Practice parameter

Practice parameter for the diagnosis and management of primary immunodeficiency

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The American Academy of Allergy, Asthma & Immunology (AAAAI) and the American College of Allergy, Asthma & 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 directed to the Executive Offices of the AAAAI, the ACAAI, and the Joint Council of Allergy, Asthma & Immunology. These parameters are not designed for use by pharmaceutical companies in drug promotion. (J Allergy Clin Immunol 2015;■■■:■■■-■■■.)

Previously published practice parameters of the Joint Task Force on Practice Parameters for Allergy & Immunology are available at http://www.JCAAI.org or http://www.allergyparameters.org.

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The Joint Task Force has made a concerted effort to acknowledge all contributors to this parameter. If any contributors have been excluded inadvertently, the Task Force will ensure that appropriate recognition of such contributions is made subsequently.

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CLASSIFICATION OF RECOMMENDATIONS AND EVIDENCE

Classification of recommendations and evidence are listed in Table I.

SUMMARY OF CONFLICT OF INTEREST DISCLOSURES

The following is a summary of interests disclosed on workgroup members' conflict of interest disclosure statements (not including information concerning family member interests). Completed conflict of interest disclosure statements are available on request.

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Abbreviations used

AAAAI: American Academy of Allergy, Asthma & Immunology
ACAAI: American College of Allergy, Asthma & Immunology
HSCT: Hematopoietic stem cell therapy
JCAAI: Joint Council of Allergy, Asthma & Immunology
PIDD: Primary immunodeficiency disease
SCID: Severe combined immunodeficiency
SS: Summary statement

RESOLUTION OF NONDISQUALIFYING INTERESTS

The Joint Task Force recognizes that experts in a field are likely to have interests that could come into conflict with the development of a completely unbiased and objective practice parameter. To take advantage of that expertise, a process has been developed to prevent potential conflicts from influencing the final document in a negative way.

At the workgroup level, members who have a potential conflict of interest either do not participate in discussions concerning topics related to the potential conflict or, if they do write a section on that topic, the workgroup completely rewrites it without their involvement to remove potential bias. In addition, the entire document is then reviewed by the Joint Task Force, and any apparent bias is removed at that level. Finally, the practice parameter is sent for review both by invited reviewers and by anyone with an interest in the topic by posting the document on the Web sites of the ACAAI and the AAAAI.

PROTOCOL FOR FINDING EVIDENCE

A search of the medical literature on PubMed was performed for a variety of terms that were considered relevant to this practice parameter. All reference types were included in the results. References identified as being relevant were searched for other relevant references. Published clinical studies were rated by category of evidence and used to establish the strength of the recommendations. The parameter was subsequently appraised by reviewers designated by the AAAAI and ACAAI. Based on this process, this parameter represents an evidence-based and broadly accepted consensus document.

PREFACE

The purpose of this "Practice parameter for the diagnosis and management of primary immunodeficiency" is to provide the consultant allergist/immunologist or other practitioner with a practical guide for the clinical recognition and diagnosis of immunodeficiency, along with the general principles that guide management of these disorders. This document was developed by a working group under the aegis of the 3 national allergy and immunology societies: the American Academy of Allergy, Asthma & Immunology (AAAAI); the American College of Allergy, Asthma & Immunology (ACAAI); and the Joint Council of Allergy, Asthma & Immunology (JCAAI). The Joint Task Force on Practice Parameters has published many practice parameters for the field of allergy/immunology. These can be found online at http://www.jcaai.org/resources/practice-paramenters/ (note that login with JCAAI membership ID and password is required for access).

The first "Practice parameter for the diagnosis and management of primary immunodeficiency" was published in 1995.[1] It was completely rewritten and updated in 2005[2] and has been brought up to date once again now. The classification of the immune deficiency disorders described herein now follows the system developed by the World Health Organization (WHO) and International Union of Immunological Societies (IUIS).[3]

This parameter was developed by a working group made up of clinical immunologists specializing in immunodeficiency. A workgroup chaired by Dr Francisco A. Bonilla prepared the initial draft, which was subsequently reviewed by the Joint Task Force. The working draft of "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 here was approved by the sponsoring organizations and represents an evidence-based and broadly accepted 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 (PIDDs). Preparation of this parameter included a review of the medical literature, mainly through 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 I).[4] There are few randomized trials in the diagnosis and management of primary immunodeficiency. Thus the great majority of these recommendations represent evidence from published case series or reports or the opinions of experts in the field.

The pathophysiology of these disorders will not be discussed in detail; ample material can be found in the literature cited. The parameter consists of 239 summary statements (SSs). Each SS is formulated in a directive manner and contains a specific

TABLE I. Classification of evidence and recommendations

Recommendation rating scale		
Statement	**Definition**	**Implication**
Strong recommendation (StrRec)	A strong recommendation means the benefits of the recommended approach clearly exceed the harms (or that the harms clearly exceed the benefits in the case of a strong negative recommendation) and that the quality of the supporting evidence is excellent (Grade A or B).* In some clearly identified circumstances, strong recommendations can be made based on lesser evidence when high-quality evidence is impossible to obtain and the anticipated benefits strongly outweigh the harms.	Clinicians should follow a strong recommendation unless a clear and compelling rationale for an alternative approach is present.
Moderate (Mod)	A recommendation means the benefits exceed the harms (or that the harms exceed the benefits in the case of a negative recommendation), but the quality of evidence is not as strong (Grade B or C).* In some clearly identified circumstances, recommendations can be made based on lesser evidence when high-quality evidence is impossible to obtain and the anticipated benefits outweigh the harms.	Clinicians should also generally follow a recommendation but should remain alert to new information and sensitive to patient preferences.
Weak	A weak recommendation means that either the quality of evidence that exists is suspect (Grade D)* or that well-done studies (Grade A, B, or C)* show little clear advantage to one approach versus another.	Clinicians should be flexible in their decision making regarding appropriate practice, although they can set bounds on alternatives; patient preference should have a substantial influencing role.
No recommendation (NoRec)	No recommendation means there is both a lack of pertinent evidence (Grade D) and an unclear balance between benefits and harms.	Clinicians should have little constraint in their decision making and be alert to new published evidence that clarifies the balance of benefit versus harm; patient preference should have a substantial influencing role.
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 quasiexperimental 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, 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,[4] with permission.

recommendation for diagnosis or management in general, for a specific disorder, or for a group of disorders. The SSs are annotated to provide a rationale or further elaboration along with literature references. The SSs and references are also "graded" according to the Classification of Recommendations and Evidence (Table I). The SSs are divided into 9 sections. The first section contains general principles of diagnosis and management of PIDDs. The remaining 8 sections provide more detail regarding specific diseases or groups of diseases. In addition to the SSs, the parameter contains annotated algorithms and tables regarding diagnostic principles in various categories of PIDDs.

Although developed principally with the consultant allergist/immunologist as the target audience, it is hoped that the 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 providers and administrators in the managed care or insurance fields might also find useful information here. The developers of this 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 subjects to an increased rate and severity of infection, immune dysregulation with autoimmune disease and aberrant inflammatory responses, and malignancy. Primary immunodeficiencies are distinct from secondary immunodeficiencies that occur, for example, during certain viral

TABLE II. Classification of primary immunodeficiencies*

Defect or disease(s)	Gene(s)
Combined B- and T-cell immunodeficiencies	
T^-B^+ severe CID	
IL-2R common gamma chain	*IL2RG*
Janus kinase 3	*JAK3*
IL-7Rα chain	*IL7RA*
IL-2Rα chain (CD25) deficiency	*IL2RA*
CD45 (protein tyrosine phosphatase, receptor type, C)	*PTPRC*
CD3δ	*CD3D*
CD3ε	*CD3E*
CD3ζ	*CD3Z*
Coronin 1A	*CORO1A*
T^-B^- SCID	
Recombinase activating genes 1 and 2	*RAG1/RAG2*
DNA cross-link repair enzyme 1C (Artemis)	*DCLRE1C*
DNA-dependent protein kinase	*PRKDC*
Adenylate kinase 2 (reticular dysgenesis)	*AK2*
Adenosine deaminase	*ADA*
DNA ligase IV	*LIG4*
Nonhomologous end-joining protein 1 (Cernunnos)	*NHEJ1*
OS	See SS 26
Less severe CID	
Purine nucleoside phosphorylase	*NP*
CD3γ	*CD3G*
CD8α	*CD8A*
ζ-Associated protein 70 kDa (ZAP-70)	*ZAP70*
Calcium channel defects	
Orai-1	*ORAI1*
Stromal interaction molecule 1 (Stim-1)	*STIM1*
Magnesium channel defects	
MAGT1 deficiency	*MAGT1*
MHC class I deficiency	
Transporters of antigenic peptides 1 and 2	*TAP1/TAP2*
TAP binding protein (tapasin)	*TAPBP*
MHC class II deficiency	
CIITA	*MHC2TA*
RFX5	*RFX5*
RFXAP	*RFXAP*
RFXANK	*RFXANK*
Winged helix deficiency (nude)	*FOXN1*
STAT5b	*STAT5B*
Cytidine triphosphate synthase 1	*CTPS1*
HIMs	
TNF superfamily member 5 (CD40L)	*TNFSF5*
TNF receptor superfamily member 5 (CD40)	*TNFRSF5*
RhoH deficiency	*RHOH*
MST1 deficiency	*STK4*
TCRα deficiency	*TRAC*
Lck deficiency	*LCK*
MALT1 deficiency	*MALT1*
IL-21R deficiency	*IL21R*
CARD11 deficiency	*CARD11*
OX40 deficiency	*OX40*
IKBKB deficiency	*IKBKB*
Syndromes with immunodeficiency	
Congenital thrombocytopenias	
WAS	*WAS*

(Continued)

TABLE II. *(Continued)*

Defect or disease(s)	Gene(s)
WAS protein–interacting protein (WIP) deficiency	*WIPF1*
Non-SCID DNA repair defects	
AT	*ATM*
AT-like disorder	*MRE11*
NBS	*NBS1*
Bloom syndrome	*BLM*
MCM4 deficiency	*MCM4*
Immunodeficiency with centromeric instability and facial anomalies (ICF syndrome)	
ICF1 (DNA methyltransferase 3b)	*DNMT3B*
ICF2 (zinc finger and BTB domain containing 24)	*ZBTB24*
PMS2 deficiency	*PMS2*
Radiosensitivity, immunodeficiency, dysmorphic features and learning difficulties (RIDDLE) syndrome	*RNF168*
DGS	*del22q11, del10p13, TBX1*
CHARGE syndrome	*CHD7, SEMA3E*
Trisomy 21 syndrome	
CD4 lymphocytopenia	
Uncoordinated 119 deficiency	*UNC119*
Immuno-osseous dysplasias	
CHH	*RMRP*
Schimke syndrome	*SMARCAL1*
CID with skeletal dysplasia	*PGM3*
Comel-Netherton syndrome	*SPINK5*
HIESs	
Autosomal dominant (type 1, Job syndrome)	*STAT3*
Autosomal recessive (type 2)	*DOCK8*
HIES variant	*TYK2*
HIES variant	*PGM3*
Loeys-Dietz syndrome	*TGFBR1*
SAM syndrome	*DSG1*
Hepatic veno-occlusive disease with immunodeficiency (VODI)	*SP110*
DKC	
X-linked DKC (Hoyeraal-Hreidarsson syndrome)	*DKC1*
Autosomal recessive DKC	*NHP2, NOP10, RTEL1*
Autosomal dominant DKC	*TERC, TERT, TINF2*
Defects of vitamin B12 and folate metabolism	
Transcobalamin II deficiency	*TCN2*
Hereditary folate malabsorption	*SLC46A1*
MTHFD1 deficiency	*MTHFD1*
IKAROS deficiency	*IKZF1*
Facial dysmorphism, immunodeficiency, livedo, and short stature (FILS) syndrome	*POLE1*
Immunodeficiency with MIA	*TTC7A*
Hoffman syndrome	
Sideroblastic anemia with immunodeficiency, fevers, and developmental delay (SIFD)	*TRNT1*
Predominantly antibody deficiencies	
Agammaglobulinemia	
X-linked (Bruton) agammaglobulinemia	*BTK*
μ Heavy chain deficiency	*IGHM*
Ig-α deficiency	*CD79A*
Ig-β deficiency	*CD79B*
Surrogate light chain (λ 5) deficiency	*CD179B*

(Continued)

TABLE II. *(Continued)*

Defect or disease(s)	Gene(s)
B-cell linker protein (BLNK) deficiency	*BLNK*
Leucine-rich repeat containing 8 deficiency	*LRRC8*
Phosphoinositide 3-kinase kinase deficiency	*PIK3R1*
E47 transcription factor deficiency	*TCF3*
Myelodysplasia with hypogammaglobulinemia	Monosomy 7, Trisomy 8
Thymoma with immunodeficiency (Good syndrome)	
CVID	
CVID-like disorders	
Inducible costimulator	*ICOS*
CD19	*CD19*
CD20	*CD20*
CD21	*CD21*
Target of antiproliferative antibody 1 (TAPA-1, CD81)	*CD81*
TACI	*TNFRSF13B*
B-cell activating factor receptor	*TNFRSF13C*
Phosphoinositol 3′ kinase catalytic subunit mutation	*PIK3CD*
Phosphoinositol 3′ kinase regulatory subunit 1 defect	*PIK3R1*
LPS-responsive beige-like anchor protein deficiency	*LRBA*
TWEAK deficiency	*TWEAK*
NF-κB2 deficiency	*NFKB2*
Protein kinase Cδ deficiency	*PRKCD*
Kabuki syndrome	*KMT2D*
SIGAD	
IGGSD	
IgA deficiency with IGGSD	
SAD	
THI	
Hypogammaglobulinemia, unspecified	
Class-switch defects	
AID deficiency	*AICDA*
Uracil-DNA glycosylase (UNG) deficiency	*UNG*
Immunoglobulin gene mutations/deletions	
Heavy chain locus deletions	*IGH*
κ-Chain deficiency	*IGLK*
Diseases of immune dysregulation	
FHL syndromes with hypopigmentation	
CHS	*LYST*
GS2	*RAB27A*
HPS type 2	*AP3B1*
FHL syndromes without hypopigmentation	
FHL1 (Unknown defect)	
Perforin deficiency (FHL2)	*PRF1*
UNC13D/Munc 13-4 deficiency (FHL3)	*UNC13D*
Syntaxin-11 deficiency (FHL4)	*STX11*
STXBP2/Munc 18-2 deficiency (FHL5)	*STXBP2*
Lymphoproliferative syndromes	
XLP1	*SH2D1A*
X-linked lymphoproliferative syndrome type 2	*XIAP*
Lymphoproliferative syndrome 1	*ITK*
Lymphoproliferative syndrome 2	*CD27*
Syndromes with autoimmunity	
ALPSs	

(Continued)

TABLE II. *(Continued)*

Defect or disease(s)	Gene(s)
Fas defect: ALPS-FAS and sFAS (somatic)	*TNFRSF6*
Fas ligand defect: ALPS-FASLG	*TNFSF6*
Caspase 10 defect: ALPS-CASP10	*CASP10*
Unknown defect: ALPS-U	
ALPS-related disorders	
Caspase 8 deficiency syndrome (CEDS)	*CASP8*
K-Ras defect	*KRAS*
N-Ras defect	*NRAS*
Fas-associated via death domain defect (FADD) deficiency	*FADD*
CARD11 gain-of-function mutations	*CARD11*
STAT3 gain-of-function mutations	*STAT3*
APECED	*AIRE*
IPEX syndrome	*FOXP3*
IPEX-like disorders, STAT1/STAT3 gain-of-function mutations	*STAT1/STAT3*
CD25 defect	*IL2RA*
E3 ubiquitin protein ligase defect	*ITCH*
Cytotoxic T lymphocyte–associated protein 4 defect	*CTLA4*
Congenital defects of phagocyte numbers, function, or both	
Defects of neutrophil differentiation	
SCNs	
SCN1 (also cyclic neutropenia), neutrophil elastase defect	*ELANE*
SCN2, growth factor–independent 1 transcription repressor defect	*GFI1*
SCN3, HCLS1-associated protein X-1 defect (Kostmann syndrome)	*HAX1*
SCN4, glucose 6 phosphatase, catalytic, 3 defect	*G6PC3*
SCN5	*VPS45*
X-linked neutropenia/myelodysplasia	*WAS*
Glycogen storage disease type 1b	*SLC37A4*
Late endosomal/lysosomal adaptor, mitogen-activated protein kinase and MTOR activator 2P14 deficiency	*LAMTOR2*
Tafazzin defect (Barth syndrome)	*TAZ*
Cohen syndrome vacuolar protein sorting 13 homolog B	*VPS13B*
Poikiloderma with neutropenia (Clericuzio syndrome)	*C16orf57*
Defects of motility	
LAD	
LAD-I, CD18 (integrin β_2) defect	*ITGB2*
LAD-II, GDP-fucose transporter 1 defect	*FUCT1*
LAD-III, fermitin family member 3	*FERMT3*
Rac-2 defect	*RAC2*
β-Actin defect	*ACTB*
Localized juvenile periodontitis (formyl peptide receptor defect)	*FPR1*
Papillon-Lefevre syndrome (cathepsin C defect)	*CTSC*
SGD (CCAAT/enhancer binding protein [C/EBP], γ defect)	*CEBPG*
Schwachman-Diamond syndrome	*SBDS*
Defects of the respiratory burst	
CGD	

(Continued)

TABLE II. *(Continued)*

Defect or disease(s)	Gene(s)
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*
p40^{phox}	*NCF4*
MSMD	
IL-12/23 receptor β1 deficiency	*IL12RB1*
IL-12 p40 deficiency	*IL12B*
IFN-γ receptor 1 deficiency	*IFNGR1*
IFN-γ receptor 2 deficiency	*IFNGR2*
STAT1 loss of function	*STAT1*
Interferon regulatory factor 8 deficiency	*IRF8*
Macrophage gp91^{phox} deficiency	*CYBB*
ISG15	*ISG15*
PAP	*CSF2RA, CSF2RB*
Defects of innate immunity	
GATA-2 deficiency (MonoMAC syndrome)	*GATA2*
Anhidrotic ectodermal dysplasia with immunodeficiency (EDA-ID)	
X-linked, nuclear factor-κB (NEMO) deficiency	*IKBKG*
Inhibitor of κB α gain of function (EDA-ID, AD)	*IKBA*
TIR signaling pathways	
IL-4 receptor–associated kinase 4 deficiency	*IRAK4*
MyD88 deficiency	*MYD88*
RBCK1 (HOIL1) deficiency	*RBCK1*
Type I interferonopathies	
Aicardi-Goutieres syndrome 1 (AGS1), TREX1 deficiency	*TREX1*
AGS2, RNASEH2B deficiency	*RNASEH2B*
AGS3, RNASEH2C deficiency	*RNASEH2C*
AGS4, RNASEH2A deficiency	*RNASEH2A*
AGS5, SAMHD1 deficiency	*SAMHD1*
AGS6, ADAR1 deficiency	*ADAR1*
SPENCD	*ACP5*
WHIM syndrome, chemokine (C-X-C motif) receptor 4 defect	*CXCR4*
EV	*TMC6, TMC8*
HSE	
Unc-93 homolog B1 *(C elegans)* defect	*UNC93B1*
TANK-binding kinase 1	*TBK1*
TLR adaptor molecule 1	*TICAM1*
TLR 3 defect	*TLR3*
TNF receptor–associated factor 3 defect	*TRAF3*
CMCC	
Caspase recruitment domain family, member 9 defect	*CARD9*
C-type lectin domain family 7, member A defect	*CLEC7A*
IL-17 receptor α chain defect	*IL17RA*
IL-17F defect	*IL17F*
STAT1 gain of function	*STAT1*
ACT1 deficiency	*ACT1*
Susceptibility to trypanosomiasis	*APOL1*
CD16 defect	*CD16*
ICA	*RPSA*
Autoinflammatory disorders	
CAPS	
FMF	*MEFV*

(Continued)

TABLE II. *(Continued)*

Defect or disease(s)	Gene(s)
MVK deficiency (hyper-IgD syndrome)	*MVK*
MWS	*NLRP3*
CINCA syndrome or NOMID	
FCAS1	
FCAS2	*NLRP12*
Noninflammasome defects	
TNF receptor–associated periodic fever syndrome (TRAPS)	*TNFRSF1A*
PAPA syndrome	*PSTPIP1*
Blau syndrome	*NOD2*
CRMO dyserythropoietic anemia (Majeed syndrome)	*LPIN2*
DIRA	*IL1RN*
Deficiency of IL-36 receptor antagonist with generalized pustular psoriasis (DITRA)	*IL36RN*
SLC29A3 deficiency	*SLC29A3*
CARD14-mediated psoriasis (CAMPS)	*CARD14*
Cherubism	*SH3BP2*
Chronic atypical neutrophilic dermatosis with lipodystrophy and increased temperature (CANDLE) syndrome or Nakajo-Nishimura syndrome (NNS), proteasome subunit, β type, 8 defect	*PSMB8*
PLAID	*PLCG2*
Stimulator of interferon genes (STING) defect	*TMEM173*
Adenosine deaminase 2 defects	*ADA2*
Early-onset inflammatory bowel disease	*IL-10, IL10RA, IL10RB*
Periodic fever associated with aphthous stomatitis, pharyngitis and cervical adenitis (PFAPA) syndrome	Unknown
Complement deficiencies	
C1	
C1q α	*C1QA*
C1q β	*C1QB*
C1q γ	*C1QC*
C1r	*C1R*
C1s	*C1S*
C2	*C2*
C3	*C3*
C4	*C4A, C4B*
C5	*C5*
C6	*C6*
C7	*C7*
C8	
C8 α	*C8A*
C8 β	*C8B*
C8 γ	*C8G*
C9	*C9*
C1 inhibitor deficiency	*SERPING1*
Factor B	*CFB*
Factor D	*CFD*
Factor H	*CFH*
Factor H–related protein deficiency	*CFHR1-5*
Factor I	*CFI*
Properdin	*CFP*
MBL deficiency	*MBL*
MBL-associated protease 1 (MASP1) deficiency	*MASP1*
MBL-associated serum protease 2 deficiency	*MASP2*
Ficolin 3 deficiency	*FCN3*

(Continued)

TABLE II. *(Continued)*

Defect or disease(s)	Gene(s)
Thrombomodulin	*THBD*
Membrane cofactor protein (CD46) deficiency	*CD46*
Membrane attack complex inhibitor (CD59) deficiency	*CD59*
COLEC11 deficiency	*COLEC11*
Complement receptor 2 deficiency	*CD21*
Complement receptor 3 deficiency	*ITGB2*
Immunodeficiency associated with autoantibodies	
Acquired angioedema	Anti–C1 inhibitor
Neutropenia/Felty syndrome	Anti–G-CSF
Cryptococcal meningitis/PAP	Anti–GM-CSF
Disseminated varicella-zoster/APECED	Anti–IFN-α/β
Disseminated infections (virus, bacteria, fungi)	Anti–IFN-γ
Recurrent bacterial skin infections/sepsis	Anti–IL-6
Disseminated *Burkholderia gladioli* infection	Anti–IL-12p70
CMCC/APECED	Anti–IL-17, anti–IL-22

*The classification is based on the format used by the WHO/IUIS.[3] The authors have attempted to use the Human Genome Organization name for each gene current at the time of publication of this document. The reader should be aware that this nomenclature is fluid, and some names might have changed.

infections, after immunosuppression to prevent graft rejection after transplantation, during treatment of systemic autoimmune disease, and in association with cancer chemotherapy. More than 200 distinct genetic disorders affecting immune system function have been identified to date (many are listed in Table II).

Primary immunodeficiencies occur in as many as 1:2000 live births. They are most often categorized according to a combination of mechanistic and clinical descriptive characteristics. These categories include the defects of specific or adaptive immunity, which are subdivided into humoral or antibody deficiencies, and the combined deficiencies affecting both humoral and cellular mechanisms. A separate category of immunodeficiency syndromes with characteristic phenotypes is distinguished, along with defects of innate immunity, disorders of immune dysregulation, autoinflammatory syndromes, and phagocyte and complement system defects. Recently, the importance of anticytokine autoantibodies has been appreciated in the pathophysiology of some Mendelian PIDD syndromes and as *prima facie* causes of PIDDs. Among these categories, the antibody deficiency group accounts for approximately half of all patients with a PIDD diagnosis.

The principal clinical manifestation of immunodeficiency is increased susceptibility to infection. The pattern of organ systems affected, as well as the characteristic pathogens, vary with the type of immune defect (Table III). Autoimmune disease and malignancy are also often seen in a variety of immunodeficiencies. In the course of 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 might predispose to infection, including anatomic defects, allergy, and metabolic disorders, should be considered where appropriate.

TABLE III. Characteristic clinical presentations of some immunodeficiency disorders

Diagnosis	Symptoms and/or clinical presentation
CIDs	
SCID	Failure to thrive, diarrhea, severe/disseminated infections, opportunistic infections, rash; abnormal newborn screen*
CD40L deficiency	Recurrent serious pyogenic infections, opportunistic infections (PCP)
Immunodeficiency syndromes	
WAS	Thrombocytopenia with bleeding and bruising, eczema, recurrent infection with encapsulated organisms, autoimmunity
AT	Chronic sinopulmonary disease, cerebellar ataxia, oculocutaneous telangiectasia, malignancy
DGS	Hypocalcemic seizures caused by hypoparathyroidism, cardiac disease, abnormal facies, infection, abnormal newborn screen*
Antibody deficiency	Recurrent sinopulmonary infections with encapsulated bacteria, recurrent viral respiratory tract and gastrointestinal infections
Immune dysregulation	Autoimmunity, lymphoproliferation, HLH
Phagocytic cell defects	
CGD	Deep-seated infection, abscess with granuloma formation
LAD	Recurrent serious bacterial infections, delayed separation of the umbilical cord; poor wound healing, lack of pus
HIES type 1	Chronic dermatitis, recurrent serious infection of the lungs with pneumatoceles; skin infections, bone fragility, failure to shed primary teeth
MSMD	Severe mycobacterial and *Salmonella* species infections
Innate immune defects	
NEMO deficiency	Severe bacterial infections, opportunistic infections, anhidrotic ectodermal dysplasia
IRAK-4 defect	Severe gram-positive bacterial infections in early childhood
CMCC	Chronic skin and mucous membrane fungal infections
HSE	Herpes simplex encephalitis
EV	Severe disseminated cutaneous papillomatosis
Autoinflammatory disorders	Episodic fever often associated with dermatitis, gastrointestinal symptoms, and arthropathy
Complement deficiency	Recurrent bacterial infections (encapsulated strains, *Neisseria* species), autoimmunity
Immunodeficiency associated with autoantibodies	
Anti–GM-CSF autoantibodies	Cryptococcal meningitis and PAP (alone or together)
Anti–IFN-γ autoantibodies	Disseminated infections with mycobacteria, *Salmonella* species, *Cryptococcus* species, *Histoplasma* species, *Penicillium* species, and varicella-zoster virus

*Many states are now screening for SCID (see SS 26). Some infants with DGS (and other disorders) might be detected by this newborn screening. See Table II for abbreviations.

However, also note that hypersensitivity to environmental allergens, food allergens, or both might be an important element of and diagnostic clue for a variety of PIDDs.

In general, initial evaluation is guided by the clinical presentation (Fig 1 and Table III). Screening tests are applied and followed by advanced tests, as indicated (Table IV). This stepwise

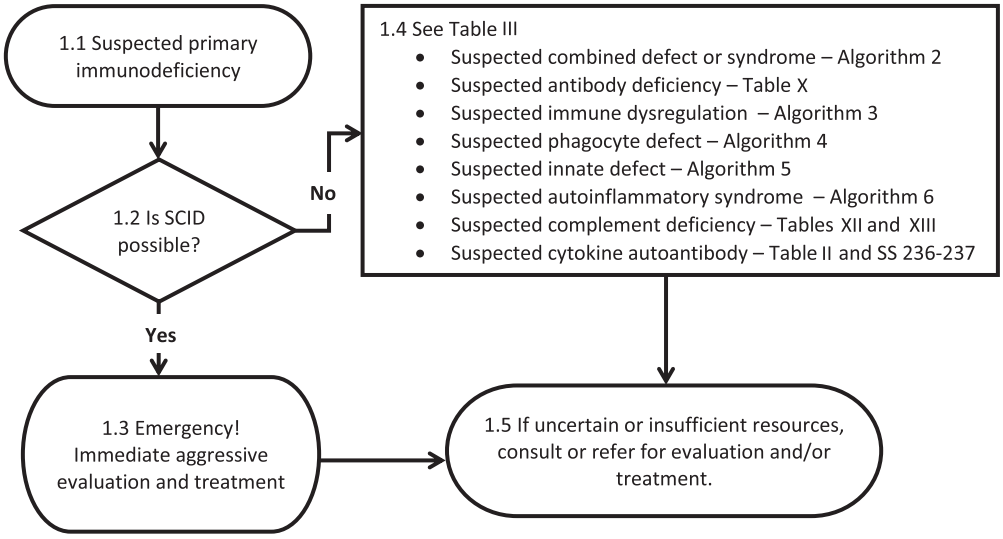

FIG 1. General approach for the diagnosis of primary immunodeficiency. *1.1*, The patient exhibits symptoms and signs consistent with a PIDD. It is assumed that immunosuppressive therapy and other medical conditions potentially resulting in secondary immunodeficiency and other anatomic or biochemical conditions potentially predisposing to infection either have been excluded or are not considered sufficient to explain the observed degree of infection susceptibility (see SS 2). *1.2*, Is the clinical presentation and initial laboratory evaluation consistent with SCID (see SS 26)? *1.3*, If the answer to 1.2 is yes, then the evaluation and management must be expedited as much as possible. Patients with SCID are fragile and extremely susceptible to infection. Early HSCT is associated with better outcomes, whereas complications before HSCT indicate poorer prognosis. *1.4*, If the answer to 1.2 is no, then another PIDD should be sought. The characteristic clinical presentations of various categories of PIDDs are summarized briefly in Table III. Diagnostic information and algorithms for these categories are presented in Figs 2 to 6; Tables II, X, XII, XIII; and SSs 236 and 237. *1.5*, If there is uncertainty or lack of resources for patient evaluation or care, consultation with or referral to a provider with experience with PIDDs should be undertaken. Although not stated explicitly in the figures that follow, this consideration is implicit in the course of evaluation and treatment of all patients with PIDDs (see SS 24).

TABLE IV. Laboratory tests of immune function

Screening tests	Advanced tests
Humoral immunity	
Serum immunoglobulin levels	Flow cytometry to enumerate B-cell subsets (eg, naive and switched memory cells)
Serum specific antibody titers	*In vitro* immunoglobulin production in response to mitogens or other stimuli
Antibody response to booster immunization	Antibody response to immunization with ϕX174
Flow cytometry to enumerate total B cells	
Cellular immunity	
TREC newborn screening	Flow cytometry to enumerate T-cell subsets (eg, naive, memory, and activated cells)
Flow cytometry to enumerate CD4 and CD8 T cells and NK cells	*In vitro* proliferative response to mitogens and antigens
Cutaneous delayed hypersensitivity	T-cell cytotoxicity
Spontaneous NK cytotoxicity	*In vitro* surface marker expression and cytokine production in response to stimuli
	Cytoplasmic protein phosphorylation in response to stimuli
Phagocytic cells	
Blood cell count with differential	Chemotaxis and/or phagocytosis assay
Neutrophil staining, morphology on a peripheral blood smear	Enzyme assays (myeloperoxidase, G6PDH)
DHR reduction or nitroblue tetrazolium	WBC turnover
Flow cytometry for adhesion molecules	Bacterial or fungal killing
	Bone marrow biopsy
Complement	
CH50 assay (total hemolytic complement activity)	Level or function of individual complement components
AH50 assay (alternative pathway hemolytic activity)	
Lectin pathway function	
Genetic tests	
Microarray for copy number variation	Targeted gene sequencing
	Whole-exome/genome sequencing

TABLE V. Internet resources for PIDDs

URL	Name/description
http://bioinf.uta.fi/idr/Immunology.shtml	ImmunoDeficiency Resource, University of Tampere, Finland
http://www.aaaai.org	American Academy of Allergy, Asthma & Immunology
http://www.esid.org	European Society for Immunodeficiencies
http://www.immunodeficiencysearch.com	Searchable database, clinical algorithms, laboratory resources
http://www.info4pi.org	Jeffrey Modell Foundation/Primary Immunodeficiency Resource Center
http://www.ipidnet.org	Immune Phenotyping in Primary Immunodeficiency
http://www.ipopi.org	International Patient Organization for Primary Immunodeficiencies
http://www.primaryimmune.org	Immune Deficiency Foundation
http://rapid.rcai.riken.jp/RAPID	Resource of Asian Primary Immunodeficiency Diseases (RAPID)
http://www.usidnet.org	US Immunodeficiency Network (USIDNET)

approach ensures efficient and thorough evaluation of mechanisms of immune dysfunction that underlie the clinical presentation, with narrowing of diagnostic options before using costly sophisticated tests that might be required to arrive at specific diagnoses. In addition to global assessment of immune development through measurement of nonspecific features, such as serum immunoglobulin levels and leukocyte and lymphocyte subpopulations, evaluation of the specific immune response is essential. This is most often directed toward evaluation of responses against vaccine antigens, but assessment of responses to natural exposure or infections is also useful.

There are a variety of resources for health care providers and patients now available on the Internet, and some are listed in Table V. Where uncertainty regarding evaluation or management occurs, consultation with physicians experienced with immunodeficiencies is essential. Where 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. General therapeutic considerations for immunodeficiency are listed in Table VI.

The combined deficiencies of specific immunity (Fig 2) 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 can include panhypogammaglobulinemia, lymphopenia, or alymphocytosis and absence of cellular immune function, as determined by using *in vitro* stimulation tests. The laboratory phenotype often depends on the specific molecular defect (Table VII). A possible diagnosis of SCID is an urgent medical condition because these infants can 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 IgG replacement. Definitive hematopoietic stem cell therapy (HSCT) should be sought as quickly as possible. A variety of additional genetic defects leading to impairment of T- and B-cell function have also been described, including hyper-IgM syndromes and others (Tables II and Table VIII).

A variety of syndromes of immunodeficiency have been described. Most prominent among these are Wiskott-Aldrich syndrome, DiGeorge syndrome, ataxia-telangiectasia, and the hyper-IgE syndromes. These disorders present with varying degrees of susceptibility to the entire spectrum of pathogenic organisms, depending on the specific disorder and on other host genetic and environmental factors (Table IX). Many of these diseases have ancillary clinical features that might influence or guide the diagnostic approach. Laboratory abnormalities of specific immune function vary depending on the specific gene defect and can include alterations in immunoglobulin levels with impaired specific antibody responses, as well as defects of specific cellular immunity, as determined by using *in vivo* and *in vitro* assays. Therapy is often supportive and anti-infective with drugs and polyclonal human IgG. HSCT has been applied in patients with many of these disorders as well (Tables VI and Table VIII).

The principal clinical manifestations of humoral immunodeficiency are recurrent bacterial infections of the upper and lower respiratory tract. Both X-linked and autosomal forms of agammaglobulinemia are associated with extremely low numbers (absence) of B cells (Table X). The X-linked form (Bruton agammaglobulinemia) accounts for the majority (85%) of cases. In patients with common variable immunodeficiency, laboratory evaluation generally shows variable reduction in 2 or more major immunoglobulin classes, impairment of specific antibody responses, and, occasionally, reductions in B-cell numbers. Milder antibody deficiencies, such as selective IgA deficiency, IgG subclass deficiency, specific antibody deficiency, or transient hypogammaglobulinemia of infancy, are associated with variably low levels of immunoglobulin classes or subclasses in serum, sometimes accompanied by impaired specific antibody formation (Table XI). For agammaglobulinemia or common variable immunodeficiency, therapy is either with antibiotic prophylaxis, IgG replacement, or both (Tables VI and VII). Milder antibody deficiencies are most often managed with antibiotic prophylaxis (SS 16 and Table VII). In some of these cases, IgG therapy can be applied.

The disorders of immune dysregulation (Fig 3) include the hemophagocytic syndromes, syndromes with autoimmunity and hypersensitivity, and lymphoproliferation. The hemophagocytic syndromes often have fulminant acute presentations triggered by viral infections. These patients usually require aggressive chemotherapy followed by HSCT to prevent immediate fatality. Other prominent disorders in this category are the autoimmune lymphoproliferative syndromes and immune deficiency, polyendocrinopathy, X-linked syndrome. These diseases also require HSCT.

Phagocytic cell defects (Fig 4) can present with severe pyogenic bacterial and fungal infections of the respiratory tract, skin, and viscera and gingivostomatitis. Laboratory evaluation might show neutropenia, normal neutrophil numbers, or marked neutrophilia (mainly in cellular adhesion defects). Functional studies show most often a defect in oxidative metabolism because chronic granulomatous disease is the most common phagocyte defect. In patients with other disorders, there might be simply severe neutropenia or variable impairment of chemotaxis

TABLE VI. Summary of therapeutic considerations for primary immunodeficiencies and their complications

Diagnosis	IgG*	HSCT	Gene therapy	
CIDs				
SCID (*IL2RG*, ADA)	Yes	Yes	Yes	• Avoid live vaccines: all • PCP prophylaxis: all SCID, CD40, CD40L • Antimicrobials as needed • Blood products irradiated, CMV^{-}: all • ADA: PEG-ADA • CD40, CD40L: G-CSF
SCID (other)	Yes	Yes	No	
CD40L deficiency	Yes	Yes	No	
Other CID	Yes	Many	No	
Immunodeficiency syndromes				
WAS	Yes	Yes	Yes	• Avoid live vaccines: many • Multidisciplinary care: many • WAS: splenectomy • DGS: thymus transplantation • Immunomodulation as needed • Chemotherapy as needed
AT	Some	No	No	
DGS	Some	No	No	
Other syndromes	Some	Some	No	
Antibody deficiency				
Agammaglobulinemia	Yes	No	No	• Avoid live vaccines: agammaglobulinemia, CVID • Antibiotics: all • Splenectomy: CVID • Immunomodulation: CVID • Chemotherapy: CVID • Pneumococcal vaccine: SIGAD, IGGSD, SAD
CVID	Yes	Rare	No	
Other antibody deficiency	Yes	No	No	
Immune dysregulation				
FHL	No	Yes	No	• Antimicrobials as needed • Chemotherapy as needed • Immunomodulators as needed
ALPS	No	Yes	No	
IPEX	No	Yes	No	
APECED	No	No	No	
Other	Some	Some	No	
Phagocytic cell defects				
Neutropenia	No	Yes	No	• Avoid live bacterial vaccines: all • Antimicrobial prophylaxis: all • IFN-γ: CGD • Surgical or dental debridement: CGD, LAD-I • Granulocyte transfusions: CGD, LAD-I • G-CSF: neutropenias • Fucose: LAD-II
CGD	No	Yes	Yes	
LAD	No	Yes	No	
HIES type 1	Some	Rare	No	
MSMD	No	Some	No	
Innate immune defects				
NEMO deficiency, other NF-κB defects	Yes	Yes	No	• Avoid live vaccines: NF-κB • PCP prophylaxis: NF-κB • Antimicrobial prophylaxis: NF-κB, CMCC • G-CSF: WHIM syndrome • Antiviral prophylaxis: HSE
CMCC	No	No	No	
WHIM syndrome	Yes	Some	No	
HSE	No	No	No	
EV	No	No	No	

(Continued)

TABLE VI. *(Continued)*

Diagnosis	IgG*	HSCT	Gene therapy	
Autoinflammatory disorders	No	No	No	• Cytokine (IL-1, TNF, IL-6) inhibitors: CAPS, DIRA, PAPA, PSMB8, TRAPS • Steroids: Blau syndrome, DITRA, HIDS, TRAPS • Retinoids: DITRA • Colchicine: TRAPS
Complement deficiency	No	No	No	• Antibiotics: all • Pneumococcal vaccine: C1, C2, C3, C4 • Meningococcal vaccine: C5-C9 • Immunomodulators: C1, C2, C4, factors H and I
Cytokine autoantibody-mediated disorders	Possible	No	No	• Plasmapheresis • Rituximab • Cytokine supplement

*Yes or No indicates whether or not IgG replacement is a component of standard therapy for this disorder.

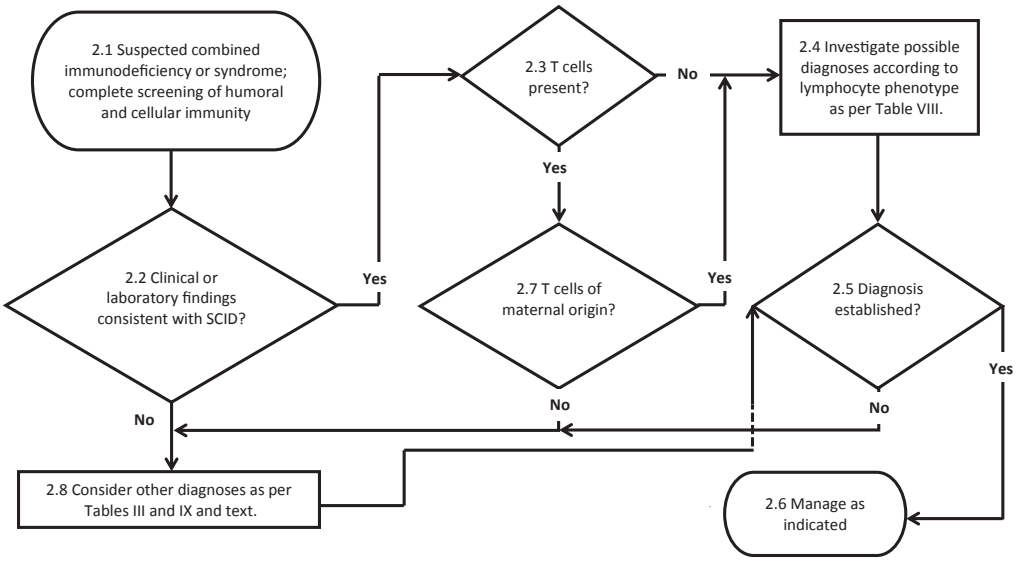

FIG 2. Diagnosis of combined or syndromic immunodeficiencies. *2.1*, In this situation it is appropriate to perform a complete screening evaluation of specific immune function, including measurement of immunoglobulin levels, specific antibody production, enumeration of lymphocyte subpopulations, measurement of T-cell proliferation with mitogens and antigens, and evaluation of NK cell cytotoxicity. *2.2*, Are the clinical presentation and laboratory evaluation consistent with SCID? Note that in some states SCID might be suspected early on the basis of newborn screening through measurement of TREC numbers in dried blood spots (see SS 24). *2.3*, If the answer to 2.2 is yes, consider the T-cell phenotype. Are T cells present? *2.4*, If the answer to 2.3 is no, this is consistent with SCID, and more specific diagnostic studies should be undertaken considering the lymphocyte phenotype, as outlined in Table VII. *2.5*, Is the diagnosis established? *2.6*, If the answer to 2.5 is yes, then proceed to manage as indicated (ultimately HSCT or gene therapy). *2.7*, If the answer to 2.3 is yes, the origin of the T cells should be determined. Are the T cells of maternal origin? If the answer to this question is yes, then this is also consistent with SCID and proceed as in 2.4. *2.8*, If the T cells are not of maternal origin, then autologous T cells are present, and the diagnosis is not classic SCID (a diagnosis of leaky SCID is still possible). Consider and investigate alternative CIDs and syndrome diagnoses as outlined in Tables III and VIII and SSs 26 to 76.

(leukocyte adhesion defects), phagocytosis, or intracellular killing. Therapy is with antibacterial and antifungal prophylaxis and IFN-γ for chronic granulomatous disease. HSCT has been applied for chronic granulomatous disease, leukocyte adhesion defects, and neutropenic syndromes. The care of patients with other forms of phagocyte defects is primarily anti-infective and supportive.

Also included in the category of phagocytic cell defects are the syndromes classified under Mendelian susceptibility to mycobacterial disease. These patients exhibit somewhat restricted susceptibility to mycobacteria and to severe salmonella infections. Therapy is with antimicrobials and IFN-γ in some forms, and HSCT has been applied in a few patients.

Disorders of innate immunity are rare and include defects of Toll-like receptor signaling, such as nuclear factor κB essential modulator syndrome, often exhibiting ectodermal dysplasia along with infection susceptibility with a narrow (eg, predominantly pyogenic bacteria or fungi) to a wide range of pathogens (Fig 5). Antimicrobial therapies are important for treatment, and some of these disorders can be managed with HSCT. This category also includes several defects associated with herpes simplex encephalitis and chronic mucocutaneous candidiasis.

TABLE VII. Regimens for prophylaxis of bacterial respiratory tract infections

Antibiotic	Regimen for children	Regimen for adults
Oral agents*		
Amoxicillin (consider with clavulanate, if necessary)	10-20 mg/kg daily or twice daily	500-1,000 mg daily or twice daily
Trimethoprim (TMP)/ sulfamethoxazole (dosing for TMP)	5 mg/kg daily or twice daily	160 mg daily or twice daily
Azithromycin	10 mg/kg weekly or 5 mg/kg every other day	500 mg weekly or 250 mg every other day
Clarithromycin	7.5 mg/kg daily or twice daily	500 mg daily or twice daily
Doxycycline	Age >8 y; 25-50 mg daily or twice daily	100 mg daily or twice daily
Inhaled agents		
Gentamicin	Age >6 y: 80 mg twice daily, 28 days on, 28 days off OR: 21 days on, 7 days off	
Tobramycin	Age >6 y: 300 mg twice daily, 28 days, on 28 days off	

*These are commonly used regimens.[57] If these agents are not effective or are not tolerated, other drugs can be considered, including cefuroxime, cefprozil, cefpodoxime, ciprofloxacin or other quinolone, or others, depending on the individual circumstances of the patient.

TABLE VIII. Lymphocyte phenotype classification of SCID

Disease	Genes	References
$T^-B^-NK^-$		
Adenosine deaminase	*ADA*	89, 90
Adenylate kinase (reticular dysgenesis)	*AK2*	91-93
$T^-B^-NK^+$		
Artemis	*DCLRE1C*	94, 95
Cernunnos	*NHEJ1*	96, 97
DNA-dependent protein kinase	*PRKDC*	98
DNA ligase IV	*LIG4*	99, 100
RAG1 and RAG2	*RAG1*, *RAG2*	101-104
$T^-B^+NK^-$		
X-linked SCID	*IL2RG*	67, 105-108
JAK3 deficiency	*JAK3*	106, 109
CD25 deficiency	*IL2RA*	110, 111
$T^-B^+NK^+$		
CD3 complex defects	*CD3D, CD3E, CD3Z*	112-115
Coronin 1A deficiency	*CORO1A*	88
CD45 deficiency	*PTPRC*	116, 117
IL-7 receptor deficiency	*IL7RA*	115, 118

These diseases are generally managed with anti-infective agents.

Autoinflammatory syndromes are also quite rare (Fig 6). These diseases are characterized by episodic fever often in association with other inflammatory manifestations that can affect the skin, joints, and gastrointestinal tract. Anti-inflammatory biologicals, such as TNF or IL-1 antagonists, might be useful, along with more routine anti-inflammatory therapies, such as corticosteroids or colchicine.

Complement deficiencies are also infrequent (Tables XII and XIII). Most early classical and alternative pathway complement defects tend to present either with systemic autoimmune disease resembling lupus erythematosus or recurrent respiratory tract bacterial infections similar to antibody deficiency. Deficiencies of terminal components can also be associated with recurrent neisserial meningitis. Some patients with low serum levels of mannose-binding lectin might be predisposed to bacterial respiratory tract infections, but there could be other host factors that interact to create such susceptibility in a patient. There is no specific therapy for complement deficiency. Antibiotic prophylaxis (SS 16 and Table VII) and immunization can be applied for recurrent infections.

Anticytokine antibodies are an important component of some PIDD syndromes. For example, there is a strong correlation of the presence and concentration of antibodies against IL-17A, IL-17F, and IL-22 with the occurrence of chronic mucocutaneous candidiasis in patients with autoimmune polyendocrinopathy–candidiasis–ectodermal dystrophy (autoimmune regulator mutations). Anti-cytokine autoantibodies might also be pathogenic by themselves, such as anti–GM-CSF antibodies in patients with pulmonary alveolar proteinosis and anti–IFN-γ antibodies in patients with adult-onset Mendelian susceptibility to mycobacterial disease. Additional examples have been described.

It is recommended that diagnosis and therapy are guided overall or performed in consultation with persons and centers with knowledge and experience diagnosing and treating a broad range of immunodeficiencies to improve consistency in evaluation and management and to have the best outcomes with respect to patient and family health, education, and planning.

All references are available in the complete parameter document pdf file included in this publication's Online Repository at www.jacionline.org or at http://www.JCAAI.org or http://www.allergyparameters.org.

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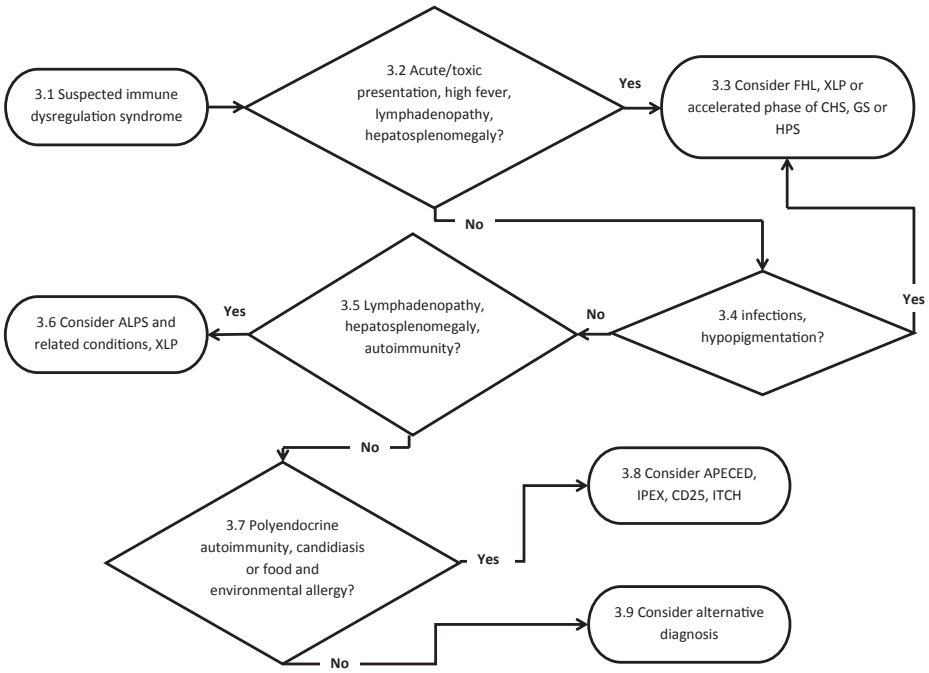

FIG 3. Diagnosis of diseases of immune dysregulation. *3.1*, A disorder of immune dysregulation is suspected because of some combination of clinical features in which 1 or more of the following are prominent: (1) autoimmunity; (2) hypersensitivity; and (3) signs of lymphoproliferation, such as diffuse lymphadenopathy, hepatosplenomegaly, or both. *3.2*, Does the patient have an acute or fulminant presentation with high fever, toxic appearance, and signs of lymphoproliferation? Alternatively, if the presentation is subacute or chronic, are features of recurrent infections and pigmentary abnormalities present? *3.3*, Either of the presentations in 3.2 is consistent with a form of HLH, either FHL or in association (as an "accelerated phase") with another syndrome, such as CHS, GS, or HPS. *3.4*, Are lymphoproliferation and autoimmune disease prominent in the presentation? *3.5*, The presentation in 3.4 suggests ALPS, ALPS-related disorders, or XLP. *3.6*, Are any of these features present: (1) polyendocrine autoimmunity; (2) CMCC; or (3) multiple food and/or environmental allergies? *3.7*, The presentation of 3.6 indicates possible APECED, IPEX, or defects of CD25 or ITCH. If none of these diagnoses is correct, the patient might have a CID or syndrome. Consider evaluation as outlined in Fig 2.

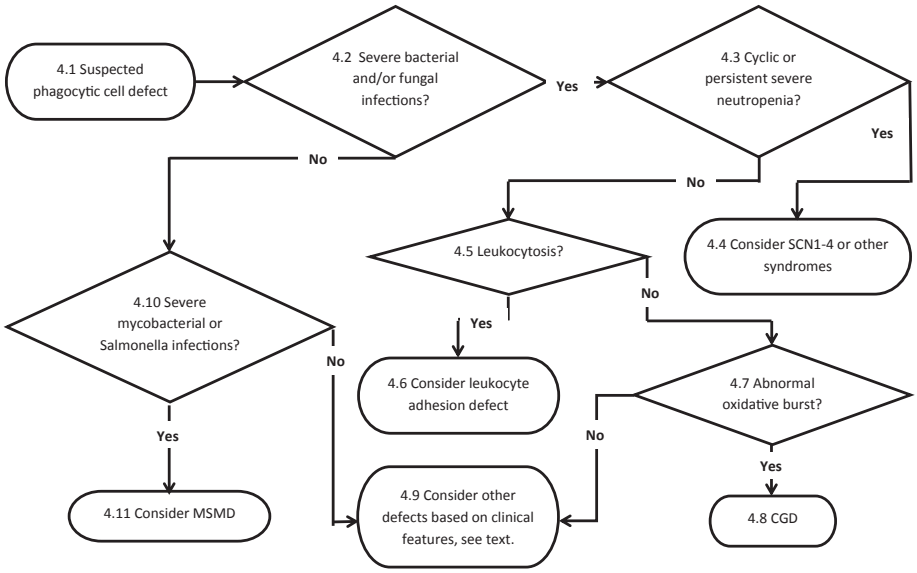

FIG 4. Diagnosis of phagocyte defects. *4.1*, The clinical presentation includes severe characteristic bacterial and/or fungal infections affecting the lungs, skin, or viscera and is primarily suggestive of a phagocyte defect, or evaluation of other immune function is thus far normal and the clinical 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*, The clinical presentation is one of infections limited to mycobacteria, severe infections with *Salmonella* species, or both. *4.3*, In the case of 4.2, consider one of the disorders of MSMD. *4.4*, There is a marked leukocytosis, even in the absence of an ongoing infection. *4.5*, In the case of 4.4, consider LAD. *4.6*, The absolute neutrophil count is normal or there is a moderate leukocytosis, perhaps with ongoing infection. *4.7*, Is neutrophil oxidative function abnormal? *4.8*, If the answer to 4.7 is yes, the diagnosis is CGD. If no, consider any of the possibilities in 4.5 or 4.10. *4.9*, There is cyclic or persistent severe neutropenia. *4.10*, In the case of 4.9, consider a diagnosis of any of the neutropenic defects.

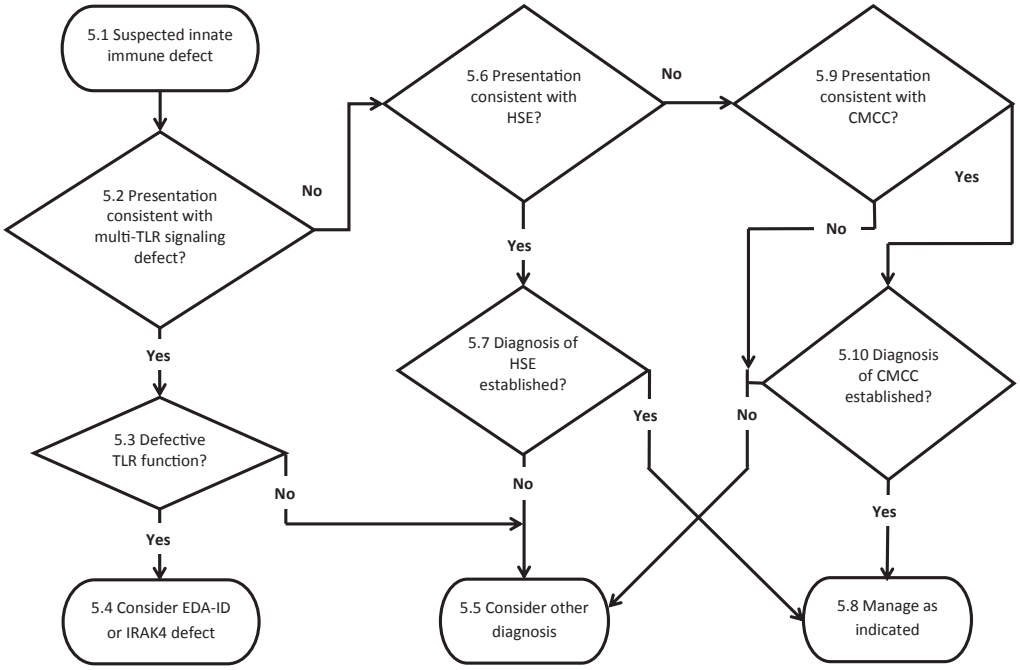

FIG 5. Diagnosis of innate immune defects. *5.1*, A defect of innate immunity is suspected according to one of the characteristic clinical presentations (Table III). *5.2*, The presentation is principally one of severe recurrent infections of all classes of pathogens together with ectodermal dysplasia, severe gram-positive bacterial infections, or other clinical features suggestive of NF-κB pathway or multiple TLR signaling defects. *5.3*, In the case of 5.2, is TLR function abnormal? *5.4*, If yes, consider defects of NF-κB signaling, anhidrotic ectodermal dysplasia with immunodeficiency, or IRAK-4. If no, go to 5.10. *5.5*, The presentation is consistent with HSE. *5.6*, In the case of 5.5, pursue a molecular diagnosis, if possible. There are no routinely available tests of TLR3 function that are informative in this setting. *5.7*, If the diagnosis of HSE or CMCC is established, manage as indicated for each disorder. If not, go to 5.10. *5.8*, The presentation is consistent with CMCC. *5.9*, In the case of 5.8, pursue a molecular diagnosis, if possible. There are no routinely available clinical tests that will be informative in this setting. If the diagnosis is confirmed, proceed as in 5.7. If not, go to 5.10. *5.10*, If TLR function is normal or HSE or CMCC diagnoses are not confirmed, consider the possibility of a CID or primary immunodeficiency syndrome (Fig 2) or phagocytic cell defect (Fig 4). A syndrome of immune dysregulation can also be considered (Fig 3). Also consider a cytokine autoantibody (Table II and SSs 236 and 237).

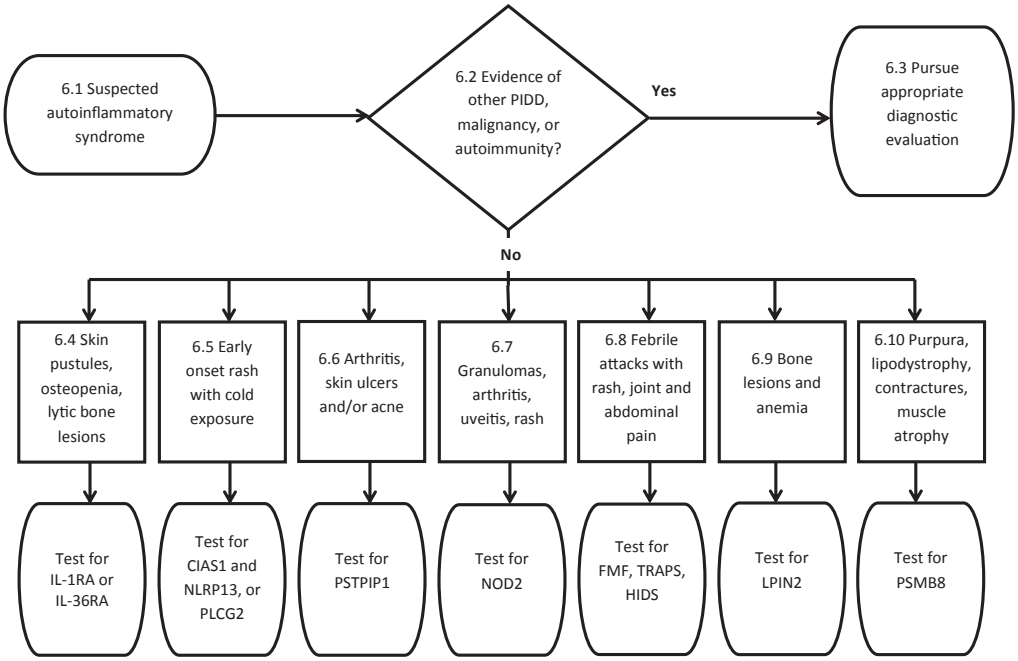

FIG 6. Diagnosis of autoinflammatory syndromes. *6.1*, A patient is suspected to have an autoinflammatory (episodic fever) syndrome. *6.2*, It is first necessary to evaluate for other causes of recurrent or continual inflammation, such as other PIDDs, autoimmune disease, or malignancy. *6.3*, If alternative (nonautoinflammatory) diagnoses are now suspected as a result of further clinical study, then these should be pursued and ruled out before additional investigation of autoinflammatory conditions is undertaken. Note that nonspecific autoantibodies (eg, anti-nuclear antibody, rheumatoid factor, anti–double-stranded DNA, antiphospholipid antibody, and anti-neutrophil cytoplasmic antibody) can be persistently or transiently present at mildly or moderately increased levels, especially in the noninflammasome defects. If the clinical presentation has features strongly suggestive of an autoinflammatory component (eg, very early onset), such a diagnosis should still be entertained. *6.4*, Early-onset severe pustular skin disease is seen in patients with DIRA and DITRA. DIRA is also associated with bone involvement with osteopenia and lytic bone lesions. Sequence analysis for *IL1RN* and *IL36RN*, as well as chromosomal analysis for deletions in the *IL1* locus, should be investigated. *6.5*, If an evanescent nonurticarial rash is present with cold exposure, genetic testing of *CIAS1* should be done to test for FCAS, as well as *NLRP13*; if the rash is a cold-induced urticarial rash, the patient should be tested for mutation of *PLCG2* (PLAID). *6.6*, If fevers are associated with pyogenic arthritis and ulcerative skin lesions (ie, pyoderma gangrenosum), cystic acne, or both, mutational analysis of the *PSTPIP1* gene should be evaluated for PAPA syndrome. *6.7*, If granulomatous disease (rash, uveitis, or arthritis) is apparent, mutational analysis of *NOD2* should be considered for Blau syndrome. *6.8*, If febrile attacks are associated with abdominal or joint pains or rash, mutation analysis of pyrin, TNF receptor I, and MVK should be undertaken. *6.9*, If bone lesions and dyserythropoietic anemia are associated with fevers, analysis of *LPIN2* for Majeed syndrome should be considered. *6.10*, If the presentation consists of purpura with 1 or more of lipodystrophy, contractures, or muscle atrophy, a defect in *PSMB8* should be investigated.

TABLE IX. Clinical and Laboratory manifestations of selected combined immunodeficiencies and syndromes

Gene defect(s) or disease(s)	Clinical features	Laboratory features	Reference(s)
Ca/Mg channel defects (*MAGT1*, *ORAI1*, *STIM1*)	Severe and opportunistic infections, autoimmune disease, anhydrotic ectodermal dysplasia, myopathy	Normal T-cell numbers, ↓ T-cell function	142-145
CARD11	Opportunistic infections	Hypogammaglobulinemia, normal lymphocyte numbers, ↓ T-cell function	146-148
CD27	Persistent symptomatic EBV viremia, recurrent infection	Hypogammaglobulinemia, impaired specific antibody response, decreased mitogen proliferation	149
CD3G	Variable severity, SCID or mild phenotype, autoimmune hemolytic anemia	Modest ↓ CD8 T cells, ↓ $CD45RA^+$ cells, ↓ TCR expression, variable immunoglobulins	113, 115
CD8	Recurrent bacterial respiratory tract infections, bronchiectasis	Absent CD8 T cells, ↑ double-negative T cells	150
CTLA4	Autosomal dominant, lymphoproliferation, organ infiltration, lymphoma, respiratory tract infections	↓ CD4 T cells, ↓ B cells, hypogammaglobulinemia, ↑ T-cell proliferation	151, 152
CTPS1	Disseminated infections with EBV and varicella-zoster virus, encapsulated bacteria, B-cell lymphoma	Lymphopenia, ↓ naive CD4 cells, ↓ IgG_2, ↓ pneumococcal response, ↓ memory B cells, absent invariant NK T cells, ↓ PHA proliferation	153
FOXN1	Athymia, reduced T-cell numbers, absence of hair, and nail dysplasia	↓ Naive T cells; ↑ double negative ($CD4^-CD8^-$) T cells	154-156
IKZF1	Prematurity, polyhydramnios with fetal hydrops, neonatal pancytopenia	Normal lymphocyte numbers, absent B cells, ↓ NK cells, ↓ $CD45RO^+$ T cells, absent mitogen proliferations, ↓ IgG	157
IL21R	Respiratory tract infections, failure to thrive, diarrhea, cryptosporidiosis	Normal lymphocyte numbers, ↑ IgE, ↓ specific antibody, normal T-cell function, ↓ NK cytotoxicity	158
ITK	EBV-associated lymphoproliferation, lymphoma	Lymphopenia, hypogammaglobulinemia	159-162
MHC class I deficiency (*TAP1*, *TAP2*, *TAPBP*), *CD8A*	Variable severity, recurrent respiratory tract infections, bronchiectasis	Complete absence of $CD8^+$ cells, normal CD4 cells, normal T-cell proliferation, normal immunoglobulins and antibody	163, 164
MHC class II deficiency (*MHC2TA*, *RFX5*, *RFXANK*, *RFXAP*), and *LCK* mutation	Severe and opportunistic infections, diarrhea, malabsorption, failure to thrive	↓ CD4 T cells, normal CD8 cells; ↓ T-cell proliferation, hypogammaglobulinemia, ↓ antibody	165-169
NP	Severe and opportunistic infections, severe varicella (including vaccine strain), neurological impairment	↓ T cells, variable ↓ in B cells, ↓ T-cell proliferation, variable immunoglobulins, and antibody	170, 171
PGM3	Recurrent infections, skeletal dysplasia, developmental delay	Neutropenia, lymphopenia (↓ T and B cells), bone marrow failure	172
POLE1	Mild facial dysmorphism, livedo, short stature, recurrent pulmonary infection with bronchiectasis, recurrent *Streptococcus pneumoniae* meningitis, long-bone abnormalities	↓ IgM, ↓ IgG_2, ↓ isohemagglutinin, ↓ $CD27^+$ memory B cells, low naive T-cell numbers	173
SLC46A1	Severe opportunistic infections, failure to thrive (reversible with folate administration)	Normocytic anemia, ↓ serum folate, hypogammaglobulinemia, ↓ T-cell proliferation	174
RHOH deficiency	Warts, molluscum, granulomatosis, Burkitt lymphoma	↓ CD4 T cells, normal immunoglobulins and antibody	175
STAT5B	Growth failure, ichthyosis/eczema, diarrhea ± bacterial or opportunistic infections, autoimmune disease	↓ Insulin-like growth factor, ↑ growth hormone, ↓ T cells, especially ↓ Treg cells	176-178
Trisomy 21	Cognitive impairment, characteristic facies, cardiac defects, gastrointestinal disorders, hypothyroidism, recurrent respiratory tract infections	Variable T- and B-cell lymphopenia, ↓ naive T and B cells, IGGSD, poor vaccine response, ↓ *in vitro* T-cell proliferation, ↓ neutrophil chemotaxis	179
TRNT1	Sideroblastic anemia, periodic fevers, developmental delay, sensorineural hearing loss, cardiomyopathy, CNS abnormalities	Variable ↓ immunoglobulins, ↓ B cells, progressive ↓ T cells and NK cells	180
ZAP70	Variable severity, SCID, and opportunistic infections, failure to thrive, mild phenotypes	↓ CD8 T cells, normal CD4 cells, ↓ T-cell proliferation, hypogammaglobulinemia, ↓ antibody	181-183

TABLE X. Summary of laboratory findings in the diagnosis of antibody deficiencies

IgG	IgA	IgM	IgG subclass	Vaccine response	B cells	Diagnosis
NL	NL	NL	NL	NL	NL	Normal*
NL	NL	NL	NL	Low†	NL	SAD
NL	NL	NL	≥1 Low	Low†	NL	IGGSD
NL	Absent	NL	Normal	NL or low	NL	SIGAD
NL	Absent	NL	≥1 Low	Low†	NL	IgA deficiency with IGGSD
Low	NL	NL		NL	NL	Possible secondary, unspecified, or transient hypogammaglobulinemia‡
Low	NL or low	NL or low		NL	NL or low	Unspecified or transient hypogammaglobulinemia
Low	Low	NL or high		Low	NL	HIM
Low	Low	NL or low		Low§	NL or low	CVID, possible transient hypogammaglobulinemia
Absent	Absent	Absent			Absent	Agammaglobulinemia or severe CVID¶

The clinical presentation is primarily suggestive of an antibody defect or any evaluation of cellular function is thus far normal, and the clinical presentation is at least consistent with a possible antibody deficiency and not suggestive of a cellular component (eg, lack of opportunistic infections). The initial laboratory examination of humoral immunity consists of measuring levels of various immunoglobulin isotypes (IgG, IgA, IgM, and possibly IgG subclasses) in serum, as well as a measure of function or specific antibody production, which should include both protein and polysaccharide antigens (see SS 6).

NL, Normal.

*Consider complement deficiency or phagocyte defect.

†Usually refers to polysaccharide response.

‡In this circumstance it is useful to measure serum total protein and/or albumin levels; if low, this is consistent with secondary hypogammaglobulinemia.

§Protein and/or polysaccharide response.

¶Cellular immunity should be evaluated as indicated by other clinical features but is often worth considering when significant impairment of humoral immunity is observed because it could be a component of a CID.

TABLE XI. Assessing serotype-specific responses to pneumococcal capsular polysaccharides

Phenotype	Age <6 y	Age >6 y
Mild	Concentration >1.3 μg/mL for >50% of types with a 2-fold increase for <50% of serotypes	Concentration >1.3 μg/mL for >70% of types with a 2-fold increase for <70% of serotypes
Moderate	Concentration >1.3 μg/mL for <50% of serotypes	Concentration >1.3 μg/mL for <70% of serotypes
Severe	Concentration >1.3 μg/mL for ≤2 serotypes	
Memory	Loss of response within 6 mo	

Adapted from Orange et al.[413]

TABLE XII. Clinical associations with complement deficiency

Component(s)	Lupus-like disease	Bacterial infections	References
C1, C2, C4	Yes	Encapsulated organisms	729, 733-735
C3	No	Encapsulated organisms (severe)	729, 733, 735
C5, C6, C7	Yes	*Neisseria* species	729, 733-735
C8, C9	No	*Neisseria* species	729, 733
C1 inhibitor (SERPING1)	No (hereditary angioedema)	None	729, 733
Factor B	No (atypical HUS)	None	729, 733, 736
Factor D	No	Encapsulated organisms	729, 733, 736
Properdin	Yes	*Neisseria* species	729, 731, 733, 736
Factor H	No (atypical HUS, macular degeneration)	Encapsulated organisms	729, 737, 738
Factor H–related protein (CFHR1-5)	No (atypical HUS)	None	739-741
Factor I	No (atypical HUS)	Encapsulated organisms	729, 737, 738, 742
MBL	No	Encapsulated organisms	730, 743
MASP1	No (3MC syndrome)	None	744, 745
MBL-associated serum protease 2	No	Encapsulated organisms	730
Ficolin 3	No	Encapsulated organisms, necrotizing enterocolitis	746, 747
Thrombomodulin	No (atypical HUS)	None	748, 749
Membrane cofactor protein (CD46)	No (atypical HUS)	None	737, 738, 750
Membrane attack complex inhibitor (CD59)	No (hemolysis, polyneuropathy)	None	751
COLEC11	No (3MC syndrome)	None	744
Complement receptor 2 (CD21)	No, CVID-like disorder	Encapsulated organisms	See SS 87
Complement receptor 3 (CD18/ITGB2)	No, LAD type 2	Encapsulated organisms	See SS 142

TABLE XIII. Summary of screening laboratory findings and diagnosis of complement deficiencies

CH50 assay	AH50 assay	Possible diagnoses
NL	NL	Normal
NL	Low	Properdin defect
NL	0	Factor B* or factor D defect
Low	NL or low	Consumption likely, regulatory component (factor H, factor I) defect possible
0	NL	C1, C2, or C4 likely absent
0	0	C3 or C5-C9 likely absent

The clinical presentation is suggestive of a complement deficiency (Table IX) or evaluation of other immune function is thus far normal, and the clinical presentation is at least consistent with complement deficiency. Note that this table does not consider possible lectin pathway defects. Both CH50 and AH50 results will be normal in the setting of MBL deficiency. See the text for discussion of lectin pathway defects and function. This algorithm can be used whether tests for the classical pathway (CH50 assay) and alternative pathway (AH50 assay) are performed simultaneously or sequentially. The CH50 assay is readily available in many hospital laboratories; the AH50 (also called the AP50) assay is not. The AH50 assay is available from the Complement Laboratory of the National Jewish Medical Center in Denver, Colorado. Genetically determined defects in the alternative pathway leading to absent activity in the presence of a normal CH50 result are very rare. Note also that complement components are unstable and tend to degrade with time, especially if blood or plasma is warmed. For the most accurate measurements, blood specimens should be placed on ice or refrigerated after drawing. If complement consumption is possible or suspected, the AH50 assay might not necessarily be helpful. A convenient way available in most hospital laboratories to test for consumption is to measure levels of factor B and C4, reflecting activation of the alternative or classical pathway, respectively. If levels of both of these (or other combination) are low, consumption of complement is assumed, and a reason should be explored. Note that deficiency of factor H, factor I, or properdin could lead to a diminished level of C3 and other components. This table has not been constructed to evaluate all of the control proteins. In the presence of an appropriate clinical history, low C4 levels in the presence of normal C3 levels might suggest hereditary angioedema, and the levels and function of C1 inhibitor should be explored. Such patients will have low CH50 results, but they will not be 0.
3MC, Carnevale-Mingarelli-Malpuech-Michels syndrome; *NL*, normal.
*Note that homozygous deficiency of factor B has never been reported.

Practice parameter for the diagnosis and management of primary immunodeficiency

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CLASSIFICATION OF RECOMMENDATIONS AND EVIDENCE

Classification of recommendations and evidence are listed in Table E1.

SUMMARY OF CONFLICT OF INTEREST DISCLOSURES

The following is a summary of interests disclosed on workgroup members' conflict of interest disclosure statements (not including information concerning family member interests). Completed conflict of interest disclosure statements are available on request.

Workgroup member	Disclosures
Francisco A. Bonilla, MD, PhD	Consultant: ADMA Biologics; Baxter; The Cowen Group; CSL Behring; Gerson-Lehrman Group; Grand Rounds Health; Immune Deficiency Foundation. DSMB: Octapharma. UpToDate in Medicine.
David A. Khan, MD	Speaker: Baxter; Genentech.
Zuhair K. Ballas, MD	UpToDate in Medicine.
Javier Chinen, MD, PhD	No conflicts.
Michael M. Frank, MD	No conflicts.
Joyce T. Hsu, MD	No conflicts.
Michael Keller, MD	Grants: NIH.
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Robert P. Nelson, Jr, MD	No conflicts.
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John M. Routes, MD	Grant: Baxter.
William T. Shearer, MD, PhD	No conflicts.
Ricardo U. Sorensen, MD	No conflicts.
James W. Verbsky, MD, PhD	No conflicts.

RESOLUTION OF NONDISQUALIFYING INTERESTS

The Joint Task Force recognizes that experts in a field are likely to have interests that could come into conflict with the development of a completely unbiased and objective practice parameter. To take advantage of that expertise, a process has been developed to prevent potential conflicts from influencing the final document in a negative way.

At the workgroup level, members who have a potential conflict of interest either do not participate in discussions concerning topics related to the potential conflict or, if they do write a section on that topic, the workgroup completely rewrites it without their involvement to remove potential bias. In addition, the entire document is then reviewed by the Joint Task Force, and any apparent bias is removed at that level. Finally, the practice parameter is sent for review both by invited reviewers and by anyone with an interest in the topic by posting the document on the Web sites of the ACAAI and the AAAAI.

PROTOCOL FOR FINDING EVIDENCE

A search of the medical literature on PubMed was performed for a variety of terms that were considered relevant to this practice parameter. All reference types were included in the results. References identified as being relevant were searched for other relevant references. Published clinical studies were rated by category of evidence and used to establish the strength of the recommendations. The parameter was subsequently appraised by reviewers designated by the AAAAI and ACAAI. Based on this

Abbreviations used:
AAGAM: Autosomal recessive agammaglobulinemia
ADA: Adenosine deaminase
AFP: α-Fetoprotein
AH50: Alternative pathway complement hemolysis 50%
AID: Activation-induced cytidine deaminase protein
AIRE: Autoimmune regulator
ALPS: Autoimmune lymphoproliferative syndrome
APECED: Autoimmune polyendocrinopathy–candidiasis–ectodermal dystrophy
APOL1: Apolipoprotein L1
AT: Ataxia-telangiectasia
BTK: Bruton tyrosine kinase
CAPS: Cryopyrin-associated periodic syndrome
CARD: Caspase recruitment domain
CASP8: Caspase 8
CASP10: Caspase 10
CBC: Complete blood count
CD40L: CD40 ligand
CFHR: Complement factor H–related protein
CGD: Chronic granulomatous disease
CH50: Classical pathway complement hemolysis 50%
CHARGE: Coloboma, heart anomaly, choanal atresia, retardation, genital and ear anomalies
CHH: Cartilage-hair hypoplasia
CHS: Chediak-Higashi syndrome
CID: Combined immunodeficiency
CINCA: Chronic infantile neurocutaneous articular
CLEC7A: C-type lectin domain family 7, member A
CMCC: Chronic mucocutaneous candidiasis
CMV: Cytomegalovirus
CNS: Central nervous system
COLEC11: Collectin subfamily member 11
CRMO: Chronic recurrent multifocal osteomyelitis
CRP: C-reactive protein
CSF: Cerebrospinal fluid
CT: Computed tomography
CVID: Common variable immunodeficiency
DGS: DiGeorge syndrome
DHR: Dihydrorhodamine 123
DIRA: Deficiency of IL-1 receptor antagonist
DITRA: Deficiency of IL-36 receptor antagonist
DKC: Dyskeratosis congenita
DOCK8: Dedicator of cytokinesis 8
ECHO: Enterocytopathic human orphan
ESR: Erythrocyte sedimentation rate
EV: Epidermodysplasia verruciformis
FCAS: Familial cold autoinflammatory syndrome
FCGR: IgG Fc receptor gene
FcγR: IgG Fc receptor (protein)
FHL: Familial hemophagocytic lymphohistiocytosis
FMF: Familial Mediterranean fever
FOXP3: Forkhead box protein 3
G-CSF: Granulocyte colony-stimulating factor
GLILD: Granulomatous and lymphocytic interstitial lung disease
GS: Griscelli syndrome
GVHD: Graft-versus-host disease
HAT: Human African trypanosomiasis
HIB: *Haemophilus influenzae* type B
HIDS: Hyper-IgD syndrome
HIES: Hyper-IgE syndrome
HIM: Hyper-IgM syndrome
HLH: Hemophagocytic lymphohistiocytosis
HPS: Hermansky-Pudlak syndrome
HPV: Human papilloma virus
HSCT: Hematopoietic stem cell therapy
HSE: Herpes simplex encephalitis
HSV: Herpes simplex virus
HUS: Hemolytic uremic syndrome
ICA: Isolated congenital asplenia
ICD4L: Idiopathic CD4 lymphopenia
ICF: Immunodeficiency, centromeric instability, and abnormal facies
IFNGR: IFN-γ receptor
IGGSD: IgG subclass deficiency
IKBA: Inhibitor of κB α chain
IKBKG: Inhibitor of κB kinase γ chain
IL17RA: IL-17 receptor α chain gene
IPEX: Immunodeficiency, polyendocrinopathy, X-linked
IRAK: IL-1 receptor–associated kinase

ITCH: Itchy E3 ubiquitin protein ligase
ITK: IL-2–inducible T-cell kinase
IVIG: Intravenous immunoglobulin
LAD: Leukocyte adhesion deficiency
LIG4: DNA ligase IV
MBL: Mannose-binding lectin
MCM4: Minichromosome maintenance complex component 4
MIA: Multiple intestinal atresia
MSMD: Mendelian susceptibility to mycobacterial disease
MST1: Macrophage stimulating 1
MTHFD1: Methylenetetrahydrofolate dehydrogenase ($NADP^+$ dependent) 1
MTOR: Mammalian target of rapamycin
MVK: Mevalonate kinase
MWS: Muckle-Wells syndrome
MyD88: Myeloid differentiation primary response 88
NBS: Nijmegen breakage syndrome
NEMO: Nuclear factor κB essential modulator
NF-κB: Nuclear factor κB
NIH: National Institutes of Health
NK: Natural killer
NOD2: Nucleotide-binding oligomerization domain–containing protein 2
NOMID: Neonatal-onset multisystem inflammatory disorder
NSAID: Nonsteroidal anti-inflammatory drug
OS: Omenn syndrome
PAP: Pulmonary alveolar proteinosis
PAPA: Pyogenic arthritis, pyoderma gangrenosum, and acne
PCP: *Pneumocystis jirovecii* pneumonia
PCV13: Conjugated 13-valent vaccine
PEG: Polyethylene glycol
PFAPA: Periodic fever with aphthous stomatitis, pharyngitis, and adenitis
PIDD: Primary immunodeficiency disease
PLAID: Phospholipase Cγ2–associated antibody deficiency and immune dysregulation
PMS2: Postmeiotic segregation increased 2
PPV23: Polysaccharide 23-valent pneumococcal vaccine
PRKCD: Protein kinase Cδ
PRP: Polyribosyl ribitol phosphate
PSTPIP1: Proline-serine-threonine phosphatase interacting protein 1
PSMB8: Proteasome catalytic subunit β type 8
RAG: Recombination-activating gene
RBCK1: RanBP-type and C3HC4-type zinc finger containing 1
RIDDLE: Radiosensitivity, immunodeficiency, dysmorphic features and difficult learning
RPSA: Ribosomal protein SA
RSV: Respiratory syncytial virus
SAA: Serum amyloid A
SAD: Specific antibody deficiency
SAM: Severe dermatitis, allergy, metabolic wasting
SAP: SLAM-associated protein
SCID: Severe combined immunodeficiency
SCIG: Subcutaneous immunoglobulin
SCN: Severe congenital neutropenia
SGD: Specific granule deficiency
SH3BP2: SH3-domain binding protein 2
SIGAD: Selective IgA deficiency
SLC46A1: Solute carrier family 46
SLE: Systemic lupus erythematosus
SPENCD: Spondyloenchondrodysplasia with immune dysregulation
SS: Summary statement
STAT: Signal transducer and activator of transcription
TACI: Transmembrane activator and CAML interactor
TBK1: TANK-binding kinase 1
TCN2: Transcobalamin II
THI: Transient hypogammaglobulinemia of infancy
TICAM1: Toll-like receptor adaptor molecule 1
TLR: Toll-like receptor
TMC6: transmembrane channel-like 6
TMEM173: Transmembrane protein 173
TNFRSF: TNF receptor superfamily
TNFSF: TNF superfamily
TRAF3: TNF receptor–associated factor 3
TRAPS: TNF receptor–associated periodic syndrome
TREC: T-cell receptor excision circle
Treg: Regulatory T
UNG: Uracil nucleoside glycosylase
WAS: Wiskott-Aldrich syndrome
WHIM: Warts, hypogammaglobulinemia, immunodeficiency, myelokathexis
XIAP: X-linked inhibitor of apoptosis
XLA: X-linked agammaglobulinemia
XLP: X-linked lymphoproliferative disease
XSCID: X-linked severe combined immunodeficiency

process, this parameter represents an evidence-based and broadly accepted consensus document.

PREFACE

The purpose of this "Practice parameter for the diagnosis and management of primary immunodeficiency" is to provide the consultant allergist/immunologist or other practitioner with a practical guide for the clinical recognition and diagnosis of immunodeficiency, along with the general principles that guide management of these disorders. This document was developed by a working group under the aegis of the 3 national allergy and immunology societies: the American Academy of Allergy, Asthma & Immunology (AAAAI); the American College of Allergy, Asthma & Immunology (ACAAI); and the Joint Council of Allergy, Asthma & Immunology (JCAAI). The Joint Task Force on Practice Parameters has published many practice parameters for the field of allergy/immunology. These can be found online at http://www.jcaai.org/resources/practice-paramenters/ (note that login with JCAAI membership ID and password is required for access).

The first "Practice parameter for the diagnosis and management of primary immunodeficiency" was published in 1995.[1] It was completely rewritten and updated in 2005[2] and has been brought up to date once again now. The classification of the immune deficiency disorders described herein now follows the system developed by the World Health Organization (WHO) and International Union of Immunological Societies (IUIS).[3]

This parameter was developed by a working group made up of clinical immunologists specializing in immunodeficiency. A workgroup chaired by Dr Francisco A. Bonilla prepared the initial draft, which was subsequently reviewed by the Joint Task Force. The working draft of "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 here was approved by the sponsoring organizations and represents an evidence-based and broadly accepted 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 (PIDDs). Preparation of this parameter included a review of the medical literature, mainly through 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 E1).[4] There are few randomized trials in the diagnosis and management of primary immunodeficiency. Thus the great majority of these recommendations represent evidence from published case series or reports or the opinions of experts in the field.

The pathophysiology of these disorders will not be discussed in detail; ample material can be found in the literature cited. The

TABLE E1. Classification of evidence and recommendations

Recommendation rating scale		
Statement	**Definition**	**Implication**
Strong recommendation (StrRec)	A strong recommendation means the benefits of the recommended approach clearly exceed the harms (or that the harms clearly exceed the benefits in the case of a strong negative recommendation) and that the quality of the supporting evidence is excellent (Grade A or B).* In some clearly identified circumstances, strong recommendations can be made based on lesser evidence when high-quality evidence is impossible to obtain and the anticipated benefits strongly outweigh the harms.	Clinicians should follow a strong recommendation unless a clear and compelling rationale for an alternative approach is present.
Moderate (Mod)	A recommendation means the benefits exceed the harms (or that the harms exceed the benefits in the case of a negative recommendation), but the quality of evidence is not as strong (Grade B or C).* In some clearly identified circumstances, recommendations can be made based on lesser evidence when high-quality evidence is impossible to obtain and the anticipated benefits outweigh the harms.	Clinicians should also generally follow a recommendation but should remain alert to new information and sensitive to patient preferences.
Weak	A weak recommendation means that either the quality of evidence that exists is suspect (Grade D)* or that well-done studies (Grade A, B, or C)* show little clear advantage to one approach versus another.	Clinicians should be flexible in their decision making regarding appropriate practice, although they can set bounds on alternatives; patient preference should have a substantial influencing role.
No recommendation (NoRec)	No recommendation means there is both a lack of pertinent evidence (Grade D) and an unclear balance between benefits and harms.	Clinicians should have little constraint in their decision making and be alert to new published evidence that clarifies the balance of benefit versus harm; patient preference should have a substantial influencing role.
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 quasiexperimental 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, 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,[4] with permission.

parameter consists of 239 summary statements (SSs). Each SS is formulated in a directive manner and contains a specific recommendation for diagnosis or management in general, for a specific disorder, or for a group of disorders. The SSs are annotated to provide a rationale or further elaboration along with literature references. The SSs and references are also "graded" according to the Classification of Recommendations and Evidence (Table E1). The SSs are divided into 9 sections. The first section contains general principles of diagnosis and management of PIDDs. The remaining 8 sections provide more detail regarding specific diseases or groups of diseases. In addition to the SSs, the parameter contains annotated algorithms and tables regarding diagnostic principles in various categories of PIDDs.

Although developed principally with the consultant allergist/immunologist as the target audience, it is hoped that the 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 providers and administrators in the managed care or insurance fields might also find useful information here. The developers of this 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.

SUMMARY STATEMENTS

General considerations

Summary statement 1. It is critical to maintain a high index of suspicion for PIDDs in patients presenting with recurrent infections, autoimmune disease, malignancy, and combinations of these conditions (D).

PIDDs result from inherited genetic defects that affect 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, environmental exposures, and anatomic factors) have been excluded. The true incidence of these disorders is unknown because this has not been studied prospectively. Individual PIDDs can be rare, but altogether, they might be relatively frequent. Estimated incidences vary from the common selective IgA deficiency (SIGAD) occurring in as many as 1 of 300 to 700 live births in American white subjects (although it is rarer in other ethnic groups, such as Asians) to the relatively rare chronic granulomatous disease (CGD; 1/200,000 live births).[5,6] However, most patients with SIGAD are asymptomatic. Altogether, registry and survey data from a variety of sources suggest an incidence for all symptomatic PIDDs ranging from 1 in 10,000 to 1 in 2,000 live births and a prevalence of 1 in 10,000 to 1 in 12,000 (or more) in the general population.[7,8] The incidence of severe combined immunodeficiency (SCID) is approximately 1:58,000 live births in the United States (also see SS 26).[9] In some consanguinous communities the incidence of PIDDs can be much higher.[8] The male/female ratio of PIDDs is approximately 5:1 in infants and children but approaches 1:1 in adults.[8,10]

PIDDs are classified according to the principal immunologic mechanisms that are disrupted, as well as their dominant clinical features. Immunologic effector mechanisms protect the host from infections, and impairment of 1 or more subsystems might be the consequence of a specific genetic lesion. Immune defense mechanisms and PIDDs can be subdivided into 2 broad categories: innate (antimicrobial factors acting at body surfaces, such as the integument and mucosa; complement and other antimicrobial elements in blood and body fluids; Toll-like receptors [TLRs]; phagocytic cells; and natural killer [NK] cells) and adaptive (lymphocyte-derived humoral and cellular mechanisms). Table E2 presents a list of PIDDs.

Antibody deficiency is the most common type of PIDD. Humoral or antibody PIDDs account for approximately half of all of these disorders.[8,10-12] Combined B- and T-cell defects, phagocyte defects, and other syndromes make up most of the remainder in varying proportions, each accounting for between 10% and 20% of the total.[8,11] Diseases of immune dysregulation, disorders of innate immunity (including NK cell defects), autoinflammatory disorders, and complement deficiencies are all relatively rare (each <1% of the total).

PIDDs usually present with signs and symptoms of infections that can be repetitive, severe, or refractory to therapy and caused by organisms of low virulence. Infection is by far the most common complication of PIDDs 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. Children with invasive pneumococcal disease should undergo immunologic investigation because up to 26% of these patients older than 2 years have an identifiable primary immunodeficiency.[13]

Severe PIDDs, such as SCID and many others, can also be associated with infections caused by low-grade or opportunistic organisms that are rarely pathogenic for immunocompetent subjects.[8,10,11]

Autoimmune diseases and malignancies are complications of many PIDDs. 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.[14] Malignancies also occur with greater frequency in patients with certain PIDDs. Most of these malignancies are hematologic in origin (lymphoma and leukemia).[15]

Many PIDDs have characteristic clinical features that can be an aid to diagnosis. Disorders of innate and adaptive immunity can each have characteristic features, although there might be considerable overlap among these diverse groups of diseases, even where distinct molecular defects have been defined (Table E3).[10,16,17]

Summary statement 2. Other conditions that can increase susceptibility to infection should be sought in patients with suspected PIDDs. (D)

Allergic inflammation can predispose patients to frequent bacterial infections, such as otitis media and sinusitis.[18,19] Adenoid hypertrophy can also be associated with frequent ear and sinus infections. Cystic fibrosis, ciliary dyskinesia, and abnormal lung anatomy can all be associated with recurrent respiratory tract infections. Lifestyle factors, such as older siblings, day care attendance, or passive (or active) smoke exposure, can also contribute to the frequency and severity of infections. Some or all of these conditions/circumstances should be investigated in patients being evaluated for PIDDs.

The physician must also exercise caution to rule out the possibility of secondary immunodeficiency (immunosuppression) underlying the patient's illness. Secondary immunodeficiency results from altered immune system function in association with immunosuppressive therapies, malnutrition, infiltrative diseases or malignancies, infectious diseases (eg, HIV infection or AIDS), protein-losing disorders, structural abnormalities or surgery, hereditary disorders, extremes of age, harsh climates, isolation, extreme stress, sleep deprivation, radiation, and idiosyncratic drug-induced adverse effects.[10,20]

Summary statement 3. It is important to confirm the precise focus of infection and organism when possible in any patient with known or suspected PIDDs. (F)

Imaging, biopsy, and/or culture data should be sought in support of a diagnosis of infection in any patient with a known or suspected PIDD. Many noninfectious conditions (eg, allergy or benign self-limiting viral infections) can cause symptoms and physical findings that might be difficult to distinguish from those caused by infectious diseases that require specific antimicrobial therapy. Identifying specific pathogens and foci of infections might provide important clues regarding a specific diagnosis of PIDD. These data are also important for accurate prescribing and for interpreting the response to therapy and might indicate the need for alteration in overall management in patients with known PIDDs.

Summary statement 4. A focused family history (eg, recurrent infections, absence of infections in siblings, early childhood deaths, and diagnosed PIDDs) should be obtained when the differential diagnosis includes a PIDD. (D)

Early in the disease course of an immunodeficient patient, the infection predisposition or susceptibility to unusually adverse outcomes might not be readily apparent, even if the PIDD symptoms are severe. Variable protection is afforded by immunoglobulin acquired from the mother during gestation, which

TABLE E2. Classification of primary immunodeficiencies*

Defect or disease(s)	Gene(s)
Combined B- and T-cell immunodeficiencies	
T^-B^+ severe CID	
IL-2R common gamma chain	*IL2RG*
Janus kinase 3	*JAK3*
IL-7Rα chain	*IL7RA*
IL-2Rα chain (CD25) deficiency	*IL2RA*
CD45 (protein tyrosine phosphatase, receptor type, C)	*PTPRC*
CD3δ	*CD3D*
CD3ε	*CD3E*
CD3ζ	*CD3Z*
Coronin 1A	*CORO1A*
T^-B^- SCID	
Recombinase activating genes 1 and 2	*RAG1/RAG2*
DNA cross-link repair enzyme 1C (Artemis)	*DCLRE1C*
DNA-dependent protein kinase	*PRKDC*
Adenylate kinase 2 (reticular dysgenesis)	*AK2*
Adenosine deaminase	*ADA*
DNA ligase IV	*LIG4*
Nonhomologous end-joining protein 1 (Cernunnos)	*NHEJ1*
OS	See SS 26
Less severe CID	
Purine nucleoside phosphorylase	*NP*
CD3γ	*CD3G*
CD8α	*CD8A*
ζ-Associated protein 70 kDa (ZAP-70)	*ZAP70*
Calcium channel defects	
Orai-1	*ORAI1*
Stromal interaction molecule 1 (Stim-1)	*STIM1*
Magnesium channel defects	
MAGT1 deficiency	*MAGT1*
MHC class I deficiency	
Transporters of antigenic peptides 1 and 2	*TAP1/TAP2*
TAP binding protein (tapasin)	*TAPBP*
MHC class II deficiency	
CIITA	*MHC2TA*
RFX5	*RFX5*
RFXAP	*RFXAP*
RFXANK	*RFXANK*
Winged helix deficiency (nude)	*FOXN1*
STAT5b	*STAT5B*
Cytidine triphosphate synthase 1	*CTPS1*
HIMs	
TNF superfamily member 5 (CD40L)	*TNFSF5*
TNF receptor superfamily member 5 (CD40)	*TNFRSF5*
RhoH deficiency	*RHOH*
MST1 deficiency	*STK4*
TCRα deficiency	*TRAC*
Lck deficiency	*LCK*
MALT1 deficiency	*MALT1*
IL-21R deficiency	*IL21R*
CARD11 deficiency	*CARD11*
OX40 deficiency	*OX40*
IKBKB deficiency	*IKBKB*
Syndromes with immunodeficiency	
Congenital thrombocytopenias	
WAS	*WAS*

(Continued)

TABLE E2. *(Continued)*

Defect or disease(s)	Gene(s)
WAS protein–interacting protein (WIP) deficiency	*WIPF1*
Non-SCID DNA repair defects	
AT	*ATM*
AT-like disorder	*MRE11*
NBS	*NBS1*
Bloom syndrome	*BLM*
MCM4 deficiency	*MCM4*
Immunodeficiency with centromeric instability and facial anomalies (ICF syndrome)	
ICF1 (DNA methyltransferase 3b)	*DNMT3B*
ICF2 (zinc finger and BTB domain containing 24)	*ZBTB24*
PMS2 deficiency	*PMS2*
Radiosensitivity, immunodeficiency, dysmorphic features and learning difficulties (RIDDLE) syndrome	*RNF168*
DGS	*del22q11, del10p13, TBX1*
CHARGE syndrome	*CHD7, SEMA3E*
Trisomy 21 syndrome	
CD4 lymphocytopenia	
Uncoordinated 119 deficiency	*UNC119*
Immuno-osseous dysplasias	
CHH	*RMRP*
Schimke syndrome	*SMARCAL1*
CID with skeletal dysplasia	*PGM3*
Comel-Netherton syndrome	*SPINK5*
HIESs	
Autosomal dominant (type 1, Job syndrome)	*STAT3*
Autosomal recessive (type 2)	*DOCK8*
HIES variant	*TYK2*
HIES variant	*PGM3*
Loeys-Dietz syndrome	*TGFBR1*
SAM syndrome	*DSG1*
Hepatic veno-occlusive disease with immunodeficiency (VODI)	*SP110*
DKC	
X-linked DKC (Hoyeraal-Hreidarsson syndrome)	*DKC1*
Autosomal recessive DKC	*NHP2, NOP10, RTEL1*
Autosomal dominant DKC	*TERC, TERT, TINF2*
Defects of vitamin B12 and folate metabolism	
Transcobalamin II deficiency	*TCN2*
Hereditary folate malabsorption	*SLC46A1*
MTHFD1 deficiency	*MTHFD1*
IKAROS deficiency	*IKZF1*
Facial dysmorphism, immunodeficiency, livedo, and short stature (FILS) syndrome	*POLE1*
Immunodeficiency with MIA	*TTC7A*
Hoffman syndrome	
Sideroblastic anemia with immunodeficiency, fevers, and developmental delay (SIFD)	*TRNT1*
Predominantly antibody deficiencies	
Agammaglobulinemia	
X-linked (Bruton) agammaglobulinemia	*BTK*
μ Heavy chain deficiency	*IGHM*
Ig-α deficiency	*CD79A*
Ig-β deficiency	*CD79B*
Surrogate light chain (λ 5) deficiency	*CD179B*

(Continued)

TABLE E2. *(Continued)*

Defect or disease(s)	Gene(s)
B-cell linker protein (BLNK) deficiency	*BLNK*
Leucine-rich repeat containing 8 deficiency	*LRRC8*
Phosphoinositide 3-kinase kinase deficiency	*PIK3R1*
E47 transcription factor deficiency	*TCF3*
Myelodysplasia with hypogammaglobulinemia	Monosomy 7, Trisomy 8
Thymoma with immunodeficiency (Good syndrome)	
CVID	
CVID-like disorders	
Inducible costimulator	*ICOS*
CD19	*CD19*
CD20	*CD20*
CD21	*CD21*
Target of antiproliferative antibody 1 (TAPA-1, CD81)	*CD81*
TACI	*TNFRSF13B*
B-cell activating factor receptor	*TNFRSF13C*
Phosphoinositol 3′ kinase catalytic subunit mutation	*PIK3CD*
Phosphoinositol 3′ kinase regulatory subunit 1 defect	*PIK3R1*
LPS-responsive beige-like anchor protein deficiency	*LRBA*
TWEAK deficiency	*TWEAK*
NF-κB2 deficiency	*NFKB2*
Protein kinase Cδ deficiency	*PRKCD*
Kabuki syndrome	*KMT2D*
SIGAD	
IGGSD	
IgA deficiency with IGGSD	
SAD	
THI	
Hypogammaglobulinemia, unspecified	
Class-switch defects	
AID deficiency	*AICDA*
Uracil-DNA glycosylase (UNG) deficiency	*UNG*
Immunoglobulin gene mutations/deletions	
Heavy chain locus deletions	*IGH*
κ-Chain deficiency	*IGLK*
Diseases of immune dysregulation	
FHL syndromes with hypopigmentation	
CHS	*LYST*
GS2	*RAB27A*
HPS type 2	*AP3B1*
FHL syndromes without hypopigmentation	
FHL1 (Unknown defect)	
Perforin deficiency (FHL2)	*PRF1*
UNC13D/Munc 13-4 deficiency (FHL3)	*UNC13D*
Syntaxin-11 deficiency (FHL4)	*STX11*
STXBP2/Munc 18-2 deficiency (FHL5)	*STXBP2*
Lymphoproliferative syndromes	
XLP1	*SH2D1A*
X-linked lymphoproliferative syndrome type 2	*XIAP*
Lymphoproliferative syndrome 1	*ITK*
Lymphoproliferative syndrome 2	*CD27*
Syndromes with autoimmunity	
ALPSs	

(Continued)

TABLE E2. *(Continued)*

Defect or disease(s)	Gene(s)
Fas defect: ALPS-FAS and sFAS (somatic)	*TNFRSF6*
Fas ligand defect: ALPS-FASLG	*TNFSF6*
Caspase 10 defect: ALPS-CASP10	*CASP10*
Unknown defect: ALPS-U	
ALPS-related disorders	
Caspase 8 deficiency syndrome (CEDS)	*CASP8*
K-Ras defect	*KRAS*
N-Ras defect	*NRAS*
Fas-associated via death domain defect (FADD) deficiency	*FADD*
CARD11 gain-of-function mutations	*CARD11*
STAT3 gain-of-function mutations	*STAT3*
APECED	*AIRE*
IPEX syndrome	*FOXP3*
IPEX-like disorders, STAT1/STAT3 gain-of-function mutations	*STAT1/STAT3*
CD25 defect	*IL2RA*
E3 ubiquitin protein ligase defect	*ITCH*
Cytotoxic T lymphocyte–associated protein 4 defect	*CTLA4*
Congenital defects of phagocyte numbers, function, or both	
Defects of neutrophil differentiation	
SCNs	
SCN1 (also cyclic neutropenia), neutrophil elastase defect	*ELANE*
SCN2, growth factor–independent 1 transcription repressor defect	*GFI1*
SCN3, HCLS1-associated protein X-1 defect (Kostmann syndrome)	*HAX1*
SCN4, glucose 6 phosphatase, catalytic, 3 defect	*G6PC3*
SCN5	*VPS45*
X-linked neutropenia/myelodysplasia	*WAS*
Glycogen storage disease type 1b	*SLC37A4*
Late endosomal/lysosomal adaptor, mitogen-activated protein kinase and MTOR activator 2P14 deficiency	*LAMTOR2*
Tafazzin defect (Barth syndrome)	*TAZ*
Cohen syndrome vacuolar protein sorting 13 homolog B	*VPS13B*
Poikiloderma with neutropenia (Clericuzio syndrome)	*C16orf57*
Defects of motility	
LAD	
LAD-I, CD18 (integrin β_2) defect	*ITGB2*
LAD-II, GDP-fucose transporter 1 defect	*FUCT1*
LAD-III, fermitin family member 3	*FERMT3*
Rac-2 defect	*RAC2*
β-Actin defect	*ACTB*
Localized juvenile periodontitis (formyl peptide receptor defect)	*FPR1*
Papillon-Lefevre syndrome (cathepsin C defect)	*CTSC*
SGD (CCAAT/enhancer binding protein [C/EBP], γ defect)	*CEBPG*
Schwachman-Diamond syndrome	*SBDS*
Defects of the respiratory burst	
CGD	

(Continued)

TABLE E2. *(Continued)*

Defect or disease(s)	Gene(s)
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*
p40^{phox}	*NCF4*
MSMD	
IL-12/23 receptor β1 deficiency	*IL12RB1*
IL-12 p40 deficiency	*IL12B*
IFN-γ receptor 1 deficiency	*IFNGR1*
IFN-γ receptor 2 deficiency	*IFNGR2*
STAT1 loss of function	*STAT1*
Interferon regulatory factor 8 deficiency	*IRF8*
Macrophage gp91^{phox} deficiency	*CYBB*
ISG15	*ISG15*
PAP	*CSF2RA, CSF2RB*
Defects of innate immunity	
GATA-2 deficiency (MonoMAC syndrome)	*GATA2*
Anhidrotic ectodermal dysplasia with immunodeficiency (EDA-ID)	
X-linked, nuclear factor-κB (NEMO) deficiency	*IKBKG*
Inhibitor of κB α gain of function (EDA-ID, AD)	*IKBA*
TIR signaling pathways	
IL-4 receptor–associated kinase 4 deficiency	*IRAK4*
MyD88 deficiency	*MYD88*
RBCK1 (HOIL1) deficiency	*RBCK1*
Type I interferonopathies	
Aicardi-Goutieres syndrome 1 (AGS1), TREX1 deficiency	*TREX1*
AGS2, RNASEH2B deficiency	*RNASEH2B*
AGS3, RNASEH2C deficiency	*RNASEH2C*
AGS4, RNASEH2A deficiency	*RNASEH2A*
AGS5, SAMHD1 deficiency	*SAMHD1*
AGS6, ADAR1 deficiency	*ADAR1*
SPENCD	*ACP5*
WHIM syndrome, chemokine (C-X-C motif) receptor 4 defect	*CXCR4*
EV	*TMC6, TMC8*
HSE	
Unc-93 homolog B1 *(C elegans)* defect	*UNC93B1*
TANK-binding kinase 1	*TBK1*
TLR adaptor molecule 1	*TICAM1*
TLR 3 defect	*TLR3*
TNF receptor–associated factor 3 defect	*TRAF3*
CMCC	
Caspase recruitment domain family, member 9 defect	*CARD9*
C-type lectin domain family 7, member A defect	*CLEC7A*
IL-17 receptor α chain defect	*IL17RA*
IL-17F defect	*IL17F*
STAT1 gain of function	*STAT1*
ACT1 deficiency	*ACT1*
Susceptibility to trypanosomiasis	*APOL1*
CD16 defect	*CD16*
ICA	*RPSA*
Autoinflammatory disorders	
CAPS	
FMF	*MEFV*

(Continued)

TABLE E2. *(Continued)*

Defect or disease(s)	Gene(s)
MVK deficiency (hyper-IgD syndrome)	*MVK*
MWS	*NLRP3*
CINCA syndrome or NOMID	
FCAS1	
FCAS2	*NLRP12*
Noninflammasome defects	
TNF receptor–associated periodic fever syndrome (TRAPS)	*TNFRSF1A*
PAPA syndrome	*PSTPIP1*
Blau syndrome	*NOD2*
CRMO dyserythropoietic anemia (Majeed syndrome)	*LPIN2*
DIRA	*IL1RN*
Deficiency of IL-36 receptor antagonist with generalized pustular psoriasis (DITRA)	*IL36RN*
SLC29A3 deficiency	*SLC29A3*
CARD14-mediated psoriasis (CAMPS)	*CARD14*
Cherubism	*SH3BP2*
Chronic atypical neutrophilic dermatosis with lipodystrophy and increased temperature (CANDLE) syndrome or Nakajo-Nishimura syndrome (NNS), proteasome subunit, β type, 8 defect	*PSMB8*
PLAID	*PLCG2*
Stimulator of interferon genes (STING) defect	*TMEM173*
Adenosine deaminase 2 defects	*ADA2*
Early-onset inflammatory bowel disease	*IL-10, IL10RA, IL10RB*
Periodic fever associated with aphthous stomatitis, pharyngitis and cervical adenitis (PFAPA) syndrome	Unknown
Complement deficiencies	
C1	
C1q α	*C1QA*
C1q β	*C1QB*
C1q γ	*C1QC*
C1r	*C1R*
C1s	*C1S*
C2	*C2*
C3	*C3*
C4	*C4A, C4B*
C5	*C5*
C6	*C6*
C7	*C7*
C8	
C8 α	*C8A*
C8 β	*C8B*
C8 γ	*C8G*
C9	*C9*
C1 inhibitor deficiency	*SERPING1*
Factor B	*CFB*
Factor D	*CFD*
Factor H	*CFH*
Factor H–related protein deficiency	*CFHR1-5*
Factor I	*CFI*
Properdin	*CFP*
MBL deficiency	*MBL*
MBL-associated protease 1 (MASP1) deficiency	*MASP1*
MBL-associated serum protease 2 deficiency	*MASP2*
Ficolin 3 deficiency	*FCN3*

(Continued)

TABLE E2. *(Continued)*

Defect or disease(s)	Gene(s)
Thrombomodulin	*THBD*
Membrane cofactor protein (CD46) deficiency	*CD46*
Membrane attack complex inhibitor (CD59) deficiency	*CD59*
COLEC11 deficiency	*COLEC11*
Complement receptor 2 deficiency	*CD21*
Complement receptor 3 deficiency	*ITGB2*
Immunodeficiency associated with autoantibodies	
Acquired angioedema	Anti–C1 inhibitor
Neutropenia/Felty syndrome	Anti–G-CSF
Cryptococcal meningitis/PAP	Anti–GM-CSF
Disseminated varicella-zoster/APECED	Anti–IFN-α/β
Disseminated infections (virus, bacteria, fungi)	Anti–IFN-γ
Recurrent bacterial skin infections/sepsis	Anti–IL-6
Disseminated *Burkholderia gladioli* infection	Anti–IL-12p70
CMCC/APECED	Anti–IL-17, anti–IL-22

*The classification is based on the format used by the WHO/IUIS.[3] The authors have attempted to use the Human Genome Organization name for each gene current at the time of publication of this document. The reader should be aware that this nomenclature is fluid, and some names might have changed.

could delay the onset of some severe infections. It is imperative to thoroughly evaluate the family history for cases of possible PIDDs to raise diagnostic suspicion and suggest screening evaluation or at least increased vigilance and monitoring in the short term.[8,10] Both a family history positive for manifestations of PIDDs and the absence of infections in siblings of a patient who is frequently sick are suggestive of an enhanced susceptibility to infection in a child.

Summary statement 5. A stepwise approach is recommended to evaluate suspected PIDDs. (D)

Screening tests used to evaluate patients with suspected PIDDs are relatively inexpensive, performed rapidly, and reasonably sensitive and specific.[8,10,21] Abnormal screening test results indicate the need for more sophisticated tests. Table E4 lists screening and advanced tests used for PIDD diagnosis. Table E5 lists Internet resources for physicians and patients with PIDDs. Fig E1 describes the fundamentals of the initial approach to the evaluation of a potentially immunodeficient patient. Approaches to the diagnosis of each category of PIDD are summarized in figures and tables that will be referenced in the respective sections of summary statements.

Summary statement 6. Evaluation of specific immune responses is essential for diagnosis of PIDDs. (C)

Measurement of serum immunoglobulin levels and lymphocyte responses to mitogens are useful indicators of global B- and T-cell development and function. However, the results of these studies might appear normal in many patients with primary immunodeficiencies because they are not sensitive indicators of specific immunity (ie, 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.[21] These substances differ in how they stimulate antibody production, and clinically significant disease can result from a selective inability to respond to polysaccharide antigens (see also SS 105). Note that in patients with findings consistent with agammaglobulinemia (see the section on antibody deficiencies), measurement of specific antibody responses might not be necessary.

Antibody levels for protein vaccine antigens, such as tetanus and diphtheria toxoids, are often determined. Antibodies against

TABLE E3. Characteristic clinical presentations of some immunodeficiency disorders

Diagnosis	Symptoms and/or clinical presentation
CIDs	
SCID	Failure to thrive, diarrhea, severe/disseminated infections, opportunistic infections, rash; abnormal newborn screen*
CD40L deficiency	Recurrent serious pyogenic infections, opportunistic infections (PCP)
Immunodeficiency syndromes	
WAS	Thrombocytopenia with bleeding and bruising, eczema, recurrent infection with encapsulated organisms, autoimmunity
AT	Chronic sinopulmonary disease, cerebellar ataxia, oculocutaneous telangiectasia, malignancy
DGS	Hypocalcemic seizures caused by hypoparathyroidism, cardiac disease, abnormal facies, infection, abnormal newborn screen*
Antibody deficiency	Recurrent sinopulmonary infections with encapsulated bacteria, recurrent viral respiratory tract and gastrointestinal infections
Immune dysregulation	Autoimmunity, lymphoproliferation, HLH
Phagocytic cell defects	
CGD	Deep-seated infection, abscess with granuloma formation
LAD	Recurrent serious bacterial infections, delayed separation of the umbilical cord; poor wound healing, lack of pus
HIES type 1	Chronic dermatitis, recurrent serious infection of the lungs with pneumatoceles; skin infections, bone fragility, failure to shed primary teeth
MSMD	Severe mycobacterial and *Salmonella* species infections
Innate immune defects	
NEMO deficiency	Severe bacterial infections, opportunistic infections, anhidrotic ectodermal dysplasia
IRAK-4 defect	Severe gram-positive bacterial infections in early childhood
CMCC	Chronic skin and mucous membrane fungal infections
HSE	Herpes simplex encephalitis
EV	Severe disseminated cutaneous papillomatosis
Autoinflammatory disorders	Episodic fever often associated with dermatitis, gastrointestinal symptoms, and arthropathy
Complement deficiency	Recurrent bacterial infections (encapsulated strains, *Neisseria* species), autoimmunity
Immunodeficiency associated with autoantibodies	
Anti–GM-CSF autoantibodies	Cryptococcal meningitis and PAP (alone or together)
Anti–IFN-γ autoantibodies	Disseminated infections with mycobacteria, *Salmonella* species, *Cryptococcus* species, *Histoplasma* species, *Penicillium* species, and varicella-zoster virus

*Many states are now screening for SCID (see SS 26). Some infants with DGS (and other disorders) might be detected by this newborn screening. See Table II for abbreviations.

TABLE E4. Laboratory tests of immune function

Screening tests	Advanced tests
Humoral immunity	
Serum immunoglobulin levels	Flow cytometry to enumerate B-cell subsets (eg, naive and switched memory cells)
Serum specific antibody titers	*In vitro* immunoglobulin production in response to mitogens or other stimuli
Antibody response to booster immunization	Antibody response to immunization with ϕX174
Flow cytometry to enumerate total B cells	
Cellular immunity	
TREC newborn screening	Flow cytometry to enumerate T-cell subsets (eg, naive, memory, and activated cells)
Flow cytometry to enumerate CD4 and CD8 T cells and NK cells	*In vitro* proliferative response to mitogens and antigens
Cutaneous delayed hypersensitivity	T-cell cytotoxicity
Spontaneous NK cytotoxicity	*In vitro* surface marker expression and cytokine production in response to stimuli
	Cytoplasmic protein phosphorylation in response to stimuli
Phagocytic cells	
Blood cell count with differential	Chemotaxis and/or phagocytosis assay
Neutrophil staining, morphology on a peripheral blood smear	Enzyme assays (myeloperoxidase, G6PDH)
DHR reduction or nitroblue tetrazolium	WBC turnover
Flow cytometry for adhesion molecules	Bacterial or fungal killing
	Bone marrow biopsy
Complement	
CH50 assay (total hemolytic complement activity)	Level or function of individual complement components
AH50 assay (alternative pathway hemolytic activity)	
Lectin pathway function	
Genetic tests	
Microarray for copy number variation	Targeted gene sequencing
	Whole-exome/genome sequencing

TABLE E5. Internet resources for PIDDs

URL	Name/description
http://bioinf.uta.fi/idr/Immunology.shtml	ImmunoDeficiency Resource, University of Tampere, Finland
http://www.aaaai.org	American Academy of Allergy, Asthma & Immunology
http://www.esid.org	European Society for Immunodeficiencies
http://www.immunodeficiencysearch.com	Searchable database, clinical algorithms, laboratory resources
http://www.info4pi.org	Jeffrey Modell Foundation/Primary Immunodeficiency Resource Center
http://www.ipidnet.org	Immune Phenotyping in Primary Immunodeficiency
http://www.ipopi.org	International Patient Organization for Primary Immunodeficiencies
http://www.primaryimmune.org	Immune Deficiency Foundation
http://rapid.rcai.riken.jp/RAPID	Resource of Asian Primary Immunodeficiency Diseases (RAPID)
http://www.usidnet.org	US Immunodeficiency Network (USIDNET)

the polyribosyl ribitol phosphate (PRP) capsular polysaccharide of *Haemophilus influenzae* type B (HIB) can 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 (Prevnar and Prevnar 13) 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 might be a useful indicator of polysaccharide immunity.[22]

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 might more clearly identify an antibody production defect. Postvaccination levels can be determined after 3 to 4 weeks. General standards of normal responses are an at least 4-fold increase for protein antigens.

IgG specific for serotypes included in currently used pneumococcal vaccines can be determined by using a standardized ELISA method and expressed in micrograms per milliliter.[23] The most accurate type-specific determinations are made with a reference standard serum (US Food and Drug Administration SF89) and preadsorption with C polysaccharide common to all types and the 22F polysaccharide, which is cross-reactive. Protection against infection and colonization is associated with antibody concentrations of 1.3 μg/mL or greater or 200 to 300 ng of antibody nitrogen per milliliter per serotype by using a conversion factor of 160 ng of antibody N/mL to 1 μ/mL.[24] This value has been adopted extensively to reflect immunocompetence, although protection against invasive pneumococcal infections, but not pneumonia and mucosal infections, such as otitis media and sinusitis, has been associated with values as low as 0.35 μg/mL.[25,26] New multiplex assays that are being used by some

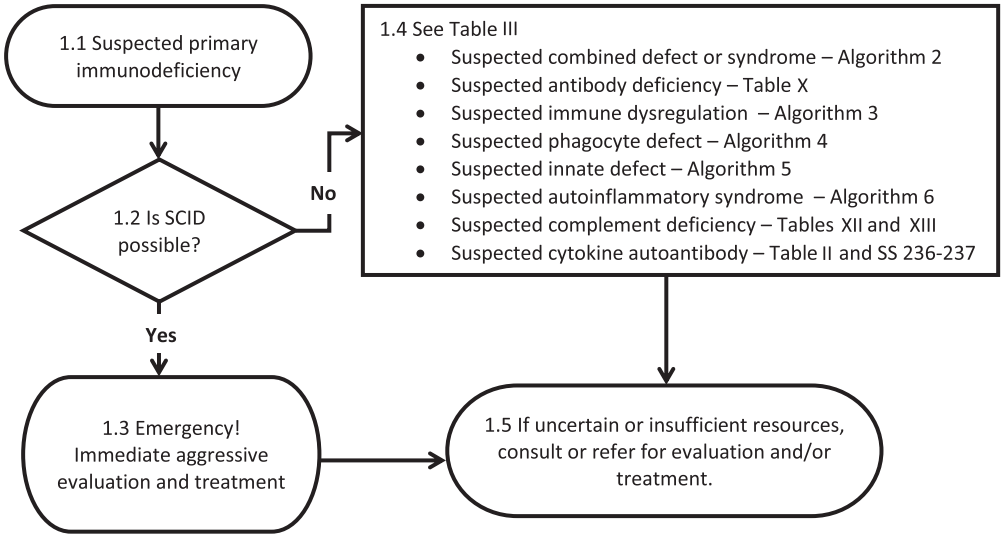

FIG E1. General approach for the diagnosis of primary immunodeficiency. *1.1*, The patient exhibits symptoms and signs consistent with a PIDD. It is assumed that immunosuppressive therapy and other medical conditions potentially resulting in secondary immunodeficiency and other anatomic or biochemical conditions potentially predisposing to infection either have been excluded or are not considered sufficient to explain the observed degree of infection susceptibility (see SS 2). *1.2*, Is the clinical presentation and initial laboratory evaluation consistent with SCID (see SS 26)? *1.3*, If the answer to 1.2 is yes, then the evaluation and management must be expedited as much as possible. Patients with SCID are fragile and extremely susceptible to infection. Early HSCT is associated with better outcomes, whereas complications before HSCT indicate poorer prognosis. *1.4*, If the answer to 1.2 is no, then another PIDD should be sought. The characteristic clinical presentations of various categories of PIDDs are summarized briefly in Table III. Diagnostic information and algorithms for these categories are presented in Figs 2 to 6; Tables II, X, XII, XIII; and SSs 236 and 237. *1.5*, If there is uncertainty or lack of resources for patient evaluation or care, consultation with or referral to a provider with experience with PIDDs should be undertaken. Although not stated explicitly in the figures that follow, this consideration is implicit in the course of evaluation and treatment of all patients with PIDDs (see SS 24).

laboratories are not yet adequately standardized, and their results cannot be interpreted according to the same criteria established for interpretation of results obtained by using ELISA.[27,28] For further discussion of assessment of pneumococcal immunity, see SS 105.

For evaluation of primary antibody responses or measurements of antibody responses in patients who might already be receiving immunoglobulin replacement, immunization with bacteriophage ϕX174 can be undertaken.[29,30] There is no natural exposure to this prokaryote virus in human subjects; it will elicit a response even in infants. The test is applied rarely for clinical diagnostic purposes and 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. These can be determined in patients of all ages, even neonates. *In vitro* proliferation to specific antigen (eg, tetanus toxoid or monilia antigen) might be a more sensitive test for cellular immunodeficiency.[21,31,32] These results can be informative in fully immunized infants beyond 6 to 12 months of age. 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.[21] As in the purified protein derivative or tuberculin reaction (Mantoux test), induration and erythema develop 48 to 72 hours after intracutaneous injection of recall antigen (eg, tetanus toxoid, monilia, or other 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, and results are suppressed by steroid therapy and intercurrent viral illnesses.

Summary statement 7. PIDDs should be defined at the molecular genetic level if management could be affected. (F)

Establishing the precise genetic lesion responsible for an immunodeficient phenotype is desirable for the following reasons: (1) unequivocal diagnosis, prognosis, and treatment; (2) accurate genetic counseling and planning for future pregnancies or their outcomes; (3) definition of genotype-phenotype associations; and (4) identification of candidates for gene-specific therapies.[33,34] If a definitive genetic diagnosis is determined, formal genetic counseling can be considered. Establishing a molecular diagnosis also permits *in utero* diagnosis in the case of future pregnancies. The cost-benefit analysis for molecular diagnosis must be assessed on a case-by-case basis.

Summary statement 8. The possibility of an X-linked PIDD should be considered, even in female patients, when other possibilities have been ruled out. (D)

Extreme nonrandom X-chromosome inactivation can lead to expression of the phenotype associated with an X-linked recessive disease in a female carrier. This has been described for CGD,[35] Wiskott-Aldrich syndrome (WAS),[36,37] X-linked agammaglobulinemia (XLA),[38] and CD40 ligand (CD40L) deficiency.[39]

Summary statement 9. Carrier status should be determined for all potentially affected relatives of patients with severe PIDDs. (D)

It is essential for informed family planning that all potential carriers of PIDDs be identified.[40] This is most important where the PIDD is potentially life-threatening or carries significant morbidity in spite of therapy (see SS 7).

Summary statement 10. After diagnosis of a PIDD, it is important to proceed quickly with preventive therapy, replacement therapy, or both. (C)

Early diagnosis and therapy are the keys to survival and a better quality of life for immunodeficient patients. Delays in immunologic reconstitution can lead to permanent organ damage (eg, bronchiectasis or bronchiolitis obliterans) or death from overwhelming infection.[8,10,20,41,42]

Summary statement 11. Immunoglobulin replacement therapy is indicated for all disorders with significantly impaired antibody production. (B)

The effectiveness of polyclonal human IgG for reducing serious bacterial infections in patients with XLA and those with common variable immunodeficiency (CVID) is well documented.[43,44] Therapeutic IgG is also used for combined defects with significantly impaired antibody production. IgG replacement therapy might be necessary even after definitive therapy, such as hematopoietic stem cell therapy (HSCT), if B-cell function is not restored.[45] Table E6 summarizes therapeutic considerations for many of the PIDD diagnoses discussed in this practice parameter. See specific content areas for more details.

Summary statement 12. In association with low IgG levels, IgA deficiency is not a contraindication to IgG therapy. (C)

Some patients with antibody deficiency alone or with combined immunodeficiency (CID) lack serum IgA (<7 mg/dL). IgG therapy will be indicated for many of these patients (except those with SIGAD, see SS 98). Very rare patients who lack serum IgA have had anaphylaxis after intravenous immunoglobulin (IVIG) administration.[46-48] Anecdotal data suggest that in some of these cases the reaction might be due to the occurrence of high levels of IgG anti-IgA antibodies in the recipient and small amounts of IgA contaminating the IVIG. However, the rarity of these events must be emphasized; the risk to any individual IgA-deficient patient is very small. Also note that some of these patients have tolerated subcutaneous IgG infusions without reactions even after having anaphylaxis with IVIG.[47]

Summary statement 13. Patients receiving IgG therapy should have regular monitoring of IgG trough levels, blood cell counts, and serum chemistry. (D)

The principles of prospective routine monitoring of patients receiving IgG replacement in general are modeled on patients with CVID (see SSs 85-93).[49] The frequency of monitoring depends on age (more frequent monitoring is advisable in younger growing children) and the clinical considerations of the individual patient. A minimum of every 6 to 12 months is standard. The adequacy of IgG replacement is determined by the trough (preinfusion) or steady-state IgG level in association with the clinical course. The dose might need to be adjusted for excessive infections (poor clinical response), growth or weight change, or other processes, such as enteric loss or increased metabolism. The steady-state IgG level is also useful for monitoring adherence of patients receiving subcutaneous immunoglobulin (SCIG) infusions.

Autoimmune cytopenias are common in many forms of immunodeficiency, and blood cell counts should be followed. The risk of transmission of hepatitis is very low, but it is considered standard to monitor liver enzymes prospectively. Furthermore, liver disease can occur in patients with some forms of immunodeficiency. IVIG can exacerbate renal disease and can occur *de novo* in patients with a variety of conditions; levels of creatinine, blood urea nitrogen, or both should also be monitored.

Additional monitoring might be indicated based on an individual patient's specific complications. Patients with paraproteins and other medical conditions affecting the cardiovascular system (eg, diabetes mellitus) are at increased risk for thrombosis.[50,51] IgG should be administered slowly or through the subcutaneous route in patients with these disorders. Hemolysis can occur, especially after high-dose IVIG infusions.[52] This is rare in replacement therapy but should be studied if suspected. Additional recommendations can be found in specific product prescribing information.

Summary statement 14. The placement of permanent central venous access solely for the purpose of IVIG administration should be discouraged. (F)

Permanent central venous catheters can be associated with thrombotic and infectious complications.[53] For patients who require intravenous access only for IgG administration every 2 to 4 weeks, permanent indwelling catheters might not represent an acceptable risk. Difficult venous access need not be a compelling indication for catheter placement with the growing availability of subcutaneous IgG infusion.[54]

Summary statement 15. Aggressive and prolonged antimicrobial therapy should be considered for immunodeficient patients. (C)

The standard dose and duration of antimicrobial regimens might not be adequate to eradicate infections in immunocompromised hosts. Early combined antimicrobial therapy and prolonged courses should be considered.[41,49]

Summary statement 16. Short- or long-term antimicrobial prophylaxis should be considered for patients with immunodeficiency. (C)

Patients with severe T-cell deficiency or dysfunction might require prophylaxis for *Pneumocystis jirovecii* pneumonia (PCP), as well as some viral, such as varicella or respiratory syncytial virus (RSV), or fungal infections. PCP prophylaxis is discussed in SS 29. Other considerations of viral and fungal prophylaxis are discussed in statements regarding specific disorders for which these are recommended.

Long-term antibiotic therapy might be required in addition to immunoglobulin replacement for preventing infection in antibody-deficient patients. Bacterial infections can continue at a reduced rate in patients with agammaglobulinemia or other antibody deficiency, even with immunoglobulin replacement.[55,56] Long-term antibiotic therapy can be added to immunoglobulin replacement in other settings as dictated by the clinical condition of the patient or disease course.[49,57] Evidence of benefit for prevention of recurrent otitis media exists in studies of immunocompetent children.[58] Meta-analysis also has shown benefit for prevention of bacterial infections after chemotherapy-induced neutropenia.[59] A higher rate of isolation of antibiotic-resistant organisms has been found in some but not all studies of otitis media prophylaxis.[58] Apart from CGD, there are no prospective studies of antibiotic prophylaxis in patients with PIDDs, and there are no reports of serious complications caused by antibiotic-resistant

TABLE E6. Summary of therapeutic considerations for primary immunodeficiencies and their complications

Diagnosis	IgG*	HSCT	Gene therapy	
CIDs				
SCID (*IL2RG*, ADA)	Yes	Yes	Yes	• Avoid live vaccines: all • PCP prophylaxis: all SCID, CD40, CD40L • Antimicrobials as needed • Blood products irradiated, CMV^{-}: all • ADA: PEG-ADA • CD40, CD40L: G-CSF
SCID (other)	Yes	Yes	No	
CD40L deficiency	Yes	Yes	No	
Other CID	Yes	Many	No	
Immunodeficiency syndromes				
WAS	Yes	Yes	Yes	• Avoid live vaccines: many • Multidisciplinary care: many • WAS: splenectomy • DGS: thymus transplantation • Immunomodulation as needed • Chemotherapy as needed
AT	Some	No	No	
DGS	Some	No	No	
Other syndromes	Some	Some	No	
Antibody deficiency				
Agammaglobulinemia	Yes	No	No	• Avoid live vaccines: agammaglobulinemia, CVID • Antibiotics: all • Splenectomy: CVID • Immunomodulation: CVID • Chemotherapy: CVID • Pneumococcal vaccine: SIGAD, IGGSD, SAD
CVID	Yes	Rare	No	
Other antibody deficiency	Yes	No	No	
Immune dysregulation				
FHL	No	Yes	No	• Antimicrobials as needed • Chemotherapy as needed • Immunomodulators as needed
ALPS	No	Yes	No	
IPEX	No	Yes	No	
APECED	No	No	No	
Other	Some	Some	No	
Phagocytic cell defects				
Neutropenia	No	Yes	No	• Avoid live bacterial vaccines: all • Antimicrobial prophylaxis: all • IFN-γ: CGD • Surgical or dental debridement: CGD, LAD-I • Granulocyte transfusions: CGD, LAD-I • G-CSF: neutropenias • Fucose: LAD-II
CGD	No	Yes	Yes	
LAD	No	Yes	No	
HIES type 1	Some	Rare	No	
MSMD	No	Some	No	
Innate immune defects				
NEMO deficiency, other NF-κB defects	Yes	Yes	No	• Avoid live vaccines: NF-κB • PCP prophylaxis: NF-κB • Antimicrobial prophylaxis: NF-κB, CMCC • G-CSF: WHIM syndrome • Antiviral prophylaxis: HSE
CMCC	No	No	No	
WHIM syndrome	Yes	Some	No	
HSE	No	No	No	
EV	No	No	No	

(Continued)

TABLE E6. *(Continued)*

Diagnosis	IgG*	HSCT	Gene therapy	
Autoinflammatory disorders	No	No	No	• Cytokine (IL-1, TNF, IL-6) inhibitors: CAPS, DIRA, PAPA, PSMB8, TRAPS • Steroids: Blau syndrome, DITRA, HIDS, TRAPS • Retinoids: DITRA • Colchicine: TRAPS
Complement deficiency	No	No	No	• Antibiotics: all • Pneumococcal vaccine: C1, C2, C3, C4 • Meningococcal vaccine: C5-C9 • Immunomodulators: C1, C2, C4, factors H and I
Cytokine autoantibody-mediated disorders	Possible	No	No	• Plasmapheresis • Rituximab • Cytokine supplement

*Yes or No indicates whether or not IgG replacement is a component of standard therapy for this disorder.

organisms in patients with antibody deficiency receiving antibiotic prophylaxis with or without concomitant IgG replacement for the prevention of respiratory tract infections. Some regimens of antibiotic prophylaxis are shown in Table E7. Specific diagnoses (eg, SCID, CGD, or CD40L deficiency) can have associated specific recommendations regarding antimicrobial prophylaxis.

Summary statement 17. Lung imaging and function should be monitored regularly in patients with a history of or who are at risk for recurrent pneumonia and/or other chronic lung damage or disease. (C)

Recurrent respiratory tract infections are the most frequent manifestations of PIDDs.[60] Bronchiectasis and a variety of other forms of infiltrative and inflammatory lung disease occur in patients with various types of PIDDs, and progression of lung disease is an important component of overall morbidity, mortality, and quality of life. High-resolution computed tomographic (CT) scanning of the chest is the most sensitive screening test to ascertain underlying pulmonary disease. If never performed or if last done in the relatively remote past, a study should be performed at the time of PIDD diagnosis.[49] Chest CT scans should be repeated as dictated by the patient's clinical situation. It is possible for lung disease to progress without overt clinical deterioration. It is unknown whether functional assessment is sufficient by itself to monitor disease status and progression. However, functional testing is noninvasive and does not involve radiation. Periodic spirometry or formal pulmonary function testing should be performed in patients with a history of or who are at risk for chronic lung disease of any type. The potential benefit of routine sequential radiographic imaging must be weighed against the potential risk of cumulative radiation exposure.

Summary statement 18. Surgical procedures undertaken with the aim of reducing infection susceptibility should be approached with caution in patients with known or suspected PIDDs. (F)

A role for surgery in the prevention and treatment of infection in immunodeficient patients has not been established. Optimal medical management, including immunoglobulin, antibiotics, and anti-inflammatory medications, might still not completely control chronic bacterial rhinosinusitis in immunodeficient patients.[61] Although there is certainly a theoretical basis for possible benefit, the efficacy of surgical procedures, such as tympanostomy tube placement, tonsillectomy/adenoidectomy, or functional endoscopic sinus surgery, for the treatment, prevention, or both of otitis media and sinusitis in immunodeficient patients has not been established. Anecdotal reports suggest that efficacy might be less than in the general population. In one study of 18 children with otorrhea of more than 6 months' duration after tympanostomy tube placement, 17 had immunologic abnormalities.[62] Most were nonspecific but included both antibody and cellular (combined) deficiencies and complement defects. In one study of functional endoscopic sinus surgery in 23 pediatric patients, 5 required intravenous antibiotics in addition to surgery for resolution of chronic rhinosinusitis.[63] Four of these 5 patients were subsequently given a diagnosis of a PIDD.

Summary statement 19. The recommended definitive therapy of cellular or combined PIDD is reconstitution by hematopoietic stem cells. (B)

Severe cellular PIDDs are much more serious than other types because of the almost certain demise early in life from infection.[8,10] Fortunately, HSCT has given hope to parents of infants with SCID and related combined B- and T-cell deficiencies, with 70% to near 95% survival depending on several factors, including the type of cellular PIDD, presence of pre-HSCT infections, age at HSCT, HLA matching, chemotherapeutic preconditioning regimen, and experience of the transplantation center.[42,64] Phagocyte deficiencies are now becoming more amenable to HSCT as experience with matched unrelated donor and cord blood donor transplants is increasing.[65,66] Gene therapy of PIDDs has met with some success, but the unexpected complication of T-cell malignancy in patients with X-linked severe combined immunodeficiency (XSCID) has tempered the initial successful results.[33,67] However, gene therapy for adenosine deaminase (ADA)–SCID has also been very successful and (thus far) without the problem of insertional mutagenesis.[68] Early results of gene therapy for WAS appear promising, but one of 8 children treated sustained a leukemogenic event.[33,69] Improvement in viral vectors that do not promote oncogenesis will avoid development of malignancies as a consequence of gene therapy.[33,34] Several other genetic repairs of PIDDs are being attempted at this time, including recombination-activating gene (RAG) 2 deficiency; Artemis deficiency; immunodeficiency, polyendocrinopathy, X-linked (IPEX) syndrome; and hemophagocytic lymphohistiocytosis (HLH).[33] A novel development for cure of the DiGeorge syndrome (DGS) and its associated primary hypoparathyroidism is the simultaneous transplantation of neonatal thymus and parental parathyroid tissue, a procedure that induces host tolerance to the parathyroid graft.[70]

TABLE E7. Regimens for prophylaxis of bacterial respiratory tract infections

Antibiotic	Regimen for children	Regimen for adults
Oral agents*		
Amoxicillin (consider with clavulanate, if necessary)	10-20 mg/kg daily or twice daily	500-1,000 mg daily or twice daily
Trimethoprim (TMP)/ sulfamethoxazole (dosing for TMP)	5 mg/kg daily or twice daily	160 mg daily or twice daily
Azithromycin	10 mg/kg weekly or 5 mg/kg every other day	500 mg weekly or 250 mg every other day
Clarithromycin	7.5 mg/kg daily or twice daily	500 mg daily or twice daily
Doxycycline	Age >8 y; 25-50 mg daily or twice daily	100 mg daily or twice daily
Inhaled agents		
Gentamicin	Age >6 y: 80 mg twice daily, 28 days on, 28 days off OR: 21 days on, 7 days off	
Tobramycin	Age >6 y: 300 mg twice daily, 28 days, on 28 days off	

*These are commonly used regimens.[57] If these agents are not effective or are not tolerated, other drugs can be considered, including cefuroxime, cefprozil, cefpodoxime, ciprofloxacin or other quinolone, or others, depending on the individual circumstances of the patient.

Improved survival of infants with SCID who underwent HSCT depends on implementation of universal neonatal screening for T-cell cytopenia. Children with SCID or related T-cell deficiencies can be rescued by early diagnosis and definitive HSCT, thus avoiding the debilitating effects of opportunistic infections.[71-73] The T-cell receptor excision circle (TREC) assay can diagnose T-cell deficiencies at birth. Drops of blood on Guthrie cards (used for routine newborn metabolic and hematologic screening) can be used to measure TREC numbers. Low numbers are indicative of T-cell PIDDs. In some forms of SCID (eg, ADA deficiency), some T cells can be present at birth but wane or disappear later. These cases can be missed by TREC screening, but there are insufficient data yet to say how often such a case might occur.[74]

Summary statement 20. Only irradiated, cytomegalovirus (CMV)–negative, lymphocyte-depleted cellular blood products should be administered to patients with cellular or combined PIDDs. (C)

Patients with impaired cellular immune function might not be able to eliminate viable lymphocytes contained in whole blood, packed red blood cells, or platelets.[75] These lymphocytes can become activated by HLA incompatibility and cause severe (sometimes fatal) graft-versus-host disease (GVHD). Irradiation renders lymphocytes incapable of undergoing cell division if they are activated and reduces the occurrence of transfusion-associated GVHD, and use of CMV-negative donors prevents opportunistic infections caused by CMV.

Summary statement 21. Live vaccines should not be administered to patients with severely impaired specific immunity. (C)

Guidelines regarding the use of live vaccines in patients with PIDDs have recently been published.[76] Currently available live viral or bacterial vaccines include BCG, oral polio virus, measles-mumps-rubella, oral typhoid, varicella, and yellow fever. Because disseminated disease with attenuated organism vaccines has been observed in severely immunocompromised patients after inoculation, these live vaccines are contraindicated in these patients.[76,77] The live rotavirus vaccine has produced severe diarrhea in several children with SCID before their diagnosis, and rotavirus vaccine is now added to that list of live virus vaccines to be avoided in immunodeficient children.[78] In general, live vaccines should also be withheld from patients with milder PIDDs because they have not been rigorously studied with respect to risk or benefit in this population. Recent data suggest that risk is low in some situations (eg, partial DGS).[79,80] Patients receiving IgG replacement therapy will have circulating antibodies 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 the vaccines would be inactivated.[81] After a single replacement IVIG dose (300-800 mg/kg), measles-mumps-rubella or varicella immunization should be delayed by 8 months. The interval should be extended to 11 months after high-dose (2 g/kg) infusion.

Summary statement 22. Inactivated or subunit vaccines can be administered to immunocompromised patients. (C)

There is no risk of disease from killed or microbial subcomponent vaccines. Because there might be some protective immunity after inoculation, even in immunocompromised hosts, these vaccines can be given according to routine indications and schedules.[77] Particular consideration should be given to those vaccine agents for which polyclonal human IgG might not provide coverage, such as influenza.[82] Immunization beyond routine guidelines can be considered therapeutic in some circumstances, such as patients with phagocytic cell defects and complement deficiency (see the relevant sections below).

Summary statement 23. Education for patients and families with PIDDs is recommended for optimal outcomes. (F)

Patients and families must understand the inheritance, causes, manifestations, and natural histories of their PIDDs. They can access organizations (Table E5) 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.

Summary statement 24. Patients with suspected or diagnosed PIDDs are recommended to have evaluation and follow-up by a clinical immunologist with experience with these disorders. (F)

Although it is appropriate for primary care physicians and other health care professionals to conduct screening evaluations for PIDDs, 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.[10,41,55] Physical examination should include careful inspection for signs of infection. Despite IgG replacement or other therapy, infections can occur. Pulmonary function should be measured serially. Deteriorating function is an indication for a chest radiograph or CT scan. Some advocate periodic chest CT scans even with preserved function because progressive abnormalities can be observed and might require intensification of treatment. Depending on the particular PIDD, symptoms and signs of autoimmune disease or malignancy should also be

sought.[83,84] The presence of lymphadenopathy or splenomegaly might be signs of lymphoproliferative disease or malignancy. For patients with established PIDD diagnoses, 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 PIDDs.

Summary statement 25. A coordinated multidisciplinary approach to management should be considered in patients with PIDDs. (F)

The multisystem nature of many PIDDs necessitates an integrated multidisciplinary approach to management. Such care optimizes medical treatment and permits integration of physical and occupational therapy, for example, 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, especially when there are multiple organ systems affected or there is any possible consideration for HSCT.

Combined B- and T-cell immunodeficiencies

Severe combined immunodeficiency.

Summary statement 26. Severe combined immunodeficiency (SCID) should be considered in the differential diagnosis when an infant presents with recurrent, persistent, or severe bacterial, viral, or fungal infections or failure to thrive. (C)

SCID designates a group of syndromes in which there is a complete lack of specific lymphocyte-dependent adaptive immunity.[85,86] These patients experience 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, although usually nonpathogenic organisms (opportunistic infections) are also seen. Infections usually do not remain localized; disseminated disease is frequent. Failure to thrive and a variety of nonspecific skin eruptions are common associations.

Physical examination often reveals the absence of lymphoid tissue, and the thymus is usually radiographically undetectable. The thymus is most often vestigial, cervically located, and lacks normal corticomedullary architecture and Hassall corpuscles. The absence of the thymus on a chest radiograph or other imaging study in an infant should prompt immunologic evaluation. Note that in some forms of SCID, such as deficiencies of CD3δ (CD3D) or coronin 1A, the thymus might appear normal on a chest imaging study.[87,88] Note also that serious infection or other metabolic stress in an infant without PIDDs can cause the thymus to shrink dramatically so that it is no longer easily seen in radiologic studies.

Characteristic laboratory abnormalities in patients with SCID include severe age-adjusted lymphopenia and low or absent IgA and IgM levels with or without low IgG levels and 1 or more reduced or absent major lymphocyte subpopulations. In particular, naive (expressing CD45RA and lacking CCR7) autologous T-cell counts are usually very low or absent and exhibit profoundly reduced proliferation to mitogens and antigens. A complete blood count (CBC) usually reveals leukopenia, lymphopenia, or both. Alterations of lymphocyte populations might be indicative of specific defects (Table E8[67,88-118] and Fig E2).

Hypogammaglobulinemia results from the lack of T-cell help, as well as from intrinsic functional abnormalities of B cells. IgG levels can be low or normal because of transplacental transfer of maternal IgG. Defects in T-cell proliferative responses to mitogens and antigens *in vitro* are the hallmark immunologic abnormalities.[85,86]

TABLE E8. Lymphocyte phenotype classification of SCID

Disease	Genes	References
$T^-B^-NK^-$		
Adenosine deaminase	*ADA*	89, 90
Adenylate kinase (reticular dysgenesis)	*AK2*	91-93
$T^-B^-NK^+$		
Artemis	*DCLRE1C*	94, 95
Cernunnos	*NHEJ1*	96, 97
DNA-dependent protein kinase	*PRKDC*	98
DNA ligase IV	*LIG4*	99, 100
RAG1 and RAG2	*RAG1*, *RAG2*	101-104
$T^-B^+NK^-$		
X-linked SCID	*IL2RG*	67, 105-108
JAK3 deficiency	*JAK3*	106, 109
CD25 deficiency	*IL2RA*	110, 111
$T^-B^+NK^+$		
CD3 complex defects	*CD3D, CD3E, CD3Z*	112-115
Coronin 1A deficiency	*CORO1A*	88
CD45 deficiency	*PTPRC*	116, 117
IL-7 receptor deficiency	*IL7RA*	115, 118

The Primary Immunodeficiency Treatment Consortium has proposed formal diagnostic criteria for SCID. "Typical" or "classic" SCID is defined as less than 300 autologous T cells/mm^3 in peripheral blood together with a less than 10% PHA response compared with control values or the presence of maternal T cells in the circulation.[119,120] Partial or "leaky" SCID, including Ommen syndrome, is defined by T lymphopenia (age <2 years, <1000 cells/mm^3; age 2-4 years, <800 cells/mm^3; age >4 years, <600 cells/mm^3) and PHA response of less than 30% of the control value.

The various forms of SCID are now most often classified according to the peripheral blood lymphocyte profile. All forms of SCID lack functional autologous T cells and are "T-negative" (T^-) by definition. Depending on the gene defect, other types of lymphocytes might or might not develop. Thus one can distinguish B^+ or B^- forms and NK^+ and NK^- forms, for example. The various forms of SCID according to this classification are listed in Table E8.

Specific mutations in genes associated with classical SCID can lead to atypical phenotypes, which are usually less severe. Variable or hypomorphic expression of mutations in genes, such as *RAG1/2* and others, can result in an SCID phenotype that is milder than "classic" (typical) SCID ("leaky" SCID, see above).[119] Patients with leaky SCID might not display all of the clinical and laboratory features, the onset of clinical disease might be later in life, and infectious complications might be less severe.

Maternal T cells can engraft in some patients with SCID and confound the interpretation of peripheral blood lymphocyte enumeration. Maternal T cells can cross the placenta and survive in the peripheral blood and lymphoid tissues of patients with SCID.[121] Because the laboratory phenotype can guide the evaluation of specific molecular defects in patients with SCID, the maternal or host origin of blood T cells should be definitively established. In male infants this is easily done by using karyotyping. For female infants, HLA typing shows the presence of more than 2 haplotypes. Typically, maternal T cells will have a memory

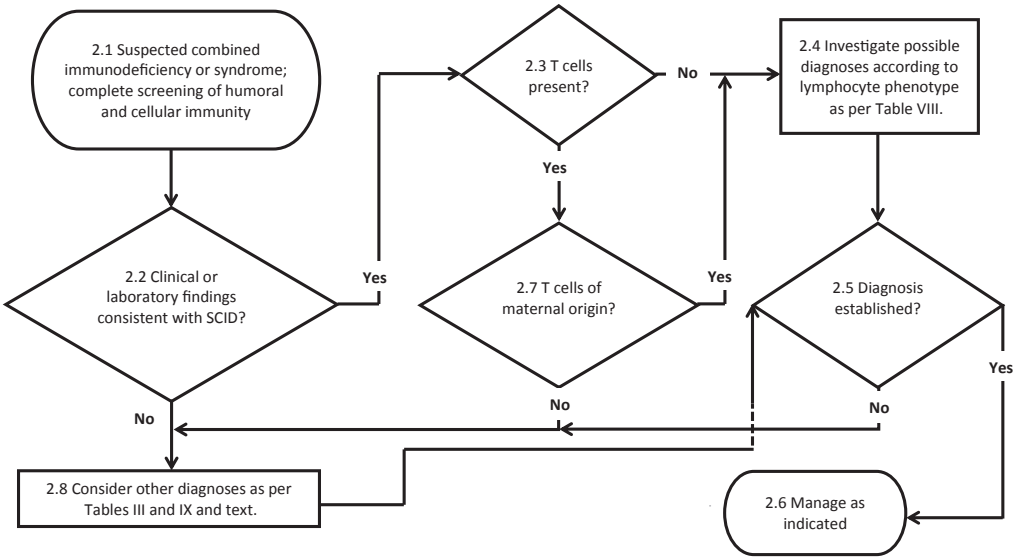

FIG E2. Diagnosis of combined or syndromic immunodeficiencies. *2.1*, In this situation it is appropriate to perform a complete screening evaluation of specific immune function, including measurement of immunoglobulin levels, specific antibody production, enumeration of lymphocyte subpopulations, measurement of T-cell proliferation with mitogens and antigens, and evaluation of NK cell cytotoxicity. *2.2*, Are the clinical presentation and laboratory evaluation consistent with SCID? Note that in some states SCID might be suspected early on the basis of newborn screening through measurement of TREC numbers in dried blood spots (see SS 24). *2.3*, If the answer to 2.2 is yes, consider the T-cell phenotype. Are T cells present? *2.4*, If the answer to 2.3 is no, this is consistent with SCID, and more specific diagnostic studies should be undertaken considering the lymphocyte phenotype, as outlined in Table VII. *2.5*, Is the diagnosis established? *2.6*, If the answer to 2.5 is yes, then proceed to manage as indicated (ultimately HSCT or gene therapy). *2.7*, If the answer to 2.3 is yes, the origin of the T cells should be determined. Are the T cells of maternal origin? If the answer to this question is yes, then this is also consistent with SCID and proceed as in 2.4. *2.8*, If the T cells are not of maternal origin, then autologous T cells are present, and the diagnosis is not classic SCID (a diagnosis of leaky SCID is still possible). Consider and investigate alternative CIDs and syndrome diagnoses as outlined in Tables III and VIII and SSs 26 to 76.

($CD45RO^+$) or activated ($HLA\text{-}DR^+$) phenotype and, in comparison with healthy newborns, will have absence or a markedly lower number of TRECs, a marker of recent thymic emigrants.[122] On occasion, engrafted maternal T cells can become activated by HLA disparities and cause clinical GVHD. Infants with diffuse cutaneous eruptions, other clinical and laboratory features of SCID, or both should be evaluated for this possibility.

Erythroderma is also associated with Omenn syndrome (OS), an SCID phenotype that is also very similar to GVHD, after HSCT. However, in patients with OS, autologous oligoclonal autoreactive T cells become activated and cause disease; GVHD is not involved. Symptoms include irritability, erythroderma, pachydermia, diarrhea, lymphadenopathy and hepatosplenomegaly, and failure to thrive. Laboratory manifestations include normal or increased lymphocyte counts with oligoclonal T cells, eosinophilia, high IgE levels, and increased inflammatory markers. OS can occur in the setting of diverse genetic forms of SCID, including defects of RAG1, RAG2, Artemis, ADA, ligase 4, IL-7 receptor α (IL-7RA), RNA component of mitochondrial RNA processing endoribonuclease (RMRP), IL-2 receptor γ (*IL2RG*, also XSCID), adenylate kinase 2, 22q11 deletion, chromodomain helicase DNA binding protein 7, and cartilage-hair hypoplasia (CHH; Table E8 and Fig E2).[91,101,102,118,123-129]

Several states have implemented newborn screening for severe T-cell lymphopenia (SCID and other conditions).[9] Newborn screening is performed through quantitative PCR to measure the number of copies of TRECs in DNA from newborn dried blood spots. Infants with SCID (classical or leaky) will have very low or absent TRECs. Other non-SCID syndromes associated with T-cell lymphopenia that might also be identified through this test include the following: DGS; Jacobsen syndrome; Trisomy 21; coloboma, heart anomaly, choanal atresia, retardation, genital and ear anomalies (CHARGE) syndrome; CD25 deficiency; Ras-related C3 botulinum toxin substrate 2 (RAC2) deficiency; dedicator of cytokinesis 8 (DOCK8) deficiency; and idiopathic CD4 lymphopenia (ICD4L).[9] Premature infants have lower TREC numbers at birth, which usually increase over time. Neonatal thymectomy during cardiac surgery, situations predisposing to lymph loss (chylothorax and lymphangiectasia), or stress associated with severe illness or infection can all be associated with low TREC counts independently of primary T-cell dysfunction. These infants should be followed prospectively until TREC counts normalize or they have secondary screening.[9]

Infants with low TREC counts should have secondary screening by using flow cytometry to enumerate T-cell numbers and the proportion of naive cells. T-cell counts of less than 1500/mm^3 or a proportion of naive cells of less than 50% should be followed up measuring the *in vitro* response to a mitogen, such as PHA.[9]

Summary statement 27. Patients with SCID or suspected SCID should receive IgG 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 patients with SCID continue to require immunoglobulin supplementation after HSCT because of failure of B-cell engraftment.[130] Also see SS 11.

Summary statement 28. 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 HSCT for SCID.[71,72,131] Prudent measures include avoidance of contact with large numbers of persons or those likely to harbor infectious agents (eg, young children in day care) and protective isolation when in the hospital setting. Prophylaxis with palivizumab can be considered during the RSV season, although therapeutic polyclonal IgG usually contains relatively high amounts of RSV antibody.[132]

Summary statement 29. Patients with SCID should receive PCP prophylaxis. (C)

PCP is a common early complication in patients with SCID.[86,133] Trimethoprim/sulfamethoxazole (5 mg/kg/d trimethoprim by mouth 3 times per week) is preferred, when possible. Alternative prophylactic regimens include pentamidine isethionate (5 mg/kg every 4 weeks), dapsone (1 mg/kg/d), and atovaquone (30 mg/kg/d).

PCP prophylaxis is indicated in other specific non-SCID diagnoses in which susceptibility is high independently of T-cell numeric or functional (mitogen response) criteria. These include CD40 and CD40L deficiencies and nuclear factor κB essential modulator (NEMO) deficiency (see the respective sections). Specific criteria for PCP prophylaxis have not been established for other non-SCID combined immunodeficiencies (eg, DGS, WAS, ataxia-telangiectasia [AT], and others), but it should be considered when T-cell numbers, function, or both decrease to less than the thresholds defining SCID established by the Primary Immunodeficiency Treatment Consortium (see SS 29).

Summary statement 30. Early signs of infection should be promptly investigated and antimicrobial regimens initiated early and for prolonged periods. (C)

Vigilance for infectious illness is essential for successful outcomes for patients with SCID. Empiric therapy should be considered if a specific pathogen diagnosis is uncertain or likely to be delayed. Therapy might need to be prolonged because clearance is usually delayed in comparison with immunocompetent hosts.[71,72,131] Also see SS 15.

Summary statement 31. Polyethylene glycol (PEG)–conjugated ADA (PEG-ADA) should be administered to patients with SCID caused by ADA deficiency if HSCT or gene therapy is unavailable. (C)

The mortality rate of patients with ADA-SCID who receive PEG-ADA (30 U/kg administered intramuscularly twice a week) is generally low (10% to 20%).[90,134,135] Most patients experience clinical improvement with a marked reduction in opportunistic infections, although immunoreconstitution based on the number of lymphocytes or antibody response is often incomplete. Antibodies to PEG-ADA develop in more than 50% of patients. Serum ADA activity and serum nucleotide levels should be used to monitor response to therapy and compliance. PEG-ADA therapy should not be used if other therapy (HSCT or gene therapy) is readily available.

Summary statement 32. A suspicion of SCID should be considered an urgent clinical condition. (C)

Once a diagnosis of SCID is confirmed, thorough immunologic evaluation and therapy must be initiated as quickly as possible. Experience clearly indicates that outcomes after HSCT for SCID depend greatly on the age of diagnosis and intervention.[71,72,131] In one study patients undergoing transplantation within the neonatal period (first 28 days of life) had significantly improved T-cell development after HSCT.[136] An earlier report from the same institution showed a strong trend toward improved survival (95% vs 76%) in infants receiving HSCT before 3.5 months of age in comparison with those who underwent transplantation later.[137] Definitive therapy before significant infectious complications arise is also associated with improved outcomes.

Summary statement 33. Patients with SCID should be immunologically reconstituted by means of HSCT or gene therapy. (B)

Most forms of SCID have been successfully treated by using a variety of techniques of HSCT (see also SSs 17 and 30). Patients with SCID caused by *IL2RG* deficiency and ADA deficiency have been successfully treated with gene therapy.[33,34,68,89,138,139] One gene therapy strategy used for the immunoreconstitution of patients with SCID consists of *ex vivo* gene transfer to autologous hematopoietic stem cells isolated from the patient's bone marrow. These modified cells are then infused back to the patient. This therapy was offered only to patients who did not have HLA-identical sibling donors because of the high rate of success of HSCT with such donors. Five of 20 patients with XSCID treated with gene therapy had T-cell leukemia caused by the integration of the corrected gene near the LIM domain only 2 *(LMO2)* oncogene.[67,140] Recently initiated clinical trials of gene therapy for XSCID use an enhancer-deleted vector.[141] None of the patients treated with gene therapy for ADA deficiency have had leukemia.[68]

Other CID syndromes.

Summary statement 34. Patients with CID with intermediate T-cell numbers and function should be studied for leaky SCID or one of several CID syndromes based on clinical and laboratory characteristics. (C)

As noted in SS 26, partial defects in genes associated with SCID might lead to less severe or variant phenotypes collectively referred to as "leaky" SCID indicating partial T-cell and/or B-cell development and function. There are also many gene defects that have been associated with CIDs that span a range of severity. Some immunologic and clinical features of these disorders are listed in Table E9.[113,115,142-183]

Summary statement 35. All forms of ancillary or supportive therapy administered to patients with SCID should be considered for patients with leaky SCID or non-SCID combined immunodeficiency. (C)

See SSs 26 to 30 and 33. Many infections and complications in these patients will be similar to those occurring in patients with SCID, and those with "milder" forms of CID will benefit from the same interventions.[102,123,125]

Summary statement 36. Patients with leaky SCID or a non-SCID combined immunodeficiency should be considered for stem cell therapy or gene therapy on a case-by-case basis. (C)

Patients with non–SCID-level immune compromise in many cases will have serious morbidity and mortality. Certainly, patients with leaky SCID should be considered for such therapy (and gene therapy, where appropriate). Many of the other CID disorders have also been successfully treated with HSCT. It is up to the team of clinicians to weigh the benefits and risks of all modes of therapy in each case.[102,123,125]

TABLE E9. Clinical and Laboratory manifestations of selected combined immunodeficiencies and syndromes

Gene defect(s) or disease(s)	Clinical features	Laboratory features	Reference(s)
Ca/Mg channel defects (*MAGT1*, *ORAI1*, *STIM1*)	Severe and opportunistic infections, autoimmune disease, anhydrotic ectodermal dysplasia, myopathy	Normal T-cell numbers, ↓ T-cell function	142-145
CARD11	Opportunistic infections	Hypogammaglobulinemia, normal lymphocyte numbers, ↓ T-cell function	146-148
CD27	Persistent symptomatic EBV viremia, recurrent infection	Hypogammaglobulinemia, impaired specific antibody response, decreased mitogen proliferation	149
CD3G	Variable severity, SCID or mild phenotype, autoimmune hemolytic anemia	Modest ↓ CD8 T cells, ↓ $CD45RA^+$ cells, ↓ TCR expression, variable immunoglobulins	113, 115
CD8	Recurrent bacterial respiratory tract infections, bronchiectasis	Absent CD8 T cells, ↑ double-negative T cells	150
CTLA4	Autosomal dominant, lymphoproliferation, organ infiltration, lymphoma, respiratory tract infections	↓ CD4 T cells, ↓ B cells, hypogammaglobulinemia, ↑ T-cell proliferation	151, 152
CTPS1	Disseminated infections with EBV and varicella-zoster virus, encapsulated bacteria, B-cell lymphoma	Lymphopenia, ↓ naive CD4 cells, ↓ IgG_2, ↓ pneumococcal response, ↓ memory B cells, absent invariant NK T cells, ↓ PHA proliferation	153
FOXN1	Athymia, reduced T-cell numbers, absence of hair, and nail dysplasia	↓ Naive T cells; ↑ double negative ($CD4^-CD8^-$) T cells	154-156
IKZF1	Prematurity, polyhydramnios with fetal hydrops, neonatal pancytopenia	Normal lymphocyte numbers, absent B cells, ↓ NK cells, ↓ $CD45RO^+$ T cells, absent mitogen proliferations, ↓ IgG	157
IL21R	Respiratory tract infections, failure to thrive, diarrhea, cryptosporidiosis	Normal lymphocyte numbers, ↑ IgE, ↓ specific antibody, normal T-cell function, ↓ NK cytotoxicity	158
ITK	EBV-associated lymphoproliferation, lymphoma	Lymphopenia, hypogammaglobulinemia	159-162
MHC class I deficiency (*TAP1*, *TAP2*, *TAPBP*), *CD8A*	Variable severity, recurrent respiratory tract infections, bronchiectasis	Complete absence of $CD8^+$ cells, normal CD4 cells, normal T-cell proliferation, normal immunoglobulins and antibody	163, 164
MHC class II deficiency (*MHC2TA*, *RFX5*, *RFXANK*, *RFXAP*), and *LCK* mutation	Severe and opportunistic infections, diarrhea, malabsorption, failure to thrive	↓ CD4 T cells, normal CD8 cells; ↓ T-cell proliferation, hypogammaglobulinemia, ↓ antibody	165-169
NP	Severe and opportunistic infections, severe varicella (including vaccine strain), neurological impairment	↓ T cells, variable ↓ in B cells, ↓ T-cell proliferation, variable immunoglobulins, and antibody	170, 171
PGM3	Recurrent infections, skeletal dysplasia, developmental delay	Neutropenia, lymphopenia (↓ T and B cells), bone marrow failure	172
POLE1	Mild facial dysmorphism, livedo, short stature, recurrent pulmonary infection with bronchiectasis, recurrent *Streptococcus pneumoniae* meningitis, long-bone abnormalities	↓ IgM, ↓ IgG_2, ↓ isohemagglutinin, ↓ $CD27^+$ memory B cells, low naive T-cell numbers	173
SLC46A1	Severe opportunistic infections, failure to thrive (reversible with folate administration)	Normocytic anemia, ↓ serum folate, hypogammaglobulinemia, ↓ T-cell proliferation	174
RHOH deficiency	Warts, molluscum, granulomatosis, Burkitt lymphoma	↓ CD4 T cells, normal immunoglobulins and antibody	175
STAT5B	Growth failure, ichthyosis/eczema, diarrhea ± bacterial or opportunistic infections, autoimmune disease	↓ Insulin-like growth factor, ↑ growth hormone, ↓ T cells, especially ↓ Treg cells	176-178
Trisomy 21	Cognitive impairment, characteristic facies, cardiac defects, gastrointestinal disorders, hypothyroidism, recurrent respiratory tract infections	Variable T- and B-cell lymphopenia, ↓ naive T and B cells, IGGSD, poor vaccine response, ↓ *in vitro* T-cell proliferation, ↓ neutrophil chemotaxis	179
TRNT1	Sideroblastic anemia, periodic fevers, developmental delay, sensorineural hearing loss, cardiomyopathy, CNS abnormalities	Variable ↓ immunoglobulins, ↓ B cells, progressive ↓ T cells and NK cells	180
ZAP70	Variable severity, SCID, and opportunistic infections, failure to thrive, mild phenotypes	↓ CD8 T cells, normal CD4 cells, ↓ T-cell proliferation, hypogammaglobulinemia, ↓ antibody	181-183

Hyper-IgM syndrome caused by defects of CD40L and CD40.

Summary statement 37. The diagnosis of a form of hyper-IgM syndrome (HIM) should be considered in patients with very low IgG, IgA, and IgE levels and normal or increased IgM levels. (C)

Mutations of TNF superfamily 5 *(TNFSF5)*, also called CD154 and CD40L, result in what has historically been referred to as the X-linked HIM, which is abbreviated XHIGM, XHIM, or HIM1.[184] Mutations of TNF receptor superfamily 5 *(TNFRSF5)*, also called CD40, result in one form of autosomal recessive HIM, which has been abbreviated HIM3. Because the eponym "hyper-IgM syndrome" is a laboratory phenotype description encompassing disorders classified as both antibody deficiencies and CIDs, some authorities argue it should be abandoned in favor of names designating molecular defects.[185]

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 (eg, PCP and disseminated fungal infections), neutropenia, chronic anemia caused by parvovirus, and cholangitis caused by *Cryptosporidium* species.[184]

Laboratory features of CD40 and CD40L deficiencies include low IgG levels with normal or increased IgM levels. IgA levels are often also low. Specific IgG antibody production is poor, although the composition of major lymphocyte subsets (CD4 and CD8 T cells, B cells, and NK cells) is most often normal. The proportion of memory ($CD27^+$) B cells, especially switched memory B cells (IgD^-CD27^+) is reduced. T cells proliferate normally *in vitro* in response to mitogenic stimuli in patients with these disorders. However, T-cell responses to recall antigens are impaired.[184]

Summary statement 38. CD40L expression should be evaluated by using flow cytometric methods on activated T cells. (C)

CD40L expression on activated T cells can be measured with mAbs, CD40-Ig fusion proteins, or both. T cells can be most conveniently activated by nonspecific stimuli, such as a combination of phorbol ester and calcium ionophore. Similar methods can also be applied to platelets. Rare patients with CD40L deficiency can have mutations that permit staining with both mAbs and fusion proteins. If clinical and laboratory features are highly suggestive of CD40L deficiency and CD40L/CD154 staining is normal, a molecular genetic diagnosis should be sought.[184]

Summary statement 39. CD40 expression should be measured by using flow cytometry on monocytes or B cells. (C)

CD40 is expressed constitutively on B cells, monocytes, and a variety of other cell types. Its presence or absence is easily determined by using flow cytometry on these cell populations, permitting presumptive diagnosis of CD40 deficiency. At present, this test is not widely available. Rare patients with CD40 deficiency can have mutations that permit staining with both mAbs and fusion proteins. If clinical and laboratory features are highly suggestive of CD40L deficiency and CD40L/CD154 deficiency has been ruled out, a diagnosis of CD40 deficiency should be sought.[184]

Summary statement 40. Female patients with the HIM phenotype should be studied for CD40L mutation if the CD40 mutation or another known mutation associated with the HIM phenotype is not found. (C)

See SS 8.

Summary statement 41. PCP prophylaxis 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 (see SS 29).[184]

Summary statement 42. Neutropenia in patients with CD40 or CD40L deficiency should be treated with granulocyte colony-stimulating factor (G-CSF). (C)

Response of neutropenia in patients with CD40L deficiency to G-CSF is inconsistent but has been observed.[184] If a sustained response is seen, G-CSF therapy should be discontinued to determine its ongoing necessity because neutropenia in patients with this disorder can resolve spontaneously. There might be an increased risk of myeloid cell proliferation or leukemia with prolonged G-CSF therapy.[186]

Summary statement 43. HSCT should be considered for CD40L and CD40 deficiency. (C)

A variety of HSCT methods have been successful in patients with CD40L defects.[184] In one case cadaveric liver transplantation was followed by HSCT from a different matched unrelated donor.[187] Liver transplantation alone in patients with CD40L deficiency has uniformly poor outcome.[188] HSCT can be curative for CD40 deficiency; experience is limited.[189]

A limited clinical trial of recombinant CD40L has been conducted in 3 patients with CD40L deficiency. Partial reconstitution of *in vivo* and *in vitro* T-cell functional reconstitution were demonstrated.[190] However, this type of treatment is not yet considered to be of established clinical efficacy and safety.

CID, unspecified.

Summary statement 45. Any patient with abnormal serum immunoglobulin levels, specific antibody production, or both and evidence of impaired cellular immunity who does not fulfill the clinical and laboratory diagnostic criteria for any of the above disorders should be given a diagnosis of unspecified CID. (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. Of course, therapy for an unspecified CID must be individualized and directed toward established infections, associated diseases (eg, autoimmune disease, lymphoproliferation, and malignancy), and the prevention of those infections for which the patient has shown predilection or for which they are considered to be at risk.

Well-defined syndromes with immunodeficiency

WAS.

Summary statement 46. A diagnosis of WAS should be considered in all male patients with clinically significant thrombocytopenia and small platelets. (C)

The classical clinical expressions of WAS are X-linked inheritance, eczema, petechiae, bruising or bleeding, recurrent and severe infections (including opportunistic organisms), autoimmune disease, and EBV-associated B-cell lymphomas. Recurrent otitis, sinopulmonary bacterial infections, and frequent viral illnesses are common in patients with WAS.[191,192] Opportunistic infections can be seen, including PCP, indicating severe immune compromise. Eczema can be absent, mild, or severe. Autoimmune colitis, vasculitis and glomerulonephritis, and other autoimmune processes are observed in older patients with WAS. Without curative therapy, patients with WAS most often succumb to overwhelming infection or massive hemorrhage. About 10% to 15% of patients with WAS have malignancy, with an average age of onset of approximately 10 years. More than 80% of these are lymphomas, often associated with EBV infection.[193,194]

The Initial presentation of WAS might be limited to bruising and easy bleeding corresponding to X-linked thrombocytopenia (XLT), with later progression to classical WAS. In a multicenter study 173 patients with a diagnosis of XLT and mutations in the *WAS* gene were reported. Serious infections occurred in 7%, autoimmunity in 12%, and malignancy in 5% of patients.[195] Very rare patients have a specific gain-of-function mutation in *WAS* that leads to a syndrome of X-linked neutropenia, which is indistinguishable from other syndromes of congenital neutropenia (see the section on severe congenital neutropenia [SCN]).[196,197]

Thrombocytopenia and small platelet size are the most consistent clinical laboratory abnormalities of WAS. Platelets are small, dysfunctional, cleared more rapidly, and produced more slowly than normal.[198] Small platelet size confirms the diagnosis of WAS in the appropriate clinical context. In healthy

subjects the platelet volume is 7.1 to 10.5 fL, whereas platelets from patients with WAS have volumes ranging from 3.8 to 5.0 fL. A blood smear should be examined when an automated blood cell counter reports normal platelet size in a patient suspected of having WAS. Small platelet size is occasionally seen in patients with other thrombocytopenias, but WAS is distinguished by the homogeneity of the platelet size and the other manifestations of the disease. However, as many as 20% of patients with WAS can have immune thrombocytopenia either before or after splenectomy.

A clinical severity scoring system of disease associated with *WAS* mutation has been developed.[199] The presence of intermittent (score <1) or persistent (score = 1) thrombocytopenia with small platelets and WAS mutations without any of the other clinical manifestations constitutes X-linked thrombocytopenia (XLT). Some patients with XLT have increased infections, and rare patients with XLT can have lymphoma (score = 5). Addition of infections, eczema, or both constitutes "classic WAS" with a clinical score of 2, 3, or 4 depending on the severity of these manifestations. The most severe form of WAS (score = 5) includes autoimmunity, malignancy (lymphoma), or both. X-linked neutropenia is defined as congenital neutropenia in the absence of any of the other manifestations and is assigned a clinical score of 0. The scoring system is not generally applied in clinical practice.

Humoral immunologic abnormalities in patients with WAS include variable dysgammaglobulinemia and impaired specific antibody production. Patients with WAS can have normal or low IgG and/or IgM levels, normal or increased IgA levels, and low, normal, or high IgE levels.[191] These abnormalities might 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 isohemagglutinin production. Additional vaccine booster doses might be required to induce protective antibody titers.

Cellular immunologic abnormalities in patients with WAS include T-cell lymphopenia, impaired *in vitro* and *in vivo* T-cell responses, and decreased NK cell activity. Approximately 20% to 30% of patients with WAS have low T-cell numbers.[191] Numbers of $CD8^+$ T cells are often disproportionately decreased and are low in more than 50% of patients with WAS. T cells have mild to moderately reduced proliferation to mitogens *in vitro* in one third to one 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.

Summary statement 47. Patients suspected to have WAS should have a definitive molecular diagnosis by finding a known deleterious *WAS* mutation and/or abnormal WAS protein expression, which might be helpful for prognosis. (C)

Both Western blot and intracytoplasmic staining and flow cytometric analyses can be performed on lymphocytes from suspected patients with WAS to determine the presence or absence of the WAS protein.[200] Abnormal findings are considered diagnostic in a patient with characteristic clinical features. The presence of normal size and amount of WAS protein does not exclude the diagnosis because some point mutations might permit protein production. Molecular analysis is required in this circumstance. Some mutant *WAS* genotypes have prognostic value.[191,200] Splice variant mutations that permit expression of a small amount of normal WAS protein or missense mutations that permit expression of a partially functional mutant WAS protein are associated with milder clinical courses. Mutations that abolish WAS protein expression or permit expression only of a truncated WAS protein lead to more severe disease. A *WAS* mutation might cause disease in some female subjects because of extreme nonrandom X-chromosome inactivation (see SS 8).[36,37]

Summary statement 48. Management of patients with WAS should include IgG replacement. (C)

IgG replacement is indicated for all but the most mildly affected patients with WAS.[191,200] Prophylactic antibiotic therapy can be used concomitantly in some (see SSs 11 and 12). Splenectomy can be considered in patients with severe WAS thrombocytopenia, although it increases the risk of infection.[201] It is preferable to have the spleen in place if stem cell therapy is planned. High-dose IVIG can also be used for thrombocytopenia in patients with WAS, although the response is variable. Glucocorticosteroids and other immunosuppressants have been used for this purpose and to control autoimmune disorders. Skin care for eczema might also be needed.

Summary statement 49. HSCT must be seriously considered for patients less than 5 years of age with suitable stem cell donors. (C)

Stem cell reconstitution of patients with WAS results in long-term improvement or resolution of thrombocytopenia and immune deficiency and lower risk of lymphoma (see SS 19).[201,202] Outcomes are superior if reconstitution is achieved at less than 5 years of age.[200]

Non-SCID DNA repair defects.

Summary statement 50. AT and other chromosomal repair disorders should be considered in all children with frequent infections and characteristic neurological, skeletal, and/or cutaneous manifestations, including ataxia, microcephaly, and telangiectasia. (C)

Deficiencies in DNA repair mechanisms result in clinical syndromes characterized by neurological, cutaneous, and immunologic abnormalities. Frequent infections in a child with neurological and cutaneous and/or skeletal symptoms might prompt the evaluating physician to consider these diagnoses. Molecular diagnosis is helpful for genetic counseling and prognosis.[203]

Cerebellar ataxia, oculocutaneous telangiectasias, growth retardation, increased risk of malignancy, and variable immune deficiency are the most prominent and consistent clinical features of AT. Most patients with AT experience growth retardation (especially in later childhood) and delayed gross motor development, such as learning to walk. Additional neurological manifestations include oculomotor apraxia, dysarthria, swallowing dyscoordination, and peripheral neuropathy. Oculocutaneous telangiectasias develop in many patients with AT at about 3 to 5 years of age. Thus they are not helpful for making an early diagnosis. Clinical immunodeficiency begins in infancy or early childhood. Bacterial respiratory tract infections predominate, although viral and fungal infections can also occur.[204] Opportunistic infections are rare. Malignancy, predominantly EBV-associated tumors, occur in the second decade of life.[205,206]

Immunologic abnormalities in patients with AT include low or increased immunoglobulin levels, IgG subclass deficiencies (IGGSDs), impaired specific antibody production, and alterations in lymphocyte populations.[203,207] Immunoglobulin levels are usually normal in patients with AT; hypogammaglobulinemia is sometimes seen. As many as 40% of patients might display

oligogammaglobulinemia or monoclonal hypergammaglobulinemia. Low IgA levels, abnormalities of IgG subclasses (eg, IgG_2 deficiency), and impairment of pneumococcal polysaccharide responses can also be seen. Lymphopenia, abnormalities of lymphocyte subsets, impaired function of $CD4^+$ and $CD8^+$ T cells *in vitro*, or decreased skin delayed hypersensitivity response can be observed. There is a highly characteristic increase in numbers of T cells bearing the γ/δ receptor.[207] Essentially identical immunologic abnormalities are found in patients with Nijmegen breakage syndrome (NBS).[208-210]

Clinical manifestations of AT-related disorders are variable. NBS, DNA ligase IV (LIG4) deficiency, DNA ligase I deficiency, and AT-like disorder are all similar but have important differences. NBS (mutation in *NBS1*) is characterized by growth retardation, characteristic facies, microcephaly, cognitive impairment, and immune deficiency.[208-210] LIG4 syndrome (mutation in *LIG4*)[99] and DNA ligase I deficiency (mutation in *LIG1*)[211] have similar phenotypes, although the central nervous system (CNS) manifestations are not found in all patients. Patients with AT-like disorders (mutation in *MRE11A*) have mild ataxia without cutaneous features or clinical immunodeficiency.[212,213] Hypogammaglobulinemia G and A with normal IgM levels are reported in about one third of patients, supporting a defect in class-switch recombination. T-cell responses to mitogens are variably affected in 90% of patients.

Bloom syndrome is characterized by growth deficiency, unusual facies, sun-sensitive telangiectatic erythema, immunodeficiency, and predisposition to cancer.[214,215] Immunologic abnormalities include low IgG and IgA levels and leukopenia. Bloom syndrome is caused by mutations in the DNA helicase gene *BLM*.

Minichromosome maintenance complex component 4 (MCM4) deficiency is characterized by adrenal insufficiency, growth retardation, and NK cell deficiency, manifesting as increased susceptibility to herpesviruses and EBV infection complications. Although the number of peripheral NK cells is markedly decreased, the number of immature $CD56^{bright}$ NK cells is preserved.[216-218]

Summary statement 51. Immunodeficiency, centromeric instability, and facial anomalies (ICF) syndrome should be considered in patients with abnormal facies, developmental delay, and immunodeficiency. (C)

In a review of 45 patients with ICF syndrome, facial anomalies were variable and occurred in about 90% of patients.[219] The most common findings were hypertelorism, epicanthal folds, low-set ears, and flat nasal bridge. Hypogammaglobulinemia also occurred in most patients (39/44). Infectious complications, including opportunistic microorganisms suggesting T-cell dysfunction, were reported in approximately 70% of patients; these presented from 3 months to 4 years of age and consisted primarily of frequent bacterial respiratory tract infections. Growth retardation occurs in about half of patients, and some degree of cognitive or developmental impairment is seen in about two thirds of patients. About 60% of patients with ICF syndrome presented with mutations in the methyl transferase *DNMT3B* gene (ICF1). Mutations in *ZBTB24* (ICF2) were found in 7 patients of 6 families with a diagnosis of ICF syndrome who presented with agammaglobulinemia and characteristic facies.[220] Humoral immunodeficiency tends to be more pronounced in patients with ICF1 syndrome; both patients with ICF1 syndrome and those with ICF2 syndrome are affected by B- and T-lymphocyte deficiency, and patients with ICF2 syndrome tend to have a higher incidence of intellectual disability.[221] HSCT reconstituted immunodeficiency in 3 patients with ICF syndrome presenting with evidence of T-cell dysfunction in addition to hypogammaglobulinemia. Two of the 3 patients had autoimmune hypothyroidism after HSCT.[222] HSCT was completed on 3 patients with ICF1 syndrome and 2 ICF syndrome–affected siblings without defined genetic mutations. Four of the patients underwent successful transplantation; 1 of the patients with ICF1 syndrome underwent transplantation for myelodysplasia and died of RSV-related complications.[219,222]

Summary statement 52. Postmeiotic segregation increased 2 *(PMS2)* defects should be sought in patients with dysgammaglobulinemia, cafe-au-lait spots, and colon and/or brain tumors. (C)

PMS2 mutations are responsible for a subset of patients with hereditary nonpolyposis colon carcinoma (Lynch syndrome) and mismatch repair syndrome (Turcot syndrome and increased risk of colon and brain neoplasia). Cells from 1 patient with recurrent infections and cafe-au-lait spots and 2 other patients with mismatch repair syndrome were found to have deficient class-switch recombination defects.[223] Only the first patient presented with increased IgM and low IgG levels; the other patients had normal immunoglobulin levels.

Summary statement 53. A diagnosis of radiosensitivity, immunodeficiency, dysmorphic features, and difficult learning (RIDDLE) syndrome should be suspected in patients with developmental delay, short stature, dysmorphic facies, and hypogammaglobulinemia. (C)

RIDDLE syndrome is a rare disorder resulting from mutations in the gene *RNF168*.[224] One patient has been reported presenting with increased IgM and low IgG levels secondary to defective class-switch recombination. Specific responses to *Escherichia coli* and herpes simplex virus (HSV) were documented, suggesting only partial impairment of humoral immunity. T-cell numbers and immune function were normal. He was treated with IgG supplementation.

Summary statement 54. Cytogenetic abnormalities, such as chromosomal translocations and chromosome fragility, support a diagnosis of AT or other chromosomal repair disorders. (C)

Chromosomal translocations involving immunoglobulin (2p12, 14q32, and 22q12) and T-cell receptor (7p15, 7q35, and 14q11) loci are highly characteristic in lymphocytes of patients with AT and NBS, and chromosomes also have increased spontaneous and radiation-induced breakage *in vitro*.[208-210,225] In patients with ICF syndrome, abnormal DNA methylation leads to anomalies of chromosomes 1, 9, and 16, which are found in lymphocytes of all patients and are pathognomonic.[219,220] These consist of multiradial chromosomes, breaks, deletions, and isochromosome formation. Cytogenetic abnormalities are common in all disorders in this category.[99,211,214,215]

Summary statement 55. Patients suspected to have AT should be screened by measuring the serum α-fetoprotein (AFP) level (C).

Increased serum AFP levels, carcinoembryonic antigen levels, or both are virtually pathognomonic for AT in the appropriate clinical and immunologic laboratory context and are seen in 95% of patients.[203,207] It is essential to use age-adjusted normal ranges for these measurements. Increased AFP levels are not seen in patients with any of the other DNA repair defects.

Summary statement 56. Imaging with radiography should be used cautiously in patients with AT or other chromosomal repair disorders. (C)

Patients with AT, NBS, and Bloom syndrome experience an extreme susceptibility to tissue damage by ionizing radiation and radiomimetic cytotoxic drugs and have a high rate of cancer.[203,209,214] Cumulative exposure to diagnostic radiation can increase the lifetime risk of malignancy. However, diagnostic sensitivity and specificity take precedence over this theoretical concern, and radiographic methods should be applied when they represent the best modality to support clinical decisions.

Summary statement 57. Antibiotic prophylaxis, IgG replacement therapy, or both are indicated for patients with AT or other chromosomal repair disorders with increased susceptibility to infections. (C)

The clinical immunodeficiency of chromosomal repair disorders is most similar to the antibody deficiencies (recurrent sinopulmonary bacterial infections), and similar therapeutic considerations apply in this regard (also see SSs 11-18 and Table E7).[99,203,208,210,212] Immune function should be reassessed periodically because it can decrease over time.

Summary statement 58. Management of malignancy in patients with AT and related disorders must be individualized. (C)

Hematologic malignancy is common in patients with any of these disorders, and toxicity and response to conventional chemotherapeutic regimens is variable.[226,227] Outcomes of standard chemotherapeutic regimens for malignancy in patients with these disorders might be inferior, and modified regimens can be associated with less morbidity and longer survival.

Summary statement 59. Stem cell transplantation can be considered in selected patients with AT and related disorders. (C)

Neurological morbidity in patients with AT and related disorders is not amenable to correction by stem cell therapy. Until recently, the toxicity of myeloablation has not been considered generally justifiable for attempted correction of immune dysfunction alone. However, newer partial ablation regimens make stem cell therapy for immune reconstitution or therapy for malignancy a therapeutic option for some patients. These have been applied in both patients with AT and those with NBS.[228,229]

DGS.

Summary statement 60. DGS should be investigated in patients with thymic hypoplasia, cardiovascular structural defects, midline craniofacial defects, and hypoparathyroidism. (C)

Most patients with DGS possess characteristic facial features of hypertelorism, saddle nose, shortened philtrum, and low-set and abnormally shaped ears, which are part of the spectrum of velocardiofacial syndrome.[230-232] The most common additional characteristics are cardiac outflow tract malformations, hypoplasia of the thymus, and parathyroid glands with hypocalcemia and immunodeficiency. Cleft palate and velopharyngeal insufficiency can also be seen.

Patients with DGS are almost always mildly to severely T-cell lymphopenic. *In vivo* and *in vitro* measures of T-cell function are usually normal. In most patients serum immunoglobulin levels are normal, as is antibody production, unless severe T-cell depletion is found.[230-232] Both CD4 and CD8 T-cell subsets are reduced, but they do not decrease significantly within the first years of life. In fact, the trend is usually toward increase, although not always to the normal range. *In vitro* lymphocyte proliferation to PHA and B-cell responses to T cell–dependent pneumococcal antigens are usually normal.

The degree of immune impairment in patients with DGS/velocardiofacial syndrome depends on the extent of thymic hypoplasia. When the naive T-cell count is greater than 50 cells/μL, the condition is termed partial DGS. When naive T cells are less than 50 cells/μL, this is called complete DGS. This is generally found in no more than 1% to 2% of patients with DGS. Patients with complete DGS require immunoreconstitution for survival.[70,233-235] In some patients with complete DGS, oligoclonal T-cell expansion can confuse the laboratory evaluation. Oligoclonal T cells developing in patients with complete DGS can be autoreactive and lead to a clinical presentation similar to that of OS. This has been called atypical complete DGS.[235] Patients with partial DGS commonly have recurrent sinopulmonary infections. Patients with complete DGS have a high risk of common and opportunistic infections.

Summary statement 61. Periodic immunologic re-evaluation is recommended for patients with DGS. (C)

As noted above, T-cell numbers and function tend to increase over time and do not usually decrease thereafter. IgA deficiency occurs in 2% to 13% of patients with DGS. Registry data from the United States and Europe suggest that approximately 6% overall are hypogammaglobulinemic and 3% receive IgG replacement.[236] Autoimmunity occurs in 8.5% of patients with DGS, predominantly autoimmune cytopenias and hypothyroidism.[237]

Summary statement 62. Patients suspected of having DGS should have molecular testing for deletion of chromosome 22q11.2 or 10p14-13 by using fluorescence *in situ* hybridization or a genomic DNA microarray. (C)

Molecular diagnosis of DGS is obtained by demonstrating deletion of one copy of the 22q11.21 chromosomal region by using fluorescence *in situ* hybridization or DNA microarray analysis.[238] Approximately 90% of patients with DGS with these features have 22q11.21 deletion. An additional fraction of patients yet to be determined have mutations in the T-box 1 *(TBX1)* gene, which is located in the 22q11.21 chromosomal region. A small number (1% to 2%) of patients have DGS caused by a chromosome 10p14-13 deletion.[231,232]

DGS also occurs in association with other general syndromes of dysmorphism, such as CHARGE syndrome.[231,232] CHARGE syndrome associated with mutations in the chromodomain helicase DNA binding protein 7 *(CHD7)* and *SEMA3E* genes has overlapping clinical characteristics with DGS and can present with immunodeficiency.[239,240] CHARGE syndrome can even present in a manner similar to OS.[124]

Summary statement 63. Treatment of infants with complete DGS requires some form of T-cell reconstitution. (C)

Patients with DGS or CHARGE syndrome should be evaluated to define the degree of immunodeficiency.[231,232] Live vaccines do not pose a risk to most patients with DGS, but they should not be administered without evidence of normal T-cell responses to mitogens and antigens and normal responses to nonviable vaccines.[79,80] Antibiotic prophylaxis is indicated to reduce the frequency of infections (see SS 16 and Table E7). Reconstitution of T-cell function in infants with complete DGS and CHARGE syndrome has been accomplished through transplantation of fetal thymus tissue, postnatal thymus tissue, HLA-identical sibling HSCT, and peripheral blood mature T-cell transplantation.[70,234] Reports of reconstitution of infants with DGS with HLA-identical bone marrow transplants were probably due to engraftment of peripheral blood T lymphocytes collected during bone marrow harvetsing.[241-243]

ICD4L.

Summary statement 64. ICD4L should be suspected in patients with opportunistic infections and persistent CD4 T-cell counts of less than 300 cells/μL in the absence of HIV infection or another cause of lymphopenia. (D)

A natural history study of 39 patients with ICD4L from the National Institutes of Health (NIH) reported that cryptococcal infection, persistent human papillomavirus infection, and nontuberculous mycobacterial infections were the most frequent presentations.[244] Twenty-nine patients presented in the third and fourth decades of life. Lymphocyte subsets other than CD4 T cells were also low in some of the patients. Immunoglobulin levels were normal. Autoimmunity occurred in 9 (23%) patients, most frequently systemic lupus erythematous (SLE). Seven patients had spontaneous resolution, whereas most remained CD4 lymphopenic. A dysregulation of CXCR4 expression in lymphocytes, but not in other cells, was described in 6 patients with idiopathic CD4 lymphocytopenia.[245] Heterozygous compound *RAG1/2* missense mutations were identified in an 18-year-old girl with a diagnosis of ICD4L who had recurrent infections since childhood.[246] A heterozygous missense mutation in *UNC119* was found to cause ICD4L in one female patient through a dominant-negative mechanism.[247]

Summary statement 65. Management of ICD4L is supportive and dictated by the degree of immune compromise. (D)

Frequent follow-up of patients with ICD4L is desirable for the early diagnosis and treatment of opportunistic infections. The role of antibiotic prophylaxis for PCP and *Mycobacterium avium* complex infection is not clear. The NIH study recorded 1 episode of PCP and 2 episodes of *Mycobacterium avium* complex in 164 patient-years of follow up.[244] Prophylaxis should be considered in those with low CD8 T-cell counts or another opportunistic infection. Successful hematopoietic stem cell transplantation with a sibling HLA-compatible donor has been reported in one case of severe ICD4L.[248]

Immuno-osseous dysplasias.

Summary statement 66. The immuno-osseous dysplasias should be considered in patients with severe growth retardation, skeletal abnormalities, and T-cell lymphopenia. (C)

Schimke syndrome (caused by mutations in the *SMARCAL1* gene) presents with growth retardation, spondyloepiphyseal dysplasia, progressive nephropathy, pigmentary skin changes, and T-cell lymphopenia. Characteristic facies include depressed and broad nasal bridge with bulbous nose. Frequent viral infections might represent defective cellular immunity, as determined by T-cell lymphopenia with very low numbers of naive T cells.[249] Other lymphocyte subsets and immunoglobulin levels are conserved.

Short-limb dwarfism, hypoplastic hair, and CID are characteristics of CHH and caused by mutations in the mitochondrial RNA processing endoribonuclease *(RMRP)* gene in most cases. Patients with CHH most frequently exhibit short-limbed dwarfism, hypoplastic hair, defective immunity with frequent infections, and anemia.[250-252] Childhood anemia can be mild or severe and might resolve with time. Hirschsprung disease, anal stenosis, and esophageal atresia can also occur.[253] Lymphopenia occurs in roughly two thirds and neutropenia in one fourth of patients. A decreased $CD4^+$ cell count is present in more than half of patients, with decreased mitogen-induced lymphoproliferation. B-cell numbers might be normal, but antibody responses are often impaired.[252,254] In 1 reported female patient, an immunologic phenotype similar to severe CVID (see SSs 85-93) manifested in adulthood (age 26 years).[255]

Summary statement 67. Medical management of immuno-osseous syndromes should include antibiotic prophylaxis and IgG supplementation appropriate to the severity of the immune dysfunction. (C)

Patients with immuno-osseous dysplasia should be evaluated for immunodeficiency. Those presenting with increased risk of infections might benefit from antibiotic prophylaxis (see SS 16 and Table E7). IgG supplementation is recommended for patients with decreased specific antibody responses.[252]

Summary statement 68. HSCT is indicated and has been successful for the correction of hematologic and immunologic defects in patients with CHH. (C)

In a European survey 16 patients with CHH and severe immunodeficiency or autoimmunity received hematopoietic stem cell transplantation. Ten of 13 patients receiving HLA-matched sibling donor survived, and all 3 patients receiving HLA-haploidentical grafts died.[256] Long-term immunoreconstitution was satisfactory, with resolution of immunodeficiency and autoimmunity. No major effect on growth and development occurred.

Comel-Netherton syndrome.

Summary statement 69. A diagnosis of Comel-Netherton syndrome (*SPINK5* gene mutation) should be sought in patients with abnormal hair structure, ichthyosis, allergic disease, and increased IgE and low IgG levels. (C)

Comel-Netherton syndrome is a rare congenital disease that usually presents in infancy with erythroderma. The diagnosis is usually made by study of the structure of the hair. The hair is often brittle and can have nodules and invaginations (trichorrhexis invaginata). Skin ichthyosis and severe allergic disease develop later. Immunologic abnormalities include increased IgE levels, hypogammaglobulinemia, and impaired antibody response to pneumococcal immunization.[257] These patients had significant improvement with reduced frequency of infections when antibiotic prophylaxis, intravenous IgG supplementation, or both were given.

Hyper-IgE syndromes.

Summary statement 70. A form of hyper-IgE syndrome (HIES) should be considered in patients with recurrent sinopulmonary and skin infections, chronic eczematous dermatitis, high serum IgE levels, and eosinophilia. (C)

Patients with HIES have chronic eczematous dermatitis with frequent superinfection by *Staphylococcus aureus* and sometimes *Candida albicans*.[218,258-260] Respiratory tract bacterial infections are frequent and can be severe.[261] Serum IgE levels range from a few thousand to several tens of thousands international units per milliliter. *S aureus* binding IgE is often present and readily measured in an immunoassay. Specific antibody responses to vaccines can be impaired. These findings are not pathognomonic for HIES; they are also observed in patients with severe atopic dermatitis, which is itself more commonly a cause of extreme increases in IgE levels in the absence of other (as yet) defined immunodeficiency. More than 90% of patients with HIES also have increased eosinophil counts.

Autosomal dominant or type 1 HIES is caused by mutations in the signal transducer and activator of transcription 3 *(STAT3)* gene.[218,258-260] This disorder is often referred to as "Job syndrome," a biblical allusion inspired by the prominent skin infections (boils). Patients with type 1 HIES are also prone to recurrent lung infections with *S aureus* (often with abscess formation), fungi (*Aspergillus* and *Candida* species), *Pseudomonas*

species, nontuberculous mycobacteria, and various opportunistic infections. These patients are prone to lung damage, including bronchiectasis and pneumatoceles.[261] Additional clinical manifestations in patients with autosomal dominant HIES include hyperextensible joints, bone fragility, scoliosis, and delayed shedding of primary teeth because of failure of root resorption. Patients can experience bone fractures with minor trauma. There is often a characteristic facies with coarse and/or asymmetric features. The facies might be absent or subtle in youth and become more prominent with age. Craniosynostosis can also be seen. Other manifestations can include neonatal dermatitis, midline anomalies, and lymphoma.[262] Although IgE levels are high, allergen-specific IgE is seen only occasionally. Other screening studies of humoral and cellular immunity are usually normal.

Heterozygous mutations in *STAT3* are identified in the majority of patients. Family members sharing the same *STAT3* mutation can present with different severity of clinical symptoms. Intermediate or variant phenotypes of autosomal dominant HIES have been described in patients with somatic mosaicism for *STAT3* mutations.[263] A scoring system based on clinical and laboratory features of autosomal dominant HIES is helpful for diagnosis.[264]

Mutations in the *DOCK8* gene are responsible for a less common autosomal recessive form of HIES (type 2).[258,265-268] These patients have some of the clinical features of autosomal dominant HIES. However, they do not have skeletal or dental abnormalities and do not tend to have pneumatoceles. Patients tend to have severe allergic manifestations, eosinophilia, and disseminated cutaneous viral infections. The most common of these are molluscum contagiosum, HSVs, and human papilloma viruses (HPVs). This group of patients has the additional feature of autoimmune vasculopathy with CNS involvement. Lymphomas also develop with increased frequency. Mutations in the *DOCK8* gene have been demonstrated in members of families with autosomal recessive HIES.[265-268] Immunologic abnormalities are variable but can include both cellular and humoral immune defects. TREC numbers have been found to be low in a few patients with DOCK8 deficiency.[269] If this is a general finding, it could aid in diagnosis and would suggest that type 2 HIES could be detected by means of newborn TREC screening (see SS 26).

Both forms of HIES are associated with defective development and function of IL-17–producing T_H17 cells.[266,270,271] T_H17 cells and IL-17 have a role in host protection from *Candida* species, as well as in chronic infectious and autoimmune inflammation.[272]

Defects in the *TYK2* gene cause a rare variant of autosomal recessive HIES. A patient who presented with skin infections, lung abscesses, and increased IgE levels were found to have a homozygous null mutation in the *TYK2* gene, resulting in absent protein expression.[273] The patient also had BCG lymphadenitis and salmonellosis, suggesting a different clinical entity than the most common presentation of autosomal recessive HIES. T-cell cytokine expression was found to be impaired. Note, however, that the HIES picture might not be a consistent association with *TYK2* mutation. One patient has been described to have a distinct *TYK2* mutation associated with severe BCG infection, neurobrucellosis, and cutaneous herpes zoster infection without atopy or high serum IgE levels.[274]

A few kindreds of patients have recently been described with some features similar to HIES and mutations in phosphoglycerate mutase 3 *(PGM3)*.[275,276] These patients have recurrent respiratory tract infections and severe eczema with skin abscesses and viral infections and food and environmental allergies. Some exhibit autoimmunity (vasculitis and neutropenia), intellectual disability, and hypomyelination. Immunologic abnormalities include markedly increased IgE levels (and other isotypes), eosinophilia with CD8 lymphopenia, and low memory B-cell counts, with generally preserved vaccine responses. Note that the *PGM3* mutation has also been described in patients with CID and skeletal dysplasia (Table E9).[172]

Another HIES-like disorder is Loeys-Dietz syndrome associated with mutations of TGF-β receptor chains 1 and 2 (*TGFBR1* and *TGFBR2*).[277] This is predominantly a connective tissue disorder characterized by vascular aneurysms similar to those seen in patients with Marfan syndrome. Some patients with particular missense mutations in *TGFBR1* also manifest severe asthma and atopic dermatitis with multiple food and environmental allergies and very high IgE levels.

Finally, the so-called severe dermatitis, allergy, metabolic wasting (SAM) syndrome can also resemble a form of HIES.[278,279] This disorder is associated with mutations of the keratinocyte tight junction component desmoglein 1 (encoded by *DSG1*). These patients also have recurrent infections, failure to thrive, severe eczematous dermatitis, and multiple food and environmental allergies with increased IgE levels.

Summary statement 71. The initial approach to HIES therapy should be directed toward management of complications. (C)

The main cause of mortality in patients with type 1 HIES is severe infections.[218,258,260] These patients can have progressive decrease of lung function secondary to frequent pneumonias.[261] Aggressive therapeutic and prophylactic antibiotic therapy are indicated. Antifungal prophylaxis can be considered. The risk of fracture with relatively minor trauma is high and should be prevented where possible. Children should be monitored carefully for scoliosis, and retained primary teeth should be extracted.[280] In patients with type 2 HIES, severe allergic manifestations can be very difficult to treat. Lymphoma and vasculopathy are the most prominent life-threatening complications. Frequent follow-up is recommended.[258,260,265,267]

Summary statement 72. Patients with DOCK8 deficiency and poor antibody production should receive IgG replacement therapy. (C)

See SS 11.[265-268]

Summary statement 73. The use of IVIG or IFN-γ in patients with type 1 autosomal dominant HIES might be helpful in selected cases. (C)

At least one series has failed to demonstrate improvement in immunologic function in patients with HIES with IVIG therapy, whereas another has reported clinical improvement with high-dose IVIG.[218,258,260] In addition to antibiotic prophylaxis, IVIG supplementation can be considered when impaired specific antibody responses are demonstrated. There are scarce reports of improvement of clinical and laboratory indicators with administration of IFN-γ.[218,258,260] However, evidence is not sufficient to consider this to be standard therapy for HIES. There are isolated case reports with rituximab (for lymphoma)[281] or omalizumab (for dermatitis)[282,283] in patients with HIES.

Summary statement 74. HSCT should be considered for both forms of HIES. (C)

Successful HSCT for patients with type 2 HIES has been reported in several cases, with restoration of immune function and resolution of eosinophilia.[284-286] In one early reported case of HSCT for type 1 HIES, the clinical manifestations reappeared.[287]

However, more recent reported cases have had successful outcomes.[288]

Hepatic veno-occlusive disease.

Summary statement 75. Mutations in the *SP110* gene should be sought in patients with hepatic veno-occlusive disease with immunodeficiency. (C)

Veno-occlusive disease with immunodeficiency is a rare CID associated with hepatic veno-occlusive disease and is most prevalent in infants from Lebanese descent in Australia.[289,290] T-cell function defects and hypogammaglobulinemia result in increased frequency of opportunistic infections. Mutations of the *SP110* gene have been identified in patients with this disorder. IgG supplementation and antibiotic prophylaxis (see SS 16 and Table E7) increase the chances of survival.

Dyskeratosis congenita.

Summary statement 76. Dyskeratosis congenita (DKC) should be investigated in patients with abnormal skin pigmentation, nail dystrophy, and leukoplakia of the oral mucosa. (C)

DKC is a disorder of telomere biology caused by mutations in any of 7 genes determining X-linked *(DKC1)*, autosomal dominant (*TERC*, *TERT*, and *TINF2*), or autosomal recessive (*NOP10*, *NHP2*, and *RTEL1*) inheritance.[291-294] Clinical diagnosis of DKC is suspected in patients presenting with the classical triad of lacy skin pigmentation, nail dystrophy, and oral leukoplakia. Pulmonary fibrosis, bone marrow failure, leukemias, and compromise of other organs can also occur.

Immunodeficiency occurs in patients with the most severe presentations and might precede the development of DKC-diagnostic clinical findings. Immunologic abnormalities were described in a single-center report of 7 patients with DKC.[295] In addition to other DKC characteristics, patients presented with lymphopenia affecting variably all subsets and hypogammaglobulinemia with impaired antigen-specific antibody and low lymphoproliferative responses, resulting in recurrent sinopulmonary infections and opportunistic infections, including PCP. Antibiotic prophylaxis and IgG supplementation can reduce the risk of infections in these patients. HSCT is curative for DKC and should be considered for patients with evidence of marrow failure.[296]

Defects of vitamin B12 and folate metabolism.

Summary statement 77. Inborn errors of folate and vitamin B12 malabsorption should be considered in the differential diagnosis of SCID. (C)

Patients with these disorders can present with all of the classic clinical and laboratory features of SCID, including PCP and disseminated CMV. Although lymphopenia might not be seen, function is poor, with absent mitogen response and hypogammaglobulinemia and impaired antibody formation. Megaloblastic anemia is also characteristic, although this could be masked by concurrent iron deficiency. Defects have been described in genes encoding transcobalamin II *(TCN2)*,[297] solute carrier family 46 (*SLC46A1*; also called the proton-coupled folate transporter),[174,298] and methylenetetrahydrofolate dehydrogenase ($NADP^+$ dependent) 1 *(MTHFD1)*.[299] The latter can be associated with leukopenia, atypical hemolytic uremic syndrome (HUS), and neurological abnormalities.

Summary statement 78. Infants with severe vitamin B12 or folate deficiency should be treated aggressively with folate or cobalamin replacement as soon as the diagnosis is made. (C)

Patients with TCN2 deficiency should receive oral or (preferably) intramuscular injection cyanocobalamin or hydroxycobalamin.[297] A lifelong regimen of weekly injections is likely to be needed. Patients with defects of *SLC46A1* should receive high-dose intravenous folinic acid.[174,298] Infants with defects of *MTHFD1* should receive supplementation with both hydroxycobalamin and folinic acid.[299]

Immunodeficiency with multiple intestinal atresia.

Summary statement 79. Patients born with multiple intestinal atresia (MIA) should be screened for CIDs. (C)

Mortality in infancy is very high in patients with MIA and can be further complicated by life-threatening infections in those patients also having an SCID-like phenotype, including a high rate of bloodstream infections with intestinal bacteria.[300-302] Patients can have variable immune defects, including lymphopenia, hypogammaglobulinemia, markedly decreased B- and T-cell counts, and decreased mitogen proliferation. Immunologic studies can be normal early in life but wane quickly over time. Defects in the tetratricopeptide repeat domain 7A gene *(TTC7A)* have been described in several of these patients.[300-302]

Summary statement 80. HSCT should be considered for treatment of MIA-SCID. (C)

Outcomes of HSCT have been mixed, although at least 3 published patients are still alive after transplantation. It is unclear whether the intestinal inflammation and atresia is secondary to the immune defect, and many of the surviving reported patients have continued to require multiple operations for intestinal atresia and remain dependent on total parenteral nutrition.[300-302]

Predominantly antibody deficiencies

Agammaglobulinemia.

Summary statement 81. Patients with very low or undetectable serum immunoglobulin concentrations and very low or undetectable circulating B lymphocytes with normal T-cell numbers and function should be given a diagnosis of agammaglobulinemia. (C)

As do patients with all forms of antibody deficiency, most patients with agammaglobulinemia present with recurrent bacterial respiratory tract infections, particularly otitis media, sinusitis, and pneumonia, in the first 2 years of life. If given an early diagnosis, many patients might have had only recurrent otitis media.[303-305] The most common organisms isolated are *Streptococcus pneumoniae* and *Haemophilus influenzae*. Some patients present with an overwhelming infection, often with associated neutropenia.

Infections that are suggestive of agammaglobulinemia specifically are CNS enterocytopathic human orphan (ECHO) viruses (although these can also occur in patients with CVID) and ecthyma or pyoderma gangrenosum caused by various species of *Helicobacter*.[305-309] Patients with agammaglobulinemia can also have a silent bacteremia with helicobacter or *Campylobacter jejuni*.[310] *Pseudomonas* species–induced sepsis can occur in patients with agammaglobulinemia.[305] Rarely, patients present with PCP or vaccine strain poliovirus infection, which is now almost nonexistent in the United States after discontinuation of routine use of attenuated polio vaccine in infancy.[311,312] *Ureaplasma* or *Mycoplasma* species–related arthritis and bacteremia or regional enteritis associated with enterovirus are also seen.[304,305,313]

A family history of affected maternal male cousins, uncles, or nephews suggestive of X-linked inheritance is frequently present

in cases of XLA, although sporadic cases are also common. Some patients are not recognized to have XLA or other forms of agammaglobulinemia until after 5 years of age despite the presence of frequent infections and recurrent antibiotic use; others have a milder clinical phenotype and are recognized only later in life.[314,315]

The physical examination of patients with agammaglobulinemia usually reveals absence of lymph nodes and tonsils distinct from other forms of antibody deficiency. Small or absent tonsils can also be seen in patients with some CIDs and other congenital agammaglobulinemias. There are no other consistent physical findings in patients with agammaglobulinemia.[304,305]

Agammaglobulinemia is characterized by a serum IgG level of usually less than 100 mg/dL, an IgM level of less than 20 mg/dL, an IgA level of less than 10 mg/dL, and peripheral blood $CD19^+$ B-cell counts of less than 2%.[304,305] The differential diagnosis of agammaglobulinemia includes X-linked and autosomal recessive forms and some patients with "severe" CVID (see below) with immunoglobulins and B cells in the agammaglobulinemic range. It can sometimes be difficult to distinguish agammaglobulinemia from CVID without molecular testing. Measurement of specific antibodies might not be necessary in patients with IgG levels in the agammaglobulinemic range. Laboratory findings and diagnostic criteria for antibody deficiencies are summarized in Table E10.

Approximately 85% of patients with agammaglobulinemia patients have the X-linked form (XLA) because of mutations in the Bruton tyrosine kinase *(BTK)* gene encoding BTK.[304,305] The absence of BTK protein in monocytes or platelets can be detected by using Western blotting or flow cytometry.

Patients with certain *BTK* mutations can have milder clinical and immunologic phenotypes with higher concentrations of serum immunoglobulins suggestive of CVID or even specific antibody deficiency (SAD).[304,305] Infections can be mild or occur late in life.[314,315] 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.[304,305] BTK deficiencies can be found in male patients with milder phenotypes with or without a family history of antibody deficiency of any phenotype. Diagnosis might require direct sequencing of *BTK* in cases in which missense mutations allow expression of normal levels of nonfunctional BTK protein. Protein and genetic tests for BTK expression and mutations are readily available from a variety of sources.

Autosomal recessive agammaglobulinemia (AAGAM) is suspected in female patients with characteristic clinical and laboratory findings, in families with an autosomal recessive pattern of inheritance or consanguinity, and in male patients in whom *BTK* mutations cannot be identified. Mutations in one of several genes that regulate B-cell maturation cause AAGAM.[316-320] Several of these are components of the pre–B-cell immunoglobulin receptor, including IgM heavy chain *(IGHM)*, part of the surrogate light chain (λ 5/14.1, *CD179B*), the immunoglobulin receptor–associated signal transducing chains Ig-α and Ig-β (*CD79A*, and *CD79B)*, and the cytoplasmic adapter molecule B-cell linker protein *(BLNK)*. All of these disorders have recessive inheritance. The only defined autosomal dominant monogenic agammaglobulinemia is caused by defects of transcription factor 3 (TCF3).[321] In addition, a translocation of a gene encoding leucine-rich repeat containing 8 *(LRRC8)* leads to a highly similar form of AAGAM.[322] Furthermore, patients with myelodysplasia with hypogammaglobulinemia might have monosomy 7 or trisomy 8, which are associated with underlying bone marrow abnormalities.[323] Molecular diagnosis of AAGAM usually requires advanced methods or genetic tests that are not routinely available in clinical reference laboratories.

Summary statement 82. Agammaglobulinemia should be managed aggressively with antimicrobials, IgG replacement, and careful attention to pulmonary status. (C)

See SSs 11 to 17.[304,305,324,325]

Summary statement 83. Enteroviral meningoencephalitis in patients with agammaglobulinemia should be treated with high doses of IVIG with measurable antibody to the infecting virus. (C)

Chronic enteroviral meningoencephalitis is usually caused by ECHO viruses and can cause serious morbidity or mortality in patients with XLA.[326] The occurrence of this complication has decreased considerably since IgG replacement has been routinely administered to patients, but it still occurs rarely, even with IgG therapy. Treatment of meningoencephalitis has been at least partly successful with IVIG given at high doses (maintaining IgG trough levels >1000 mg/dL). The product or lot of IgG should be selected to contain relatively high-titer antibody to the particular infecting ECHO virus. Intraventricular IgG has resulted in a cure in 1 reported case.[327]

Summary statement 84. Lung transplantation should be considered for patients with agammaglobulinemia and life-threatening chronic lung disease. (C)

In patients with XLA who have severe bronchiectasis, lung transplantation has been performed with at least initial success.[328] Survival of 6 and 12 months in 2 patients with XLA after double lung transplantation for end-stage lung disease has been reported. Experience is too limited to permit generalization regarding the application of lung transplantation in patients with XLA or other forms of agammaglobulinemia.

CVID.

Summary statement 85. The diagnosis of CVID should be considered in male or female subjects older than 4 years who have low IgG and IgA levels and impaired antibody response but do not have genetic lesions or other causes of primary or secondary antibody deficiency. (C)

CVID is a primary immunodeficiency of uncertain cause affecting approximately 1:30,000 persons.[329-332] Recurrent and chronic bacterial respiratory tract infections, including otitis media, sinusitis, bronchitis, and pneumonias, are the most frequent infectious complications (as with all forms of antibody deficiency). Common pathogens include encapsulated (nontypeable *H influenzae* and *S pneumococcus*) or atypical (*Mycoplasma* and *Ureaplasma* species) bacteria. Recurrent and/or persistent viral respiratory tract infections, in particular secondary to rhinovirus, are also increased in patients with CVID.[333]

A universally accepted consensus definition of CVID does not exist.[329] It has been proposed that a definitive diagnosis of CVID should include a serum IgG level of less than 450 to 500 mg/dL and a serum IgA or IgM level of less than the fifth percentile. Some authorities require that IgA levels must be low in addition to IgG levels. All agree that patients must have decreased ability to make specific antibodies and the exclusion of other primary (eg, XLA and X-linked lymphoproliferative disease [XLP]) and secondary (eg, medications; protein loss through the gastrointestinal tract, lymphatics, or kidney; B-cell lymphomas, and bone marrow failure) causes of

TABLE E10. Summary of laboratory findings in the diagnosis of antibody deficiencies

IgG	IgA	IgM	IgG subclass	Vaccine response	B cells	Diagnosis
NL	NL	NL	NL	NL	NL	Normal*
NL	NL	NL	NL	Low†	NL	SAD
NL	NL	NL	≥1 Low	Low†	NL	IGGSD
NL	Absent	NL	Normal	NL or low	NL	SIGAD
NL	Absent	NL	≥1 Low	Low†	NL	IgA deficiency with IGGSD
Low	NL	NL		NL	NL	Possible secondary, unspecified, or transient hypogammaglobulinemia‡
Low	NL or low	NL or low		NL	NL or low	Unspecified or transient hypogammaglobulinemia
Low	Low	NL or high		Low	NL	HIM
Low	Low	NL or low		Low§	NL or low	CVID, possible transient hypogammaglobulinemia
Absent	Absent	Absent			Absent	Agammaglobulinemia or severe CVID¶

The clinical presentation is primarily suggestive of an antibody defect or any evaluation of cellular function is thus far normal, and the clinical presentation is at least consistent with a possible antibody deficiency and not suggestive of a cellular component (eg, lack of opportunistic infections). The initial laboratory examination of humoral immunity consists of measuring levels of various immunoglobulin isotypes (IgG, IgA, IgM, and possibly IgG subclasses) in serum, as well as a measure of function or specific antibody production, which should include both protein and polysaccharide antigens (see SS 6).

NL, Normal.

*Consider complement deficiency or phagocyte defect.

†Usually refers to polysaccharide response.

‡In this circumstance it is useful to measure serum total protein and/or albumin levels; if low, this is consistent with secondary hypogammaglobulinemia.

§Protein and/or polysaccharide response.

¶Cellular immunity should be evaluated as indicated by other clinical features but is often worth considering when significant impairment of humoral immunity is observed because it could be a component of a CID.

hypogammaglobulinemia.[329,334] Documenting impaired production of specific antibodies (in response to protein or polysaccharide antigens) is essential for diagnosis (Table E10). Hypogammaglobulinemia in young children resolves as they age (see below). For this reason, it is not considered appropriate to confer a diagnosis of CVID before age 4 years.

B-cell numbers in the peripheral blood of patients with CVID might be normal or reduced; about 13% of patients will have less than 3% B cells among peripheral blood lymphocytes.[329-332] Although it is classified as a form of predominantly humoral immunodeficiency, T-cell abnormalities are frequently found in patients with CVID.[329,331,332,335,336] These include reductions in peripheral blood T-cell populations, as well as functional defects, such as reduced *in vitro* proliferative responses, defects in cytokine production, decreased T_H cell function, abnormalities in T-cell signaling, diminished expression of the costimulatory molecule CD40L, decreased numbers of naive T cells, increased suppressor T-cell function, and decreased numbers of regulatory T (Treg) cells.

Summary statement 86. Grouping of patients with CVID based on analysis of B-cell subsets in the periphery might be useful and should be considered. (C)

Proportions of peripheral B-cell subtypes correlate with clinical phenotypes. The Freiburg,[337] Paris,[338] and EUROclass[339,340] classification schemes group patients with CVID based on enumeration by means of flow cytometry of various B-cell parameters, such as total numbers of B cells and B-cell subsets (switched memory B cells, marginal zone B cells, transitional B cells, and $CD21^{low}$ cells present in the peripheral blood). The most recent classification (EUROclass) incorporates features of the Freiburg and Paris classifications. Increased granulomatous diseases correlates with a decreased number of marginal zone ($IgD^+IgM^+CD27^+$) and class-switched B cells ($IgD^-IgM^-CD27^+$). Granulomatous disease and splenomegaly also correlate with increased expansion of $CD21^{low}$ B cells. Expansion of transitional B cells ($IgM^{high}CD38^{high}$) is associated with lymphadenopathy. Specific B-cell subsets are developmentally regulated, and age-adjusted values should be used in these instances.[341,342]

Summary statement 87. Selected diseases, molecular defects, or both should be considered in patients presenting with symptoms and signs consistent with CVID. (C)

Several different gene mutations have been discovered in patients with a phenotype consistent with or similar to CVID. Most of these genetic abnormalities are rare, with the exception of mutations in *TNFRSF13B* (TNF receptor superfamily 13B encoding transmembrane activator and CAML interactor [TACI]), which occur in approximately 10% of patients.[343-345] TACI polymorphisms are not entirely disease causing by themselves, but the presence of one of these TACI polymorphisms does appear to confer increased risk of lymphoproliferation and autoimmunity.

Rare cases of monogenic autosomal recessive forms of hypogammaglobulinemia have been described. Mutations of inducible T-cell costimulator *(ICOS)* lead to all of the clinical manifestations of CVID.[346] Other monogenic forms of CVID can result from mutations in *CD19*,[347] *CD20*,[348] *CD21*,[349] *CD81*,[350] and B-cell activating factor receptor *(BAFFR)* and others.[351] In general, these disorders are characterized by the variable age of onset and hypogammaglobulinemia and impaired antibody formation characteristic of CVID. However, autoimmune, lymphoproliferative, and malignant complications are not seen. The clinical utility of identifying these mutations in patients given a diagnosis of CVID is not entirely clear, although the prognosis might be different and general considerations of genetic counseling apply (see SS 7).

Many other forms of PIDs can have clinical and laboratory manifestations that overlap CVID.[323] Some examples include XLP1 and XLP2, immunoglobulin class-switch defects, XLA, Good syndrome (see below), and myelodysplasia with hypogammaglobulinemia.[323] Recent additions to CVID-like genetic diagnoses include gain-of-function mutations of phosphoinositol 3′ kinase catalytic subunit *(PIK3CD)*,[352] loss- or gain-of-function mutations of the p85 regulatory subunit of phosphoinositide 3-kinase *(PIK3R1)*,[317,353,354] LRBA deficiency,[355-357] mutations in TNF superfamily member 12 (*TNFS12*; also known as TWEAK, TNF-related weak inducer of apoptosis),[358] nuclear factor κB (NF-κB) 2 deficiency,[301] and protein kinase Cδ (PRKCD) deficiency.[359] Management might not change as a

result of the identification of one of these specific genetic lesions. However, when resources are available, specific diagnosis might be desirable for other reasons (see SS 7). Mutations of *KMT2D* are found in 60% of patients with a form of Kabuki syndrome in which the characteristic cleft palate, abnormal facies, and developmental delay are seen in association with hypogammaglobulinemia and impaired antibody formation and poor memory B-cell development similar to that seen in patients with CVID.[360]

Summary statement 88. CVID should be managed aggressively with antimicrobials, IgG replacement, and careful attention to pulmonary status. (C)

See SSs 11 to 17.

Infectious lung disease occurs in the majority of patients with CVID.[329-332] A clinical presentation very similar to that of allergic asthma can occur in as many as 10% to 15% of patients, usually in the absence of allergen-specific IgE.[361] Noninfectious chronic pulmonary disease occurs in nearly 30% of patients and is associated with reduced survival.[55,362-364] Bronchiectasis is the most common pulmonary complication of CVID, occurring in 10% to 20% of patients. A form of interstitial lung disease termed granulomatous and lymphocytic interstitial lung disease (GLILD) is found in approximately 10% of patients. GLILD is frequently accompanied by splenomegaly and diffuse adenopathy and can be associated with increased mortality. Lung transplantation has been attempted in very few patients with CVID.[365]

Even with IgG replacement that is adequate to prevent invasive bacterial infections (eg, pneumonia), many patients with CVID will have recurrent sinusitis, otitis media, and bronchitis.[329-332] Frequent bronchitis and pneumonia are more likely to be associated with bronchiectasis. These patients often benefit from the addition of antibiotic prophylaxis to their maintenance regimen for periods of months or years or permanently (see SS 16 and Table E7).

Summary statement 89. Gastrointestinal status should be monitored regularly in patients with CVID. (C)

Approximately 20% to 25% of patients with CVID have gastrointestinal complications.[329-332,366] Most prominent among these are chronic gastritis with or without pernicious anemia, lymphoid nodular hyperplasia, villous atrophy, inflammatory bowel disease, and enteropathy. Giardiasis and enteritis with *C jejuni* and salmonellosis are the most common enteric infections. Chronic viral enteritis caused by CMV, norovirus, or parechovirus can also occur. Approximately 40% of patients with CVID have abnormalities in liver function tests, with an increase in levels of alkaline phosphatase the most frequent abnormality. Nodular regenerative hyperplasia, which frequently leads to nonicteric portal hypertension, is the most common chronic liver disease in patients with CVID.[364,367,368] Patients with CVID are more prone to progressive liver disease after infection with hepatitis. Liver transplantation has been performed in only very few patients with CVID.[368]

Summary statement 90. Vigilance for possible autoimmune diseases should be maintained during follow-up of patients with CVID. (C)

The overall prevalence of autoimmune diseases in patients with CVID is approximately 20%.[323,329-332,364,369,370] The spectrum of autoimmune diseases found in patients with CVID is broad. Autoimmune cytopenias (autoimmune thrombocytopenic purpura and autoimmune hemolytic anemia) are the most common autoimmune disorders, occurring in 11% to 12% patients. Patients with autoimmune cytopenias are more likely to have splenomegaly and mutations in TACI. Other autoimmune diseases, such as seronegative arthritis and vasculitides, have also been observed. There are no standardized specific recommendations for routine or scheduled testing or imaging with respect to autoimmune manifestations in patients with CVID, other than the routine monitoring studies related to IgG replacement and lung status discussed in SSs 11 to 15.[49,331] The clinician must maintain a high index of suspicion when new symptoms arise.

Summary statement 91. Vigilance for nonmalignant and malignant lymphoproliferative disease should be maintained during follow-up of patients with CVID. (C)

As many as one third of patients with CVID will have a lymphoproliferative disorder that can be manifested by splenomegaly, intestinal lymphoid hyperplasia, or abdominal, mediastinal, or peripheral lymphadenopathy and is associated with an increased frequency in the development of B-cell malignancies and a worse prognosis.[329-332] Additionally, between 8% and 22% of patients have granulomatous infiltration in 1 or more organ systems (eg, lung, bone marrow, spleen, liver, and gastrointestinal tract). These patients have an increased incidence of autoimmunity.

B-cell lymphomas and other malignancies occur with increased frequency in patients with CVID.[329-332] The prevalence of B-cell lymphomas (predominantly non-Hodgkin lymphoma) and lymphoma of mucosa-associated lymphoid tissue is approximately 1.8% to 8.2%. Estimates of the relative risk of non-Hodgkin lymphoma range from 30- to 400-fold greater than in the general population. It can be difficult to distinguish malignant from nonmalignant disease in patients with CVID. There is also an approximately 10-fold increase in the relative risk for gastric cancer compared with the healthy population.[371] The prevalence in this population is approximately 0.8% to 1.7%. There are no standardized specific recommendations for routine or scheduled testing or imaging with respect to lymphoproliferative or malignant manifestations in patients with CVID other than the routine monitoring studies related to IgG replacement and lung status discussed in SSs 11 to 15. The clinician must maintain a high index of suspicion when new symptoms arise.

Summary statement 92. 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.[372-374] When choosing among therapeutic options for a particular complication, the degree of immune suppression might become a more prominent consideration than it might be in other settings. At this time, there are no regimens, modifications, or specific approaches considered "standard" for therapy of autoimmune or malignant complications of CVID.

Summary statement 93. Stem cell transplantation can be considered for patients with CVID with malignancy or severe organ damage. (C)

Experience is very limited in this regard. One group recently reported outcomes for 4 patients (2 with lymphoma and 2 with GLILD) who received allogeneic hematopoietic stem cells after reduced-intensity conditioning.[375] There was 1 death during the procedure, 1 patient had full immune reconstitution ("cure"), and 2 patients had improvement with partial immune reconstitution but ongoing morbidity caused by complications of CVID.

Summary statement 94. Patients having hypogammaglobulinemia and thymoma should be given a diagnosis of Good syndrome. (C)

"Common variable immunodeficiency with thymoma," "immunodeficiency with thymoma," and "Good syndrome" all denote a form of adult-onset hypogammaglobulinemia/agammaglobulinemia in association with thymoma.[376,377] The spectrum of bacterial sinopulmonary infections and pathogens is similar to that associated with the more prevalent form of CVID. However, Good syndrome is associated more frequently with opportunistic infections, including mucocutaneous candidiasis, severe varicella infection, PCP, CMV, and recurrent HSV. Lymphadenopathy and splenomegaly, which are commonly seen in patients with CVID, are not characteristic features of Good syndrome. Because thymomas frequently go undetected on routine chest radiography, diagnosis might require chest CT.

Autoimmune disease is a frequent complication of Good syndrome, most notably pure red cell aplasia and neutropenia.[376,377] Patients with Good syndrome often have chronic diarrhea of unclear cause.

Panhypogammaglobulinemia is a consistent finding in patients with Good syndrome.[376,377] Unlike the majority of patients with CVID, immunophenotypic analysis of peripheral blood lymphocytes frequently shows absent or very low numbers of B cells, reduced $CD4^+$ T-cell counts, absent cutaneous delayed hypersensitivity responses, and a reduced *in vitro* T-cell response to mitogen.

As many as 9% of patients in a large French study of patients with CVID had late sudden onset of opportunistic infections, gastrointestinal tract disease, splenomegaly, lymphomas, and granulomas, many in association with a CD4 count of less than 200 cells/μL.[378] This has been called late-onset combined immunodeficiency.[379] This phenotype is very similar to Good syndrome, with the exception of thymoma.

The general principles of management of Good syndrome are the same as for CVID, including IgG replacement; aggressive, prolonged, or prophylactic antibiotics as necessary; and monitoring of lung, liver, gastrointestinal, and kidney function and vigilance for symptoms and signs of autoimmune disease.

Summary statement 95. 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.[376,377]

SIGAD.

Summary statement 96. Subjects older than 4 years with a serum IgA level of less than 7 mg/dL and normal serum IgG and IgM levels and in whom other causes of hypogammaglobulinemia have been excluded should be given a diagnosis of SIGAD. (C)

Note that this definition is restricted to very low or absent circulating IgA concentrations (Table E10).[380,381] Only methods capable of detecting IgA concentrations of less than 7 mg/dL can determine whether IgA is truly absent or present at very low concentrations. Approximately two thirds of subjects with IgA levels of less than 7 mg/dL have a lower detectable level of IgA; in one third of subjects, it appears to be completely absent.[47] Most clinical laboratories do not measure IgA levels of less than 7 mg/dL, although such testing is available in some specialty laboratories. Some patients with SIGAD have CVID later in life.[382] SIGAD is a common immunologic abnormality affecting approximately 1 in 300 to 700 white subjects in the United States.[380,381] SIGAD is relatively rare in Asian populations (about 1:18,000). There is a family history of either SIGAD or CVID in 20% to 25% of affected subjects of the same family. The prevalence of SIGAD might be higher in male patients.

A molecular cause of IgA deficiency has not been clearly described. Genetic linkage studies implicate a multifactorial genetic basis, including contributions from a variety of MHC and non-MHC loci.[381] Some large-scale genetic deletions, such as 18q deletion syndrome, have been associated with IgA deficiency, sometimes in association with other abnormalities, such as IgG_4 deficiency, and autoimmune manifestations, such as diabetes or thyroiditis.[383]

Summary statement 97. Patients with serum IgA levels of less than the normal range for age but greater than 7 mg/dL should not be given a diagnosis of IgA deficiency. (C)

There are no consistently identified clinical associations in those with IgA concentrations of greater than 7 mg/dL but less than the lower limit of normal.[384] It is not appropriate to refer to these patients as having SIGAD.

Summary statement 98. Patients with SIGAD should be monitored over time for the occurrence of complications. (C)

Most affected patients with SIGAD are asymptomatic, but some do have problems over time. Clinical manifestations can include respiratory and gastrointestinal tract infections, atopy, autoimmune diseases, celiac disease, and malignancy. Long-term vigilance is recommended.[380,381,385,386]

Up to one third of symptomatic patients experience recurrent infections. 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.

In addition to infections, IgA-deficient patients are 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.[380,381,385,386] Several studies have reported a higher prevalence of celiac disease in patients with SIGAD, as well as a higher frequency of SIGAD among patients with confirmed celiac disease. Patients with SIGAD are also at higher risk for gastrointestinal and lymphoid malignancies later in life. They also have a higher prevalence of allergies and asthma.

Several studies suggest an increased incidence of IGGSD (see below) among patients with symptomatic SIGAD.[380,381] Impaired specific antibody responses (particularly to pneumococcal polysaccharide) are also seen in patients with SIGAD. However, one study did not document correlation between a history of infections and response to pneumococcal polysaccharide vaccine.[387] One study reported that the proportion of switched memory B cells were lower in patients with SIGAD, with higher rates of pneumonia, bronchiectasis, and autoimmune disease.[388] T-cell populations and function are normal in patients with SIGAD.

Patients with IgA deficiency are considered by many to be at risk for anaphylactic reactions to blood products (eg, red cells and platelets) because of the possible occurrence of antibodies to IgA (see SS 12).[389] However, the risk to an individual patient is unclear (likely small), and practices vary. However, some centers will transfuse products from IgA-deficient donors for IgA-deficient recipients or wash cells before they are transfused.

Summary statement 99. Medication use should be investigated in patients with IgA deficiency. (C)

SIGAD can be acquired as a result of certain medications. Examples of these medications include phenytoin, carbamazepine, valproic acid, zonisamide, sulfasalazine, gold, penicillamine, hydroxychloroquine, and nonsteroidal anti-inflammatory drugs (NSAIDs).[390,391] A thorough history of medication use is needed for patients with SIGAD because in many cases this is reversible with cessation of the drug therapy. Hypogammaglobulinemia and IGGSD can also be caused by similar drug-induced adverse effects.

Summary statement 100. Aggressive antimicrobial therapy, prophylaxis, or both should be used in patients with SIGAD and recurrent sinopulmonary infections. (C)

No definitive therapy for SIGAD exists. Some patients with frequent infections might benefit from longer-term prophylactic antibiotics.[381]

Summary statement 101. Atopic disease should be treated aggressively in patients with SIGAD. (C)

Atopy occurs frequently in association with SIGAD.[387] Because allergic inflammation can predispose patients to respiratory tract infection (especially sinusitis and otitis media), allergy should be diagnosed with standard techniques. If present, it should be treated vigorously with all standard modalities, where applicable.[381]

Summary statement 102. Rare patients with SIGAD might benefit from IVIG replacement therapy. (C)

Use of IgG replacement therapy in patients with SIGAD is controversial. The majority of these patients will have minimal (if any) clinical response. The demonstration of impaired antibody production can be construed to support such use, but the lack of clear a correlation of impaired vaccine response with infection in patients with SIGAD might render such reasoning questionable.[381] In patients with recurrent infections that negatively affect quality of life and in whom aggressive antibiotic therapy and prophylaxis fail or who have intolerable side effects or hypersensitivity to antibiotics, a trial of IgG therapy can be considered.[392] See SS 12 regarding anti-IgA antibodies and their possible effect on use of IgG in these patients.

IgG subclass deficiency.

Summary statement 103. A diagnosis of IGGSD should be considered for a patient with recurrent infections, 1 or more IgG subclass levels less than the fifth percentile, and normal total concentrations of IgG, IgM, and IgA. (C)

A clinical diagnosis of IGGSD is controversial.[393] Measurement of IgG subclass levels is not universally recommended as part of the evaluation of antibody-mediated immunity. Recall that by definition, normal IgG subclass values are defined as within −2 SDs of the mean, and thus approximately 2.5% of the population will automatically be "deficient" in at least 1 IgG subclass.[394] Measuring IgG subclasses adds cost and is frequently unnecessary when total immunoglobulins and specific antibodies are measured. When a decision is made to measure IgG subclasses, all 4 should be determined at the same time. A 1-time low level of 1 or more IgG subclasses is not considered sufficient for a diagnosis of IGGSD. All abnormal IgG subclass concentrations should be confirmed by at least 1 additional measurement at least 1 month apart from the first.[395]

IgG2 or IgG3 deficiencies are the most commonly diagnosed forms of IGGSD.[396-399] Because IgG1 comprises ± 60% of the total IgG level, "selective" deficiency of IgG1 is usually (not always) associated with a low total IgG level, which defines hypogammaglobulinemia. IgG4 is present in very low concentrations in children younger than 10 years of age, and therefore IgG4 deficiencies should not be diagnosed before age 10 years.[395] Furthermore, normal ranges for IgG4 are poorly defined. Low IgG2 levels are sometimes associated with low IgG4 levels (and/or low IgA levels, see below). Low IgG1 levels are sometimes associated with low IgG3 levels.

Measurement of IgG subclasses can be considered in patients with recurrent respiratory tract infections, particularly if IgG, IgA, and IgM levels are normal.[396-399] If a diagnosis of SAD is being considered because of poor vaccine response (see below), IgG subclasses should be determined because a diagnosis of IGGSD might be more appropriate (Table E10). IGGSD has been observed in association with other primary immunodeficiencies, such as AT[400] and WAS[401]; secondary immunodeficiencies, such as HIV infection or AIDS[402]; and after HSCT.[403] Secondary IGGSD has also been described in patients treated with antiepileptic drugs (see SS 99).[404]

In one study of patients with respiratory tract infections, IgA deficiency was found in 9.3%, IgG subclass deficiency in 8.4%, and combined IgA and IGGSDs only in 1.4%.[398] The functional significance of IGGSD in addition to SIGAD is not well understood.[392] Patients with this combination of abnormalities are usually given diagnoses during evaluation for antibody deficiencies. The clinical implications of this combination of abnormalities need to be evaluated in the context of the severity of infections, autoimmunity, and other manifestations of abnormal immunity and of the progression of symptoms over time.[405]

Some patients with IGGSD exhibit impaired specific antibody production.[396-399] Impaired polysaccharide responses are observed commonly among young patients with IgG_2 subclass deficiency. Several abnormalities of specific polysaccharide antibody production have been described in patients with IGGSD (see section on SAD below).[406] Impaired antibody production against polysaccharide antigens is not often seen in adults with IgG3 subclass deficiency.

IGGSD with impaired vaccine responses and predisposition to recurrent respiratory tract infections can occasionally be seen in association with various syndromes, such as Trisomy 21.[179] Trisomy 21 can also be associated with other variable immunologic abnormalities (Table E9), but frequent or severe infections beyond the respiratory tract are uncommon.

Summary statement 104. The principles of management of IGGSD should follow those presented for SIGAD and SAD. (C)

Recurrent respiratory tract viral and encapsulated bacterial infections are the most common clinical associations with IGGSD.[396-399] The frequency and severity of infections might wane over time, even when the immunologic abnormality persists. On the other hand, infections could persist, but the subclass abnormality might not. Rare patients can present early with IGGSD and evolve into more severe phenotypes, such as CVID, later in life. Other clinical conditions associated with IGGSD include atopy and autoimmune disease. A higher incidence of malignancy is generally not associated with IGGSD.

The principles of management of IGGSD include therapy of allergy, if present; prophylactic antibiotics; and cautious use of polyclonal human IgG in selected patients.[407,408] These considerations are as already outlined for SIGAD above (SSs 100-102; see also SSs 11-17). In some patients additional immunization with

TABLE E11. Assessing serotype-specific responses to pneumococcal capsular polysaccharides

Phenotype	Age <6 y	Age >6 y
Mild	Concentration >1.3 μg/mL for >50% of types with a 2-fold increase for <50% of serotypes	Concentration >1.3 μg/mL for >70% of types with a 2-fold increase for <70% of serotypes
Moderate	Concentration >1.3 μg/mL for <50% of serotypes	Concentration >1.3 μg/mL for <70% of serotypes
Severe	Concentration >1.3 μg/mL for ≤2 serotypes	
Memory	Loss of response within 6 mo	

Adapted from Orange et al.[413]

pneumococcal vaccines should also be used to enhance immunity. This has been shown to be effective in patients with associated IgG2 deficiency who require 2 doses of the conjugate vaccine at ages when one dose is usually sufficient.[409]

SAD.

Summary statement 105. The diagnosis of SAD should be given to patients older than 2 years with recurrent respiratory tract infections, normal immunoglobulin and IgG subclass levels, and impaired response to pneumococcal capsular polysaccharide. (C)

The prevalence of SAD is unknown, but it can be a frequent finding in patients evaluated for recurrent respiratory tract infections.[410-412] SAD is characterized by normal concentrations of IgG, IgA, IgM, and IgG subclasses and abnormal IgG antibody responses to polysaccharide vaccines (Table E10). Patients with SAD have normal responses to protein antigens and can have normal responses to conjugate polysaccharide vaccines, including conjugate pneumococcal polysaccharides. The diagnosis of SAD requires the demonstration of poor IgG response to polysaccharide antigens in the context of normal serum immunoglobulin concentrations. When a concomitant IGGSD is present, the abnormality should be classified as a subclass deficiency because abnormal antibody responses to polysaccharides are frequently part of IGGSDs (see SS 103).

The diagnosis of SAD is based on the level of antibodies present after receiving the 23-valent polysaccharide vaccine.[410-412] In patients who have previously received 1 or more doses of any of the conjugate vaccines, normal antibodies against the conjugate vaccine serotypes do not exclude the diagnosis of SAD. A diagnosis of SAD is not possible without taking into account the record of immunization with conjugate pneumococcal vaccines. As the number of serotypes included in conjugate pneumococcal vaccines increases, it is important to request testing of at least 6 serotypes present in the 23-valent polysaccharide vaccine only. Both the final postimmunization antibody concentrations are considered for the diagnosis of SAD, along with the increase from preimmunization to postimmunization specific antibody concentrations. Patients who already have high baseline antibody concentrations of specific antibodies to a pneumococcal serotype are less likely to have a significant increase in antibody concentrations after immunization.[413]

Recently, a classification of severe, moderate, and mild forms of SAD has been proposed. This classification takes into account the patient's age to assess how the number of normal responses to individual serotypes defines the level of immunologic severity of SAD.[413] This classification also accepts a form of SAD in which there is an initial serologic and clinical response to the 23-valent polysaccharide vaccine followed by the loss of protective antibodies within 6 months. This form of SAD is generally referred to as "memory SAD." This classification is summarized in Table E11.[413] A low level of switched memory B cells might be a further indication of impaired specific humoral immunity.[414]

It must be understood that the current methods of measuring antibodies to pneumococcal serotypes do not measure function but rather antibody concentration in terms of protein. Additional measures of antibody quality or function include measurement of antibody avidity or activity in an opsonophagocytic assay.[415-417] Tests of antibody avidity are available for clinical use, but there is still insufficient experience to know how to apply this in the diagnosis of antibody deficiency. The opsonophagocytic assay is a true functional assay but is not yet available for clinical use. It is possible that these additional methods will lead to establishment of more accurate criteria for diagnosis of antibody deficiency and more clearly justified use of IgG replacement therapy in patients with antibody deficiency.[418]

Summary statement 106. Patients with SAD might benefit from additional immunization with conjugate pneumococcal vaccines, intensified use of antibiotics, and in some cases a period of IgG replacement therapy. (C)

Treatment decisions should be based on the immunologic classification of mild, moderate, severe, and memory SAD.[413] The mild phenotype represents a group that can be followed clinically. However, a determination can be made that IgG replacement is needed if they do not respond to other medical treatment. If patients have not received the conjugate pneumococcal vaccine, immunization with the conjugate vaccine with the largest number of serotypes available is recommended in all patients with recurrent infections. In considering IgG replacement therapy, immunologic and clinical severity are the determining factors.[407,408] For patients who have responded to IgG replacement, selected patients who are deemed stable enough and are not likely to have a severe recurrence of symptoms can discontinue treatment after 1 to 2 years for a period of 4 to 6 months and then be re-evaluated. However, such treatment discontinuation must be deemed appropriate by the treating physician.

Transient hypogammaglobulinemia of infancy.

Summary statement 107. Infants and young children with frequent viral and bacterial respiratory illnesses and low IgG levels with normal vaccine responses should be given a diagnosis of transient hypogammaglobulinemia of infancy (THI). (C)

Infants are normally protected by transplacentally acquired maternal IgG for the first 3 to 6 months of life until the natural degradation of 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. This period of hypogammaglobulinemia can be associated with recurrent infections.[419-422] In one study 18 patients with THI were followed prospectively; IgG levels spontaneously corrected to

normal at a mean age of 27 months, with all patients reaching normal levels by 59 months.[423]

The definitive diagnosis of THI can only be made after IgG (and in some cases IgA, IgM, or both) levels have corrected; before that, infants with a decreased IgG concentration have hypogammaglobulinemia of infancy that can become THI (Table E10). Although most children with THI spontaneously recover their IgG values and have a benign clinical course, some of them do not recover and have SIGAD, CVID, or other forms of dysgammaglobulinemia.[419-422]

Clinical manifestations of THI include bacterial sinopulmonary infections and other respiratory tract infections. THI is rarely associated with sepsis, meningitis, or invasive infections. Case reports have documented these more severe infections,[424] but studies of larger cohorts indicate that this is uncommon. Some patients are asymptomatic, and some exhibit atopy or autoimmune diseases.[420] 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.

In patients with THI, immunoglobulin levels are repeatedly less than the age-specific normal range for a period of time during infancy and early childhood. IgM levels, IgA levels, or both can also be transiently low; specific antibody production is usually preserved; and cellular immunity is intact.[419-422] Isolated transient deficiencies of IgA, IgG2, and SADs do exist but are not presently identified as a different form of antibody-like deficiency, as is THI (see also sections on SIGAD, IGGSD, and SAD).[425] Some authors stipulate that measurements should be repeated to eliminate misdiagnosis because of laboratory error. However, this standard is not universally applied.

Evaluation includes measurement of specific antibody production and enumeration of lymphocyte subsets by means of flow cytometry.[419-422] Most children have normal booster responses to protein vaccines and normal isohemagglutinin concentrations. Some patients have transient suppression of vaccine responses, which recover by the age of 3 to 4 years.[423] Some patients have reduced memory B-cell counts.[426,427] Decreased numbers of circulating T cells were noted in some patients with THI, but this is also not a prominent feature in most patients.

Prediction of the eventual outcome of hypogammaglobulinemia toward THI as opposed to a persistent form of immunodeficiency is based on clinical severity and ability to respond to specific antigens despite low IgG concentrations.[428] Recently, evaluation of memory B cells has been used to predict the evolution of hypogammaglobulinemia of infancy with patients, with low IgM levels, class-switched memory B-cell counts, or both being more likely to have a permanent form of immunodeficiency.[420]

Summary statement 108. The principles of management of THI should follow those for antibody deficiency. (C)

Antibiotic prophylaxis should be the initial mode of preventive therapy for THI (see SS 16 and Table E7).[399,419-422] If this fails or is not tolerated, some patients might benefit from IgG administration, particularly during seasons when respiratory illnesses are more frequent.[429] An increase in the patient's own IgG production can be monitored by keeping the IgG dose and infusion intervals constant; IgG production is clearly reflected by increasing IgG trough levels. When levels of IgA, IgM, or both are also low when IgG replacement begins, they should also be monitored regularly. An increase into the normal range is a clear sign of improvement and might allow discontinuation of IgG replacement therapy based on objective data. Another recommendation is to stop IgG therapy after 3 to 6 months to reassess the status of the patient's humoral immune function (also see SSs 11-17).[407,408]

Immunoglobulin class-switch defects.

Summary statement 109. Patients with immunoglobulin class-switch defects should be clearly differentiated from those with other forms of CID with similar screening laboratory findings. (C)

The clinical phenotypes of deficiencies of activation-induced cytidine deaminase (AID) or uracil nucleoside glycosylase (UNG) are similar to other forms of antibody deficiency, with recurrent upper and lower respiratory tract infections being the most common presentation.[430-432] Opportunistic infections are rare. Nonmalignant lymphoid hyperplasia occurs in approximately 70% of patients. Autoimmunity/inflammatory disorders (eg, autoimmune hemolytic anemia and inflammatory bowel disease) can be seen in approximately 20% of patients with a deficiency in AID.[433]

Serum IgM levels are increased along with severely reduced serum IgG and IgA levels in nearly all patients with AID or UNG deficiencies.[430-432] Serum IgM levels might decrease with the initiation of IgG replacement therapy. Total numbers of T cells and $CD4^+$ and $CD8^+$ subsets, as well as results of T-cell functional studies, are typically normal. The total numbers of B cells and unswitched memory B cells ($CD27^+IgD^+IgM^+$) are normal, whereas numbers of class-switched memory B cells ($CD27^+IgM^-IgD^-$) are reduced.[431]

AID and UNG deficiencies have been referred to as forms of HIM (types 2 and 5, respectively).[430-432] Other forms of CID have a class-switch defect as part of their phenotype and are also often referred to as HIM. These include the X-linked form (CD40L defect, type 1) and an autosomal recessive form (CD40 defect, type 3, see SSs 37-43). Defects in CD40 or CD40L (and other disorders, such as NEMO deficiency) can present with laboratory findings similar to those of patients with AID and UNG defects. The opportunistic infections associated with CIDs are usually not seen in patients with AID and UNG deficiencies, but these clinical distinctions cannot always be relied on to avoid diagnostic confusion. Defining these groups of patients clearly at the molecular level is necessary because prognosis and therapy are distinct for these disorders.

Summary statement 110. The principles of management of immunoglobulin class-switch defects should follow those for antibody deficiency. (C)

IgG therapy and antibiotics are the mainstays of therapy for AID and UNG deficiencies, as with other predominantly antibody deficiencies (see SSs 11-17).[430-432]

Summary statement 111. Autoimmune, lymphoproliferative, or malignant diseases associated with immunoglobulin class-switch defects are treated as they would be in other clinical settings. (C)

See SS 92. There are no therapeutic modalities for these complications of class-switch defects distinct from those generally applicable in other clinical contexts.[430-432]

Unspecified hypogammaglobulinemia.

Summary statement 112. Any patient with primary hypogammaglobulinemia and normal cellular immunity who does not fulfill the diagnostic criteria for the above disorders should be given a diagnosis of unspecified hypogammaglobulinemia. (D)

A diagnosis of unspecified hypogammaglobulinemia can be applied in patients who have (1) significant morbidity from infections, (2) abnormal levels of serum immunoglobulins not conforming to any of the diagnoses above, (3) normal cellular immunity, (4) no other potential immune deficiency diagnosis, and (5) no other conditions predisposing to humoral immunodeficiency.[405,419,421] The diagnosis should be one of exclusion, and it might often need to be qualified, at least temporarily, because molecular genetic analysis for some disorders might not be readily available.

Summary statement 113. Management of unspecified hypogammaglobulinemia should adhere to the general principles presented for antibody deficiency. (D)

See SSs 11-17. If other treatments (eg, antibiotic prophylaxis) fail and a trial of IgG therapy is undertaken, the continuation of such therapy must be based on the objective clinical response.[407,408]

Diseases of immune dysregulation

The general approach to the evaluation and diagnosis of disorders of immune dysregulation is summarized in Fig E3.

Chediak-Higashi syndrome.

Summary statement 114. Chediak-Higashi syndrome (CHS) should be suspected in patients with partial oculocutaneous albinism, bacterial infections, and progressive neurological symptoms. (C)

The infections of CHS are pyogenic and affect mainly the skin, respiratory tract, and, occasionally, other organs. Patients with CHS also exhibit partial oculocutaneous albinism and pleomorphic neurological manifestations that can include cognitive impairment, photophobia, and nystagmus, as well as cerebellar, spinal, and peripheral neuropathies.[434,435] Gingivitis, oral ulcerations, and periodontal disease occur frequently, as does a mild coagulation defect that results in a bleeding diathesis that can become severe during the accelerated phase (see below).

CHS is associated with mutations in lysosomal trafficking regulator *(LYST)*, which encodes lysosomal trafficking regulator, a ubiquitous cytosolic protein. The precise function of LYST is unknown; it is thought to act as a vesicle trafficking regulatory protein involved in lysosome fusion or the sorting of lysosomal proteins to endosomes. Proteins accumulate in lysosomes and cause the characteristic enlargement of these and related organelles, including melanosomes, platelet-dense bodies, and cytolytic granules.

CHS is a member of the group of disorders known as familial hemophagocytic lymphohistiocytosis (FHL). Virtually all patients with CHS who do not die of infection eventually have HLH, as characterized by a high unremitting fever with hepatosplenomegaly and neurological signs ranging from confusion and seizures to coma. In patients with CHS, this is referred to as the accelerated phase. These clinical signs are associated with pancytopenia (usually including anemia and thrombocytopenia), hepatitis with high levels of liver enzymes, hypertriglyceridemia, hypofibrinogenemia, hyponatremia, and high ferritin levels.[434-437] Without aggressive treatment, it is usually fatal.

Summary statement 115. Examination of a peripheral blood smear should be the first diagnostic test for suspected CHS. (C)

Patients with CHS have giant azurophilic lysosomal granules in all granulated cells, including hematopoietic cells and melanocytes. These are pathognomonic for CHS with the clinical features described above.[434,435]

Summary statement 116. The treatment of HLH in patients with CHS is identical in principle to the treatment of HLH in other contexts (FHL). (C)

See SS 121.[438,439] The oculocutaneous albinism and neurological manifestations associated with CHS are not corrected by HSCT.[440]

Griscelli syndrome type 2.

Summary statement 117. Griscelli syndrome (GS) type 2 should be suspected in patients with pigmentary dilution, neurological abnormalities, and pyogenic infections. (C)

The pigmentary changes in patients with GS involve the hair (large melanin clumps in the shaft) and skin (retention of melanosomes in melanocytes).[441,442] These changes are diagnostic in association with the other manifestations of this group of diseases. GS is a rare autosomal recessive disorder that has 3 subtypes. GS1 is characterized by hypopigmentation and neurological abnormalities with little or no infections and is associated with mutations in myosin Va *(MYO5A)*. GS3 is characterized by hypopigmentation associated with mutations in melanophilin *(MLPH)* with minimal or no infection or neurological signs. GS2 is characterized by oculocutaneous hypopigmentation, silvery grey hair, and recurrent pyogenic infections; GS2 is associated with mutations in the *RAB27A* gene.[443,444]

The neurological symptoms occur more frequently in patients with GS1 but can occur also in patients with GS2 and include seizures, ataxia, and oculomotor and reflex abnormalities.[443,444] Infections are not consistent in all patients but are mainly pyogenic bacterial infections involving the respiratory tract, skin, or other organs. Hepatosplenomegaly is frequent at presentation. Almost all patients eventually have an "accelerated phase" of HLH, which is often fatal (similar to CHS). This is the most common clinical presentation of GS. The pigmentary changes are present from birth. Infections, neurological symptoms, and hepatosplenomegaly generally begin in infancy. The accelerated phase usually occurs in infancy or childhood. Infrequently, it can be delayed until the second decade of life.

Many patients with GS2 have normal screening tests of immune function.[443,444] Even in the presence of infections, laboratory immunologic abnormalities are variable and not always seen in these patients. 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 can be more pronounced during the HLH phase.

The accelerated phase of GS2 is another form of FHL and is fatal without standard chemotherapy and immunosuppression (see SS 121).[445-447]

Hermansky-Pudlak syndrome.

Summary statement 118. Hermansky-Pudlak syndrome (HPS) type 2 should be suspected in patients with hypopigmentation, thrombocytopenia, neutropenia, and recurrent infections. (C)

HPS denotes a group of diseases whose principal clinical manifestations are oculocutaneous albinism and severe thrombocytopenia, thrombasthenia, or both. Nine distinct gene defects have been described (HPS1-9).[435,448,449] All lead to abnormalities of cellular granules somewhat similar to what is seen in patients with CHS and GS2. However, only HPS2 has been associated with immune deficiency caused by the frequent finding of severe

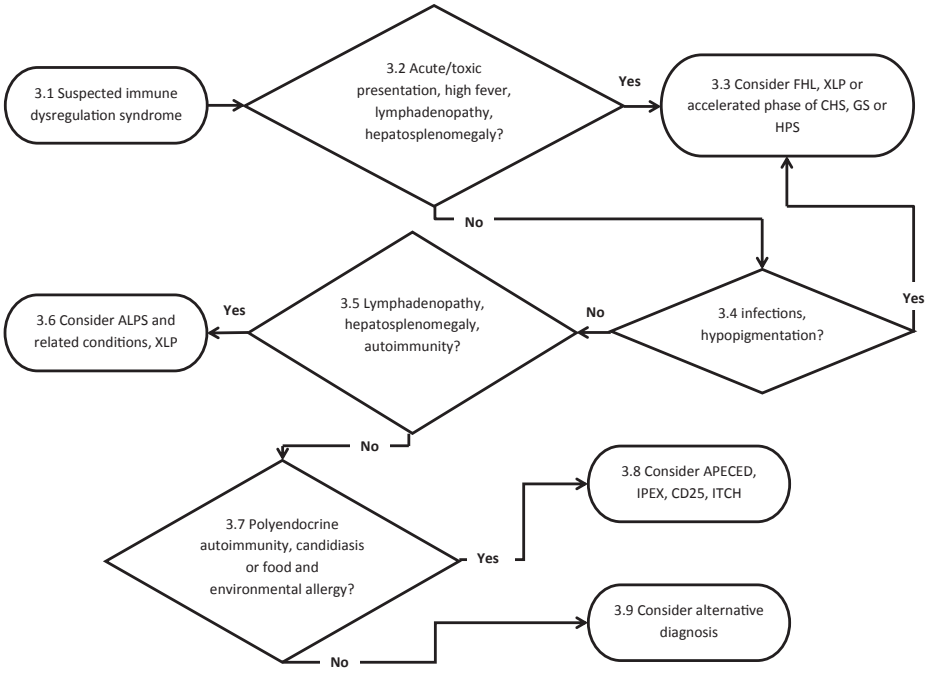

FIG E3. Diagnosis of diseases of immune dysregulation. *3.1,* A disorder of immune dysregulation is suspected because of some combination of clinical features in which 1 or more of the following are prominent: (1) autoimmunity; (2) hypersensitivity; and (3) signs of lymphoproliferation, such as diffuse lymphadenopathy, hepatosplenomegaly, or both. *3.2,* Does the patient have an acute or fulminant presentation with high fever, toxic appearance, and signs of lymphoproliferation? Alternatively, if the presentation is subacute or chronic, are features of recurrent infections and pigmentary abnormalities present? *3.3,* Either of the presentations in 3.2 is consistent with a form of HLH, either FHL or in association (as an "accelerated phase") with another syndrome, such as CHS, GS, or HPS. *3.4,* Are lymphoproliferation and autoimmune disease prominent in the presentation? *3.5,* The presentation in 3.4 suggests ALPS, ALPS-related disorders, or XLP. *3.6,* Are any of these features present: (1) polyendocrine autoimmunity; (2) CMCC; or (3) multiple food and/or environmental allergies? *3.7,* The presentation of 3.6 indicates possible APECED, IPEX, or defects of CD25 or ITCH. If none of these diagnoses is correct, the patient might have a CID or syndrome. Consider evaluation as outlined in Fig 2.

neutropenia.[450,451] HPS is also an important cause of idiopathic pulmonary fibrosis; this complication is infrequently seen in patients with HPS2.[452]

Although the immune defect in patients with HPS2 is not well characterized, the main abnormalities that are noted include congenital neutropenia, as well as marked defects in antigen presentation and T-cell cytotoxicity.[450,451] HPS2 results from defects in the gene encoding the β1 subunit of the adaptor protein complex 3 *(AP3B1)* with loss of microtubule-mediated movement of lytic granules to immunologic synapses and loss of cytotoxic T lymphocyte–mediated killing. Recently, a case of HPS2 was associated with a defect in the *PLDN* gene (encoding the protein palladin), which is the defect in *pallid* mice and is also involved in intracellular transport of pigment-containing vesicles and in cellular cytotoxicity.[453]

To date, only a limited number of cases of HPS2 have been associated with HLH.[454,455] Evaluation and treatment is as with other forms of FHL (see below).

FHL syndromes.

Summary statement 119. FHL should be suspected in patients with fever, hepatosplenomegaly, and neurological symptoms. (C)

FHL syndromes are heritable forms of the more generic HLH. HLH syndromes are classified as primary (genetic) or secondary. Primary HLH is often called FHL. HLH syndromes are caused by uncontrolled activation of cytotoxic cells, including NK cells, $CD8^+$ cytotoxic T cells, and macrophages, as well as overproduction of IFN-γ and TNF.[454,455] Both secondary HLH and acute attacks of FHL usually have an infectious trigger, particularly viruses, such as EBV. The loss of control of cytotoxic activity is frequently caused by dysfunction in fusion of cytotoxic granules at the membranes of cytotoxic and phagocytic cells because of a number of distinct defects. It can also be caused by overwhelming uncontrolled responses to viral infections. FHL has autosomal recessive inheritance (incidence of approximately 1:50,000); secondary HLH is frequently associated with an underlying chronic illness (eg, juvenile inflammatory arthritis, Still disease, and malignancy).

All HLH syndromes are characterized by well-defined clinical and laboratory parameters. Symptoms and signs include high unremitting fever, hepatitis with hepatosplenomegaly, and central neurological symptoms ranging from confusion to seizures and coma.[454,455] Additional features can include lymphadenopathy, jaundice, edema, and a nonspecific skin rash.

There are established diagnostic criteria for HLH.[454] These include (1) fever; (2) splenomegaly; (3) cytopenias affecting at least 2 lineages; (4) hypertriglyceridemia of greater than 3 mmol/L or 265 mg/dL, hypofibrinogenemia of less than 1.5 g/L, or both; (5) hemophagocytosis in bone marrow, spleen, or lymph nodes; (6) low or absent NK cell activity; (7) hyperferritinemia of greater than 500 mg/L; and (8) an increased soluble CD25 level (IL-2 receptor α chain) of greater than 2400 U/mL.

Increased cerebrospinal fluid (CSF) protein levels and pleocytosis in association with CNS symptoms are adjunct diagnostic criteria. Liver biopsy will frequently demonstrate chronic persistent hepatitis. Other abnormal laboratory findings consistent with the diagnosis are hypoproteinemia, hyponatremia, and increased very low-density lipoprotein or decreased high-density lipoprotein levels.[456]

The genetic defect in patients with FHL1 has been localized to chromosome 9q21.3-22 near the perforin locus, but the defect is unknown.[454,455] FHL2 is associated with a defect in perforin (gene *PRF1*) and accounts for about 30% to 35% of FHL cases, although there is some variability in different ethnic groups. Flow cytometric detection of perforin is a good screening tool for FHL2. FHL3 is associated with a defect in Munc13-4 protein (gene *UNC13D*) and accounts for 30% to 35% of FHL cases. FHL4 is associated with a defect in the syntaxin 11 protein (gene *STX11*), predominantly in Turkish and Kurdish populations. FHL4 presents later in life than other forms. FHL5 is associated with a defect in Munc18-2 protein (gene *STXBP2*), which accounts for 6% to 14% of FHL cases, mainly of Saudi Arabian or Turkish origin. Note that CHS, GS2, HPS2 (see above), and XLP (see below) are also often included in the list of genetic associations with FHL.

Summary statement 120. Laboratory screening for FHL should be performed before genetic testing. (C)

Flow cytometry alone or in combination with functional cellular assays can be used to screen for the absence of specific proteins or the occurrence of characteristic functional abnormalities in patients with FHL. A European consortium evaluated screening patients' cells for intracellular perforin, SLAM-associated protein (SAP), and X-linked inhibitor of apoptosis (XIAP, see below) and a modified functional NK cell/cytotoxic T-cell assay based on detection of CD107a (lysosomal-associated membrane protein 1).[457] Overall, the occurrence of degranulation in more than 5% of resting NK cells had 96% sensitivity and 88% specificity in favor of primary FHL.

Summary statement 121. HLH should be treated with high-dose glucocorticosteroids, chemotherapeutic and other immunosuppressive agents, and HSCT. (C)

The treatment of HLH is based on the HLH-2004 consensus statement.[456] The recommended regimen includes high-dose dexamethasone, etoposide, and cyclosporine and in selected patients, intrathecal methotrexate. Other commonly used therapies include antithymocyte globulin, other T-cell depletion modalities, and anti-CD20 therapy (rituximab). In spite of this, relapses are frequent.

Allogeneic HSCT is the only potentially curative therapy for FHL.[454,455] As with all immunologic defects, early transplantation is more successful. Transplantation in patients with HLH has had an overall poor outcome, but reduced-intensity conditioning might improve outcomes.[458,459]

Lymphoproliferative syndromes.

Summary statement 122. XLP should be suspected in boys with fulminant infectious mononucleosis with HLH, lymphoma, and dysgammaglobulinemia. (C)

XLP1 is caused by mutations in the gene *SH2D1A* (encoding SAP). XLP2 is caused by mutations in *XIAP*. Approximately 40% of patients with XLP1 present with fulminant infectious mononucleosis, often with HLH.[446,458,460,461] The incidence of HLH in EBV-negative patients is much lower than that in EBV-positive patients. However, it is clear that immune dysregulation is present in patients even before EBV infection. About 15% of patients present with lymphoma (immunoblastic sarcoma), and another 20% to 25% present with dysgammaglobulinemia. There is considerable overlap, and patients can have 1, 2, or all 3 manifestations at one time or another. The onset of symptomatic disease can be as early as 5 months or in later adulthood. In patients with XLP2, HLH is milder, dysgammaglobulinemia is common, and lymphoma has not been described.

The immunologic findings in patients with XLP1 are variable and depend on EBV exposure.[460,462] Before EBV exposure, immunologic laboratory abnormalities are limited mainly to hypogammaglobulinemia, 1 or more low IgG subclasses, or increased IgA and IgM levels. After EBV infection, there can be hypogammaglobulinemia with impaired specific antibody production, an inverted CD4/CD8 ratio (caused by expansion of CD8 cells), and diminished T-cell proliferative responses to mitogens and antigens *in vitro*. There is also often a striking decrease in NK cell cytotoxicity. Some patients with XLP have received a diagnosis of CVID.

Autosomal recessive disorders, including IL-2–inducible T-cell kinase (ITK) deficiency[159,162] and CD27 deficiency,[149,359,463] should also be considered in the differential diagnosis of lymphoproliferative syndromes. These patients might also present with chronic and symptomatic EBV infection, late hypogammaglobulinemia, HLH, and increased risk of EBV-driven lymphoma and other malignancy. EBV-driven lymphoproliferation has a variable response to immunosuppression, including steroids and rituximab. The mortality in the reported cases is quite high, with one patient with ITK deficiency and one patient with CD27 deficiency undergoing successful transplantation.

Summary statement 123. Patients with suspected XLP should be screened by using flow cytometric testing before genetic testing. (C)

When XLP is suspected, flow cytometric analysis of SAP and XIAP can be performed.[464,465] SAP expression levels correlate well with genetic alterations in *SH2D1A*; normal XIAP expression despite *XIAP* mutations is more frequent. Therefore detection of normal protein expression does not exclude the diagnosis of XLP2.

Summary statement 124. IVIG should be given to patients with XLP and hypogammaglobulinemia/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.[446,460-462] Some have advocated IgG therapy in asymptomatic patients in an attempt to prevent primary or recurrent EBV infections. The effectiveness of this approach is unknown, but primary infection and relapses of EBV disease have occurred in patients receiving IVIG.

Summary statement 125. Patients with XLP and HLH should be treated with chemotherapy, followed by HSCT. (C)

The treatment of HLH in patients with XLP is identical in principle to the treatment of HLH in other contexts (FHL; see SS 121).[446,461] HSCT for XLP before clinically evident disease is controversial; however, mortality in patients with XLP1 who underwent transplantation after recovery from HLH is approximately 50%, whereas the success rate is close to 80% in patients with XLP1 undergoing transplantation before HLH or fulminant infectious mononucleosis. Some patients have been successfully treated with rituximab before chemotherapy and HSCT.[466,467]

Syndromes with autoimmunity.

Autoimmune lymphoproliferative syndrome and autoimmune lymphoproliferative syndrome–related disorders.

Summary statement 126. Autoimmune lymphoproliferative syndrome (ALPS) or an ALPS-related disorder should be suspected in patients who exhibit lymphoproliferation and autoimmunity. (C)

The lymphoproliferation and hepatosplenomegaly observed in patients with ALPS is noninfectious and nonmalignant.[468-470] The defect in patients with ALPS is in the Fas pathway, which controls apoptosis of T and B lymphocytes. This leads to uncontrolled lymphocyte proliferation and increased lymphocyte counts. Patients with ALPS are susceptible to autoimmune cytopenias, including autoimmune hemolytic anemia, autoimmune thrombocytopenia, and neutropenia.[468-471] These can be severe and unremitting, especially in early childhood. The autoimmune cytopenias are often worsened by hypersplenism. Other autoimmune conditions that have been associated with ALPS include glomerulonephritis, autoimmune hepatitis, vasculitis, uveitis, aplastic anemia, chronic pancreatitis, severe osteopenia, angioedema, and transient alopecia. These manifestations are much less common than autoimmune cytopenias.

Most patients with ALPS (60% to 70%) have germline mutations in the gene encoding the Fas molecule *(TNFRSF6)*. The next most common finding (10% of patients) is somatic mutations affecting Fas. Rarely, patients have mutations in the gene encoding Fas ligand *(TNFSF6*, <1% of patients) and caspase 10 (CASP10; 2% to 3% of patients).[468-471]

The classification of ALPS has changed to reflect these genetic phenotypes more closely.[468-471] In the initial classification of ALPS, patients with mutations in genes encoding caspase 8 *(CASP8)*, as well as Kirsten rat sarcoma viral oncogene homolog *(KRAS)* and neuroblastoma RAS viral oncogene homolog *(NRAS)*, were included. Because there are distinct differences in the phenotypes of these 2 lymphoproliferation syndromes from ALPS, they are now classified as ALPS-related disorders. Patients with mutations in *CASP8* were originally classified as having ALPS because *CASP8* and *CASP10* have similar functions, and *CASP8* mutant patients present with lymphadenopathy and defective Fas-mediated apoptosis. Patients with *CASP8* mutations (caspase 8 deficiency state) frequently have lymphopenia, and although the defect is primarily in T cells in patients with ALPS, in the caspase 8 deficiency state the defect is in function and activation of T, B, and NK cells. Additionally, patients with *CASP8* mutations are predisposed to significant recurrent bacterial infections and mucocutaneous infections with herpes viruses.

Ras-associated leukoproliferative disorders are lymphoproliferative diseases characterized by impaired cytokine withdrawal–induced apoptosis in T cells. This is due to various gain-of function somatic mutations in RAS family genes, including *KRAS* and *NRAS*. Fewer than 10 patients with Ras-associated leukoproliferative disorder have been reported.[468-471]

Caspase recruitment domain family, member 11 *(CARD11)* gain-of-function mutations have also been implicated in patients with ALPS-related disease; several cases were reported with polyclonal lymphocytosis since infancy, hepatosplenomegaly and lymphadenopathy, recurrent infection, defective response to polysaccharide vaccines, autoimmunity, and late lymphoma.[146] PRKCD deficiency, which results in a CVID-like phenotype, can also present with lymphoproliferation resulting from defective B-cell apoptosis (see SS 87).

Recently, gain-of-function mutations in *STAT3* have also been associated with clinical presentations similar to an overlap of ALPS and IPEX syndrome with either diabetes, autoimmune enteropathy, autoimmune cytopenias, lymphoproliferation, and leukemia or lymphoma.[472-474] Some patients have exhibited fungal or mycobacterial infections. Immunologic findings vary but can include lymphopenia, hypogammaglobulinemia, and increased double-negative T-cell counts (see SS 127) and impaired Fas-mediated apoptosis.

Summary statement 127. Measurement of T cells expressing the α/β T-cell receptor (TCR) without either CD4 or CD8 should be the first screening test for ALPS. (C)

Normal T cells express a receptor for a complex of MHC molecules and antigenic peptide. The antigen TCR is a heterodimer of γ and δ chains (TCR1) or α and β chains (TCR2). T cells that express α/β constitute the majority (usually >90%) of T cells in the peripheral blood. These T cells normally also express either CD4 or CD8. In patients with ALPS, α/β T cells that express neither CD4 nor CD8 ($CD3^+CD4^-CD8^-$ double-negative T cells) can be found in high numbers.[468-471] The origin and mechanism of expansion of these cells have not yet been determined.

The diagnosis of ALPS is based on fulfilling the following criteria based on the 2009 NIH consensus statement.[468-471] These include (1) chronic (>6 months), nonmalignant, noninfectious lymphadenopathy, splenomegaly, or both and (2) increased $CD3^+TCR\alpha\beta^+CD4^-CD8^-$ double-negative T cells (>1.5% of total lymphocytes or 2.5% of $CD3^+$ lymphocytes) in the setting of normal or increased lymphocyte counts. This criterion might not hold for lymphopenic patients. In addition, 1 or both of these accessory criteria must be fulfilled: (1) defective lymphocyte apoptosis (in 2 separate assays) or (2) somatic or germline pathogenic mutation in *TNFRSF6, TNFSF6* (encoding Fas and Fas ligand, respectively), or *CASP10*.[468-471]

In addition to the cardinal symptoms, serologic markers might assist in suggesting the diagnosis of ALPS.[468-471] The accessory criteria (Fas apoptosis assay or genetic testing) are only available through specialized laboratories. Additionally, the apoptosis assay is subject to interlaboratory variability and sample transport problems. Thus serologic criteria have been established to guide which patients require further increased for genetic causes of ALPS. These include increased plasma soluble Fas ligand levels (>200 pg/mL), increased plasma IL-10 levels (>20 pg/mL), increased serum or plasma vitamin B12 levels (>1500 ng/L), or increased plasma IL-18 levels (>00 pg/mL). Increased immunoglobulin levels (especially IgG) are also associated with ALPS. There are well-characterized typical immunohistologic findings in lymph node or spleens that, in the hands of an experienced hematopathologist, can assist in diagnosis. Finally, a family history of lymphoproliferation can help guide diagnosis and treatment.

Summary statement 128. Treatment of ALPS should be tailored to address life-threatening complications. (C)

Lymphoproliferation and splenomegaly are relatively resistant to treatment and unless there are specific other factors, do not require treatment.[470,475,476] Autoimmune cytopenias can be difficult to treat because they do not respond as easily to corticosteroid or IgG therapy. Mycophenolate mofetil can improve the symptoms of autoimmunity. More recently, rapamycin (sirolimus) has been successfully used to arrest progression of the cytopenias. Treatment with rituximab has not been helpful for

autoimmune hemolytic anemia and has also led to more prolonged B-cell lymphopenia in these patients. HSCT is infrequently used, except for those with refractory cytopenias.

Infectious complications are infrequent in patients with ALPS.[468-471] However, splenectomized patients with ALPS have a high risk of sepsis and mortality because of infectious complications. The incidence of sepsis in patients with ALPS after splenectomy has been reported to be as high as 30%. Thus long-term antibiotic prophylaxis is clearly indicated in patients with ALPS after splenectomy (see SS 16 and Table E7). Patients with ALPS do not otherwise appear to be at an increased risk for infections.

Patients with ALPS have a high risk of malignancy. B-cell lyphomas (Hodgkin and non-Hodgkin lymphoma) occur in up to 10% of patients with ALPS.[468-471] Surveillance for these malignancies is clearly indicated.

Autoimmune polyendocrinopathy–candidiasis–ectodermal dysplasia.

Summary statement 129. Autoimmune polyendocrinopathy–candidiasis–ectodermal dystrophy (APECED) should be suspected in patients with immune-mediated destruction of endocrine tissue, chronic candidiasis, and ectodermal dystrophy. (C)

APECED, also known as autoimmune polyglandular syndrome type 1 (APS1), is an autosomal recessive disorder with a highly variable clinical phenotype.[477-480] A high prevalence has been identified in 3 ethnic groups, Sardinians, Finns, and Iranian Jews, although lower prevalence can be found in multiple other ethnic groups. Candidiasis is commonly seen in most patients but is rare in Iranian Jews carrying the Y85C mutation. The endocrinopathy is immune mediated, with hypoparathyroidism and adrenal failure the most prevalent. Other autoimmune phenomena seen include alopecia areata, gonadal failure, autoimmune hepatitis, autoimmune enteritis, vitiligo, pernicious anemia, Hashimoto thyroiditis, and type I diabetes. Ectodermal dystrophies include keratopathy and nail dystrophy. All elements might not be present in a given patient.

Patients with APECED or isolated thymoma should be observed for the development of CMCC, which can arise in the setting of anti–IL-17A, anti–IL-17F, and anti–IL-22 autoantibodies. CMCC is a prominent clinical component of Mendelian immunodeficiencies that include a component of defective T_H17 function (mainly defects of *STAT1*, *STAT3*, *DOCK8*, and *CARD9*; see SSs 70 and 188). Anti–IL-17A, anti–IL-17F, and anti–IL-22 autoantibodies neutralize the IL-17 pathway, which appears to be critical for T_H17 lymphocyte control of *Candida* species. Currently, only patients with APECED or thymoma have been identified with these autoantibodies and CMCC.[481,482] Also see SSs 235 and 236.

Summary statement 130. Patients with clinical features consistent with autoimmune regulator *(AIRE)* mutation should be screened for this defect, when possible. (C)

APECED (APS1) is caused by a mutation in the gene *AIRE*.[477-480] More than 60 *AIRE* mutations have been reported and often cluster by population group. There are some correlates between mutation and clinical presentation (eg, the lower incidence of candidiasis among Iranian Jews with the Y85C mutation), but the structure-function correlation is not well established for most of the features of the disease. Detecting autoantibodies against various cytokines, most commonly interferon types 1 and 2 and omega[483-486] and IL-17 and IL-22,[482] might assist diagnosis in the absence of genetic testing. Also see SSs 235 and 236.

Summary statement 131. Immunosuppressive therapy should be considered in patients with APECED. (C)

Immunomodulating drugs can suppress clinical manifestations, but care must be taken to avoid severe infectious complications caused by underlying host defense abnormalities.[479,487,488] Management of AIRE requires thorough evaluation of infectious, endocrinologic, and gastrointestinal manifestations. The evaluation of patients with APECED is complex because of the large number of potentially affected organs. The primary treatments for affected patients include hormone replacement for endocrinopathies and antifungals to treat mucocutaneous candidiasis.

Summary statement 132. Other specific genetic lesions should be sought in patients with chronic mucocutaneous candidiasis (CMCC) without other manifestations of APECED. (C)

Mutations of *CARD9*; C-type lectin domain family 7, member A *(CLEC7A)*; *IL17F*; IL-17 receptor α chain *(IL17RA)*; and *STAT1* have also been described in association with syndromes of CMCC. See SSs 187 to 189.

IPEX syndrome.

Summary statement 133. IPEX syndrome should be suspected in patients with severe enteritis and food allergy, infantile diabetes or thyroiditis, and eczema. (C)

IPEX syndrome is a rare systemic autoimmune disorder resulting from mutations in the forkhead box protein 3 *(FOXP3)* gene, which encodes the DNA-binding transcriptional regulator considered to be the master controller for $CD4^+CD25^+$ Treg cells.[489,490] The lack of Treg cells leads to allergic and autoimmune manifestations, including severe eczema and food allergies with enteritis and early-onset endocrine autoimmunity, with diabetes and thyroiditis being most common. It is frequently fatal in the first year of life. However, milder phenotypes have been identified, and patients have lived into adulthood with severe but not life-threatening disease. Clinical syndromes very similar to IPEX syndrome have also been associated with gain-of-function mutations in *STAT1* and *STAT3*.[472-474,491]

Summary statement 134. A diagnosis of IPEX syndrome should be sought by enumerating Treg cells in the peripheral blood or genetic analysis of *FOXP3*. (C)

The *FOXP3* gene encodes a crucial DNA-binding transcriptional regulator that is critically required for the differentiation and function of $CD4^+$ naturally occurring Treg cells and subsets of inducible Treg cells.[489,490] The genetic defects lead to a deficiency in a cell population that is required to regulate effector T cells, diminish inflammatory cytokine production, and mitigate against autoimmune processes.

IPEX syndrome can be suspected on the basis of flow cytometric detection of total FOXP3-expressing cells; however, confirmatory genetic testing is required. Although IPEX syndrome is frequently associated with genetic defects that manifest as low or absent FOXP3 protein in T cells, mutations that present with defective (truncated or misfolded) protein have been reported. Thus if a patient presents with manifestations consistent with IPEX syndrome but detectable FOXP3 in $CD4^+CD25^+$ T cells, further testing is mandatory to eliminate the possibility of IPEX syndrome. Specifically, genetic analysis and functional characterization of Treg cells are necessary when clinical manifestations of IPEX syndrome are present but FOXP3 protein is detected by using flow cytometry. These tests are available in specialized centers.[489,490]

Summary statement 135. Initial treatment of IPEX syndrome should include immune suppression with a calcineurin inhibitor or mammalian target of rapamycin (MTOR) inhibitor. (C)

Calcineurin inhibitors, such as cyclosporine or tacrolimus, diminish effector T-cell function and can suppress inflammatory and some autoimmune features of IPEX syndrome. An MTOR inhibitor, such as rapamycin (sirolimus), increases Treg cell numbers and function both *in vitro* and *in vivo* and can transiently improve the clinical manifestations of IPEX syndrome.[492,493] Because IPEX syndrome often has an extremely accelerated course, earlier diagnosis and treatment are recommended and are in general more successful.

Summary statement 136. HSCT should be considered early in the course of IPEX syndrome. (C)

The only potential definitive treatment for IPEX syndrome is HSCT.[490,494] Early treatment improves outcomes because autoimmune and endocrinologic manifestations can persist after transplantation. Myeloablative conditioning has been associated with transient reconstitution and mortality caused by graft failure, viral infections, and hemophagocytic syndromes. More recently, nonmyeloablative conditioning regimens have been used with better outcomes. To date, the published experience remains primarily in case reports or small series. These regimens are associated with lower toxicity, rapid engraftment, and potentially lower posttransplantation infectious complications. Most of these reports detail incomplete donor chimerism but relatively good outcome with resolution of enteritis, diabetes, and other pretransplantation complications. The precise degree of chimerism required for successful engraftment is unknown, but considering that the host immune system appears to have normal effector function, sustained engraftment of only the Treg cell compartment has been speculated to be sufficient for successful long-term reconstitution.[495]

Summary statement 137. Other specific genetic lesions should be sought in patients with features of IPEX syndrome with normal FOXP3 expression and gene sequences. (C)

Clinical features of IPEX syndrome can be associated with defects in the *IL2RA* gene and in the gene encoding itchy E3 ubiquitin protein ligase *(ITCH)*. Two patients with a defect in the expression of CD25, the α chain of the IL-2 receptor, have had features similar to those of patients with IPEX syndrome, with onset in infancy; dermatologic, gastrointestinal, and endocrine manifestations; and frequent infections.[110,111] However, the marked increase in IgE levels seen in the FOXP3-deficient patients was not described in CD25 deficiency. HSCT was attempted successfully in 1 patient, primarily because of severe frequent infections. Some patients with mutations in *STAT5B* might also present with features similar to those of IPEX syndrome.[490]

Patients with ITCH defects have been found in 1 large Amish family.[496] They exhibit very characteristic facial features (triangular-shaped face, macrocephaly, hypertelorism, and micrognathia), failure to thrive, and developmental delay. The features similar to IPEX syndrome include chronic diarrhea, diabetes and thyroid disease, and autoimmune hepatitis. A unique feature associated with the ITCH/AIP4 defect is susceptibility to chronic lung disease that is also seen in patients with the IPEX-like disorder caused by mutations in *STAT5B* (see Table E9).[490]

Summary statement 138. Complement deficiency should be considered in the evaluation of patients with autoimmune disease. (C)

Complement deficiency disorders are discussed in SSs 228 to 237. We mention here only that many complement component deficiencies are associated with a significant propensity toward autoimmune disease. Complement function should be considered in patients presenting with autoimmune disease.

Phagocytic cell defects

The general approach to the diagnosis and evaluation of suspected phagocytic cell disorders is summarized in Fig E4.

Defects of neutrophil differentiation.

Severe congenital neutropenia (SCN).

Summary statement 139. Patients with recurrent bacterial respiratory tract and soft tissue infections, gingivostomatitis, and vaginal or rectal mucosal ulceration should be screened with serial CBCs. (C)

Infections in neutropenic patients are generally associated with fever and malaise.[497,498] Pharyngitis with lymphadenopathy is common; pneumonia, mastoiditis, and cellulitis also occur. Periodontitis can 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.

Cyclic neutropenia is also referred to as SCN type 1 (SCN1) (elastase, neutrophil expressed [ELANE] defect) and can be cyclic or persistent.[499] SCN2 is caused by defects of growth factor independent 1 transcription repressor (GFI1)[500]; Kostmann syndrome (also SCN3) is caused by defects in HCLS1-associated protein X-1 (HAX1)[501]; SCN4 results from defects in glucose 6 phosphatase, catalytic, 3 (G6PC3)[498,502]; and SCN5 arises from defects in vacuolar protein sorting 45 homolog (VPS45).[503,504] Rare patients can have the WAS variant X-linked neutropenia (see SS 46).

Additional genetic lesions have recently been identified in patients with various syndromes in which neutropenia is a component. Glycogen storage disease 1b caused by mutation in solute carrier family 37, member 4 *(SLC37A4)* has a broad range of sequelae, including infantile hepatomegaly, hypoglycemia, and lactic acidosis.[505,506] It is also characterized by recurrent infection caused by neutropenia, abnormal neutrophil motility, and defective oxidative burst. Inflammatory bowel disease is frequently seen and is thought to be secondary to defective leukocytes. Barth syndrome is a triad of neutropenia, growth failure, and cardiomyopathy caused by mutations in the mitochondrial protein tafazzin gene *(TAZ)*.[507,508] Cohen syndrome consists of abnormal facies, cognitive impairment, and retinal dystrophy in association with neutropenia and results from mutations in the *VPS13B* (vacuolar protein sorting 13 homolog B) gene, which is important for lysosome function.[509] Neutropenia also arises from mutations in the gene encoding the late endosomal/lysosomal adaptor mitogen-activated protein kinase and MTOR activator 2 (LAMTOR2), which is also important for lysosome function.[510] Finally, the syndrome of poikiloderma with neutropenia arises from mutations in the U6 snRNA biogenesis 1 *(USB1)* gene, which encodes a nuclear RNA processing enzyme.[498,511]

Patients with a decreased neutrophil count should have serial measurements of neutrophils to distinguish between cyclic and persistent or chronic neutropenia. CBCs should be obtained 2 or 3 times weekly for 6 to 8 weeks. The periodicity of cyclic neutropenia is usually about 21 days but can range from 14 to 36 days. Infections occur only during the nadirs of the neutrophil count, but there is a lag between the nadir of the neutrophil count and the onset of clinical symptoms so that quite often neutrophil counts are normal when the patients are seen for symptoms.

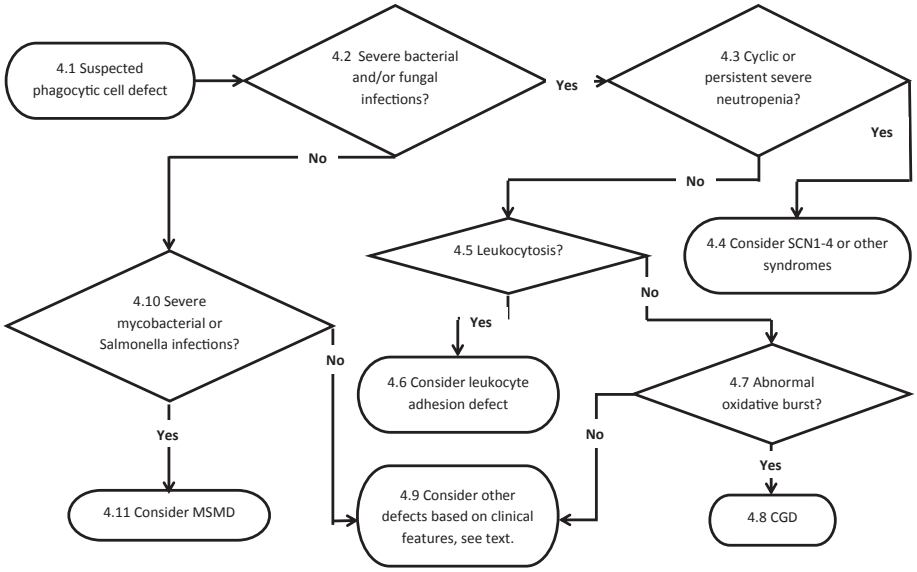

FIG E4. Diagnosis of phagocyte defects. *4.1*, The clinical presentation includes severe characteristic bacterial and/or fungal infections affecting the lungs, skin, or viscera and is primarily suggestive of a phagocyte defect, or evaluation of other immune function is thus far normal and the clinical 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*, The clinical presentation is one of infections limited to mycobacteria, severe infections with *Salmonella* species, or both. *4.3*, In the case of 4.2, consider one of the disorders of MSMD. *4.4*, There is a marked leukocytosis, even in the absence of an ongoing infection. *4.5*, In the case of 4.4, consider LAD. *4.6*, The absolute neutrophil count is normal or there is a moderate leukocytosis, perhaps with ongoing infection. *4.7*, Is neutrophil oxidative function abnormal? *4.8*, If the answer to 4.7 is yes, the diagnosis is CGD. If no, consider any of the possibilities in 4.5 or 4.10. *4.9*, There is cyclic or persistent severe neutropenia. *4.10*, In the case of 4.9, consider a diagnosis of any of the neutropenic defects.

Summary statement 140. Patients with neutropenia should receive G-CSF. (C)

G-CSF is recommended for all patients with cyclic neutropenia.[498] Approximately 90% of patients with cyclic neutropenia or severe chronic neutropenia (defect known or unknown) will respond to G-CSF with increased neutrophil counts. In the case of glycogen storage disease 1b, treatment with GM-CSF or G-CSF improved the neutrophil defect, infection rate, and gastrointestinal inflammation.[498]

Summary statement 141. HSCT should be considered for patients with severe chronic neutropenia. (C)

HSCT should be considered for patients with severe neutropenia who either do not respond to G-CSF or who continue to have severe infections despite increased counts.[512,513] Success has been reported with both HLA-identical sibling donors and HLA-matched unrelated donors.

Patients with severe chronic neutropenia (but not those with cyclic neutropenia) have an increased incidence of acute myeloid leukemia or myeloid dysplasia. Long-term follow-up data from the Severe Chronic Neutropenia International Registry found an incidence of acute myeloid leukemia/myeloid dysplasia of 2.3% per year, with a cumulative incidence after 15 years follow-up of 22%.[514]

Defects of neutrophil motility.

Leukocyte adhesion deficiency types I, II, and III.

Summary statement 142. Leukocyte adhesion deficiency (LAD) should be suspected in patients with cellulitis, abscesses, or bacterial and fungal respiratory tract infections and markedly increased white blood cell counts. (C)

Patients with LAD-I are severely affected early in life with the infectious complications characteristic of neutropenia listed above.[515-517] Delayed separation of the umbilical cord can be seen in patients with LAD-I. Although delayed cord separation can occur in healthy infants, in patients with LAD-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 can be considered. A partial or moderate form of LAD-I has a milder clinical course. These patients have poor wound healing and severe periodontitis. Other pyogenic infections are not as severe as in the classical form, and patients might not receive a diagnosis until childhood or later.

Patients with LAD-II principally have pulmonary infections and chronic severe periodontitis.[515,516] Characteristic facies, growth and developmental delay, and mental retardation are also seen in patients with LAD-II. The facies of patients with LAD-II consist of coarse features with puffy eyelids, brachycephaly, broad nasal tip, long upper lip, everted lower lip, low hair line, and short webbed neck. Reduced growth and cognitive impairment are pronounced. Delayed umbilical cord separation is not a feature of LAD-II.

Patients with LAD-III, in addition to infections, display dysfunctional platelet aggregation, leading to bleeding complications, including cerebral hemorrhage at birth and a bleeding diathesis similar to that seen in patients with Glanzmann thrombasthenia.[515,516]

Summary statement 143. A blood cell count should be the first screening test for LAD. (C)

A CBC with differential is the best initial screening test for LAD.[515,516] Neutrophil counts are increased to greater than normal values even in the absence of infection in the great majority of patients with LAD. When bacterial infection is present, neutrophil counts can increase to as high as 100,000 cells/mm^3. These patients are sometimes thought to have myeloid leukemia or leukemoid reactions.

Summary statement 144. LAD-I/II should be diagnosed by using 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 and sialyl Lewis-X (CD15s) on the neutrophil or monocyte surface.[515-517] The absence of or decreased expression of CD18 and the inability to upregulate CD18 on the neutrophil cell surface after phorbol 12-myristate 13-acetate or N-formylmethionine-leucyl-phenylalanine (fMLP) stimulation is usually diagnostic for LAD-I. 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-I with normal (or near-normal) levels of expression of nonfunctional CD18 have been reported. Genetic analysis is necessary for diagnosis in this situation. The absence of sialyl Lewis-X/CD15s on myeloid cells is diagnostic of LAD-II.[515,516]

LAD-III is clinically similar to LAD-I, but these patients can have normal flow cytometric findings. LAD-III is caused by mutations in fermitin family member 3 *(FERMT3)*, which leads to functional impairment of neutrophil migration but with normal expression of CD18 and CD15. Diagnosis depends on the demonstration of impaired integrin function and requires genetic analysis for mutations in FERMT3.[515,516]

Summary statement 145. Therapy for LAD-I/II should be supportive and dictated by aggressive prevention and management of infections. (C)

Supportive treatment for LAD-I consists of prompt use of antibiotics for infection and surgical debridement of wounds.[515-517] Granulocyte transfusion is indicated for severe therapy-resistant infections in patients with LAD-I. Neutrophil infusion is probably futile for patients with LAD-II because the cells will not be able to exit the circulation to the site of infection and will only serve to sensitize the recipients, making future HSCT problematic.[515,516] Consideration can be given to the use of antibacterial and/or antifungal prophylactic treatment. The same general approach is true for other neutrophil defects that might or might not be amenable to HSCT or even when the genetic defect is unknown.

Summary statement 146. Fucose supplementation can ameliorate the course of LAD-II. (C)

LAD-II is caused by a general defect in fucosylation of macromolecules, and thus nonimmune manifestations are common and play a role in the long-term outcome.[515,516] 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-II. Discontinuation of fucose supplements results in a rapid loss of selectin ligands and increases in peripheral neutrophil counts. Patients with LAD-II tend to have less of the infectious complications and more of the metabolic complications as they get older.

Summary statement 147. HSCT is curative for LAD-I and LAD-III and should be considered early. (C)

HSCT is curative for LAD-I and should be considered early in the course of disease for patients with complete LAD-I. Allogeneic HSCT leading to a mixed chimeric population of normal and LAD-I myeloid stem cells can achieve a clinical cure.[513,518,519] This is also the only reported therapy that seems to work in patients with LAD-III.[520,521]

Specific granule deficiency.

Summary statement 148. Specific granule deficiency (SGD) should be considered in patients with recurrent severe bacterial infections of the skin and respiratory tract and normal neutrophil counts. (C)

Few patients have been reported to date. Skin infections are usually indolent, and severe infections with abscess formation can also affect the lungs, lymph nodes, ears, and mastoids.[522] Pathogens include *S aureus*, *Pseudomonas* species, and *Candida* species. SGD can also present with severe chronic diarrhea.[523] Homozygous mutations in the gene encoding the C/EBPε transcription factor underlie this disorder.

Microscopic examination of stained neutrophils can establish the diagnosis of SGD.[522] In patients with SGD, the neutrophils have abnormal, bilobed, or cleft nuclei. The specific granules are devoid of most of their contents and are not visible after Wright staining. Laboratory abnormalities in patients with SGD include impaired chemotaxis and bacterial killing.

Summary statement 149. Management of SGD should be supportive, but HSCT might have a role. (C)

Management is supportive, with intensive antibiotic coverage and prophylactic antibiotic use.[522] There is one case report in which HSCT was curative.[523]

Other syndromes of defective neutrophil motility.

Summary statement 150. Additional genetic lesions should be investigated in patients with clinical and laboratory features consistent with neutrophil defects who are not found to have any of the disorders listed previously. (C)

Ras-related C3 botulinum toxin substrate 2 (Rac2) deficiency leads to a clinical presentation very similar to that of LAD, with severe bacterial infections, poor pus formation, poor wound healing, and neutrophilia.[524] β-Actin (gene *ACTB*) defects are better known in association with severe juvenile dystonia, although it has been described in association with neutrophil dysfunction and cognitive impairment in a single female patient.[525] As the name implies, localized juvenile periodontitis is a syndrome of aggressive gum disease in childhood that has been associated with a polymorphism (Thr348Cys) in the major formyl peptide receptor (gene *FPR1*) of neutrophils. In patients with this disease, neutrophils have reduced capacity to undergo chemotactic migration in response to fMLP produced by bacteria.[526] Papillon-Lefevre syndrome with severe periodontitis and palmoplantar hyperkeratosis arises from mutations in *CTSC* encoding cathepsin C (dipeptidyl peptidase), a major proteolytic enzyme contained in neutrophil azurophilic granules.[527-529] Patients with Schwachman-Diamond syndrome (also called Schwachman-Bodian-Diamond syndrome) have pancytopenia associated with growth failure and pancreatic insufficiency.[530,531] These patients also have a high risk for myeloid leukemia. This disorder is caused by mutations in the *SBDS* gene encoding a product important for ribosome function.

Defects of the respiratory burst.

Chronic granulomatous disease (CGD).

Summary statement 151. CGD should be suspected in patients with deep-seated granulomatous infections with bacteria and fungi. (C)

CGD occurs in about 1:200,000 births in the United States.[532-534] The X-linked form is generally more severe and accounts for about 70% of cases, whereas autosomal recessive forms make up the remainder (Table E2). Disease onset is usually in infancy. Granulomatous abscesses occur in the lungs (approximately 75% of patients), lymph nodes (50%), skin (40%), liver (25%), and bones (25%). Sepsis can occur in about 20% of patients. The principal bacterial pathogens are usually catalase producing and include *S aureus* and *Salmonella*, *Klebsiella*, *Aerobacter*, *Serratia*, *Nocardia*, and *Burkholderia* species. Infection with *Aspergillus fumigatus* occurs in a majority of patients; *C albicans* is another prominent fungal pathogen.[535-537] A colitis similar to Crohn disease occurs in about 17% of patients. Granulomatous inflammation can lead to obstruction of the stomach, ureter, or esophagus in some patients. Physical examination can reveal growth failure, evidence of abscesses or other infection in any region, or lymphadenopathy, organomegaly, or both.

Although most patients are affected as infants or young children, adults occasionally present with acute severe fungal pneumonia.[535] CGD should be suspected in any patient presenting with characteristic infections and complications, regardless of age of onset. Also, X-linked CGD presents rarely in female patients with extreme skewing of X-chromosome lyonization (also see SS 8).[35]

Summary statement 152. Measurement of phagocyte oxidase activity should be the first screening test for CGD. (C)

Screening diagnostic tests rely on various measures of neutrophil superoxide production and include direct measurement of superoxide production, the nitroblue tetrazolium reduction test, and the dihydrorhodamine 123 (DHR) oxidation test.[538] The DHR test depends on the ability of phagocytes on stimulation to oxidize the DHR dye to a green fluorescent molecule by the generated superoxide; this fluorescence is measured by means of flow cytometry and is thus objective and quantitative. The nitroblue tetrazolium test relies on visual scoring and is thus qualitative and highly subjective in addition to having a higher rate of false-negative results. Both can also be used for determination of carrier status of X-linked CGD in female patients, although interpretation of the DHR assay might be more straightforward for this purpose. Cytoplasmic flow cytometric methods to detect phagocyte oxidase subunits have been developed but are not yet generally available.[539] Ultimate confirmation is done by testing for the genetic mutation in the genes that make up the NADPH (reduced form of nicotinamide adenine dinucleotide phosphate) oxidase complex (gp91phox, p22phox, p47phox, p67phox, and p40phox).[540]

Summary statement 153. Patients with CGD should be given prophylaxis with antimicrobial agents and IFN-γ. (A)

Therapy for phagocytic defects is aimed at preventing recurrent infections and reducing morbidity and mortality from these infections through very aggressive treatment. Careful personal hygiene is generally considered an important adjunct for the prevention of infections in patients with CGD and other phagocyte defects. Prophylactic treatment with trimethoprim-sulfamethoxazole, 5 mg/kg divided twice daily, has been shown to reduce the rate of severe bacterial infections in patients with CGD by 50%.[533,540] Prophylactic treatment with itraconazole (100 mg daily up to 50 kg body weight, 200 mg daily thereafter) reduces the rate of infections with *Aspergillus* species. Prophylactic IFN-γ, 50 $\mu g/m^2$, administered subcutaneously 3 times per week reduces severe infections in both patients with X-linked and those with autosomal recessive CGD. However, adherence might be an issue because of side effects, and breakthrough infections still occur.

Summary statement 154. Granulocyte transfusions should be considered as a last-resort therapy for the treatment of life-threatening infections in patients with CGD. (C)

Granulocyte transfusions can be used, although only as a last resort, for treatment of life-threatening infections or those refractory to other medical and surgical treatments. Granulocyte transfusion can lead to alloimmunization, which might adversely affect the odds of a successful HSCT in the future.[541]

Summary statement 155. 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.[542]

Summary statement 156. HSCT should be considered early in the course of CGD, where possible. (C)

HSCT has successfully been performed to treat CGD. Long-term survival with HLA-identical sibling donors is approximately 80%.[66,533,543] Outcomes with other modes of stem cell transplantation are improving and should be considered. Gene therapy correction of CGD is being studied but is not generally available.[544-546]

Mendelian susceptibility to mycobacterial disease.

Summary statement 157. Patients with severe tuberculous or atypical mycobacterial infections, *Salmonella* species infections, or herpesvirus infections and normal results on screening studies of humoral and cellular immunity should be tested for genetic defects and autoantibodies associated with Mendelian susceptibility to mycobacterial disease (MSMD). (C)

Extreme susceptibilities to all types of mycobacteria, *Salmonella* species, and herpesviruses (CMV, HSV, and varicella-zoster virus) have been reported in patients with defects in type 1 cytokine pathways. These defects result from genetic mutations in genes encoding IFN-γ receptor chains 1 and 2 (IFN-γ receptor 1/2 *[IFNGR1/2]*), the IL-12 p40 subunit, the IL-12 receptor β1 chain (also a component of the IL-23 receptor), STAT1, ISG15 (ISG15 ubiquitin-like modifier), and the IFN-γ response factor interferon regulatory factor 8 (IRF8).[532,547-550] These conditions are autosomal recessive except for specific *IFNGR1* and *STAT1* mutations, which can be autosomal dominant. A family pedigree might be helpful in diagnosis.

Adults with late onset of infections suggestive of MSMD defects should be evaluated for anti–IFN-γ autoantibodies (also see SSs 237-239).[551] Patients with anti–IFN-γ autoantibodies present with adult-onset infections similar to those seen in patients with IFN-γ and IL-12 axis gene mutations.[552] Patients affected by these autoantibodies are more likely to be adult native Asians with HLA-DRB1*1602 and HLA-DQB1*0502 alleles.[553]

The autoantibody titers also tend to be extremely high (unlike the nonpathogenic low-titer autoantibodies found in patients with latent or active pulmonary tuberculosis) and are actively neutralizing for IFN-γ pathway signaling and activation.

Autoantibodies to IL-12 have also been described, although their pathologic association is not clear in all cases. At least 1 patient has been described with recurrent disseminated *Burkholderia gladioli* infection who had neutralizing autoantibodies to IL-12p70.[554]

Standard screening measures of cellular and humoral immune function are normal in patients with MSMD. Serum immunoglobulin, IgG subclass, 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. Some patients with anti-interferon autoantibodies can have hypergammaglobulinemia.[552]

Summary statement 158. Patients suspected of having MSMD should have measurement of serum IFN-γ levels. (C)

A markedly increased serum IFN-γ level can be used as a screening test to prompt further evaluation for *IFNGR1/2* gene defects. Serum IFN-γ levels are increased (>80 pg/mL) in patients with a mutation in the genes that code for the components of the IFN-γ receptor.[549] This can be used as a screening assay before pursuit of *IFNGR1/2* gene sequencing when a defect is suspected.

Summary statement 159. Management of MSMD should include vigilance for infection and aggressive and prolonged therapy of infections when they occur. (C)

Avoidance of infection is desirable. For example, heavy exposure to soil should be avoided. Early detection of infection and specific identification of the pathogen and its antimicrobial susceptibility are critical for favorable outcome.[532,547-549] Multidrug regimens should be applied for prolonged periods to ensure eradication, which should be confirmed, when feasible. The need for long-term prophylaxis depends on the frequency with which individual patients become infected. Prophylaxis is not considered necessary for all subjects or at all times.

The same principles of therapy apply to adult-onset disease caused by autoantibodies to IFN-γ. There have been a few case reports of successful treatment using plasmapheresis with cytotoxic immunosuppression or rituximab.[555,556]

Summary statement 160. Patients with partial *IFNGR1/2* mutations and IL-12p40 or IL-12 receptor β1 defects with nontuberculous mycobacterial disease might benefit from adjunct therapy with subcutaneous IFN-γ. (C)

Subcutaneous treatment with IFN-γ is an accepted adjunct therapy for mycobacterial disease. Because of the impaired ability of patients with IL-12p40 or IL-12 receptor β1 mutations to produce IFN-γ in response to physiologic stimuli, this treatment might be useful for these patients and should be used in addition to standard antimycobacterial chemotherapies.[549]

Summary statement 161. HLA-identical sibling HSCT can be considered for therapy of the *IFNGR1/2* mutation. (C)

One group reported their experience with various techniques of HSCT for 8 patients with *IFNGR1* defects.[557] Four patients died within 4 months or transplantation, and only 2 were in remission 5 years later. These 2 patients received non–T cell–depleted bone marrow from HLA-matched siblings.

Pulmonary alveolar proteinosis.

Summary statement 162. Patients with pulmonary alveolar proteinosis (PAP) should be tested for mutations in the genes encoding the macrophage GM-CSF receptor, antibodies to GM-CSF, or both. (C)

Patients with PAP have increased susceptibility to both the usual respiratory pathogens and opportunistic infections. Most of the opportunistic pathogens are those primarily controlled by phagocytes, including nontuberculous mycobacteria, and endemic fungi, such as *Aspergillus*, *Cryptococcus*, *Histoplasma*, *Nocardia*, and *Proteus* species. Pulmonary, CNS, arthritic, and disseminated infections with these organisms have been described.[558-560]

Although PAP is a relatively uncommon chronic lung disease, it can be progressive, and determination of its underlying pathogenesis has significant relevance to treatment and prognosis. There are several causes of PAP. Severe early-onset disease is caused by defects of the GM-CSF receptor α and β subunits.[561,562] PAP also occurs in some patients with GATA-2 deficiency.[563] PAP can also be secondary to hematologic malignancy, immunosuppressive medication, or toxin inhalation.[558-560] The majority of patients given a diagnosis of PAP are adults who have neutralizing autoantibodies against GM-CSF (also see SSs 237-239).[564]

In addition to anti-infective and anti-inflammatory therapy for PAP, patients given a diagnosis of clinically significant anti–GM-CSF autoantibodies can be treated with exogenous GM-CSF or rituximab. Several trials have examined the efficacy of either inhaled or subcutaneous GM-CSF in patients with PAP with anti–GM-CSF antibodies.[565-567] Therapy does not seem to affect autoantibody titers, and both routes of administration were effective, possibly by complexing with (consuming) the autoantibody. Long-term administration appears to be both effective and safe.[568] Rituximab was also found to be effective in small trials.[569]

Neutrophil/phagocytic cell defect, unspecified.

Summary statement 163. Any patient with recurrent infections and a demonstrable isolated defect of phagocytic cell function who does not have any of the above disorders 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 can have recurrent infections characteristic of phagocytic cell defects, along with diminished neutrophil numbers 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. Therapy for unspecified phagocytic cell dysfunction must be individualized. See SSs 149 and 153 to 155.

GATA-2 deficiency.

Summary statement 164. Patients with recurrent severe infections with bacteria, mycobacteria, fungi, and viruses (especially papillomaviruses) and very low numbers of monocytes, B cells, and NK cells should be studied for *GATA2* mutation. (C)

GATA-2 deficiency (also called MonoMAC syndrome) has autosomal dominant inheritance and is thought to be a time-dependent progression starting with an infection-susceptible phenotype, progressing through myelodysplasia and ending with hematologic or other malignancies.[570-572] Clinical presentation is usually in late childhood/adolescence or adulthood. The infectious diseases to which patients are susceptible include respiratory tract bacterial and fungal infections, mycobacterial infections, and viral infections, most commonly with papilloma

viruses. HPV infections are particularly severe and often present in populations exposed to genital infection with HPV11 and HPV16 (the latter frequently leads to severe genital cancers in these patients). Abnormal physical characteristics have been described in some patients, including hypotelorism, epicanthal folds, webbed neck, long tapering fingers, and high-frequency deafness. Monocyte and lymphocyte counts are low, especially B and NK cells (and dendritic cells), and T-cell numbers and function are variable. Immunoglobulin levels are normal. HSCT can be curative.

Defects of innate immunity

The general approach to the evaluation and diagnosis of defects of innate immunity is summarized in Fig E5.

Defects of NEMO.

Summary statement 165. NEMO defects and related syndromes should be suspected in patients with ectodermal dysplasia and severe viral, bacterial, and atypical mycobacterial infections. (C)

NEMO syndrome results from mutations in the inhibitor of κB kinase γ chain *(IKBKG)* gene encoding the NEMO protein[547,573,574] and is phenocopied by mutations in the inhibitor of κB α chain *(IKBA)* gene encoding the I-κB α protein.[573,575,576] *IKBKG* mutations are X-linked recessive, and *IKBA* mutations are autosomal dominant. Because they both impair the function of the NEMO protein and share characteristics, they are collectively referred to as NEMO syndrome.

Aside from resulting in immunodeficiency, NEMO syndrome is best and originally known for causing ectodermal dysplasia, which is characterized by conical or absent teeth, fine sparse hair, frontal bossing, and abnormal thermal regulation because of decreased eccrine sweat glands.[573-576] The occurrence and penetrance of ectodermal dysplasia in patients with NEMO syndrome is incomplete and affects approximately 75% of patients in some form. However, patients without any evidence of ectodermal dysplasia are well known. A small subset of the X-linked cases also have lymphedema and osteopetrosis. Almost all known patients have had susceptibility to infection, with most experiencing bacterial infections, just less than half having mycobacterial infections, approximately one quarter having DNA viral infections, and less than one tenth having pneumocystis.

Autoimmunity/autoinflammation is also common in patients with NEMO syndrome and affects approximately 25% of patients.[573-577] The most frequently occurring condition is a nondescript intestinal inflammatory disorder presenting as diarrhea and abdominal pain. This condition can be difficult to manage and has been steroid dependent in several cases.[577,578]

Summary statement 166. Patients suspected of having NEMO syndrome should have measurement of NK cell and TLR responses in addition to routine studies of humoral and cellular specific immune function. (C)

Laboratory abnormalities in patients with NEMO syndrome include the following in order of frequency: (1) impaired NK cell function; (2) impaired pneumococcal specific antibodies; (3) abnormal TLR response; (4) hypogammaglobulinemia; (5) antigen-specific T-cell proliferative abnormalities; and (6) increased serum IgA levels.[575,577] Although originally defined as an alternative cause of hyper-IgM, this is present in less than 20% of patients.

Summary statement 167. Mycobacterial infection in patients with NEMO syndrome should be treated with an aggressive antimicrobial regimen. (C)

Mycobacterial infection in patients with *IKBKG* mutation can be severe and difficult to treat.[575,577] 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 can 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.

Summary statement 168. Patients with NEMO syndrome should receive IgG replacement. (C)

Because of the prevalence of impaired antibody production, specific antibody generation, and B-cell function, patients with IKBKG or NEMO deficiency should be given immunoglobulin replacement (see SSs 11-17).[575,577] In many patients, however, significant bacterial infections still occur. IVIG has been applied extensively in patients with NEMO syndrome, but there is less experience with SCIG. The abnormal ectoderm present in many patients should prompt caution in approaching the use of SCIG. That said, anecdotal experience with this method of therapy has been described.[579]

Summary statement 169. Antibacterial, antimycobacterial, *Pneumocystis* species, and antiviral prophylaxis should be considered for patients with NEMO syndrome. (C)

Decreased cellular immune function, including TLR response, NK cell cytotoxicity, and specific T-cell functions, might predispose patients with an *IKBKG* mutation to severe and recurrent viral infections, particularly herpesviruses.[575,577] Chronic herpes antiviral prophylaxis should be considered in patients who have experienced these infections. Because significant bacterial infections can occur in spite of IgG replacement, antibacterial prophylaxis should be considered (see SS 16 and Table E7). Antimycobacterial (atypical) prophylaxis in young patients who have not yet been given a diagnosis of such infection should also be considered. Finally, the increasingly appreciated susceptibility to pneumocystis (8% of patients) should prompt consideration of specific pneumocystis prophylaxis in patients with NEMO syndrome.

Summary statement 170. HSCT should be considered for patients with NEMO syndrome. (C)

NEMO syndrome can be a severe primary immunodeficiency with a relatively large number of early fatalities, despite tertiary medical care.[575,577] Thus HSCT should be considered in all patients with NEMO syndrome.[580,581] Factors hypothesized to improve likelihood of success are young age, absence of mycobacterial infection, and an HLA-identical sibling donor. Overall outcomes have been mixed, and additional experience is needed. Even when successful, transplantation will not ameliorate all comorbidities attributable to NEMO syndrome, including the ectodermal dysplasia phenotype, if present. A patient with persistent intestinal inflammation after transplantation has also been described.[582] Thus transplantation should be approached cautiously until additional data are available.

Other TLR signaling pathway defects.

Summary statement 171. IL-1 receptor–associated kinase 4 (IRAK-4) and myeloid differentiation primary response 88 (MyD88) deficiencies should be considered in patients with recurrent serious infections with gram-positive bacteria and normal levels of immunoglobulins, complement, and phagocytic cells. (C)

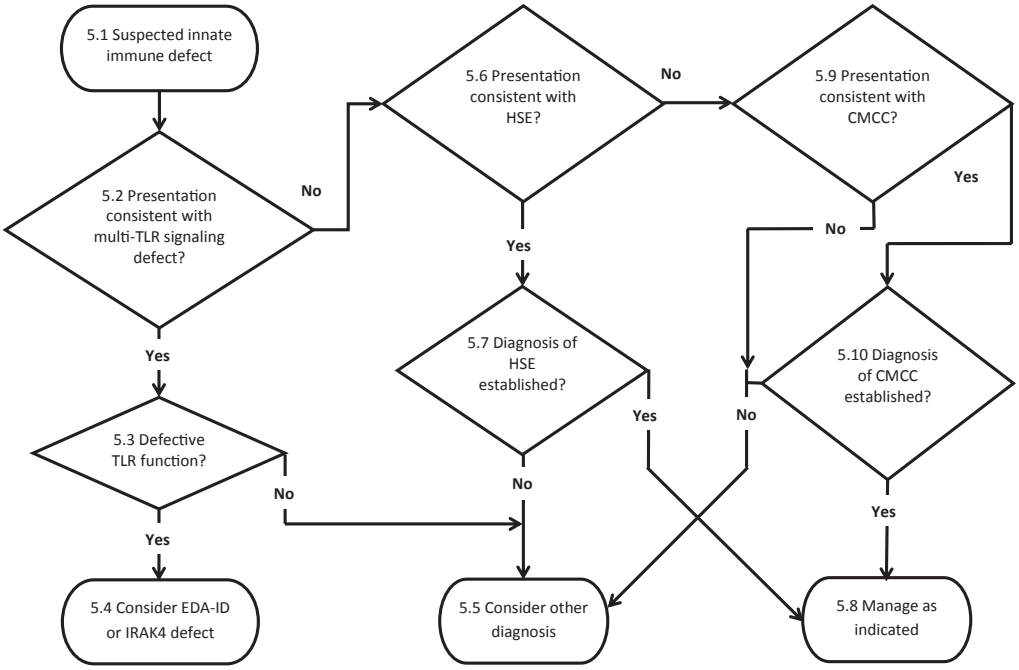

FIG E5. Diagnosis of innate immune defects. *5.1*, A defect of innate immunity is suspected according to one of the characteristic clinical presentations (Table III). *5.2*, The presentation is principally one of severe recurrent infections of all classes of pathogens together with ectodermal dysplasia, severe gram-positive bacterial infections, or other clinical features suggestive of NF-κB pathway or multiple TLR signaling defects. *5.3*, In the case of 5.2, is TLR function abnormal? *5.4*, If yes, consider defects of NF-κB signaling, anhidrotic ectodermal dysplasia with immunodeficiency, or IRAK-4. If no, go to 5.10. *5.5*, The presentation is consistent with HSE. *5.6*, In the case of 5.5, pursue a molecular diagnosis, if possible. There are no routinely available tests of TLR3 function that are informative in this setting. *5.7*, If the diagnosis of HSE or CMCC is established, manage as indicated for each disorder. If not, go to 5.10. *5.8*, The presentation is consistent with CMCC. *5.9*, In the case of 5.8, pursue a molecular diagnosis, if possible. There are no routinely available clinical tests that will be informative in this setting. If the diagnosis is confirmed, proceed as in 5.7. If not, go to 5.10. *5.10*, If TLR function is normal or HSE or CMCC diagnoses are not confirmed, consider the possibility of a CID or primary immunodeficiency syndrome (Fig 2) or phagocytic cell defect (Fig 4). A syndrome of immune dysregulation can also be considered (Fig 3). Also consider a cytokine autoantibody (Table II and SSs 236 and 237).

IRAK4 encodes an essential catalytic unit of the IRAK complex, which mediates downstream signaling from the TLRs, with the exception of TLR3.[576,583] Rare autosomal recessive mutations in this gene have been identified in patients with susceptibility to severe invasive bacterial infections. A recent summary of 48 patients with IRAK-4 deficiency described meningitis in roughly 40% of cases, bacteremia/septicemia in 23%, septic arthritis in 15%, deep tissue abscesses in 15%, and osteomyelitis in 6%.[584] Noninvasive bacterial infections also occur, which primarily involved the skin (cellulitis and folliculitis) and upper respiratory tract (sinusitis, recurrent otitis media, and tonsillar abscesses). These infections often begin in the neonatal period (31% of cases), and the vast majority present before 2 years of age (88%, including 74% of invasive infections).

Streptococcus pneumoniae is the leading pathogen and accounts for more than half of invasive infections. Other common isolates include *S aureus* (25%) and *Pseudomonas aeruginosa* (20%). Less common pathogens include *H influenzae*, *Shigella sonnei*, *Neisseria meningitidis*, and *Clostridium septicum*.[576,584] Pneumonia or bronchitis is rarely described, and viral infections are rare and generally uncomplicated. A single case of pulmonary *Mycobacterium avium* was described in an adolescent with IRAK-4 deficiency.[584] Opportunistic infections with parasites or fungi have not been described. Atopic and/or autoimmune diseases have not been described in these patients.

Most reported deaths caused by invasive bacterial infection occurred before 2 years of age, with invasive pneumococcal disease being the leading cause of death.[584] In survivors no deaths and few infections have been seen outside the first decade of life, although reports exist of persistent SAD in some patients. It has been hypothesized that maturation in adaptive immunity and possibly alterations in innate signaling with age can facilitate improvement in most patients.

MyD88 is a cytosolic adaptor protein that bridges both the TLRs and IL-1 receptors to the IRAK complex, allowing downstream production of cytokines, including TNF, IL-6, and IL-8. Rare autosomal recessive mutations in MyD88 are associated with recurrent invasive bacterial infections.[585] The spectrum of disease in patients with MyD88 deficiency is indistinguishable from that in patients with IRAK-4 deficiency.[576,584]

The results of standard screening tests of immune function are normal in patients with IRAK-4 or MyD88 deficiency, with the possible exception of humoral responses to pneumococcal polysaccharides. Lymphocyte subpopulations are normal, as is proliferation to mitogens and recall antigens. Immunoglobulin levels are generally normal, although hypergammaglobulinemia and increased IgE levels have been described in many cases. Increased

IgM levels have also been noted in some cases. Vaccine responses to protein antigens are usually intact, although roughly one half of patients show a degree of impaired protection against T-independent antigens, most notably to *S pneumoniae*.[584] However, the majority of patients studied demonstrated a response to vaccine boosting against *S pneumoniae*. It should be noted that in IRAK-4- and MyD88-deficient patients, no correlation was seen between pneumococcal titers and risk of invasive pneumococcal disease.

Summary statement 172. Deficiency of RanBP-type and C3HC4-type zinc finger containing 1 (RBCK1) should be suspected in patients exhibiting features of both autoinflammation and immunodeficiency. (C)

RBCK1 (previously called HOIL1) is involved in some pathways of canonical NF-κB activation in response to some cytokines, such as IL-1β.[586] Hyperresponsiveness or hyporesponsiveness can be observed depending on the cell type. These patients presented very early in life with recurrent fever and systemic inflammation, as well as hepatosplenomegaly and lymphadenopathy, without other signs of mucosal inflammation. In addition, they were affected by recurrent infection, although not until steroid therapy was initiated for the autoinflammatory episodes. Patients also had amylopectin-like deposits in muscle tissue.[586]

Summary statement 173. Patients with suspected defects of TLR signaling should be screened by measurement of TLR response *in vitro*. (C)

PBMCs from patients with IRAK-4 deficiency show decreased production of TNF, IL-6, IL-12, G-CSF, GM-CSF, and IFN-γ when stimulated with IL-1 or IL-18 or through TLR2, TLR3, TLR4, TLR5, and TLR9. However, production of type I Interferon is spared.[587] This is similar to what is found in patients with NEMO syndrome, as well as in patients with other defects affecting the signaling pathways downstream of the TLR. Like IRAK-4 deficiency, MyD88 is required for production of TNF, IL-6, and IFN-γ after ligation of TLRs (with the exception of TLR3) or IL-1 receptor. This was shown to be detectable by means of *in vitro* stimulation of PBMCs.[583] Patients with RBCK1 defects can have abnormal (high or low) responses to TLR stimulation and have not been well studied with respect to these types of assays applied clinically.[586]

Summary statement 174. Therapy for defects of TLR signaling should be directed toward treatment and prevention of infection. (C)

Infections in patients with these disorders are caused by a narrow range of bacteria, with *S pneumoniae* and *S aureus* responsible in the majority of cases.[576,583-585,587] These infections can present as early as the neonatal period and are recurrent in many cases. Prophylactic antibiotics, hyperimmunization, and immunoglobulin replacement have been used to attempt to reduce infection rates. Cotrimoxazole and penicillin V are the primary antibiotics used. Vaccination against *N meningitidis*, *H influenzae*, and *S pneumoniae* should be performed, with serologic confirmation of response. If poor response to vaccination is noted, immunoglobulin replacement should be strongly considered. It has been reported that in patients with IRAK-4 or MyD88 deficiency who received prophylaxis of any sort, invasive infections were reduced by half.[584] Subgroup analysis regarding different forms of prophylaxis was unfortunately not performed, although roughly one third of the described patients were receiving immunoglobulin. Of note, for 7 patients older than 14 years who were not receiving prophylaxis, no further invasive infections were described. Thus reducing or discontinuing prophylaxis might be considered in well patients during this age period.

Rapid recognition and treatment of bacterial infections is essential for reduction of both morbidity and mortality in IRAK-4–deficient patients. Signs of inflammation might be lacking in early infection, particularly in neonates. Nearly all neonates and roughly half of infants and children will lack fever (>38°C) in the setting of invasive bacterial infections. Laboratory markers of inflammation might also be lacking or delayed, including C-reactive protein (CRP) and total leukocytes. Antibiotic treatment should not be withheld based on lack of inflammatory features.[584]

HSCT has not been reported for IRAK-4 or MyD88 defects. HSCT has been attempted for a few extremely ill children with RBCK1 deficiency.[586] None have survived, but experience is too limited to permit generalization.

Type I interferonopathies.

Summary statement 175. Aicardi-Goutieres syndrome should be considered in cases of neonatal presentation consistent with *in utero* toxoplasmosis, other (syphilis, varicella, parvovirus B19), rubella, CMV, HSV (TORCH) infection without evidence of infectious cause. (C)

Aicardi-Goutieres syndrome is a relatively rare autoinflammatory disease with a worldwide prevalence of about 200 cases, with underlying defects in 6 known genes: *TREX1* (3′ repair exonuclease 1), *RNASEH2B*, *RNASEH2C*, *RNASEH2A*, *SAMHD1* (SAM domain and HD domain 1), and *ADAR1* (ADA, RNA-specific).[358,588,589] Presentation is usually in the neonatal-infant period and similar to that seen in congenital viral infection, with severe encephalopathy, acquired microcephaly, and some symptoms overlapping with SLE. Brain magnetic resonance imaging usually reveals calcification, white matter changes, and atrophy, with CSF lymphocytosis and a signature of markedly increased IFN-α levels in the CSF and possibly also in whole blood. However, serologic test results for evidence of infection are negative. Because the majority of patients seem to have an initial encephalopathic period followed by neurological deterioration during a limited period of a few months with subsequent stabilization, early diagnosis and symptom control might be critical to minimizing clinical decline during this critical progressive stage. There is also significant variability in the disease between patients and even within families.[358,588,589]

Summary statement 176. Spondyloenchondrodysplasia with immune dysregulation (SPENCD) should be suspected in patients presenting with characteristic osseous lesions, CIDs, autoimmunity, and neurological disorders. (C)

SPENCD results from mutations in acid phosphatase 5, tartrate resistant *(ACP5)*.[590,591] Patients are affected by a triad of metaphyseal and vertebral spondyloenchondrodysplasia, combined immune dysfunction with a variety of recurrent infections and SLE-like systemic autoimmunity, and neurological abnormalities, including cerebral calcifications and developmental delay. Patients exhibited increased IFN-α levels in serum.[590,591]

Summary statement 177. Therapy of type 1 interferonopathies should be directed toward infectious and autoimmune complications. (C)

Treatment efficacy has been variable and includes the use of various immunosuppressants, such as prednisone, IVIG, and azathioprine; however, there is currently some work investigating the possibility of anti–IFN-α agents.[358,588-591]

Warts, hypogammaglobulinemia, immunodeficiency, and myelokathexis syndrome.

Summary statement 178. Warts, hypogammaglobulinemia, immunodeficiency, myelokathexis (WHIM) syndrome should be suspected in patients who manifest the principal characteristics. (C)

WHIM syndrome is a rare congenital immunodeficiency defined by high susceptibility to papilloma viruses, lymphocytopenia with markedly decreased memory B-cell counts, hypogammaglobulinemia, and peripheral neutropenia with retention of mature neutrophils in the bone marrow.[592] In most, but not all, patients this disorder is caused by an autosomal dominant gain-of-function mutation in the chemokine receptor CXCR4. To date, more than 37 patients with WHIM syndrome have been reported.

Patients present at a variety of ages with any or all of the cardinal features.[592] Infection with papilloma viruses often causes widespread recalcitrant warts, which can occur on the trunk, extremities, or anogenital regions. Condyloma accuminata can occur, as can dysplastic lesions with risk of malignant transformation. Recurrent pneumonias are common, which in some cases might contribute to the development of bronchiectasis. Other infections include sinusitis, cellulitis, urinary tract infection, thrombophlebitis, osteomyelitis, and deep tissue abscesses. Common pathogens include *H influenzae*, *S pneumoniae*, *Klebsiella pneumoniae*, *S aureus*, and *Proteus mirabilis*. Aside from human papillomaviruses, other viruses are rarely implicated in patients with severe infections. A noted exception is the occurrence of EBV-associated lymphoproliferative disorder in 2 patients with WHIM syndrome.[592]

Laboratory findings in patients with WHIM syndrome include neutropenia and variably decreased humoral and cellular immunity.[592] Lymphocytopenia in patients with WHIM syndrome is often marked, with near-uniform decreases in B-cell counts and frequently decreased T-cell and NK cell counts. T-cell function is intact in response to mitogens and recall antigens. Total leukocyte counts are often less than 1×10^9/L. Peripheral neutrophil counts are often less than 0.5×10^9/L but increase with infection and also respond to exogenous epinephrine, corticosteroids, or G-CSF with rapid increases to near-normal numbers. Levels of IgG, IgA, or both are often less than normal levels; IgM levels are more often normal. Humoral responses to vaccination are present but often transient, with rapid waning of protection over time.[592]

Summary statement 179. Treatment of WHIM syndrome should include IgG replacement, G-CSF therapy, or both to reduce the incidence of infection. (C)

IgG replacement therapy has been successful in reducing infections in patients with WHIM syndrome.[592] Both G-CSF and GM-CSF have been reported to result in 4- to 100-fold increases in peripheral blood neutrophil counts. Adverse effects can limit therapy, and G-CSF is recommended given its milder side effect profile. Interestingly, serum IgA and IgG levels might normalize after G-CSF or GM-CSF therapy. Additionally, 2 trials of the CXCR4 antagonist plerixafor in patients with WHIM syndrome have shown rapid increases in neutrophil, monocyte, and lymphocyte counts, with normalization of B-cell counts.[593,594] The clinical efficacy of this treatment with respect to infection is not yet known.

Summary statement 180. Vaccination against HPV should be considered in patients with WHIM syndrome. (C)

A response to quadrivalent HPV vaccine was recorded in a patient with WHIM syndrome who mounted a transient humoral response but showed evidence of a sustained cellular response to the vaccine.[595] Although the clinical benefit remains uncertain, its use should be strongly considered given the established safety of the vaccine and the severity of papillomavirus infections in patients with WHIM syndrome.

Summary statement 181. Hematopoietic stem cell transplantation should be considered for patients with WHIM syndrome. (C)

A single case of hematopoietic stem cell transplantation through matched umbilical cord blood has been described in a child with WHIM syndrome.[596] This transplantation was successful, with near full-donor chimerism and complete resolution of all clinical symptoms without further need for immunoglobulin or G-CSF therapy.

Epidermodysplasia verruciformis.

Summary statement 182. Epidermodysplasia verruciformis (EV) should be suspected in patients with diffuse verrucosis caused by HPV. (C)

EV is associated with diffuse chronic warts caused by HPVs and carries a high risk of nonmelanoma skin cancer.[597] EV is a rare genetic condition involving persistent refractory skin lesions beginning in early childhood. Skin lesions present as disseminated macules or flat warts that are concentrated in areas of sun exposure and often change slowly over time. Typical warts or anogenital warts are uncommon. Lesions are caused by β-papillomaviruses, which rarely cause symptomatic disease in immunocompetent hosts, with HPV5 being the most common isolate.[598] No other viral, bacterial, or fungal susceptibility has been described in patients with EV. Malignant transformation in patients with EV usually occurs in actinic keratosis lesions and can occur as early as the second decade of life. Only a subset of β-HPVs, most notably HPV5, HPV8, HPV14, HPV17, HPV20, and HPV47 have been associated with skin cancers in patients with EV.[599]

It has been reported that some patients with EV have decreased T-cell numbers, as well as decreased *in vitro* lymphocyte proliferation, in response to mitogens.[600] It is unclear whether this might be due to the underlying molecular defect in patients with EV or is reflective of chronic HPV infection. NK cell cytotoxicity and antibody-dependent cytotoxicity have been described as intact or even increased.[601]

Autosomal recessive fully penetrant nonsense mutations in transmembrane channel-like 6 *(TMC6)* and *TMC8* have been identified in 75% of kindreds with EV.[602] TMC6 and TMC8 are expressed in keratinocytes, as well as lymphocytes. There is evidence that they are involved in intracellular zinc regulation,[603] although their exact role in defense against β-HPV remains unknown.

A small number of autosomal recessive familial cases of EV have been identified that lack mutations in *TMC6/8*.[604] X-linked recessive inheritance has also been reported.[605] Homozygous nonsense mutations in the atypical Rho GTPase *RHOH* have also been identified in 2 siblings with EV.[175] Unlike typical EV, they also had bronchopulmonary disease, and 1 sibling had Burkitt lymphoma. Immunologic studies in these siblings showed decreased T-cell proliferation *in vitro*, as well as markedly decreased numbers of naive T cells. Mutations in macrophage stimulating 1 *(MST1)* are usually associated with severe T-cell deficiency.[606] Two siblings with an EV phenotype with *MST1* mutations have been reported.[175]

Summary statement 183. Primary therapy for EV should involve avoidance of UVB and radiation exposure and frequent dermatologic screening for skin cancer. (C)

Treatment with retinoids and α-interferon have not produced sustained improvements in patients with EV.[598,607] Given that lesions tend to occur in sun-exposed areas and radiation has been noted to worsen skin lesions, UVB and radiation avoidance is essential. Monitoring for premalignant lesions through regular dermatologic screening is recommended.

Summary statement 184. Patients with severe viral illnesses (especially disseminated vaccine strain measles) should be studied for mutations in *STAT2*. (C)

One kindred has been described with variable-penetrance deleterious homozygous mutations of *STAT2* leading to impaired signaling through type 1 interferons.[608] The most severely affected patients were siblings: one had disseminated vaccine strain measles infection after routine immunization, and the other died after a presumed viral infection of unknown type.

Susceptibility to herpes simplex encephalitis.

Summary statement 185. Patients with herpes simplex encephalitis (HSE) should be tested for one of the known associated gene defects. (C)

HSE is a rare and severe consequence of primary HSV-1 infection. The incidence of HSE peaks between 3 months and 6 years of age, with most cases occurring in children less than 3 years of age, and it has been estimated to occur in 1 in 250,000 patient years.[609] Acquired through neurotropic spread through the cranial nerves, viremia and cutaneous disease are often absent. Genetic defects in the TLR3 pathway causing susceptibility to HSE have been discovered in both familial and sporadic cases.

Autosomal recessive susceptibility to HSE is caused by defects in TLR3, UNC93b (unc-93 homolog B1), and Toll-like receptor adaptor molecule 1 (TICAM1), and autosomal dominant susceptibility results from defects in TNF receptor–associated factor 3 (TRAF3), TANK-binding kinase 1 (TBK1), TLR3, and TICAM1.[609-614] Penetrance is complete in patients with autosomal recessive *TLR3*, autosomal recessive *TICAM1*, and autosomal dominant *TRAF3* mutations, whereas incomplete penetrance has been noted in patients with *UNC93b*, autosomal dominant *TLR3*, and autosomal dominant *TICAM1* mutations. These mutations result in selective susceptibility to HSE because resistance to other viruses and bacteria has been noted to be normal in affected patients. An association between a rare mutation in TLR3 and coxsackie B virus–associated viral myocarditis has been reported,[615] although predisposition to viral myocarditis has not been reported in patients affected by HSE-associated mutations.

Defects in *UNC93B1*, *TLR3*, *TBK1*, *TICAM1*, and *TRAF3* might not be detectable by using available *in vitro* functional assays.[609-614] Studies of HSE susceptibility genes have shown that the associated mutations selectively alter the generation of interferon types I and III, as well as IL-6, by fibroblasts in response to the TLR3 agonist polyinosinic-polycytidylic acid. Increased HSV-1 replication and cytolysis have also been demonstrated *in vitro*, which were correctable by addition of exogenous type I interferon. However, it has been demonstrated that leukocytes and keratinocytes of affected patients respond normally to polyinosinic-polycytidylic acid through TLR3-independent mechanisms.[614] These findings speak to the importance of innate fibroblast immunity in resistance to HSE. It should be noted that defective *in vitro* TLR responses can be seen with defects in STAT1, NEMO, and I-κB α, which also cause predisposition to HSE.[609] However, these defects cause multiple susceptibilities beyond HSV. In suspected cases of HSE-causing gene defects, genetic analysis is recommended for definitive diagnosis.[616]

Summary statement 186. Antiviral prophylaxis should be considered for patients with defects in *UNC93B1*, *TLR3*, *TBK1*, *TRIF*, and *TRAF3*. (F)

TLR3 pathway defects selectively predispose patients to HSE during primary HSV-1 infection, making prior detection of patients difficult in the absence of a suggestive family history. After primary infection, serologic evidence of immunity against HSV-1 is often detectable.[609,610] Given the higher incidence of HSE in children less than 3 years of age and the high incidence of neurological sequelae after HSE, antiviral prophylaxis is advisable for identified infants and young children until HSV seroconversion is confirmed.

CMCC.

Summary statement 187. Patients who present exclusively with recurrent *Candida* species infection of nails, skin, and mucous membranes should be considered for the diagnosis of CMCC. (C)

The diagnosis of CMCC can be applied to a heterogeneous group of patients having an apparent selective susceptibility to chronic, recurrent, and sometimes exuberant *Candida* species infections of the skin and mucous membranes.[617] Dermatophytosis of the nails is also common. Autosomal recessive forms caused by mutations in *CARD9* and *IL17RA* have been described, and autosomal dominant forms are caused by dominant negative mutations in *IL17F* and gain-of-function mutations in *STAT1*.[618-620] Defects of the adapter molecule TRAF3 interacting protein 2 (TRAF3IP2) also abolishes IL-17 receptor activity.[621] Incomplete penetrance has been noted in dominant *IL17F* mutations, whereas the other mutations appear to be fully penetrant.

CMCC has also been described in patients with homozygous Tyr238Stop polymorphisms in the gene encoding the pattern recognition receptor CLEC7A.[622] However, subsequent studies have identified the polymorphism in healthy subjects, suggesting that *CLEC7A* might represent a risk gene rather than a monogenic cause.[617,623] Note that CARD9 is a signaling intermediate in the CLEC7A pathway. Candidiasis and polyendocrinopathy can be seen in association with autosomal recessive mutations in *AIRE* (see section on APECED, SSs 129-132).

Although mostly limited to mucocutaneous disease, invasive fungal disease occurs in rare cases of CMCC. Candidal meningitis and deep dermatophytosis have been described in patients with CARD9 deficiency.[618,624,625] Disseminated infections with *Histoplasma* and *Coccidioides* species occur in patients with *STAT1* gain-of-function mutations.[109,626] Autoimmune thyroiditis and hepatitis have been described in patients with associated *STAT1* mutations.[619] Rare cases of squamous cell carcinoma and cerebral aneurysms have also been reported.

Summary statement 188. Evaluation of patients with suspected CMCC should include NK cell numbers and functional studies and assessment of T-cell response to *Candida* species. (C)

Laboratory abnormalities in patients with CMCC can include defective cutaneous or *in vitro* T-cell response to *Candida* species and low NK cell counts, function, or both.[627] Patients with CMCC associated with *CARD9*, *IL17RA*, *IL17F*, and *STAT1* mutations will not have other identifiable cellular or humoral immunodeficiencies.[628,629] Laboratory testing might reveal impaired *in vitro* lymphocyte proliferation and cytokine secretion in response to *Candida* species, and delayed-type hypersensitivity test results to *Candida* species might be negative.[628] Other antigen responses are usually intact. A decrease in

T_H17 cell counts has been observed with mutations in *CARD9* and *STAT1*, although they are at normal levels with mutations in *IL17RA* and *IL17F*.[618-620]

Summary statement 189. Antifungal agents should be the mainstays of therapy for CMCC. (C)

Prolonged treatment with antifungal agents might be required, depending on the extent of *Candida* species infection. Prophylaxis should also be strongly considered in association with mutations in *CARD9*, given the higher incidence of invasive fungal infections.[618] No other therapies are known to affect the course of this disorder. Recently, a patient with CARD9 deficiency and relapsing meningoencephalitis was found to have an impaired GM-CSF response and was subsequently treated successfully with long-term antifungals and GM-CSF.[630]

Susceptibility to trypanosomiasis.

Summary statement 190. Patients with sleeping sickness caused by *Trypanosoma evansi* should be studied for mutation in the apolipoprotein L1 *(APOL1)* gene. (C)

Rare autosomal recessive mutations in *APOL1* cause susceptibility to human African trypanosomiasis (HAT; also commonly known as sleeping sickness).[631] *APOL1* encodes a high-density lipoprotein–associated protein with trypanolytic activity and is active against *Trypanosoma brucei brucei* and *Trypanosoma evansi*. Two subspecies of African trypanosomes (*Trypanosoma brucei gambiense* and *Trypanosoma brucei rhodesiense*) are resistant to APOL1-mediated lysis, which is mediated by the serum resistance protein.[632,633] These latter species are the causative parasites for HAT, whereas human subjects are naturally resistant to *T brucei brucei* and *T evansi*. A single case of HAT caused by *T evansi* infection was described in India.[634] Subsequent investigation showed that the patient's serum had no trypanolytic activity. Compound heterozygous frameshift mutations resulting in premature stop codons in *APOL1* were discovered.[631] Addition of normal human serum restored trypanolytic activity.

Standard treatment of HAT per WHO guidelines was successful in the single case of trypanosomiasis caused by *T evansi* associated with APOL1 deficiency. WHO guidelines for treatment of HAT involve the use of suramin or pentamidine for stage I (hemolymphatic) trypanosomiasis and melarsoprol or enflornithine for stage II (neurological) disease.[635] The APOL1-deficient patient was treated successfully with suramin with complete cure.[636]

Selective NK cell defects.

Summary statement 191. Patients with severe disease caused by herpesviruses or papillomaviruses who do not have another defined immunodeficiency should have phenotypic and functional assessments of NK cells. (C)

A number of patients have been identified who have a susceptibility to certain viral infections and have an isolated deficiency in NK cell numbers or function without other substantive identifiable immunologic defects.[637-639] There are 2 phenotypic labels used to describe these patients: (1) classical NK cell deficiency and (2) functional NK cell deficiency.[638] In classical NK cell deficiency, patients have a near-absolute and stable absence of $CD56^+/CD3^-$ NK cells, as well as NK cell cytotoxicity. Patients with functional NK cell deficiency have $CD56^+/CD3^-$ NK cells but stably deficient NK cell cytotoxicity. In all cases results must be consistent on at least 3 separate occasions separated by at least 1 month and preferably in the absence of infection or significant other illness because there is notable variation in NK cell populations.[637] Care should be taken to exclude other immunodeficiencies known to be associated with defects in NK cell numbers or function. These include but are not limited to various forms of SCID, CHS, XLP, CD40L deficiency, WAS, XLA, and NEMO syndrome.[638] Consideration should also be given to the known single-gene defects that can cause classical or functional NK deficiency, including *MCM4*,[217] *GATA2* (see *SS 164*),[640] and IgG Fc receptor (FcγR) 3A *(FCGR3A)*.[216]

Summary statement 192. Patients with a selective functional NK cell defect should be screened for mutations affecting CD16 by using flow cytometry with the anti-CD16 clone B73.1. (C)

CD16A encoded by the *FCGR3A* gene is an IgG receptor used by NK cells to mediate antibody-dependent cell-mediated cytotoxicity. A mutation in the *FCGR3A* gene results in impaired NK cell cytotoxicity and susceptibility to recurrent or severe herpesvirus infections.[216] Standard evaluations of B- and T-cell function are normal in these patients. The number of NK cells in an affected patient can be low or normal, but spontaneous NK cell cytotoxicity is reduced.

When severe or recurrent infection caused by herpesvirus, papillomavirus, or both is encountered in patients with decreased NK cell function in the absence of other defined immunodeficiencies, NK cells should be specifically evaluated by means of flow cytometry with the anti-CD16 clone B73.1 alone because of failure of the most commonly used reagents to detect the mutated receptor.[216] This assay appears to be sensitive but of indeterminate specificity, and thus NK cell functional evaluation and CD16 gene sequencing are important when the diagnosis is being formally entertained.[216]

Summary statement 193. Patients with growth retardation, adrenal insufficiency, and NK cell deficiency should be tested for the *MCM4* mutation. (C)

Three consanguineous Irish cohorts have been identified with a syndrome of growth retardation, adrenal insufficiency, and NK cell deficiency resulting from homozygous mutations in the *MCM4* gene.[217,641] Not all affected patients were affected by all 3 parts of this clinical triad. There was a susceptibility to EBV infection and other herpesviruses, as well as complications of other viral infections. A majority of affected patients had very low (<1%) NK cell counts, defining this syndrome as a "classical" NK cell deficiency. Interestingly, patients had an abundance of $CD56^{bright}$ NK cells, which represent a developmental precursor to the major $CD56^{dim}$ NK cell subset.[642] $CD56^{bright}$ NK cells typically constitute approximately 5% of total NK cells, and in the patients studied, they approached 50%.[217] It is presently unclear as to the mechanism linking this gene defect to the immunologic phenotype, and the known role of the MCM complex (unwinding of chromosomal DNA) does not provide particular clues. It is also presently unclear as to what the specificity and sensitivity of evaluating patients for $CD56^{bright}$ NK cells will be when considering the clinical diagnosis.

Summary statement 194. Patients with selective NK cell defects might benefit from specific chemoprophylaxis against herpesviruses and vaccination against HPV. (C)

Varicella-zoster virus, HSV, or CMV infections associated with NK cell deficiencies are reduced by appropriate chemoprophylaxis. This is considered the standard of care in patients rendered immunocompromised because of HSCT or solid-organ transplantation. Such therapy should be considered in patients with primary immunodeficiency and susceptibility to herpesvirus

infection.[216,637,638,640] Should disease occur while a patient is receiving prophylaxis, antiviral sensitivity testing should be performed to rule out resistance. In addition to receiving chemoprophylaxis for herpesviruses, patients with identifiable NK cell defects should be vaccinated with HPV vaccine at the first opportunity, given the susceptibility to this viral family in patients with reduced NK cell functions. Although HPV vaccines only include selected HPV types, additional protection against these especially virulent viruses is of at least theoretic value, particularly because adaptive immunity appears largely intact in these patients.

Varicella-zoster virus vaccines are viable and could, at least theoretically, cause disease in patients with severe NK cell deficiency. There are insufficient data to determine the safety of these vaccines for these patients. Therefore they should not be administered in this setting.

Isolated congenital asplenia.

Summary statement 195. Patients presenting with a family history of asplenia or sepsis caused by encapsulated bacteria, most frequently *S pneumoniae*, should be evaluated for congenital asplenia.

Isolated congenital asplenia (ICA) has been recognized as a hereditary condition for some time. It is often a silent disease until presentation with sudden invasive disease, most frequently as pneumococcal sepsis. This contrasts with asplenia syndrome (Ivemark syndrome), which presents primarily with symptomatic congenital heart disease in early infancy. Initial presentation of ICA can be at any age and is not limited to childhood. Diagnosis is made by means of ultrasound of the abdomen and examination for Howell-Jolly bodies on peripheral blood smear.[643]

The inheritance of ICA is generally autosomal dominant within families, although a significant portion of cases arise spontaneously. Recently, ribosomal protein SA (RPSA) haploinsufficiency has been identified as the first genetic mutation underlying more than half of the ICA cases in the study cohort. Clinical penetrance in the affected kindreds was complete. *RPSA* encodes a component of the ribosome.[644]

Summary statement 196. Patients with ICA should be started immediately on antibiotic prophylaxis and receive vaccination for encapsulated organisms.

Antibiotic coverage should be initiated immediately on diagnosis, with coverage for encapsulated bacteria (see SS 16 and Table E7). Prophylaxis should be continued at least until the age of 5 years in fully vaccinated children. Some experts recommend lifelong prophylaxis, although the optimal duration of antibiotic prophylaxis is unknown. *S pneumoniae* accounts for more than half of invasive infections in patients with ICA. Both the conjugated 13-valent vaccine (PCV13) and polysaccharide 23-valent pneumococcal vaccine (PPV23) should be administered. For patients younger than 2 years, PCV13 should be given, followed by PPV23 at age 2 years. For patients older than 2 years, PCV13 should be given as per usual vaccination schedules, followed by PPV23 immunization 6 to 8 weeks after the final dose of PCV13. Vaccination for *HIB* and *N meningitidis* is also recommended.[645]

Autoinflammatory disorders

Autoinflammatory disorders are a group of syndromes characterized by recurrent bouts of inflammation without features of autoimmunity (ie, autoantibodies or autoreactive T cells). These disorders are also often referred to as periodic fever syndromes, although this designation is not entirely accurate because it is possible to have an autoinflammatory disorder without fevers and the fevers tend to be more episodic than periodic. The general approach to the evaluation and diagnosis of autoinflammatory disorders is summarized in Fig E6.

Summary statement 197. Patients with episodic fever should be screened for other PIDDs, autoimmune disease, or malignancy. (C)

When presented with a patient with recurrent bouts of fever or signs of inflammation, such as an increased erythrocyte sedimentation rate (ESR) or CRP level, it is first necessary to evaluate for other causes of recurrent or continual inflammation. Autoinflammatory disorders are very rare, and organ damage caused by these disorders typically takes some time to develop. Thus it is essential to rule out other causes of recurrent fevers or recurrent/ongoing inflammation.

A careful evaluation for malignancies, recurrent infections, and autoimmunity should first be done before a workup of autoinflammatory disorders is undertaken. Abnormal CBCs or physical signs of malignancy (eg, mass) should be investigated. Careful assessment for infections is necessary, and if episodes are associated with infections, a workup for immune deficiency should be undertaken. Rash, arthritis, uveitis, serositis, nephritis, diarrhea with weight loss, or other organ involvement should point to a possible autoimmune cause. If these workups are nonrevealing, measurement of inflammatory markers can be helpful. Measurements of ESR and CRP levels are relatively nonspecific tests, but these should be done and repeated to determine whether the inflammation is due to an ongoing process or whether the process is truly episodic. Although a consistently increased ESR or CRP level can be seen in patients with autoinflammatory disorders, this finding should direct the workup toward a malignant or autoimmune process that is not apparent on physical examination (eg, lymphoma or vasculitis). Note that nonspecific autoantibodies (eg, antinuclear antibody, rheumatoid factor, anti–double-stranded DNA, anti-phospholipid antibody, and anti-neutrophil cytoplasmic antibody) can occasionally be persistently or transiently present at mildly or moderately increased levels, especially in patients with noninflammasome defects. If the clinical presentation has features strongly suggestive of an autoinflammatory component (eg, early onset), such a diagnosis should still be entertained.

Cryopyrin-associated periodic syndromes.

Summary statement 198. Cryopyrin-associated periodic syndrome (CAPS) should be suspected in patients presenting with bouts of systemic inflammation resulting in rash, fevers, arthritis, neurological deficits, and amyloidosis. (C)

Neonatal-onset multisystem inflammatory disorder (NOMID), also called chronic infantile neurocutaneous articular (CINCA) syndrome; Muckle-Wells syndrome (MWS); and familial cold autoinflammatory syndrome (FCAS) 1 represent a spectrum of diseases characterized by recurrent bouts of inflammation caused by mutations in the NLR family, pyrin domain containing 3 *(NLRP3)* gene.[646-649] All forms are inherited in an autosomal dominant manner, and onset of disease typically occurs early in life. In terms of severity of symptoms, FCAS is the mildest and NOMID/CINCA syndrome is the most severe. A positive family history can be helpful, but *de novo* mutations do occur in patients with the most severe symptoms (ie, NOMID/CINCA syndrome). In addition, there are rare reports of reduced penetrance, with

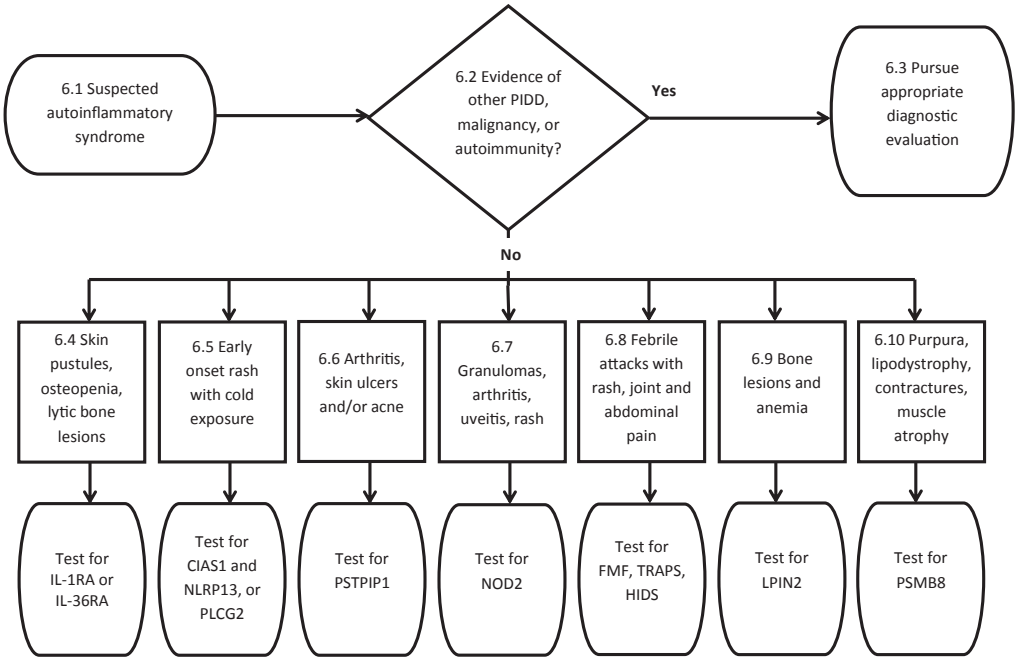

FIG E6. Diagnosis of autoinflammatory syndromes. *6.1*, A patient is suspected to have an autoinflammatory (episodic fever) syndrome. *6.2*, It is first necessary to evaluate for other causes of recurrent or continual inflammation, such as other PIDDs, autoimmune disease, or malignancy. *6.3*, If alternative (nonautoinflammatory) diagnoses are now suspected as a result of further clinical study, then these should be pursued and ruled out before additional investigation of autoinflammatory conditions is undertaken. Note that nonspecific autoantibodies (eg, anti-nuclear antibody, rheumatoid factor, anti–double-stranded DNA, antiphospholipid antibody, and anti-neutrophil cytoplasmic antibody) can be persistently or transiently present at mildly or moderately increased levels, especially in the noninflammasome defects. If the clinical presentation has features strongly suggestive of an autoinflammatory component (eg, very early onset), such a diagnosis should still be entertained. *6.4*, Early-onset severe pustular skin disease is seen in patients with DIRA and DITRA. DIRA is also associated with bone involvement with osteopenia and lytic bone lesions. Sequence analysis for *IL1RN* and *IL36RN*, as well as chromosomal analysis for deletions in the *IL1* locus, should be investigated. *6.5*, If an evanescent nonurticarial rash is present with cold exposure, genetic testing of *CIAS1* should be done to test for FCAS, as well as *NLRP13*; if the rash is a cold-induced urticarial rash, the patient should be tested for mutation of *PLCG2* (PLAID). *6.6*, If fevers are associated with pyogenic arthritis and ulcerative skin lesions (ie, pyoderma gangrenosum), cystic acne, or both, mutational analysis of the *PSTPIP1* gene should be evaluated for PAPA syndrome. *6.7*, If granulomatous disease (rash, uveitis, or arthritis) is apparent, mutational analysis of *NOD2* should be considered for Blau syndrome. *6.8*, If febrile attacks are associated with abdominal or joint pains or rash, mutation analysis of pyrin, TNF receptor I, and MVK should be undertaken. *6.9*, If bone lesions and dyserythropoietic anemia are associated with fevers, analysis of *LPIN2* for Majeed syndrome should be considered. *6.10*, If the presentation consists of purpura with 1 or more of lipodystrophy, contractures, or muscle atrophy, a defect in *PSMB8* should be investigated.

patients carrying the mutation not expressing the typical clinical phenotype.

The mildest form of CAPS is FCAS1, which typically presents with fever, rash, headache, conjunctivitis, and arthralgias, predominantly after cold exposure.[646-649] Unlike cold-induced urticaria (a form of physical urticaria), localized cold challenge (ie, ice cube test) will not precipitate an attack in patients with FCAS1 because full-body cold exposure is necessary. The rash can be described as nonurticarial erythematous papules or plaques that typically resolve within 24 hours. The rash lacks characteristic features of urticaria (eg, angioedema) and signs of mast cell proliferation or degranulation and is caused by neutrophilic infiltrates. Neurological symptoms and amyloidosis are rare.

Mutations in the *NLRP12* gene give rise to the clinical phenotype of fever, rash, arthralgias, myalgias, and headache on generalized cold exposure.[649] This disease, termed FCAS type 2 (FCAS2) presents within the first year of life, with attacks occurring at least monthly. Headache, abdominal pain, lymphadenopathy, and aphthous ulcers can also been seen, whereas sensorineural hearing loss and other CNS manifestations occurred variably.

Patients with MWS will present very early in life with fevers, rash, and articular symptoms that are not typically precipitated by cold exposure.[646-648] Unlike FCAS1, chronic meningitis occurs with papilledema and sensorineural hearing loss, articular symptoms are more severe, and amyloidosis occurs over time.

NOMID/CINCA syndrome is the most severe form of CAPS, presenting at birth with the most rapid progression.[646-648] All affected patients exhibit a rash, with the majority presenting at birth. CNS manifestations, including aseptic meningitis, headache, cerebral atrophy, uveitis, hearing loss, and mental retardation, occur variably. Severely affected infants can present with failure to thrive with poor growth. The chronic arthropathy in patients with NOMID is severe and deforming because of recurrent bouts of inflammation leading to epiphyseal and patellar

overgrowth. Historically, approximately 20% of affected infants died before adulthood. However, effective therapies might be reducing mortality.

Summary statement 199. Patients suspected of having CAPS or FCAS2 should be screened for persistent systemic signs of inflammation in the absence of demonstrable infection, autoimmune disease, or malignancy. (C)

FCAS1, MWS, and NOMID present with a robust acute-phase response, with leukocytosis, neutrophilia, anemia, and thrombocytosis.[646-648] ESR and CRP levels are typically persistently increased. Infants or young children with a characteristic rash and laboratory markers demonstrating inflammation should be evaluated for CAPS once infectious and autoimmune causes have been ruled out. Infants presenting with these symptoms should be initially evaluated for sepsis, neonatal infections, and congenital (ie, toxoplasma, rubella, cytomegalovirus, and herpes simplex virus 2) infections. Systemic-onset juvenile idiopathic arthritis can present in the first year of life with a similar rash, fevers, and arthritis, although systemic-onset juvenile idiopathic arthritis rarely presents before 6 months of age. Sequence analysis of the *NLRP3* gene will confirm the diagnosis, although waiting for this result might delay effective treatment. A trial of IL-1 blockade with anakinra, rilonacept, or canakinumab can be tried and can help aid in the diagnosis.

Summary statement 200. IL-1 inhibitors (anakinra, rilonacept, and canakinumab) should be given to all patients with CAPS and might be effective for FCAS2. (B)

Several treatments have been proposed for CAPS with variable effectiveness before the discovery of IL-1–inhibitory biologics. High-dose steroids, colchicine, and androgens have been tried with mild-to-moderate success. IL-1 inhibitors were shown to induce rapid and sustained response in patients with CAPS.[650-653] Subsequently, rilonacept (IL-1R–IgG Fc fusion protein) and canakinumab (anti–IL-1β mAb) have been shown to be effective.[651-655] Laboratory abnormalities (ESR, CRP, and leukocytosis) typically normalize in days, and the rash responds rapidly. Importantly, IL-1 blockade improves long-term morbidity, such as hearing loss, joint deformity, and amyloidosis.[650,656]

Limiting cold exposure appears effective to prevent attacks of FCAS1 and FCAS2. Low-dose steroids, antihistamines, or NSAIDs were reported to be moderately effective in some of the families with FCAS2.[649] Anakinra was effective in 1 patient with FCAS2, although the response waned over time.[657]

Deficiency of IL-1 receptor antagonist.

Summary statement 201. Patients presenting at or soon after birth with a pustular rash, joint swelling, and profound osteopenia and bone lesions should be suspected of having deficiency of IL-1 receptor antagonist (DIRA). (C)

DIRA is a severe autoinflammatory disorder with the predominant features of cutaneous pustulosis and bone involvement.[658,659] Most infants presented within the first 2 weeks of life, several exhibited prenatal distress, and most were born mildly premature (at 33-38 weeks of gestational age). Several other features observed include respiratory distress, aphthous ulcers, hepatomegaly, and failure to thrive. Bone changes include diffuse osteopenia, multiple osteolytic lesions, rib widening, and epiphyseal expansion somewhat similar to what is seen in patients with NOMID. Approximately a third of infants died from multiorgan failure.[658]

Laboratory abnormalities in patients with DIRA typically reflect an acute-phase response with increased ESR and CRP levels, leukocytosis, anemia, and thrombocytosis. Infants born with DIRA exhibit a persistently increased acute-phase response from birth.[658,659] Monocytes stimulated with IL-1β exhibited increased production of inflammatory cytokines caused by the lack of inhibition of IL-1 receptor antagonist.[658]

Summary statement 202. Anakinra or other IL-1 antagonists should be used therapeutically and can also be helpful in the diagnosis of DIRA. (C)

Numerous anti-inflammatory and immunosuppressive medications have been tried in patients with DIRA with limited efficacy.[658] Corticosteroid therapy reduced the length of the episodes but did not affect frequency, nor did it prevent the complications of the disease. Three of the original 10 infants reported died despite treatment with prednisone and NSAIDs. Anakinra treatment results in a rapid and sustained response, with correction of laboratory abnormalities, resolution of rash, and healing of bone lesions in all but 1 affected patient.[658,659]

Blau syndrome.

Summary statement 203. Blau syndrome should be suspected in patients presenting with noncaseating granulomas in the skin, eyes, and joints. (C)

Blau syndrome was originally described as a granulomatous disease affecting the skin, joints, and uveal tract.[660,661] The original description affected 11 family members and was inherited in an autosomal dominant manner. Nucleotide-binding oligomerization domain–containing protein 2 *(NOD2)/CARD15* mutations in patients with Blau syndrome result in spontaneous activation of the NOD2 protein, activation of NF-κB, and production of proinflammatory cytokines.

Joint involvement in patients with Blau syndrome presents with a boggy synovitis and tenosynovitis, with cystic swelling of the large joints, particularly the wrists and ankles.[660,661] Unlike rheumatoid arthritis, bone resorption is not a prominent feature, although this can be seen in the proximal interphalangeal joints. Campylodactyly (interphalangeal contractures) is common. The rash seen in patients with Blau syndrome is described as erythematous maculopapular, lichenoid papules, or similar to erythema nodosum. Biopsy specimens show noncaseating granulomas. Less frequent involvement includes granulomatous liver disease, cranial neuropathies, large-vessel vasculitis, and interstitial lung disease. Unlike sarcoidosis, respiratory involvement is rare in patients with Blau syndrome.

Results of laboratory studies in patients with Blau syndrome are typically normal. Antinuclear antibodies are either negative or of low titer, and rheumatoid factor is typically negative.[660,661] Angiotensin-converting enzyme levels can be normal or increased, and hypergammaglobulinemia can be seen. ESRs are typically normal but can be increased.

Summary statement 204. Corticosteroids should be the mainstay of treatment for patients with Blau syndrome. (C)

Most patients with Blau syndrome have been treated with corticosteroids.[660,661] Limited reports have demonstrated the effectiveness of infliximab[662] and thalidomide.[663] Anakinra was reported to be effective in 1 patient, although this was not confirmed in a second study.[664,665]

Deficiency of IL-36 receptor antagonist.

Summary statement 205. Patients presenting with generalized pustular psoriasis should be suspected of having deficiency of IL-36 receptor antagonist (DITRA). (C)

A syndrome of generalized pustular psoriasis with autosomal recessive inheritance is caused by mutations in the gene encoding

the IL-36 receptor antagonist (IL-36ra, which is related to IL-1ra).[666,667] DITRA usually presents in the first 2 decades of life with recurrent pustular rashes. The age of onset varied greatly in patients with this disorder, from several weeks of life to young adulthood. All affected patients exhibited episodes characterized by high-grade fevers and erythematous skin eruption, which evolves into pustules similar to those seen in patients with DIRA.[658,659] A variety of other symptoms were described, including geographic tongue, nail dystrophy, arthritis, and cholangitis.[666,667]

DITRA is episodic, with a variety of triggers. Infectious triggers are associated with disease flares.[666,667] Viral and bacterial infections were the most common trigger, followed by withdrawal of retinoids, menstruation, and pregnancy. The patients with episodes with infections after pregnancy were given a diagnosis of impetigo herpetiformis, an uncommon complication of pregnancy.

Laboratory evaluation during attacks in patients with DITRA demonstrated leukocytosis and increased CRP levels. During attacks, increased white blood cell counts, ESRs, and CRP levels are detected. It was not reported whether these values normalize between episodes. It was also not reported whether affected patients exhibited laboratory evidence of autoimmunity.[666,667]

Summary statement 206. Retinoids should be the mainstay of treatment for DITRA, although steroids and IL-1 inhibitors have also been used. (C)

The majority of patients with this disorder were treated with acitretin, an oral retinoid, which was beneficial because withdrawal of the medication was associated with recurrence of symptoms.[666] Some patients were also treated with oral and topical steroids, cyclosporine, methotrexate, and TNF antagonists, with variable results.[667]

Familial Mediterranean fever and TNF receptor–associated periodic syndrome.

Summary statement 207. Familial Mediterranean fever (FMF) or TNF receptor–associated periodic syndrome (TRAPS) should be suspected in patients presenting with recurrent and often prolonged fever attacks associated with serosal, cutaneous, and synovial manifestations. (C)

FMF is the most common Mendelian autoinflammatory syndrome.[646,648,668,669] FMF has autosomal recessive inheritance and is caused by mutations in the *MEFV* (Mediterranean fever) gene, which encodes the pyrin/marenostrin protein. Although FMF is considered a recessive disorder, a substantial percentage of patients with clinical FMF have only 1 demonstrable mutation in *MEFV*.

FMF occurs most frequently among Sephardic Jewish, Armenian, and Turkish populations and, to a lesser extent, in Italian, Ashkenazi Jewish, and Arab populations. Mediterranean and Middle Eastern populations have a higher carrier frequency of different mutations, suggesting a heterozygous advantage for pathogens endemic to this region.[670]

Most patients have onset by age 20 years, and there is a slight male predominance.[646,648,668,669] Attacks are variable in severity and episodic, lasting 1 to 3 days and manifesting with inflammation of the peritoneum, pleura, joints, and/or skin. Between attacks, patient are generally symptom free. Fever is often the only symptom of FMF in children, but over time, other symptoms generally develop. The mechanism that invokes an attack is not well understood, although reported triggers include stress and menstruation. Abdominal symptoms include distention, rigidity, and severe pain, which can mimic acute appendicitis. Joint symptoms, including arthralgia and arthritis, are common and can be a presenting sign in children. Synovial aspirates from joint effusions are sterile, with a predominance of neutrophils (>100,000/mm^3). Muscle pain in the lower extremities after exercise is a common finding. Classically, an erysipeloid erythematous rash can occur on the lower legs as an isolated sign or in conjunction with other manifestations.[671]

Amyloidosis is the most severe complication of FMF. The increase in serum amyloid A (SAA) levels depends on the genetic and environmental susceptibility factors, such as the specific mutation, country of origin, male sex, SAA genotype (SAA1 α/α), positive family history of amyloidosis, and compliance with colchicine therapy.[646,648,668,669]

TRAPS is an autosomal dominant autoinflammatory disease associated with heterozygous missense mutations in the extracellular domain of the gene encoding TNF receptor 1. Patients with TRAPS exhibit symptomatology very similar to that of FMF. During a febrile flare, patients with TRAPS can exhibit severe abdominal pain, pleurisy, migratory rash, myalgia from inflammation of the underlying fascia, arthralgia, and/or periorbital edema.[646,648,668,669] Febrile flares are longer lasting than in patients with FMF and are generally unprovoked, although stress, exercise, trauma, and hormonal changes are reported triggers.[672]

Summary statement 208. Patients suspected of having FMF or TRAPS should be screened for persistent systemic signs of inflammation in the absence of demonstrable infection or autoimmune disease. (C)

Increased serum levels of CRP, ESR, SAA, and complement, often with leukocytosis and thrombocytosis, are evident during attacks. Chronic increased SAA levels can result in systemic amyloidosis and life-threatening organ damage. Sustained SAA levels of greater than 10 mg/L are associated with development of amyloidosis.[646,648,668,669]

Summary statement 209. Colchicine should be the mainstay of therapy for FMF. (B)

Daily use of colchicine results in symptomatic relief in 95% of patients with FMF, with nearly 75% achieving near-complete remission, thus significantly reducing the risk of amyloidosis.[673] The recommended maintenance adult dose is 1.2 to 1.8 mg/d orally, which can be adjusted for body weight in younger patients. Abdominal pain and diarrhea are the most common side effects, and gradually increasing the dose can help this. Colchicine can also cause lactose intolerance. More recently, IL-1 antagonists have been used successfully in some patients unresponsive to colchicine.[674-676]

Summary statement 210. Corticosteroids, TNF blockers, and IL-1 antagonists should be used in therapy for TRAPS. (B)

For infrequent attacks, short courses of prednisone at the time of a flare might be effective. For more severe disease, etanercept reduces symptoms of inflammation in a dose-dependent manner, but failure of sustained efficacy and lack of normalization of acute-phase reactants has been reported.[677] However, infliximab can cause a paradoxical inflammatory response.[678] Beneficial effects of anakinra have been noted.[651-653,679] Response to anti–IL-6 receptor antibody (tocilizumab) has also been encouraging.[680]

Mevalonate kinase deficiency (hyper-IgD syndrome).

Summary statement 211. Hyper-IgD syndrome (HIDS) should be suspected in patients presenting with fevers with lymphadenopathy, abdominal pain, diarrhea, vomiting, arthralgia, rash, aphthous ulcers, and splenomegaly. (C)

Mevalonate kinase (MVK) is an enzyme involved in the biosynthesis of cholesterol and isoprenoids. Mutations in the *MVK* gene are associated with a spectrum of clinical phenotypes ranging from HIDS and fevers to mevalonic aciduria based on the level of MVK enzyme activity.[681-683] Patients with HIDS have low but detectable enzyme activity and manifest with lifelong bouts of systemic inflammation. At an early age, patients present with recurrent fever spikes lasting 4 to 6 days accompanied by lymphadenopathy, abdominal pain, diarrhea, vomiting, arthralgia, rash, aphthous ulcers, and splenomegaly.[684] Nonmigratory painful erythematous macules can develop during an attack. Patients with mevalonic aciduria have nondetectable enzyme activity and severe symptomatology, including psychomotor retardation, facial dysmorphism, and failure to thrive.[681] MVK loses enzymatic activity in patients with HIDS at increased temperatures, which might provide a rationale for immunizations, infection, trauma, and surgery as noted precipitants of an attack. *Ex vivo* studies indicate a central role of IL-1β in the pathogenesis of disease.[681-683]

Summary statement 212. Patients with suspected HIDS should be screened by measuring serum IgD and urine mevalonic acid levels. (C)

Between attacks, increased serum IgD levels can be detected and are generally accompanied by increased IgA levels. However, in one report 22% of patients with HIDS had normal IgD levels, and therefore a normal result cannot exclude the diagnosis.[684] The clinical relevance and predictive value of IgD has been questioned in several studies. Increased levels of mevalonic acid can be detected in urine during attacks.[681-683]

HIDS occurs primarily in patients of European ancestry; approximately half of the reported cases are in patients of Dutch ancestry.[681-683] Clinical diagnostic criteria with high sensitivity and justifying genetic testing includes early onset of disease and joint pain during an attack, which lasts less than 14 days.[685] Other suggestive criteria include increased serum IgD levels (>100 IU/L) and the first recorded attack occurring after childhood vaccinations.[684] Definitive diagnosis might require genetic testing. Clinical criteria to warrant genetic tests include early-onset disease, lymphadenopathy, skin rash, transient joint pain, and white ethnic background. Genetic screening for HIDS should target V377I, the most frequent *MVK* mutation, with a carrier frequency of 1 in 65 in Dutch populations.

Summary statement 213. Therapeutic trials of corticosteroids and inflammatory cytokine inhibitors should be undertaken for patients with HIDS. (C)

Corticosteroid, when administered in high doses at the first sign of an attack, decrease the severity and duration of symptoms in some patients.[684] Most reports indicate a significant beneficial effect from inhibitors of TNF-α and IL-1β.[686] Other agents tried with limited benefit include IVIG, colchicine, cyclosporine, and cholesterol inhibitors, such as simvastatin.[687]

Pyogenic arthritis, pyoderma gangrenosum, and acne.

Summary statement 214. Pyogenic arthritis, pyoderma gangrenosum, and acne (PAPA) syndrome should be suspected in patients presenting with the characteristic recurrent episodes of severe joint and skin inflammation. (C)

PAPA syndrome is caused by gain-of-function mutations in the gene encoding proline-serine-threonine phosphatase interacting protein 1 (PSTPIP1).[688,689] PAPA syndrome is a rare autosomal dominant autoinflammatory syndrome that typically presents in early childhood with recurrent sterile erosive arthritis that sometimes results in significant joint destruction. By the time of puberty, debilitating ulcerative skin lesions similar to pyoderma gangrenosum develop, often on the lower extremities, and cystic acne occurs, which persists into adulthood. Culture of skin lesions and joints are sterile.

Summary statement 215. Treatment of patients with PAPA syndrome with cytokine inhibitors should be attempted. (C)

The arthritis can respond to corticosteroid therapy; however, the associated adverse effects often limit their use. Consistent with the evidence for increased inflammatory mediators, there are several reports of successful treatment with IL-1 receptor antagonists (anakinra)[690,691] and the TNF-α inhibitors etanercept[692] and infliximab.[693] There are reports that IL-1 blockade might be more beneficial for the treatment of joint manifestations[691] and TNF inhibition for cutaneous symptoms.[694] However, to date, there is no consistently successful treatment for this syndrome.

Proteasome catalytic subunit β type 8 (*PSMB8* gene) and transmembrane protein 173 (TMEM173; stimulator of interferon) defects.

Summary statement 216. These disorders should be suspected in patients with early-onset fevers, systemic inflammation, and purpuric plaques caused by cutaneous leukocytoclastic vasculitis. (C)

Additional features of *PSMB8* defects include lipodystrophy, contractures, and muscle atrophy (including cardiomyopathy); periorbital edema; hepatomegaly; lymphadenopathy; and failure to thrive. The disorder has several eponyms, including Nakajo-Nishimura syndrome, Japanese autoinflammatory syndrome with lipodystrophy,[695] joint contractures, muscle atrophy, panniculitis-induced lipodystrophy syndrome,[696,697] and chronic atypical neutrophilic dermatitis with lipodystrophy and increased temperatures.[698] Laboratory signs of *PSMB8* mutations include anemia and increased levels of inflammatory markers. All acute-phase reactants are increased in these patients. The level of IFN-γ–induced protein is also high.[699] Biopsy specimens of the purpuric skin plaques show dermal neutrophilic infiltrates.

The defects of TMEM173 described to date are expressed as dominant gain-of-function mutations in heterozygous patients.[700,701] In addition to systemic inflammation and cutaneous vasculitis (often with nail dystrophy), these patients can present with interstitial lung disease with fibrosis and mediastinal adenopathy. Some patients can also have arthritis, muscle atrophy, or both.

Summary statement 217. A variety of anti-inflammatory modalities should be tried in patients with *PSMB8* or *TMEM173* defects.

Treatment is primarily anti-inflammatory and can include steroids; inhibitors of TNF-α, IL-6, and IL-1; or both. These have shown variable responses based on small sample sizes. More effective targeted therapy, such as interferon signaling blockade, is worthy of investigation.[699] Standard anti-inflammatory therapies, such as NSAIDs, corticosteroids, disease-modifying antirheumatic drugs, and biologics, have had disappointing results in the therapy of this disorder.[701] *In vitro* data suggest that Janus kinase inhibitors might be a promising therapeutic modality.

Chronic recurrent multifocal osteomyelitis dyserythropoietic anemia (or Majeed) syndrome.

Summary statement 218. Majeed syndrome should be suspected in patients presenting in early childhood with chronic recurrent multifocal osteomyelitis (CRMO), congenital dyserythropoietic anemia, and dermatosis. (C)

CRMO can occur sporadically or as an autosomal recessive autoinflammatory syndrome (Majeed syndrome) and is caused by

mutations in the lipin 2 *(LPIN2)* gene.[702] The clinical features of Majeed syndrome consist of early-onset relapsing CRMO with severe episodic bouts of bone pain, swelling, and often associated fever. Lytic lesions and sclerosis most commonly affecting metaphyses of the long bones can be seen on plain radiographs. Congenital dyserythropoietic anemia is common and severe, often requiring frequent transfusions. Neutrophilic dermatosis, also called Sweet syndrome, can also be a presenting feature. Failure to thrive and hepatomegaly have also been reported in most patients. Increased ESR is a clinical marker of disease.[702]

Summary statement 219. A variety of anti-inflammatory modalities should be tried in patients with Majeed syndrome. (C)

Treatment with oral steroids and NSAIDs are variably effective.[702] A recent report indicated the efficacy of IL-1 inhibitors used in 2 patients, highlighting the involvement of autoinflammatory pathways.[703]

Other autoinflammatory syndromes.

Summary statement 220. Patients presenting with features of H syndrome, including cardiac anomalies, cutaneous hyperpigmentation, hypertrichosis, hepatosplenomegaly, short status, and contractures of the fingers and toes, should be screened for sensorineural hearing loss and insulin-dependent diabetes.

Mutations of the gene encoding solute carrier family 29 (equilibrative nucleoside transporter), member 3 (SLC29A3) lead to histiocytic infiltration of many organs.[704,705] The spectrum of disease includes H syndrome (cutaneous hyperpigmentation, hypertrichosis, hepatosplenomegaly, heart anomalies, early sensorineural hearing loss, hypogonadism, short stature, hallux valgus, fixed flexion contractures of the toe joints and proximal interphalangeal joints), pigmented hypertrichosis with insulin-dependent diabetes mellitus, familial histiocytosis syndrome (Faisalabad histiocytosis), and sinus histiocytosis with massive lymphadenopathy (Rosai-Dorfman disease).[706] It can present with recurrent febrile episodes with systemic autoinflammation.[707] Onset is in childhood with autosomal recessive inheritance, and prenatal molecular diagnosis can be performed on chorionic villi and amniotic cells. Management is primarily supportive, but early diagnosis of sensorineural hearing loss and diabetes mellitus is important.

Summary statement 221. *CARD14* mutations should be considered in patients with generalized pustular psoriasis and familial pityriasis rubra pilari. (C)

CARD14 gain-of-function mutations can lead to the sporadic occurrence of typical plaques, generalized pustular psoriasis, and familial pityriasis rubra pilari.[708] Management of moderate-to-severe psoriasis includes systemic immunosuppression with methotrexate, cyclosporine, TNF inhibitors, and anti–IL-17 and anti–IL-23 mAbs.

Summary statement 222. A diagnosis of cherubism should be considered in children presenting with bilateral, symmetric, painless enlargement of the cheeks and mandible. (C)

Cherubism is a rare bone dysplasia that usually presents between the ages of 2 and 7 years, although most cases regress spontaneously at puberty.[709,710] Rarely, bone lesions and facial changes will progress into adulthood and require corrective surgery. The facial changes associated with cherubism usually begin between the ages of 2 and 4 years, with swelling of the jaw and symmetric cervical and submandibular lymphadenopathy. Fibro-osseous masses displace the ocular globe and result in the characteristic upward gaze. Less commonly, the disease can affect dental development (including early loss of primary teeth and abnormal secondary dental eruption), result in cystic lesions in the ribs, or cause upper airway obstruction secondary to displacement of the tongue. Cherubism can be mistaken for Noonan syndrome when the clinical findings are limited to symmetric mandibular enlargement.[709,710]

The majority of cases of cherubism are due to germline mutations in SH3-domain binding protein 2 *(SH3BP2)*. *SH3BP2* is expressed in osteoclasts and is an important regulator of bone resorption and remodeling.[710] Gene sequencing for *SH3BP2* is available commercially, and identification of mutation can confirm the diagnosis.

Management of cherubism is largely expectant, with surgical intervention for severe cases or those with airway obstruction.[709] Radiographic panoramic imaging every 2 to 5 years is useful after the disease stabilized. The bone lesions might not regress until early adulthood and in rare cases can continue to expand.

Summary statement 223. Patients with inherited atypical cold urticaria should be studied for phospholipase Cγ2–associated antibody deficiency and immune dysregulation (PLAID). (C)

Patients with PLAID have cold-induced urticaria that flares with evaporation and rewarming.[711-713] Urticaria tends to be localized, although there can be oropharyngeal edema with ingestion of cold food or drink. Recently, patients with PLAID have also been described with recurrent infections, low IgA and IgM levels, decreased circulating B-cell numbers, low NK cell numbers, and autoantibody production. Many patients will have impaired neutrophil chemotaxis *in vitro*.[714] Familial cases have also been affected with bullous skin lesions.[711-713]

Summary statement 224. Children with early-onset medium-vessel vasculitis (polyarteritis nodosa) should be screened for mutations of *ADA2*. (C)

Several patients exhibiting childhood (<5 years of age)–onset chronic fevers with vasculopathy (some consistent with polyarteritis nodosa) have been found to have recessive mutations in *ADA2*.[715-717] Additional features of these patients include myalgia/arthralgia, livedo rash, cerebral, cardiac, and visceral aneurysms and infarcts and panniculitis. Biopsy specimens show medium- and small-vessel leukocytoclastic vasculitis. Some patients had low levels of anti-nuclear antibody, and several had low serum IgM levels. Authors of these reports suggest trials of treatment with anti-TNF agents or replacement with exogenous ADA2 in plasma.

At least 1 patient has presented with more severe immunodeficiency with pancytopenia, hypogammaglobulinemia, poor vaccine response, and diffuse lymphadenopathy and hepatosplenomegaly.[716] This patient was successfully treated with HSCT.

Summary statement 225. Children with early-onset (<4 years of age) inflammatory bowel disease should be screened for mutations of *IL10* or its receptor. (C)

Mutations of *IL10* or either chain of the IL-10 receptor (*IL10RA* or *IL10RB*) account for 15% to 45% of cases of inflammatory bowel disease with onset before 4 years of age.[718,719] The histologic pattern is that of Crohn colitis. Patients with *IL10* pathway defects have more severe disease in comparison with those who do not. *IL10* pathway defects have a very high rate of perianal fistulas, more severe inflammation, and generally poor response to standard therapies. At least 1 patient was successfully treated with HSCT.[719]

Summary statement 226. Periodic fever with aphthous stomatitis, pharyngitis, and adenitis (PFAPA) should be suspected in

young children presenting with the characteristic clinical features. (C)

PFAPA syndrome is the most common autoinflammatory condition.[720-722] A relatively benign, self-limiting, and sporadic autoinflammatory disease, PFAPA primarily affects children with onset usually before age 5 years. Febrile flares last an average of 5 days and occur with precise periodicity approximately every 28 days. Clinical manifestations are characterized by a prodrome of cardinal features, including fatigue, chills, and oral ulcers on the lips and buccal mucosa, followed by cervical adenitis, pharyngitis, and high fever. Consistent with other autoinflammatory syndromes, white blood cell counts and acute-phase reactant and inflammatory cytokine (INF-γ, IL-6, and TNF-α) levels are increased during febrile episodes.[723] There is no specific diagnostic laboratory test for PFAPA, and a genetic basis has not been determined.

Summary statement 227. Initial management of PFAPA syndrome should be with oral glucocorticoids during acute episodes. (C)

Unlike other autoinflammatory syndromes, the use of a single dose of 1 to 2 mg/kg oral prednisone given immediately at the onset of symptoms is highly effective in aborting febrile episodes, although it does not prevent recurrence and might indeed diminish the interval between flares.[720-722] Additional doses of prednisone can be used for symptom recurrence. Cimetidine (20-40 mg/kg/d) in divided doses has been reported to prevent recurrence. The benefits of tonsillectomy,[724-726] administration of IL-1β receptor antagonist,[723] and vitamin D supplementation[727,728] on recurrence (and in some cases remission) of symptoms has also been highlighted in clinical studies. NSAIDS, antibiotics, and colchicine are generally less effective in treating and preventing inflammatory flares. Prognosis is good, with a strong trend toward resolution of symptoms on the average of 5 years after onset.[720-722]

Complement deficiencies

Many of the specific complement protein deficiencies have only been seen in a handful of patients. However, deficiencies of mannose-binding lectin (MBL), C2, and C9 are relatively more common, the latter particularly among Japanese subjects.[729,730] The genes for all complement proteins (except properdin) are autosomal.[729,731] The estimated prevalence of a complete complement component deficiency is 0.03%.[732] The reason for the rarity of complement deficiency is unknown.

Hereditary angioedema is due to defects in the plasma protein C1 esterase inhibitor. This protein regulates the complement, kinin-generating, clotting, and fibrinolytic mediator pathways. Current evidence indicates that kinin system activation with generation of bradykinin is responsible for attacks.[733] This entity will not be discussed here.

Summary statement 228. Patients with recurrent bacterial sinopulmonary infections with or without autoimmune disease and with normal humoral immunity should be screened for complement deficiency (C).

Table E12[729-731,733-751] shows the major clinical associations with specific complement protein deficiencies. Partial deficiencies of C2 and C4 are the most common in this category and are found in patients with null alleles of C2, C4A, or C4B. Some patients with C2 deficiency present with recurrent bacterial respiratory tract infections resembling those of patients with antibody deficiencies.[732] A higher prevalence of autoimmune disease resembling SLE is seen in C2- and C4-deficient patients as well.[734]

All pathways of complement activation converge on C3, and thus C3-deficient patients are at the greatest risk for infection. These patients might appear similar to those with severe antibody deficiencies or defects of phagocyte function.[732,735,752] Factor I deficiency is inherited as an autosomal recessive trait. In the absence of factor I, the alternative pathway is continually activated. Plasma C3 levels are depleted, leading to a similar propensity toward bacterial (mainly respiratory tract) infection.[737,742]

Defects of the lectin complement activation pathway might be associated with increased susceptibility to bacterial infections.[730] MBL is very similar structurally to C1. MBL-associated serum protease 2 is homologous to C1s. Defects of either have been associated with recurrent bacterial respiratory tract infections. Defects of MBL and MBL-associated serum protease 2 most often have autosomal recessive inheritance. However, because of structural features of the MBL protein, heterozygous patients with certain amino acid substitutions, as well as homozygous deficient patients, have abnormally low MBL levels (<100 ng/mL).[730] Homozygous MBL deficiency can be found in as many as 3% of subjects. Some of these might be at increased risk of infection, particularly as infants. One study found an approximately 2-fold higher rate of low serum MBL levels in children with a history of recurrent bacterial respiratory tract infections.[743] The association was strongest in a subgroup with a variety of abnormalities of immunoglobulin classes or subclasses. Lupus-like autoimmune disease can also be seen, although very infrequently. The clinical significance or predictive value of low serum MBL levels with or without abnormal immunoglobulin or IgG subclass levels requires further clarification and is not considered part of a standard evaluation for immunodeficiency.

Ficolin 3 is another member of the collectin family having structural similarity to MBL and C1q and capable of activating the lectin complement pathway.[746,747] Defects of ficolin 3 have been associated with bacterial respiratory tract infections and necrotizing enterocolitis in infants.

The extremely rare patients with alternative pathway complement defects (factor B, factor D, and properdin) might also be at risk for infection.[732,752] Susceptibility to autoimmunity in patients with these deficiencies does not appear to be as great as with classical pathway defects.

Summary statement 229. Patients with characteristics of Carnevale-Mingarelli-Malpuech-Michels syndrome (facial dysmorphism, growth deficiency, cognitive impairment, hearing loss, craniosynostosis, radioulnar synostosis, and eye and ear abnormalities) should be evaluated based on defects in the lectin pathway of complement activation. (C)

MBL-associated serine protease 1 *(MASP1)* and collectin subfamily member 11 *(COLEC11)* are 2 genes in the lectin pathway that are mutated in patients with Carnevale-Mingarelli-Malpuech-Michels syndrome.[744] Although *COLEC11* mutations do not affect downstream complement factor production (normal C2, C3, and C4 levels), *MASP1* mutations lead to defects in its isoform, MASP3, resulting in defect cleavage of C2 and C4. In these cases C3 convertase might not be formed, and the downstream complement cascade is inhibited.[745]

Summary statement 230. Patients with susceptibility to neisserial infections should be suspected of having a terminal pathway complement deficiency. (C)

Increased susceptibility to infections with *N meningitidis* and *N gonorrhoeae* is seen in patients with deficiencies of C5 to

TABLE E12. Clinical associations with complement deficiency

Component(s)	Lupus-like disease	Bacterial infections	References
C1, C2, C4	Yes	Encapsulated organisms	729, 733-735
C3	No	Encapsulated organisms (severe)	729, 733, 735
C5, C6, C7	Yes	*Neisseria* species	729, 733-735
C8, C9	No	*Neisseria* species	729, 733
C1 inhibitor (SERPING1)	No (hereditary angioedema)	None	729, 733
Factor B	No (atypical HUS)	None	729, 733, 736
Factor D	No	Encapsulated organisms	729, 733, 736
Properdin	Yes	*Neisseria* species	729, 731, 733, 736
Factor H	No (atypical HUS, macular degeneration)	Encapsulated organisms	729, 737, 738
Factor H–related protein (CFHR1-5)	No (atypical HUS)	None	739-741
Factor I	No (atypical HUS)	Encapsulated organisms	729, 737, 738, 742
MBL	No	Encapsulated organisms	730, 743
MASP1	No (3MC syndrome)	None	744, 745
MBL-associated serum protease 2	No	Encapsulated organisms	730
Ficolin 3	No	Encapsulated organisms, necrotizing enterocolitis	746, 747
Thrombomodulin	No (atypical HUS)	None	748, 749
Membrane cofactor protein (CD46)	No (atypical HUS)	None	737, 738, 750
Membrane attack complex inhibitor (CD59)	No (hemolysis, polyneuropathy)	None	751
COLEC11	No (3MC syndrome)	None	744
Complement receptor 2 (CD21)	No, CVID-like disorder	Encapsulated organisms	See SS 87
Complement receptor 3 (CD18/ITGB2)	No, LAD type 2	Encapsulated organisms	See SS 142

C9.[732,752] This has also been described in association with deficiency of the alternative pathway component properdin.[731]

Summary statement 231. Patients with atypical HUS should be screened for abnormalities of a complement regulatory protein. (C)

Atypical HUS occurs in the absence of infection with any of the characteristic HUS-inducing bacteria. Defects in the complement regulatory components factor H, factor I, thrombomodulin, and CD46 can predispose to atypical HUS.[737,738,748,749] Deficiency of factor H, a C3 regulatory protein, is inherited as an autosomal recessive trait and has been found in a number of patients with the inherited form of HUS. Defects in other C3 regulatory proteins (CD46 and factor I) are also associated with the development of atypical HUS. In addition, gain-of-function mutations of C3 and factor B have been associated with atypical HUS.[736] Furthermore, allelic modifications in factor H are now known to be associated with macular degeneration in the elderly, a disease in which complement is known to be deposited in the retina.[753]

Summary statement 232. Patients with Shiga toxin–negative HUS should be evaluated for atypical HUS and tested for anti–factor H protein (CFH) autoantibodies and deficiency of complement factor H–related protein (CFHR) 1 to 5. (C)

Factor H acts as a complement regulator, and circulating autoantibodies to factor H can results in autoimmune atypical HUS. Diagnosis of these autoantibodies is important because patients will respond to plasma exchange treatment. Exogenous CFHR1 might also help in the treatment of atypical HUS.[741] One patient with antibody-mediated rejection after renal transplantation for spina bifida–associated reflux nephropathy was found to be deficient in CFHR3/1 and responded to eculizumab (monoclonal C5 inhibitor) therapy.[740] About one fourth of pediatric patients with atypical HUS are positive for CFH antibody, many of whom are CFHR1 deficient.[739]

Summary statement 233. Screening for defects of classical and terminal pathway complement components should be performed by using the classical pathway complement hemolysis 50% (CH50) assay. (C)

Patients with recurrent pyogenic infections and normal humoral immunity should be studied for complement deficiency.[732] Laboratory findings and diagnosis of complement deficiencies are summarized in Table E13. The original CH50 assay measures the lysis of antibody-sensitized sheep erythrocytes by fresh serum. The result is expressed as the reciprocal of the dilution yielding 50% red cell lysis. This test is relatively insensitive compared with functional tests of single complement proteins. The level of a single complement protein can be markedly reduced, for example, if the patient is heterozygous with a deletion of one of the alleles for a single complement protein; there might be no change in the CH50 result, and the deletion might have no clinical consequences. If the CH50 result is 0 or close to 0, there is often a genetic defect affecting one of the complement proteins. If the titer is less than normal but not 0, often this implies that the level of several complement proteins are decreased, which in turn implies that a complement pathway has been activated.

Newer methods of determining classical pathway activity might use liposomes containing glucose-6-phosphate dehydrogenase and labeled with a defined antigen, such as dinitrophenyl. Liposomes are lysed by complement-fixing anti-dinitrophenyl antibody and serum. The released enzyme acts on glucose-6-phosphate and nicotinamide adenine dinucleotide in solution, and the color change is measured in a spectrophotometer.[754]

Because most of the complement deficiencies are inherited as autosomal recessive traits and because heterozygotes are usually normal clinically, one can make the diagnosis of most of the significant defects by determining that the patient's CH50 result is 0; that is, there is no lysis of the red cells. Subsequently, levels of individual proteins can be tested separately.[732] Complement component levels are measured by using standard nephelometric or ELISA techniques. Individual component function can be determined by complementation of control serum that has been selectively depleted

TABLE E13. Summary of screening laboratory findings and diagnosis of complement deficiencies

CH50 assay	AH50 assay	Possible diagnoses
NL	NL	Normal
NL	Low	Properdin defect
NL	0	Factor B* or factor D defect
Low	NL or low	Consumption likely, regulatory component (factor H, factor I) defect possible
0	NL	C1, C2, or C4 likely absent
0	0	C3 or C5-C9 likely absent

The clinical presentation is suggestive of a complement deficiency (Table IX) or evaluation of other immune function is thus far normal, and the clinical presentation is at least consistent with complement deficiency. Note that this table does not consider possible lectin pathway defects. Both CH50 and AH50 results will be normal in the setting of MBL deficiency. See the text for discussion of lectin pathway defects and function. This algorithm can be used whether tests for the classical pathway (CH50 assay) and alternative pathway (AH50 assay) are performed simultaneously or sequentially. The CH50 assay is readily available in many hospital laboratories; the AH50 (also called the AP50) assay is not. The AH50 assay is available from the Complement Laboratory of the National Jewish Medical Center in Denver, Colorado. Genetically determined defects in the alternative pathway leading to absent activity in the presence of a normal CH50 result are very rare. Note also that complement components are unstable and tend to degrade with time, especially if blood or plasma is warmed. For the most accurate measurements, blood specimens should be placed on ice or refrigerated after drawing. If complement consumption is possible or suspected, the AH50 assay might not necessarily be helpful. A convenient way available in most hospital laboratories to test for consumption is to measure levels of factor B and C4, reflecting activation of the alternative or classical pathway, respectively. If levels of both of these (or other combination) are low, consumption of complement is assumed, and a reason should be explored. Note that deficiency of factor H, factor I, or properdin could lead to a diminished level of C3 and other components. This table has not been constructed to evaluate all of the control proteins. In the presence of an appropriate clinical history, low C4 levels in the presence of normal C3 levels might suggest hereditary angioedema, and the levels and function of C1 inhibitor should be explored. Such patients will have low CH50 results, but they will not be 0.
3MC, Carnevale-Mingarelli-Malpuech-Michels syndrome; *NL*, normal.
*Note that homozygous deficiency of factor B has never been reported.

of one component. Occasionally, complement component deficiency must be distinguished from complement consumption, as can occur during infection or autoimmune disease (see below). This can be assessed by determining reductions in the level or activity of 2 or more individual components (usually C4 and C3).

It is important to bear in mind that hypocomplementemia usually results from complement component use caused by activation, as can occur in autoimmune disease or during infection. Complement levels are often low in patients with autoimmune diseases, such as SLE,[755] and less frequently in patients with rheumatoid arthritis[756] and some vasculitides[757] because complement is frequently activated and used during the course of these antibody-mediated inflammatory processes. Antibody formation during acute infection can create immune complexes, which can decrease levels of circulating plasma complement proteins. Immune complexes can also be deposited in the kidney, leading to complement deposition with glomerulonephritis.[758] Examples include poststreptococcal glomerulonephritis,[752] bacterial endocarditis with glomerulonephritis,[759] and viral infections, such as with erythrovirus B19, which might be associated with glomerulonephritis.[760] Reduced levels of C4 and C3 (as occur in SLE) 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 like poststreptococcal glomerulonephritis.

Summary statement 234. Screening for possible defects of the alternative pathway of complement should be with the alternative pathway complement hemolysis 50% (AH50) assay. (C)

The AH50 (also called the AP50) assay 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 can then be lysed through an alternative pathway (complement attack through the alternative pathway does not require IgG for activation). As with the CH50 assay, the result is the reciprocal of the dilution yielding 50% lysis. In an alternative method serum is placed in a well in agar containing RBCs. As complement components diffuse into the agar, they cause lysis of the RBCs. The result is determined by the diameter of the ring of lysis around the well. A very low AH50 result suggests an alternative pathway defect (factor B, factor D, or properdin).[732] The AH50 assay has the same considerations of lack of sensitivity discussed above for the CH50 assay.

Summary statement 235. Consideration can be given to screening lectin pathway function in patients with recurrent bacterial sinopulmonary infections who have normal humoral immunity and normal classical and alternative complement function. (C)

Lectin pathway function can also be assessed by using hemolytic methods similar to the CH50 and AH50 assays.[761] In a solid-phase method plates are coated with mannan and incubated with serum under conditions that permit MBL to be fixed and activated while C1q binding is inhibited. Purified C4 is added and converted to soluble C4a and C4b, which adheres to the plate. The amount of C4b deposited can be measured with a labeled mAb to C4b.

Summary statement 236. Immunization and antibiotic therapy should be the major modes of treatment for complement deficiencies associated with recurrent infections. (C)

Patients with complement deficiencies require immunization with relevant vaccines (*S pneumoniae*, *H influenzae*, and *N meningitidis*). Consideration should be given to maintenance of protective immunity to these bacteria beyond what is routinely recommended. Chronic antibiotic therapy might be required in patients with frequent infections but is usually not needed.[729,752]

Summary statement 237. Autoimmune diseases associated with complement deficiency are treated as they would be in other clinical settings. (C)

The autoimmune diseases that arise in patients with complement deficiencies are treated with the appropriate standard therapy. There is no available gene therapy at the present time, and in most situations, supplying the missing complement protein is not beneficial.[734,752,762]

Anti-cytokine autoantibodies

Summary statement 238. Patients with certain PIDD phenotypes who do not have mutations in the genes known to be causative should be studied for associated anti-cytokine autoantibodies. (C)

Autoantibodies against cytokines can result in clinical phenocopies of known genetic mutations that result in immune deficiency and autoimmunity.[763] Table E2 lists the PIDD phenotypes associated with specific anti-cytokine autoantibodies. Antibodies to C1 esterase inhibitor (technically not a cytokine) lead to an acquired form of episodic angioedema clinically very similar to the hereditary form (see SS 227).

As a group, these disorders tend to most closely resemble those entities grouped together under the heading of defects of innate immunity. Antibodies to G-CSF have been associated with a single reported case of neutropenia and a lupus-like syndrome (Felty syndrome).[764] Antibodies to GM-CSF lead to PAP in association with opportunistic infections, such as cryptococcal

meningitis, or infections with *Nocardia* species, *Proteus* species, or atypical mycobacteria. Anti-type I interferon antibodies have been seen in patients with thymoma and APECED (SSs 129-132) and have been associated with disseminated varicella-zoster infection.[765,766] Autoantibodies to IFN-γ lead to disseminated infections with mycobacteria, *Salmonella* species, *Cryptococcus* species, *Histoplasma* species, *Penicillium* species, and varicella-zoster virus.[552,555,556] Antibodies to IL-6 have been reported in patients with recurrent skin infections, sepsis, or both caused by both gram-positive (*S aureus* and *Staphylococcus intermedius*) and gram-negative *(E coli)* organisms.[92-94] One patient with anti–IL-12p70 antibodies has been found to have *Burkholderia gladioli* lymphadenitis.[554] Finally, autoantibodies to IL-17A, IL-17F, and IL-22 are found in patients with CMCC in the setting of APECED caused by *AIRE* mutation (SSs 129-132).[481,482]

Summary statement 239. In addition to therapy directed toward infectious and/or non–cytokine-directed autoimmune complications in patients with these disorders, patients with anti-cytokine autoantibodies might benefit from therapy targeted to the anticytokine autoimmune response. (C)

In these patients the principal pathophysiology is the immune dysregulation exerted by autoantibody consumption of the cytokine autoantigen. Therefore therapies directed toward depleting autoantibody (eg, plasmapheresis) or reducing its formation (eg, rituximab), supplementing the target cytokine, or both can ameliorate the disease course.[763] These approaches have had some success in cases of patients with autoantibodies to GM-CSF or type I and II interferons.[552,555,556,763,767] High-dose/immunomodulatory therapy with IgG could be considered because it has been effective for therapy of other disorders caused by autoantibodies to humoral components, such as clotting factors.[768] However, to our knowledge, this has not yet been reported for the treatment of cytokine autoantibody–mediated disorders.

EXECUTIVE SUMMARY

Primary immunodeficiencies are inherited disorders of immune system function that predispose affected subjects to an increased rate and severity of infection, immune dysregulation with autoimmune disease and aberrant inflammatory responses, and malignancy. Primary immunodeficiencies are distinct from secondary immunodeficiencies that occur, for example, during certain viral infections, after immunosuppression to prevent graft rejection after transplantation, during treatment of systemic autoimmune disease, and in association with cancer chemotherapy. More than 200 distinct genetic disorders affecting immune system function have been identified to date (many are listed in Table E2).

Primary immunodeficiencies occur in as many as 1:2000 live births. They are most often categorized according to a combination of mechanistic and clinical descriptive characteristics. These categories include the defects of specific or adaptive immunity, which are subdivided into humoral or antibody deficiencies, and the combined deficiencies affecting both humoral and cellular mechanisms. A separate category of immunodeficiency syndromes with characteristic phenotypes is distinguished, along with defects of innate immunity, disorders of immune dysregulation, autoinflammatory syndromes, and phagocyte and complement system defects. Recently, the importance of anticytokine autoantibodies has been appreciated in the pathophysiology of some Mendelian PIDD syndromes and as *prima facie* causes of PIDDs. Among these categories, the antibody deficiency group accounts for approximately half of all patients with a PIDD diagnosis.

The principal clinical manifestation of immunodeficiency is increased susceptibility to infection. The pattern of organ systems affected, as well as the characteristic pathogens, vary with the type of immune defect (Table E3). Autoimmune disease and malignancy are also often seen in a variety of immunodeficiencies. In the course of 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 might predispose to infection, including anatomic defects, allergy, and metabolic disorders, should be considered where appropriate. However, also note that hypersensitivity to environmental allergens, food allergens, or both might be an important element of and diagnostic clue for a variety of PIDDs.

In general, initial evaluation is guided by the clinical presentation (Fig E1 and Table E3). Screening tests are applied and followed by advanced tests, as indicated (Table E4). This stepwise approach ensures efficient and thorough evaluation of mechanisms of immune dysfunction that underlie the clinical presentation, with narrowing of diagnostic options before using costly sophisticated tests that might be required to arrive at specific diagnoses. In addition to global assessment of immune development through measurement of nonspecific features, such as serum immunoglobulin levels and leukocyte and lymphocyte subpopulations, evaluation of the specific immune response is essential. This is most often directed toward evaluation of responses against vaccine antigens, but assessment of responses to natural exposure or infections is also useful.

There are a variety of resources for health care providers and patients now available on the Internet, and some are listed in Table E5. Where uncertainty regarding evaluation or management occurs, consultation with physicians experienced with immunodeficiencies is essential. Where 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. General therapeutic considerations for immunodeficiency are listed in Table E6.

The combined deficiencies of specific immunity (Fig E2) 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 can include panhypogammaglobulinemia, lymphopenia, or alymphocytosis and absence of cellular immune function, as determined by using *in vitro* stimulation tests. The laboratory phenotype often depends on the specific molecular defect (Table E7). A possible diagnosis of SCID is an urgent medical condition because these infants can 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 IgG replacement. Definitive hematopoietic stem cell therapy (HSCT) should be sought as quickly as possible. A variety of

additional genetic defects leading to impairment of T- and B-cell function have also been described, including hyper-IgM syndromes and others (Tables E2 and E8).

A variety of syndromes of immunodeficiency have been described. Most prominent among these are Wiskott-Aldrich syndrome, DiGeorge syndrome, ataxia-telangiectasia, and the hyper-IgE syndromes. These disorders present with varying degrees of susceptibility to the entire spectrum of pathogenic organisms, depending on the specific disorder and on other host genetic and environmental factors. Many of these diseases have ancillary clinical features that might influence or guide the diagnostic approach. Laboratory abnormalities of specific immune function vary depending on the specific gene defect and can include alterations in immunoglobulin levels with impaired specific antibody responses, as well as defects of specific cellular immunity, as determined by using *in vivo* and *in vitro* assays. Therapy is often supportive and anti-infective with drugs and polyclonal human IgG. HSCT has been applied in patients with many of these disorders as well (Tables E6 and E8).

The principal clinical manifestations of humoral immunodeficiency are recurrent bacterial infections of the upper and lower respiratory tract. Both X-linked and autosomal forms of agammaglobulinemia are associated with extremely low numbers (absence) of B cells. The X-linked form (Bruton agammaglobulinemia) accounts for the majority (85%) of cases. In patients with common variable immunodeficiency, laboratory evaluation generally shows variable reduction in 2 or more major immunoglobulin classes, impairment of specific antibody responses, and, occasionally, reductions in B-cell numbers. Milder antibody deficiencies, such as selective IgA deficiency, IgG subclass deficiency, specific antibody deficiency, or THI, are associated with variably low levels of immunoglobulin classes or subclasses in serum, sometimes accompanied by impaired specific antibody formation. For agammaglobulinemia or common variable immunodeficiency, therapy is either with antibiotic prophylaxis, IgG replacement, or both (Tables E6 and E7). Milder antibody deficiencies are most often managed with antibiotic prophylaxis (SS 16 and Table E7). In some of these cases, IgG therapy can be applied.

The disorders of immune dysregulation (Fig E3) include the hemophagocytic syndromes, syndromes with autoimmunity and hypersensitivity, and lymphoproliferation. The hemophagocytic syndromes often have fulminant acute presentations triggered by viral infections. These patients usually require aggressive chemotherapy followed by HSCT to prevent immediate fatality. Other prominent disorders in this category are the autoimmune lymphoproliferative syndromes and immune deficiency, polyendocrinopathy, X-linked syndrome. These diseases also require HSCT.

Phagocytic cell defects (Fig E4) can present with severe pyogenic bacterial and fungal infections of the respiratory tract, skin, and viscera and gingivostomatitis. Laboratory evaluation might show neutropenia, normal neutrophil numbers, or marked neutrophilia (mainly in cellular adhesion defects). Functional studies show most often a defect in oxidative metabolism because chronic granulomatous disease is the most common phagocyte defect. In patients with other disorders, there might be simply severe neutropenia or variable impairment of chemotaxis (leukocyte adhesion defects), phagocytosis, or intracellular killing. Therapy is with antibacterial and antifungal prophylaxis and IFN-γ for chronic granulomatous disease. HSCT has been applied for chronic granulomatous disease, leukocyte adhesion defects, and neutropenic syndromes. The care of patients with other forms of phagocyte defects is primarily anti-infective and supportive.

Also included in the category of phagocytic cell defects are the syndromes classified under Mendelian susceptibility to mycobacterial disease. These patients exhibit somewhat restricted susceptibility to mycobacteria and to severe salmonella infections. Therapy is with antimicrobials and IFN-γ in some forms, and HSCT has been applied in a few patients.

Disorders of innate immunity are rare and include defects of Toll-like receptor signaling, such as nuclear factor κB essential modulator syndrome, often exhibiting ectodermal dysplasia along with infection susceptibility with a narrow (eg, predominantly pyogenic bacteria or fungi) to a wide range of pathogens (Fig E5). Antimicrobial therapies are important for treatment, and some of these disorders can be managed with HSCT. This category also includes several defects associated with HSE and chronic mucocutaneous candidiasis. These diseases are generally managed with anti-infective agents.

Autoinflammatory syndromes are also quite rare (Fig E6). These diseases are characterized by episodic fever often in association with other inflammatory manifestations that can affect the skin, joints, and gastrointestinal tract. Anti-inflammatory biologicals, such as TNF or IL-1 antagonists, might be useful, along with more routine anti-inflammatory therapies, such as corticosteroids or colchicine.

Complement deficiencies are also infrequent (Tables E12 and E13). Most early classical and alternative pathway complement defects tend to present either with systemic autoimmune disease resembling lupus erythematosus or recurrent respiratory tract bacterial infections similar to antibody deficiency. Deficiencies of terminal components can also be associated with recurrent neisserial meningitis. Some patients with low serum levels of mannose-binding lectin might be predisposed to bacterial respiratory tract infections, but there could be other host factors that interact to create such susceptibility in a patient. There is no specific therapy for complement deficiency. Antibiotic prophylaxis (SS 16 and Table E7) and immunization can be applied for recurrent infections.

Anticytokine antibodies are an important component of some PIDD syndromes. For example, there is a strong correlation of the presence and concentration of antibodies against IL-17A, IL-17F, and IL-22 with the occurrence of chronic mucocutaneous candidiasis in patients with autoimmune polyendocrinopathy–candidiasis–ectodermal dystrophy (autoimmune regulator mutations). Anti-cytokine autoantibodies might also be pathogenic by themselves, such as anti–GM-CSF antibodies in patients with PAP and anti–IFN-γ antibodies in patients with adult-onset Mendelian susceptibility to mycobacterial disease. Additional examples have been described.

It is recommended that diagnosis and therapy are guided overall or performed in consultation with persons and centers with knowledge and experience diagnosing and treating a broad range of immunodeficiencies to improve consistency in evaluation and management and to have the best outcomes with respect to patient and family health, education, and planning.

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