Practice parameter

Practice parameter for the diagnosis and management of primary immunodeficiency

Francisco A. Bonilla, MD, PhD*; I. Leonard Bernstein, MD†; David A. Khan, MD‡; Zuhair K. Ballas, MD§; Javier Chinen, MD, PhD¶; Michael M. Frank, MD‖; Lisa J. Kobrynski, MD**; Arnold I. Levinson, MD††; Bruce Mazer, MD‡‡; Robert P. Nelson, Jr, MD§§; Jordan S. Orange, MD, PhD¶¶; John M. Routes, MD‖‖; William T. Shearer, MD, PhD***; and Ricardo U. Sorensen, MD†††

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PREFACE

The purpose of this Practice Parameter for the Diagnosis and Management of Primary Immunodeficiency is to provide the consultant allergist/immunologist with a practical guide for the clinical recognition and diagnosis of immunodeficiency, along with the general principles that guide management of

* Department of Medicine, Children's Hospital Boston, and Department of Pediatrics, Harvard Medical School, Boston, Massachusetts.
† Department of Medicine and Environmental Health, University of Cincinnati College of Medicine, Cincinnati, Ohio.
‡ Department of Internal Medicine, University of Texas Southwestern Medical Center, Dallas, Texas.
§ Division of Allergy/Immunology, Department of Internal Medicine, University of Iowa and the Iowa City Veteran's Administration Medical Center, Iowa City, Iowa.
¶ National Human Genome Research Institute, National Institutes of Health, Bethesda, Maryland.
‖ Department of Pediatrics, Children's Health Center, Duke University Medical Center, Durham, North Carolina.
** Department of Pediatrics, Emory University School of Medicine, Atlanta, Georgia.
†† Section of Allergy and Immunology, Department of Medicine and Neurology, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania.
‡‡ Division of Allergy and Immunology, Montreal Children's Hospital, and Department of Pediatrics, McGill University, Montreal, Quebec.
§§ Department of Medicine, Division of Hematology/Oncology Hematological Malignancy Program/Immunology, Indianapolis, Indiana.
¶¶ Children's Hospital of Philadelphia, Division of Immunology, and Department of Pediatrics, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania.
‖‖ National Jewish Medical Research Center, Associate Professor of Medicine and Immunology, University of Colorado Health Sciences Center, Denver, Colorado.
*** Allergy and Immunology Service, Texas Children's Hospital, Professor of Pediatrics and Immunology, Baylor College of Medicine, Houston, Texas.
††† Department of Pediatrics, Louisiana State University Health Science Center, New Orleans, Louisiana.

The American Academy of Allergy, Asthma and Immunology (AAAAI) and the American College of Allergy, Asthma and Immunology (ACAAI) have jointly accepted responsibility for establishing the *Practice Parameter for the Diagnosis and Management of Primary Immunodeficiency.* This is a complete and comprehensive document at the current time. The medical environment is a changing environment and not all recommendations will be appropriate for all patients. Because this document incorporated the efforts of many participants, no single individual, including those who served on the Joint Task Force, is authorized to provide an official AAAAI or ACAAI interpretation of these practice parameters. Any request for information about or an interpretation of these practice parameters by the AAAAI or ACAAI should be direct to the Executive Offices of the AAAAI, the ACAAI, and the Joint Council of Allergy, Asthma and Immunology. These parameters are not designed for use by pharmaceutical companies in drug promotion. This parameter was edited by Dr Nicklas in his private capacity and not in his capacity as a medical officer with the Food and Drug Administration. No official support or endorsement by the Food and Drug Administration is intended or should be inferred.
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these disorders. This document was developed by a Working Group under the aegis of the Joint Task Force on Practice Parameters, which has published 12 practice parameters for the field of allergy/immunology. (These can be found online at http://www.jcaai.org/Param/index.htm.) The 3 national allergy and immunology societies—the American Academy of Allergy, Asthma, and Immunology (AAAAI), the American College of Allergy, Asthma and Immunology (ACAAI), and the Joint Council of Allergy, Asthma and Immunology (JCAAI)—have given the Joint Task Force the responsibility for both creating new parameters and updating existing parameters. The first Parameter for Primary Immunodeficiency was published in 1995. This document represents the first major revision since its original publication; the entire Practice Parameter has been rewritten. The Practice Parameter was developed by a Working Group made up of clinical immunologists who specialize in immunodeficiency. A working group chaired by Dr Francisco A. Bonilla prepared the initial draft, which was subsequently reviewed by the Joint Task Force. The working draft of the Practice Parameter for the Diagnosis and Management of Primary Immunodeficiency was reviewed by several experts in allergy and immunology. These experts included reviewers appointed by the ACAAI and AAAAI. The revised final document presented herein was approved by the sponsoring organizations and represents an evidence-based consensus parameter. The project was exclusively funded by the 3 allergy and immunology societies noted above.

A principal aim of this Practice Parameter is to organize current knowledge and practice in the diagnosis and management of primary immunodeficiency diseases. Preparation of this Practice Parameter included a review of the medical literature, mainly via the PubMed database. Published clinical studies or reports were rated by category of evidence and used to establish the strength of a clinical recommendation (Table 1). There are few randomized trials in the diagnosis and management of primary immunodeficiency. Thus, most of these recommendations represent evidence from published case series or reports or the opinions of experts in the field.

Table 1. Classification of Evidence and Recommendations*

Category of evidence	
Ia	Evidence from meta-analysis of randomized controlled trials
Ib	Evidence from at least 1 randomized controlled trial
IIa	Evidence from at least 1 controlled study without randomization
IIb	Evidence from at least 1 other type of quasi-experimental study
III	Evidence from nonexperimental descriptive studies, such as comparative studies, correlation studies, and case-control studies
IV	Evidence from expert committee reports or opinions or clinical experience of respected authorities or both
LB	Evidence from laboratory-based studies
Strength of recommendation	
A	Directly based on category I evidence
B	Directly based on category II evidence or extrapolated from category I evidence
C	Directly based on category III evidence or extrapolated from category I or II evidence
D	Directly based on category IV evidence or extrapolated from category I, II, or III evidence
E	Directly based on category LB evidence
F	Based on consensus of the Joint Task Force on Practice Parameters

*Adapted from Shekelle et al[1] by permission of *BMJ*.

The pathophysiology of these disorders will not be discussed in detail; ample material can be found in the literature cited. The Practice Parameter consists of 224 summary statements, each intended to convey an important concept or point of information related to immunodeficiency in general, a specific disorder, or group of disorders. The summary statements are annotated to give a rationale or further elaboration along with literature references. The summary statements and references are also graded according to the Classification of Recommendations and Evidence (Table 1). The Practice Parameter is divided into 6 sections. The first section contains general principles of diagnosis and management of primary immunodeficiency diseases. The remaining 5 sections provide more detail regarding specific diseases or groups of diseases. Within each of these sections, the summary statements describe the principal clinical and laboratory features of each disorder or group of disorders, as well as principles of management that apply to that specific disease or group.

In addition to the annotated summary statements, the Practice Parameter contains 6 annotated algorithms that display decision trees regarding the diagnosis and general principles of therapy of the primary immunodeficiencies. There is also an Appendix with prescribing guidelines for gammaglobulin replacement therapy.

Although developed principally with the consultant allergist/immunologist as the target audience, it is hoped that the Practice Parameter will also serve as a useful reference tool for physicians at all levels of training and in other disciplines as well. Other health care professionals and administrators in managed care or insurance fields may also find useful information here. The developers of this Practice Parameter hope to encourage wider recognition of primary immunodeficiency, increase uniformity and efficiency in evaluation, and enhance consistent application of specific diagnoses. Furthermore, it is hoped that improved understanding of the principles of management of these diseases will lead to better outcomes for these patients and their families.

EXECUTIVE SUMMARY

Primary immunodeficiencies are inherited disorders of immune system function that predispose affected individuals to increased rate and severity of infection, immune dysregulation with autoimmune disease, and malignancy. Primary immunodeficiencies have many clinical similarities with, but are distinct from, secondary immunodeficiencies that may occur during certain viral infections, after immunosuppression to prevent graft rejection after transplantation, during treatment of systemic autoimmune disease, or in association with cancer chemotherapy. More than 100 distinct genetic

Table 2. Classification of Primary Immunodeficiencies

Disease	Gene
Humoral immunodeficiency	
Known genetic basis	
X-linked (Bruton) agammaglobulinemia	
Bruton tyrosine kinase	*BTK*
Autosomal recessive agammaglobulinemia	
IgM heavy chain	*IGHM*
Igα	*CD79A*
Surrogate light chain (λ5)	*CD179B*
B-cell linker protein	*BLNK*
Leucine-rich repeat containing 8	*LRRC8*
Autosomal recessive hyper-IgM syndrome	
Activation-induced cytidine deaminase	*AICDA*
Uracil-DNA glycosylase	*UNG*
Late-onset hypogammaglobulinemia	
Inducible T-cell costimulator	*ICOS*
Immunodeficiency, centromeric instability, and facial anomalies syndrome	
DNA methyltransferase 3B	*DNMT3B*
Unknown genetic basis	
Common variable immunodeficiency	
Selective IgA deficiency	
IgG subclass deficiency	
Specific antibody deficiency	
Transient hypogammaglobulinemia of infancy	
Hypogammaglobulinemia, unspecified	
Cellular immunodeficiency	
Known genetic basis	
Defects of the IL-12/IFN-γ axis	
IFN-γ receptor α chain	*IFNGR1*
IFN-γ receptor β chain	*IFNGR2*
IL-12 p40	*IL12B*
IL-12 receptor β1 chain	*IL12RB1*
Signal transducer and activator of transcription 1	*STAT1*
Chronic mucocutaneous candidiasis	
Autoimmune regulator	*AIRE*
CD16 deficiency	*FCGR3A*
Unknown genetic basis	
Idiopathic $CD4^+$ T lymphocytopenia	
Chronic mucocutaneous candidiasis due to unknown defect	
Natural killer cell deficiency due to unknown defect	
Cellular immunodeficiency, unspecified	
Combined immunodeficiency	
Known genetic basis	
Severe combined immunodeficiency	
X-linked SCID	
Cytokine receptor common γ chain (γ_c)	*IL2RG*
Janus kinase 3	*JAK3*
IL-7 receptor α chain (CD127)	*IL7RA*
IL-2 receptor α chain (CD25)	*IL2RA*
Recombinase activating genes 1 and 2 (includes Omenn syndrome)	*RAG1, RAG2*
Artemis	*DCCRE1C*
MHC class II gene transcription complex	
CIITA (complementation group A)	*MHC2TA*
RFXANK (complementation group B)	*RFXANK*
RFX5 (complementation group C)	*RFX5*
RFXAP (complementation group D)	*RFXAP*
MHC class I	
Transporters of antigenic peptides 1 and 2	*TAP1, TAP2*
TAP-binding protein (tapasin)	*TAPBP*
CD3 complex components	
CD3δ	*CD3D*
CD3ε	*CD3E*
CD3γ	*CD3G*
ζ associated protein of 70 kDa	*ZAP70*
CD45	*PTPRC*
Adenosine deaminase	*ADA*
Purine nucleoside phosphorylase	*NP*
Wiskott-Aldrich syndrome	
Wiskott-Aldrich syndrome protein	*WASP*
Ataxia-telangiectasia and related disorders	
Ataxia–telangiectasia mutated	*ATM*
Ataxia–telangiectasia related disorder	*HMRE11*
Nijmegen breakage syndrome	*NBS1*
DNA ligase IV	*LIG4*
DNA ligase I	*LIG1*
DiGeorge syndrome	*22q11 del (TBX-1)* *10p13 del* *Other*
Hyper-IgM syndrome	
Tumor necrosis factor superfamily member 5 (CD40L, CD154)	*TNFSF5*
Tumor necrosis factor receptor superfamily member 5 (CD40)	*TNFRSF5*
X-linked lymphoproliferative syndrome	
SH2D1A/SLAM-associated protein (SAP)	*SH2D1A*
Warts, hypogammaglobulinemia, infections, and myelokathexis syndrome	
CXC chemokine receptor 4	*CXCR4*
Defects of NF-κB regulation	
IκB kinase γ chain (IKKγ) or NF-κB essential modifier (NEMO)	*IKBKG*
IκBα chain	*IKBA*
Defects of Toll-like receptor signaling	
IL-1 receptor–associated kinase 4	*IRAK4*
Caspase 8 deficiency	*CASP8*
Unknown genetic basis	
Severe combined immunodeficiency with unknown defect	
Combined immunodeficiency with unknown defect	
Phagocytic cell disorders	
Known genetic basis	
Chronic granulomatous disease	
X-linked due to mutation of $gp91^{phox}$ (cytochrome b_{558} β chain)	*CYBB*
Autosomal recessive	
$p22^{phox}$ (cytochrome b_{558} α)	*CYBA*
$p47^{phox}$	*NCF1*
$p67^{phox}$	*NCF2*
Chediak-Higashi syndrome	

Table 2. Continued

Disease	Gene
Lysosomal transporter	*LYST*
Griscelli syndrome	*RAB27A*
Hermansky-Pudlak syndrome type 2	*AP3B1*
Leukocyte adhesion deficiency	
Type 1, CD18 (integrin β_2)	*ITGB2*
Type 2, GDP-fucose transporter 1	*FLJ11320*
Neutrophil-specific granule deficiency	
Transcription factor C/EBPε	*CEBPE*
Congenital cyclic or chronic neutropenia (Kostmann syndrome)	
Elastase 2 deficiency	*ELA2*
X-linked neutropenia due to *WASP* mutation	*WASP*
Unknown genetic basis	
Hyper-IgE syndrome	
Complement deficiencies	
C1	
C1q	
C1q β chain	*C1QB*
C1q γ chain	*C1QG*
C1r	*C1R*
C2	*C2*
C3	*C3*
C4	*C4A, C4B*
C5	*C5*
C6	*C6*
C7	*C7*
C8	
C8α	*C8A*
C8β	*C8B*
C9	*C9*
Factor D	*DF*
Factor H	*HF1*
Factor I	*IF*
Properdin	*PFC*
Mannose binding lectin–associated protease 2	*MASP2*

Abbreviations: IFN-γ, interferon-γ; IL, interleukin; MHC, major histocompatibility complex; SCID, severe combined immunodeficiency; WASP, Wiskott-Aldrich syndrome protein.

disorders that affect immune system function have been identified to date (a selection is listed in Table 2).

Primary immunodeficiencies occur in as many as 1 in 2,000 live births. They are most often categorized according to the immune mechanisms that are disrupted. These categories include the defects of specific immunity that are subdivided into humoral or antibody deficiencies, cellular deficiencies, and the combined deficiencies that affect both humoral and cellular mechanisms. There are also defects of innate immunity and the phagocyte and complement system defects. Of all of these categories, antibody deficiencies together account for approximately half of all primary immunodeficiency.

The principal clinical manifestation of immunodeficiency is increased susceptibility to infection. The pattern of organ systems affected and the characteristic pathogens vary with the type of immune defect (Table 3). Autoimmune disease and malignancy are also often seen in a variety of immunodeficiencies. A careful family history may provide important clues regarding potential X-linked or autosomal recessive patterns of inheritance.

In evaluating immunodeficiency, it is critical as, much as possible, to document carefully the foci of infections, the organisms, and the response to treatment. This is necessary to distinguish infectious disease from other noninfectious conditions such as allergy or to distinguish viral infection from bacterial infection. Any other conditions that may predispose the patient to infection, including anatomic defects, allergy, and metabolic disorders, should be considered wherever appropriate

In general, initial evaluation is guided by the clinical presentation (Algorithm 1). Screening tests are applied followed by advanced tests as indicated (Table 4). This stepwise approach ensures efficient and thorough evaluation of mechanisms of immune dysfunction that may underlie the clinical presentation, with narrowing of diagnostic options before using costly sophisticated tests that may be required to arrive at specific diagnoses. In addition to global evaluation of immune development via measurement of nonspecific features such as serum immunoglobulin levels and leukocyte and lymphocyte subpopulations, evaluation of specific immune response is essential. This is most often directed toward evaluation of responses against vaccine antigens, but evaluation of responses to natural exposure or infections is also useful.

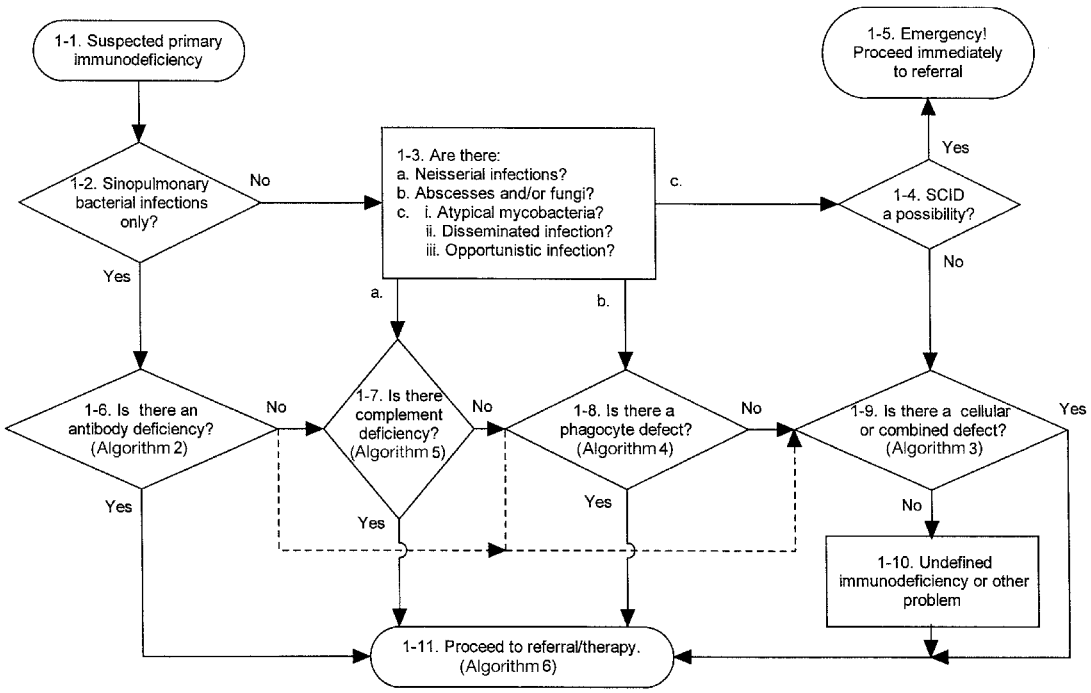
Wherever uncertainty regarding evaluation occurs, consultation with physicians experienced in the diagnosis of immunodeficiencies is essential for establishing the most specific and accurate diagnosis as quickly as possible to enable directed therapy. Wherever possible, diagnosis at the molecular level is desirable to (1) establish unequivocal diagnosis; (2) permit accurate genetic counseling; (3) allow planning of future pregnancies or their outcomes; (4) better define genotype-phenotype associations; and (5) identify candidates for gene-specific therapies.

The principal clinical manifestations of humoral immunodeficiency (Algorithm 2) are recurrent bacterial infections of the upper and lower respiratory tract. Both X-linked and autosomal recessive forms of agammaglobulinemia are associated with extremely low B-cell counts (absent). The X-linked form (Bruton agammaglobulinemia) is most common. In common variable immunodeficiency (CVID), laboratory evaluation generally shows variable reduction in one or more immunoglobulin classes, impairment of specific antibody responses, and, occasionally, reduction of B-cell counts. Milder antibody deficiencies, such as selective IgA deficiency (SIGAD), IgG subclass deficiency (IGGSD), specific antibody deficiency (SAD), or transient hypogammaglobulinemia of infancy (THI), are associated with variably low levels of an immunoglobulin class or subclass in serum, sometimes

Table 3. Primary Immunodeficiency Disorders: Examples of Typical Clinical Presentations

Category of immunodeficiency and examples	Characteristic presentation
Antibody deficiencies	
XLA, ARA, CVID, SIGAD, IGGSD, SAD, THI, hypogam	Recurrent sinopulmonary infections with encapsulated bacteria
Cellular deficiencies	
IL-12/IFN-γ axis	Atypical mycobacterial and salmonella infections
AIRE mutations	Mucocutaneous candidiasis and autoimmune endocrinopathy
Combined deficiencies	
SCID	Failure to thrive, diarrhea, opportunistic infection, rash
Wiskott-Aldrich syndrome	Thrombocytopenia with bleeding and bruising, eczema, recurrent infection with encapsulated organisms
Ataxia telangiectasia	Chronic sinopulmonary disease, cerebellar ataxia, oculocutaneous telangiectasia, malignancy
DiGeorge syndrome	Hypocalcemic seizures due to hypoparathyroidism, cardiac disease, abnormal facies, infection
CD40 ligand deficiency	Recurrent, serious pyogenic infections (also opportunistic infections)
Phagocyte defects	
Chronic granulomatous disease	Deep-seated infection, abscess with granuloma formation
Leukocyte adhesion deficiency	Recurrent serious bacterial infections, delayed separation of the umbilical cord; poor wound healing, lack of pus
Hyper-IgE syndrome	Chronic dermatitis, recurrent serious infection of lungs with pneumatoceles; skin infections, bone fragility, failure to shed primary teeth
Complement deficiencies	
Early classical pathway components	Autoimmune disease and bacterial infections
Late components	Neisserial infection
C3 and regulatory components	Recurrent infections with encapsulated bacterial

Abbreviations: AIRE, autoimmune regulator; ARA, autosomal recessive agammaglobulinemia; CVID, common variable immunodeficiency; hypogam, hypogammaglobulinemia; IFN-γ, interferon-γ; IGGSD, IgG subclass deficiency; IL-12, interleukin 12; SAD, specific antibody deficiency; SCID, severe combined immunodeficiency; SIGAD, selective IgA deficiency; THI, transient hypergammaglobulinemia of infancy; XLA, X-linked agammaglobulinemia.



Algorithm 1. General approach for the diagnosis of primary immunodeficiency. SCID indicates severe combined immunodeficiency.

Table 4. Laboratory Tests for Evaluation of Immunodeficiency

- B-cell function
  - Screening tests
    - Serum immunoglobulin levels
    - Serum specific antibody titers
  - Advanced tests
    - Antibody response to booster immunization
    - Flow cytometry to enumerate B cells
    - In vitro immunoglobulin production in response to mitogen
    - In vitro immunoglobulin production in response to anti-CD40 and cytokines
    - Antibody response to immunization with ϕ X174
- Cellular immune function
  - Screening tests
    - Flow cytometry to enumerate T cells and natural killer cells
    - Cutaneous delayed hypersensitivity
  - Advanced tests
    - Enzyme assays (ADA, PNP)
    - FISH for 22q11 and 10p11 deletion
    - In vitro proliferative response to mitogens and antigens
    - Natural killer cell cytotoxicity
    - Cytokine production in response to mitogen or antigen stimulation
    - Expression of surface markers after mitogen stimulation
- Phagocytic cell function
  - Screening tests
    - Blood cell count with differential
    - Neutrophil staining, morphology
  - Advanced tests
    - Oxidase function (dihydrorhodamine, nitroblue tetrazolium, chemiluminescence)
    - Flow cytometry for adhesion molecules
    - Chemotaxis
    - Phagocytosis
    - Enzyme assays (myeloperoxidase, G6PDH)
    - WBC turnover
    - Bacterial or fungal killing
    - Bone marrow biopsy
- Complement function
  - Screening tests
    - CH_{50} (total hemolytic complement activity)
    - AH_{50} (alternative pathway hemolytic activity)
  - Advanced tests
    - Level or function of individual complement components
    - Chemotactic activity of complement split products
- General
  - Advanced tests
    - Molecular methods including Southern, Northern, and Western blots, PCR/SSCP, DNA fingerprinting, and nucleotide sequencing

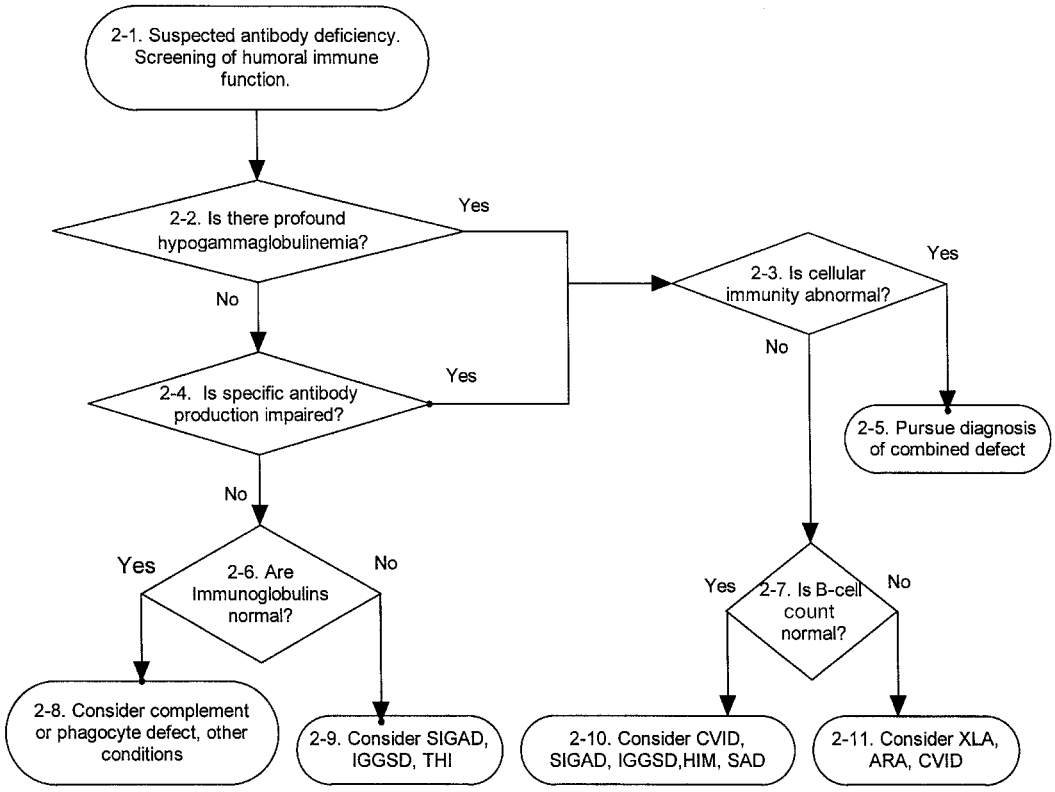
Abbreviations: ADA, adenosine deaminase; FISH, fluorescent in situ hybridization; G6PDH, glucose-6-phosphate dehydrogenase; PCR, polymerase chain reaction; PNP, purine nucleoside phosphorylase; SSCP, single-strand conformation polymorphism; WBC, white blood cell.

accompanied by impaired specific antibody formation. For agammaglobulinemia or CVID, therapy is with gammaglobulin, often with the addition of antibiotic prophylaxis. (Table 5). Milder antibody deficiencies are most often managed with antibiotic prophylaxis. In rare cases, gammaglobulin therapy may be applied.

Selective defects of cell-mediated immunity (Algorithm 3) characteristically present with recurrent infections with pathogens that replicate intracellularly, such as mycobacteria or salmonella. Most of the disorders defined at the molecular level involve defects of the interferon-γ (IFN-γ)/interleukin 12 (IL-12) axis. In the cellular deficiencies with a significant component of natural killer (NK) cell dysfunction, recurrent and/or severe herpesvirus infections may be seen. Laboratory abnormalities may be subtle and often require specialized research tests or molecular genetic analysis for diagnosis. Therapy of these disorders may include anti-infection prophylaxis, cytokines (eg, IFN-γ), and/or bone marrow transplantation (BMT) (Table 5).

The combined deficiencies of specific immunity (Algorithm 3) are somewhat arbitrarily classified as severe combined immunodeficiency (SCID) or among a variety of other less severe disorders. Patients with SCID have complete absence of specific immunity and experience the most extreme susceptibility to the entire range of possible pathogens, including opportunistic organisms. These children often present initially with chronic diarrhea and failure to thrive. Laboratory abnormalities may include panhypogammaglobulinemia, lymphopenia or alymphocytosis, and absence of cellular immune function as determined by in vitro stimulation tests. The laboratory phenotype often depends on the specific molecular defect (Table 6). A possible diagnosis of SCID is a medical emergency, since these infants may succumb to severe infection at any time, and outcomes are greatly improved by the earliest possible intervention. Initial therapy is supportive and anti-infective with antimicrobials and gammaglobulin. Definitive therapy with BMT should be sought as quickly as possible.

A variety of less severe defects of combined immunodeficiency (CID) have been described (Algorithm 3). Most prominent among these are Wiskott-Aldrich syndrome (WAS), DiGeorge syndrome (DGS), ataxia-telangiectasia (A-T), nuclear factor of κB essential modifier (NEMO) deficiency, hyper-IgM syndromes (HIM), and X-linked lymphoproliferative disease (XLP). These disorders present with varying degrees of susceptibility to the entire spectrum of organisms, depending on the specific disorder and on other host genetic and environmental factors that are still poorly understood. Many of these diseases have ancillary clinical features that may influence or guide the diagnostic approach. Laboratory abnormalities of specific immune function vary, depending on the specific gene defect, and may include alterations in immunoglobulin levels with impaired specific antibody responses, as well as defects of specific cellular immunity as determined by in vivo and in vitro assays. Therapy is often supportive and anti-infective with drugs and gammaglobulin. BMT has been applied in many of these disorders as well (Table 5).



Algorithm 2. Diagnosis of humoral immunodeficiency. ARA indicates autosomal recessive agammaglobulinemia; CVID, common variable immunodeficiency; HIM, hyper-IgM syndrome; IGGSD, IgG subclass deficiency; SAD, specific antibody deficiency; SIGAD, selective IgA deficiency; THI, transient hypogammaglobulinemia of infancy; and XLA, X-linked agammaglobulinemia.

Phagocytic cell defects (Algorithm 4) may present with severe pyogenic bacterial and fungal infections of the respiratory tract, skin, viscera, and gingivostomatitis. Laboratory evaluation shows neutropenia, normal numbers, or neutrophilia (in cellular adhesion defects). Functional studies show most often a defect in oxidative metabolism, since chronic granulomatous disease is the most common phagocyte defect. In other disorders, there may be simply severe neutropenia or variable impairment of chemotaxis, phagocytosis, or intracellular killing. Therapy is with antibacterial and antifungal prophylaxis and cytokines (IFN-γ) for chronic granulomatous disease (CGD). BMT has also been applied for CGD. The care of patients with other forms of phagocyte defects is primarily anti-infective and supportive. BMT has been applied in some, but experience is limited (Table 5).

Complement deficiencies are the rarest of the primary immunodeficiencies, accounting for less than 1%. Most early classical and alternative pathway complement defects tend to present with either systemic autoimmune disease that resembles lupus erythematosus or recurrent respiratory tract bacterial infections similar to antibody deficiency (Table 7). Deficiencies of terminal components may also be associated with recurrent neisserial meningitis. Some patients with low serum levels of mannose-binding lectin (MBL) may be predisposed to bacterial respiratory tract infections, but there may be other host factors that interact to create such susceptibility in an individual. There is no specific therapy for complement deficiency. Antibiotic prophylaxis may be considered for recurrent infections (Table 5).

To improve consistency in evaluation and management and to have the best outcomes with respect to patient and family health, education, and planning, it is imperative that diagnosis and therapy are guided overall by individuals with direct experience with a broad range of immunodeficiencies.

ALGORITHMS

Annotations to Algorithm 1: General Approach for the Diagnosis of Primary Immunodeficiency

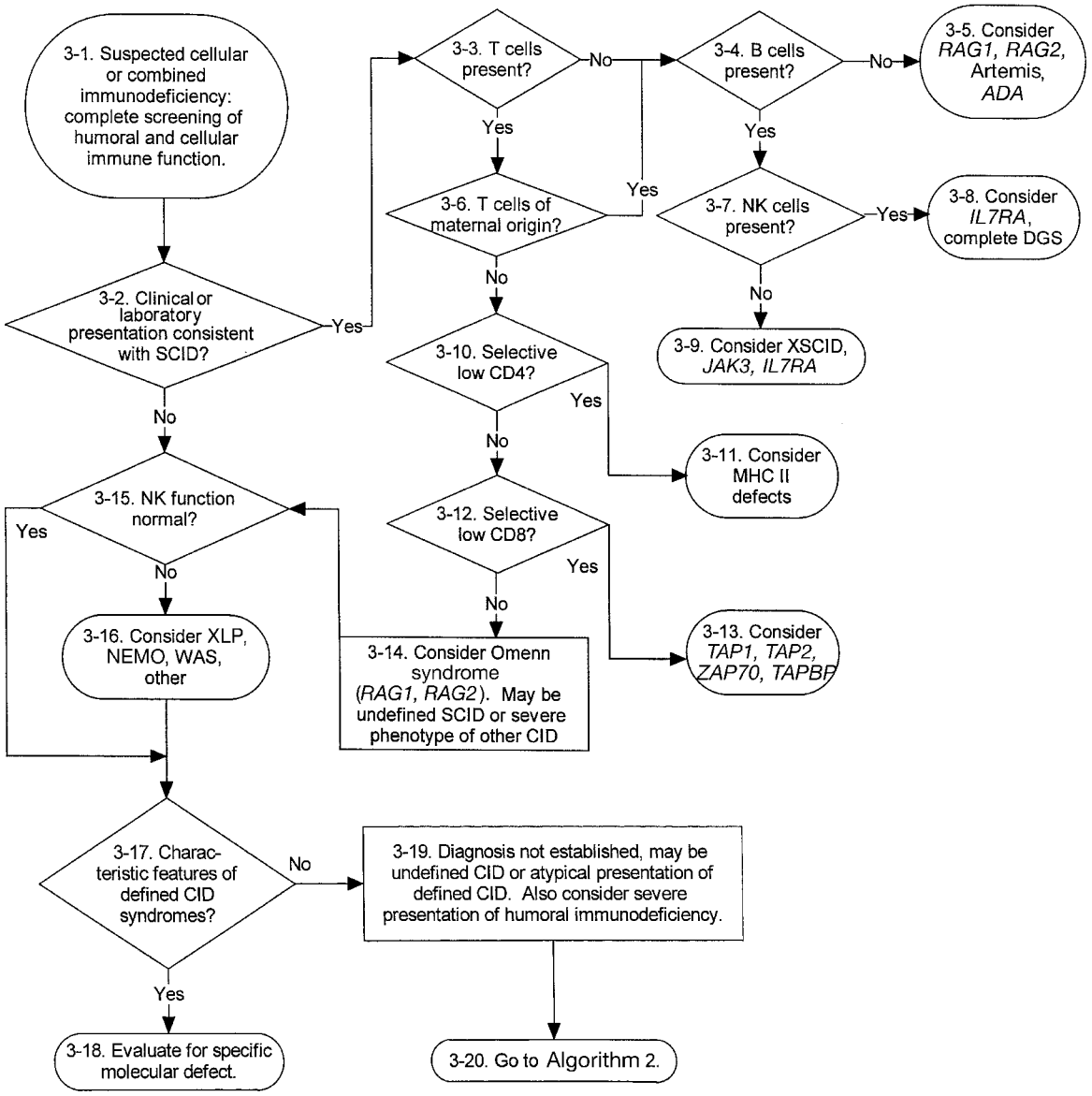
1-1. The patient exhibits symptoms and signs consistent with primary immunodeficiency. It is assumed that immunosuppressive therapies and other medical conditions potentially resulting in secondary immunodeficiency and other anatomic or biochemical conditions potentially predisposing to infection either have been excluded or are not considered sufficient to explain the observed degree of infectious susceptibility.

1-2. Antibody deficiency is most frequently encountered and commonly presents with sinopulmonary bacterial infec-

Table 5. Summary of Therapeutic Considerations for Primary Immunodeficiencies and Their Complications

Category of immunodeficiency	IVIG	BMT	Gene therapy	Other treatments
Humoral immunodeficiency				
XLA, ARA, *AICDA*, *UNG*, *ICOS*, CVID, SAD, hypogam	Yes	No	No	Avoidance of live vaccines: all except SIGAD, IGGSD, THI
IGGSD, SIGAD, THI	?	No	No	Antibiotics: all Immunomodulators: CVID, SIGAD, IGGSD Splenectomy: CVID Chemotherapy: CVID Pneumococcal vaccines: SAD
Cellular Immunodeficiency				
IFN-γRA/B	No	Yes	No	Avoidance of live vaccines: all
IL-12R, *AIRE*, NK (CD16), ICD4L, CMCC, NK (unknown), unspecified	?	No	No	Antibiotics: all IFN-γ: partial IFN-γR, IL-12R Anti-mycobacterials: IFN-γ, IL-12R Immunomodulators: *AIRE*, ICD4L IL-2: ICD4L Antifungals: *AIRE*, ICD4L, CMCC Antivirals: NK (CD16), ICD4, NK (unknown)
Combined Immunodeficiency				
SCID (*IL-2RG, ADA*)	Yes	Yes	Yes	Avoidance of live vaccines: all (partial DGS?)
SCID (*JAK3, IL-2RA, IL7RA, RAG1/2,* CD45, MHC I/II, CD3, *ZAP70*, Artemis, *NP* (unknown)	Yes	Yes	No	Avoidance of nonirradiated blood or products: all Avoidance of CMV-positive blood or cells: all Antibiotics: all
WAS, A-T, NBS, DGS, *TNFSF5, TNFRSF5*, XLP, GS, NEMO, WHIM, syndrome caspase 8, Unknown	Yes	Yes	No	Pneumocystis prophylaxis: all SCID, *TNFSF5, TNFRSF5* PEG-ADA: ADA Splenectomy: WAS Anti-inflammatory: WAS G-CSF: *TNFSF5*, *TNFRSF5*, WHIM syndrome GM-CSF: WHIM syndrome Chemotherapy: XLP, GS Thymus transplantation: DGS Multidisciplinary care: DGS, A-T
Phagocyte defects				
CGD	No	Yes	?	Avoidance of live bacterial vaccines: all
CHS, LAD type I, neutropenias	No	Yes	No	Antibiotic prophylaxis: all
LAD type II	No	No	No	IFN-γ: CGD
HIES	?	No	No	Surgical or dental debridement: CGD, LAD type I Granulocytic transfusions: CGD, LAD type I Antifungals: CGD, LAD type I, HIES G-CSF: neutropenias Fucose: LAD type II Chemotherapy: CHS
Complement deficiencies				
C1q, C1r, C2, C3, C4, C5, C6, C7, C8, C9, factors D, H, and I, properdin	No	No	No	Antibiotics: all Pneumococcal vaccine: C1a, C1r, C2, C3, C4 Meningococcal vaccine: C5, C6, C7, C8, C9 Immunomodulators: C1a, C2, C4

Abbreviations: A-T, ataxia-telangiectasia; ADA, adenosine deaminase; AICDA, activation-induced cytidine deaminase; AIRE, autoimmune regulator; ARA, autosomal recessive agammaglobulinemia; BMT, bone marrow transplantation; CGD, chronic granulomatous disease; CHS, Chediak-Higashi syndrome; CMCC, chronic mucocutaneous candidiasis; CMV, cytomegalovirus; CVID, common variable immunodeficiency; DGS, DiGeorge syndrome; G-CSF, granulocyte colony-stimulating factor; GM-CSF, granulocyte-macrophage colony stimulating factor; GS, Griscelli syndrome; HIES, hyper-IgE syndrome; hypogam, hypogammaglobulinemia; ICD4L, idiopathic CD4 lymphocytopenia; ICOS, inducible T-cell costimulator; IFN-γ, interferon-γ; IFN-γR, interferon-γ receptor; IGGSD, IgG subclass deficiency; IL, interleukin; IL-12R, interleukin 12 receptor; IVIG, intravenous immunoglobulin; LAD, leukocyte adhesion deficiency; MHC, major histocompatibility complex; NBS, Nijmegen breakage syndrome; NEMO, nuclear factor of κB essential modifier; NK, natural killer; NP, nucleoside phosphorylase; PEG, polyethylene glycol; RAG, recombinase activating gene; SAD, specific antibody deficiency; SCID, severe combined immunodeficiency; SIGAD, selective IgA deficiency; THI, transient hypogammaglobulinemia of infancy; TNFSF5, tumor necrosis factor superfamily member 5; TNFRSF5, tumor necrosis factor receptor superfamily member 5; UNG, uracil nucleoside glycosylase; WAS, Wiskott-Aldrich syndrome; WHIM, warts, hypogammaglobulinemia, immunodeficiency, and myelokathexis; XLA, X-linked agammaglobulinemia.



Algorithm 3. Diagnosis of cellular and combined immunodeficiencies. ADA indicates adenosine deaminase; CID, combined immunodeficiency; DGS, DiGeorge syndrome; IKBKG, IκB kinase γ chain; IL-2Ra, interleukin 2 receptor agonist; MHC, major histocompatibility complex; NK, natural killer; SAP, SLAM-associated protein; SCID, severe combined immunodeficiency; WAS, Wiskott-Aldrich syndrome; and XSCID, X-linked severe combined immunodeficiency.

tions. If these are the only types of infections under consideration, screening for antibody deficiency is appropriate.

1-3. Other forms of primary immunodeficiency may present with distinct infectious complications with or without sinopulmonary bacterial disease. Some of these forms of infection are more or less characteristic of specific categories of immunodeficiency (Table 2). Neisserial infections characterize terminal complement component deficiencies, abscesses and fungal pathogens are seen in phagocyte defects, and mycobacterial, disseminated, or opportunistic infections occur in cellular or combined deficiencies.

1-4. If the clinical presentation is consistent with SCID, then immediate referral for expedited evaluation and treatment (BMT) is indicated.

1-5. Successful outcomes depend on timely intervention.

1-6. Suspected antibody deficiency may be evaluated according to Algorithm 2. Complement deficiency, phagocyte defects, and some combined deficiencies may have a clinical presentation similar to antibody deficiency and should be sought when there is not a definitive diagnosis of such. Depending on the clinical presentation, any of these could be an appropriate subsequent focus of investigation.

Table 6. Abnormalities of Lymphocyte Populations in Some Defined SCID Syndromes*

Gene	CD4	CD8	B cells	Natural killer cells	Lymph nodes	Thymus	Other features	Reference(s)
IL2RG	↓	↓	NL	↓	−	−		18, 326
JAK3	↓	↓	NL	↓	−	−		329–333
IL2RA	↓	↓	NL	↓	+	+		334, 335
IL7RA	↓	↓	NL	NL	+	−		336
CD3D	↓	↓	NL	NL		+		337
RAG1, RAG2	↓	↓	↓	NL	−	−	May have oligoclonal host T cells with graft-vs-host disease–like phenotype (Omenn syndrome)	338–340
DCCRE1C	↓	↓	↓	NL	−	−	Radiation sensitivity	341, 342
MHCIID	↓	NL	NL	NL			Sclerosing cholangitis	343–345
MHCID	NL	↓	NL	NL	+	+	Milder phenotype, mainly respiratory bacterial infections	346–348
ZAP70	NL	↓	NL	NL	+	+		349–351
ADA	↓	↓	↓	±	±	−	Skeletal abnormalities	352
NP		Variable			±	±	Central nervous system disease	36, 353
PTPRC	↓	↓	NL					354, 355

*Downward arrow indicates decrease; minus sign, negative; and plus sign, positive.

1-7. Suspected complement deficiency may be evaluated according to Algorithm 5.

1-8. Suspected phagocyte defects may be evaluated using Algorithm 4.

1-9. Suspected cellular or combined immunodeficiencies may be evaluated according to Algorithm 3.

1-10. Depending on the specific characteristics of the infections and other medical problems that occur in a given patient, one or all of these immune effector mechanisms may require evaluation. In some cases, no definitive immunologic defect is ascertained. These patients either have an undefined form of compromised immunity or some other medical problem predisposing them to infection.

1-11. Whenever possible, the evaluation and/or management of suspected primary immunodeficiency should be performed by, or in close consultation with, a clinician with experience in this area. At some time during evaluation or after diagnosis is established, referral should be made for further evaluation and/or guidance during therapy.

Annotations to Algorithm 2: Diagnosis of Humoral Immunodeficiency

2-1. The clinical presentation is primarily suggestive of an antibody defect or any evaluation of cellular function is so far normal, and the clinical presentation is at least consistent with a possible antibody deficiency. The initial laboratory examination of humoral immunity consists of measuring the levels of various immunoglobulin isotypes (IgG, IgA, IgM) in serum, as well as a measure of function, or specific antibody production.

2-2. Profound hypogammaglobulinemia with serum IgG levels less than 100 mg/dL in an infant or less than 2 to 3 g/L in an older child or adult should prompt additional evaluation of lymphocyte populations and cellular immune function **(2-3)** to investigate CID and B-cell count.

2-4. Specific antibody responses may be impaired as a result of a B-cell defect or failure of T-cell help for antibody production, even if serum immunoglobulin levels are normal or near normal. This situation should also prompt evaluation of lymphocyte subsets and cellular immunity **(2-3)**.

2-5. Cellular immunity is evaluated either because of severe hypogammaglobulinemia or impaired specific antibody production (or both). If cellular immunity is abnormal, then the eventual diagnosis will be a form of CID. If cellular immunity is normal, it is important to determine whether there appears to be a significant impairment of B-cell development **(2-7)**.

2-6. There is no profound hypogammaglobulinemia or demonstrable impairment of specific antibody production. Is there any abnormality of serum immunoglobulins or IgG subclasses? Yes **(2-8)** or No **(2-9)**.

2-7. Is B-cell count normal? Yes **(2-10)** or No **(2-11)**.

2-8. All measurements are normal, and alternative explanations for recurrent infections should be sought.

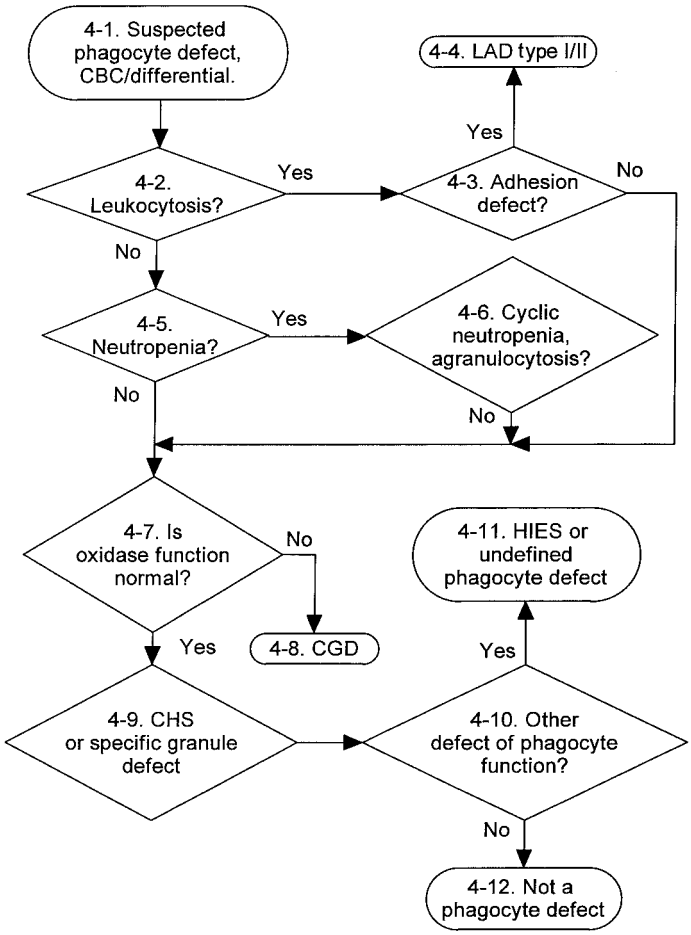
2-9. Mild hypogammaglobulinemia in infants, low serum IgA or IgG subclasses, or other poorly defined immunoglobulin abnormalities may exist with normal levels of specific antibodies as measured by standard assays. Potential diagnoses include SIGAD, IGGSD, or THI.

2-10. Hypogammaglobulinemia and/or impaired specific antibody formation are seen in CVID, SIGAD, IGGSD, SAD, and some forms of HIM, such as activation-induced cytidine deaminase (AID) or uracil nucleoside glycosylase (UNG) deficiencies.

2-11. Hypogammaglobulinemia or agammaglobulinemia associated with low or absent B-cell counts is seen in X-linked agammaglobulinemia (XLA) or autosomal recessive agammaglobulinemia (ARA) and in CVID.

Annotations to Algorithm 3: Diagnosis of Cellular and Combined Immunodeficiencies

3-1. In this situation, it is appropriate to perform a complete screening evaluation of specific immune function, including measurement of immunoglobulin levels, specific antibody pro-



Algorithm 4. Diagnosis of phagocyte defects. CBC indicates complete blood cell count; CGD, chronic granulomatous disease; CHS, Chediak-Higashi syndrome; HIES, hyper-IgE syndrome; and LAD, leukocyte adhesion deficiency.

duction, enumeration of lymphocyte subpopulations, evaluation of NK cell cytotoxicity, and measurement of T-cell function.

3-2. If the clinical and laboratory phenotype is consistent with SCID, every effort must be made to expedite definitive therapy (BMT). It is desirable to know the actual molecular defect, but this should not delay therapy.

3-3 through 3-14. The particular form of SCID may often be suspected based on the lymphocyte phenotype (Table 5). If T cells are present, their origin (mother or patient) should be determined.

3-4. If T cells are absent or only of maternal origin **(3-6)** and B cells are also absent, then one of the alymphocytic SCID syndromes should be considered **(3-5)**. If B cells are present, along with NK cells **(3-7),** consider IL-7 receptor α *(IL7RA)* mutation or complete DGS **(3-8)**.

3-9. If B cells are present but NK cells absent, consider mutations that involve common γ chain, *JAK3*, or *IL2RA*.

3-10. If host T cells are present and there is selective depletion of $CD4^+$ cells, consider defects of major histocompatibility complex (MHC) class II expression **(3-11)**.

3-12. If there is selective depletion of $CD8^+$ cells, consider defects involving MHC class I expression or ZAP70 deficiency **(3-13)**.

3-14. Omenn syndrome is associated with a variable host T-cell phenotype, although there is not usually extreme preponderance of one cell type. One should also consider the possibility of a less common (possibly undefined) form of SCID or a severe phenotype of other CID, such as CD40 ligand (CD40L) deficiency.

3-15. If there is at least partial T-cell function, evaluation of NK cell cytotoxicity may partly guide the subsequent evaluation. It has been recently recognized that a few CID syndromes may be associated with depressed NK cytotoxicity. These include (but are not limited to) XLP, NEMO deficiency and WAS. **(3-16)**.

3-17. Whether NK function is abnormal or not, there may be characteristic clinical or laboratory features that may suggest a particular molecular diagnosis (Table 3).

3-18. The clinical presentation and laboratory evaluation so far is suggestive of 1 or more particular disorders. Ad-

Table 7. Clinical Associations With Complement Component Deficiencies

Component(s)	SLE-like autoimmune disease	Bacterial infections
C1, C2, C4	Yes	Multiple species
C3	No	Multiple species, severe
C5, C6, C7	Yes	*Neisseria*
C8, C9	No	*Neisseria*
Properdin	Yes	*Neisseria*
Factor D	No	Multiple species

Abbreviation: SLE, systemic lupus erythematosus.

vanced molecular methods (Table 4) may be applied to detect particular defects.

3-19. If there are no such distinguishing clinical or laboratory features or if the suspected diagnosis is proven incorrect, one should consider **(3-20)** an undefined CID, an atypical clinical presentation of a defined CID, or a severe presentation of a primary humoral immunodeficiency **(3-21)** (Algorithm 2).

Annotations to Algorithm 4: Diagnosis of Phagocyte Defects

4-1. The clinical presentation is primarily suggestive of a phagocyte defect or evaluation of other immune function is so far normal, and the clinical presentation is at least consistent with a possible phagocyte defect. A complete blood cell count with differential is necessary to show the absolute neutrophil count.

4-2. Marked leukocytosis is observed in most cases of leukocyte adhesion defects and should raise suspicion in the appropriate setting.

4-3. Defects associated with leukocyte adhesion deficiency (LAD) are readily screened by flow cytometry, which may establish the diagnosis **(4-4)**.

4-5. Severe neutropenia may be associated with congenital agranulocytosis or cyclic neutropenia **(4-6)**.

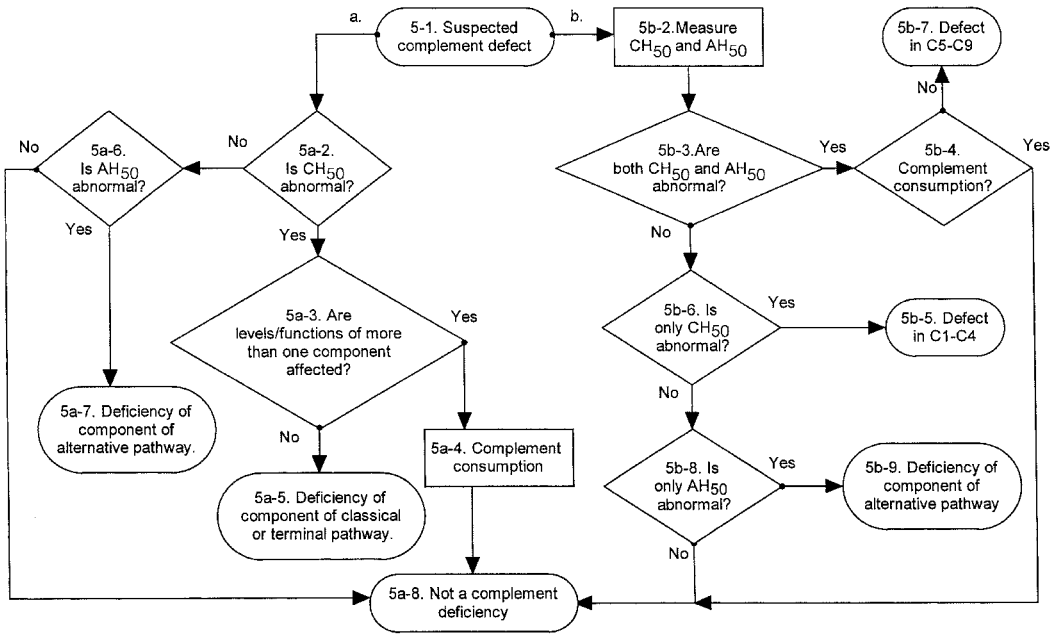
4-7. If leukocyte count is not abnormal and the clinical features are consistent, neutrophil oxidase function may be evaluated by dihydrorhodamine reduction, nitroblue tetrazolium, or chemiluminescence. Abnormal oxidase function is indicative of CGD **(4-8).**

4-9. Chediak-Higashi syndrome (CHS) and specific granule deficiency (SGD) are suspected based on clinical presentation and neutrophil appearance under microscopy.

4-10. In the absence of a known syndrome of phagocyte deficiency, it is necessary to establish a functional defect more precisely. These tests include assays of chemotaxis, adhesion, migration, and intracellular killing. If such a functional deficit is reproducible, then a diagnosis of a clinically defined or unspecified phagocyte defect may be considered **(4-11)**. Hyper-IgE syndrome (HIES) is usually suspected based on the characteristic clinical presentation. If the presentation is not consistent with this or any of the above, another form of immunodeficiency should be sought **(4-12)**.

Annotations to Algorithm 5: Diagnosis of Complement Deficiency

5-1. The clinical presentation is primarily suggestive of a complement deficiency or evaluation of other immune func-



Algorithm 5. Diagnosis of complement deficiency. AH_{50} indicates alternative pathway hemolytic activity; CH_{50}, total hemolytic complement assay.

tion is so far normal, and the clinical presentation is at least consistent with a possible complement deficiency. Two distinct algorithms are presented, depending on whether total hemolytic complement assay (CH_{50}) and alternative pathway hemolytic activity (AH_{50}) are measured sequentially (5a) or simultaneously (5b). The CH_{50} is available in many clinical laboratories; the AH_{50} is not so widely available (it is available from the Complement Laboratory of the National Jewish Medical Center, Denver, CO). Note that both will be normal in the setting of MBL deficiency

5a-2. Classical pathway function is measured first by the CH_{50}.

5a-3. Following determination of diminished classical pathway function, it is necessary to determine if there is complement consumption.

5a-4. More than one complement component level is diminished, indicating complement consumption. Another cause of immunodeficiency should be sought.

5a-5. A single complement component level or function is absent, indicative of deficiency of either an early classical pathway component or a terminal pathway component. Note that deficiency of factor H or factor I could lead to a diminished level of C3. The level of each component may be measured by enzyme-linked immunosorbent assay (ELISA), or function may be determined in a lysis assay.

5a-6. The CH_{50} is normal. If complement deficiency is still suspected, function of the alternative pathway is measured by the AH_{50}.

5a-7. Since it has already been determined that the CH_{50} is normal, isolated abnormal AH_{50} is indicative of a defect of a component of the alternative pathway. Each component may be measured by ELISA or functional assay.

5a-8. CH_{50} and AH_{50} are normal.

5b-2. CH_{50} and AH_{50} are measured at the same time.

5b-3. If both are abnormal, this may be due to complement consumption not a primary complement abnormality. Note that deficiency of factor H or factor I could lead to a diminished level of C3.

5b-4. Low levels of multiple complement proteins are indicative of consumption.

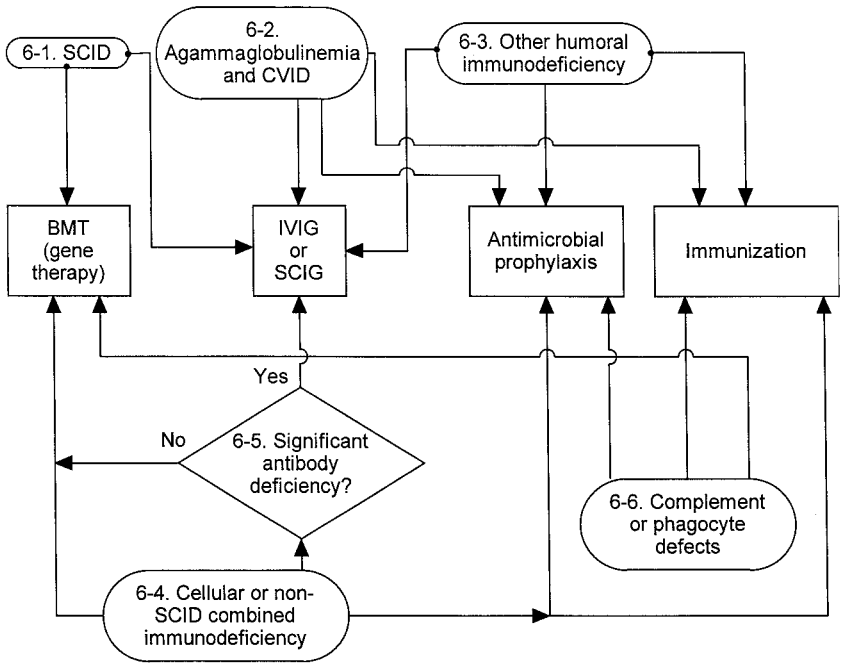
5b-5. If there is no complement consumption, simultaneous abnormality of CH_{50} and AH_{50} is indicative of a terminal pathway deficiency (ie, C3, C5 to C9).

5b-6. If the CH_{50} is abnormal and AH_{50} is normal, this suggests a classical pathway component deficiency (C1, C2, C4) **(5b-7)**.

5b-8. If the AH_{50} is abnormal and the CH_{50} is normal, this is indicative of a defect of a component of the alternative pathway (properdin, factor D) **(5b-9)**. Note that homozygous deficiency of factor B has not been reported.

Annotations to Algorithm 6: General Considerations for Therapy of Primary Immunodeficiency

Four principal general categories of therapy are indicated: BMT or gene therapy, intravenous immunoglobulin (IVIG) or subcutaneous immunoglobulin (SCIG), antimicrobial prophylaxis for any pathogen to which the host is susceptible and for which preventive therapy is available, and immunization where appropriate (Table 4).



Algorithm 6. General considerations for therapy of primary immunodeficiency. BMT indicates bone marrow transplantation; CVID, common variable immunodeficiency; IVIG, intravenous immunoglobulin; and SCIG, subcutaneous immunoglobulin.

6-1. For SCID, BMT should be pursued as expeditiously as possible. IVIG or SCIG is indicated before BMT and as necessary afterward for persistent humoral immunodeficiency. (Note that the latter could be similar to either **6-2** or **6-3**.) For some diseases, now or in the future, gene therapy is or may be a possibility.

6-2. For XLA, ARA, or CVID, IVIG or SCIG is appropriate at the time the diagnosis is established. Many also recommend routine initiation of antibacterial prophylaxis at this time. Some prescribe preventive antibiotics when IVIG or SCIG is inadequate for prevention of infection or when other conditions such as bronchiectasis are present. Immunization may be considered, particularly with inactivated vaccines for which coverage by IVIG or SCIG is not reliable (eg, influenza).

6-3. For milder antibody deficiencies (SIGAD, IGGSD, SAD), therapy is often initially with preventive antimicrobials and immunization. Depending on all of the clinical and laboratory features, IVIG or SCIG may be considered.

6-4. For specific cellular deficiencies or for non-SCID combined deficiencies, BMT is often considered. BMT may not be appropriate for milder forms or if a suitable donor is not available. Wherever there is significant impairment of specific antibody production (**6-5**), IVIG or SCIG should be given. Antimicrobial prophylaxis and immunization may also be appropriate, depending on the specific defect.

6-6. For some phagocyte defects (eg, CGD), BMT should be considered. IVIG or SCIG is generally not appropriate for complement or phagocyte defects. Antimicrobial prophylaxis is essential for phagocyte defects and may be considered for complement deficiency. Immunization may be helpful.

SUMMARY STATEMENTS

General Considerations

Summary statement 1. Individual immunodeficiencies are rare, but altogether they occur in more than 1 in 2,000 live births. (C)

Summary statement 2. Immunodeficiencies are classified according to the principal immunologic mechanisms that are disrupted. (D)

Summary statement 3. Antibody deficiency is the most common type of primary immunodeficiency. (C)

Summary statement 4. Immunodeficiency usually presents with signs and symptoms of infections that may be repetitive, severe, or refractory to therapy and caused by organisms of low virulence. (C)

Summary statement 5. It is critically important to confirm the precise focus of infection and organism whenever possible. (D)

Summary statement 6. Other conditions that may increase susceptibility to infection should be sought in patients with suspected immunodeficiency. (D)

Summary statement 7. The physician must exercise caution to rule out the possibility of secondary immunodeficiency underlying the patient's illness. (D)

Summary statement 8. Autoimmune diseases and malignancies are complications of many immunodeficiencies. (C)

Summary statement 9. Many immunodeficiency disorders have characteristic clinical features. (C)

Summary statement 10. The family history may be a critical diagnostic clue for the presence of immunodeficiency. (C)

Summary statement 11. A stepwise approach is used to evaluate suspected immunodeficiency. (D)

Summary statement 12. Evaluation of specific immune response is essential. (C)

Summary statement 13. Patients suspected of having a primary immunodeficiency require evaluation by a clinical immunologist with experience with these disorders. (D)

Summary statement 14. Wherever possible, immunodeficiency should be defined at the molecular genetic level. (D)

Summary statement 15. The possibility of a X-linked disease should be considered in female patients when other possibilities have been ruled out. (D)

Summary statement 16. Female carrier status should be determined for all potentially affected female relatives of male patients with X-linked immunodeficiencies. (D)

Summary statement 17. Following diagnosis, it is important to proceed quickly with preventive and/or replacement therapy. (C)

Summary statement 18. Immunodeficient patients often require more aggressive and prolonged antimicrobial therapy. (C)

Summary statement 19. Antibody replacement therapy is indicated for all disorders with significantly impaired antibody production. (B)

Summary statement 20. Antibiotics may be needed in addition to immunoglobulin replacement for preventing infection in antibody-deficient patients. (C)

Summary statement 21. Mild antibody deficiencies are treated initially with antibiotic prophylaxis. (C)

Summary statement 22. Immunoglobulin replacement therapy may be considered for milder forms of antibody deficiency where other therapies have failed or are not tolerated. (D)

Summary statement 23. The placement of permanent central venous access solely for the purpose of IVIG administration should be discouraged. (F)

Summary statement 24. A role for surgery in the prevention and treatment of infection in immunodeficient patients has not been established. (C)

Summary statement 25. Definitive therapy of cellular or CID requires reconstitution by hematopoietic stem cells. (C)

Summary statement 26. Only irradiated, cytomegalovirus (CMV)–negative, lymphocyte-depleted cellular blood products should be administered to patients with cellular immunodeficiency or CID. (C)

Summary statement 27. No live vaccines should be administered to patients with severely impaired specific immunity. (C)

Summary statement 28. Inactivated or subunit vaccines may be administered to immunocompromised patients. (C)

Summary statement 29. Frequent evaluation by a clinical immunologist with applicable experience is important for patients with immunodeficiencies. (D)

Summary statement 30. Education is important for optimal outcomes for patients and families with immunodeficiency. (D)

Humoral Immunodeficiencies

Summary statement 31. Most patients with XLA present with recurrent bacterial infections, particularly otitis media, sinusitis, and pneumonia, in the first 2 years of life. (C)

Summary statement 32. The physical examination of patients with XLA usually reveals absent lymph nodes and tonsils. (C)

Summary statement 33. Characteristic laboratory abnormalities of XLA include agammaglobulinemia and very low or absent B-cell counts. (C)

Summary statement 34. Bruton tyrosine kinase (BTK) protein is absent in most patients with XLA. (C)

Summary statement 35. Certain *BTK* mutations are associated with variant (milder) phenotypes. (C)

Summary statement 36. Antimicrobial agents are often required in addition to IVIG for therapy of XLA. (C)

Summary statement 37. Chronic enteroviral meningoencephalitis in XLA responds to treatment with high doses of IVIG and with the antiviral drug pleconaril. (C)

Summary statement 38. Lung transplantation has been performed successfully in patients with XLA. (C)

Summary statement 39. Symptoms, signs, laboratory abnormalities, and therapy of the agammaglobulinemias due to autosomal gene defects are generally identical to those of XLA. (C)

Summary statement 40. Prominent clinical features of AID or UNG deficiency include bacterial sinopulmonary infections, gastrointestinal infections, and lymphoid hyperplasia. (C)

Summary statement 41. Laboratory evaluation of humoral immunity in AID or UNG deficiency may reveal low IgG, IgA, and IgE levels together with elevated IgM levels. Specific antibody responses may be impaired. (C)

Summary statement 42. IVIG replacement therapy is indicated for all patients with AID or UNG deficiency. (C)

Summary statement 43. Inducible T-cell costimulator (ICOS) deficiency is characterized by recurrent respiratory tract bacterial infections and gastrointestinal infections. (C)

Summary statement 44. Patients with ICOS deficiency generally have panhypogammaglobulinemia and impaired specific antibody production, along with reduced B-cell counts. (C)

Summary statement 45. Absence of ICOS expression can be determined by flow cytometric methods. (C)

Summary statement 46. Gammaglobulin replacement and antimicrobial agents are the major elements of therapy for ICOS deficiency. (C)

Summary statement 47. The main clinical features of immunodeficiency, centromeric instability, and facial anomalies (ICF) syndrome include abnormal facies and respiratory tract infections. (C)

Summary statement 48. Immunologic abnormalities in ICF syndrome may include hypogammaglobulinemia and mild defects of T-cell function. (C)

Summary statement 49. Characteristic abnormalities of chromosomes 1, 9, and 16 are diagnostic of ICF syndrome. (C)

Summary statement 50. Gammaglobulin replacement is indicated for patients with ICF syndrome and hypogammaglobulinemia. (C)

Summary statement 51. The predominant clinical manifestations of CVID are recurrent upper and/or lower respiratory tract infections with encapsulated or atypical bacteria. (C)

Summary statement 52. Gastrointestinal tract disease is common in patients with CVID. (C)

Summary statement 53. Autoimmune diseases occur with increased frequency in patients with CVID. (C)

Summary statement 54. Nonmalignant lymphoproliferative disease is seen frequently in CVID. (C)

Summary statement 55. Hematologic and other malignancies occur with increased frequency in patients with CVID. (C)

Summary statement 56. Hypogammaglobulinemia and impaired specific antibody production are the hallmarks of CVID. (C)

Summary statement 57. T-cell abnormalities are frequently found in patients with CVID. (C)

Summary statement 58. Selected molecular genetic defects should be ruled out in patients who meet diagnostic criteria for CVID, whenever possible. (C)

Summary statement 59. CVID with thymoma may be a distinct syndrome (Good syndrome). (C)

Summary statement 60. Gammaglobulin replacement therapy and antimicrobial agents are the mainstays of therapy for CVID. (B)

Summary statement 61. Autoimmune, lymphoproliferative, or malignant diseases associated with CVID are treated as they would be in other clinical settings. (C)

Summary statement 62. In patients with Good syndrome, thymomas should be excised. (C)

Summary statement 63. SIGAD is defined as a serum IgA level of less than 0.07 g/L but normal serum IgG and IgM levels in a patient older than 4 years in whom other causes of hypogammaglobulinemia have been excluded. (C)

Summary statement 64. Clinical manifestations of SIGAD include respiratory and gastrointestinal tract infections, atopy, autoimmune diseases, and malignancy. (C)

Summary statement 65. Laboratory evaluation in SIGAD may reveal associated IGGSD and impaired specific antibody formation (C).

Summary statement 66. Atopic disease should be treated aggressively in patients with SIGAD. (C)

Summary statement 67. Aggressive antimicrobial therapy and prophylaxis are often indicated in patients with SIGAD. (C)

Summary statement 68. Rare patients with SIGAD may benefit from IVIG replacement therapy. (C)

Summary statement 69. IGGSD is defined as an abnormally low level of 1 or more IgG subclasses in patients with normal levels of total IgG and IgM; IgA level may also be low. (C)

Summary statement 70. The diagnosis of IGGSD is controversial. (D)

Summary statement 71. Some patients with IGGSD exhibit impaired specific antibody production. (C)

Summary statement 72. The major clinical association with IGGSD is recurrent sinopulmonary bacterial infection. (C)

Summary statement 73. IGGSD may be seen in a variety of primary and secondary immunodeficiencies and with a variety of additional clinical associations. (C)

Summary statement 74. The principles of management of IGGSD include therapy of allergy, preventive antibiotics, and cautious use of gammaglobulin in selected patients. (C)

Summary statement 75. The diagnosis of SAD should be considered in patients older than 2 years with recurrent upper and/or lower respiratory tract infections. (C)

Summary statement 76. SAD is characterized by normal concentrations of IgG, IgA, IgM, and IgG subclasses and abnormal IgG antibody responses to polysaccharide vaccines. (C)

Summary statement 77. Patients with SAD may benefit from additional immunization with conjugate pneumococcal vaccines. (C)

Summary statement 78. The clinical presentation of THI is in infants and young children with recurrent bacterial sinopulmonary infections and frequent viral illnesses. (C)

Summary statement 79. In THI, immunoglobulin levels are below the age-specific normal range, specific antibody production is usually preserved, and cellular immunity is intact. (C)

Summary statement 80. Preventive antibiotic therapy may be indicated for patients with THI. A period of IVIG replacement may be considered. (C)

Summary statement 81. Any patient with primary hypogammaglobulinemia and normal cellular immunity who does not fulfill diagnostic criteria for the above disorders has hypogammaglobulinemia of an unspecified type. (D)

Summary statement 82. Management of unspecified hypogammaglobulinemia may include antimicrobial therapy and gammaglobulin replacement. (D)

Cellular Immunodeficiencies

Summary statement 83. Clinical manifestations of defects that involve the IFN-γ/IL-12 axis are mainly diseases caused by bacille Calmette-Guérin (BCG) or other poorly pathogenic mycobacteria, disseminated tuberculosis, systemic and/or persistent nontyphi *Salmonella*, or severe herpesvirus infection. (C)

Summary statement 84. Standard screening measures of cellular and humoral immune function are normal in patients with defects of the IFN-γ/IL-12 axis. (C)

Summary statement 85. Markedly increased serum IFN-γ level can be used as a screening test to prompt further evaluation for IFN-γ receptor (IFN-γR) defects. (C)

Summary statement 86. Individuals with partial IFN-γR mutations and IL-12 p40 or IL-12Rβ1 mutations with nontuberculous mycobacterial disease may benefit from adjunct therapy with subcutaneous interferon gamma. (C)

Summary statement 87. HLA-identical sibling BMT may be considered for therapy of IFN-γR mutation (C).

Summary statement 88. The principal clinical manifestations of chronic mucocutaneous candidiasis (CMCC) due to autoimmune regulator (*AIRE*) mutation are immune-mediated destruction of endocrine tissue, chronic candidiasis, and ectodermal dystrophy. (C)

Summary statement 89. Patients with clinical features consistent with *AIRE* mutation should be screened for this defect, when possible. (C)

Summary statement 90. Patients with *AIRE* mutation may benefit from immunosuppressive therapy. (C)

Summary statement 91. Patients with NK cell deficiency due to mutations of CD16 (FcγRIII) may have severe or recurrent herpesvirus disease. (C)

Summary statement 92. Patients with isolated defects of cellular immunity who do not have mutations that affect the IFN-γ/IL-12 axis should be screened for mutation in FcγRIII by flow cytometry using anti-CD16 clone B73.1. (C)

Summary statement 93. Patients with recurrent disease caused by herpesviruses associated with *FCGR3A* mutation may benefit from specific chemoprophylaxis against herpesviruses. (C)

Summary statement 94. Acquired immunodeficiency syndrome (AIDS)–like opportunistic infections are often seen in individuals with idiopathic CD4 lymphocytopenia (ICD4L). (C)

Summary statement 95. Laboratory criteria for ICD4L include a $CD4^+$ T-cell count of less than 300 cells/mm^3 with no evidence of human immunodeficiency virus (HIV) or other retroviral infection by both serologic and molecular testing. (C)

Summary statement 96. Measurement of adenosine deaminase (ADA) activity should be considered in patients diagnosed as having ICD4L. (C)

Summary statement 97. Antimicrobial prophylaxis and IL-2 may be considered for therapy of ICD4L. (C)

Summary statement 98. Patients who present only with recurrent candidal infection of nails, skin, and mucous membranes should be considered for the diagnosis of CMCC. (C)

Summary statement 99. Laboratory abnormalities in CMCC may include defective cutaneous or in vitro T-cell response to *Candida* and low NK cell count and/or function. (C)

Summary statement 100. Antifungal agents are the mainstays of therapy for CMCC. (C)

Summary statement 101. Individuals with severe disease caused by herpesviruses or papillomaviruses who do not have

another defined immunodeficiency should have phenotypic and functional assessments of NK cells performed. (C)

Summary statement 102. Patients with undefined NK cell defects may benefit from chemoprophylaxis against herpesviruses. (D)

Summary statement 103. Any patient with normal serum immunoglobulin levels and specific antibody production and evidence of impaired cellular immunity who does not fulfill clinical and laboratory diagnostic criteria for any of the above disorders may be considered to have a cellular immunodeficiency of an unspecified type. (D)

Summary statement 104. Therapy for unspecified cellular immunodeficiency must be individualized. (D)

Combined Immunodeficiencies

Summary statement 105. Patients with SCID present within the first few months of life with recurrent, persistent, or severe bacterial, viral, or fungal infections and failure to thrive, diarrhea, and rashes (C).

Summary statement 106. A suspicion of SCID should be considered an emergent condition. (C)

Summary statement 107. Physical examination reveals absence of lymphoid tissue and the thymus is radiographically undetectable. (C)

Summary statement 108. Characteristic laboratory abnormalities may include severe, age-adjusted lymphopenia and panhypogammaglobulinemia, 1 or more reduced or absent major lymphocyte subpopulations, and absent or profoundly reduced T-cell proliferation to mitogens and antigens. (C)

Summary statement 109. Some mutations in genes associated with SCID may lead to atypical (milder) phenotypes. (C)

Summary statement 110. Maternal T cells may engraft in some patients with SCID and obscure the peripheral blood lymphocyte phenotype. (C)

Summary statement 111. An established diagnosis of SCID should be considered a medical emergency. (C)

Summary statement 112. Patients with SCID may be immunologically reconstituted by BMT or gene therapy. (C)

Summary statement 113. Patients with SCID due to IL-2R γ chain (common γ chain) deficiency and ADA deficiency have been successfully treated with gene therapy. (C)

Summary statement 114. Patients with SCID or suspected SCID should receive gammaglobulin replacement therapy. (C)

Summary statement 115. Patients with SCID or suspected SCID should be protected from exposure to infectious agents. (C)

Summary statement 116. Patients with SCID or suspected SCID should receive prophylaxis for *Pneumocystis carinii* pneumonia (PCP). (C)

Summary statement 117. Early signs of infection should be promptly recognized, and antimicrobial regimens initiated early and for prolonged periods. (C).

Summary statement 118. Patients with SCID due to ADA deficiency may benefit from the administration of polyethylene glycol (PEG) ADA. (C)

Summary statement 119. The classic clinical expressions of WAS are X-linked inheritance, an eczematous skin eruption, petechiae, bruising or bleeding, and recurrent and severe infections, including opportunistic organisms, autoimmune diseases, and Epstein-Barr virus (EBV)–related B-cell lymphomas. (C)

Summary statement 120. Thrombocytopenia and small platelet size are the most characteristic laboratory abnormalities of WAS. (C)

Summary statement 121. Humoral immunologic abnormalities in WAS include dysgammaglobulinemia and impaired specific antibody production. (C)

Summary statement 122. Cellular immunologic abnormalities in WAS include T lymphocytopenia, impaired in vitro and in vivo T-cell responses, and decreased NK cell activity. (C)

Summary statement 123. A WAS protein (*WASP*) mutation is expressed in some female patients due to extreme nonrandom X-chromosome inactivation. (C)

Summary statement 124. WASP is measurable by Western blot or flow cytometry to establish a diagnosis. (C)

Summary statement 125. A molecular diagnosis should be established in every case of WAS for its prognostic value. (C)

Summary statement 126. The only curative therapy for WAS is BMT. (C)

Summary statement 127. Before BMT, WAS is managed by a combination of splenectomy, antibiotics, and gammaglobulin replacement. (C)

Summary statement 128. Gait ataxia, oculocutaneous telangiectasias, growth retardation, and immune deficiency are the most prominent and consistent clinical features of A-T. (C)

Summary statement 129. Immunologic abnormalities in A-T include low or elevated immunoglobulin levels, IgG subclass deficiencies, impaired specific antibody production, and alterations in lymphocyte populations. (C)

Summary statement 130. Cytogenetic abnormalities, such as chromosomal translocations and chromosome fragility, support a diagnosis of A-T and related disorders. (C)

Summary statement 131. Patients with A-T and related disorders experience an extreme susceptibility to ionizing radiation and radiomimetic drugs and have a high rate of cancer. (C)

Summary statement 132. Elevated levels of oncofetoproteins are highly characteristic of A-T but not related disorders. (C)

Summary statement 133. All children with persistent ataxia should have determination of serum α-fetoprotein (AFP) levels. (C)

Summary statement 134. A-T and related disorders should be considered in all children with persistent characteristic neurologic and/or cutaneous manifestations. (D)

Summary statement 135. Patients with A-T and related disorders benefit from a coordinated multidisciplinary approach to management. (D)

Summary statement 136. Antibiotic prophylaxis and/or gammaglobulin replacement therapy may be indicated for A-T and related disorders. (C)

Summary statement 137. Therapy of hematologic malignancy in A-T and related disorders should be administered by physicians with prior direct experience with this complication. (C)

Summary statement 138. Thymic dysplasia, cardiovascular structural defects, and hypoparathyroidism mark the triad of congenital defects in DGS. (C)

Summary statement 139. T-cell lymphopenia is the most common laboratory feature of DGS. (C)

Summary statement 140. Treatment of infants with complete DGS requires some form of cellular reconstitution. (C)

Summary statement 141. Patients with DGS require multispecialty care. (D)

Summary statement 142. Clinical features of CD40 and CD40L deficiencies include infections with viral, bacterial, fungal, and opportunistic pathogens and cytopenias. (C)

Summary statement 143. Immunologic abnormalities of CD40 and CD40L deficiencies affect both humoral and cell-mediated immunity. (C)

Summary statement 144. CD40L expression is most readily evaluated by flow cytometric methods on activated T cells. (C)

Summary statement 145. CD40 expression may be measured by flow cytometry on monocytes or B cells. (C)

Summary statement 146. Female patients with the HIM phenotype should be studied for CD40L mutation if CD40 mutation or other known autosomal recessive mutation associated with the HIM phenotype is not found. (C)

Summary statement 147. Prophylaxis for PCP is indicated for all patients with known or suspected CD40 or CD40L deficiency. (C)

Summary statement 148. Neutropenia in CD40 or CD40L deficiency should be treated with granulocyte colony-stimulating factor (G-CSF). (C)

Summary statement 149. BMT is curative for CD40L deficiency. (C)

Summary statement 150. Three characteristic phenotypes of XLP are fulminant infectious mononucleosis, lymphoma, and dysgammaglobulinemia. (C)

Summary statement 151. The immunologic findings in XLP are variable and depend on EBV exposure. (C)

Summary statement 152. Some patients with XLP have been diagnosed as having CVID. (C)

Summary statement 153. IVIG should be given to patients with XLP and hypogammaglobulinemia or dysgammaglobulinemia and infections. (C)

Summary statement 154. BMT can cure XLP. (C)

Summary statement 155. Patients with XLP and lymphoproliferative disease may be treated with chemotherapy followed by BMT. (C)

Summary statement 156. The warts, hypogammaglobulinemia, immunodeficiency, and myelokathexis (WHIM) syndrome is named for its cardinal clinical features. (C)

Summary statement 157. Laboratory findings in WHIM syndrome include neutropenia and variably depressed humoral and cellular immunity. (C)

Summary statement 158. IVIG replacement may reduce the rate of respiratory tract bacterial infections in WHIM syndrome. (C)

Summary statement 159. G-CSF and granulocyte-macrophage colony-stimulating factor (GM-CSF) increase neutrophil counts in patients with WHIM syndrome. (C)

Summary statement 160. The major clinical manifestations of defects in NF-κB regulation include ectodermal dysplasia and severe infections with viruses, bacteria, and atypical mycobacteria. (C)

Summary statement 161. Dysgammaglobulinemia and altered cellular immune function are observed in patients with defects of NF-κB regulation. (C)

Summary statement 162. Mycobacterial infection in patients with an *IKBKG* mutation should be treated with an aggressive antimicrobial regimen. (C)

Summary statement 163. Patients with *IKBKG* mutation should receive gammaglobulin replacement. (C)

Summary statement 164. Antimycobacterial and antiviral prophylaxis should be considered for patients with *IKBKG* mutation. (C)

Summary statement 165. Consider BMT for patients with defects of NF-κB regulation not infected with mycobacteria. (C)

Summary statement 166. The main clinical manifestation of IL-1R–associated kinase (IRAK-4) deficiency is serious infection with gram-positive bacteria. (C)

Summary statement 167. The results of screening tests of immune function are normal in patients with IRAK-4 deficiency. (C)

Summary statement 168. Defects of toll-like receptor (TLR) signaling are seen in IRAK-4 deficiency. (C)

Summary statement 169. Therapy in IRAK-4 deficiency is directed toward treatment and prevention of infection. (C)

Summary statement 170. Clinical features of caspase 8 deficiency include failure to thrive, respiratory tract bacterial infections, and viral infections. (C)

Summary statement 171. Laboratory features of caspase 8 deficiency include impaired pneumococcal vaccine response and relative CD4 lymphocytopenia. (C)

Summary statement 172. Management for caspase 8 deficiency is individualized. (D)

Summary statement 173. Any patient with abnormal serum immunoglobulin levels and/or specific antibody production and evidence of impaired cellular immunity who does not fulfill clinical and laboratory diagnostic criteria for any of the above disorders may be considered to have a CID of an unspecified type. (D)

Summary statement 174. Therapy for unspecified CID must be individualized. (D)

Phagocyte Defects

Summary statement 175. Deep-seated granulomatous infections with bacteria and fungi are characteristic of CGD. (C)

Summary statement 176. The diagnosis of CGD may be established by measurement of phagocyte oxidase activity. (C)

Summary statement 177. Antimicrobial agents and IFN-γ reduce the rate of infections in patients with CGD. (A)

Summary statement 178. Granulocyte transfusions may be indicated for the treatment of infections in patients with CGD. (C)

Summary statement 179. In patients with CGD, aggressive surgical debridement is indicated for abscesses unresponsive to medical therapy. (C)

Summary statement 180. CGD may be cured by BMT. (C)

Summary statement 181. Partial oculocutaneous albinism and neurologic symptoms are characteristic of CHS. (C)

Summary statement 182. Giant azurophil granules are characteristic of neutrophils in CHS. (C)

Summary statement 183. Virtually all patients with CHS who do not die of infection eventually develop a lymphoproliferative disorder known as the accelerated phase. (C)

Summary statement 184. The accelerated phase may be treated with high-dose glucocorticosteroids and chemotherapeutic agents. (C)

Summary statement 185. BMT is curative for CHS, even in the accelerated phase. (C)

Summary statement 186. Clinical manifestations of Griscelli syndrome (GS) include pigmentary dilution, neurologic abnormalities, pyogenic infections, and a hemophagocytic syndrome. (C)

Summary statement 187. Most patients with GS have normal results on screening tests of immunodeficiency. (C)

Summary statement 188. The accelerated phase of GS should be treated with chemotherapy. (C)

Summary statement 189. GS is curable by BMT. (C)

Summary statement 190. Patients with LAD type I or II present with cellulitis, abscesses, and bacterial and fungal respiratory tract infections. (C)

Summary statement 191. Delayed separation of the umbilical cord may be seen in LAD type I. (C)

Summary statement 192. A partial or moderate form of LAD type I has a milder clinical course. (C)

Summary statement 193. Characteristic facies, growth, and developmental delay and mental retardation are seen in LAD type II. (C)

Summary statement 194. Significant neutrophilia is almost always present in patients with LAD. (C)

Summary statement 195. LAD types I and II may be diagnosed by flow cytometric measurement of relevant phagocyte surface molecules. (C)

Summary statement 196. Therapy for LAD types I and II is supportive and dictated by aggressive prevention and management of infections. (C)

Summary statement 197. Fucose supplementation may ameliorate the course of LAD type II. (C)

Summary statement 198. BMT is curative of LAD type I. (C)

Summary statement 199. The main clinical manifestation of SGD is recurrent bacterial infections of the skin and respiratory tract. (C)

Summary statement 200. Microscopic examination of stained neutrophils can establish the diagnosis of SGD. (C)

Summary statement 201. Management of SGD is supportive. (C)

Summary statement 202. The clinical manifestations of neutropenia include bacterial respiratory tract and soft tissue infections, gingivostomatitis, and vaginal or rectal mucosal ulceration. (C)

Summary statement 203. Serial measurements of neutrophil counts are necessary to distinguish persistent from cyclic neutropenia. (C)

Summary statement 204. G-CSF may increase neutrophil counts. (C)

Summary statement 205. BMT may be curative for severe chronic neutropenia. (C)

Summary statement 206. The major clinical manifestations of HIES include recurrent lung and skin infections and chronic dermatitis. (C)

Summary statement 207. Elevated serum IgE level and staphylococcus-binding IgE and eosinophilia are characteristic of HIES. (C)

Summary statement 208. The initial approach to therapy of HIES is directed toward management of its characteristic complications. (C)

Summary statement 209. The use of IVIG or IFN-γ in HIES is controversial. (C)

Summary statement 210. BMT is not curative of HIES. (C)

Summary statement 211. Any patient with recurrent infections and a demonstrable isolated defect of phagocytic cell function who does not have any of the disorders above should be considered to have an unspecified phagocytic cell defect. (D)

Summary statement 212. Therapy for unspecified phagocytic cell dysfunction must be individualized. (D)

Complement Deficiencies

Summary statement 213. Total deficiencies of a complement protein are rare. (C)

Summary statement 214. Usually, hypocomplementemia results from complement component consumption caused by activation, as may occur in autoimmune disease or during infection. (C)

Summary statement 215. In general, absence of a component of the classical pathway of complement is associated with autoimmunity or frequent infection. (C)

Summary statement 216. Defects of the MBL and the alternative complement activation pathways may be associated with increased susceptibility to bacterial infections. (C)

Summary statement 217. C3 deficiency is associated with high susceptibility to bacterial infections. (C)

Summary statement 218. Terminal pathway complement deficiencies are associated with susceptibility to neisserial infections. (C)

Summary statement 219. A patient with factor I deficiency may present with frequent infections and urticaria. (C)

Summary statement 220. Some patients with hemolytic uremic syndrome have abnormalities of the complement regulatory protein factor H. (C)

Summary statement 221. The rare deficiencies of numbered complement components can be detected with a laboratory test (CH_{50}). (C)

Summary statement 222. Alternative pathway complement function is measured by the AH_{50}. (C)

Summary statement 223. Immunization and antibiotic therapy are the major modes of treatment for complement deficiencies associated with recurrent infections. (C)

Summary statement 224. Anti-inflammatory therapies are indicated for treatment of autoimmune disease associated with complement deficiency. (C)

GENERAL CONSIDERATIONS

Summary statement 1. Individual immunodeficiencies are rare, but altogether they occur in more than 1 to 2,000 live births. (C)

Primary immunodeficiency results from inherited genetic defects that involve the immune system and immune responses. The origins of some of the diagnoses discussed in this Practice Parameter are not yet defined at the molecular level. In these instances, the disorder is considered primary if all other potential contributors to immune dysfunction (eg, drugs, infections) have been excluded. The true incidence of these disorders is unknown, because this has not been studied prospectively. Estimated incidences vary from the common SIGAD (1 of 300 to 700 live births) to the relatively rare CGD (1 of 200,000 live births). X-linked SCID (XSCID) has an incidence of 1 of 50,000 to 100,000 live births and CVID an incidence of 1 of 75,000 live births. Aside from SIGAD, registry and survey data from a variety of sources suggest an incidence for all immunodeficiencies together ranging from 1 in 10,000 to 1 in 2,000 live births and a prevalence of 1 in 10,000 in the general population (see, for example, the studies by Stray-Pedersen et al[2] and Zelazko et al[3] and literature cited therein). These incidences are likely underestimated, since these diagnoses may be missed altogether and some affected individuals die before a diagnosis is made. The male-female ratio of these defects is approximately 5:1 in infants and children, but the ratio approaches 1:1 in adults.[4–10]

Summary statement 2. Immunodeficiencies are classified according to the principal immunologic mechanisms that are disrupted. (D)

Immunologic effector mechanisms operate in concert to fight infections, but impairment of 1 or more subsystems may be the consequence of a specific genetic lesion. Immune defense mechanisms and immunodeficiencies may be subdivided into 2 broad categories: innate (complement and phagocytic cells) and adaptive (lymphocyte-derived humoral and cellular mechanisms).[10–12] Table 2 presents a list of selected defined immunodeficiencies grouped according to this system. Note that the specific immunodeficiencies are usually subdivided into 3 categories: defects of humoral immunity, defects of cellular immunity, and combined defects involving both.

Summary statement 3. Antibody deficiency is the most common type of primary immunodeficiency. (C)

Humoral or antibody immunodeficiency accounts for approximately half of all primary immunodeficiency.[2,3,10] Complement deficiency is the rarest, comprising less than 1% of all primary immunodeficiency.[13] Cellular, combined, and phagocyte defects make up the remainder in varying proportions, each accounting for between 10% and 20% of the total.

Summary statement 4. Immunodeficiency usually presents with signs and symptoms of infections that may be repetitive, severe, or refractory to therapy and caused by organisms of low virulence. (C)

Infection is by far the most common complication of primary immunodeficiency and the most frequent problem that leads to medical evaluation. Infections in immunodeficient patients usually occur with pathogens that are prevalent in the community but are of unusual severity, frequency, and duration. They also tend to respond poorly to therapy. Severe immunodeficiency is also associated with infections caused by low-grade or opportunistic organisms that are rarely pathogenic for immunocompetent individuals.[5,6,12,14–17]

Summary statement 5. It is critically important to confirm the precise focus of infection and organism whenever possible. (D)

Imaging, biopsy, and/or culture data should be sought in support of a diagnosis of infection in any patient with known or suspected immunodeficiency. Many noninfectious conditions (for example, allergy or benign self-limiting viral infections) may cause symptoms and physical findings that may be difficult to distinguish from those due to infectious diseases that require specific antimicrobial therapy. Identifying specific pathogens and foci of infections may give important clues regarding a possible diagnosis of immunodeficiency. These data are also important for accurate prescribing and interpretation of response to therapy and may indicate the need for alteration in overall management in patients with known immunodeficiency.[17,18] (Also see Practice Parameter for the Diagnosis and Management of Sinusitis.)

Summary statement 6. Other conditions that may increase susceptibility to infection should be sought in patients with suspected immunodeficiency. (D)

Allergic inflammation may predispose patients to frequent bacterial infections such as otitis media and sinusitis.[19,20] Adenoid hypertrophy may also be associated with frequent ear and sinus infections.[21,22] Cystic fibrosis,[23] ciliary dyskinesia,[24] and abnormal lung anatomy[25] may all be associated with recurrent respiratory tract infections. Some or all of these conditions should be investigated in patients being evaluated

for immunodeficiency. (Also see Practice Parameter for the Diagnosis and Management of Sinusitis.)

Summary statement 7. The physician must exercise caution to rule out the possibility of secondary immunodeficiency underlying the patient's illness. (D)

Secondary immunodeficiency results from altered immune system function in association with immunosuppressive therapies, malnutrition, infiltrative diseases or malignancies, infectious diseases (such as HIV infection or AIDS), protein-losing disorders, structural abnormalities or surgery, hereditary disorders, and idiosyncratic drug adverse effects.[26–30]

Summary statement 8. Autoimmune diseases and malignancies are complications of many immunodeficiencies. (C)

In many instances, autoimmune diseases arise as a result of the same immunologic defect or dysregulation that predisposes the patient to infection. Examples include autoimmune cytopenias, inflammatory arthropathies, and vasculitides. Malignancies also occur with great frequency in certain immunodeficiencies. Most of these are hematologic in origin (lymphoma, leukemia).[5,6,12,15,31–38]

Summary statement 9. Many immunodeficiency disorders have characteristic clinical features. (C)

Disorders of specific and nonspecific immunity may each have characteristic features, although there may be considerable overlap among these diverse groups of diseases, even where distinct molecular defects have been defined (Table 3). For example, the usual clinical features of genetically determined antibody deficiencies are (1) onset after 6 months of age when maternal antibodies have dissipated; (2) recurrent or persistent upper and lower respiratory tract infections; (3) severe bacterial infections; and (4) normal growth. The usual clinical features of genetically determined SCID is (1) onset soon after birth; (2) diarrhea and malabsorption with failure to thrive; and (3) recurrent infections with bacteria, viruses, fungi, protozoa, mycobacteria, and opportunistic organisms.[4,39,40] Additional examples are listed in Table 3.

Summary statement 10. The family history may be a critical diagnostic clue for the presence of immunodeficiency. (C)

Early in the disease course of an immunodeficient patient, the infection predisposition or susceptibility to unusually adverse outcome may not be readily apparent, even if the immunodeficiency is severe. Variable protection is afforded by immunoglobulin acquired from the mother during gestation, which may delay the onset of some severe infections. If there are no siblings or day care attendance, exposure to infections may not be frequent. It is imperative to thoroughly evaluate the family history for cases of possible immunodeficiency to raise diagnostic suspicion and suggest screening evaluation or at least increased vigilance and monitoring in the short term.[4,10]

Summary statement 11. A stepwise approach is used to evaluate suspected immunodeficiency. (D)

Screening tests used to evaluate patients with suspected immunodeficiency are relatively inexpensive, performed rapidly, and reasonably sensitive and specific. Abnormal screening test results indicate the need for more sophisticated tests. Table 4 lists screening and advanced tests used for diagnosis of immunodeficiency. Algorithm 1 is an algorithm for initial considerations in the evaluation of a potentially immunodeficient patient. Algorithms 2 and 3 are algorithms that suggest an approach for the evaluation of B-cell and T-cell specific immune dysfunction. Phagocyte defects and complement disorders have fairly characteristic clinical presentations, although there also may be some overlap, especially with antibody deficiency. Algorithms 4 and 5 present algorithms for the evaluation of these disorders.

Summary statement 12. Evaluation of specific immune response is essential. (C)

Measurement of serum immunoglobulin levels and lymphocyte responses to mitogens are useful indicators of global B-cell and T-cell development and function. However, these studies may appear normal in many primary immunodeficiencies, because they are not sensitive indicators of specific immunity: the responses of T and B cells to antigen. For evaluation of humoral immune function, specific antibody titers to both protein and polysaccharide antigens should be measured.[17,41–43] These substances differ in how they stimulate antibody production, and clinically significant disease may result from a selective inability to respond to polysaccharide antigens.

Antibody levels for protein vaccine antigens such as tetanus and diphtheria are often determined. Antibodies against the polyribose phosphate (PRP) capsular polysaccharide of *Haemophilus influenzae* type B (HIB) may also be measured. Current HIB vaccines couple the PRP to a protein carrier, and PRP titers in immunized children, although specific for a polysaccharide, are indicative of immune response to a protein. Similar considerations apply to measurement of antibodies against pneumococcal capsular polysaccharides. Antibody levels measured after natural exposure or immunization with unconjugated pneumococcal vaccines are indicative of polysaccharide responses. Newer pneumococcal vaccines also couple the polysaccharide to a protein carrier, and responses to these vaccines are indicative of protein antigen response.

Serum isohemagglutinins are naturally occurring antibodies against ABO blood group antigens. They are produced in response to polysaccharide antigens of gut flora, and measurement of IgG isohemagglutinins may be a useful indicator of polysaccharide immunity.[44]

Specific antibody levels must be interpreted in the context of the patient's immunization history. If levels are low at initial evaluation, even if the patient is not remote from immunization, response to a booster may show more clearly an antibody production defect. Postvaccination levels may be determined after 3 to 4 weeks. General standards of normal responses are at least a 4-fold increase for protein antigens and at least 2-fold for polysaccharide antigens,[17,41,42] but these criteria have not been well studied with respect to sensitivity and specificity in primary immunodeficiency. One must bear in mind that polysaccharide antibody responses are not reliable in healthy children younger than 2 years, and negative

responses to these antigens in these patients should be interpreted with caution.[45] See summary statement 76 for further discussion.

For evaluation of primary antibody responses or for measurement of antibody responses in patients who may already be receiving immunoglobulin replacement, immunization with bacteriophage X174 may be undertaken. There is no natural exposure to this prokaryote virus in humans; it will elicit a response even in infants.[46,47] The test is only rarely applied for clinical diagnostic purposes; it exists mainly as a research tool. (This test is not generally available. For information, contact Dr Hans Ochs, Department of Pediatrics, University of Washington, Seattle, WA 98195.)

In vitro lymphocyte responses to mitogens are nonspecific and indicate the ability of T cells to be activated by powerful stimuli. In vitro proliferation to specific antigen is a more sensitive test for cellular immunodeficiency.[17,41,42] Normal ranges for in vitro T-cell responses to mitogens and antigens are determined in each laboratory. Cutaneous delayed hypersensitivity is an in vivo T-cell specific antigen response.[17,41–43] As in the purified protein derivative reaction, induration and erythema develop 48 to 72 hours after intracutaneous injection of recall antigen (eg, tetanus, monilia, or mumps antigen). A normal response is at least 2 to 5 mm of induration; smaller reactions are seen in young children. The test is less reliable for patients younger than 1 year.

Summary statement 13. Patients suspected of having a primary immunodeficiency require evaluation by a clinical immunologist with experience with these disorders. (D)

Although it is appropriate for primary care physicians and other health care professionals to conduct screening evaluations for primary immunodeficiency diseases, consultation with a clinical immunologist is imperative when there is any question regarding interpretation of screening test results and in determining which advanced tests to pursue.[40,42]

Summary statement 14. Wherever possible, immunodeficiency should be defined at the molecular genetic level. (D)

Establishing the precise genetic lesion responsible for an immunodeficient phenotype is desirable for the following reasons: (1) unequivocal diagnosis, (2) accurate genetic counseling, (3) planning future pregnancies or their outcomes, (4) definition of genotype-phenotype associations, and (5) identification of candidates for gene-specific therapies. An online directory of molecular genetic and other specialized testing for immunodeficiencies has recently become available.[48] It may be found on the Internet at http://bioinf.uta.fi/IDdiagnostics. The Immune Deficiency Foundation (http://www.primaryimmune.org) and the Jeffrey Model Foundation (http://www.jmfworld.org) also have information regarding availability of molecular diagnostic tests.

Summary statement 15. The possibility of a X-linked disease should be considered in female patients when other possibilities have been ruled out. (D)

Extreme nonrandom X-chromosome inactivation may lead to expression of the phenotype associated with a X-linked recessive disease in a female carrier. This has been described for CGD,[49] WAS,[50,51] XLA,[52] and CD40L deficiency.[53]

Summary statement 16. Female carrier status should be determined for all potentially affected female relatives of male patients with X-linked immunodeficiencies. (D)

It is essential for informed family planning that all potential female carriers of X-linked immunodeficiencies (XLA, XSCID, WAS, NEMO deficiency, XLP, CGD) be identified. A variety of molecular methods may be applied, depending on the particular defect.[54–60]

Summary statement 17. Following diagnosis, it is important to proceed quickly with preventive and/or replacement therapy. (C)

Early diagnosis and therapy are the keys to survival and a better quality of life for immunodeficient patients. Delays in immunologic reconstitution may lead to permanent organ damage (eg, bronchiectasis or bronchiolitis obliterans) or death from overwhelming infection.[5,6,10,12,16]

Summary statement 18. Immunodeficient patients often require more aggressive and prolonged antimicrobial therapy. (C)

Standard dose and duration of antimicrobial regimens may not be adequate to eradicate infections in immunocompromised hosts. Early combined antimicrobial therapy, prolonged courses, and prophylaxis should be considered.[10,12]

Summary statement 19. Antibody replacement therapy is indicated for all disorders with significantly impaired antibody production. (B)

The effectiveness of gammaglobulin for reducing serious bacterial infections in XLA[61,62] and CVID[34,63] is well documented.[64–66] Gammaglobulin is also used for combined defects with significantly impaired antibody production. Gammaglobulin therapy may be necessary even after definitive therapy such as BMT if B-cell function is not restored.[67] Table 5 and Algorithm 6 summarize therapeutic considerations for many of the immunodeficiency diagnoses discussed in this Practice Parameter. See specific content areas for more details. Guidelines for gammaglobulin prescribing and administration are presented in the Appendix.

Summary statement 20. Antibiotics may be needed in addition to immunoglobulin replacement for preventing infection in antibody-deficient patients. (C)

Bacterial infections may continue at a reduced rate in patients with agammaglobulinemia or other antibody deficiency, even with immunoglobulin replacement.[5,34,61–65,68–72] Some authorities recommend continual therapy with immunoglobulin and long-term preventive or therapeutic dose antibiotics when a diagnosis of agammaglobulinemia or severe hypogammaglobulinemia (eg, CVID) is made. Long-term antibiotic therapy may be added to immunoglobulin replacement in other settings as dictated by the clinical condition of the patient or course of the disease.

Summary statement 21. Mild antibody deficiencies are treated initially with antibiotic prophylaxis. (C)

Milder clinically defined antibody deficiencies such as IGGSD, SAD, or THI generally do not require IVIG replace-

ment for control of recurrent bacterial infections.[64,65,73,74] Infections must be documented carefully, and other conditions that may predispose to infection should be sought and treated. Aggressive management of established infection is a necessary first step. After resolution, antibiotic use may be continued as preventive therapy. There are no controlled studies that compare effectiveness of any antibiotic prophylaxis regimen in patients with established immunodeficiency. Regimens derived from studies of preventing otitis media in children include (1) sulfisoxazole, 50 mg/kg daily; (2) amoxicillin, 20 mg/kg daily or divided bid; (3) trimethoprim-sulfamethoxazole, 3 to 5 mg/kg as trimethoprim once daily or divided into twice-daily dosages; and (4) azithromycin, 10 mg/kg weekly.[75–77]

Summary statement 22. Immunoglobulin replacement therapy may be considered for milder forms of antibody deficiency where other therapies have failed or are not tolerated. (D)

Considerable controversy exists regarding gammaglobulin prescribing for therapy of SIGAD, IGGSD, SAD, or THI. Most experts in this area consider demonstration of impaired antibody production essential. Rare patients may have susceptibility to infection with vaccine responses that are normal by laboratory criteria but may, nevertheless, benefit from gammaglobulin administration.[73,74,78,79] It *must be demonstrated* that (1) the patient has significant and clearly documented infectious morbidity (eg, recurrent pneumonias, frequent episodes of documented bacterial sinusitis, and not just isolated chronic sinusitis) (see summary statement 5); (2) other disorders (allergy, anatomic defects) have been sought and treated aggressively if present (see summary statement 6); and (3) other modes of therapy (antimicrobial, anti-inflammatory) are inadequate or poorly tolerated. If administered to children with milder antibody deficiencies, gammaglobulin therapy should be discontinued if there has been an extended period of significant improvement, because the susceptibility to infection may decrease over time.[80] Humoral immune function should be reassessed no sooner than 3 months (preferably 4–6 months) after the last infusion. Patients must be followed up closely, and therapy should be discontinued, generally after no more than 3 to 6 months, if there is lack of clinical efficacy.

Summary statement 23. The placement of permanent central venous access solely for the purpose of IVIG administration should be discouraged. (F)

Permanent central venous catheters may be associated with thrombotic and infectious complications.[81–83] For patients who require intravenous access only for gammaglobulin administration every 2 to 4 weeks, permanent indwelling catheters may not represent an acceptable risk. Difficult venous access need not be a compelling indication for catheter placement with the growing availability of subcutaneous gammaglobulin infusion[84] (Appendix).

Summary statement 24. A role for surgery in the prevention and treatment of infection in immunodeficient patients has not been established. (C)

Optimal medical management, including immunoglobulin, antibiotics, and anti-inflammatory medications, may still fail to completely control chronic bacterial rhinosinusitis in immunodeficient patients.[85] Consideration may be given to surgical procedures such as tympanostomy tube placement or tonsillectomy and adenoidectomy for the treatment and/or prevention of otitis media and sinusitis in immunodeficient patients. These procedures are not well studied in this population, although, theoretically, they could be of benefit for some patients. The role of endoscopic sinus surgery in pediatrics is somewhat controversial; experience in immunodeficient children or adults is limited and has not been studied. Theoretically, at least in some patients, this also could be of benefit.[18,86]

Summary statement 25. Definitive therapy of cellular or CID requires reconstitution by hematopoietic stem cells. (C)

BMT has been applied successfully in cellular immunodeficiencies (defects of the IL-12/IFN-γ axis), virtually all SCIDs, and many other combined immunodeficiencies.[6,87–100] Phagocytic cell disorders have also been treated with BMT.[94,101–105] The best outcomes are obtained with HLA-identical sibling bone marrow donors. Unfortunately, only 25% to 35% of patients have such a donor. Factors associated with good prognosis include young age ($<$3 months), absence of infections, and HLA matching. The use of myeloablation for SCID patients without significant numbers of T cells is still controversial,[106,107] and BMT has been applied with or without myeloablation in a variety of circumstances, depending mainly on the specific form of SCID. Potential sources of stem cells include haploidentical parents, HLA-matched unrelated donors, and umbilical cord blood. Patients with severe immunodeficiencies should be referred to tertiary care centers with experience in hematopoietic stem cell transplantation for primary immunodeficiencies.

Cytokine replacement therapy is being investigated for some diseases (eg, IL-12 or IFN-γ for defects of this cytokine axis). Gene therapy can correct the genetic defect in XSCID but is considered investigational at this time (see summary statement 113).

Summary statement 26. Only irradiated, CMV-negative, lymphocyte-depleted cellular blood products should be administered to patients with cellular immunodeficiency or CID. (C)

Patients with impaired cellular immune function may not be able to eliminate viable lymphocytes contained in whole blood, packed red blood cells, or platelets.[108] These lymphocytes may become activated by HLA incompatibility and cause severe (sometimes fatal) graft-vs-host disease. Irradiation renders lymphocytes incapable of undergoing cell division, if they are activated, and reduces the occurrence of transfusion-associated graft-vs-host disease; use of CMV-negative donors prevents opportunistic infections caused by CMV.[109,110]

Summary statement 27. No live vaccines should be administered to patients with severely impaired specific immunity. (C)

Currently available live viral or bacterial vaccines include BCG, oral polio virus, measles-mumps-rubella, oral typhoid, varicella, and yellow fever. Disseminated disease with attenuated organism vaccines has been observed in severely immunocompromised patients after inoculation.[111–113] Thus, live vaccines are absolutely contraindicated in these patients. In general, live vaccines should also be withheld from patients with milder immunodeficiency, because they have not been rigorously studied with respect to risk or benefit in this population.[114] Recent data suggest that in some situations risk is low (partial DGS, for example).[115,116] Patients receiving gammaglobulin replacement therapy will have circulating antibody against polio, measles, mumps, rubella, and varicella. The Advisory Committee on Immunization Practices does not recommend administration of measles-mumps-rubella or varicella vaccines to patients receiving immunoglobulin, because they would be inactivated.[117]

Summary statement 28. Inactivated or subunit vaccines may be administered to immunocompromised patients. (C)

There is no risk of disease from killed or microbial subcomponent vaccines. Since there may be some protective immunity after inoculation, even in immunocompromised hosts, these vaccines may be given according to routine indications and schedules.[114,117] Particular consideration should be given to those vaccine agents for which gammaglobulin might not provide coverage, for example, influenza.[118]

Summary statement 29. Frequent evaluation by a clinical immunologist with applicable experience is important for patients with immunodeficiencies. (D)

Evaluations should be conducted regularly (at least every 6–12 months) by a clinical immunologist with training and experience in the care of patients with primary immunodeficiency. Physical examination should include careful inspection for signs of infection. Despite gammaglobulin replacement, respiratory tract infections may occur.[119,120] Pulmonary function should be measured serially. Deteriorating function is an indication for a chest radiograph or computed tomogram (CT). Some advocate periodic chest CTs even with preserved function, because progressive abnormalities may be observed and may require intensification of treatment.[121]

Depending on the particular immunodeficiency, symptoms and signs of autoimmune disease or malignancy should also be sought. The presence of lymphadenopathy or splenomegaly may be signs of lymphoproliferative disease or malignancy.[34]

Summary statement 30. Education is important for optimal outcomes for patients and families with immunodeficiency. (D)

Patients and families must understand the inheritance, causes, manifestations, and natural histories of their immunodeficiencies. They may access organizations such as the Immune Deficiency Foundation (www.primaryimmune.org) and the Jeffrey Model Foundation (www.jmfworld.org) for advocacy and support from other patients and families, education regarding new developments and treatments, and government or private support of research programs. Patients and families should establish long-term relationships with health care professionals, including physicians, nurses, and social workers, to obtain the best outcomes for their diseases.

HUMORAL IMMUNODEFICIENCIES

X-linked Agammaglobulinemia

Summary statement 31. Most patients with XLA present with recurrent bacterial infections, particularly otitis media, sinusitis and pneumonia, in the first 2 years of life. (C)

The most common organisms isolated are *Streptococcus pneumoniae* and HIB.[61,122] Some patients present with an overwhelming infection, often with neutropenia.[123] Central nervous system enterocytopathic human orphan (ECHO) virus infections are characteristic of XLA.[124] Occasionally, patients present with PCP, vaccine strain poliovirus infection, *Ureaplasma urealyticum* arthritis and bacteremia, or regional enteritis associated with enterovirus.[125–128] A family history of affected maternal male cousins, uncles, or nephews is frequently present, although sporadic cases are also common. Some patients are not recognized to have XLA until after 5 years of age despite the presence of frequent infections and recurrent antibiotic use.

Summary statement 32. The physical examination of patients with XLA usually reveals absent lymph nodes and tonsils. (C)

Small tonsils are seen in combined immunodeficiencies and other congenital agammaglobulinemias. This feature and absence of peripheral lymph nodes are the only consistent physical findings in XLA.[61,122]

Summary statement 33. Characteristic laboratory abnormalities of XLA include agammaglobulinemia and very low or absent B-cell counts. (C)

XLA is characterized by a serum IgG level usually less than 2 g/L, IgM and IgA levels less than 0.2 g/L, and peripheral blood $CD19^+$ B-cell counts below 2%.[61,122]

Summary statement 34. BTK protein is absent in most patients with XLA. (C)

The differential diagnosis of XLA includes ARA. Approximately 85% of agammaglobulinemic patients have XLA.[129] Mutation in *BTK* results in absent BTK messenger RNA in leukocytes.[130–132] The absence of BTK protein in monocytes or platelets may be detected by Western blots or flow cytometry.[55,56]

Summary statement 35. Certain *BTK* mutations are associated with variant (milder) phenotypes. (C)

Patients with *BTK* mutations may have milder clinical and immunologic phenotypes with higher concentrations of serum immunoglobulins suggestive of CVID or even SAD.[133] Infections may be mild or occur late in life.[134–136] In all cases, the number of peripheral blood $CD19^+$ B cells is low. Discordant phenotypes can also be observed in siblings and families with identical *BTK* mutations.[137,138] BTK deficiencies may be found in male patients with milder phenotypes with or without a family history of antibody deficiency of any

phenotype.[139] Diagnosis may require direct sequencing of *BTK*.[140]

Summary statement 36. Antimicrobial agents are often required in addition to IVIG for therapy of XLA. (C)

Long-term follow up of XLA patients reveals that bronchiectasis[121] and gastroenteritis[141] may occur despite IVIG treatment.[62] Close monitoring and aggressive treatment of acute or chronic infections are essential (see summary statement 20).

Summary statement 37. Chronic enteroviral meningoencephalitis in XLA responds to treatment with high doses of IVIG and with the antiviral drug pleconaril. (C)

Chronic enteroviral meningoencephalitis may cause serious morbidity or mortality in XLA patients. This complication is usually caused by ECHO viruses. Its occurrence has dropped considerably since IVIG has been routinely administered to patients but does occur rarely, even with replacement. Therapy has been at least partly successful with IVIG given at high doses (maintaining IgG trough levels of >1,000 mg/dL) and selected to contain relatively high titer antibody to the particular infecting ECHO virus.[62,124,142,143] Intrathecal gammaglobulin has also been used. Despite initial responses to these treatments, relapses have occurred. Some patients have been treated successfully with the antiviral drug pleconaril.[144,145] The drug is not approved by the Food and Drug Administration and is currently available only via compassionate use release from ViroPharma Inc (www.viropharma.com).

Summary statement 38. Lung transplantation has been performed successfully in patients with XLA. (C)

Survival of 6 and 12 months in 2 patients with XLA following double lung transplantation for end-stage lung disease has been reported.[146] Experience is too limited to permit generalization regarding the application of lung transplantation in XLA.

Autosomal Recessive Agammaglobulinemia

Summary statement 39. Symptoms, signs, laboratory abnormalities, and therapy of the agammaglobulinemias due to autosomal gene defects are generally identical to those of XLA. (C)

Approximately 10% to 15% of agammaglobulinemic patients have an autosomal recessive form of the disease.[129] ARA is characterized by recurrent sinopulmonary bacterial infections, extremely low or absent IgG, IgM, and IgA, and peripheral blood $CD19^+$ B-cell counts below 2%.[129] The physical examination typically reveals small or absent lymph nodes and tonsils. ARA is suspected in female patients with agammaglobulinemia, in families with an autosomal recessive pattern of inheritance, or with consanguinity[147] and in agammaglobulinemic male patients in whom *BTK* mutations cannot be identified. Mutations in one of several genes that regulate B-cell maturation cause ARA. Several of these are components of the pre–B-cell immunoglobulin receptor including μ heavy chain (Cμ, *IGHM*[148]), part of the surrogate light chain (λ5/14.1, IGLL1, *CD179B*[149]), and the immunoglobulin-associated signal transducing chain Igα (*CD79A*[150,151]). Mutation of the gene that encodes the cytoplasmic adapter B-cell linker protein (*BLNK*[152]) also causes ARA. In addition, mutation of the gene that encodes the leucine-rich repeat containing 8 (*LRRC8*) leads to a highly similar form of ARA.[153,154] The principles of diagnosis and therapy for XLA outlined above also apply to patients with known or suspected ARA.

HIM Due to Mutation of AICDA *or* UNG

Summary statement 40. Prominent clinical features of AID or UNG deficiency include bacterial sinopulmonary infections, gastrointestinal infections, and lymphoid hyperplasia. (C)

HIM is an eponym for a group of diseases characterized by normal or elevated levels of serum IgM, together with low or absent IgG and IgA levels. Because of the clinical and molecular heterogeneity of these disorders, they will be referred to herein mainly according to their molecular defects. One form of HIM results from deficiency of AID (gene designation *AICDA*).[155,156] This has been called HIM type 2. This syndrome is characterized by recurrent upper and lower respiratory tract infections caused by encapsulated bacteria. Approximately half of patients have prominent lymphadenopathy and tonsillar hypertrophy. An indistinguishable syndrome arises from mutations of *UNG*.[157]

Summary statement 41. Laboratory evaluation of humoral immunity in AID or UNG deficiency may reveal low IgG, IgA, and IgE levels together with elevated IgM levels. Specific antibody responses may be impaired. (C)

In 29 patients described with AID deficiency, IgG levels ranged from 0 to 1.5 g/L, IgA levels ranged from 0 to 0.2 g/L, and IgM levels ranged from 1 to 37 g/L.[155,156] Tetanus-specific IgG antibodies were absent in all, whereas IgM isohemagglutinins were present in most. T-cell subpopulations in these patients and in vitro proliferative responses to mitogens and antigens were normal.[155,156] Laboratory findings in UNG deficiency are similar.[157]

Summary statement 42. IVIG replacement therapy is indicated for all patients with AID or UNG deficiency. (C)

IVIG therapy effectively reduces the incidence and severity of infectious illnesses in patients with AID deficiency.[155,156] Therapy for UNG deficiency is not well established. Since it has similar pathophysiology to AID deficiency, therapy is expected to be similar (see summary statement 19).

Late-Onset Hypogammaglobulinemia Due to Mutation of ICOS

Summary statement 43. ICOS deficiency is characterized by recurrent respiratory tract bacterial infections and gastrointestinal infections. (C)

In a group of 32 patients initially diagnosed as having CVID, 4 were found to have a mutation in ICOS.[158] These individuals had the characteristic infectious complications associated with CVID but without lymphoproliferative or autoimmune disease. One patient developed a papilloma virus–associated carcinoma of the vulva at an early age. In

another cohort of 194 CVID patients, 5 were found to have ICOS mutations.[159] All 9 patients described to date have the same genetic deletion, indicative of a founder effect (all have origins in the Black Forest region of Germany).

Summary statement 44. Patients with ICOS deficiency generally have low IgG and IgA, and impaired specific antibody production. (C)

All patients with ICOS deficiency fulfilled accepted diagnostic criteria for CVID.[12,34,122] In the 49 patients described, all had low levels of IgG and IgA, while 5 had low and 4 had normal IgM levels at diagnosis.[158,159] B-cell counts were low in 5 and normal in 4. In these 9 patients, only 1 had a mildly low T cell number (629 cells/μL). Of the initial 4 patients reported, memory ($CD27^+$) B-cell counts were severely reduced; all had normal T cell function in vitro (proliferation to mitogens or antigens, production of IL-2, IL-4, IL-5, IL-10, IL-13, IFN-γ, tumor necrosis factor [TNF]). One patient had an inverted CD4/CD8 ratio.[158]

Summary statement 45. Absence of ICOS expression can be determined by flow cytometric methods. (C)

ICOS is induced on normal T cells by stimulation with mitogens such as phytohemagglutinin. It may be detected by flow cytometry using a monoclonal antibody or an ICOS-ligand-immunoglobulin fusion protein.[158]

Summary statement 46. Gammaglobulin replacement and antimicrobial agents are the major elements of therapy for ICOS deficiency. (C)

Therapy of ICOS deficiency adheres to the same general principles established for agammaglobulinemia (see summary statement 19).[158]

ICF Syndrome

Summary statement 47. The main clinical features of ICF syndrome include abnormal facies and respiratory tract infections. (C)

More than 30 patients with ICF syndrome have been described in the literature to date.[160] Facial anomalies are variable and occur in approximately 70% of patients. The most common are hypertelorism, epicanthal folds, and flat nasal bridge. Infectious complications are also reported in approximately 70% of patients; these may have their onset anywhere from 3 months to 4 years of age and consist primarily of frequent bacterial respiratory tract infections. One patient has been reported to have HIV infection.[161] Growth retardation occurs in approximately half of patients, and some degree of cognitive or developmental impairment is seen in approximately two thirds.

Summary statement 48. Immunologic abnormalities in ICF syndrome may include hypogammaglobulinemia and mild defects of T-cell function. (C)

Immunologic abnormalities are seen in almost all patients.[160,162,163] Hypogammaglobulinemia is most common. It may be mild or severe and may involve any or all isotypes. Data regarding specific antibody responses have generally been omitted from case reports. B-cell count has been low only in a few patients; approximately half have variable abnormalities of peripheral T-cell subsets, including low total T-cell counts or selective low CD4 with inversion of the CD4/CD8 ratio. In vitro T-cell responses to mitogens have been measured in approximately 10 patients and have been found to be variably depressed in half of these. Hypogammaglobulinemia is usually found at presentation; cellular immunologic abnormalities may develop later.

Summary statement 49. Characteristic abnormalities of chromosomes 1, 9, and 16 are diagnostic of ICF syndrome. (C)

Approximately 75% of cases of ICF syndrome result from mutation of the DNA methyltransferase 3B gene (*DNMT3B*).[163] Abnormal DNA methylation leads to anomalies of chromosomes 1, 9, and 16. These consist of multiradial chromosomes, breaks, deletions, and isochromosome formation. These abnormalities are found in lymphocytes of all patients and are pathognomonic for this disorder.

Summary statement 50. Gammaglobulin replacement is indicated for patients with ICF syndrome and hypogammaglobulinemia. (C)

There is no specific therapy for ICF syndrome; care is supportive. Gammaglobulin replacement has been administered and may reduce the frequency and severity of infections.[160,162,163]

Common Variable Immunodeficiency

Summary statement 51. The predominant clinical manifestations of CVID are recurrent upper and/or lower respiratory tract infections with encapsulated or atypical bacteria. (C)

CVID is a primary immunodeficiency of uncertain origin that affects approximately 1 in 50,000 to 1 in 75,000 individuals.[164] Respiratory tract infections, including otitis media, sinusitis, bronchitis, and recurrent pneumonias, are the most frequent infectious complications. The diagnosis of CVID should be considered in male and female patients older than 2 years with recurrent upper and/or lower respiratory tract infections with encapsulated (*H influenzae*, *S pneumoniae*) or atypical (*Mycoplasma* sp) bacteria.[34,122,165] Additional abnormalities of the lower respiratory tract, including bronchiectasis, granulomatous lung disease, and lymphocytic interstitial pneumonitis, are frequent causes of morbidity and mortality.[34,165–167]

Summary statement 52. Gastrointestinal tract disease is common in patients with CVID. (C)

Approximately 20% to 25% of patients with CVID have gastrointestinal complications.[34] Most prominent among these are lymphonodular hyperplasia, inflammatory bowel disease, and nonspecific malabsorption. Giardiasis and enteritis with *Campylobacter jejuni* and salmonellosis are the most common enteric infections. Viral hepatitis and severe CMV enteritis may also occur.[34,168]

Summary statement 53. Autoimmune diseases occur with increased frequency in patients with CVID. (C)

The overall prevalence of autoimmune diseases in CVID is approximately 20%.[34] The spectrum of autoimmune diseases found in CVID is wide, although autoimmune thrombocyto-

penic purpura (6%) and autoimmune hemolytic anemia (5%) are the most common disorders. Seronegative arthritis and vasculitides have also been observed.

Summary statement 54. Nonmalignant lymphoproliferative disease is seen frequently in CVID. (C)

As many as one third of patients will develop a lymphoproliferative disorder that may be manifested by splenomegaly, intestinal lymphoid hyperplasia, or abdominal, mediastinal, or peripheral lymphadenopathy.[34,169,170] Lymphoid interstitial pneumonitis has been reported in a few patients.[171,172] Care must be taken to distinguish these processes from true malignancy.

Summary statement 55. Hematologic and other malignancies occur with increased frequency in patients with CVID. (C)

The prevalences of non-Hodgkin lymphoma (B-cell lymphoma) (2.2%–7.7%) and gastric cancer (0.8%–1.7%) are increased in CVID.[34,165,170,173–175] Estimates of the relative risk of non-Hodgkin lymphoma range from 30- to 400-fold above the general population. There is at least a 10-fold increase in the relative risk for developing gastric cancer compared with the normal population.

Summary statement 56. Hypogammaglobulinemia and impaired specific antibody production are the hallmarks of CVID. (C)

In patients with CVID, IgG levels are reduced to greater than 2 SDs below the mean.[12,122] Most patients have low levels of IgA, and many will have reduced IgM levels. Some authorities recommend that low serum IgA levels must be included in the diagnostic criteria for CVID,[34,122,165] although there may not be universal agreement in this regard.[11,13] Documenting impaired production of specific antibodies (isohemagglutinins and/or poor responses to one or more vaccines) is essential for diagnosis. Numbers of B cells in the peripheral blood may be normal or reduced; approximately 13% of patients will have a B-cell count of less than 3% among peripheral blood lymphocytes.[34,169]

Summary statement 57. T-cell abnormalities are frequently found in patients with CVID. (C)

Although classified as a form of predominantly humoral immunodeficiency, T-cell abnormalities are common.[34] These include reductions in peripheral blood T-cell populations, as well as functional defects such as reduced in vitro proliferative responses,[176] defects in cytokine production,[69,177,178] decreased T-helper cell function,[179] abnormalities in T-cell signaling,[180,181] diminished expression of the costimulatory molecule CD40L,[182] and increased suppressor T-cell function.[183]

Summary statement 58. Selected molecular genetic defects should be ruled out in patients who meet diagnostic criteria for CVID, whenever possible. (C)

At least 4 different gene mutations have been discovered in patients with a phenotype consistent with CVID. These include *BTK* (mutated in XLA),[136,139] *SH2D1A* (SAP, mutated in XLP),[184] *ICOS*,[158] and *TNFSF5* (X-linked HIM).[53] ICOS deficiency is autosomal recessive and appears to be restricted to individuals with ancestors who originate from the Black Forest region of Germany. The other conditions are all X-linked, and mutations may occur sporadically. These defects should be sought, if possible, in male patients who meet the criteria for CVID (see summary statement 14).

Summary statement 59. CVID with thymoma may be a distinct syndrome (Good syndrome). (C)

CVID with thymoma, immunodeficiency with thymoma, and Good syndrome all denote a form of adult-onset hypogammaglobulinemia or agammaglobulinemia in association with thymoma.[185,186] The spectrum of bacterial sinopulmonary infections and pathogens is similar to those associated with CVID. However, Good syndrome is associated more frequently with opportunistic infections, including mucocutaneous candidiasis, varicella-zoster virus (VZV), PCP, CMV, and recurrent herpes simplex virus (HSV). Lymphadenopathy and splenomegaly, commonly seen in CVID, are not characteristic features of this syndrome. Since thymomas frequently go undetected on routine chest x-ray examination, diagnosis may require chest CT.

Like CVID, autoimmune disease is a frequent complication of Good syndrome, most notably pure red cell aplasia and neutropenia. Patients with Good syndrome often experience chronic diarrhea of unclear origin. The mean age of presentation of the first manifestation of this syndrome was 56 years in the most recent large survey (age range, 29–75 years).[185] There is a single reported pediatric case in an 8-year-old girl.[187]

Panhypogammaglobulinemia is a consistent finding. In Good syndrome, unlike CVID, immunophenotypic analysis of peripheral blood lymphocytes consistently shows absent or very low B-cell counts (87% of patients, $n = 38$).[188] Patients also frequently exhibit reduced $CD4^+$ T cells (45% of patients, $n = 20$), absent cutaneous delayed hypersensitivity responses (86% of patients, $n = 14$), and reduced in vitro T-cell response to mitogen (40% of patients, $n = 20$).[188]

Summary statement 60. Gammaglobulin replacement therapy and antimicrobial agents are the mainstays of therapy for CVID. (B)

See summary statements 18–20.

Summary statement 61. Autoimmune, lymphoproliferative, or malignant diseases associated with CVID are treated as they would be in other clinical settings. (C)

Immunosuppressive, anti-inflammatory, cytotoxic, and antineoplastic therapies are all used for the treatment of autoimmune or malignant complications of CVID. When choosing among therapeutic options for a particular complication, the degree of immune suppression may become a more prominent consideration than it might be in other settings. Adjunct antimicrobial prophylaxis may be added. At this time, there are no regimens, modifications, or specific approaches considered standard for therapy of autoimmune or malignant complications of CVID.[5,34,69]

Summary statement 62. In patients with Good syndrome, thymomas should be excised. (C)

Although thymomas are usually slow growing, their locally invasive potential dictates surgical resection. Thymectomy is not followed by normalization of immune phenotype or function or remission of associated autoimmune diseases.[185,186]

Selective IgA Deficiency

Summary statement 63. SIGAD is defined as a serum IgA level of less than 0.07 g/L but normal serum IgG and IgM levels in a patient older than 4 years in whom other causes of hypogammaglobulinemia have been excluded. (C)

Note that this definition is restricted to absence of serum IgA. There is no known clinical association with IgA levels between the lower detection limit and the lower limit of the normal range. It is not appropriate to refer to patients with these nonzero low IgA values as IgA deficient. Note also that the definition requires persistence of low IgA values beyond early childhood. Young children may have a delay in the development of significant amounts of IgA in serum; this does not, by itself, constitute an immunodeficiency.

SIGAD is a common immunologic abnormality, affecting approximately 1 in 300 to 700 individuals.[5,12] Most affected individuals are asymptomatic.[189,190] There is a family history of either SIGAD or CVID in 20% to 25% of affected individuals.[189,191,192] The prevalence of SIGAD may be higher in male patients and may even have a seasonal pattern, with highest levels occurring in winter, in one report.[193] The same group showed that IgA levels continue to rise slowly throughout life.

SIGAD may be acquired due to certain medications. Examples of these medications include phenytoin, carbamazepine, valproic acid, zonisamide, sulfasalazine, gold, penicillamine, hydroxychloroquine, and nonsteroidal anti-inflammatory drugs.[189,194,195] A thorough history of medication use is needed for individuals with SIGAD, because in many cases this is reversible with cessation of the drug therapy.

Summary statement 64. Clinical manifestations of SIGAD include respiratory and gastrointestinal tract infections, atopy, autoimmune diseases, and malignancy. (C)

Up to one third of patients experience recurrent infections.[196,197] These infections include recurrent viral infections, recurrent otitis media, and frequent sinopulmonary infections, as well as gastrointestinal infections. Invasive infections such as septicemia and meningitis are not generally features of SIGAD.[190] Some patients develop CVID later in life.[189] IgA-deficient individuals are also at increased risk for autoimmune diseases, including lupus-like illnesses and arthritis; hematologic disorders, including neutropenia and thrombocytopenia; and gastrointestinal illnesses, including Crohn disease, ulcerative colitis, and celiac disease.[198] They are also at higher risk for gastrointestinal and lymphoid malignancies later in life.[192] Patients with IgA deficiency also have a higher prevalence of allergies and asthma.[197]

Summary statement 65. Laboratory evaluation in SIGAD may reveal associated IGGSD and impaired specific antibody formation. (C)

Several studies suggest an increased incidence of IGGSD and/or impaired specific antibody responses among patients with SIGAD.[196] To determine if these patients would benefit from IVIG, IgG antibody responses to protein and polysaccharide vaccines should be performed.[189] The functional significance of IGGSD in addition to SIGAD is not well understood, and a decision regarding IVIG replacement should be based on inadequate responses to vaccines or infections and the clinical course.[199] However, one study did not document correlation between history of infections and response to pneumococcal polysaccharide vaccine.[197] Cell-mediated immunity is normal in SIGAD.

Summary statement 66. Atopic disease should be treated aggressively in patients with SIGAD. (C)

Atopy occurs frequently in association with SIGAD.[189,190,197] Since allergic inflammation can predispose patients to respiratory tract infection (especially sinusitis and otitis media), allergy should be diagnosed and treated aggressively in these patients using all standard modalities (environmental control or avoidance, medication, immunotherapy) where applicable.

Summary statement 67. Aggressive antimicrobial therapy and prophylaxis are often indicated in SIGAD. (C)

No definitive therapy for SIGAD is known. Some patients who have frequent infection may benefit from longer-term prophylactic antibiotics.[12,192,196]

Summary statement 68. Rare patients with SIGAD may benefit from IVIG replacement therapy. (C)

The use of IVIG in SIGAD without a demonstrable impairment of specific antibody formation is extremely controversial.[5,189,192,196] If there is inadequate response to antimicrobial therapy, one may consider a trial of IVIG in patients with SIGAD who have a concomitant specific antibody defect[197] (see summary statement 22).

IgG Subclass Deficiency

Summary statement 69. IGGSD is defined as an abnormally low level of 1 or more IgG subclasses in patients with normal levels of total IgG and IgM; IgA level may also be low. (C)

IGGSD is defined as 1 or more IgG subclass levels 2 SDs below the age-adjusted mean.[200] In most patients who are given this diagnosis, the total IgG level is normal. In some cases, the total IgG level may be low, but the clinician should be careful to determine whether a diagnosis of CVID might be more appropriate in such a circumstance, especially where there is impaired specific antibody production. In most patients, the IgM level is normal. A low level of IgA is seen in some patients with abnormal IgG subclasses (see summary statement 65).[201]

Summary statement 70. The diagnosis of IGGSD is controversial. (D)

The clinical significance of abnormal IgG subclass levels in patients with recurrent infections is unclear.[200,202] By definition, a low level of at least 1 IgG subclass will be found in approximately 2.3% of a given population. One study of 575 healthy children found 11 (1.9%) with low IgG2 levels.[203] The frequency with which abnormalities of more than 1 IgG

subclass occur together are not well established. A low level of 1 or more IgG subclasses alone is generally not considered sufficient for a diagnosis of immunodeficiency.

Summary statement 71. Some patients with IGGSD exhibit impaired specific antibody production. (C)

Impaired polysaccharide responses are observed commonly among young patients with IgG2 subclass deficiency.[204,205] Impaired antibody production may not be seen among adult patients with IgG3 subclass deficiency.[206] In individuals with recurrent infections and 1 or more low levels of IgG subclasses, a demonstrable impairment in antibody response to vaccination or natural exposure is considered the most important determinant of disease.[202] Susceptibility to infection may wane over time, although immunologic abnormalities may persist.[80]

Summary statement 72. Major clinical associations with IGGSD include recurrent sinopulmonary bacterial infection and allergy. (C)

Sinopulmonary bacterial infection with encapsulated organisms is the most frequent complication observed in patients with low levels of 1 or more IgG subclasses.[204,205,207,208] Some patients also exhibit frequent viral illnesses. Environmental allergy is also frequently encountered in patients with IGGSD.[209]

Summary statement 73. IGGSD may be seen in a variety of primary and secondary immunodeficiencies and with a variety of additional clinical associations. (C)

IGGSD has been observed in association with other primary immunodeficiencies such as A-T,[210] WAS,[211] secondary immunodeficiencies such as HIV infection or AIDS,[212] and following BMT.[213] Other clinical conditions associated with IGGSD include atopy and autoimmune disease.[209]

Summary statement 74. The principles of management of IGGSD include therapy of allergy, preventive antibiotics, and cautious use of gammaglobulin in selected patients. (C)

These considerations are as already outlined for SIGAD above (summary statement 68).[74,206,209,214] Also see summary statement 22.

Specific Antibody Deficiency

Summary statement 75. The diagnosis of SAD should be considered in patients older than 2 years with recurrent upper and/or lower respiratory tract infections. (C)

SAD with normal immunoglobulin levels is a primary immunodeficiency of unknown origin.[215–220] The prevalence of this disorder is unknown, but it may be a frequent finding in patients evaluated for recurrent respiratory tract infections.[221–223]

Summary statement 76. SAD is characterized by normal concentrations of IgG, IgA, IgM, and IgG subclasses and abnormal IgG antibody responses to polysaccharide vaccines. (C)

The diagnosis of SAD requires the demonstration of poor response to polysaccharide antigens in the context of normal serum immunoglobulin concentrations.[79,224,225] Methods that measure IgG and IgM antibodies simultaneously may give falsely normal antibody concentrations due to short-lived increases in IgM antibodies. IgG specific for serotypes included in currently used pneumococcal vaccines may be determined by a standardized ELISA method and expressed in micrograms per milliliter.[219] The most accurate type-specific determinations are made using a reference standard serum (Food and Drug Administration SF89) and preadsorption with C polysaccharide common to all types and the 22F polysaccharide, which is cross-reactive.[226] (Laboratories that meet these standards include Louisiana State University Children's Hospital, New Orleans, LA; ARUP Laboratories, University of Utah, Salt Lake City, UT; and IBT Reference Laboratory, Progene Biomedical Inc, Lenexa, KS.) Protection against infection and colonization is associated with antibody concentrations of 1.3 μg/mL or higher or 200 to 300 ng of antibody nitrogen per milliliter (N/ml) per serotype. The conversion factor is 160 ng of antibody N/ml to 1 μg/mL.[227,228]

The interpretation of antipneumococcal antibody concentration results is based on antibody increases over preimmunization concentrations (immune response) and on final concentrations following immunization. High preimmunization antibody concentrations to a specific serotype are less likely to rise after immunization.[220] Adequate responses to individual pneumococcal serotypes are defined as a postimmunization antibody concentration of 1.3 μg/mL or higher or at least 4-fold over baseline.[220] In patients immunized with heptavalent pneumococcal conjugate vaccine, it is important to measure antibody responses against at least 6 serotypes present only in the polysaccharide vaccine.

Age also plays a significant role in the interpretation of responses to polysaccharide immunization. Well-validated age-adjusted criteria that define normal responsiveness to pure polysaccharides are yet to be developed. In general, responses to pure polysaccharide antigens are unreliable in patients younger than 2 years.[220] Between the ages of 2 to 5 years, individuals should respond to approximately half or more of the pneumococcal type-specific polysaccharides. Although controversy exists regarding the actual number of pneumococcal serotypes needed to determine a normal response, a consensus of this work group recommends that for patients older than 5 years, individuals should respond to at least approximately 70% of pneumococcal serotypes.

As discussed in summary statement 12, pneumococcal conjugate vaccines stimulate antibody responses as would other protein immunogens. Criteria regarding the magnitude and number of serotypes in responses to conjugate pneumococcal vaccines with respect to diagnosis of primary immunodeficiency have not been established.

Summary statement 77. Patients with SAD may benefit from additional immunization with conjugate pneumococcal vaccines. (C)

Patients who fail to respond to the polysaccharide vaccine when immunized after 2 years of age usually respond to the conjugate vaccine[219] Also see summary statements 18 to 22.

Transient Hypogammaglobulinemia of Infancy

Summary statement 78. The clinical presentation of THI is in infants and young children with recurrent bacterial sinopulmonary infections and frequent viral illnesses. (C)

Infants are normally protected by transplacentally acquired maternal IgG for the first 3 to 4 months of life, until the natural degradation of the maternal antibodies (half-life of approximately 21 days). In some infants, production of IgG (and in some cases IgA and IgM) does not reach normal levels until early childhood (as long as 36 months).[12] This delay in antibody production may be associated with recurrent infections.

Clinical manifestations of THI include bacterial sinopulmonary infections and other respiratory tract infections.[229] THI is rarely associated with sepsis, meningitis, or invasive infections.[229] Case reports have documented these more severe infections,[230,231] but studies of larger cohorts indicate that this is uncommon.[232] Sixty percent of patients are male. There is no known genetic basis for THI, although an increased incidence is reported in families with other immunodeficient patients.[12] Patients with THI have an increased incidence of atopic diseases.[233]

Summary statement 79. In THI, immunoglobulin levels are below the age-specific normal range, specific antibody production is usually preserved, and cellular immunity is intact. (C)

Laboratory evaluation in THI reveals IgG levels below the fifth percentile for age.[234] Some authors stipulate that measurements be repeated to eliminate misdiagnosis due to laboratory error[235]; this standard is not universally applied. Decreased IgG level is frequently associated with decreased IgA level and, less often, with decreased IgM level.[232] Evaluation includes measurement of specific antibody production and enumeration of lymphocyte subsets by flow cytometry. Most children have normal booster responses to protein vaccines and normal isohemagglutinin concentrations. Transient impairment of antibody responses to viral infections was noted in one report, but measurement of antiviral antibody titers is not usually part of the evaluation.[236] Rare individuals have transient suppression of vaccine responses, which recovers by the age of 3 to 4 years.[237] Decreased numbers of circulating T cells were noted in some patients with THI, but this is also not a prominent feature in most patients.[238]

Summary statement 80. Preventive antibiotic therapy may be indicated for patients with THI. A period of IVIG replacement may be considered. (C)

Antibiotic prophylaxis should be the initial mode of preventive therapy. If this fails or is not tolerated, some patients may benefit from gammaglobulin administration, particularly during seasons when respiratory illnesses are more frequent. If administered, gammaglobulin therapy should be stopped after 3 to 6 months to reassess the status of the patient's humoral immune function[5,237] (see summary statement 22).

Hypogammaglobulinemia, Unspecified

Summary statement 81. Any patient with primary hypogammaglobulinemia and normal cellular immunity who does not fulfill diagnostic criteria for the above disorders has hypogammaglobulinemia of an unspecified type. (D)

Hypogammaglobulinemia occurs in association with a variety of clinical conditions or in circumstances where its relevance to the overall clinical picture is unclear. There is increased susceptibility to infectious illnesses (mainly sinopulmonary bacterial infections) in some individuals. However, hypogammaglobulinemia is occasionally discovered incidentally in persons for whom it is believed to be clinically insignificant.

Some case reports describe small numbers of individuals with immunoglobulin abnormalities and variable impairment of specific antibody formation such as IgM deficiency[239–242] or IgE deficiency.[243] These are not considered specific diagnostic entities. A diagnosis of unspecified hypogammaglobulinemia may be applied in patients who have (1) significant morbidity from infections, (2) abnormal levels of serum immunoglobulins and/or antibody production not conforming to any of the diagnoses above, (3) evidence of normal cellular immunity, (4) none of the genetic lesions known to be associated with immune deficiency, or (5) no other conditions predisposing to humoral immunodeficiency. As much as possible, the diagnosis should be one of exclusion. It may often need to be qualified, at least temporarily, because molecular genetic analysis for some disorders may not be readily available.

Summary statement 82. Management of unspecified hypogammaglobulinemia may include antimicrobial therapy and gammaglobulin replacement. (D)

For these patients, few published data exist to guide management, which must, therefore, be individualized (see summary statements 18 to 22). Some individuals without apparent predisposition to infection may be found incidentally to have low serum immunoglobulin levels. The prognosis in this situation is unknown. There is no standard with respect to therapy, although close follow-up and periodic reevaluation would seem prudent.

CELLULAR IMMUNODEFICIENCIES

Defects of the IFN-γ/IL-12 Axis

Summary statement 83. Clinical manifestations of defects that involve the IFN-γ/IL-12 axis are mainly diseases caused by BCG or other poorly pathogenic mycobacteria, disseminated tuberculosis, systemic and/or persistent nontyphi *Salmonella*, or severe herpesvirus infection. (C)

Extreme susceptibilities to mycobacteria, *Salmonella*, and herpesviruses (CMV, HSV, and VZV) have been reported in patients with defects in type 1 cytokine pathways.[244–246] These defects result from genetic mutations in genes encoding IFN-γRα,[113,247–250] IFN-γRβ,[251,252] the IL-12 p40 subunit,[112] IL-12Rβ1[253–258] (also a component of the IL-23R.[259]), and signal transducer and activator of transcription 1 (STAT-1).[260] Mutations result in partial (IFN-γRs and STAT-1) or complete (IFN-γRs, IL-12 p40, and IL-12Rβ1) deficiencies. These conditions are inherited as autosomal recessive conditions except for partial IFN-γRα and partial STAT-1 deficiency,

which can be autosomal dominant. A family pedigree may be helpful in diagnosis.

Summary statement 84. Standard screening measures of cellular and humoral immune function are normal in patients with defects of the IFN-γ/IL-12 axis. (C)

Serum immunoglobulins, IgG subclasses and specific antibody production, peripheral blood lymphocyte numbers, and T-cell proliferative responses to mitogens and antigens are generally normal in this group of patients.[244,245]

Summary statement 85. Markedly increased serum IFN-γ level can be used as a screening test to prompt further evaluation for *IFN-γR* gene defects. (C)

Serum IFN-γ measured by ELISA is elevated (>80 pg/mL) in patients with a mutation in the genes that code for the components of the IFN-γR.[261] The ELISA may be used as a screening assay before pursuit of *IFNGR1* or *IFNGR2* gene sequencing when a defect is suspected.

Summary statement 86. Individuals with partial IFN-γR mutations and IL-12 p40 or IL-12Rβ1 mutations with nontuberculous mycobacterial disease may benefit from adjunct therapy with subcutaneous IFN-γ. (C)

Subcutaneous treatment with IFN-γ is an accepted adjunct therapy for mycobacterial disease.[262] Because of the impaired ability of patients with IL-12 p40 or IL-12Rβ1 mutations to produce IFN-γ in response to physiologic stimuli, this treatment may be useful for these patients and should be used in addition to standard antimycobacterial chemotherapies.

Summary statement 87. HLA-identical sibling BMT may be considered for therapy of IFN-γR mutation (C)

There is at least one reported case of successful BMT from an HLA-identical sibling for a patient with complete *IFNGR1* deficiency.[98]

CMCC Due to Mutation of AIRE

Summary statement 88. The principal clinical manifestations of CMCC due to *AIRE* mutation are immune-mediated destruction of endocrine tissue, chronic candidiasis, and ectodermal dystrophy. (C)

APECED, also known as autoimmune polyglandular syndrome type 1, is an autosomal recessive disorder that has a highly variable clinical phenotype.[35,263,264] A high prevalence has been identified in 3 ethnic groups: Sardinians, Finns, and Iranian Jews. Candidiasis is periodically seen in most patients but is rare in Iranian Jews. The endocrinopathy is immune mediated, with hypoparathyroidism and adrenal failure the most prevalent. Other autoimmune phenomena seen include alopecia areata, gonadal failure, autoimmune hepatitis, vitiligo, pernicious anemia, Hashimoto thyroiditis, and type 1 diabetes mellitus. Ectodermal dystrophies include keratopathy and nail dystrophy.[265–271] The clinical phenotype of *AIRE* mutations is highly variable and differs among ethnic groups. All elements (multiple endocrinopathy, ectodermal dystrophy, and candidiasis) may not be present in all patients.[272–274]

Summary statement 89. Patients with clinical features consistent with *AIRE* mutation should be screened for this defect, when possible. (C)

There is no convenient biomarker for this disease; diagnosis rests on demonstration of a mutation in the *AIRE* gene.[35,263–272]

Summary statement 90. Patients with *AIRE* mutation may benefit from immunosuppressive therapy. (C)

Immunosuppressive therapy may be helpful in reducing the onset or progression of autoimmune disease.[272]

Defective NK Cell Cytotoxicity Due to a Defect in CD16 (FcγRIII)

Summary statement 91. Patients with NK cell deficiency due to mutations of CD16 (FcγRIII) may have severe or recurrent herpesvirus disease. (C)

A mutation in the gene (*FCGR3A*) that codes for CD16 and causes a L48H amino acid substitution results in impaired NK cell cytotoxicity and susceptibility to recurrent or severe herpesvirus infections.[275,276] One patient also had BCG infection that required therapy.[276] Standard evaluations of B-cell and T-cell function are normal. The number of NK cells may be low or normal, spontaneous cytotoxicity may be low or normal, and antibody-dependent cellular cytotoxicity is not affected. The pathophysiologic basis of this disease is unclear.

Summary statement 92. Patients with isolated defects of cellular immunity who do not have mutations that affect the IFN-γ/IL-12 axis should be screened for mutation affecting FcγRIII by flow cytometry using anti-CD16 clone B73.1. (C)

Patients homozygous for this mutation have NK cells that fail to react with a commonly used anti-CD16 monoclonal antibody (clone B73.1) and thus will appear as $CD56^+/CD16^-/CD3^-$. In many clinical immunology laboratories, flow cytometry evaluation of NK cells uses anti-CD16 clone B73.1 and anti-CD56 conjugated with the same fluorophore in the same tube (identifies cells $CD16^+$ *or* $CD56^+$). In this type of assay, patients with the L48H substitution will not be identified. Thus, when severe or recurrent infection due to herpesvirus is encountered in patients with decreased NK cell function in the absence of other defined immunodeficiency, NK cells should be specifically evaluated by flow cytometry using anti-CD16 clone B73.1 alone.[275,276]

Summary statement 93. Patients with recurrent disease caused by herpesviruses associated with *FCGR3A* mutation may benefit from specific chemoprophylaxis against herpesviruses. (C)

VZV, HSV or CMV infections associated with NK cell deficiencies are reduced by appropriate chemoprophylaxis. This is considered standard of care in patients rendered immunocompromised due to BMT or solid organ transplantation.[277–280] Such therapy should be considered in patients with primary immunodeficiency and susceptibility to herpesvirus infection. Should disease occur while a patient is receiving prophylaxis, antiviral sensitivity testing should be performed to rule out resistance.

Idiopathic CD4 Lymphocytopenia

Summary statement 94. AIDS-like opportunistic infections are often seen in individuals with ICD4L. (C)

Among the variety of infections reported in this disorder are PCP,[281] disseminated tuberculosis,[282] diffuse verrucosis,[283] histoplasmosis,[284] cryptococcosis,[285–287] mucocutaneous candidiasis,[288,289] and persistent or relapsing herpes zoster.[289,290]

Additional conditions associated with ICD4L include vasculitis,[291] progressive multifocal leukoencephalopathy,[292,293] inflammatory demyelinating polyneuropathy,[294] and vitiligo.[295] Malignancies such as non-Hodgkin lymphoma[296] and mycosis fungoides[297] have also been observed. Some conditions are discovered incidentally and the individuals are asymptomatic.

Summary statement 95. Laboratory criteria for ICD4L include a $CD4^+$ T-cell count less than 300 cells/mm^3 with no evidence of HIV or other retroviral infection by both serologic and molecular testing. (C)

A patient with persistently decreased $CD4^+$ lymphocyte populations ($<$300 cells/mm^3) who repeatedly tests negative for HIV-1, HIV-2, human T-cell lymphotrophic virus 1, and human T-cell lymphotrophic virus 2 by serologic analysis, culture, and polymerase chain reaction and who has evidence of normal humoral immunity can be given the diagnosis of ICD4L.[298–301] Patients who fulfill these criteria may experience opportunistic infections but may also be asymptomatic.[302]

Summary statement 96. Measurement of ADA activity should be considered in patients diagnosed as having ICD4L. (C)

At least 2 individuals have been described to have idiopathic $CD4^+$ T lymphocytopenia that resulted from partial deficiency of ADA.[303]

Summary statement 97. Antimicrobial prophylaxis and IL-2 may be considered for therapy of ICD4L. (C)

Guidelines for antimicrobial prophylaxis are best made on an individual basis. There are no data concerning application of specific prophylactic regimens in this small patient population; regimens used in patients with HIV infection may be considered. One patient has been treated with extended clinical and immunologic improvement with regular injections of PEG-conjugated IL-2.[304]

Chronic Mucocutaneous Candidiasis

Summary statement 98. Patients who present only with recurrent candidal infection of nails, skin, and mucous membranes should be considered for the diagnosis of CMCC. (C)

The diagnosis of CMCC may be applied to a heterogeneous group of patients having an apparent selective susceptibility to chronic, recurrent, and sometimes exuberant candidal infections of the skin and its appendages and mucous membranes.[305–307] Invasive or systemic candidiasis is rare. There is an autosomal recessive form that may be associated with endocrinopathy and *AIRE* gene mutations. There is an autosomal dominant form for which no genetic abnormality has been found. In addition, many patients have a sporadic form(s) with no definite pattern of inheritance.

Summary statement 99. Laboratory abnormalities in CMCC may include defective cutaneous or in vitro T-cell response to *Candida* and low NK cell count and/or function. (C)

Patients with CMCC will not have other identifiable cellular or humoral immunodeficiencies. Laboratory testing may reveal impaired in vitro lymphocyte proliferation and cytokine secretion in response to *Candida*, and delayed-type hypersensitivity test results to *Candida* may be negative.[308,309] Other antigen responses are usually intact. A number of patients with CMCC also have decreased NK cell cytotoxic activity and decreased NK cell counts.[310–312] Thus, a complete laboratory evaluation should include NK cell phenotype and functional studies.

Summary statement 100. Antifungal agents are the mainstays of therapy for CMCC. (C)

Prolonged treatment with antifungal agents may be required, depending on the extent of candidal disease. No other therapies are known to affect the course of this disorder.[305–307]

NK Cell Deficiency Due to Unknown Defects

Summary statement 101. Individuals with severe disease caused by herpesviruses or papillomaviruses who do not have another defined immunodeficiency should have phenotypic and functional assessments of NK cells performed. (C)

A number of patients have been identified who have a susceptibility to certain viral infections and have an isolated deficiency in NK cells or NK cell activities without other identifiable immunologic defects.[313–317] These individuals should be evaluated for complete absence of all NK cells (absolute NK cell deficiency—determined by absence of all $CD56^+$ cells and NK cell cytotoxicity), absence of classic NK cells (classic NK cell deficiency—determined by absence of $CD56^+/CD3^-$ and NK cell cytotoxicity but presence of $CD56^+/CD3^+$ cells), and defective NK cell function (functional NK cell deficiency—determined by presence of $CD56^+/CD3^-$ lymphocytes but absence of NK cell cytotoxicity). In all cases, results must be consistent on at least 3 separate occasions separated by at least 1 month, because there is notable variation in NK cell populations. Care should be taken to exclude other immunodeficiencies known to be associated with defects of NK cell number or function. These include, but are not limited to, various forms of SCID,[8,318,319] CHS,[320] XLP,[321] CD40L deficiency,[322] WAS,[323] XLA,[324] and NEMO deficiency.[325]

Summary statement 102. Patients with undefined NK cell defects may benefit from chemoprophylaxis against herpesviruses. (D)

See summary statement 93.

Cellular Immunodeficiency, Unspecified

Summary statement 103. Any patient with normal serum immunoglobulin levels and specific antibody production and evidence of impaired cellular immunity who does not fulfill clinical and laboratory diagnostic criteria for any of the above disorders may be considered to have a cellular immunodeficiency of an unspecified type. (D)

Clearly, this would be a diagnosis of exclusion and must be conferred ultimately only after careful investigation of all other possibilities. It is extremely important to rule out mild or early forms of known cellular or combined deficiencies to maximize the likelihood of their detection and provide the best opportunities for definitive diagnosis and therapy and accurate genetic counseling.

Summary statement 104. Therapy for unspecified cellular immunodeficiency must be individualized. (D)

There are no standard recommendations for patients who fall into this category. Therapy must be directed toward established infections, associated diseases (eg, autoimmune disease), and prevention of those infections for which patients have shown predilection or for which they are considered to be at risk.

COMBINED IMMUNODEFICIENCIES

Severe Combined Immunodeficiency

Summary statement 105. Patients with SCID present within the first few months of life with recurrent, persistent, or severe bacterial, viral, or fungal infections and failure to thrive, diarrhea, and rashes. (C)

SCID designates a group of syndromes in which there is a complete lack of specific lymphocyte-dependent adaptive immunity.[8,326] These patients have the most extreme susceptibility to infection and characteristically present early in life with some or all of the symptoms listed above. Common pathogens are most often seen; usually nonpathogenic organisms (opportunistic infections) are also seen. Infections usually do not remain localized; disseminated disease is frequent.

Summary statement 106. A suspicion of SCID should be considered an emergent condition. (C)

SCID is an emergent medical problem because of the rapidity with which these infants succumb to life-threatening infections.[327] Thorough immunologic evaluation must be accomplished as quickly as possible.

Summary statement 107. Physical examination reveals absence of lymphoid tissue and the thymus is radiographically undetectable. (C)

The absence of tonsils and palpable lymph nodes may be noted on physical examination. The thymus is vestigial, usually cervical, and lacks normal corticomedullary architecture and Hassall corpuscles.[328] The absence of the thymus on a chest x-ray film or other imaging study in an infant with serious infection should prompt immunologic evaluation.

Summary statement 108. Characteristic laboratory abnormalities include severe, age-adjusted lymphopenia and panhypogammaglobulinemia, 1 or more reduced or absent major lymphocyte subpopulations, and absent or profoundly reduced T-cell proliferation to mitogens and antigens. (C)

A complete blood cell count usually reveals leukopenia and/or lymphopenia. Alterations of lymphocyte populations may be indicative of 1 or a few specific genetic defects (Table 6 and Algorithm 3). Hypogammaglobulinemia results from lack of T-cell help, as well as from intrinsic functional abnormalities of B cells. Defects in T-cell proliferative responses to mitogens and antigens in vitro are the hallmark immunologic abnormalities.[8,326]

Summary statement 109. Some mutations in genes associated with SCID may lead to atypical (milder) phenotypes. (C)

Atypical or partial milder expressions of disease are sometimes seen in association with gene defects usually associated with classic SCID.[329,342,356–358] Also, some of the gene defects commonly grouped with SCID do not lead to the most severe classic phenotype (for example, MHC class I deficiency). Individuals may not display all of the clinical and laboratory features, onset of clinical disease may be later in life, and infectious complications may be less severe.

Summary statement 110. Maternal T cells may engraft in some patients with SCID and obscure the peripheral blood lymphocyte phenotype. (C)

Maternal T cells may cross the placenta and survive in the peripheral blood and lymphoid tissues of SCID patients.[359] Since the laboratory phenotype may guide the evaluation of specific molecular defects in SCID patients, the maternal or host origin of blood T cells should be definitively established. In male infants, this is easily done by karyotyping. For female infants, HLA typing shows the presence of more than 2 haplotypes.

On occasion, engrafted maternal T cells may become activated by HLA disparities and cause clinical graft-vs-host disease. Infants with diffuse cutaneous eruptions and/or other clinical and laboratory features of SCID should be evaluated for this possibility. Note that erythrodermia is also associated with a form of SCID known as Omenn syndrome, a subset of SCID due to mutations of *RAG1* or *RAG2* (Table 6, Algorithm 3). Peripheral blood T cells in patients with Omenn syndrome are of host origin; graft-vs-host disease is not involved.

Summary statement 111. An established diagnosis of SCID should be considered a medical emergency. (C)

Once a diagnosis of SCID is confirmed, therapy must be initiated as quickly as possible. Experience clearly indicates that outcome after BMT for SCID depends greatly on the age of diagnosis and intervention.[8,107,327,360] In one study, patients who received transplants within the neonatal period (first 28 days of life) had significantly improved T-cell development after BMT.[360] An earlier report from the same institution showed a trend toward improved survival (95% vs 76%) in infants undergoing BMT before 3.5 months of age compared with those who received transplants later.[107]

Summary statement 112. Patients with SCID may be immunologically reconstituted by BMT or gene therapy. (C)

See summary statement 25.

Summary statement 113. Patients with SCID due to IL-2R γ chain (common γ chain) deficiency and ADA deficiency have been successfully treated with gene therapy. (C)

The gene therapy strategy used for the immunoreconstitution of patients with SCID consisted of ex vivo gene transfer to autologous hematopoietic stem cells isolated from the patient bone marrow. These modified cells were then infused

back to the patient without any preparative chemotherapeutic conditioning regimen.[361–363] This therapy was offered only to patients who did not have HLA-identical sibling donors because of the high rate of success of BMT with such donors.

Gene therapy has also been successful for reconstitution of ADA-deficient SCID. Two patients have had immune reconstitution following infusion of stem cells transduced ex vivo with a retroviral vector.[364] These patients received a nonmyeloablative conditioning regimen prior to stem cell infusion.

Three cases of leukemia have occurred among the XSCID patients that received gene therapy.[362,365] For this reason, all gene therapy trials are currently being closely evaluated.

Summary statement 114. Patients with SCID or suspected SCID should receive gammaglobulin replacement therapy. (C)

Patients with SCID are unable to mount specific antibody responses. Immunoglobulin replacement therapy instituted at the earliest opportunity affords protection from many common bacterial and viral pathogens. A significant number of SCID patients continue to require immunoglobulin supplementation after hematopoietic stem cell transplantation because of the failure of B-cell engraftment (see summary statement 19).[67,366,367]

Summary statement 115. Patients with SCID or suspected SCID should be protected from exposure to infectious agents. (C)

The absence of serious infection is an important element for a favorable prognosis for the success of BMT for SCID.[107] Prudent measures include avoidance of contacts with large numbers of people or those likely to harbor infectious agents (eg, young children in day care) and protective isolation when in the hospital setting.

Summary statement 116. Patients with SCID or suspected SCID should receive prophylaxis for PCP. (C)

PCP is a common early complication in patients with SCID.[8,352] Trimethoprim-sulfamethoxazole (5 mg/kg of trimethoprim given orally once daily 3 times a week) is preferred, whenever possible. Alternative prophylactic regimens include pentamidine isethionate (5 mg/kg every 4 weeks), dapsone (1 mg/kg daily), and atovaquone (30 mg/kg daily).

Summary statement 117. Early signs of infection should be promptly recognized, and antimicrobial regimens initiated early and for prolonged periods. (C)

Vigilance for infectious illness is essential for successful outcomes for SCID patients.[106,107] Empiric therapy should be considered, if a specific pathogen diagnosis is uncertain or likely to be delayed. Therapy may need to be prolonged, because clearance is usually slower compared with immunocompetent hosts (see summary statement 18).

Summary statement 118. Patients with SCID due to ADA deficiency may benefit from the administration of PEG-ADA. (C)

The mortality rate of 48 ADA-SCID patients who received PEG-ADA (30 U/kg intramuscularly twice a week) was 15%.[368] All experienced clinical improvement with marked reduction of opportunistic infections, although immunoreconstitution based on the number of lymphocytes or antibody response was incomplete. Serum ADA activity and serum nucleotide levels should be used to monitor response to therapy and compliance. Antibodies to PEG-ADA develop in 65% of patients.[368] PEG-ADA should not be administered to patients for whom BMT is planned.

Wiskott-Aldrich Syndrome

Summary statement 119. The classic clinical expressions of WAS are X-linked inheritance, an eczematous skin eruption, petechiae, bruising or bleeding, recurrent and severe infections, including opportunistic organisms, autoimmune diseases, and EBV-related B-cell lymphomas. (C)

Recurrent otitis, sinopulmonary bacterial infections, and frequent viral illnesses are common in WAS.[211,369] Opportunistic infections may be seen, particularly PCP. Eczema may be absent, mild, or severe. Autoimmune colitis, vasculitis and glomerulonephritis, and other autoimmune processes are observed in WAS.[33] Patients most often succumb to overwhelming infection or massive hemorrhage. Approximately 10% to 15% of WAS patients develop malignancy, with an average age of onset of approximately 10 years.[369] More than 80% of these are lymphomas, often associated with EBV.

Summary statement 120. Thrombocytopenia and small platelet size are the most characteristic laboratory abnormalities of WAS. (C)

Platelets are small, dysfunctional, and cleared more rapidly and produced more slowly than normal.[370] Small platelet size confirms the diagnosis of WAS in the appropriate clinical context. In healthy individuals, the platelet volume is 7.1 to 10.5 fL, with a diameter of $2.3 \pm 0.12 \times 10^{-6}$M, whereas platelets from WAS patients have volumes ranging from 3.8 to 5.0 fL, with diameters of $1.82 \pm 0.12 \times 10^{-6}$M.[370,371] Small platelet size is occasionally seen in immune thrombocytopenias, but WAS is distinguished by its other manifestations. However, as many as 20% of WAS patients may develop immune thrombocytopenia either before or after splenectomy.[372]

Summary statement 121. Humoral immunologic abnormalities in WAS include dysgammaglobulinemia and impaired specific antibody production. (C)

Patients with WAS have low IgG, IgM, and IgE levels and sometimes elevated IgA levels.[211,369,370] These abnormalities may not appear until late in the course of the disease. More than 50% of patients display some degree of impairment in vaccine antibody responses or in isohemagglutinin production.

Summary statement 122. Cellular immunologic abnormalities in WAS include T lymphocytopenia, impaired in vitro and in vivo T-cell responses, and decreased NK cell activity. (C)

Approximately 20% to 30% of WAS patients have low T-cell counts.[211,369,370] $CD8^+$ T-cell counts are often disproportionately depressed and are low in more than 50% of patients with WAS. T cells have reduced proliferation to

mitogens in vitro in one third to half of patients. Diminished cutaneous antigen responses are observed in more than 80% of patients. Defects in spontaneous NK cell cytotoxic function are also seen.[323]

Summary statement 123. A *WASP* mutation is expressed in some female patients due to extreme nonrandom X-chromosome inactivation. (C)

Female patients with characteristic clinical and laboratory features of WAS should be studied for mutations in *WASP*. One female patient had clinical WAS as a result of carrying a *WASP* mutation and having extreme nonrandom lyonization of her X-chromosome bearing the functional *WASP* gene.[373] Another heterozygous female patient exhibited clinical features of WAS, despite having a *WASP* mutation on only 1 X chromosome and random X-inactivation.[51]

Summary statement 124. WASP is measurable by Western blot or flow cytometry to establish a diagnosis. (C)

Both Western blot and intracytoplasmic staining and flow cytometry analyses may be performed on lymphocytes from patients suspected of having WAS to determine the presence or absence of WASP.[374] This is considered diagnostic in a patient with characteristic clinical features. The presence of normal size and amount of WASP by protein-based analysis does not exclude the diagnosis, since some point mutations may permit protein production. Molecular analysis is required in this circumstance.

Summary statement 125. A molecular diagnosis should be established in every case of WAS for its prognostic value. (C)

Some mutant *WASP* genotypes have prognostic value.[375–379] Splice variant mutations that permit expression of a small amount of normal WASP or missense mutations that permit expression of a partially functional mutant WASP are associated with milder clinical courses. Mutations that abolish WASP expression or permit expression only of a truncated WASP lead to more severe disease (see summary statement 14).

Summary statement 126. The only curative therapy for WAS is BMT. (C)

See summary statement 25. HLA-identical sibling donor transplants have a high success rate (5 year probability of survival of 87%).[92] HLA-matched unrelated donor transplants under age 5 years have a similar success rate. Unrelated donor transplants after age 5 years have a lower rate of survival.

Summary statement 127. Before BMT, WAS is managed by a combination of splenectomy, antibiotics, and gammaglobulin replacement. (C)

Gammaglobulin replacement is indicated for all patients with WAS.[70,211,369] Preventive antibiotic therapy may be used concomitantly in some. Thrombocytopenia of WAS is best managed by splenectomy.[369,372,380] This intervention alone increases median survival significantly. High-dose IVIG may also be used for thrombocytopenia in WAS, although the response is variable. Glucocorticosteroids are successful for this purpose, but the immune suppression is undesirable.

A-T and Related Disorders

Summary statement 128. Gait ataxia, oculocutaneous telangiectasias, growth retardation, and immune deficiency are the most prominent and consistent clinical features of A-T. (C)

Most patients with A-T experience growth retardation (especially in later childhood) and delayed gross motor development, especially learning to walk.[381] Additional neurologic manifestations include oculomotor apraxia, dysarthria, swallowing dyscoordination, and peripheral neuropathy. Oculocutaneous telangiectasias develop in many patients with A-T at approximately 3 to 5 years of age. Thus, they are not helpful for making a timely diagnosis.[381] Clinical immunodeficiency begins in infancy or early childhood. Respiratory tract bacterial infections predominate; viral and fungal infections may also occur.[382] Opportunistic infections are rare.

Clinical features of Nijmegen breakage syndrome (NBS), DNA ligase IV deficiency (LIG4 syndrome), DNA ligase I deficiency, and A-T–like disorder (ATLD) are similar but have important differences. NBS (mutation in *NBS1*) is characterized by growth retardation, characteristic facies, microcephaly, cognitive impairment, and immune deficiency.[383] LIG4 syndrome (mutation in *LIG4*[384]) and DNA ligase I deficiency (mutation in *LIG1*[385]) have similar phenotypes. Patients with ATLD (mutation in *HMRE11*) have ataxia without cutaneous features or clinical immunodeficiency.[386]

Summary statement 129. Immunologic abnormalities in A-T include low or elevated immunoglobulin levels, IgG subclass deficiencies, impaired specific antibody production, and alterations in lymphocyte populations. (C)

Immunoglobulin levels are usually normal in A-T; hypogammaglobulinemia is sometimes seen.[381] As many as 40% of patients may display oligoclonal or monoclonal hypergammaglobulinemia.[387] Low IgA levels and abnormalities of IgG subclasses such as IgG2 deficiency,[210,381,382,388] and impairment of pneumococcal polysaccharide responses[389] may also be seen. Lymphopenia, abnormalities of lymphocyte subsets, impaired function of $CD4^+$ and $CD8^+$ T cells in vitro, or depressed skin delayed hypersensitivity response may be observed.[381,382,390] There is a highly characteristic increase in T cells that bear the $\gamma\delta$ receptor.[391] Essentially identical immunologic abnormalities are found in NBS[383] and DNA ligase I deficiency.[385] Immunodeficiency of LIG4 syndrome is reported as pancytopenia and respiratory tract infections.[384] ATLD is not associated with immunodeficiency or altered laboratory measures of immune function.[386]

Summary statement 130. Cytogenetic abnormalities such as chromosomal translocations and chromosome fragility support a diagnosis of A-T or related disorders. (C)

Chromosomal translocations that involve immunoglobulin (2p12, 14q32, 22q12) and T-cell receptor (7p15, 7q35, 14q11) loci are highly characteristic in lymphocytes of patients with A-T, NBS, or ATLD, and chromosomes also have increased spontaneous and radiation-induced breakage in vitro.[136,383,392] There is increased chromosomal damage with radiation in LIG4 syndrome, but the immunoglobulin and

T-cell receptor translocations are not seen.[384] Ligase I deficiency leads to DNA sensitivity to a wider range of damaging agents.[385,393]

Summary statement 131. Patients with A-T and related disorders experience an extreme susceptibility to ionizing radiation and radiomimetic drugs and have a high rate of cancer. (C)

A-T, NBS, LIG4 syndrome, DNA ligase I deficiency, and ATLD are all associated with sensitivity to toxic effects of ionizing radiation.[136,383–385,392] In A-T, NBS, and DNA ligase I deficiency, there is a high rate of malignancy. Lymphomas predominantly occur before the age of 15 years, and epithelial tumors occur in older patients. Malignancy may be part of the clinical presentation of A-T.[394] Malignancy has not been observed in ATLD or LIG4 syndrome.[384,386]

Summary statement 132. Elevated levels of oncofetoproteins are highly characteristic of A-T but not related disorders. (C)

Elevated serum carcinoembryonic antigen[395] and AFP[396] levels are virtually pathognomonic for A-T and are seen in 95% of patients. Elevated AFP levels are not seen in NBS or ATLD.[136,383,392] It is essential to use age-adjusted normal ranges for these measurements. These laboratory abnormalities have not been sought in syndromes of ligase I or ligase IV deficiency.

Summary statement 133. All children with persistent ataxia should have determination of serum AFP levels. (C)

Oculocutaneous telangiectasias may not appear until 3 to 5 years of age, whereas ataxia is present early. Delayed diagnosis of A-T is associated with significant morbidity and missed opportunities for informed family planning.[381]

Summary statement 134. A-T and related disorders should be considered in all children with persistent characteristic neurologic and/or cutaneous manifestations. (D)

Particular *ATM* mutations may be associated with mild phenotypes or unusual manifestations such as cutaneous granulomas or mixed hypopigmentation and hyperpigmentation in the absence of telangiectasias.[397–402]

Summary statement 135. Patients with A-T and related disorders benefit from a coordinated multidisciplinary approach to management. (D)

The multisystem nature of these disorders necessitates an integrated multidisciplinary approach to management. Such care optimizes medical treatment and permits integration of physical and occupational therapy into the overall care of the patient. Referral to a tertiary care center with experience in the evaluation and management of these diseases is desirable.

Summary statement 136. Antibiotic prophylaxis and/or gammaglobulin replacement therapy may be indicated for A-T and related disorders. (C)

The clinical immunodeficiency of A-T early in its course is most similar to the antibody deficiencies (recurrent sinopulmonary bacterial infections) and similar therapeutic considerations apply in this regard[381] (see summary statements 18 to 22). Immune function should be reassessed periodically, because it may decline over time.

Summary statement 137. Therapy of hematologic malignancy in A-T and related disorders should be administered by physicians with prior direct experience with this complication. (C)

Outcomes of standard chemotherapeutic regimens for malignancy in A-T are poor due to the toxic effects of these regimens in these patients.[403–405] Modified regimens are associated with less morbidity and longer survival.[406,407]

DiGeorge Syndrome

Summary statement 138. Thymic dysplasia, cardiovascular structural defects, and hypoparathyroidism mark the triad of congenital defects in DGS. (C)

Most patients with DGS possess characteristic facial features of hypertelorism, saddle nose, shortened philtrum, and low-set and abnormally shaped ears, part of the spectrum of velocardiofacial syndrome (VCFS).[408] The most common additional characteristics are cardiac outflow tract malformations, hypoplasia of the thymus and parathyroid glands with hypocalcemia, and immunodeficiency.[409] Cleft palate and velopharyngeal insufficiency may also be seen. Approximately 80% to 90% of patients with DGS with these features have 22q11.2 deletion.[408,409] An additional fraction yet to be determined have mutations in the *TBX1* gene.[410,411] A small number (1%–2%) of patients have DGS without the features of VCFS due to a chromosome 10p14 deletion.[408] The remainder have DGS in association with other general syndromes of dysmorphism, such as the CHARGE (coloboma, heart anomaly, choanal atresia, retardation, genital and ear anomalies) association.[412,413]

Summary statement 139. T-cell lymphopenia is the most common laboratory feature of DGS. (C)

The degree of immune impairment in DGS and VCFS depends on the extent of thymic hypoplasia. It is the rare (no more than 1%–2% of the total) DGS patient who has compromised T-cell immunity so severe as to require immunoreconstitution.[414] Patients with extreme T-cell lymphopenia are referred to as those with complete DGS, whereas those patients with intermediate levels of T-cell immunity are said to have partial DGS.[6] Most patients with complete DGS have no T cells; in a small number of these patients, oligoclonal T cells may develop, making diagnosis complex.[415] Patients with partial DGS are usually mildly to moderately lymphopenic. In vivo and in vitro measures of T-cell function are usually normal. Serum immunoglobulin levels are normal, as is antibody production.[416] IgA deficiency occurs in 2% to 13% of DGS patients[416,417]; some of these develop autoimmune disease.[409]

In patients with partial DGS, T-cell subsets (CD3, CD4, CD8), although generally lower than those of controls, were not observed to decline with age, up to 120 months.[414] Furthermore, lymphocyte proliferation to phytohemagglutinin did not decline with age in 41 of 45 patients. No patients had impaired specific antibody production.

Summary statement 140. Treatment of infants with complete DGS requires some form of cellular reconstitution. (C)

Reconstitution of T-cell function in complete DGS infants has been accomplished by transplantation of fetal thymus, postnatal thymus tissue, HLA-identical sibling BMT, and peripheral blood mature T-cell transplantation.[88,415,418,419] Reports of reconstitution of DGS infants with HLA-identical BMTs were probably due to engraftment of peripheral blood T lymphocytes collected during harvesting of bone marrow.[6]

Summary statement 141. Patients with DGS require multispecialty care. (D)

The constellation of congenital defects in patients with DGS poses special health problems that require coordinated care from a variety of subspecialties.[409] Comprehensive pediatric medical care at a medical center with experience treating DGS is desirable.

HIM Due to Defects of CD40L (CD154, TNFSF5*) and CD40 (*TNFRSF5*)*

Summary statement 142. Clinical features of CD40 and CD40L deficiencies include infections with viral, bacterial, fungal, and opportunistic pathogens and cytopenias. (C)

Mutations of *TNFSF5*, also called CD154 and CD40L, result in what has historically been referred to as the X-linked HIM, abbreviated XHIGM, XHIM, or HIM1. Mutations of *TNFRSF5*, also called CD40, result in 1 form of autosomal recessive HIM, which has been abbreviated HIM3. Because the eponym HIM is a laboratory phenotypic description that encompasses disorders classified as both antibody deficiencies and combined immunodeficiencies, some authorities argue it should be abandoned in favor of names that designate molecular defects.

Clinical features of deficiencies of CD40 and CD40L include presentation in infancy with recurrent and severe bacterial upper and lower respiratory tract infections, gastrointestinal infections, opportunistic infections such as PCP and disseminated fungal infections, neutropenia, chronic anemia due to parvovirus, and cholangitis due to *Cryptosporidium*.[37,420,422]

Summary statement 143. Immunologic abnormalities of CD40 and CD40L deficiencies affect both humoral and cell-mediated immunity. (C)

Laboratory features of CD40 and CD40L deficiencies include low IgG levels with normal or elevated IgM levels. The IgA level is often also low. Specific IgG antibody production is poor, although lymphocyte subset composition is most often normal. T cells proliferate normally in vitro in response to mitogenic stimuli in these disorders. However, T-cell responses to recall antigens are impaired.[37,420,421,423]

Summary statement 144. CD40L expression is most readily evaluated by flow cytometric methods on activated T cells. (C)

CD40L expression on activated T cells may be measured using monoclonal antibodies, CD40-immunoglobulin fusion proteins, or both.[424,425] T cells may be most conveniently activated by nonspecific stimuli such as a combination of phorbol ester and calcium ionophore. Similar methods may also be applied to platelets.[426] A few patients with CD40L deficiency may have mutations that permit some staining with both monoclonal antibodies and fusion proteins.[424] If clinical and laboratory features are highly suggestive of CD40L deficiency and CD40L/CD154 staining is inconclusive, a molecular diagnosis should be sought.

Summary statement 145. CD40 expression may be measured by flow cytometry on monocytes or B cells. (C)

CD40 is expressed constitutively on B cells, monocytes, and a variety of other cell types.[37] Its presence or absence is easily determined by flow cytometry on these cell populations, permitting presumptive diagnosis of CD40 deficiency. Currently, this test is not widely available.

Summary statement 146. Female patients with the HIM phenotype should be studied for CD40L mutation if CD40 mutation or other known mutation associated with the HIM phenotype is not found. (C)

Rare female carriers may express CD40L mutations in the hemizygous state due to extreme nonrandom X chromosome inactivation.[53]

Summary statement 147. Prophylaxis for PCP is indicated for all patients with known or suspected CD40 or CD40L deficiency. (C)

PCP occurs in 30% to 40% of patients with defects of CD40 or CD40L.[37,420,421]

Summary statement 148. Neutropenia in CD40 or CD40L deficiency should be treated with G-CSF. (C)

Response of neutropenia in patients with CD40L deficiency to G-CSF is inconsistent but has been observed.[37,420,421] If a sustained response is seen, G-CSF therapy should be discontinued to determine its ongoing necessity, because neutropenia in this disorder may resolve spontaneously.

Summary statement 149. BMT is curative for CD40L deficiency. (C)

A variety of BMT methods have been successful in patients with CD40L defects.[87,89,91,95,96,99,100,420,427] In one case, cadaveric liver transplantation was followed by BMT from a different matched unrelated donor.[93] Liver transplantation alone in CD40L deficiency has uniformly poor outcome.[428] There is no experience with BMT as therapy for CD40 deficiency.

X-linked Lymphoproliferative Disease

Summary statement 150. Three characteristic phenotypes of XLP are fulminant infectious mononucleosis, lymphoma, and dysgammaglobulinemia. (C)

Several early reported cases of XLP followed several infections with EBV. However, it is now clear that prior EBV infection is not necessary to activate the trigger for onset of this debilitating and progressive disease.[429,430] Almost 60% of patients present with fulminant infectious mononucleosis. An additional 30% will develop lymphoma (immunoblastic sarcoma), whereas another 30% have dysgammaglobulinemia. There is considerable overlap, and patients may have 1, 2, or all 3 manifestations at one time or another. A few patients with familial hemophagocytic lymphohistiocytosis have been

found to have XLP.[431] The onset of symptomatic disease may be as early as 5 months or later than 20 years of age.

Summary statement 151. The immunologic findings in XLP are variable and depend on EBV exposure. (C)

Before EBV exposure, immunologic laboratory abnormalities are limited mainly to hypogammaglobulinemia, 1 or more low IgG subclasses, or elevated IgA and IgM levels.[430] Following EBV infection, there may be hypogammaglobulinemia with impaired specific antibody production, an inverted CD4/CD8 ratio, and diminished T-cell proliferative responses to mitogens and antigens in vitro. There is also often a striking decrease in NK cell cytotoxicity.[321]

Summary statement 152. Some patients with XLP have been diagnosed as having CVID. (C)

As many as 10% of male patients diagnosed as having CVID may have mutations in *SH2D1A*, the gene mutated in XLP.[184,432,433]

Summary statement 153. IVIG should be given to patients with XLP and hypogammaglobulinemia or dysgammaglobulinemia and infections. (C)

It is likely that IVIG will provide some protection from infection in patients with XLP, although there are no controlled trials to establish efficacy.[430] Some have advocated attempts to prevent primary or recurrent EBV infections.[434] The effectiveness of this approach is unknown, but primary infection and relapses of EBV disease occur in patients while receiving IVIG.[435]

Summary statement 154. BMT can cure XLP. (C)

Several patients have been successfully treated with BMT.[436–438] This is indicated for any patient who has experienced at least 1 life-threatening manifestation of XLP. BMT before clinically evident disease is controversial.

Summary statement 155. Patients with XLP and lymphoproliferative disease may be treated with chemotherapy followed by BMT. (C)

A regimen of chemotherapy designated HLH-94 consists of etoposide, corticosteroids, cyclosporine A, and, in selected patients, intrathecal methotrexate and is successful for treatment of hemophagocytosis and lymphoproliferation in XLP.[439] The patient may proceed immediately afterward to BMT.

WHIM Syndrome

Summary statement 156. The WHIM syndrome is named for its cardinal clinical features. (C)

Approximately 25 patients have been reported to have this syndrome as a result of mutations in the chemokine receptor gene *CXCR4*.[440–443] Individuals are affected to varying degrees with verrucosis, hypogammaglobulinemia with recurrent sinopulmonary bacterial infections, and myelokathexis (retention of mature neutrophils in the bone marrow with resulting peripheral neutropenia).

Summary statement 157. Laboratory findings in WHIM syndrome include neutropenia and variably depressed humoral and cellular immunity. (C)

Peripheral blood neutrophil counts are generally less than 0.5×10^9/L.[440–443] Neutrophil counts rise with infection, and neutrophil functional test results are normal. Bone marrow biopsy specimens show the presence of mature neutrophils. Levels of IgG and/or IgA may be below normal; IgM levels are more often normal. Vaccine antibody responses are generally preserved. Lymphocyte subsets are generally normal, but in vitro proliferative responses to mitogens and antigens may be impaired, and cutaneous anergy to recall antigens has also been reported.

Summary statement 158. IVIG replacement may reduce the rate of respiratory tract bacterial infections in WHIM syndrome. (C)

Gammaglobulin may be effective for reducing bacterial infections in patients with WHIM syndrome.[441]

Summary statement 159. G-CSF and GM-CSF increase neutrophil counts in patients with WHIM syndrome. (C)

Both G-CSF and GM-CSF have been reported to result in 4- to 100-fold increases in peripheral blood neutrophil counts.[441] Adverse effects may limit therapy. Interestingly, serum IgA and IgG levels may normalize following G-CSF or GM-CSF administration.

Defects of NF-κB Regulation

Summary statement 160. The major clinical manifestations of defects in NF-κB regulation include ectodermal dysplasia and severe infections with viruses, bacteria, and atypical mycobacteria. (C)

Ectodermal dysplasia is characterized by conical or absent teeth, fine sparse hair, frontal bossing, and abnormal thermal regulation due to decreased eccrine sweat glands.[444] A small subset of X-linked cases has immunodeficiency, and some have lymphedema and osteopetrosis. To date, most have been associated with a mutation in *IKBKG*.[325,445–450] This gene on the X-chromosome encodes the IκB kinase γ chain, also called NEMO. Individuals with *IKBKG* mutations experience severe bacterial or viral infections early in life and atypical mycobacterial infection.

A single patient has been described with mutation of the *IKBA* gene encoding the IκB α chain.[451] This individual exhibited ectodermal dysplasia, bacterial respiratory tract infections, chronic diarrhea, and failure to thrive. Up to the age of 1 year when he underwent BMT, infection with mycobacteria had not occurred.

Not all *IKBKG* mutations result in overt ectodermal dysplasia.[452,453] Thus, male patients with atypical mycobacterial infections with immunologic laboratory findings consistent with those that result from *IKBKG* mutation, including hypogammaglobulinemia, absent protective antibody responses to vaccines, hyper-IgM, or hyper-IgA, should be evaluated for *IKBKG* or NEMO deficiency.

Summary statement 161. Dysgammaglobulinemia and altered cellular immune function are observed in patients with defects of NF-κB regulation. (C)

Laboratory studies in patients with *IKBG* or NEMO deficiency may reveal hypogammaglobulinemia, poor specific

antibody production, either hyper-IgM or hyper-IgA, depressed NK cell cytotoxicity, and deficient in vitro proinflammatory cytokine responses.[325,445–450] Cellular responses to T-cell mitogens and recall antigens in vitro are variable. The single patient with IκBα deficiency had high IgM with low IgG and IgA levels, no specific antibody responses, polyclonal lymphocytosis with normal subset distribution (although γδ T cells were absent and all blood T cells were $CD45RA^+$), and normal mitogen proliferation but absent T-cell responses to recall antigens.[451]

Summary statement 162. Mycobacterial infection in patients with an *IKBKG* mutation should be treated with an aggressive antimicrobial regimen. (C)

Mycobacterial infection in patients with *IKBKG* mutation can be severe and difficult to treat.[325,446,448,450] Some of the immunologic deficits resulting from *IKBKG* mutation may decrease the effectiveness of certain immune-based treatments, such as injections of IFN-γ. Thus, it is important to use a multidrug regimen based on the sensitivities of the mycobacterial isolate obtained from the patient. Cessation of antimycobacterial therapies may permit rapid relapse. Thus, therapy should be considered long term, but should be adjusted according to disease severity and antimicrobial sensitivity of serial mycobacterial isolates. Surgical treatment of identified foci of infection should be considered.

Summary statement 163. Patients with *IKBKG* mutation should receive gammaglobulin replacement. (C)

Due to the propensity toward ineffective antibody production and susceptibility to bacterial infections.[325,445–450] patients with *IKBKG* or NEMO deficiency should be given regular IVIG infusions. In many patients, however, significant bacterial infections may still occur, despite IVIG replacement.

Summary statement 164. Antibacterial, antimycobacterial and antiviral prophylaxis should be considered for patients with *IKBKG* mutation. (C)

Decreased cellular immune function, including NK cell cytotoxicity, may predispose patients with an *IKBKG* mutation toward severe and recurrent viral infections, particularly herpesviruses.[325,446,454] Chronic herpes antiviral prophylaxis should be considered in patients who have experienced these infections. Since significant bacterial infections may occur in spite of gammaglobulin replacement, antibacterial prophylaxis should be considered. Antimycobacterial (*Mycobacterium avium*) prophylaxis in young patients who have not yet been diagnosed as having such infection should also be considered.

Summary statement 165. Consider BMT for patients with defects of NF-κB regulation not infected with mycobacteria. (C)

The natural history of patients with *IKBKG* mutations is incompletely understood. A relatively large number of early fatalities has been seen, despite tertiary medical care.[446,450] Thus, the identification of an *IKBKG* mutation in an individual with immunodeficiency should raise consideration of BMT. Limited experience exists; however, anticipated outcomes of BMT would be favorable in younger children who have not yet experienced mycobacterial infection. BMT will not ameliorate some morbidities attributable to *IKBKG* or NEMO deficiency, including the ectodermal dysplasia phenotype, if present. The single known patient with *IKBA* mutation was treated successfully with BMT.[451]

IRAK-4 Deficiency

Summary statement 166. The main clinical manifestation of IRAK-4 deficiency is serious infection with gram-positive bacteria. (C)

Three patients with IRAK-4 deficiency have been described.[455] They experienced recurrent episodes of cellulitis, arthritis, meningitis, osteomyelitis, organ abscesses, and sepsis caused mainly by *Staphylococcus aureus* and *Streptococcus pneumoniae*. Serious infections with other bacteria also occurred.

Summary statement 167. The results of screening tests of immune function are normal in patients with IRAK-4 deficiency. (C)

Serum immunoglobulin levels, specific antibody formation, and T-cell responses to mitogens and recall antigens are all normal in these patients.[455] Peripheral eosinophilia and elevated serum IgE levels may also be observed.

Summary statement 168. Defects of TLR signaling are seen in IRAK-4 deficiency. (C)

Peripheral blood mononuclear cells from patients with IRAK-4 deficiency do not produce TNF when stimulated via IL-1 or IL-18Rs or TLRs 2, 3, 4, 5, and 9.[455] Western blotting may reveal absence of IRAK-4 protein.

Summary statement 169. Therapy in IRAK-4 deficiency is directed toward treatment and prevention of infection. (C)

Antibiotic or other therapy is dictated by specific pathogen sensitivity and the focus of infection. Antibiotic prophylaxis and/or IVIG replacement may be considered.[455]

Caspase 8 Deficiency

Summary statement 170. Clinical features of caspase 8 deficiency include failure to thrive, respiratory tract bacterial infections, and viral infections. (C)

Only 2 patients have been described to date.[456] These patients are male and female siblings who presented at 11 and 12 years of age, respectively, with recurrent sinopulmonary bacterial infections, poor growth, lymphadenopathy and splenomegaly, eczema, asthma, and herpesvirus infection.

Summary statement 171. Laboratory features of caspase 8 deficiency include impaired pneumococcal vaccine response and relative CD4 lymphocytopenia. (C)

Immunoglobulin levels are normal in 2 patients with caspase 8 deficiency, although they have poor responses to immunization with pneumococcal vaccine (type not specified) and diminished production of IgG and IgM in vitro after stimulation with pokeweed mitogen or *S aureus* Cowan strain.[456] The percentage of $CD4^+$ T cells is low (approximately 25% of lymphocytes), and the CD4/C8 ratio is 0.5. T cells showed decreased proliferation in vitro with phytohemagglutinin and decreased IL-2 production with anti-CD3

stimulation. NK cells did not respond to anti-CD16 or anti-2B4 stimulation.

Summary statement 172. Management for caspase 8 deficiency is individualized. (D)

No published data exist regarding therapy for these patients. Management is directed toward infectious complications; gammaglobulin replacement is reasonable. Caspase 8 is ubiquitously expressed; thus, one cannot predict that BMT would be curative.

Combined Immunodeficiency of an Unspecified Type

Summary statement 173. Any patient with abnormal serum immunoglobulin levels and/or specific antibody production and evidence of impaired cellular immunity who does not fulfill clinical and laboratory diagnostic criteria for any of the above disorders may be considered to have a CID of an unspecified type. (D)

Clearly, this would be a diagnosis of exclusion and must be conferred ultimately only after careful investigation of all other possibilities. It is extremely important to rule out mild or early forms of known humoral or combined deficiencies to maximize the likelihood of their detection and provide the best opportunities for definitive diagnosis and therapy and accurate genetic counseling.

Summary statement 174. Therapy for unspecified CID must be individualized. (D)

There are no standard recommendations for patients who fall into this category. Therapy must be directed toward established infections, associated diseases (eg, autoimmune disease), and the prevention of those infections for which the patients have shown predilection or for which they are considered to be at risk.

PHAGOCYTIC CELL DISORDERS

Chronic Granulomatous Disease

Summary statement 175. Deep-seated granulomatous infections with bacteria and fungi are characteristic of CGD. (C)

CGD occurs in approximately 1 in 200,000 births in the United States.[9,457] The X-linked form is generally more severe and accounts for approximately 70% of cases, whereas the autosomal recessive forms make up the remainder (Table 2). Disease onset is usually in infancy. Granulomatous abscesses occur in the lungs (79% of patients), lymph nodes (53%), skin (42%), liver (27%), and bones (25%).[9] Sepsis occurs in 18% of patients. The principal bacterial pathogens are *S aureus*, *Salmonella*, *Klebsiella*, *Aerobacter*, *Serratia*, and *Burkholderia*. Infection with *Aspergillus fumigatus* occurs in most patients; *Candida albicans* is another prominent fungal pathogen.[9,457,458] A colitis similar to Crohn disease occurs in approximately 17% of patients. Granulomatous inflammation may lead to obstruction of the stomach, ureter, or esophagus in some patients. Physical examination may reveal growth failure, evidence of abscesses or other infection in any region, or lymphadenopathy and/or organomegaly.

Summary statement 176. The diagnosis of CGD may be established by measurement of phagocyte oxidase activity. (C)

This is readily accomplished by a variety of methods. The nitroblue tetrazolium test, the chemiluminescence assay, and the dihydrorhodamine reduction assay are the most widely applied. The nitroblue tetrazolium test is scored visually and comparison made to a control. Dihydrorhodamine reduction is a quantitative flow cytometric assay.[54,459] Both may also be used for determination of carrier status of X-linked CGD in female relatives, although interpretation of the dihydrorhodamine assay may be more straightforward for this purpose.[457]

Summary statement 177. Antimicrobial agents and IFN-γ reduce the rate of infections in patients with CGD. (A)

Therapy for phagocytic defects is aimed at preventing recurrent infections and reducing morbidity and mortality from these infections through aggressive treatment. Careful personal hygiene is generally considered to be an important adjunct for the prevention of infection in CGD and other phagocyte defects. Prophylactic treatment with trimethoprim-sulfamethoxazole, 5 mg/kg divided into twice-daily dosages, has been shown to reduce the rate of severe bacterial infections in patients with CGD by 50%.[9,460] Prophylactic treatment with itraconazole (100 mg/d up to 50 kg of body weight, 200 mg/d thereafter) reduces the rate of infections with *Aspergillus*.[461] Prophylactic IFN-γ, 50 μg/m^2 administered subcutaneously 3 times per week, reduces severe infections in both X-linked and autosomal recessive CGD.[462–464]

Summary statement 178. Granulocyte transfusions may be indicated for the treatment of infections in patients with CGD. (C)

Granulocyte transfusions may be used for treatment of life-threatening infections or those refractory to other medical and surgical treatments. Adverse effects are frequent and limit the usefulness of this therapy.[465]

Summary statement 179. In patients with CGD, aggressive surgical debridement is indicated for abscesses unresponsive to medical therapy. (C)

Many deep-seated granulomatous infections in patients with CGD do not respond readily to intravenous antibiotic therapy, even with granulocyte transfusions. If there is not a prompt clinical response to medical therapy, aggressive surgical debridement is necessary.[464,466]

Summary statement 180. CGD may be cured by BMT. (C)

CGD has been successfully treated with BMT. Long-term survival using HLA-identical sibling donors is approximately 80%.[467] BMT should be considered for patients with recurrent, severe infections despite supportive treatment and those who have HLA-matched siblings.[94,464]

Chediak-Higashi Syndrome

Summary statement 181. Partial oculocutaneous albinism and neurologic symptoms are characteristic of CHS. (C)

The infections of CHS are pyogenic and affect mainly the skin, respiratory tract, and, occasionally, other organs. Pa-

tients with CHS also exhibit partial oculocutaneous albinism and pleomorphic neurologic manifestations, which may include cognitive impairment, photophobia, and nystagmus, as well as cerebellar, spinal, and peripheral neuropathies.[468,469]

Summary statement 182. Giant azurophil granules are characteristic of neutrophils in CHS. (C)

Patients with features of a neutrophil defect plus oculocutaneous albinism or lymphoproliferative disease require a microscopic examination of peripheral blood neutrophils to demonstrate the presence of giant azurophilic granules, diagnostic of CHS.[468]

Summary statement 183. Virtually all patients with CHS who do not die of infection eventually develop a lymphoproliferative disorder known as the accelerated phase. (C)

In the so-called accelerated phase, there is proliferation of T cells and massive infiltration of lymphoid compartments, causing lymphadenopathy, hepatosplenomegaly, and bone marrow failure. Without aggressive treatment, it is usually fatal.[468–470]

Summary statement 184. The accelerated phase may be treated with high-dose glucocorticosteroids and chemotherapeutic agents. (C)

Chemotherapy and high-dose methylprednisolone can be of use in treating the accelerated phase of CHS. However, relapses are frequent.[470]

Summary statement 185. BMT is curative for CHS, even in the accelerated phase. (C)

Allogeneic BMT is the only curative therapy for the accelerated phase and the immunologic defect in CHS. The oculocutaneous albinism and neurologic manifestations associated with CHS are not corrected by BMT.[104]

Griscelli Syndrome

Summary statement 186. Clinical manifestations of GS include pigmentary dilution, neurologic abnormalities, pyogenic infections, and a hemophagocytic syndrome. (C)

The pigmentary changes in GS involve the hair (large melanin clumps in the shaft) and skin (retention of melanosomes in melanocytes).[471,472] These changes are diagnostic in association with the other manifestations of this group of diseases. The neurologic symptoms include seizures, ataxia, and oculomotor and reflex abnormalities. Infections are not consistent in all individuals but are mainly pyogenic bacterial infections that involve the respiratory tract, skin, or other organs. Hepatosplenomegaly is frequent at presentation. Almost all patients eventually develop an accelerated phase of lymphoproliferation and hemophagocytosis, which is often fatal (similar to CHS). This is the most common clinical presentation of GS.[471,472] The pigmentary changes are present from birth. Infections, neurologic symptoms, and hepatosplenomegaly generally begin in infancy. The accelerated phase usually occurs in infancy or childhood. Infrequently, it may be delayed until the second decade of life.

The full clinical spectrum of GS is associated with mutations in the *RAB27A* gene.[472] This has been called GS2.[473] A form of GS with pigmentary change and neurologic disease without immunodeficiency or accelerated phase is associated with mutations of *MYO5A* (GS1).[472,473] A third form of GS (GS3) with only hair and skin pigment changes is associated with mutations of melanophilin (*MLPH*).[473]

Hermansky-Pudlak syndrome denotes a group of diseases whose principal clinical manifestations are oculocutaneous albinism and severe thrombasthenia. Seven distinct gene defects have been described.[474,475] All lead to abnormalities of cellular granules somewhat similar to those of CHS and GS. Patients with Hermansky-Pudlak syndrome type 2 (mutations of the β1 subunit of the adaptor protein complex 3) may present with mild immunodeficiency. Abnormalities of cytotoxic T-cell function in vitro have been described in some of these patients as well.

Summary statement 187. Most patients with GS have normal results on screening tests of immunodeficiency. (C)

Laboratory immunologic abnormalities are variable and not always seen in these patients.[471,472] Reported defects have included hypogammaglobulinemia, impaired delayed cutaneous hypersensitivity to recall antigens, impaired NK cell cytotoxicity, and neutropenia. Some patients have decreased in vitro T-cell responses to mitogens and antigens. Immunologic abnormalities may be more pronounced during the accelerated phase.

Summary statement 188. The accelerated phase of GS should be treated with chemotherapy. (C)

The accelerated phase of GS is fatal without cytotoxic chemotherapy.[472] The HLH-94 protocol may be used but is not curative.[476]

Summary statement 189. GS is curable by BMT. (C)

BMT offers the only hope for long-term survival for GS patients.[472,476,477]

LAD Types I and II

Summary statement 190. Patients with LAD type I or II present with cellulitis, abscesses, and bacterial and fungal respiratory tract infections. (C)

Patients with LAD type I are severely affected early in life with infectious complications characteristic of neutropenia. Patients with LAD type II principally have pulmonary infections and chronic severe periodontitis.[478,479]

Summary statement 191. Delayed separation of the umbilical cord may be seen in LAD type I. (C)

Delayed cord separation may occur in healthy infants. In patients with LAD type I, this finding is often accompanied by acute omphalitis. After 4 weeks with no evidence of even the beginning of cord separation from the umbilicus, an evaluation for LAD may be considered. This is best done initially with a complete blood cell count with differential. Delayed umbilical cord separation is not a feature of LAD type II.[479]

Summary statement 192. A partial or moderate form of LAD type I has a milder clinical course. (C)

These patients have poor wound healing and severe periodontitis. Other pyogenic infections are not as severe as in the

classic form, and patients may not have their conditions diagnosed until childhood or later.[480–482]

Summary statement 193. Characteristic facies, growth and developmental delay, and mental retardation are seen in LAD type II. (C)

The facies of LAD type II consist of coarse facial appearance with puffy eyelids, brachycephaly, broad nasal tip, long upper lip, an everted lower lip, low hair line, and a short, webbed neck.[483] Reduced growth and cognitive impairment are pronounced.

Summary statement 194. Significant neutrophilia is almost always present in patients with LAD. (C)

Neutrophil counts are elevated above normal even in the absence of infection in most patients with LAD, and a complete blood cell count with differential is an appropriate screening test.[478,479,483] When bacterial infection is present, neutrophil counts may rise as high as 100,000 cells/mm^3. These patients are sometimes thought to have myelogenous leukemia or leukemoid reactions.

Summary statement 195. LAD types I and II may be diagnosed by flow cytometric measurement of relevant phagocyte surface molecules. (C)

Patients with neutrophilia and recurrent infections along with the absence of pus formation should be tested for defects in leukocyte adhesion by measurement of CD18 or sialyl Lewis X proteins on the neutrophil surface. Absence or decreased expression of CD18 and inability to up-regulate CD18 on the neutrophil cell surface following phorbol myristate acetate or f-Met-Leu-Phe stimulation is usually diagnostic for LAD type I.[478,479,483–485] Patients with the severe or classic form have 1% or less cell surface CD18 expression. Patients with the milder variant have 1% to 30% normal levels of surface CD18. Patients with LAD type I with normal (or near-normal) levels of expression of nonfunctional CD18 have been described.[485–487] Genetic analysis is necessary for diagnosis in this situation. The absence of sialyl Lewis X proteins (CD15s) is diagnostic of LAD type II.[485]

Summary statement 196. Therapy for LAD types I and II is supportive and dictated by aggressive prevention and management of infections. (C)

Supportive treatment for LAD type I consists of prompt use of antibiotics for infection and surgical debridement of wounds. Granulocyte transfusions may be useful to treat infections otherwise unresponsive to therapy. Consideration may be given to the use of antibacterial and/or antifungal prophylactic treatment. The same general approach is true for other neutrophil defects that may or may not be amenable to BMT or even when the genetic defect is unknown.[478,479,483]

Summary statement 197. Fucose supplementation may ameliorate the course of LAD type II. (C)

Oral fucose supplementation can induce expression of fucosylated selectin ligands on neutrophils, resulting in normalization of neutrophil counts, decreased infections, and improvement in psychomotor abilities in a few patients with LAD type II. Discontinuation of fucose supplements results in a rapid loss of selectin ligands and increases in peripheral neutrophil counts.[488,489]

Summary statement 198. BMT is curative of LAD type I. (C)

BMT is curative for LAD type I and should be considered early in the course of disease for patients with complete LAD type I. Allogeneic BMT leading to a mixed chimeric population of normal and LAD type I myeloid stem cells can achieve a clinical cure.[103,105]

Specific Granule Deficiency

Summary statement 199. The main clinical manifestation of SGD is recurrent bacterial infections of the skin and respiratory tract. (C)

Only 5 patients have been described to date. Skin infections may be indolent, and severe infections with abscess formation may also affect lungs, lymph nodes, ears, and mastoids. Pathogens include *S aureus, Pseudomonas*, and *Candida*. Mutations in the C/EBPε transcription factor have been identified in 2 patients.[466,490,491]

Summary statement 200. Microscopic examination of stained neutrophils can establish the diagnosis of SGD. (C)

Laboratory abnormalities in SGD include impaired chemotaxis and bacterial killing. These findings are nonspecific. In SGD, the neutrophils have abnormal, bilobed, or clefted nuclei.[466,490,491] The specific granules are devoid of most of their contents and are not visible after Wright staining.

Summary statement 201. Management of SGD is supportive. (C)

See summary statement 196.

Cyclic or Chronic (Kostmann Syndrome) Neutropenia and X-linked Neutropenia

Summary statement 202. The clinical manifestations of neutropenia include bacterial respiratory tract and soft tissue infections, gingivostomatitis, and vaginal or rectal mucosal ulceration. (C)

Infections in neutropenic patients are generally associated with fever and malaise. Pharyngitis with lymphadenopathy is common; pneumonia, mastoiditis, and cellulitis also occur. Periodontitis may accompany oral ulceration and gingivitis; vaginal and rectal mucosal ulcers are also seen. The severity of the infectious complications tends to parallel the severity of the neutropenia.[491–493]

Summary statement 203. Serial measurements of neutrophil counts are necessary to distinguish persistent from cyclic neutropenia. (C)

Patients with a decreased neutrophil count should have serial measurements of neutrophils to distinguish among cyclic neutropenia (elastase 2 defect),[492] congenital agranulocytosis (Kostmann syndrome, only a subset associated with elastase 2 mutation),[493] and the rare WAS variant X-linked neutropenia due to *WASP* mutation.[494] Complete blood cell counts should be obtained 2 or 3 times weekly for 6 to 8 weeks. The periodicity of cyclic neutropenia is usually approximately 21 days but may range from 14 to 36 days.[492]

Infections occur only during the nadirs of the neutrophil count. Neutropenia in Kostmann syndrome or due to *WASP* mutation is persistent.[493,494]

Summary statement 204. G-CSF may increase neutrophil counts. (C)

G-CSF is recommended for all patients with cyclic neutropenia.[491] Approximately 90% of patients with cyclic neutropenia or severe chronic neutropenia (defect known or unknown) will respond to G-CSF with increased neutrophil counts[493] As with other neutrophil defects, preventive and supportive measures are important elements of therapy of neutropenia(see summary statement 196).

Summary statement 205. BMT may be curative for severe chronic neutropenia. (C)

BMT should be considered for patients with severe neutropenia who either do not respond to G-CSF or continue to have severe infections despite increased counts. Success has been reported with both HLA-identical sibling donors[101] and HLA-matched unrelated donors.[102]

Hyper-IgE Syndrome

Summary statement 206. The major clinical manifestations of HIES include recurrent lung and skin infections and chronic dermatitis. (C)

This disorder is often referred to as Job syndrome, a biblical allusion inspired by the prominent skin infections in this disease. Patients with HIES have chronic eczematous dermatitis with frequent superinfection by *S aureus.* [495] Recurrent lung infections with *Staphylococcus* (often with abscess formation) and especially *Aspergillus* are common. These individuals are prone to lung damage, including bronchiectasis and pneumatoceles. Additional clinical manifestations include hyperextensible joints, bone fragility, scoliosis, and delayed shedding of primary teeth due to failure of root resorption. There is often a characteristic facies with coarse and/or asymmetric features. Craniosynostosis may also be seen. This constellation of features is associated with an autosomal dominant pattern of inheritance.

A group of patients with an autosomal recessive form of HIES has recently been described.[496] These patients have clinical features similar to those of the autosomal dominant form. However, they do not have skeletal or dental abnormalities and do not tend to develop pneumatoceles. This group of patients has the additional feature of autoimmune vasculopathy with CNS involvement.

Summary statement 207. Elevated serum IgE level and staphylococcus-binding IgE and eosinophilia are characteristic of HIES. (C)

Serum IgE level ranges from a few thousand to several tens of thousands units per milliliter. *S aureus* binding IgE is often present and is readily measured in an immunoassay.[497,498] These findings are not pathognomonic for HIES; they are also observed in patients with severe atopic dermatitis. More than 90% of patients with HIES also have elevated eosinophil counts.[495] A scoring system based on clinical and laboratory criteria for establishing a diagnosis of HIES has been published.[499]

Summary statement 208. The initial approach to therapy of HIES is directed toward management of its characteristic complications. (C)

Aggressive and prophylactic antibiotic therapy is indicated. Antifungal prophylaxis may be considered. The possibility of fracture should be considered even with relatively minor trauma. Children should be monitored carefully for scoliosis, and retained primary teeth should be extracted[495] (see summary statements 179 and 196).

Summary statement 209. The use of IVIG or interferon gamma in HIES is controversial. (C)

A least one series has failed to demonstrate improvement in immunologic function in HIES with IVIG therapy,[500] whereas another has reported clinical improvement with high-dose IVIG.[501] There are scarce reports of improvement of clinical and laboratory indicators with administration of IFN-γ.[502,503] However, evidence is not sufficient to consider this to be standard therapy for HIES.

Summary statement 210. BMT is not curative of HIES. (C)

The immune defects in HIES reappear after BMT.[504] Note that the phenotype of this patient was consistent with the autosomal dominant form of HIES described above.

Neutrophil or Phagocytic Cell Defect, Unspecified

Summary statement 211. Any patient with recurrent infections and a demonstrable isolated defect of phagocytic cell function who does not have any of the disorders above should be considered to have an unspecified phagocytic cell defect. (D)

It is assumed that defects of specific immunity and complement have been ruled out. Some patients may have recurrent infections characteristic of phagocytic cell defects, along with diminished neutrophil number or function (chemotaxis, diapedesis, phagocytosis, respiratory burst, microbial killing, or a combination of these) but not have any of the known genetically determined defects described above. These patients should be considered to have an unspecified phagocytic cell defect.

Summary statement 212. Therapy for unspecified phagocytic cell dysfunction must be individualized. (D)

See summary statements 179 and 196.

COMPLEMENT DEFICIENCIES

Summary statement 213. Total deficiencies of a complement protein are rare. (C)

Many of the specific complement protein deficiencies have only been seen in a handful of cases; however, this is not true of the relatively more common deficiencies of MBL, C2, and C9. The C9 deficiency is common in some Japanese populations. The complement deficiencies are usually inherited as autosomal recessive traits. The genes for all complement proteins, except properdin, are autosomal. The estimated prevalence of a complete complement component deficiency

is 0.03%.[13] The reason for the rarity of complement deficiency is unclear.[505]

Hereditary angioedema is due to defects of the complement protein C1 esterase inhibitor. Although this is technically a complement deficiency, the clinical phenotype does not include predisposition to infection or autoimmune disease. This entity will not be discussed here (see Practice Parameter for the Diagnosis and Management of Urticaria and Angioedema).

Summary statement 214. Usually, hypocomplementemia results from complement component consumption caused by activation, as may occur in autoimmune disease or during infection. (C)

Complement levels may be low in autoimmune diseases, such as systemic lupus erythematosus,[506] rheumatoid arthritis,[507] or some vasculitides,[508] since complement is frequently activated and consumed during these antibody-mediated inflammatory processes. Antibody formation during acute infection can create immune complexes that may deposit in the kidney and result in complement consumption with glomerulonephritis, examples include poststreptococcal glomerulonephritis,[43,509] bacterial endocarditis with glomerulonephritis,[510] or even viral infections such as with parvovirus B19, which may be associated with glomerulonephritis.[511] Reduced levels of C4 and C3 (as occurs in systemic lupus erythematosus) generally imply classical pathway activation. Low levels of properdin or factor B and C3 point to activation of the alternative pathway as seen in diseases such as poststreptococcal glomerulonephritis.

Summary statement 215. In general, absence of a component of the classical pathway of complement is associated with autoimmunity or frequent infection. (C)

Table 7 shows the major clinical associations with specific complement proteins. Selective complete deficiencies of classical pathway components are also associated with autoimmune disease (Table 7). Partial deficiencies of C2 and C4 are found in individuals with null alleles of C2, C4A, or C4B. Some patients with C2 deficiency present with recurrent respiratory tract bacterial infections, resembling patients with antibody deficiencies.[13] A higher prevalence of autoimmune disease resembling systemic lupus erythematosus is seen in C2- and C4-deficient individuals as well.[509,512]

Summary statement 216. Defects of the MBL and the alternative complement activation pathways may be associated with increased susceptibility to bacterial infections. (C)

Defects of MBL are inherited as an autosomal recessive trait, but due to structural features of the protein, heterozygous individuals with certain amino acid substitutions, as well as homozygous deficient individuals, have abnormally low MBL levels.[509,512,513] Homozygous MBL deficiency may be found in as many as 3% of individuals. Some of these individuals may be at increased risk of infection, particularly as infants. Lupus-like autoimmune disease may also be seen. One recent study found an approximately 2-fold higher rate of low serum MBL level in children with a history of recurrent respiratory tract bacterial infections. The association was strongest in a subgroup with a variety of abnormalities of immunoglobulin classes or subclasses.[513] The clinical significance of low serum MBL requires further clarification. The rare individuals with alternative pathway complement defects may also be at risk for infection.[13,509]

Summary statement 217. C3 deficiency is associated with high susceptibility to bacterial infections. (C)

Since all pathways of complement activation converge on C3, C3-deficient individuals are at greatest risk for infection. These patients may appear similar to those with severe antibody deficiencies or defects of phagocyte function.[13,32,509,512,514,515]

Summary statement 218. Terminal pathway complement deficiencies are associated with susceptibility to neisserial infections. (C)

Increased susceptibility to infections with *Neisseria meningitidis* and *Neisseria gonorrhoeae* is seen in individuals with deficiencies of C5 to C9.[13,509,514] This has also been described in association with deficiency of the alternative pathway component properdin.

Summary statement 219. A patient with factor I deficiency may present with frequent infections and urticaria. (C)

Factor I deficiency is inherited as an autosomal recessive trait. In the absence of factor I, the alternative pathway is continually activated. Plasma C3 is depleted, leading to propensity toward infection. Anaphylatoxins are generated by complement activation, leading to urticaria.[509]

Summary statement 220. Some patients with hemolytic uremic syndrome have abnormalities of the complement regulatory protein factor H. (C)

Factor H deficiency is inherited as an autosomal recessive trait. A number of patients with the inherited form of hemolytic uremic syndrome have deficiency of factor H.[516,517]

Summary statement 221. Deficiencies of classical and terminal pathway complement components can be detected with a laboratory test (CH_{50}). (C)

Patients with recurrent pyogenic infections and normal humoral immunity should be studied for complement deficiency. The CH_{50} measures the lysis of antibody-sensitized sheep erythrocytes by fresh serum. The result is expressed as the reciprocal of the dilution that yields 50% red cell lysis. Reference ranges are determined for each laboratory. Since most of the complement deficiencies are inherited as autosomal recessive genes and since heterozygotes are usually normal clinically, one can make the diagnosis of most of the significant defects by determining whether the patient's CH_{50} is 0, that is, there is no lysis of the red cells. If it is 0 or below the level of detection of the reporting laboratory, this suggests a defect of a classical or terminal pathway component, and levels of individual proteins may be tested separately.[13,43] Complement component levels are measured by standard nephelometric or ELISA techniques. Individual component function may be determined by complementation of control serum that has been selectively depleted of one component. Occasionally, complement component deficiency must be distinguished from complement consumption as may occur during infection or autoimmune disease. This can be evalu-

ated by determining reduction in the level or activity of 2 or more individual components (eg, C2, C4, C3).

Summary statement 222. Alternative pathway complement function is measured by the AH_{50}. (C)

The AH_{50} measures the function of the alternative pathway of complement activation. A calcium chelator is added to serum to inactivate the classical pathway of activation. Unsensitized red blood cells may then be lysed via alternative pathway complement attack (the alternative pathway does not require IgG for activation). A very low level suggests an alternative pathway defect.[13,43]

Summary statement 223. Immunization and antibiotic therapy are the major modes of treatment for complement deficiencies associated with recurrent infections. (C)

Individuals with complement deficiencies require immunization with the relevant vaccines available. Long-term antibiotic therapy is required in some individuals with frequent infection but is usually not needed.[509]

Summary statement 224. Anti-inflammatory therapies are indicated for treatment of autoimmune disease associated with complement deficiency. (C)

The autoimmune diseases that arise in patients with complement deficiency are treated by the appropriate respective therapy. There is currently no available gene therapy, and in most situations treatment by supplying the missing complement protein is not appropriate.[509]

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Requests for reprints should be addressed to:
Joint Council of Allergy, Asthma and Immunology
50 N Brockway St
#3-3
Palatine, IL 60067

Appendix. Prescribing Information and Guidelines for Administration of Immunoglobulin Replacement Therapy for Primary Immunodeficiency Diseases

I. Indications

Immunoglobulin replacement is indicated for all patients with the following diagnoses. Therapy should be continued indefinitely or until definitive correction of the underlying disorder (by bone marrow transplantation, for example).

A. Severe combined immunodeficiency
B. X-linked or autosomal recessive agammaglobulinemia
C. Common variable immunodeficiency
D. Other combined immunodeficiencies with a significant hypogammaglobulinemia or antibody production defect including but not limited to the following:
   1. Wiskott-Aldrich syndrome
   2. CD40 ligand deficiency (X-linked hyper-IgM syndrome)
   3. Nuclear factor of κB essential modifier deficiency
   4. Ataxia-telangiectasia
   5. DiGeorge syndrome

Immunoglobulin may be considered under rare circumstances for patients with recurrent infections and carrying 1 of the following diagnoses (see summary statement 22).

A. IgG subclass deficiency
B. IgA deficiency
C. Specific antibody deficiency
D. Transient hypogammaglobulinemia of infancy
E. Unspecified hypogammaglobulinemia

II. Products

Product choice is often determined by availability. The physician may choose among available products at his/her discretion. Currently, no evidence exists that any product is clearly superior with respect to efficacy, safety, or tolerability as replacement therapy for immunodeficiency. Some products are available as both 5% and 10% solutions. The choice of concentration is sometimes determined by availability and on occasion by the patient's history of tolerance of immunoglobulin or a specific product. Table 8 lists some characteristics of gammaglobulin products licensed by the Food and Drug Administration in the United States.

Table 8. Characteristics of Gammaglobulin Preparations Licensed in the United States

Name	Preparation*	Form	Stabilizer
Carimune	Acid/pepsin, nanofiltration	Lyophilized, 3%, 6%, 9%, 12%	Sucrose
Flebogamma	Pasteurization, PEG precipitation	Liquid, 5%	Sorbitol
Gamimune-N, 5%	Diafiltration, pH 4.0, solvent/detergent	Liquid, 5%	Maltose
Gamimune-N, 10%	Diafiltration, pH 4.0, solvent/detergent	Liquid, 10%	Glycine
Gammagard	Ultrafiltration, ion-exchange chromatography, solvent/detergent	Lyophilized 5%, 10%	Albumin, glycine, glucose, PEG
Gammar-P I.V.	Pasteurization ultrafiltration	Lyophilized, 5%	Albumin sucrose
Gamunex	Caprylate precipitation, ion exchange chromatography	Liquid, 10%	Glycine
IVEEGAM-EN	Trypsin, PEG precipitation	Lyophilized, 5%	Glucose
OCTAGAM	Ultrafiltration, ion exchange chromatography, solvent/detergent	Liquid, 5%	Maltose
Panglobulin	Ultrafiltration	Lyophilized, 3%, 6%, 9%, 12%	Sucrose
Polygam S/D	Ultrafiltration ion exchange chromatography solvent/detergent	Lyophilized, 5%, 10%	Albumin, glycine, glucose, PEG
Venoglobulin-S	Ion exchange chromatography, PEG/bentonite precipitation, solvent/detergent	Lyophilized 5%, 10%	Sorbitol

Abbreviation: PEG, polyethylene glycol.
*All preparations begin with cold ethanol fractionation.

Appendix. Continued

III. Route of administration

Immunoglobulin may be administered intravenously (IVIG) or subcutaneously (SCIG). IVIG therapy is generally available in hospitals, many secondary health care settings, and many home care nursing agencies. SCIG is not yet widely available, although popularity is growing.

Based on the published data to date, IVIG and SCIG are considered generally equivalent with respect to safety and efficacy.[367,518,519] For standard replacement dosing, subcutaneous and intravenous replacement administration results in roughly equivalent trough IgG concentrations (over time). Clinical circumstances may necessitate maintaining higher trough levels, which may require intravenous therapy. The occurrence of acute and delayed adverse effects with SCIG may be less than with IVIG; the occurrence of acute or delayed local effects may be greater with SCIG than with IVIG. SCIG may be given to individuals who lack convenient venous access. The placement of central venous access devices for the sole purpose of administering IVIG should be discouraged. The choice between IVIG and SCIG routes of administration may be influenced by the following:

A. Patient preference
B. Problems with intravenous access
C. Systemic adverse effects with intravenous administration
D. Trough IgG levels
E. Physician preference

IV. Prescribing

The following must be specified when ordering immunoglobulin replacement:

A. Product
B. Dose (grams)
C. Route of administration (intravenous vs subcutaneous)
D. Premedication (if any)
E. Dosage interval (days or weeks)

Dosing guidelines:

1. IVIG[5,63–66,71,72,119,120,366,520]
   a. For agammaglobulinemia or severe hypogammaglobulinemia, consider a loading dose of 1 g/kg of body mass intravenously.
   b. To start, 300 to 400 mg/kg every 3 weeks or 400 to 500 mg/kg every 4 weeks.
   c. Maximum dose is generally 600 mg/kg every 3 weeks or 800 mg/kg every 4 weeks.
   d. Dose interval may be reduced as necessary, generally not less than 2 weeks except under unusual circumstances. Extending the interval beyond 4 weeks is not recommended.
   e. Depending on the product dosage form and the size of the patient, an attempt should be made to round doses to the nearest unit dose to avoid waste of immunoglobulin.
2. SCIG[84,367,518,519,521.522]

Note that Baygam (16% solution) is suitable for subcutaneous administration. Some standard IVIG products are available as 10% to 12% solutions that are packaged in powder form and some may be reconstituted at 15% for subcutaneous administration, although experience is limited. Standard 10% solutions formulated for intravenous use may also be given subcutaneously. Note that published data regarding safety, efficacy, and tolerability do not exist for all gammaglobulin products with respect to administration by the subcutaneous route.

   a. For agammaglobulinemia or severe hypogammaglobulinemia, consider a loading dose of 1 gm/kg intravenously.
   b. To start, 100 mg/kg every week or 50 mg/kg twice per week.
   c. Maximum dose is 200 mg/kg every week or 100 mg/kg twice per week.
   d. Dose interval may be reduced as necessary, generally not less than twice per week except under unusual circumstances. Extending the interval beyond 2 weeks is not recommended.
   e. Depending on the product and the size of the patient, an attempt should be made to round doses to the nearest unit dose to avoid waste of immunoglobulin.

V. Premedication

Premedication is not required for all patients. The decision to prescribe premedication may be based on the following:

A. Patient preference
B. Route of administration
C. History of adverse effects with immunoglobulin administration
D. Physician preference

Typical premedications are listed below. Medications may be used alone or in combination. Additional medications in these classes may be considered at physician and patient discretion. Steroids should only be used if antihistamines and nonsteroidal anti-inflammatory drugs (NSAIDs) in combination fail to control adverse effects.

1. Antihistamines
   a. Diphenydramine (Benadryl), 1 mg/kg, 25 to 50 mg maximum
   b. Hydroxyzine (Atarax), 0.6 mg/kg, 25 to 50 mg maximum
   c. Cyproheptadine (Periactin) 1 mg, 2 mg, or 4 mg (maximum)
2. NSAIDs
   a. Acetaminophen (Tylenol), 10 to 15 mg/kg, 1,000 mg maximum
   b. Ibuprofen (Motrin, Advil), 10 mg/kg, 400 to 600 mg maximum

Appendix. Continued

3. Corticosteroids
   a. Prednisone or prednisolone 1 to 2 mg/kg orally, 40 to 80 mg maximum
   b. Solu-medrol, 1 to 2 mg/kg intravenously, 40–80 mg maximum
   c. Hydrocortisone, 10 mg/kg intravenously, 500 mg maximum
   d. Decadron, 0.1–0.5 mg/kg intravenously, 9 mg maximum

VI. Adverse Reactions

A. Acute adverse reactions (during infusion)
   1. Mild: headache, malaise, fatigue, flushing, pruritus. Intervention: slow infusion, consider antihistamines and NSAIDs as above.
   2. Moderate: severe headache, dizziness or nausea, vomiting, myalgia, arthralgia, back pain, urticaria. Intervention: stop infusion and administer antihistamines and NSAIDs as above. Consider steroids.
   3. Severe: altered mental status, hypotension, bronchospasm, anaphylaxis. Intervention: stop infusion and administer epinephrine, antihistamines, steroids, and supportive care or resuscitation as necessitated by the patient's condition.

B. Delayed adverse reactions (within 72 hours of administration)
   1. Mild: headache, malaise, fatigue, flushing, pruritus. Intervention: give antihistamines and NSAIDs as above until symptoms subside.
   2. Moderate to severe: severe headache, dizziness or nausea, vomiting, myalgia, arthralgia, back pain, urticaria, aseptic meningitis syndrome. Intervention: administer antihistamines and NSAIDs as above until symptoms subside. Consider antimigraine medications such as sumatriptan.[523] Consider steroids.

For patients experiencing adverse reactions, subsequent infusions may be administered differently. Premedication may be initiated, doses increased, or medications added. Infusions may be given more slowly. Doses may be reduced (this may necessitate decreasing the dosing interval). An alternative gammaglobulin product or route of administration may be considered. Acute adverse effects may be more frequent when patients change to a gammaglobulin product with a different formulation.[524] Some patients with CVID and absent serum IgA have measurable anti-IgA antibodies in serum. If IVIG is used, some recommend use of a preparation with low IgA concentrations to decrease the risk of adverse reactions.[189] However, the magnitude of this risk (ie, the rate of adverse reactions of this type) is unknown, and recommendations in this regard are not uniform.[525,526] Many centers do not routinely screen for anti-IgA antibodies. Severe acute reactions are rare; in one 2-year study, there were no life-threatening adverse reactions documented in 13,508 infusions.[527]

VI. Monitoring

For patients with severe hypogammaglobulinemia or agammaglobulinemia, trough IgG levels should be maintained at least at 500 to 600 mg/dL. At least one study indicates that maintaining trough levels at greater than 700 mg/dL further reduces occurrence of infections.[120] Levels should be checked every 3 to 6 months in growing children and every 6 to 12 months in adults. There are no uniform guidelines for screening with respect to diseases potentially transmissible by blood products. Measurement of serum transaminase levels every 3 to 6 months is routine in many centers. Patients receiving products stabilized with sucrose should have serum creatinine monitored every 3 to 6 months due to possible renal adverse effects with these preparations.[528,529] Some suggest that renal function should be monitored in all patients, since nephrotoxicity has been observed in some patients treated with IVIG products that did not contain sucrose.[530]