to a hematologist or other specialist for management. In individuals with a primary immunodeficiency disease affecting phagocytic cells, prophylactic antibiotics are appropriate. These antibiotics include trimethoprim sulfamethoxazole and cephalexin. CD40 Ligand deficient patients are often profoundly neutropenic. Individuals with Kostmann's Syndrome may be responsive to granulocyte colony stimulating factor (G-CSF), as may be the neutropenia associated with CD40 Ligand deficiency. Prophylactic antifungal agents are often administered in patients with CGD.

It is important to obtain bacterial and fungal cultures in these patients to direct antibiotic treatment. With appropriate antibiotic therapy, individuals with CGD should live into their 40's or older. However, there are differences in infection susceptibility in terms of the X-linked and

autosomal recessive types, with somewhat more frequent infections in the X-linked type. Meticulous medical care from an expert in immunology will increase the patient's chances of longer survival. Typically, hemoglobin, hematocrit, ESR (erythrocyte sedimentation rate) and/or CRP (C-reactive protein) and a chest X-ray should be followed regularly in CGD. If there is any fever, malaise or change in health status, the patient requires immediate medical evaluation. Patients with CGD have normal T cell and B cell function. Therefore, they are not susceptible to viral infections, can receive live virus (but not BCG) vaccines, and can attend school and visit public areas such as malls.

Gamma-interferon has been used to treat CGD. There is no change in in vitro tests of phagocytic cell function with this treatment, although some clinical benefit (e.g. reduced number of serious infections) has been reported. Bone marrow transplantation has been successful in children with CGD when there is a matched sibling donor.

Part C: Practical Aspects of Genetic Counseling

The genetic basis is known for most of the phagocytic cell immune defects. However, as with SCID, mutations in multiple genes are responsible for a clinically similar condition. For example, four genes (when mutated) are known to cause Chronic Granulomatous Disease. The most common form of this disorder follows X-linked recessive inheritance and the other forms follow autosomal recessive inheritance. A detailed family history may be helpful in

determining the type of CGD. However, genetic testing is again crucial in determining the specific gene involved. With this information, the clinical prognosis can be assessed and patterns of inheritance determined in the family. Genetic testing for the phagocytic cell immune defects is only available in specialized laboratories. Please see the general section on genetic counseling for more information about testing.

PHAGOCYtic CELL IMMUNE DEFECTS

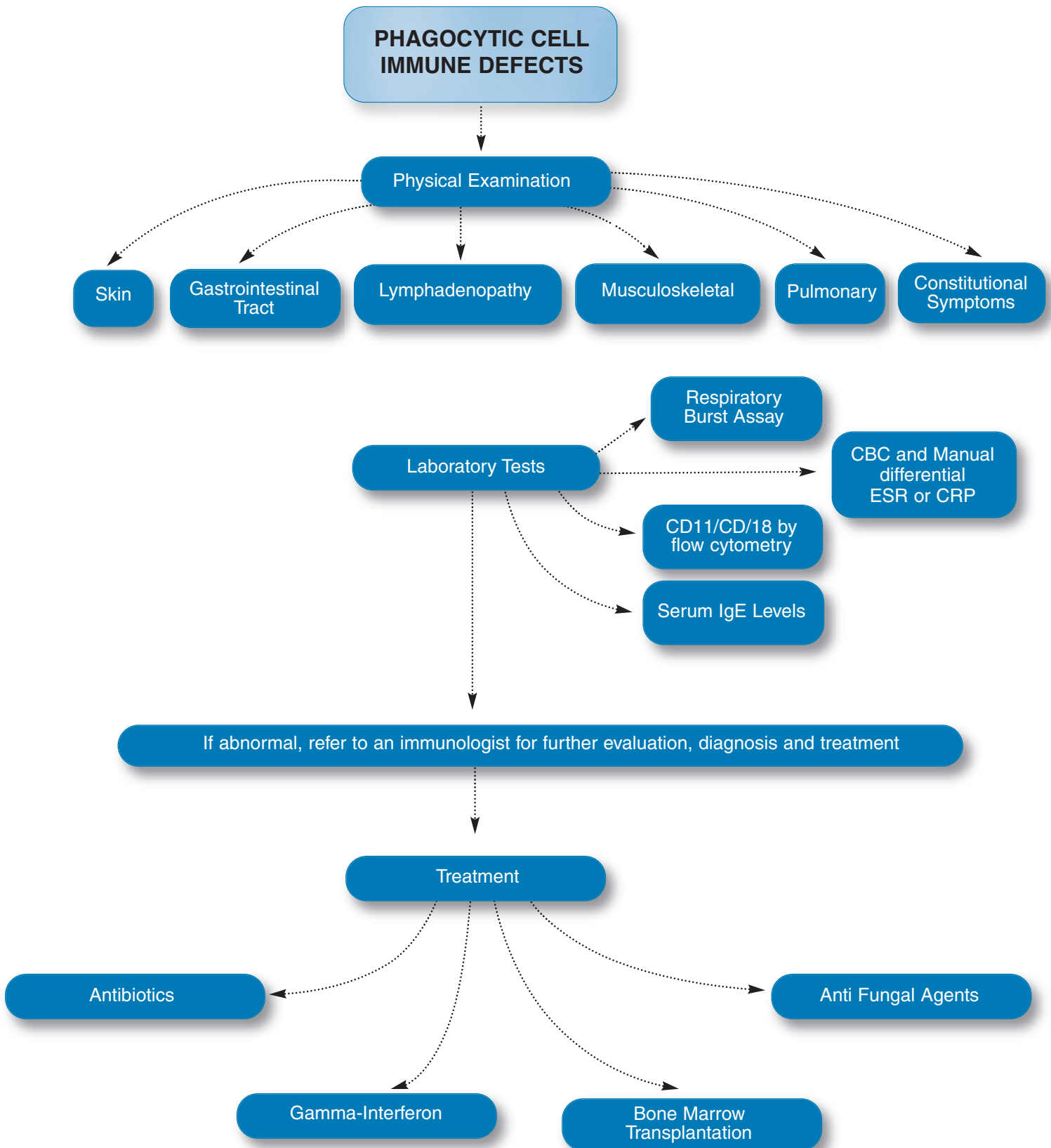
Part D: Frequently Asked Questions

1. What activities and places should my child avoid?

There is no general recommendation for avoiding infections. However, swimming in lakes or ponds should be avoided. Exposure to aspergillus and mold that is associated with gardening that involves digging and handling or being around mulch should also be avoided. These and any other activities that will expose the child with a phagocytic cell primary immunodeficiency to potentially harmful bacteria or fungi should be avoided.

2. Can my child receive all types of vaccines?

Yes, except for Bacille Calmette Guerin (BCG), because patients with CGD have normal T and B cell function.



COMPLEMENT DEFECTS

Part A: Recognition and Assessment

Evaluation of the complement system is appropriate for patients with episodes of bacteremia, meningitis or systemic Neisserial (either *N. meningitidis* or *N. gonorrhoea*) infections. A single systemic Neisserial infection warrants immediate testing of the complement system.

- ❖ C1, C4 or C2 deficiencies may present with recurrent pneumococcal disease, i.e. otitis, pneumonia or bacteremia. There can also be concomitant antibody deficiency due to poor antigen uptake by dendritic cells, which normally interact with antigen-antibody complexes bearing complement components. Systemic lupus erythematosus is much more common than infections as a manifestation of early complement component deficiencies.
- ❖ C3 deficiency is very rare, but is characterized by recurrent serious bacterial infections, such as pneumonia or bacteremia, and development of membranoproliferative glomerulonephritis.
- ❖ Systemic Neisserial infections in children and adolescents suggest C5-7 deficiencies:
 - » Recurrent Central Nervous System (CNS) infections are more common in African Americans than Caucasians with complement component deficiencies.
 - » Genitourinary tract infections are also seen.
 - » Cutaneous lupus and other manifestations of autoimmunity are observed, particularly with deficiencies of C1, C2, or C4.

Hereditary Angioedema is due to a deficiency of C1 esterase inhibitor. Patients may experience recurrent episodes of abdominal pain, vomiting and laryngeal edema. The diagnosis can be made based on the clinical occurrence of angioedema (swelling) and the repeated finding of decreased quantities of C1 inhibitor protein or activity and reduced levels of C4. C1q when measured concomitantly is normal.

Laboratory Tests

Diagnosis: CH50 and AH50

- ❖ In the work up for complement deficiency, the CH50 is an excellent screening test, but the blood needs to be handled carefully—see below. Alternative Pathway defects can be screened for with the AH50 test. Identification of the particular component that is missing will require studies in a research or specialized laboratory.
- ❖ For diagnosis, proper specimen collection of blood samples is very important. Complement is very heat labile. In general, if the CH50 is undetectable, the patient likely has a deficiency in a complement component, however, if the CH50 is just low, it is more likely that the specimen was not handled properly or that the patient has an autoimmune disease.

COMPLEMENT DEFECTS

| DISEASE | COMMON NAME | ICD 9 CODE |
|---|-----------------------|------------|
| C1 Esterase Inhibitor Deficiency | Hereditary Angioedema | 277.6 |
| Complement Component Deficiencies (e.g. C1, C2, C3, C4, C5, C6, C7, etc.) | Complement Deficiency | 279.8 |

Part B: Management, Expectations, Complications and Long Term Monitoring

Prophylactic antibiotics may be appropriate for deficiencies of any of the components of the complement cascade. Meningococcal vaccine and/or antibiotic prophylaxis may be helpful for any person diagnosed with a C5 through C9 deficiency.

All complement deficient patients should receive immunization with Prevnar® or Pneumovax or both for pneumococcal infection prevention. Early recognition of fevers and prompt evaluation (including blood cultures) is very important.

Complications of complement deficiency include autoimmune disease, especially systemic lupus erythematosus, lupus-like syndromes, glomerulonephritis, and infections.

Mannose binding lectin, a protein of the innate immune system, is involved in opsonisation and phagocytosis of micro-organisms. Most of those with the Mannose Binding Lectin defect are healthy except for skin infections, but some resemble patients with early complement component defects. In the setting of recurrent infection with suspected mannose binding lectin deficiency, a specialty laboratory (not a commercial one) must diagnose this defect.

Part C: Practical Aspects of Genetic Counseling

The genetic basis is known for all of the complement defects but testing is only available in specialized laboratories. All forms of inheritance have been reported for the complement defects and it is very important to determine the specific complement factor involved as well as its molecular basis.

The genetic basis of hereditary angioedema is known and follows autosomal dominant inheritance. Please see the general genetics section for a more complete description of autosomal dominant inheritance. Family history is important in the evaluation of angioedema. Genetic testing is available for C1 Esterase Inhibitor deficiency and can be important in distinguishing the hereditary form of the disorder from the acquired forms.

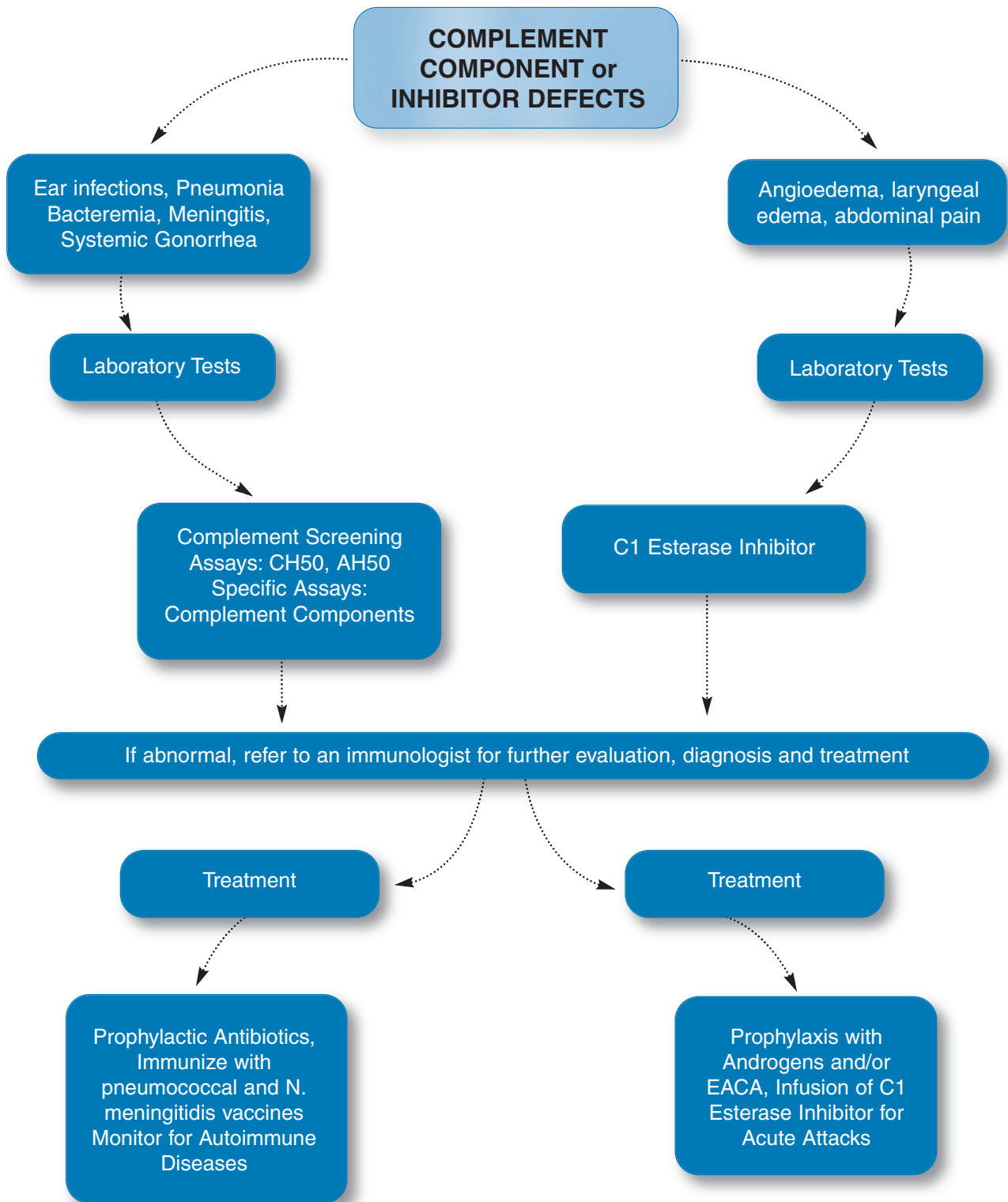
Part D: Frequently Asked Questions

1. Can my child receive all types of vaccines?

Yes, individuals with complement defects usually have normal T and B cell function.

2. Are there infection risks if my child with a complement defect attends public school or goes to public places?

No, in general the problems with infections are due to those that your child would come in contact with in a variety of physical settings. However, if there is a known outbreak of pneumonia or meningitis in your community, it may be prudent to keep your child at home out of the school environment and administer antibiotics recommended by the public health authorities.



PRACTICAL ASPECTS OF GENETIC COUNSELING: GENERAL CONSIDERATIONS

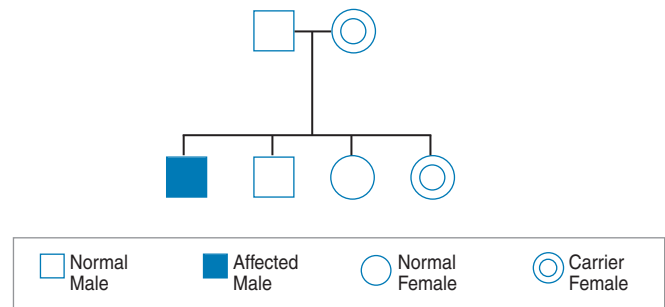
Due to the genetic nature of the primary immunodeficiency diseases, genetic counseling for the individual affected by these diseases, as well as family members, is very important in providing comprehensive care. Genetic counseling is typically provided once the individual has been diagnosed with a specific primary immunodeficiency disease. While most immunologists are knowledgeable about the genetic aspects of primary immunodeficiency disease, it is sometimes helpful to refer the individual or family member to a genetic counselor who has expertise in providing complex information in an unbiased and easily understood manner. Issues addressed in genetic counseling for a primary immunodeficiency disease should include:

- ❖ Discussion of the diagnosis and the gene(s) responsible for the disorder, if known.
- ❖ Determination of available molecular genetic testing for confirmation of the diagnosis, if applicable, depending on the disorder in question.
- ❖ An accurate intake of the patient's family history, preferably in the form of a pedigree.
- ❖ Determination and discussion of inheritance pattern and recurrence risk for future children.
- ❖ Identification of family members who may be at risk of being affected with the disorder or at risk of being carriers.
- ❖ Brief discussion of the availability of prenatal diagnosis options for the particular primary immunodeficiency. This can be discussed again in more detail in future genetic counseling sessions when appropriate.
- ❖ Discussion of whether the family should save the cord blood of future infants born to them. If the infant is affected, this would not be helpful. If the infant is normal, the cord blood could be used as a source of stem cells for affected HLA-identical members of the family who might need a transplant for immune reconstitution.

Patterns of Inheritance

The pattern of inheritance is very important when evaluating the patient with a primary immunodeficiency disease. Many of the primary immunodeficiency diseases follow X-linked recessive inheritance. This means that the genes responsible for these disorders are located on the X chromosome and these conditions predominantly affect males. Affected males have either inherited the gene defect from their mothers who were carriers of the gene defect or the gene defect occurred as a new mutation for the first time in the affected male.

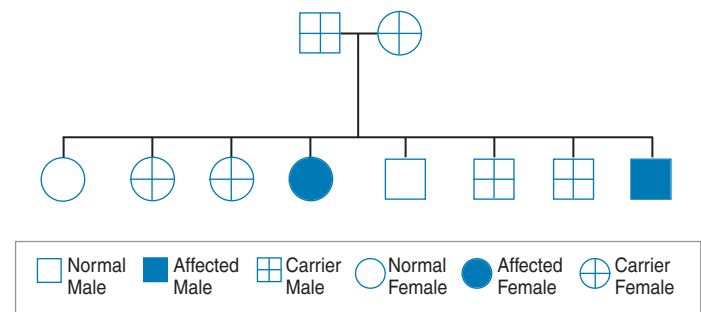
X-LINKED RECESSIVE INHERITANCE



About one third of all X-linked defects are identified as new mutations. In these cases, the mothers are not carriers or are the first affected (carrier) member of the family and the family history is otherwise negative. Female carriers of the gene defect do not typically show clinical symptoms. However, half of all boys born to female carriers may be affected with the disorder and half of the daughters may be carriers like their mothers. Therefore, in families with X-linked disorders, it is important to determine whether the gene defect is inherited or is a new mutation, because this will greatly affect the recurrence risk to other family members.

The other most common pattern of inheritance for primary immunodeficiency diseases is autosomal recessive. Disorders following this pattern are caused by gene defects on any of the 22 pairs of numbered chromosomes (not the X or Y) and therefore, affect both males and females. In this type of inheritance, the condition is only expressed when both parents are carriers of the gene defect and both have passed the defective gene on to their child. These couples have a one in four chance of having an affected child with each pregnancy.

AUTOSOMAL RECESSIVE INHERITANCE



PRACTICAL ASPECTS OF GENETIC COUNSELING: GENERAL CONSIDERATIONS

Some primary immunodeficiency diseases follow autosomal dominant inheritance. These disorders are caused by gene defects on any of the numbered chromosomes and affect both males and females. Unlike autosomal recessive inheritance, only one copy of the gene defect needs to be present for the condition to be expressed in an individual. The defective copy overrides the individual's normal copy of the gene. Individuals affected with these disorders have a 50% chance of passing the gene defect on to each of their children, regardless of gender. It is important to note that some of these disorders occur as new mutations in the affected individual and a family history may be negative.

A number of factors complicates genetic counseling for primary immunodeficiency diseases. It is important that the process of genetic counseling for primary immunodeficiency diseases be done by either an immunologist or genetic counselor knowledgeable about the specific intricacies of these disorders. Some of the complicating factors include:

- ❖ Primary immunodeficiency diseases are a group of more than 150 different disorders and there are at least that many genes involved in these disorders.
- ❖ Some primary immunodeficiency diseases have the same or similar clinical presentation, but different genetic causes. This impacts the accurate determination of inheritance pattern and recurrence risk to other family members.
- ❖ The genetic basis is still not known for many of the primary immunodeficiency diseases, including some of the most common disorders, making it difficult to accurately determine inheritance patterns and risk to other family members. This also makes it difficult to offer prenatal diagnostic options.
- ❖ Very few commercial laboratories perform molecular diagnostic procedures for primary immunodeficiency diseases and, for those that do, costs may be \$2500-\$3000 or more per family. Genetic testing is also possible in some research laboratories. These considerations may influence accessibility to testing as well as timely receipt of test results. For a current list of laboratories performing genetic testing of primary immunodeficiency diseases, consult your immunologist or contact the Immune Deficiency Foundation.

Genetic counseling also involves a psychosocial component. This is true when providing genetic counseling to families affected by the primary immunodeficiency disorders. The emotional aspect of having a genetic disease in the family can be a heavy burden and this can be explored in a genetic counseling session. In addition, the discussion of prenatal diagnostic options can be a sensitive topic, since interruption of a pregnancy may be a consideration. Prenatal diagnosis for primary immunodeficiency diseases may be an option if the genetic defect is known in the family. This could be done through a chorionic villus sampling performed in the first trimester of pregnancy or through amniocentesis performed in the second trimester. Each of these procedures has a risk of miscarriage of the pregnancy associated with it, so these risks need to be discussed thoroughly by the genetic counselor. Prenatal diagnosis for a primary immunodeficiency disease may be considered when a couple wants to better prepare for the birth of an infant with the disease in question. For example, knowing that a fetus is affected can give a couple time to start looking for a match for a bone marrow donor if this is the therapy for the disease. Knowing that a fetus is unaffected can offer great relief to the couple for the rest of the pregnancy. Prenatal diagnosis may also be considered when a couple would choose to terminate a pregnancy of an affected fetus. Again, these considerations are thoroughly discussed in a genetic counseling session.

Finally, the discussion of gene therapy may be addressed in the genetic counseling of a family affected by a primary immunodeficiency disease. The anticipation is that gene therapy will become available for several diseases over the coming years. However, even if the treatment is perfected and found to be safe, it cannot be done unless the abnormal gene is known in the family.

LIFE MANAGEMENT CONSIDERATIONS

Diagnosis Information

Patients need a hard copy description of their diagnosis and therapy and/or a MedicAlert badge (if applicable, are available at www.medicalert.org). In addition, individuals should consider acquiring a Personal Health Key from the MedicAlert organization. This USB enabled key stores your health record and can be carried on a key chain or in a purse.

Travel Recommendations

Travel outside the United States may require medical regimens or vaccinations. Patients should consult with their immunologist to determine which vaccines can be safely administered and about the advisability of travel to various geographic areas of the world. As an example, be aware that yellow fever vaccine is a live vaccine so it should not be given to patients with T cell defects or members of their immediate household. In addition, IVIG would be of no benefit for protection against yellow fever, as it lacks antibody to this viral agent.

Psychosocial Concerns

The challenges of living with a primary immunodeficiency disease can cause significant stress and have a great impact on the psychological well being of the person affected with the disease and his/her caregivers and family members. Learning effective coping strategies can benefit all who are affected by these chronic illnesses. Establishing a good support system through family members, friends, health care team members and other peers affected by primary immunodeficiency disease is essential to coping effectively with the disease. It is important for health care providers to pay close attention to signs of more serious psychological concerns, such as clinical depression, in a patient affected by a primary immunodeficiency or his/her caregiver. This recognition can help the individual and family seek appropriate intervention in a timely manner. The Immune Deficiency Foundation provides peer support by connecting patients and their families with trained volunteers who have gone through similar situation to share experiences, encouragement and understanding. Please contact the Immune Deficiency Foundation for more information on this resource.

Education

The transition from infant/toddler to school aged child can be particularly challenging for a family affected by a primary immunodeficiency disease. Communication between parents and caregivers, the health care team and school professionals is very important. This should include educating school personnel about the child's particular disease, management of infections, vaccine restrictions, prescribed therapy and precautionary measures that can be taken to minimize infection in the school. Parents and health care providers should be familiar with the federal regulations enacted to promote equal education for children with chronic diseases, such as primary immunodeficiency diseases, that may qualify as disabilities. For more information about these regulations, please contact the Immune Deficiency Foundation.

Employment

Adults with primary immunodeficiency diseases are sometimes faced with the problem of employment discrimination because of their diseases. Both patients and health care providers should be familiar with the Americans with Disabilities Act. It protects U.S. citizens with health conditions such as primary immunodeficiency diseases that may qualify as disabling conditions. For more information about federal regulations, please contact the Immune Deficiency Foundation.

HEALTH INSURANCE

Great progress has been made in the treatment of primary immunodeficiency diseases. Life-saving therapies are now available for many of the primary immunodeficiency diseases. However, primary immunodeficiency diseases differ from acute health conditions, as many of the therapies necessary to treat these conditions are life-long. Therefore, it is essential that patients affected by these diseases have adequate health insurance coverage for these chronic therapies. In many cases, if therapy is not administered on a regular basis, the cost of health complications and subsequent hospitalizations could be extremely burdensome.

Reimbursement and coverage of the treatments and services for primary immunodeficiency diseases can vary considerably, depending on the type of health insurance a patient has. Therefore, maintenance of health insurance coverage requires a close working relationship on the part of the patient, the health care provider and the health insurance administrator. Patients or their caregivers need to pay particular attention to the following issues when working with their health insurance providers:

- ❖ Obtain a complete copy of the patient's health insurance policy and understand services and treatments that are covered under the policy and those that are excluded.
- ❖ Know the patient's specific diagnosis, including the ICD-9 code for the diagnosis. This information is available through the physician's office.
- ❖ Know if the insurance policy requires physician referrals and/or prior authorization for coverage of medical treatments, services or procedures before administration of the treatment is scheduled to take place.
- ❖ Consider establishing a case manager through the health insurance provider to maintain consistency when seeking advice on the patient's policy.
- ❖ Maintain a good understanding of out-of-pocket expenses, including annual deductible amount, coinsurance amount and copayments for prescription drugs, office visits and any other services.
- ❖ Know if the health insurance policy has a lifetime limit/maximum on benefits and if so, know the maximum amount.
- ❖ Know if the health insurance policy has any pre-existing condition waiting periods.
- ❖ Know patients' rights under the Health Insurance Portability and Accountability Act (HIPAA) and how these protect insurance coverage.

- ❖ If the patient is covered by Medicare, selecting the option of Part B coverage is necessary for proper reimbursement of many of the therapies for primary immunodeficiency diseases. Additionally, since coverage of these therapies is usually limited to 80%, it is also important that a patient consider selecting a Medigap policy to help defray the cost of the 20% for which the patient is typically responsible.

Since reimbursement for therapies is constantly changing, it is important to keep up with any changes in each individual's health insurance policy. In some cases, coverage for therapies may be denied and the patient may have to appeal for reconsideration of coverage. Patients should read their health plan's Summary Plan Document to know the appeals process and timelines associated with filing an appeal. Resources are often available for this type of assistance through manufacturers of the therapies. In addition, the resources below can be of assistance to patients going through this process. Sample letters for patients and providers are attached below for guidance through the insurance appeals process.

- ❖ Immune Deficiency Foundation:
www.primaryimmune.org or (800) 296-4433
- ❖ State Departments of Insurance:
www.naic.org/state_web_map.htm
- ❖ www.cms.hhs.gov

How to Appeal Health Insurance Immunoglobulin Denials

Immunoglobulin (IG) therapy is an expensive therapy. Unfortunately, some insurance companies deny IG therapy for patients with primary immunodeficiency until the insurer understands the rationale behind this life sustaining therapy. Insurers are very reluctant to approve expensive payments per year where indications are not substantiated.

Listed below are tips that have been successful in helping to overturn health insurance IG denials. The appeal should be short, succinct and carefully documented.

- ❖ Keep in mind that you have a very short amount of time (probably only a few minutes) of the Medical Director's attention.
- ❖ Provide well-accepted diagnostic studies, which are in the practice guidelines.
- ❖ Provide standards of practical criteria to support the laboratory studies.

HEALTH INSURANCE

- ❖ Provide proof and documentation of serious infections and complications, which have not been responsive to appropriate medical and /or surgical intervention; include clear radiographic evidence of persistent disease, e.g. lungs, sinuses et al, and clinical documentation of infections etc.
 - ❖ Focus on the rationale for IG therapy; a doctor's letter that states, "because it is medically necessary" is not specific enough. Precise statements, such as *3 episodes of pneumonia with fever to 102, or chest x-ray showed lobar pneumonia and xx days of antibiotics were required*, are needed.
 - ❖ Keep in mind that the insurance companies are reviewing thousands of appeals; therefore, the larger appeal packets will be put to the side. Remember, the shorter the appeal, the shorter the turn-around-time for a response.
 - ❖ When concluding the letter, add the names of immunologists that have completed the scientific research on the diagnosis in question, should the insurer request a peer review. For example *"Should you have any questions, I would request a peer review by either Dr. John Smith or Dr. Ann Jones from the University School of Medicine."*
4. The American Academy of Allergy, Asthma and Immunology (AAAAI) Primary Immunodeficiency Diseases Committee created an IVIG toolkit to educate payers and regulators who are responsible for coverage determinations and aid physicians in the safe, effective and appropriate use of IVIG for patients with primary immunodeficiency diseases. The IVIG toolkit has been approved by the AAAAI Board of Directors, and endorsed by the Clinical Immunology Society and the Immune Deficiency Foundation. The IVIG toolkit includes:
 - ❖ Eight guiding principles for safe, effective and appropriate use of IVIG
 - ❖ Guidelines for the site of care of the administration of IVIG therapy for patients with PIDD
 - ❖ AAAAI Work Group Report: The Appropriate Use of Intravenously Administered Immunoglobulin (IGIV) "Use of intravenous immunoglobulin in human disease: A review of evidence by members of the primary immunodeficiency committee of the American Academy of Allergy Asthma & Immunology," published as a *supplement to The Journal of Allergy and Clinical Immunology in April, 2006*
 - ❖ Letter to contract and medical directors to advocate for the coverage of IVIG

For additional information:

1. To view sample appeal letters, visit the IDF Website at www.primaryimmune.org
2. References to attach to appeal letter can be found at www.pubmed.com PubMed is a service of the U.S. National Library of Medicine that includes over 18 million citations from MEDLINE and other life science journals for biomedical articles back to 1948.
3. The IDF Consulting Immunologist Program offers free physician-to-physician consults; consults or second opinions on issues of diagnosis, treatment and disease management; and access to a faculty of recognized leaders in clinical immunology 1-800-296-4433.

The toolkit can be found at:

<http://www.aaaai.org/members/resources/initiatives/ivig.stm>

SAMPLE PHYSICIAN INSURANCE APPEAL LETTER

Letter should be tailored to patient's clinical history.

Insurance Company Name
Address
City, State, Zip code

Re: Patient Name
Date of Birth:
Appeal Account #:

Dear Insurance Company:

I am appealing the decision and request immunoglobulin be approved for this patient.

Disease: Common Variable Immune Deficiency (279.06); severe recurrent infections (listed below), hypothyroidism, allergies

Clinical History:

- ❖ Types of infections:
 - Severe recurrent sinopulmonary infections, but has been on chronic antibiotics for the past 11 months with partial benefit but constant relapse.
 - Sinus x-rays demonstrated clear-cut pansinusitis with opacification, systemic antibiotics together with nasal irrigation gentamicin and an empiric course of Diflucan.
 - Patient also had chronic bronchitis with copious mucus.
- ❖ Hospitalizations & Surgeries: 2 (Sinus surgery & total thyroid removal)

Laboratory Studies:

- ❖ After four doses of Prevnar and two doses of the pneumococcal vaccine, patient did not respond to any of the pneumococcal serotypes. In addition, he responded to only three out of seven of the Prevnar (protein behaving antigens). Therefore, using the well accepted, classic definition of poor antibody response to less than 50% (in this case zero), patient falls into the severe phenotype.
- ❖ Despite repeated infections, patient's quantitative immunoglobulins are low.

Patient Fulfills the criteria for IVIG on the following:

- ✓ Repeated, chronic, poorly responsive respiratory disease to aggressive antibiotic and other anti-infectious measures.
- ✓ Patient has objective data indicating persistent infection with chronic inflammation, pansinusitis with opacification despite aggressive systemic antibiotics, antifungal and antibiotic irrigation
- ✓ Patient has clear-cut, well documented laboratory studies indicating immunodeficiency.

Therefore, IVIG is warranted.

Should you have any questions, I would request a peer review by members* of the Primary Immunodeficiency Committee of the American Academy of Allergy, Asthma and Immunology that contributed to "Use of intravenous immunoglobulin in human disease."

With very best wishes.

Sincerely,

John Smith, M.D.
List credentials

Enclosures

*Orange JS, Hossny EM, Weiler CR, Ballow M, Berger M, Bonilla FA, Buckley R, Chinen J, El-Gamal Y, Mazer BD, Nelson RP Jr, Patel DD, Secord E, Sorensen RU, Wasserman RL, Cunningham-Rundles C; Primary Immunodeficiency Committee of the American Academy of Allergy, Asthma and Immunology. Use of intravenous immunoglobulin in human disease: a review of evidence by members of the Primary Immunodeficiency Committee of the American Academy of Allergy, Asthma and Immunology. J Allergy Clin Immunol. 2006 Apr;117(4 Suppl):S525-53.

GLOSSARY

A

Acute – a descriptive term used to describe an illness which is usually short in duration

Agammaglobulinemia – an almost total lack of immunoglobulins or antibodies

Amniocentesis – involves the withdrawal of fluid surrounding a fetus usually in order to perform prenatal genetic testing

Antibodies – protein molecules that are produced and secreted by certain types of white cells (lymphocytes) in response to stimulation by an antigen; their primary function is to bind and help eliminate or neutralize bacteria, viruses, toxins, and other substances foreign to the body

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

Autoimmune disease – a disease that results when the body's immune system reacts against a person's own tissue

Autosomes – any chromosome (numbered 1-22) other than a sex chromosome (X or Y)

B

Bacteria – single cell organisms (microorganisms) that can be seen only under a microscope; while bacteria can be useful, many bacteria can cause disease in humans

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 that contain developing red and white blood cells, platelets and cells of the immune system

Bronchiectasis – damage to the tubes (bronchi) leading to the air sacs of the lung; usually the consequence of recurrent infection

C

CD 40 ligand – a protein found on the surface of activated T lymphocytes; Individuals with X-linked Hyper IgM Syndrome have a deficiency in this protein

Cellular immunity – immune protection provided by the direct action of the immune cells

Chromosomes – physical structures in the cell's nucleus that house genes; each human has 23 pairs of chromosomes – 22 pairs of autosomes and a pair of sex chromosomes

Chronic – descriptive term used to describe an illness or infection that may be recurrent or lasting a long time

Chorionic villus sampling – involves the retrieval of a sample of the developing placenta from the womb in order to perform prenatal genetic or biochemical testing

Combined immunodeficiency – immunodeficiency resulting from when both T and B cells are inadequate or lacking

Complement – a complex series of blood proteins that act in a definite sequence to effect the destruction of bacteria, viruses and fungi

Congenital – present at birth

Cord blood – blood obtained from the placenta at birth, usually by removal from the umbilical cord

Cryptosporidium – an organism that can cause severe gastrointestinal symptoms and severe liver disease; may be present in drinking water; the organism is resistant to chlorine, so even chlorinated water can carry this organism

GLOSSARY

D

DNA (deoxyribonucleic acid) – the carrier of genetic information contained in chromosomes found in the cell nucleus

E

Eczema – skin inflammation with redness, itching, encrustations and scaling

F

Fungus – member of a class of relatively primitive microorganisms including mushrooms, yeast and mold

G

Gamma interferon – a cytokine primarily produced by T-cells that improves bacterial killing by phagocytes; used as treatment for Chronic Granulomatous Disease

Gene – a unit of genetic material (DNA)

Gene (or genetic) testing – testing performed to determine if an individual possesses a specific gene or genetic trait; may include studies of whether the gene is altered (mutated) in any way

Gene therapy – treatment of genetic diseases by providing the correct or normal form of the abnormal gene causing the disease

Graft-versus-host disease – a life-threatening reaction in which transplanted or transfused immunocompetent T cells attack the tissue of the recipient

Graft rejection – the immunologic response of the recipient to the transplanted tissue resulting in rejection of the transplant

Granulocyte – a white cell of the immune system characterized by the ability to ingest (phagocytize) foreign material; a granulocyte is identified by the presence of many granules when seen under a microscope; neutrophils, eosinophils, and basophils are examples of granulocytes

H

Haplotype – a series of gene clusters on one human chromosome 6 that encodes a set of histocompatibility (HLA) antigens

Helper lymphocytes (Helper T cells) – a subset of T cells that help B cells and other immune cells to function optimally

Humoral immunity – immune protection provided by soluble factors, such as antibodies, which circulate in the body's fluid

Hypogammaglobulinemia – lower than normal levels of immunoglobulins and antibodies in the blood; low levels need to be assessed as to whether the level requires replacement immune globulin therapy; this assessment is best made by a qualified experienced immunologist

I

IgA – an immunoglobulin found in blood, tears, saliva, and fluids bathing the mucous membranes of respiratory and intestinal tracts

IgD – an immunoglobulin whose function is poorly understood at this time

IgE – an immunoglobulin found in trace amounts in the blood; antibodies of this type are 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 immunoglobulin that can cross the placenta

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 activity or response of the immune system against foreign substances

Immunodeficiency – a state of either a congenital (present at birth) or an acquired abnormality of the immune system that prevents adequate immune responsiveness

Immunoglobulins (Ig) – the antibody proteins; there are five major classes: IgG, IgA, IgM, IgD, and IgE

Intravenous immunoglobulin – immune globulin therapy injected directly into the vein

GLOSSARY

K

Killer lymphocytes – T lymphocytes that directly kill microorganisms or cells that are infected with microorganisms, also called “cytotoxic T lymphocytes”

L

Leukemia – type of cancer of the immune system

Live vaccines – live viruses are used in the vaccine; live vaccines (particularly oral polio and the chickenpox vaccine) when injected into immunodeficient individuals, can transmit the diseases they were designed to prevent

Less virulent agents – organisms that do not generally infect humans; they may cause disease in individuals with weak immune systems, these are called “opportunistic infections”

Leukocyte (white blood cell) – a group of small colorless blood cells that play a major role in the body's immune system; there are five basic white blood cells: monocytes, lymphocytes, neutrophils, eosinophils and basophils

Lymph – fluid made up of various components of the immune system; it 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 cells, T cells and macrophages; lymph nodes unite in one location the several factors needed to produce an immune response

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 three major forms of lymphocytes, B cells, T cells and natural killer (NK) cells, each of which have distinct but related functions in generating an immune response

Lymphoma – type of cancer of the immune system

M

Macrophages – phagocytic cells found in the tissue, able to destroy invading bacteria or foreign material

Metabolism – a general term which summarizes the chemical changes within a cell resulting 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

Mucosal surfaces – surfaces that come in close contact with the environment, such as mouth, nose, gastrointestinal tract, eyes, etc. IgA antibodies protect these surfaces from infection

N

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

GLOSSARY

O

Opportunistic infection – an infection caused by a usually benign or less virulent agent, but resulting when those organisms become established under certain conditions, such as in immunodeficient individuals

Organism – an individual living thing

Osteomyelitis – infection of the bone

P

Parasite – a plant or animal that lives, grows and feeds on or within another living organism

Persistent infections – infections marked by the continuance of an infectious episode despite appropriate medical interventions

Petechiae – pinhead sized red spots resulting from bleeding into the skin, usually caused by low platelet numbers (thrombocytopenia)

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

Plasma cells – antibody-producing cells descended from B cells

Platelets – smallest of the blood cells; their primary function is associated with the process of blood clotting

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

Prophylactic – 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

R

Recurrent infections – infections, such as otitis, sinusitis, pneumonia, deep-seated abscess, osteomyelitis, bacteremia or meningitis, that occur repeatedly

S

Secondary immunodeficiency – immunodeficiency due to another illness or agent, such as human immunodeficiency virus (HIV), cancer or chemotherapy

Sepsis – an infection of the blood

Spleen – an organ in the abdominal cavity; it is directly connected to the blood stream and like lymph nodes contains B cells, T cells, and macrophages

Stem cells – cells from which all blood cells and immune cells are derived; bone marrow is rich in stem cells. The stem cells referred to in this glossary, do not include embryonic stem cells, which are involved in the generation of all cells and tissues

Subcutaneous infusion – administration of a drug or biologic (e.g. immunoglobulin) slowly, directly under the skin often using a small pump

GLOSSARY

T

Telangiectasia – dilation of small blood vessels

Thrombocytopenia – low platelet count

Thrush – a fungal disease on mucous membranes caused by *Candida albicans* infections

Thymus gland – a lymphoid organ located behind the upper portion of the sternum (breastbone) where T cells develop; this organ increases in size from infancy to adolescence and then begins to shrink

T lymphocytes (or T cells) – lymphocytes that are processed in the thymus; they have a central role in carrying out the immune response

U

Unusual infectious agents – these are normally non-pathogenic agents or those not generally found in humans which can cause serious disease in immunocompromised patients

V

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

Virus – a submicroscopic microbe causing infectious disease which can only reproduce in living cells

W

White blood cells – see leukocyte

This publication was made possible by an unrestricted educational grant from Talecris Biotherapeutics

