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KEY REVIEW ARTICLE

ICON: The Early Diagnosis of Congenital Immunodeficiencies

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Abstract Primary immunodeficiencies are intrinsic defects in the immune system that result in a predisposition to infection and are frequently accompanied by a propensity to autoimmunity and/or immunedysregulation. Primary immunodeficiencies can be divided into innate immunodeficiencies, phagocytic deficiencies, complement deficiencies, disorders of T cells and B cells (combined immunodeficiencies), antibody deficiencies and immunodeficiencies associated with syndromes. Diseases of immune dysregulation and autoinflammatory disorder are many times also included

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although the immunodeficiency in these disorders are often secondary to the autoimmunity or immune dysregulation and/or secondary immunosuppression used to control these disorders. Congenital primary immunodeficiencies typically manifest early in life although delayed onset are increasingly recognized. The early diagnosis of congenital immunodeficiencies is essential for optimal management and improved outcomes. In this International Consensus (ICON) document, we provide the salient features of the most common congenital immunodeficiencies.

Keywords Primary immunodeficiencies · combined immunodeficiencies · severe combined immunodeficiencies · diagnosis · treatment · consensus · global-consensus

Abbreviations

AD-EDA-ID	Autosomal dominant anhidrotic ectodermal dysplasia with immunodeficiency
AD-HIES	Autosomal dominant hyper IgE syndrome
AR-HIES	Autosomal recessive hyper IgE syndrome
AT	Ataxia telangiectasia
ATM	Ataxia-telangiectasia mutated
BCG	Bacillus Calmette-Guérin
CGD	Chronic granulomatous disease
CID	Combined immunodeficiencies
CMC	Chronic Mucocutaneous Candidiasis
CSR	Class switch recombination
DHR	Dihydrorhodamine–1,2,3
EDA	Anhidrotic ectodermal dysplasia
G-CSF	Granulocyte colony-stimulating factor
GVHD	Graft-versus-host disease
HSCT	Hematopoietic stem-cell transplantation
HSE	Herpes simplex encephalitis
HSV1	Herpes simplex virus type 1
ICON	International consensus
IVIG	Intravenous immunoglobulin
LAD-I	Leukocyte adhesion deficiency type I
LAD-II	Leukocyte adhesion deficiency type II
LAD-III	Leukocyte adhesion deficiency type III
MSMD	Mendelian susceptibility to mycobacterial diseases
NBS	Newborn screening
NBT	Nitroblue tetrazolium
OSM	Oncostatin M
PID	Primary immunodeficiency
SCID	Severe combined immunodeficiency
SHM	Somatic hyper mutation
STAT3	Signal transducer and activator of transcription 3
TIR	Toll-IL-1R
TLR	Toll-like receptors
TREC	T cell receptor excision circle
WAS	Wiskott-Aldrich syndrome
WASp	Wiskott-Aldrich syndrome protein
XHIGM	X-linked hyper IgM
XLA	X-linked agammaglobulinemia
XLT	X-linked thrombocytopenia
XR-EDA-ID	X-linked recessive anhidrotic ectodermal dysplasia with immunodeficiency

This International Consensus Document (ICON) was written at the request of the Steering Committee of the International Collaborative in Asthma ALlergy and ImmunoLogy (iCAALL). iCAALL initiated coalition between the American Academy of Allergy, Asthma & Immunology; European Academy of Allergy and Clinical Immunology; World Allergy Organization; and American College of Allergy, Asthma and Immunology to create consensus documents that will encompass the state of the

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art of allergy and immunology from a global perspective. The information contained in this manuscript represents the consensus expert opinion of the authors.

Introduction

Newborn screening (NBS) for severe combined immunodeficiency (SCID) has been introduced in several states throughout the United States. If more widely implemented, NBS should result in an increase in the early diagnosis and successful treatment of this disorder. However, SCID is only one of several primary immunodeficiencies (PIDs) that present early in life. Although not completely sensitive, the NBS test for SCID is able to identify some other primary immunodeficiencies characterized by a profound reduction of naïve T cells (e.g. complete DiGeorge syndrome, leaky SCID, ataxia telangiectasia). The development of powerful diagnostic tools and technologies such as the use of next-generation DNA sequencing, has resulted in a tremendous increase in the number newly recognized PIDs in which the genetic cause is known. Consequently, practicing pediatricians should be aware of *genetic heterogeneity*, (i.e. the situation when a single phenotype could be caused by any one of multiple alleles or non-allelic (different locus) mutations). The novel clinical presentations [1] and new gene mutations underlying these disorders are being reported 'as we speak' [2]. This further highlights the emerging need for better classification of PIDs [3], which permits the physician to determine a diagnosis before end-organ damage occurs. Although the early diagnosis of these PIDs should lead to a better outcome, the lack of knowledge of many physicians of congenital PID frequently delays the diagnosis, leading to an unfavorable outcome. The purpose of this consensus document is to familiarize physicians with the typical clinical manifestations of congenital PID and diagnostic studies that can lead to the specific diagnosis.

Disorders of Innate Immunity

Genetic Defects of TLR/IL-1R Signaling Pathways

Toll-like receptors (TLRs) sense microbial products and play an important role in innate immunity. TLRs recognize conserved motifs in microbial pathogens, which, upon binding, trigger downstream signaling events that lead to the production of inflammatory cytokines (Fig. 1). TLRs, and members of the interleukin-1 receptor (IL-1Rs) family, contain an intracellular domain known as the Toll-IL-1R (TIR). The TIR domain is critical to the pro-inflammatory signaling pathway, which activates map kinases (MAPKs), and classical NF-κB pathway [4, 5].

The canonical TIR pathway, which is used by all TLRs except TLR3, is dependent on signaling through MyD88 and IRAK-4. Mutations in *MYD88* (OMIM#612260) or *IRAK4* (OMIM#607676) cause a PIDs with impaired signaling of all the affected TLRs. In contrast, the alternative TIR pathway signals through the adaptor TRIF [6]. Defects in the TLR3 pathway include mutations in *TLR3* (OMIM#613002), *UNC93B1* (OMIM#610551), *TRIF* (OMIM#614850), *TBK1* (OMIM#604834) or *TRAF3* (OMIM#601896) [7, 8].

Impaired signaling of the NF-κB signaling pathway may also occur as a result of mutations in *NEMO* (OMIM#300291), IKBA (OMIM#612132) or *IKBKB* [6] *NEMO*, *IKBA* and *IKBKB* are core molecules in the NF-κB pathway downstream from various receptors, including those triggered by members of the (tumor necrosis factor receptor) TNF-R, TIRs, TCR and BCR (Fig. 1) [5, 7–13]. As discussed below, the clinical phenotypes of abnormalities in the canonical TLR pathway, alternative TLR pathway and or as a result of mutations in *NEMO*, *IKBA* and *IKBKB* result in distinct clinical phenotypes.

IRAK-4 and MyD88 Deficiencies: Inborn Errors of the TIR Signaling Pathways

To date, 52 patients with autosomal recessive (AR) IRAK-4 deficiency, and 24 AR MyD88-deficient patients have been identified [6, 14–17]. Patients with MyD88 and IRAK-4 deficiency show a predisposition to invasive bacterial infections (meningitis, sepsis, arthritis, osteomyelitis and abscesses), often in the absence of fever. The predominant pathogens associated with invasive bacterial infections are unexpectedly narrow and include *Streptococcus pneumoniae*, *Staphylococcus aureus* and *Pseudomonas aeruginosa*. Non-invasive bacterial infections include skin infections and upper respiratory tract infections. Both PIDs improve with age and patients often have no further invasive bacterial infections beyond their teenage years [18]. These patients should receive conjugated and non-conjugated bacterial vaccines, antibiotic prophylaxis, and immunoglobulin (IgG) replacement during the first decade of life [18]. Importantly, families or physicians need to initiate empiric parenteral antibiotic treatment, as soon as an infection is suspected, or if the patient develops a moderate fever because patients may die from rapid invasive bacterial infection despite appropriate prophylaxis [6]. Routine screening tests of immune function in these patients are usually normal. Specific screening tests for MyD88 and IRAK-4 deficiency (e.g. lack of proinflammatory cytokine production and CD62L shedding) are available only in specialized clinical immunology laboratories [18].

TLR3, UNC93B1, TRIF, TBK1 and TRAF3 Mutations: Inborn Errors of the TLR3-IFN-α/β and -λ Pathway

This group of inherited disorders leads to impaired TLR3 signaling, with affected patients bearing mutations in *TLR3*, *UNC93B1*, *TRIF*, *TBK1* or *TRAF3* [7, 8, 10–13]. Ten symptomatic patients with AR and autosomal dominant (AD)

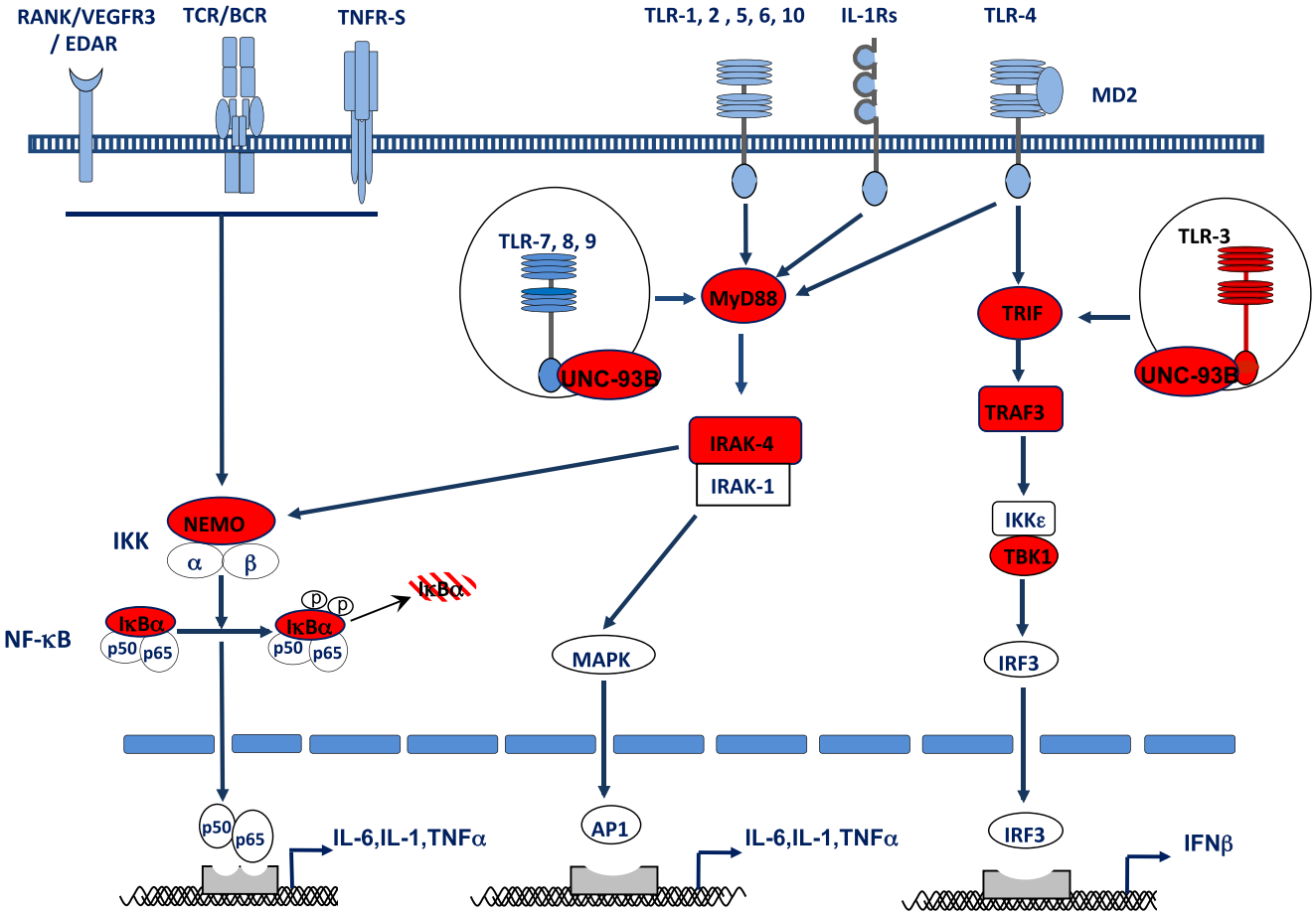

Fig. 1 Genetic defects of TLR/IL-1R signaling pathways: the receptor signaling pathways leading to NF-κB activation can be grouped into four categories on the basis of the surface receptors involved: developmental receptors RANK, VEGFR3 and EDAR; antigen receptors (TCR and BCR); members of the TNF receptor superfamily (TNF-Rs) and members of the TIR superfamily (IL-1Rs/TLRs); TIRs signaling pathway leading to MAPK activation. The two proteins of the TIR signaling pathway (MyD88, IRAK-4) and the two proteins of the NF-κB signaling pathway (NEMO and IκBα) responsible for PIDs are shown in *red*. The TLR3 signaling pathway leading to IRF3 activation and the production of type 1 and 3 IFN. The defect in UNC-93B abolishes cellular responses to TLR3 and 7–9 agonists. The defect in TRAF3 impairs cellular responses to TLR3 and other pathways. The four proteins of the TLR3 signaling pathway (TLR3, UNC-93B, TRAF3 and TBK1) responsible for PIDs are shown in *red*

TLR3 deficiencies; AR UNC93B1-deficiency; AR and AD TRIF deficiencies; AD TBK1deficiency; or AD TRAF3 deficiency have been reported [7, 8, 10–13]. The dominant clinical phenotype is herpes simplex encephalitis (HSE) during primary infection with herpes simplex virus type 1 (HSV1), usually between 3 months and 6 years of age [7, 8, 10–13]. Treatment consists of prophylactic acyclovir and the use of recombinant. IFN-α may also be beneficial. Referral to a clinical immunologist is essential as routine screening tests of immune function are normal, and more specific tests examining the TLR3 pathway are not routinely available in commercial laboratories. Functional abnormalities of immune function include a marked decrease in the ability of patient's fibroblasts to produce IFN-β/-λ in response to TLR3 agonists and HSV1 infection. Specific diagnosis requires DNA sequencing of the genes in the TLR3-IFN-α/β and -λ pathway.

NEMO Deficiency, *IKBA* Mutation and IKK2 Deficiency: Inborn Errors of NF-κB-Mediated Immunity

X-linked recessive anhidrotic ectodermal dysplasia (EDA) with immunodeficiency (XR-EDA-ID) is caused by hypomorphic *IKBKG*/*NEMO* mutations impairing NF-κB activation [19, 20]. Over 100 male patients have been reported with over 40 different mutations leading to impaired NF-κB activation [6, 21–24]. About 90 % of the NEMO-deficient patients described to date have EDA, with sparse hair, conical teeth or tooth agenesis, and hypohidrosis [6, 21]. In some NEMO-deficient patients, associated osteopetrosis and/or lymphedema have been described in addition to EDA [20, 21]. Colitis is the most frequent autoinflammatory disorder occurring in approximately 20 % of patients. About 10 % of NEMO-deficient patients have no developmental phenotype

[21, 25]. NEMO deficiency is associated with susceptibility to invasive pyogenic bacteria caused by *S. pneumoniae*, *Haemophilus influenzae*, *Staphylcoccus aureus*, *Pseudomonas aeruginosa*, environmental mycobacteria (*Mycobacterium avium* or *Mycobacterium kansasii*, see Mendelian susceptibility to mycobacterial diseases) and, occasionally, parasites, fungi and viruses [6, 21, 24].

Treatment includes antibiotic prophylaxis. IgG replacement is indicated in patients with hypogammaglobulinemia and these patients should also be immunized with conjugated and non-conjugated bacterial vaccines. In case of infection, the same clinical management as with IRAK-4 and MyD88-deficient patients is recommended. HSCT should be performed only for selected patients with severe immunodeficiency [6, 21, 24]. HSCT can correct the immunodeficiency, but some inflammatory signs may persist and the EDA phenotype remains unmodified [6, 21, 24]. Common screening tests of immune function may be normal in NEMO deficiency. Half the patients have hypogammaglobulinemia and 15 % have high serum IgM levels [21]. Most patients also have impaired antibody response to pneumococcal polysaccharides [6]. The definitive diagnosis of NEMO deficiency requires DNA sequencing of the *IKBKG*/*NEMO* gene.

An AD form of EDA-ID (AD-EDA-ID) is caused by heterozygous gain-of-function mutation of *NFKBIA/IKBA*, impairing phosphorylation and degradation of NF-κB inhibitor α (IκBα) [26]. Seven patients with three different *IKBA* mutations have been identified [27–30]. All patients with AD-EDA-ID develop recurrent bacterial infections [6, 24], and are prone to opportunistic infections including pulmonary pneumocystosis and chronic mucocutaneous candidiasis. Four patients developed diarrhea and/or colitis. All patients without mosaicism have EDA phenotype [6] while a patients with complex mosaicism do not display EDA These patients have hypogammaglobulinemia with no production of specific antibodies; some also have low numbers of memory T cells, no TCRγ/δ T cells and displayed severe impairment of T-cell proliferation in response to anti-CD3 [6, 24, 31, 27]. Treatment is similar to NEMO-deficient patients and HSCT has been performed for two patients with severe combined immunodeficiency [32, 33].

AR IKK2 deficiency was recently reported in four patients as a new form of SCID [34]. All patients carried a homozygous duplication of *IKBKB*, which encodes IκB kinase 2 (IKK2, also known as IKKβ), leading to loss of expression of IKK2, a component of the IKK–NF-κB pathway. IKK2 deficiency causes an impaired response to activation stimuli in a variety of immune cells, leading to impairment of adaptive and innate immunity [34]. IKK2 deficiency is associated with susceptibility to invasive pyogenic bacteria caused by *Escherichia coli*, *Serratia marcescens*. *Listeria monocytogenes*, chronic mucocutaneous candidiasis (CMC) and parainfluenzae viral infections. Immunological phenotype is characterized by profound hypogammaglobulinemia, with B and T cells almost exclusively with naive phenotype [34]. Regulatory T cells and γδ T cells were absent [34]. Immune cells from the patients had impaired responses to stimulation through T-cell receptors, B-cell receptors, and TLR.

In summary, defects in the TLRs, TLR signaling pathways, and NF-κB-mediated immunity lead to PIDs. Because the typical screening assays of immune function may be normal in these PIDs, a high index of suspicion is needed and early referral to a clinical immunologist is necessary for a timely diagnosis. DNA sequencing of the relevant genes based on clinical phenotype makes definitive diagnosis of these PIDs.

Chronic Granulomatous Disease

Chronic Granulomatous Disease (CGD), (OMIM # 306400, 233690, 233700, 233710, 608203) is a congenital immunologic disorder characterized by early onset of severe and recurrent infections affecting initially the natural barriers of the organism such as the lungs, lymph nodes, skin, and eventually inner structures, such as the liver, spleen, bones, and brain. The occurrence of hepatic abscess is a hallmark of CGD. The estimated incidence of this disease is 1/250,000 live births per year [35–37].

The pathogens found in CGD are typically catalase negative bacteria such as *Staphylcoccus aureus* and gram-negative bacilli, and fungi species such as *Aspergillus and Candida* [35–37]. Other pathogens include *Burkholderia cepacia*, *Chromobacterium violaceum*, *Nocardia*, and invasive *Serratia marcescens*. In developing countries, Bacillus Calmette–Guérin (BCG) vaccine causes adverse effects in up to 20 % of CGD patients [38]. Tissue examination typically shows microscopic granulomas [35–37]. Inflammatory complications are frequent in CGD patients. Granulomata obstructing the respiratory, urinary or gastrointestinal tracts are frequent complications [35–37]. Inflammatory bowel disease (Crohn's like disease) and perianal disease may affect up to 30 % of CGD cases [39]. The development of chronic inflammatory lung disease leading to respiratory insufficiency is also a frequent complication of CGD patients [35–37].

The underlying immunopathological mechanism in CGD is a defective microbicidal activity of phagocytes associated with a failure of the phagocyte NADPH oxidase to produce superoxide and other reactive oxygen intermediates (ROI). The molecular defects causing CGD are a consequence of absence, low expression, or malfunctioning of one of the NADPH oxidase components, which leads to an impaired respiratory burst [35–37]. The X-linked form of the disease is the most frequent (approximately 60 %) and is caused by defects in *CYBB* encoding for gp91-phox [40–44]. The AR forms are caused by defects in one of the cytosolic components of the NADPH oxidase: *NCF1* encoding for p47-phox (approximately 30 % of the cases), or *NCF2* encoding for p67-

phox, in *CYBA* encoding for p22-phox, and *NCF4* encoding for p40-phox (together 10 % of the cases) [40–44]. There are two reported cases of Rac2 deficiency associated with a defective respiratory burst (OMIM#608203) [45, 46]. The diversity of these mutations and the multiple affected genes provide an explanation for the clinical and genetic heterogeneity of CGD [47–51]. The severity of the clinical phenotype relates to the residual function of the NADPH oxidase; the greater ability to generate ROI the better prognosis [52].

Currently, the most frequent laboratory tests used for diagnosing CGD are the dihydrorhodamine -1,2,3 (DHR) and the nitroblue tetrazolium (NBT) tests. Flow-cytometry evaluation of the respiratory burst uses DHR as the fluorescent detector of hydrogen peroxide. The DHR assay has proven to be highly reliable and sensitive and is able to detect female carriers of the X-linked form of CGD. The DHR has replaced ROI measurements and the NBT slide tests as the primary screening assay for CGD in most laboratories [35–37].

The management of CGD includes prophylactic antibiotics and antifungals, along with aggressive and prolonged treatment of infections as they occur [35–37]. Prophylactic trimethoprim/sulfamethoxazole (5 mg/kg/day-trimethoprim) reduces the occurrence of major infections. Itraconazole prophylaxis showed marked efficacy in the prevention of fungal infection in CGD (100 mg daily for patients <13 years or <50 kg; 200 mg daily for those ≥13 years or ≥50 kg). IFN-γ is widely used in North America but less so in other areas of the world. IFN-γ is well tolerated and reduces the occurrence of severe infections in 70 % [53–55].

Myeloablative transplantation using either cord blood or bone marrow leads to immune recovery, high long-term donor chimerism, and good survival in chronic granulomatous disease. By contrast, gene therapy has been attempted only in a few patients. In most cases, it has been unsuccessful or only partially successful. Use of conditioning regimen has shown to be necessary, but in some patients adverse events such as myelodysplasia and AML have been observed. The development of new and safer vectors currently brings promising perspectives for gene therapy in CGD, especially in developing countries where it may be difficult to identify matched donors for HSCT [52, 56–58].

Severe Congenital Neutropenia

Severe Congenital Neutropenia (SCN) is a congenital defect of phagocyte number, characterized by persistent severe neutropenia and maturation arrest of myeloid differentiation at the promyelocyte-myelocyte stage, which lead to a variety of manifestations, mainly serious recurrent infections [59, 60]. Although single gene defects are well described, in some cases SCN is thought to be multigenic disorder with a common hematological phenotype [61, 62].

Mutations in the neutrophil-expressed elastase (*ELANE*) gene (OMIM#130130) is the only defect identified in approximately half of SCN cases and can be inherited either in AD or sporadic manner [63, 64]. Mutations in the HCLS1-associated protein X1 (*HAX1*) gene (OMIM#605998) are the main cause of AR SCN in 2007 [65]. A syndromic variant of SCN has recently been identified due to hemizygous mutations of the glucose-6-phosphatase, catalytic, 3 (*G6PC3*) gene (OMIM#611045). Mutations in G6PC3 can lead to various developmental defects, especially cardiac and/or urogenital malformations [66, 67]. An AD variant of SCN has also been described due to heterozygous mutations in the proto-oncogene growth factor-independent 1 (*GFI1*) gene (OMIM#600871) [68]. X-linked neutropenia is due to constitutively activating mutations in the Wiskott-Aldrich syndrome (*WAS*) gene (OMIM#300392) [69]. Increased apoptosis of myeloid cells are thought to be responsible for the neutropenia due to mutations in the*HAX1*gene, *ELANE* gene or the*G6PC3* gene. Mutations in the *GFI1* and the *WAS* lead to defective neutrophil production [62].

Patients with SCN mainly suffer from recurrent infections beginning in early infancy. Respiratory tract infections, diarrhea, abscesses, oral lesions, and mucocutaneous problems are the main clinical manifestations [59, 60, 70]. During the course of disease, the patients usually develop abscesses at different sites [59, 70, 71]; while neurological disorders have also been reported in some cases due to *HAX1* mutations [72]. All children who suffer from severe infections should have a CBC and differential as a first screening test [60]. Early onset recurrent infections associated with severe persistent neutropenia (<500/mm^3) should raise suspicions for SCN [59, 60, 73–75].

Granulocyte colony-stimulating factor (G-CSF) is first line therapy for SCN. Administration of G-CSF increases the production of neutrophils with a concomitant decrease in the severity and frequency of infections [61]. Myelodysplasia, which has been described in patients with the mutations in the ELANE gene following the long-term administration of G-CSF, is a serious complication of disease and is likely due to an acquired mutation in the granulocyte colony-stimulating factor receptor (*GCSF-R*) gene (OMIM#138971) [61, 76]. HSCT should be performed on patients who do not respond well to G-CSF therapy, and continue to have severe bacterial infections or develop myelodysplasia.

Leukocyte Adhesion Deficiencies

Leukocyte Adhesion Deficiency Type I

LAD-I (OMIM#116920) is a form of adhesion defect characterized by life-threatening recurrent bacterial infections. It is the most common of the LADs and occurs in 1 in 1 million individuals. The clinical manifestations of the disease occur in infancy or early childhood. Delayed umbilical cord separation

with omphalitis is a common presenting feature and should always raise the possibility of LAD-I. Skin infections may evolve to large ulcers and severe periodontitis is often present later in life and leads to early loss of teeth. A lack of inflammation is observed in the area of infection.

LAD-I is an AR disorder and is caused by mutations in the *ITGB2*gene (21q22.3), encoding the beta-2-integrin CD18 that is essential for firm adhesion of leukocytes to the endothelium [77]. The severity of the disease correlates with the degree of deficiency in CD18. The severe form occurs when CD18 expression is less than 5 %, while in the moderate form the expression is up to 20 %. Diagnosis is based on the clinical presentation and the presence of leukocytosis with neutrophilia (WBC 20,000–150,000 with 60–85 % neutrophils). There is a reduced CD18 expression as determined by flow cytometry on leukocytes and mutations in the *ITGB2* gene confirm the diagnosis [78].

Management of LAD-I focuses on controlling infections. HSCT represents the only cure of LAD-I, but gene therapy may be available in the future. Prognosis depends on the severity of the disease. Death in patients with the severe form of LAD-I occurs from infection within the first few years of life. Consequently, HSCT is the treatment of choice in severe forms of LAD-1 with a survival rate around 75 %. Patients with a moderate form of the LAD-1 have a better chance to survive into adulthood.

Leukocyte Adhesion Deficiency Type II (Congenital Disorder of Glycosylation IIc (CDG IIc))

LAD-II (OMIM#266265) is an extremely rare form of LAD characterized by recurrent infections with marked leukocytosis, severe growth delay and severe intellectual deficit. Facial dysmorphism is common, mainly depressed nasal bridge. Severe periodontitis is often present later in life. In adulthood, intellectual deficit and growth retardation govern the clinical picture LAD-II results from mutations in the *SLC35C1*gene (11p11.2), a fucose-transporter localized in the Golgi apparatus. All fucose containing glycoproteins are thus absent from the cell surface, including Sialyl Lewis X, the ligand for the selectin, leading to a defect in the first phase of the adhesion process, the rolling of leukocytes on the endothelium [79]. Diagnosis is based on clinical findings and complete blood count, revealing leukocytosis with neutrophilia. Blood typing is essential to look for Bombay group, which exist in all patients with LAD-II and confirmation is based on genetic analyses. Management should focus on controlling infections and includes antibiotics. Fucose replacement may improve leukocyte function in some cases. Infections in LAD-II are rarely life threatening and thus patients may live to adulthood.

Leukocyte Adhesion Deficiency Type III

LAD-III (OMIM#612840) is an extremely rare immunodeficiency characterized by both severe bacterial infections and severe bleeding disorder. Patients present with classical LAD-I features and Glanzmann thrombasthenia-like bleeding disorder. LAD-III is caused by mutations in the *FERMT3* gene encoding kindlin-3. Mutations in *FERMT3* gene result in an activation defect of all beta–integrins, leading to a defect in platelet aggregation [80].

Diagnosis is based on clinical findings and complete blood count revealing leukocytosis with neutrophilia (at the same level as in LAD 1, see above). Platelet aggregation assay and genetic analysis confirm the diagnosis. Management should focus on controlling infections and includes antibiotics, and blood transfusion as needed. Prognosis is poor and death occurs in early infancy if HSCT is not performed.

Mendelian Susceptibility to Mycobacterial Diseases (MSMD)

Mendelian susceptibility to mycobacterial diseases (MSMD) (OMIM#209950) refers to a group of PIDs characterized by severe and unexplained infections caused by poorly virulent mycobacteria, such as the bacilli Calmette-Guérin (BCG) vaccine and environmental mycobacteria [81]. Initially this group of PIDs was thought to be exclusively sensitive to mycobacterial infections and non-typhoidal extra-intestinal salmonellosis, now it is apparent these patients also have infections by other intracellular microorganisms such as *Cryptoccus neoformans* and *Paracoccidioides brasiliensis* [82, 83]. In endemic areas, they are highly prone to tuberculosis (TB) upon exposure to *Mycobacterium tuberculosis* [84–86]. Surprisingly, these patients are not prone to infections with other intracellular agents, including most viruses, or extracellular bacteria such as *Streptococcus pneumoniae* or *Haemophilus influenza* [87]. One early clue to the presence of a defect that lead to MSMD is the development of complications, after BCG vaccination, in countries where this vaccine is administered soon after birth.

The genetic defects underlying MSMD are physiologically related, and result in an impairment of interleukin-12-23 (IL-12, IL-23)- interferon gamma (IFN-γ) mediated immunity [87]. Mutations in seven autosomal genes (*IFNGR1*, *IFNGR2*, *IL12B*, *IL12RB1*, *STAT1*, *IRF8*, *ISG15*)–and in two X-linked genes (*NEMO*, *CYBB*) have since been discovered, accounting for only about half the known cases [88–91]. Mutations affecting *IFNGR1*, *IFNGR2* and *STAT1* impair cellular responses to IFN-γ [87, 92] (Fig. 2). Mutations affecting *IL12B* and *IL12RB1* impair the IL-12-dependent induction of IFN-γ, accounting for MSMD. Patients deficient in IL12B and IL12Rβ1 also have a deficiency in IL-17 production, accounting for the mild chronic mucocutaneous candidiasis in some of these patients [82, 83]. Mutations of *ISG15*,

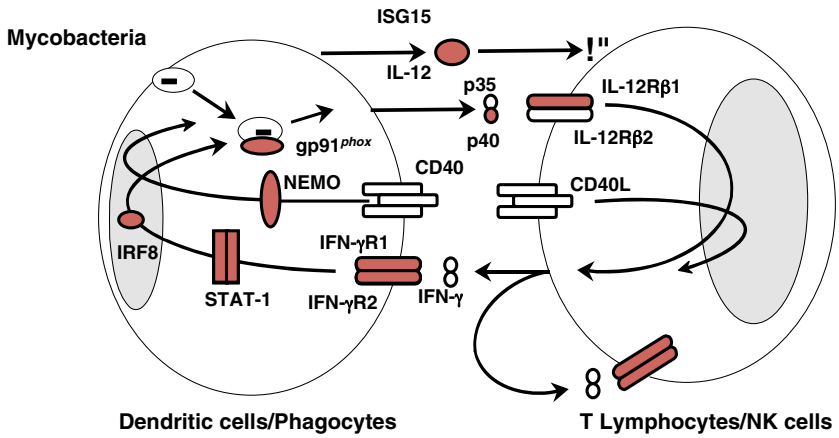

Fig. 2 MSMD: MSMD-causing gene products in the IL-12/23-IFN-γ circuit. Schematic representation of cytokine production and cooperation between monocytes/macrophages/dendritic cells and NK/T cells. Mutant molecules in patients with MSMD are indicated in *red*. Allelic heterogeneity of the nine genes results in the definition of 17 genetic disorders. The IL12/IFN-γ loop and the CD40L-activated CD40 pathway, mediating cooperation between T cells and monocyte/cells, are crucial for protective immunity to mycobacterial infection in humans. The *NEMO* mutations in the LF domain mostly impair CD40-NEMO-dependent pathways. The *CYBB* mutations, T1787 and Q231P, specifically abolish the respiratory burst in monocyte-derived macrophages. IRF8 is an IFN-γ-inducible transcription factor required for the induction of various genes, including IL-12. Mutations of *ISG15* impair the induction of IFN-γ

disrupting a circuit involving principally granulocytes and NK cells, also impair the induction of IFN-γ by IL-12 [91]. MSMD-causing mutations of *NEMO* impair the T cell- and CD40L-dependent induction of IL-12 by dendritic cells [93]. MSMD-causing mutations in *CYBB* impair the IFN-γ-dependent respiratory burst in macrophages [90]. Heterozygous mutations of the *IRF8* gene prevent the development of IL-12-producing $CD1c^+$ $CD11c^+$ dendritic cells [89].

MSMD due to AR complete IFNγR1 and IFNγR2 deficiencies are the most serious etiologies with onset in early childhood and first infections generally occurring around the age of three [94]. Serious disseminated infections with BCG and environmental mycobacteria are observed and can involve soft tissue, bone marrow, lungs, skin, bones and lymph nodes. Other infections with *Salmonella spp*., *Listeria monocytogenes* and viruses have been reported in these immunodeficiencies. MSMD due to partial IFNγR1, partial IFNγR2, complete IL-12Rβ1, complete IL-12B, complete ISG15, partial STAT1 and partial IRF8 deficiencies and MSMD due to partial X-linked recessive mutations are usually less severe [82, 83, 88, 95, 96]. They also have minor symptoms and some occur after the age of three to adulthood. Multifocal or unifocal mycobacterial osteomyelitis is a common presentation of AD IFNγR1 [97]. AR IL-12Rβ1 deficiency was the first genetic etiology of the severe forms of pediatric TB to be identified [86, 92]. Severe infections caused by non-typhoidal Salmonella species have been reported in half of patients, especially in those with IL-12Rβ1 or IL-12B deficiencies [82, 83, 98]. Other infections with *Paracoccidiodes brasiliensis*, *Leishmania and Klebsiella* have been reported in single patients [99–101].

Patients with a history compatible with MSMD should be referred to a clinical immunologist for definitive diagnosis, as general screening tests of immune function may be normal. Identification of the genetic defect underlying MSMD is crucial to the optimal management of patients. BCG vaccination should be avoided in those with MSMD or family history compatible with MSMD. Patients with complete IL-12B, IL-12Rβ1 or ISG15 deficiencies, and partial IFNγR1 or IFNγR2, IRF8 and STAT1 deficiencies respond well to antibiotic therapy and can also be treated with IFN-γ therapy [102]. HSCT should be considered in those with complete IFNγR1 and IFNγR2 deficiencies, but rates of engraftment are low. The failure to engraft following HSCT in complete IFNγR1 and IFNγR2 deficiencies is probably due to high levels of IFN-γ in the serum of these patients, which can affect homing of HSCs to the bone marrow niche [103, 104]. Prognosis depends on the specific mutation involved and the corresponding associated disorder.

Congenital Asplenia

Congenital asplenia is a very serious immune deficiency with the main clinical phenotype of sepsis. Impaired splenic function can have multiple causes and the correct identification of congenital asplenia is extremely important due to the high risk of death from infection. A simple review of the complete blood count for Howell Jolly bodies can be informative. Causes of functional hyposplenism are shown in Table I. Congenital asplenia may occur in isolation, or may be part of a heterotaxy syndrome. Heterotaxy syndromes can be sporadic or familial and have a variable genetic background and penetrance. Because the penetrance of these gene defects can be highly variable, it is possible that some of these may be involved in isolated congenital asplenia. To date, however, the only genes that have been identified in familial congenital

Table I Causes of functional hyposplenia

Autoimmune
Vasculitis
Systemic lupus erythematosus
Rheumatoid arthritis
Sjogren syndrome
Sarcoidosis
Autoimmune polyglandular syndrome I
Gastrointestinal
Celiac disease
Inflammatory bowel disease
Intestinal lymphangiectasia
Whipple disease
Hepatitis
Cirrhosis
Hematologic
Hemoglobinopathies
Histiocytosis
Fanconi anemia
Heme-oxygenase I deficiency
Metabolic
Storage diseases
Amyloidosis
Vascular
Splenic artery or venous occlusion
Celiacartery occlusion
Miscellaneous
HIV
Graft versus host disease
Corticosteroids
Splenic irradiation

isolated asplenia are NKX2-5 deficiency and RPSA deficiency [105, 106].

The importance of identification of the asplenic state cannot be overstated. In a study of children who died unexpectedly, approximately 2 % of the deaths were associated with asplenia [107]. One percent of all invasive pneumococcal infections are associated with asplenia [108].

Much of what we know regarding infections in asplenic patients comes from the study of patients with hemoglobinopathies. In the older infants, children and adults who are asplenic, the most common pathogens are *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Escherichia coli*, and *Neisseria meningitidis* Other fairly common bacterial infections in asplenic patients include *Staphylcoccus aureus*, *Pseudomonas sps*, *Klebsiella sps* and *Salmonella sps* [108]. In addition, asplenic patients are at unique risk of severe infection with *Capnocytophaga canimorsus*, a bacterium that has been associated with rapid onset sepsis and death after cat or dog bites [109]. Finally, asplenic patients seem to be particularly susceptible to babesiosis. In addition to the increased risk of bacterial sepsis in patients with asplenia, the mortality rate specifically from *Streptococcus pneumoniae* is approximately 30–50 % [108, 110].

Patients with heterotaxy syndromes and asplenia, as well as those who have hyposplenism due to other medical conditions, should have a liver-spleen scan. The liver-spleen scan is both sensitive and specific, however, it can be difficult to quantitate. A study of patients with sickle cell anemia demonstrated excellent correlation between a technetium sulfur colloid scans, pitted red cell count, and Howell-Jolly bodies [111]. Pitted red cell analyses are quantitative and reproducible, however, are not widely available. In the study of patients with sickle cell anemia, ultrasound did not predict spleen function. In the setting of herotaxy syndromes, both polysplenia and asplenia states can be associated with functional asplenia and the function can change over time [112].

In addition to the usual schedule of vaccines, *S. pneumonia*, *H. influenza* and *N. meningitidis* vaccines should be given [113]. It is preferable to give the conjugate vaccines prior to the polysaccharide vaccines. Antibiotic prophylaxis should be used for invasive dental procedures and specific recommendations should be made for travel. A letter documenting the urgency of treatment for fever and contact information should be provided. Alternatively, a medical alert bracelet could be worn.

Complement Deficiencies

Infections associated with complement deficiency are nearly always due to encapsulated organisms. There are three pathways: classical, lectin activation, and alternative. Each activation arm recognizes pathogens or waste products. C3 acts as a powerful opsonin and also activates B cells [114]. C3 binds to C5 to initiate the integration of the terminal or membrane attack components, C6, C7, C8, and C9. Defects in the activation arms are primarily associated with invasive infections with encapsulated bacteria such as *Haemophilus influenzae*, *Streptococcus pneumonia*e, and *Neisseria meningitidis* (Table II). Deficiencies of the early components are strongly associated with systemic lupus erythematosus. Patients with C3 deficiency also have an extremely high rate of membranous glomerulonephritis due to an inability to clear immune complexes. Deficiencies of the terminal components (C5-9), whose role it is to destabilize the bacterial cell membrane are associated with *Neisseria sp*. infections, in particular *Neisseria meningitidis* [115–117]. Early onset SLE, or SLE associated with deep infections with encapsulated organisms are a clue to complement deficiencies.

The identification of a specific defect is not always essential, however, in most cases it will facilitate management planning. The AH50 measures the intactness of the alternative pathway from factor B through C9. A CH50 measures the intactness of the classical pathway components from C1 through C9 and is the appropriate initial test for patients with

Table II Inherited complement deficiencies

Deficiency	Number of cases reported	Clinical features, diagnostic strategy
C1q	10–100	SLE, infections, CH50 near zero
C1r/s	10–100	SLE, infections, CH50 near zero
C4	10–100	SLE, infections, CH50 near zero
C2	Many	SLE, infections, some asymptomatic, CH50 near zero
C3	10–100	Infections frequent and severe, glomerulonephritis, CH50 near zero. Activating mutations are associated with aHUS.
Factor D	<10	Neisseria, AH50 near zero
Factor B	<10	Neisseria, AH50 near zero. Activating mutations are associated with aHUS.
Properdin	>100	Neisseria, AH50 diminished
MBL	Millions	Most asymptomatic, infections, SLE, CH50 normal, MBL assay required
C5	10–100	Neisseria, CH50 near zero
C6	>100	Neisseria, CH50 near zero
C7	>100	Neisseria, CH50 near zero
C8	>100	Neisseria, CH50 near zero
C9	Many	Neisseria, CH50 diminished
Factor I	10–100	Neisseria, HUS, C3 may be diminished, many require mutation analysis
Factor H	10–100	Neisseria, HUS, C3 may be diminished, many require mutation analysis
MCP	<10	HUS, mutation analysis required
C1 inhibitor	Many	Angioedema, C1 antigen and functional levels
CR3/CR4	>100	Leukocyte adhesion deficiency, very severe systemic infections, lack of pus, flow cytometry
CD59	<10	Paroxysmal nocturnal hemoglobinuria, flow cytometry

encapsulated organism infections. Slightly low CH50 levels are seen with chronic liver disease (most complement components are produced by the liver), in early infancy, and with poor sample handling. Deficiencies of early classical pathway components will be associated with an absent or nearly absent CH50 level. Therefore, slightly low levels are not helpful in this setting. To specifically identify the defective component, the next step is to obtain antigen levels of those components most likely to be involved, i.e., C1q, C1r, C1s, C4, C2, and C3. Not all mutations lead to diminished levels of protein and if the protein levels are all normal, labor intensive mixing experiments must be done where patient sera is supplemented with other purified components until the hemolytic activity has been restored. Mutation testing is not often undertaken.

At a minimum, all patients infected with unusual serotypes of *N. meningitidis*, with a positive family history of neisserial disease, or with recurrent neisserial disease should be evaluated for a complement component deficiency. C9 deficiency is associated with a CH50 approximately 1/3 of the normal range. There are several regulatory defects that are associated with neisserial infections where the CH50 is not diagnostic. In the case of alternative pathway defects, the CH50 may be slightly low due to consumption of C3; however, an AH50 will be near zero. Finally, certain mutations in factor H and factor I are associated with neisserial infections, and often the only clue is a slightly low CH50. In this specific setting, mutation analysis is often required.

For classical complement deficiencies *Haemophilus influenzae*, *Streptococcus pneumoniae*, *and Neisseria meningitidis* vaccines are usually administered. Prophylactic antibodies may be used for young children. C1 esterase inhibitor deficiency can be treated on demand for problematic episodes of angioedema or using prophylactic replacement of C1 esterase inhibitor. The defects associated with atypical hemolytic uremic syndrome have highly variable severity and treatment must be individualized, ranging from education to renal transplantation.

Disorders of T Cells and/or B Cells

Combined Immunodeficiencies (CID) and Severe Combined Immunodeficiency (SCID)

Combined immunodeficiencies (CID) including severe combined immunodeficiency (SCID) (OMIM #102700; #602450, #611291; #601457, #300400, #600802, #608971) are a group of rare genetic disorders characterized by profound deficiencies of T cell counts and/or function with or without intrinsic defects in B cell function. Several types of SCID/CID have been defined on the basis of immunologic and genetic criteria and mutations in 39 different genes have been found to cause these conditions [118].

According to newborn screening data, the incidence of SCID (including typical, leaky and variant SCID) is higher than expected and is now estimated to be at least 1 in 50,000 live births. In the Hispanic population, this incidence is higher and reaches 2.4/50000 [119, 120] Since most forms of CID are inherited as AR traits, they would be expected to be more common in areas with high rate of consanguinity [121]. Unfortunately, the diagnosis is often delayed due to the lack of recognized family history; absence of distinguishing ("classical") physical characteristics and/or their variability; and the lack of awareness among pediatricians about "early suspicion" and the work-up needed to confirm the diagnosis.

The CID, and in particular the SCID, have been rightfully recognized as pediatric emergency [122]. Early diagnosis of

CID is crucial so that life-saving treatment and precautions can be implemented to reduce the risk of early death and to improve the long-term quality of life [123]. These precautions include antimicrobial prophylaxis (in particular against *Pneumocystis jiroveci*), regular administration of IgG, and avoidance of live vaccines such as oral polio vaccine (OPV), BCG, rotavirus and measles, mumps and rubella (MMR). Furthermore, in cases where red blood cell and platelet transfusions are needed, they should be CMV negative and irradiated to avoid the risk of graft-versus-host disease (GVHD). However, survival ultimately depends on reconstitution of immune function that is usually achieved by means of HSCT and/or gene therapy in the case of X-linked SCID due to common gamma chain deficiency and adenosine deaminase (ADA) deficiency [124]. In the latter, enzyme replacement therapy may be an option in the interim [125]. There is strong evidence that the outcomes of HSCT are better if they are performed at an earlier age, emphasizing the need for an early diagnosis [126].

SCID, a genetically heterogeneous group of disorders affecting early T cell development is the most severe form of primary immunodeficiency [118]. Patients usually present in early infancy, typically with pneumonitis, chronic diarrhea and failure to thrive. Affected newborns may appear healthy, although engraftment of maternal T cells can lead to symptoms of GVHD such as erythroderma or chronic liver disease. However, when patients are exposed to pathogens they are unable to clear the (usually viral) infection(s) leading to persistent respiratory and gastrointestinal tract infections, most often presenting with bronchiolitis-like signs, malabsorption and malnutrition with classical 'falling off' the centile growth chart. Localized or disseminated BCG-osis may be the presenting feature in immunized infants; persistent superficial candidiasis is common. The isolation of several pathogens is common. For example, one classical feature of SCID is insidiously progressive respiratory distress with radiological evidence of interstitial pneumonitis and hyperinflation. Isolation of *Pneumocystis jirovecii,* as well as respiratory viruses, is common in these patients. Besides the variable degree of respiratory distress, malabsorption and superficial thrush, physical examination reveals no palpable lymph nodes and there is a lack of thymic shadow on chest radiography. A family history of early deaths due to infections (or unexplained) may be important, particularly in consanguineous families.

Over the last decade a significant number of patients have been reported presenting with profound combined immunodeficiency beyond the age 1 year. These patients present with atypical features of inflammation and autoimmunity, such as: prominent skin rash or erythroderma; granulomatous infiltrations (skin, lungs, etc.); lymphadenopathy; hepatosplenomegaly; evidence of thymic presence on chest radiography; autoimmune cytopenias (haemolytic anemia, thrombocytopenia, neutropenia); and/or lymphoproliferative disease and malignancy. The pathogens causing recurrent and persistent opportunistic infections in these 'SCID variants' are usually the same as in classical SCID [127, 128].

Most of the SCID variants are due to hypomorphic mutations of the same genes that cause classical SCID [118]. In contrast to null mutations, hypomorphic mutations code for proteins with residual function. Thus, hypomorphic mutations lead to residual T cell immunity and are presumably responsible for eosinophilia and elevated IgE levels as frequently seen in Omenn syndrome [129]. Another group of patients has either underlying defects in genes involved in late T cell development and/or T cell activation [118, 130], or defects that affect T cell survival (e.g. MST1 deficiency, Coronin-1A mutations) [131], and present with features of functional CID with a severe impairment of immune response to pathogens, prominent signs of immune dysregulation and increased risk of malignancy, in particular EBV driven lymphoproliferative disease. Depending on the underlying gene defect, some patients may present with clinical features as severe as SCID patients, or other clinical features such as ectodermal dysplasia and congenital myopathy, delayed development, warts, chronic mucocutaneous candidiasis, severe allergy/food intolerance, and heart defects [131].

A complete and differential blood count is crucial to detect lymphopenia, which is observed in many CID patients, in particular within the 'classical SCID' group. Importantly, lymphocyte count has to be accurately interpreted according to the age matched normal values as neonates and young infants have a higher absolute lymphocyte count compared to older children and adults [132]. However, a normal lymphocyte count does not exclude SCID/CID diagnosis. Neutropenia, thrombocytopenia and anemia can also be detected and could constitute an autoimmune manifestation of the disease that should alert the pediatrician especially in a young child.

Measurement of serum IgG, IgA, IgM and IgE levels has to be interpreted according the age of the patient. Severe hypogammaglobulinemia is a typical finding, but normal immunoglobulin level does not exclude the diagnosis. If the patient has received any vaccine, the assessment of the specific antibody production (tetanus and diphtheria toxoid, *Haemophilus influenzae type b*) will complete the evaluation of humoral immunity, even if the immunoglobulin levels are normal.

If clinical manifestations and/or biological investigations give rise to any suspicion of SCID/CID, the patient has to be rapidly referred to a specialized center because a deeper immunologic investigation is required to assess the diagnosis and type of SCID/CID. Enumeration of T cells subsets, B cells and NK cells constitutes the first step. The absolute numbers of T cells, B cells and NK cells need to be compared with the normal age-matched range. The absence, or a profound decrease, in the number of naïve T cells is consistent with classical SCID. The presence or absence of B cell and NK cells is useful in narrowing the likely genetic causes for SCID.

Finally, it should be noted that a normal T cell count does not exclude a SCID/CID. Maternal engraftment or transfusion of blood products with viable T cells can lead to a graft versus host like disease with normal or elevated numbers of T cells. Enumeration of naïve T cells and T cell functional studies can be helpful in these cases to further clarify immune status in cases where T cell numbers are normal.

NBS Using the TREC Assay for the Early Diagnosis of SCID

Beginning with Wisconsin in 2008, several states in the United States have begun statewide newborn screening for SCID using the T cell receptor excision circle (TREC) assay. TRECs are small pieces of circular DNA that are formed in the process of generating a mature T cell receptor in the thymus. The TREC assay enumerates the number of TRECs by real-time PCR on DNA extracted from the dried blood spot of a newborn screening card [133]. As TRECs do not replicate, TRECs serve as a biomarker for the number of newly formed naïve T cells, which are profoundly decreased in all molecular forms of typical SCID [133, 134]. The results of an abnormal TREC assay must be confirmed by the enumeration of the number of naïve T cells in peripheral blood by flow cytometry. The early identification and HSCT of infants with SCID has been shown to improve prognosis [135]. Therefore, it is likely that NBS for SCID will substantially improve the overall outcome of infants with SCID in states and countries in which it is performed.

The TREC assay has been shown to be a highly sensitive assay to detect SCID with severe T cell lymphopenia and in some cases other causes severe T cell lymphopenia [136, 137]. The sensitivity of the TREC assay for severe T cell lymphopenia or SCID variants is not absolute, and negative (normal) TREC assays have been reported in MHC II deficiency and delayed-onset ADA deficiency [119]. Furthermore, it is likely that other patients with leaky or variant SCID or other CID may not be reliably identified by NBS using the TREC assay. For example, in the CID caused ZAP-70 deficiency circulating CD8 T cell numbers are extremely low but CD4 T cell numbers are normal, which could result in a negative NBS using the TREC assay. Therefore, in an infant that has clinical features suggestive of SCID, the diagnosis must be pursued even in states or countries that perform NBS using the TREC assay.

Hyper- IgM Syndromes or Defects in Class Switch Recombination

The hyper-IgM syndromes comprise a group of heterogeneous disorders currently named, defects in class switch recombination [138]. X-linked, autosomal recessive and autosomal dominant forms of inheritance exist and five distinct molecular forms have been recognized. Such molecular characterization has provided insights into how B cells produce different antibody isotypes of high affinity and specificity. Two mechanisms define this process: 1) class switch recombination (CSR) and 2) somatic hyper mutation (SHM). In the former, the binding of CD40 (on B cells) to its ligand CD40Ligand (on activated T cells) allows B-cells to switch from generating only IgM antibodies to producing different high affinity immunoglobulin isotypes, IgG, IgA or IgE. Simultaneously, SHM improves antibody specificity by creating mutations within the variable regions of the antibody molecule. These two events allow for the selection and proliferation of B-cells capable of producing specific and high affinity antibodies to a particular antigen. Consequently, effective antigen clearance and development of both antigen specific memory B-cells and long-lived plasma cells occurs [139].

At times, patients with hyper IgM syndromes may be confused with patients with CVID. Close attention to the clinical phenotype and associated laboratory studies can alert the practitioner towards the correct diagnosis. The laboratory findings common to most hyper IgM (HIGM) syndromes include low or borderline levels of IgG, usually absent IgA with elevated or normal levels of IgM in the setting of either recurrent infections or opportunistic infections such as *Pneumocystis jirovecii* pneumonia and respiratory failure. It is important to note that IgM levels can vary depending on the molecular defect (see below), and age of presentation: the younger the child, the more "normal" the IgM level. Children less than 3 months may have IgG levels that reflect maternal transfer. There is usually a lack of response to routine childhood vaccinations, while isohemagglutinins are usually normal or elevated. Standard flow cytometry analyses of peripheral blood lymphocytes, reported by most commercial laboratories, including T, B, and NK populations are usually normal. If B cell subpopulations are analyzed, there may be a lack of class switched memory B cells (CD27+ IgM−), which can be similar to that seen in patients with CVID. Proliferation studies to mitogens will be normal but T-cell cytokine production of INF-γ and TNF-α is defective [140]. Patients with XHIGM will not express CD40L when T cells are activated in functional studies. These should be performed in laboratories with experience in PID analysis, as use of anti-human CD40L monoclonal antibody alone can miss up to 32 % of CD40L mutations [141]. In addition, rare patients with mutations in the intracytoplasmic tail of CD40L may have normal CD40L expression by flow [141]. Defects in CD40 may be easily recognized if the lymphocyte subpopulation flow analysis includes CD40. Finally, neutropenia can be present in 50 % of cases of X-linked HIGM (XHIGM) and should not be confused with neutropenia seen in XLA or CVID.

The following is a summary of the different molecular forms that comprise the hyper-IgM syndromes, their clinical presentation, unique laboratory findings, and treatments.

X-Linked Hyper IgM (XHIGM; HIGM Type 1)

XHIGM (OMIM#308230) was the first of the hyper-IgM syndromes described and has an estimated prevalence of 1:1,000,000 [142] and is caused by mutations in CD40 Ligand (*CD40LG*) gene [143–147]. In addition to controlling immunoglobulin class switching, CD40L enables antigen priming of T cells, activates macrophages and allows for maturation of dendritic cells [140, 148]. Due to the lack of CD40L, lymph nodes lack germinal center formation [149].

Clinical presentation includes recurrent sinopulmonary and gastrointestinal infections caused by intracellular and extracellular pathogens [142, 150]. Susceptibility to rare fungal pathogens has been recently noted [151]. Opportunistic infections such as *Pneumocystis jirovecii* can be the initial presenting illness in up to 32 % of patients [152]. *Cryptosporidium* is also common and has been associated with sclerosing cholangitis contributing to significant morbidity and mortality [142, 150, 153]. Parvovirus induced aplastic anemia has been reported, and neutropenia can occur in up to 50 % of patients [142]. In addition, susceptibility to autoimmune diseases and malignancies are recognized [150, 154, 155].

The treatment of HIGM syndrome includes the use of IgG antibody replacement and prevention of opportunistic infections such as *Pneumocystis* with trimethroprim-sulfamethoxazole. Despite improved diagnosis, the overall survival of XHIGM remains poor, with 40 % of patients surviving into the third decade of life [142, 150, 156]. Because of the morbidity and mortality related to this condition, HSCT has been performed since the mid 1990's. Initial case reports or small series were very encouraging [142, 157–166]. In 2004, Gennery et al., reported data collected on 38 patients with XHIGM who had undergone HSCT in different European centers. Twenty-six of 38 patients were surviving 1.2 to 9.3 years post transplantation. Of these 22/26 (58 %) showed normal CD40L expression and were considered cured from the disease. All deaths were associated with infection and in 50 % of cases cryptosporidium had been identified [167]. Comparative analysis of HSCT and medical management has not been performed and long-term clinical outcomes data are necessary to establish best therapeutic options. Recently, recombinant CD40L (rCD40L) was administered to three patients with XHIGM leading to specific delayed type hypersensitivity, adequate IFN-γ and TNF-α production by mitogen activated T-cells and changes in lymph node architecture [168]. rCD40L is not currently available clinically and the long-term utility of this approach remains to be determined.

AR Type 2 (HIGM Type 2)

HIGM type 2 (OMIM#605258) is due to mutation in activation-induced cytidine deaminase (*AICDA; AID*). The inheritance pattern is AR and the gene is located in chromosome 12p13. In contrast to XHIGM, the defect is intrinsic to B-cells, which are not able to isotype switch despite normal CD40 and CD40L binding [169]. In the absence of functional AICDA, dsDNA breaks, necessary for CSR does not occur, and both isotype switching and SHM are impaired. As a result, patients have a profound decrease in IgG, and IgA with elevated IgM. Isohemagglutinins are present.

Clinical presentation is similar to XHIGM, except that opportunistic infections are the exception; diffuse lymphoid hyperplasia and lymphadenopathy are commonly encountered. This is thought to be the consequence of constant stimulation and expansion of B-cells within lymphoid organs. Autoimmunity has been described in up to 25 % of patients and hemolytic anemia and thrombocytopenia are most common [170–173]. Diagnosis tends to occur later than in XHIGM as gamma-globulin replacement therapy provides clinical improvement, including the lymphadenopathy [169, 173].

AR Hyper IgM Type 3 (HIGM Type 3)

HIGM type 3 (OMIM#606843) is due to mutations in *CD40 (TNFSFR5)*. The inheritance pattern is AR and the gene is located on chromosome 20q12-q13.2. CD40 is expressed on antigen presenting cells such as B-cells, dendritic cells and macrophages. In addition, CD40 is present on endothelial cells and bronchial epithelial cells [174]. The clinical phenotype is similar to those with mutations in CD40L and, to date, several families have been characterized, with the largest series comprising a total of 11 patients [175–177]. Treatment includes gamma-globulin infusions either subcutaneously or intravenously along with antibiotic prophylaxis for opportunistic infections such as *P. jirovecii.* HSCT has been successfully performed [178, 179].

Hyper IgM Type 4 (HIGM Type 4)

In contrast to AID defects, patients with HIGM type 4 (OMIM#608184) have impaired CSR but maintain normal SHM. Mutations are localized to the C-terminal domain of the AID [180]. Less than 20 patients have been carefully described. Most were sporadic mutations and age at presentation is older than classic XHIGM. Clinically, patients resemble HIGM type 2 but appear to have a milder course as some may have residual IgG production. Recurrent sinopulmonary infections, sepsis, lymphadenitis, osteomyelitis and autoimmune cytopenias have been reported [181]. Similar to HIGM type 2, lymphadenopathy can occur but appears to be less

pronounced than in HIGM type 2. B cells are present and, like HIGM type 2, these patients are not susceptible to opportunistic infections [181]. Management is similar to HIGM type 2. An AD form of type 2 HIGM has also been described when the defect in the C-terminal region of AID behaves as a dominant negative deficiency [182].

AR Hyper IgM Type 5 (HIGM Type 5)

HIGM type 5 (OMIM#608106) is due to mutations in the gene encoding uracil-DNA-glycosylase (UNG) and is inherited as an AR pattern. Patients with this defect have impaired CSR but retain an abnormal pattern of SHM [183]. In the absence of UNG, genomic uracil accumulates in the nucleus and while the initiation steps in CSR appear intact, DNA double stranded breaks do not form within switch region (Sμ), preventing effective CSR [184]. The clinical characteristics of the initial 3 patients described are similar to AID defects: susceptibility to bacterial infections, lymphoid hyperplasia and elevated levels of IgM with variable levels of IgG [183]. Treatment for this type of HIGM is similar to HIGM type 2.

Other differential diagnoses to consider when patients with recurring infections have elevated levels of IgM along with low IgG and IgA are: ataxia telangiectasia (AT), MHC class II deficiency, Lig4/cernunnos deficiency and defects in NEMO, also known as IKK-γ. In the former case, the diagnosis may be difficult, as telangiectasias may lag behind the ataxia. In these cases the alpha-fetoprotein can be helpful as it is invariably elevated in AT. Standard flow based assays can identify MHC class II expression on circulating B cells and thus provide fairly quick diagnosis for MHC class II defects. Finally patients with NEMO defects have features of ectodermal dysplasia including presence of conical teeth that allow their recognition (see In born errors of NF-κB-mediated immunity section).

Activated PI3 Kinase δ Syndrome

Recently, dominant activating mutations of the *PI3KD* gene (phosphatidylinositol-3-OH δ, PI3K δ gene) (OMIM#602839) were found to cause a CID characterized by recurrent sinopulmonary infections, lymphadenopathy, splenomegaly, nodular lymphoid hyperplasia of mucosal surfaces and severe infections due to herpes group viruses (CMV, HSV, EBV, VZV) [124, 185]. The age of onset is variable but can be quite early with recurrent respiratory tract infections in the first few months of life. Many patients have severe pulmonary disease with progressive bronchiectasis. In terms of readily available screening tests of immune function, the majority of the patients were lymphopenic with low numbers of circulating CD4- or CD8-T cells, decreased numbers of naïve CD4 T cells, decreased numbers of B cells including isotype class switched memory B cells. Low total serum IgG, low IgG2 and high IgM as well as impaired specific antibody responses to vaccines were found in many patients. The optimal treatment of these patients is unknown but antibody replacement therapy and antimicrobial therapy were used in many patients that continued to have progressive pulmonary disease. HSCT resulted in marked improvement in one patient whereas another patient improved using rapamycin.

X-Linked Agammaglobulinemia (XLA) and AR Agammaglobulinemia

X-linked agammaglobulinemia (XLA; OMIM #300755; gene *BTK*) was first described over 50 years ago by Colonel Ogden Bruton [186]. The estimated prevalence is 1:100–379,000 live births [187, 188]; is caused by mutations in the Bruton's tyrosine kinase (*BTK*) gene [189, 190]; and affects all ethnic groups.

Clinical presentations were first compiled for a group of 96 patients by Lederman et al., almost 30 years ago [191]. Twenty years later, despite a family history of XLA, over 50 % of affected children are not diagnosed promptly at birth but when clinical manifestations of the disease arise [188]; most patients will present clinical symptoms as maternal antibodies wane between 3 and 6 months. Over 50 % will come to medical attention by 1 year and >85 % of patients will have developed symptoms by 5 years. In an era of antibiotics, these patients come to medical attention due to recurrent infections; classically otitis media, sinusitis and pneumonias. *Pseudomonas sps.* sepsis may be the initial presentation and in such patients neutropenia is frequently encountered. A common pathogen causing meningitis is *Streptococcus pneumoniae*, whereas it is rare to isolate a pathogen in patients with pneumonia. Pyoderma gangrenosum and skin infections are not uncommon and chronic diarrhea is caused by *Giardia lamblia* 50 % of the time. Most patients with XLA can clear viral infections with one exception, enteroviruses. Vaccine induced polio identified both patients with XLA and SCID in the past. Unfortunately, due to contaminated IgG preparations with Hepatitis C, some patients became infected which resulted in liver failure, liver transplant and death. Inflammatory bowel disease and arthralgias are not uncommon. Pathogens such as *Ureaplasma urealyticum* can cause arthritis and must be investigated. As patients survive into adulthood, reports of malignancies have been described and the potential importance of colorectal surveillance should be entertained [188, 192].

The diagnosis of XLA should be pursued in children with frequent upper and lower respiratory tract infection, in particular respiratory tract infections that occur out of proportion to what is normally expected or are poorly responsive to medical therapy. Invasive bacterial infections such as sepsis or meningitis should also prompt an evaluation. Apart from a complete blood count, which should be performed on any patient suspected of having a PIDD, quantitative serum immunoglobulins is the single best test to identify patients with XLA. In XLA IgG concentrations are usually <200 mg/dl, but in some

cases may be higher but are almost always <400 mg/dl [193]. IgA and IgM are very low or undetectable. The results of the specific immunoglobulin isotypes must always be adjusted according to the age of the child. Patients with XLA will not make specific antibodies to vaccines like tetanus, diphtheria, *Streptococcus pneumococcus* or *Haemophilus influenza* type B, and cannot make isohemagglutinins. However, if tested before 6 months of age, maternal IgG levels can be present. In a patient with panhypogammablobulinemia, a lymphocyte subset analysis by flow cytometry should be performed. Patients with XLA will show profoundly decreased numbers of circulating B cells (<2 %) with normal levels of T cells and NK cells. Ten to 20 % of patients with XLA may have neutropenia with infection, which resolves with therapy [188]. Sequencing the *BTK* gene provides confirmatory testing. Many commercial laboratories offer this diagnosis as part of standard of care, and can identify approximately 90 % of reported mutations and allow for prompt carrier detection.

Treatment of XLA consists of infusions of pooled gammaglobulin products. This can be administered weekly via a subcutaneous route or intravenously (IVIG) every 3–4 weeks, which is based on the half-life of IgG molecules. Some centers will use prophylactic antibiotics, but the prompt use of antibiotics for intercurrent infections is indicated. Live vaccines should not be administered, particularly oral polio. Complications including inflammatory bowel disease and enteroviral infections may be difficult to manage and may contribute to mortality.

Autosomal recessive agammaglobulinemia (ARA) represent a group of rare disorders of early B cell development and comprise 7–8 % of all patients with agammaglobulinemia who have absent B cells [194]. The defects result from mutations in the gènes that encode for molecules essential for the assembly of an effective B-cell receptor complex and include: the μ heavy chain (OMIM # 147020; Chr 14q32.33), λ5 (OMIM# 146770; Chr. 22q11.23), Igα (OMIM# 613501; CD79A; Chr. 19q13.2), Igβ (OMIM#147245; CD79B; Chr 17q23.3) along with an adaptor protein called BLNK (OMIM#613502; Chr.10p24.1). Clinical manifestations and treatment is similar to XLA. The molecular form of a severe and early defect in B cell development was recently reported in a patient lacking the p85α subunit of PI3K [195].

Immunodeficiencies Associated with Syndromes

Ataxia Telangiectasia

Ataxia Telangiectasia (AT) is an AR chromosomal breakage syndrome (OMIM#208900), with progressive cerebellar neurodegeneration, immunodeficiency, radiosensitivity, and increased cancer susceptibility. AT results from a defect in the DNA repair response due to mutations in the ataxia-telangiectasia mutated (*ATM*) gene. The ATM protein mediates the cellular response to double strand breaks in DNA, also known as the DNA damage response. The defect in *ATM* results in defective DNA repair during cellular processes including the recombination of T and B lymphocyte receptors, cell cycle checkpoints in dividing cells, and *ATM* dependent apoptosis during CNS development. These defects lead to susceptibility to recurrent infections, genomic instability in proliferating cells, and neuronal damage. Individuals of all races and ethnicities are affected equally. Impaired DNA damage signaling due to mutations in *ATM* defines the pathogenesis of AT, but other diverse cellular functions of *ATM* are described [196]. The incidence worldwide is estimated to be between 1 in 40,000 and 1 in 100,000 people. Ataxia telangiectasia is probably the second most frequent AR cerebellar ataxia worldwide (1 case per 150,000 persons to 1 case per 200,000 persons) [197].

In AT, the associated neurologic features include progressive cerebellar ataxia, generalized hypotonia, intention tremor, dysarthria, abnormal eye movements, choreoathetosis, diminished or absent deep tendon reflexes, positive Babinski sign, loss of vibration sense, and axonal degeneration of peripheral nerves. In AT-like disorder (ATLD), the features are limited to progressive cerebellar ataxia, abnormal eye movements and dysarthria [198]. Progressive cerebellar neurodegeneration is a distinguishing feature of AT. The symptoms become apparent often as the child learns to walk, with development of gait abnormalities. Later, the other features mentioned above become more apparent. Patients with AT eventually become reliant on a wheelchair, usually by 10 years of age. Causes of death in AT include diseases of the respiratory system, such as chronic lung disease, or cancer [196].

Recurrent infections tend to be of the upper respiratory tract, and the frequency worsens over time with increased risk of aspiration pneumonia. Other infections are otitis, sinusitis, upper and lower respiratory infections with *Haemophilus infuenzae or Streptococcus pneumonia*. Patients with recurrent infections are managed with prophylactic antibiotics and immune globulin replacement therapy. Cancer occurs in AT with a lifetime risk of approximately 30 % (mostly leukemia and lymphoma). Children afflicted with AT can develop acute lymphocytic leukemia of T cell origin, and leukemia in older AT patients is usually an aggressive T cell cancer similar to a chronic lymphoblastic leukemia. *ATM* mutations in heterozygote carriers are considered cancer predisposing, and these mutations have been strongly linked to breast and other cancers.

AT must be considered in any child with progressive ataxia. Low or absent IgA, IgE and IgG2 are common findings. Lymphopenia with low CD4 T-cell numbers is also observed. Alpha-fetoprotein is elevated in >90 % of affected patients. Immunoblot for the ATM protein is a sensitive and specific clinical test, (>90 % of patients have no detectable ATM in peripheral blood lymphocytes). Significantly decreased

viability after radiation of AT cells in culture is observed compared to normal controls. Over 600 mutations are identified so far; therefore whole gene sequencing may be required to identify a specific definitive mutation [199]. Patients may initially present to the neurologist. In a recent retrospective review of pediatric cerebellar atrophy, 300 cases over a 10-year period at a tertiary children's hospital, were evaluated. The etiology of the majority (53 %) of cases remained unknown, and the diagnosis of AT ranked 3rd most common (11/300) of the group with known diagnosis, after mitochondrial disorders and neuronal ceroid lipofuscinosis. Of the AT cases, the average age of onset was 2 years, and in all cases the AFP (alpha-fetoprotein) was elevated, immunoglobulins decreased, and diagnosis confirmed via ATM mutation or protein assay [200].

There is no cure for AT. Antibiotic prophylaxis and IgG replacement comprise the usual approach to management of recurrent infections [201]. Radiographic studies should be used only when absolutely necessary, to avoid excess radiation. The use of certain chemotherapies for cancers in AT is also challenging. Physical, occupational, and speech therapy provide support to the patient for activities of daily living. Genetic counseling should be offered to relatives at risk and parents of an affected child. Psychological support and rehabilitation for the families and patients is recommended.

Wiskott-Aldrich Syndrome (OMIM#301000)

Wiskott-Aldrich syndrome (WAS) is an X-linked primary immunodeficiency disease that is classically characterized by the triad of thrombocytopenia with small-size platelets, eczema, and immune deficiency [202, 203]. The WAS gene, responsible for WAS, encodes a protein called the Wiskott-Aldrich syndrome protein (WASp) [204] that is expressed only in cells of the hematopoietic lineage [205]. WASp is involved in cytoskeletal reorganization and plays a role in T cell development, T cell function, immune synapse stabilization, trafficking of hematopoietic cells (reviewed in [206]), B cell homeostasis [207, 208] and dendritic cell function [209, 210]. WAS gene mutations are also responsible for X-linked thrombocytopenia (XLT), characterized by congenital thrombocytopenia and small platelets, without immunodeficiency. Mutations leading to unregulated activation of WASp are responsible for X-linked neutropenia [69].

The clinical presentation of WAS can be very diverse, and the disease severity can range from a life threatening condition with opportunistic infections combined with autoimmune manifestations (severe classical WAS), to a chronic but mild thrombocytopenia with few or no clinical hemorrhagic manifestations. The initial clinical signs may be present early during the neonatal period or the first year of life. Patients may have hemorrhagic manifestations such as epistaxis, purpura, petechiae, bruising, prolonged bleeding after circumcision, gastrointestinal bleeding (bloody diarrhea, hematemesis, melena), or rarely, intracranial hemorrhage [211]. Eczema, which usually develops during the first year of life, can be severe, generalized and difficult to manage, or mild and localized [211], and can also be complicated by secondary infections such as abscess, cellulitis or Herpes simplex (varicella). Eczema, although frequent, is not a consistent feature and its absence should absolutely not lead one to rule out WAS.

Patients with WAS have increased infections such as recurrent otitis media, sinusitis and pneumonia due to common bacterial pathogens. WAS patients also are uniquely predisposed to infection due to encapsulated organisms that can lead to life threatening meningitis or sepsis. Infections with *Pneumocystis jiroveci*, CMV, EBV, *Candida albicans* as well as severe molluscum contagiousum occur [211]. Autoimmune and inflammatory complications have been reported in 40 to 72 % of patients [211, 212] and include autoimmune hemolytic anemia, non-specific vasculitis, arthritis, inflammatory bowel disease and Henoch-Schönlein purpura alone or together with IgA nephropathy. Malignancies are usually described in older patients (adolescent and young adults) and are frequently associated with a poor prognosis [211].

A diagnosis of WAS should be considered in any boy with congenital thrombocytopenia, thrombocytopenia early in life, or chronic thrombocytopenia. Intermittent thrombocytopenia uncommonly occurs and this disease has been named intermittent XLT (iXLT) [213]. In XLT and WAS, platelets are typically small with a mean volume of platelets (MPV) of 3.8 to 5.0 fl (normal range is 7.1 to 10.5 fl) [214]. However, MPVs are frequently misclassified as being normal when measured using clinical hematology analyzers. Therefore, one should ask that a hematologist assess platelet volume using microscopy.

In addition to the thrombocytopenia, WAS patients have an immunodeficiency that involves both cellular and humoral immunity. Patients usually have normal serum IgG, low serum IgM and elevated levels of serum IgA and IgE [214–216]. Isohemagglutinin titers are low and antibody responses to polysaccharides are depressed [211, 214–216]. Antibody responses to protein antigens are frequently reduced with decreased isotype switching. Lymphopenia becomes more severe over the years and affects most lymphocyte subsets [211, 214]. T-cell function is depressed but not absent, with a decreased lymphoproliferative response to anti-CD3 antibody, mitogens or antigens in vitro [211, 217]. When a diagnosis of WAS or XLT is considered, it should be confirmed by sequencing of the WAS gene. Depending on the clinical situation, the assessment of WASp expression may be useful in helping to evaluate the severity of the disease.

Importantly, in a patient with congenital thrombocytopenia, the detection of a mutation in the *WAS* gene does not necessarily mean that the patient has a classical WAS. The patient

may also have XLT. The difference is crucial because in WAS, HSCT is highly recommended, and usually as soon as possible since the overall survival after HSCT is better if performed in younger patients [218, 219]. More recently, gene therapy has been successfully performed in *WAS* [220]. Before -HSCT, the patient should be managed with IVIG, *P jiroveci* prophylaxis, and sometimes with immunosuppressive drugs to manage autoimmune manifestations. On the other hand, in XLT, HSCT is generally not recommended [221], neither is IVIG substitution, nor *Pneumocystis jiroveci* prophylaxis. However, patients with refractory severe thrombocytopenia before the age of 2 have a poor prognosis and should also receive an HSCT, even in the absence of other signs [222]. In addition, it is important to consider that a definitive diagnosis of XLT can only be made after several years of follow-up, and, in any case, after the age of two because the immunodeficiency and its consequences may appear progressively. The characterization of the WASp mutation can be helpful in difficult situations because null mutations with no WASp expression are usually associated with WAS, while milder mutations with persistent WASp expression are associated with XLT with a relatively good genotype/phenotype correlation [221, 223, 224]. Nevertheless, the rule is not absolute and, in some cases, comprehensive evaluation of the immune system is required to distinguish XLT from WAS. A scoring system has been developed to help delineate those patients that would most benefit from conservative management or a HSCT (Table III).

In the situation of a young boy with a severe infection (CMV, for instance) and a thrombocytopenia, a normal initial basic immunological work-up could be falsely reassuring leading one to believe that the thrombocytopenia was autoimmune or related to the infection. In this situation, one must always think about a possible diagnosis of WAS and consider assessing the size of the platelets, asking for specialized advice and/or testing for WASp mutations.

Table III Scoring system for WAS

	XLT	Classic WAS			
Score	1	2	3	4	5
Thrombocytopenia	+	+	+	+	+
Small platelets	+	+	+	+	+
Eczema	−	(+)	+	++	(+)/+/++
Immunodeficiency	−/(+)	(+)	+	+	(+)/+
Infections	−	(+)	+	+/++	(+)/+/++
Autoimmunity and/or malignancy	−	−	−	−	+

−/(+) absent or mild

(+) mild, transient eczema or mild, infrequent infections not resulting in sequelae

+ persistent but therapy-responsive eczema and recurrent infections requiring antibiotics

++ eczema that is difficult to control and severe, life-threatening infections

Because patients with XLT may develop autoimmune disorders or lymphoma, although at a lower rate than those with classical WAS, a progression from a score of 1 or 2 to a score of 5 is possible for XLT

Hyper IgE Syndrome (HIES)

Hyper IgE syndrome was initially described in two girls with recurrent, "cold" (non-inflammatory) Staphylococcal abscesses, pneumonias, and eczema. Elevated IgE was not found to be a feature of the syndrome until sometime later. As family kindreds began to be identified, it became clear that there were two modes of inheritance with similar but discernable phenotypes: An AD form (AD-HIES) characterized by a combination of bacterial infections, eczema, and systemic features including atraumatic fractures, scoliosis, and vascular aneurysms [225] and an AR form (AR-HIES) characterized by bacterial infections, cutaneous viral infections, eczema, and susceptibility to malignancy.

AD-HIES

In 2007, AD-HIES was linked to heterozygous, autosomal-dominant mutations in the Signal Transducer and Activator of Transcription 3 (*STAT3*), a transcription factor that plays a critical role in cellular responses to a wide array of cytokines (IL-6, IL-21, etc.) and growth factors (Oncostatin M (OSM), Leukemia Inhibitory Factor (LIF), etc.) (OMIM#147060) [226]. All identified mutations create a dysfunctional protein that has a dominant-negative effect when it dimerizes with either mutant or wild-type STAT proteins in the cell.

Virtually all patients with STAT3 defects develop *Staphylcoccus aureus* pneumonia. This may occur in childhood and frequently leads to development of large pneumatoceles. This is the most significant cause of morbidity and mortality in most patients. Eczema occurs in almost all patients, with 80 % having a pustular eczematous rash as newborns. Boils and skin abscesses, primarily caused by *Staphylcoccus aureus*, occur in 87 %. Candidal infections of the mucosa and nails develop in 83 %. Other frequent manifestations include retained primary teeth, atraumatic fractures, scoliosis, joint hyperextensibility, vascular aneurysms, and characteristic "coarse" facial features. IgG, IgA and IgM levels are usually normal, but IgE is frequently elevated in infancy and ultimately reaches a peak serum level >2,000 IU/mL in most patients. Despite this, atopic asthma is relatively uncommon in this disease. Patients typically have low Th17 cell numbers [106, 227]. AD-HIES can present sporadically with no family history. Despite the systemic nature of the disease, most patients survive into adulthood and many have a normal lifespan.

AR-HIES

AR-HIES was initially linked to mutations in the tyrosine kinase TYK2 in a single patient with high IgE and invasive mycobacterial infections (OMIM#306400) [228]. Identification of a second patient with TYK2 deficiency, who had mycobacterial infections but normal IgE levels, linked this disorder more with undue susceptibility to mycobacterial infections rather than a Hyper-IgE phenotype n. TYK2, a member of the Janus tyrosine kinase family, interacts with multiple cytokine receptors and mediates signaling to STAT proteins. In 2009, dedicator of cytokinesis 8 (DOCK8) deficiency was identified as the cause of AR-HIES in most patients (OMIM#614113) [229]. DOCK8, a guanine nucleotide exchange factor (GEF) that interacts with small GTPases, including Cdc42, can act as an adapter protein to link signaling pathways within the cell [230]. The DOCK8 locus contains a large number of CpG islands and is therefore genomically labile, such that most identified patients have large deletions in at least one allele of the gene.

Patients with *DOCK8* mutations have a combined immunodeficiency that usually presents in the first 1–2 years of life. Eczema and frequent bacterial sinopulmonary infections are often the first symptoms. MCC is almost universal and patients can have Staphylococcal pneumonias but the characteristic features that differentiate this disease from STAT3 deficiency are severe, early onset papilloma and herpes virus infections, a tremendous propensity to malignancy (lymphoid and squamous cell) that can occur in childhood, and significant allergic disease including food allergies and asthma. Systemic features of STAT3 deficiency, including retained primary teeth, coarse facies, and fractures, are uncommon in DOCK8 deficiency. IgE is significantly elevated (>2,000 IU/ml) in almost all reported patients [229]. Th17 cell numbers are low and most patients have T cell lymphopenia that may be significant enough to allow them to be identified by TREC-based newborn screening at birth. Most patients die of malignancies or infections in the second or third decades of life if they do not undergo hematopoietic stem cell transplant.

The population prevalence is not known for STAT3 or DOCK8 deficiency. Males and females appear to be equally affected in both disorders. There is no known ethnic predisposition to either disorder although a significant percentage of the DOCK8 deficient patients currently described in the literature are from consanguineous families.

The gold standard for diagnosis of either STAT3 or DOCK8 deficiency is identification of a mutation in the respective gene. Sequencing of both genes and copy number variation analysis are available in commercial labs. Measurement of STAT3 protein is not diagnostic. Patients with mutations in the SH2 or transactivation domains of the STAT3 protein (~50 % of patients) can be identified by demonstrating decreased tyrosine phosphorylation of STAT3 in response to IL-6 stimulation, an assay that can be performed by flow cytometry. In the case of DOCK8, almost all mutations lead to absence of protein, which can be evaluated either by Western blotting or by flow cytometry. Both STAT3 and DOCK8 deficiency are associated with decreased Th17 cells so evaluation of stimulated peripheral blood lymphocytes by flow cytometry to identify IL-17 expressing CD4+ T cells can be a valuable screening tool for both disorders [106, 227].

For both STAT3 and DOCK8 deficiency, aggressive treatment of active infections is critically important. Antibacterial and antifungal prophylaxis appears to be effective at decreasing infections, although there have been no randomized trials to verify their efficacy in these populations. Diluted bleach baths have been used to reduce staphylococcal colonization of the skin. B cell dysfunction has been described in both STAT3 and DOCK8 deficiency but the marked T cell dysfunction in DOCK8 deficiency combines to create a significant humoral immune deficiency in this disorder. IgG replacement therapy is therefore clearly indicated in DOCK8 deficiency but its role in STAT3 deficiency is more controversial. As a result of the combined immunodeficiency and propensity to develop malignancy, patients with DOCK8 deficiency rarely survive past the third decade of life. HSCT is successful in this disorder and is recommended early in life [231]. The role of HSCT in STAT3 deficiency remains controversial. The initial report suggested that it was not successful in resolving many features of the disease [232], however subsequent reports have been more encouraging, demonstrating resolution of the immunologic defects and the infectious susceptibility post-HSCT [233]. Because STAT3 deficiency is a systemic disease, there are features such as vascular aneurysms that are not expected to improve following HSCT. In the majority of cases however, premature death is caused by severe infections or pulmonary complications arising after cavitating Staphylococcal pneumonias, both of which should be preventable after successful transplant.

Chromosome 22q11.2 Deletion Syndrome

The main phenotype of chromosome 22q11.2 deletion syndrome is cardiac not immunologic. The most common infections are sinopulmonary. The features of chromosome 22q11.2 deletion syndrome vary dramatically from patient to patient, even within families. By far the most common manifestations are speech delay, nasal speech, conotruncal cardiac anomalies and low T cell numbers. The speech issues are a common method of ascertainment in older children while cardiac anomalies, hypocalcemia, and infection are the major ascertainment pathways for infants. The main types of cardiac defects include tetralogy of Fallot, pulmonary atresia, truncus arteriosus, interrupted aortic arch and ventricular septal defect [234–236]. Collectively, structural cardiac defects are seen in

approximately 80 % of patients. Tetralogy of Fallot and interrupted aortic arch type B in particular have a strong positive predictive value for chromosome 22q11.2 deletion syndrome.

The immune system is affected in approximately 75 % of the patients and the effects are due to thymic hypoplasia. The size of the thymus does not predict circulating T cell counts partly due to microscopic nests of thymic epithelial cells at aberrant locations [237]. The severity ranges from absent thymic tissue and no circulating T cells, to completely normal T cell counts. It is now not uncommon for children with chromosome 22q11.2 deletion syndrome and low T cells to be identified via newborn screening for severe combined immune deficiency. Many infants with low T cell counts will demonstrate improvement in the first year of life but after that, T cell counts decline, as is seen in unaffected children [238, 239]. Most pediatric patients have a mild to moderate decrease in the mean number of CD3+ T cells compared to age matched controls [239, 240]. T cell proliferation is normal in the majority of patients and, when decreased, is simply reflecting the low frequency of responder cells. The majority of patients with the deletion are modestly immunocompromised and do not develop opportunistic infections. Viral infections can be prolonged and abnormal palatal anatomy may lead to compromised drainage and an increased susceptibility to upper airway bacterial infections. With the exception of very immune compromised children, live viral vaccines may be safely given. No special precautions need to be taken to prevent graft versus host disease or opportunistic infections except in those patients with very severe immunocompromise. There are secondary consequences to the T cell defect. Antibody production and function are largely intact, however, there are patients with significant antibody defects who require immunoglobulin replacement. A more severe infection pattern may correlate with immunoglobulin abnormalities [241–243]. Additional features in this syndrome are shown in Table IV [244]. Those features that are most often helpful diagnostically are indicated with an asterisk. Fluorescent in situ hybridization (FISH) is often used to identify the heterozygous deletion but rapid PCR methods and SNP arrays are becoming more widely used. Some patients are also identified on prenatal ultrasound due to the identification of suspicious clinical features.

Management of patients requires a flexible multidisciplinary approach. The changing needs of patients can tax a single specialist. Early in life, concerns about hypocalcemia and the cardiac anomaly dominate the picture. At this point, the focus for the immunologist is to identify patients who will need a T cell or thymus transplant [245]. Later in life, development, socialization, and psychiatric concerns are prominent. Older children and adults require immunologic monitoring focused on immunoglobulin production and function. Atopy and autoimmune disease are increased in this population, but there is no prospective monitoring that has been demonstrated to predict patients who will evolve atopic or autoimmune disease [239, 246].

Table IV Major phenotypic features

Feature		Frequency
Cardiac anomalies		77 %
	Tetralogy of Fallot	20 %
	Ventriculoseptal defect	21 %
	Interrupted aortic arch	12 %
	Truncus arteriosus	6 %
Immune deficiency		77 %
	T cell lymphopenia	67 %
	Delayed IgG production	10 %
	Thymic aplasia with absent T cells	<0.5 %
Palatal defects		
	Velopharyngeal insufficiency	42 %
	Submucous cleft palate	16 %
	Overt cleft palate	11 %
	Cleft lip and palate	2 %
Endocrine		
	Hypocalcemia	49 %

Immune Dysregulation, Polyendocrinopathy, Enteropathy, X-Linked (IPEX)

Immune dysregulation, Polyendocrinopathy, Enteropathy, X-linked (IPEX) is an inherited syndrome of systemic autoimmunity (OMIM#304790) and the prototype of severe, early onset immune dysregulation disorders. It is caused by mutations in the *FOXP3* gene located on the X chromosome and encoding a key transcription factor for naturally occurring regulatory T cells (nTreg). IPEX is characterized by severe, early-onset, systemic autoimmunity that is the result of absence of functional regulatory T cells.

Almost all patients with IPEX present with enteropathy within the first 6 months of life. The enteropathy is typically characterized by profuse watery diarrhea (often non-bloody) and villus atrophy. The majority of patients have an eczematous dermatitis that typically begins in the first months of life. 60–70 % of patients also develop an early onset endocrinopathy that is almost exclusively either thyroiditis or Type I diabetes. The most consistent laboratory abnormality among patients is a significantly elevated serum IgE level. In addition to these characteristic clinical and lab features, patients also have a high incidence of other severe autoimmune disorders including: hemolytic anemia, thrombocytopenia, neutropenia, hepatitis, renal disease, and others. Recently hypotonia at birth with dysmorphic facial appearance was also observed in some cases.

Many patients who have symptoms suggestive of IPEX lack FOXP3 mutations. A subset of these "IPEX-like"

patients, have been found to have mutations in CD25 (IL2RA), STAT5B, or STAT1 but many do not yet have a clearly identified molecular etiology [247, 248]. Some patients with leaky SCID variants caused by hypomorphic mutations in *RAG1*, *RAG2*, or related genes may also have symptomatic overlap with IPEX.

Recognition of the clinical features of IPEX is the first step in diagnosing this disorder. Sequencing of the *FOXP3* gene remains the gold standard for making a diagnosis of IPEX although sequencing needs to encompass non-coding areas of the gene, including the upstream non-coding exon and the polyadenylation signal sequence in order to cover all regions in which pathogenic mutations have been identified [249–251]. To date, no copy number variants (duplications/deletions) within the *FOXP3* gene have been identified in patients with IPEX. Flow cytometry to measure FOXP3 protein expression and FOXP3+ regulatory T cells (Treg) is a helpful adjunct to gene sequencing although only ~25 % of patients have mutations that are predicted to completely abrogate FOXP3 protein expression. The remainder of patients has varying degrees of FOXP3+ Treg deficiency due to the fact that mutant FOXP3 may not support normal Treg development. As a result, flow cytometry by itself is not considered to be a sufficiently reliable screening test for IPEX.

Initial therapy for IPEX typically consists of aggressive supportive care (parenteral nutrition, insulin, thyroid hormone, etc.) combined with T cell-directed immune suppression using agents such as tacrolimus, cyclosporine or rapamycin. HSCT is currently the only curative therapy for IPEX. Early HSCT using a non-myeloablative conditioning regimen prior to the onset of autoimmune-mediated organ damage, usually leads to the best outcome and limits the adverse effects of therapy [252, 253]. Since Tregs constitutively express the high-affinity IL-2 receptor, they have a selective growth advantage in vivo. As a result, complete donor engraftment in all hematopoietic lineages may not be necessary because preferential engraftment of donor Treg cells can be sufficient to control the disease [254].

Conclusion

The number of specific PIDs and the molecular basis for these disorders has grown tremendously over the last decade. Similarly, the ability to treat congenital immunodeficiencies has improved and long-term survival is achievable for most PIDs. Consequently, the early diagnosis of congenital PID is essential to improve the outcomes of these children. A high index of suspicion for PID is necessary in particular in young children that present with unusual or severe infections, autoimmunity or immune dysregulation. Early referral to a clinical immunologist should be made in these cases for definitive diagnosis and treatment.

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