An Introduction to Primary Immunodeficiency Diseases 1

Nima Rezaei, Francisco A. Bonilla, Kathleen E. Sullivan, Esther de Vries, and Jordan S. Orange

Core Messages

- Primary immunodeficiency diseases are a heterogeneous group of inherited disorders with defects in one or more components of the immune system.
- Primary immunodeficiency diseases are not as rare as once believed.
- Infections are the hallmark of immunodeficiency.
- Delays in diagnosis can lead to irreparable organ system damage and thus immunodeficiency should be promptly considered.
- Other symptoms may be more prominent at first, and this can be misleading.
- Family history is of paramount importance.
- Pattern recognition among clinical presentations is an efficient means of identifying primary immunodeficiency diseases within the large pool of patients with infections.
- Abnormal patterns in host defense can only be identified by having a firm grasp of what is considered "normal".
- Severe defects should be considered and identified promptly using widely available screening tests such as the absolute peripheral blood lymphocyte count.

1.1 Definition

1.1.1 Background

The immune system is a complex network of cells and organs which cooperate to protect people against infectious microorganisms, as well as internally-derived threats such as cancer. The immune system specializes in identifying danger, containing and ultimately eradicating it. It is composed of highly specialized cells, proteins, tissues, and organs. B and T lymphocytes, phagocytic cells and soluble factors such as complement are some of the major components of the immune system, and have specific critical functions in immune defense.

When part of the immune system is missing or does not work correctly, immunodeficiency occurs; it may be either congenital (primary) or acquired (secondary). Secondary immunodeficiency diseases are caused by environmental factors, such as infection with HIV, chemotherapy, irradiation, malnutrition, and others, while primary immunodeficiency diseases (PID) are hereditary disorders, caused by mutations of specific genes.

Primary immunodeficiency diseases are a heterogeneous group of inherited disorders with defects in one or more components of the immune system. These diseases have a wide spectrum of clinical manifestations and laboratory findings. However, in the vast majority of cases, they result in an unusually increased susceptibility to infections and a predisposition to autoimmune diseases and malignancies [23, 45, 46, 77, 151, 155, 180, 193].

More than 150 different types of PID have been reported to date [77, 155, 193]. Although some of them are relatively common, others are quite rare. The exact prevalence of PID in the general population is unknown. Although the overall prevalence of PID has been estimated to be 1 per 10,000 individuals, excluding asymptomatic IgA deficiency, recent reports indicate a higher prevalence of PID [25, 193]; this prevalence may differ among different ethnic groups and countries [193]. While the number of patients diagnosed with PID is growing, many physicians still know little about these disorders. Thus, many patients are diagnosed late; many cases suffer complications by chronic infections, irretrievable end-organ damage, or even death before the definitive diagnosis is made. Timely diagnosis and appropriate treatment remain the keys to the successful management of patients with PID [37, 98, 176].

1.1.2 History

The birth of the primary immunodeficiency field is attributed to Col. Ogden Bruton in 1952, who reported a male patient with early onset recurrent infections and an absent gammaglobulin peak on serum protein electrophoresis. This child had an excellent response to immunoglobulin replacement therapy [26]; later, the condition ultimately became known as X-linked agammaglobulinemia (XLA) or Btk (Bruton's tyrosine kinase) deficiency. However, several patients with characteristic clinical manifestations of immunodeficiency disorders had been reported before 1950: Ataxia-telangiectasia (A-T) in 1926 [200], chronic mucocutaneous candidiasis (CMC) in 1929 [203], and Wiskott–Aldrich syndrome (WAS) in 1937 [220]. The first patient with cellular deficiency was initially reported in 1950 [80], the first case of a phagocytic defect (severe congenital neutropenia: SCN) was reported in 1956 [119], and the first case of complement deficiency (C2 deficiency) was reported in 1966 [114].

The discovery of PID and characterization of these diseases led to crucial contributions to understanding the functional organization of the immune system and molecular biology. Thus, the study of PID has contributed to progress in immunological and molecular diagnostic techniques. These advances enabled increased recognition and characterization of new types of PID, and identification of more than 150 different types of PID in the ensuing years [77, 151, 155, 193] (Tables 1.1–1.8).

1.1.3 Registries

Several PID registries have been established in different countries during the last two decades [1, 2, 4, 7, 8, 63, 66, 68, 83, 86, 94, 109, 112, 115, 123, 125, 129, 133, 141, 176, 177, 182, 185, 194]. They provide valuable epidemiological information and demonstrate wide geographical and racial variations in the prevalence of PID in general and of its different types (Table 1.9). Considering the recent reports from four major registries describing more than 10,000 patients, including ESID (European Society for Immunodeficiencies), LAGID (Latin American Group for Primary Immunodeficiency Diseases), Australia and New Zealand, and Iran, antibody deficiencies are the most common PID and comprise more than half of all patients (Fig. 1.1) [66, 112, 125, 176]. Other well-defined immunodeficiencies, phagocytes defects, and combined T and B cell immunodeficiencies are also relatively common. Among them, common variable immunodeficiency (CVID) is the most common PID, with a relative frequency of approximately 20%, followed by selective IgA and/or IgG subclass deficiencies, agammaglobulinemia with absent B cells, AT, chronic granulomatous disease (CGD), and severe combined immunodeficiency (SCID). Other diseases have lower relative frequencies [66, 112, 125, 176].

1.2 Etiology

1.2.1 Classification

There is no single system of classification for the large and heterogeneous group of PID that suffices for every educational or clinical purpose [22, 33]. Most texts utilize a functional classification wherein distinct disease entities are grouped according to the disturbed immunological mechanism responsible for the principal clinical and laboratory manifestations of those diseases or syndromes [24, 77, 151]. One may distinguish, for example, antibody or humoral-specific immune defects, specific cellular immune deficiencies, combined immunodeficiencies (affecting both specific humoral and cellular immunity), phagocytic cell defects, complement deficiencies, and other defects of innate immunity. Note that these types of descriptive functional categories may overlap to varying degrees; for example, phagocytic cells and complement may be considered elements of innate immunity, but are usually considered separately due to the convenience of their mechanistic distinction. The assignment of one entity to a particular category is occasionally arbitrary and may have a historical basis.

The foundation for the organization of this text is the most recent classification of immunological diseases reported by the World Health Organization (WHO) in conjunction with the International Union of Immunological Societies (IUIS) [77]. This classification is conveyed in Tables 1.1–1.8. This scheme includes more or less "classic" PID listed in Table 1.1 (combined T and B cell immunodeficiencies), Table 1.2 (predominantly antibody deficiencies), Table 1.3 (phagocytes defects), Table 1.4 (genetic disorders of immune regulation), Table 1.5 (defects in innate

Table 1.1 Modified IUIS classification of combined T and B cell immunodeficiencies

Diseases		Inheritance	Genetic defects
T-B+ Severe combined immunodeficiency	*γc deficiency*	XL	IL-2 receptor gamma (*IL2RG*)
	JAK3 deficiency	AR	Janus-associated kinase 3 (*JAK3*)
	IL7-Rα deficiency	AR	IL-7 receptor (*IL7-R*) alpha
	CD45 deficiency	AR	Leukocyte-common antigen (*LCA*) or *CD45*
	CD3γ deficiency	AR	T cell antigen receptor, Gamma subunit of T3 (*CD3G*)
	CD3δ deficiency	AR	T cell antigen receptor, Delta subunit of T3 (*CD3D*)
	CD3ε deficiency	AR	T cell antigen receptor, Epsilon subunit of T3 (*CD3E*)
	CD3ξ deficiency	AR	T cell antigen receptor, Zeta subunit of T3 (*CD3Z*) or *CD247*
T-B- Severe combined immunodeficiency	*RAG1 deficiency*	AR	Recombination-activating gene 1 (*RAG1*)
	RAG2 deficiency	AR	Recombination-activating gene 2 (*RAG2*)
	Artemis deficiency	AR	Artemis or DNA cross-link repair protein 1C (*DCLRE1C*)
	ADA deficiency	AR	Adenosine deaminase (*ADA*)
	Reticular dysgenesis	AR	Defective maturation of immune cells from stem cell
Omenn syndrome		AR	*RAG1/2, Artemis* and *IL7-R*
DNA ligase IV deficiency		AR	DNA ligase IV (*LIG4*)
Cernunnos/XLF deficiency		AR	Non-homologous end-joining 1 (*NHEJ1*) or *CERNUNNOS*
Purine nucleoside phosphorylase (PNP) deficiency		AR	Purine nucleoside phosphorylase (*PNP*)
Immunoglobulin class switch recombination deficiencies (affecting CD40-CD40L)	*CD40 ligand deficiency*	XL	Tumor necrosis factor ligand superfamily, member 5 (*TNFS5B*) or CD40 antigen ligand (*CD40L*)
	CD40 deficiency	AR	Tumor necrosis factor receptor superfamily, member 5 (*TNFRSF5*)
MHC class II deficiency	*CIITA deficiency*	AR	Class II transactivator (*CIITA*)
	RFX5 deficiency	AR	MHCII promoter X box regulatory factor 5 (*RFX5*)
	RFXAP deficiency	AR	Regulatory factor X-associated protein (*RFXAP*)
	RFXANK deficiency	AR	Ankyrin repeat containing regulatory factor X-associated protein (*RFXANK*)
MHC class I deficiency	*TAP1 deficiency*	AR	Transporter associated with antigen processing 1 (*TAP1*)
	TAP2 deficiency	AR	Transporter associated with antigen processing 2 (*TAP2*)
	Tapasin deficiency	AR	Tap-binding protein (*TAPBP*)
CD8 deficiency	*CD8α chain defect*	AR	CD8 antigen, alpha polypeptide (*CD8A*)
	ZAP-70 deficiency	AR	Zeta-chain-associated protein of 70 kd signaling kinase (*ZAP-70*)
CD4 deficiency	*p56lck deficiency*	AR	Lymphocyte-specific protein-tyrosine kinase (*LCK*)
	Idiopathic CD4 lymphocytopenia	Variable	Unknown
CRAC deficiency		AR	ORAI1 or Calcium release-activated calcium modulator 1 (*CRACM1*) or Transmembrane protein 142A (*TMEM142A*)
Winged-helix-nude (WHN) deficiency		AR	Winged-helix-nude (*WHN*) or Forkhead box N1 (*FoxN1*)
CD25 deficiency		AR	Interleukin 2 receptor, alpha (*IL2RA*) or *CD25*
STAT5B deficiency		AR	Signal transducer and activator of transcription 5B (*STAT5B*)

AR autosomal recessive, *XL* X-linked

Table 1.2 Modified IUIS classification of predominantly antibody deficiencies

Diseases		Inheritance	Genetic defects
Agammaglobulinemia with absent B cells	*Btk deficiency*	XL	Bruton tyrosine kinase (*BTK*)
	μ heavy chain deficiency	AR	Ig heavy mu chain (*IGHM*)
	λ5/14.1 deficiency	AR	Immunoglobulin lambda-like polypeptide 1 (*IGLL1*)
	Igα deficiency	AR	CD79A antigen (*CD79A*)
	Igβ deficiency	AR	CD79B antigen (*CD79B*)
	BLNK deficiency	AR	B cell liker protein (*BLNK*) or SH2 domain containing leukocyte protein, 65-KD (*SLP65*)
	LRRC8 deficiency	AD	Leucine-rich repeat-containing protein 8 (*LRRC8*)
	Other forms of agammaglobulinemia	Variable	Unknown
Hypogammaglobulinemia with normal/low number of B cells	*Common variable immunodeficiency*	Variable	Unknown
	ICOS deficiency	AR	Inducible costimulator (*ICOS*)
	TACI deficiency	AR	Tumor necrosis factor receptor super-family, member 13b (*TNFRSF13B*) or transmembrane activator and calcium modulator and cyclophilin ligand interactor (*TACI*)
	CD19 deficiency	AR	CD19 antigen (*CD19*)
	Other forms of hypogammaglobulinemia	Variable	Variable, Unknown
Immunoglobulin class switch recombination deficiencies (due to Intrinsic B Cell Defects)	*AID deficiency*	AR	Activation-induced cytidine deaminase (*AICDA*)
	UNG deficiency	AR	Uracil-DNA glycosylase (*UNG*)
	Other CSR selective deficiencies	AR	Unknown; Selective deficiency in Ig class-switch recombination (CSR)
Selective IgA deficiency		Variable	Unknown
Other immunoglobulin isotypes or light chain deficiencies	*Isolated IgG subclass deficiency*	Variable	Unknown
	IgA with IgG subclass deficiency	Variable	Unknown
	Ig heavy chain deletions	AR	Chromosomal deletion at 14q32
	κ light chain deficiency	AR	Ig kappa constant region (*IGKC*)
Specific antibody deficiency with normal immunoglobulin levels		Variable	Unknown
Transient hypogammaglobulinemia of infancy		Variable	Unknown

AR autosomal recessive, *AD* autosomal dominant, *XL* X-linked

Table 1.3 Modified IUIS classification of phagocytes defects

Diseases		Inheritance	Genetic defects
Severe congenital neutropenias (SCN)	*ELA2 deficiency*	AD	Elastase 2 (*ELA2*)
	GFI1 deficiency	AD	Growth factor-independent 1 (*GFI1*)
	HAX1 deficiency	AR	HCLS1-associated protein X1 (*HAX1*)
	GCSFR deficiency	AD	Granulocyte colony-stimulating factor receptor (*GCSFR*) or Colony-stimulating factor 3 receptor (*CSF3R*)
	Neutropenia with myelodysplasia	XL	Wiskott–Aldrich syndrome protein (*WASP*)

(continued)

Table 1.3 (continued)

Diseases		Inheritance	Genetic defects
Cyclic neutropenia		AD	Elastase 2 (*ELA2*)
Leukocyte adhesion deficiency (LAD)	*LAD type 1*	AR	Integrin, beta-2 (*ITGB2*)
	LAD type 2	AR	Solute carrier family 35, member C1 (*SLC35C1*) or GDP-fucose transporter 1 (*FUCT1*)
	LAD type 3	AR	Calcium-Diacylglycerol Guanine Nucleotide Exchange Factor I (*CalDAG-GEFI*), defective Rap1-activation of integrins
RAC-2 deficiency		AD	Ras-related C3 botulinum toxin substrate 2 (*RAC2*)
β-Actin deficiency		AD	Actin, beta (*ACTB*)
Chronic granulomatous disease (CGD)	*gp91 ^{phox} deficiency*	XL	Cytochrome b(-245), beta subunit (*CYBB*)
	p22 ^{phox} deficiency	AR	Cytochrome b(-245), alpha subunit (*CYBA*)
	p47 ^{phox} deficiency	AR	Neutrphil cytosolic factor 1 (*NCF1*)
	p67 ^{phox} deficiency	AR	Neutrophil cytosolic factor 2 (*NCF2*)
Neutrophil G-6PD deficiency		XL	Glucose-6-phosphate dehydrogenase (*G6PD*)
Myeloperoxidase deficiency		AR	Myeloperoxidase (*MPO*)
Specific granule deficiency		AR	CCAAT/enhancer-binding protein, epsilon (*CEBPE*)
Shwachman–Diamond syndrome		AR	Shwachman–Bodian–Diamond syndrome (*SBDS*)
Localized juvenile periodontitis		AR	Formyl peptide receptor 1 (*FRP1*)
Papillon–Lefèvre syndrome		AR	Cathepsin c (*CTSC*)

AR autosomal recessive, *AD* autosomal dominant, *XL* X-linked

Table 1.4 Modified IUIS classification of genetic disorders of immune regulation

Diseases		Inheritance	Genetic defects
Familial hemophagocytic lymphohistiocytosis	*Perforin deficiency*	AR	Perforin 1 (*PRF1*)
	MUNC 13-4 deficiency	AR	*MUNC13–4* or *UNC13D*
	Syntaxin 11 deficiency	AR	Syntaxin 11 (*STX11*)
Immunodeficiency with hypopigmentation	*Chediak-Higashi syndrome*	AR	Lysosomal trafficking regulator (*LYST*)
	Griscelli syndrome, type II		Ras-associated protein rab27a (*RAB27A*)
	Hermansky–Pudlak syndrome, type II	AR	Adaptor-related protein complex 3, beta-1 subunit (*AP3B1*)
	P14 deficiency	AR	MAPBP-interacting protein (*MAPBPIP*) or *P14*
X-linked lymphoproliferative syndrome (XLP)	*XLP1 (SAP deficiency)*	XL	src homology 2-domain protein (*SH2D1A*)
	XLP2 (XIAP deficiency)	XL	Inhibitor-of-apotosis, X-linked (*XIAP*) or Baculoviral IAP repeat-containing protein 4 (*BIRC4*)

(continued)

Table 1.4 (continued)

Diseases		Inheritance	Genetic defects
Autoimmune lymphoproliferative syndrome (ALPS)	*ALPS Ia (CD95 deficiency)*	AD, AR	Tumor necrosis factor receptor superfamily, member 6 (*TNFRSF6*) or *CD95* or *FAS*
	ALPS Ib (CD95L deficiency	AD, AR	Tumor necrosis factor ligand superfamily, member 6 (*TNFSF6*) or *CD95L* or *FASL*
	ALPS IIa (Caspase 10 deficiency	AD	Caspase 10, apoptosis-related cysteine protease (*CASP10*)
	ALPS IIb (Caspase 8 deficiency	AD	Caspase 8, apoptosis-related cysteine protease (*CASP8*)
	ALPS III	AD	Unknown, Neuroblastome RAS viral oncogene homologu (*NRAS*)
Autoimmune polyendocrinopathy with candidiasis and ectodermal dystrophy (APECED)		AR	Autoimmune regulator (*AIRE*)
Immunodysregulation, polyendocrinopathy, enteropathy, X-linked (IPEX)		XL	Forkhead box P3 (*FOXP3*)

AR autosomal recessive, *AD* autosomal dominant, *XL*, X-linked

Table 1.5 Modified IUIS classification of defects in innate immunity: receptors and signaling components

Diseases		Inheritance	Genetic defects
Defective TLR signaling without ectodermal dysplasia	*Interleukin-1 receptor-associated kinase-4 (IRAK-4) deficiency*	AR	Interleukin 1 receptor-associated kinase 4 (*IRAK4*)
	TLR3 deficiency	AD	Toll-like receptor 3 (*TLR3*)
	UNC-93B deficiency	AR	*UNC-93B*
Defective TLR signaling with ectodermal dysplasia	*X-linked anhidrotic ectodermal dysplasia with immunodeficiency (XL-EDA-ID)*	XL	Inhibitor of kappa light polypeptide gene enhancer in B cells, kinase of, gamma (*IKBKG*) or NF-kappa-B essential modulator (*NEMO*)
	Autosomal dominant anhidrotic ectodermal dysplasia with immunodeficiency (AD-EDA-ID)	AD	Inhibitor of kappa light polypeptide gene enhancer in B cells, kinase of, alpha (*IKBA*)
Mendelian susceptibility to mycobacterial diseases	*IFN-γ receptor 1 deficiency*	AR, AD	Interferon, gamma, receptor 1 (*IFNGR1*)
	IFN-γ receptor 2 deficiency	AR, AD	Interferon, gamma, receptor 2 (*IFNGR2*)
	IL-12/IL-23 receptor β1 chain deficiency	AR	Interleukin 12 receptor, beta-1 (*IL12RB1*)
	IL-12p40 deficiency	AR	Interleukin 12B (*IL12B*)
	STAT1 deficiency	AR, AD	Signal transducer and activator of transcription 1 (*STAT1*)
Warts, hypogammaglobulinemia, infections, myelokathexis (WHIM) syndrome		AD	Chemokine, CXC motif, receptor 4 (*CXCR4*)
Epidermodysplasia verruciformis (EV)	*EV type 1*	AR	Epidermodysplasia verruciformis gene 1 (*EVER1*)
	EV type 2	AR	Epidermodysplasia verruciformis gene 2 (*EVER2*)

AR autosomal recessive, *AD* autosomal dominant, *XL* X-linked

Table 1.6 Modified IUIS classification of autoinflammatory disorders

Diseases		Inheritance	Genetic defects
Familial Mediterranean fever (FMF)		AR	Mediterranean fever (*MEFV*)
TNF receptor-associated periodic syndrome (TRAPS)		AD	Tumor necrosis factor receptor superfamily, member 1a (*TNFRSF1A*)
Mevalonate kinase deficiency (MVD)	*Hyper-IgD and periodic fever syndrome (HIDS)*	AR	Mevalonate kinase (*MVK*)
	Mevalonic aciduria (MVA)	AR	Mevalonate kinase (*MVK*)
Cryopyrin-associated periodic syndrome (CAPS)	*Chronic infantile neurological cutaneous articular syndrome (CINCAS)*	AD	Cias1 gene (*CIAS1*) or sNacht domain-, leucine-rich repeat-, and pyd-containing protein 3 (*NALP3*) or Pyrin domain- containing APAF1-like protein 1 (*PYPAF1*)
	Muckle–Wells syndrome (MWS)	AD	Cias1 gene (*CIAS1*) or Nacht domain-, leucine-rich repeat-, and pyd-containing protein 3 (*NALP3*) or Pyrin domain-containing APAF1-like protein 1 (*PYPAF1*)
	Familial cold autoinflammatory syndrome (FCAS)	AD	Cias1 gene (*CIAS1*) or Nacht domain-, leucine-rich repeat-, and pyd-containing protein 3 (*NALP3*) or Pyrin domain- containing APAF1-like protein 1 (*PYPAF1*)
Blau syndrome		AD	Caspase recruitment domain-containing protein 15 (*CARD15*) or Nucleotide-binding oligomerization domain protein 2 (*NOD2*)
Pyogenic arthritis, pyoderma gangrenosum and acne (PAPA) syndrome		AD	Proline/Serine/Threonine phosphatase-interacting protein 1 (*PSTPIP1*) or CD2 antigen-binding protein 1 (*CD2BP1*)
Polygenic/multifactorial autoinflammatory diseases		Variable	Variable

AR autosomal recessive, *AD* autosomal dominant

Table 1.7 Modified IUIS classification of complement deficiencies

Diseases		Inheritance	Genetic defects
Deficiencies of classical pathway components	*C1q deficiency*	AR	Complement component 1, q subcomponent, alpha, beta and gamma polypeptides (*C1QA, C1QB, C1QG*)
	C1r deficiency	AR	Complement component *C1R*
	C1s deficiency	AR	Complement component 1, s subcomponent (*C1S*)
	C4 deficiency	AR	Complement component 4A and 4B (*C4A, C4B*)
	C2 deficiency	AR	Complement component 2
Deficiencies of lectin pathway components	*MBL deficiency*	AR	Lectin, mannose-binding, soluble, 2 (*MBL2*) or Mannose-binding protein, Serum (*MBP1*)
	MASP2 deficiency	AR	Mannan-binding lectin serine protease 2 (*MASP2*)

(continued)

Table 1.7 (continued)

Diseases		Inheritance	Genetic defects
Deficiencies of alternative pathway components	*Factor D deficiency*	AR	Complement factor D (*CFD*)
	Properdin deficiency	XL	Properdin P factor, complement (*PFC*)
Deficiency of complement component C3		AR	Complement component 3 (*C3*)
Deficiencies of terminal pathway components	*C5 deficiency*	AR	Complement component 5
	C6 deficiency	AR	Complement component 6
	C7 deficiency	AR	Complement component 7
	C8a deficiency	AR	Complement component 8, alpha subunit (*C8A*)
	C8b deficiency	AR	Complement component 8, beta subunit (*C8B*)
	C9 deficiency	AR	Complement component 9
Deficiencies of complement regulatory proteins	*C1 inhibitor deficiency*	AD	Complement component 1 inhibitor (*C1NH*)
	Factor I deficiency	AR	Complement factor I (*CFI*)
	Factor H deficiency	AR	Complement factor H (*CFH*)
	CD46 deficiency	AD	Membrane cofactor protein (*MCP*) or *CD46*
	CD55 deficiency	AR	Decay-accelerating factor for complement (*DAF*) or *CD55* antigen
	CD59 deficiency	AR	CD59 antigen p18–20 (*CD59*)
	CD18 deficiency	AR	Integrin, beta-2 (*ITGB2*)

AR autosomal recessive, *AD* autosomal dominant, *XL*, X-linked

Table 1.8 Modified IUIS classification of other well-defined immunodeficiencies

Diseases		Inheritance	Genetic defects
Other syndromes associated with defective DNA repair	*Ataxia-telangiectasia*	AR	Ataxia-telangiectasia mutated gene (*ATM*)
	Ataxia-like syndrome	AR	Meiotic recombination 11, S. cerevisiae, homolog of, A (*MRE11A*)
	Nijmegen breakage syndrome	AR	Nijmegen breakage syndrome gene (*NBS1*)
	Bloom's syndrome	AR	Bloom syndrome (*BLM*)
	Immunodeficiency, centromere instability and facial abnormalities (ICF) syndrome	AR	DNA methyltransferase 3b (*DNMT3B*)
Di George syndrome		AD	Deletion of chromosome 22q11.2
Wiskott–Aldrich syndrome		XL	Wiskott–Aldrich syndrome protein (*WASP*)
Hyper-IgE syndrome (HIES)	*Stat3 deficiency (Job's syndrome)*	AD	Signal transducer and activator of transcription 3 (*STAT3*)
	Tyk2 deficiency	AR	Protein-tyrosin kinase 2 (*TYK2*)
	HIES with unknown origin	AR	Unknown

(continued)

Table 1.8 (continued)

Diseases		Inheritance	Genetic defects
Immuno-osseous dysplasias	*Schimke syndrome*	AR	SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily A-like (*SMARCAL1*)
	Cartilage hair hypoplasia	AR	RNA component of mitochondrial RNA-processing endoribonuclease (*RMRP*)
Chronic mucocutaneous candidiasis		AD, AR, Sporadic	Unknown
Netherton syndrome		AR, XL	Serine protease inhibitor, Kazal-type, 5 (*SPINK5*)
Høyeraal–Hreidarsson syndrome		XL	Dyskerin (*DKC1*)

AR autosomal recessive, *AD* autosomal dominant, *XL*, X-linked

Table 1.9 Prevalence of different types of primary immunodeficiency diseases, reported in several registries

	Region/ report	Year of Report	Number of patients[a]	Combined T and B cell immuno-deficiencies (%)	Predomi-nantly antibody deficiencies (%)	Phago-cytes defects (%)	Comple-ment deficiencies (%)	Other immuno-deficien-cies[b] (%)	Reference
1	JMF referral centers	2007	30,283	7.5	54.5	6.9	1.9	29.2	[109][c]
2	ESID	2008	6,118	8.5	53.9	9.1	1.8	26.7	[66][d]
3	LAGID	2007	3,321	9.5	53.2	8.6	2.8	25.9	[125]
4	Spain	2001	2,050	7.3	66.8	4.5	10.1	11.3	[141]
5	UK	2000	1,544	13.8	72.0	5.6	6.3	2.3	[1]
6	Argentina	2007	1,246	5.5	68.4	4.2	1.0	20.9	[125]
7	Australia and New Zealand	2007	1,209	6.3	77.0	3.3	5.9	7.5	[112]
8	Sweden	2000	934	7.4	87.1	4.8	0.0	0.7	[1]
9	Iran	2006	930	11.0	38.4	28.3	2.4	19.9	[176]
10	Italy	1983	797	14.2	65.9	4.9	1.7	13.3	[133]
11	Brazil	2007	790	9.5	51.1	14.2	6.3	18.9	[125]
12	Japan	1981	628	4.2	61.8	7.3	0.3	26.4	[94]
13	Netherlands	2000	624	22.1	66.5	6.9	0.5	4.0	[1]
14	Switzerland	2000	548	13.1	55.7	12.0	17.7	1.5	[1]
15	Czech	2000	518	8.1	78.0	1.2	11.5	1.2	[1]
16	France	2000	425	44.7	27.5	22.6	0.7	4.5	[1]
17	Mexico	2007	399	10.5	36.3	14.1	1.5	37.6	[125]
18	Norway	2000	372	3.5	50.8	6.7	21.0	18.0	[194]
19	Germany	2000	327	42.0	39.5	14.7	3.3	0.5	[1]
20	Greece	2000	323	10.2	84.5	3.4	0.3	1.6	[1]
21	Polonia	2000	322	24.8	55.0	14.3	0.3	5.6	[1]

(continued)

Table 1.9 (continued)

	Region/ report	Year of Report	Number of patients[a]	Combined T and B cell immuno-deficiencies (%)	Predomi-nantly antibody deficiencies (%)	Phago-cytes defects (%)	Comple-ment deficiencies (%)	Other immuno-deficien-cies[b] (%)	Reference
22	Chile	2007	279	14.7	43.0	6.8	1.8	33.7	[125]
23	Portugal	2000	208	6.3	76.9	3.8	6.7	6.3	[1]
24	Costa Rica	2007	193	17.6	24.9	4.2	0.5	52.8	[125]
25	Russia	2000	161	29.8	59.6	6.2	0.0	4.4	30
26	Colombia	2007	145	19.3	46.2	8.3	2.8	23.4	[125]
27	Republic Ireland	2005	115	9.6	46.1	9.6	27.8	6.9	[2]
28	Uruguay	2007	95	9.1	40.9	4.5	9.1	36.4	[125]
29	Hungary	2000	90	0.0	22.2	14.5	63.3	0.0	[1]
30	Kuwait	2007	76	21.1	30.3	7.9	3.9	36.8	[8]
31	Austria	2000	71	26.8	67.6	2.8	1.4	1.4	[1]
32	Belgium	2000	64	10.9	64.1	17.2	4.7	3.1	[1]
33	Panama	2007	59	15.3	55.9	8.5	3.4	16.9	[125]
34	Finland	2000	48	8.3	71.1	10.4	4.2	0.0	[1]
35	Singapore	2003	39	10.3	41.0	15.4	33.3	0.0	[129]
36	Paraguay	2007	39	7.7	38.5	33.3	0.0	20.5	[125]
37	Taiwan	2005	37	13.5	45.9	24.4	16.2	0.0	[123]
38	Honduras	2007	37	10.8	32.5	10.8	0.0	45.9	[125]
39	Croatia	2000	30	6.7	63.3	0.0	30.0	0.0	[1]
40	Denmark	2000	29	37.9	31.0	13.8	6.9	10.2	[1]
41	Turkey	2000	25	24.0	40.0	4.0	24.0	8.0	[1]
42	Venezuela	2007	22	9.5	53.2	8.6	2.8	25.9	[125]
43	Peru	2007	17	11.8	17.6	5.9	11.8	52.9	[125]
44	Iceland	2000	15	6.7	80.0	6.7	0.0	6.6	[1]

JMF Jeffrey Modell Foundation Diagnostic and Referral Centers, *ESID* European Society for Immunodeficiencies, *LAGID* Latin American Group for Primary Immunodeficiency Diseases

[a]There may be some overlapping between registries; i.e. JMF Referral Centers, ESID, LAGID and other databases

[b]Although some registries use different classification, in this table we consider the term of other immunodeficiencies for genetic disorders of immune regulation, defects in innate immunity, autoinflammatory disorders, and other well-defined immunodeficiencies

[c]Updated based on global survey results for 2007 by 116 JMF diagnostic/referral centers

[d]Updated based on ESID report by 49 documenting centers

immunity: receptors and signaling components), Table 1.6 (autoinflammatory disorders), Table 1.7 (complement deficiencies), and Table 1.8 (other well-defined immunodeficiencies not conveniently placed into any of the other categories). Note that different authors may use different classification systems [24], and that the WHO/IUIS classification itself undergoes periodic revisions wherein individual disease entities may be completely reassigned even to previously well-established distinct "categories" [77, 151, 152]. In addition to the well-recognized primary immunodeficiency diseases, the WHO/IUIS classification also includes genetic disorders of immune regulation (Table 1.4), and "autoinflammatory" disorders (Table 1.6).

The usefulness of any classification scheme depends mainly on the ultimate purpose for which it is developed [22]. The WHO/IUIS system is well suited as a framework for organizing a knowledge base on the

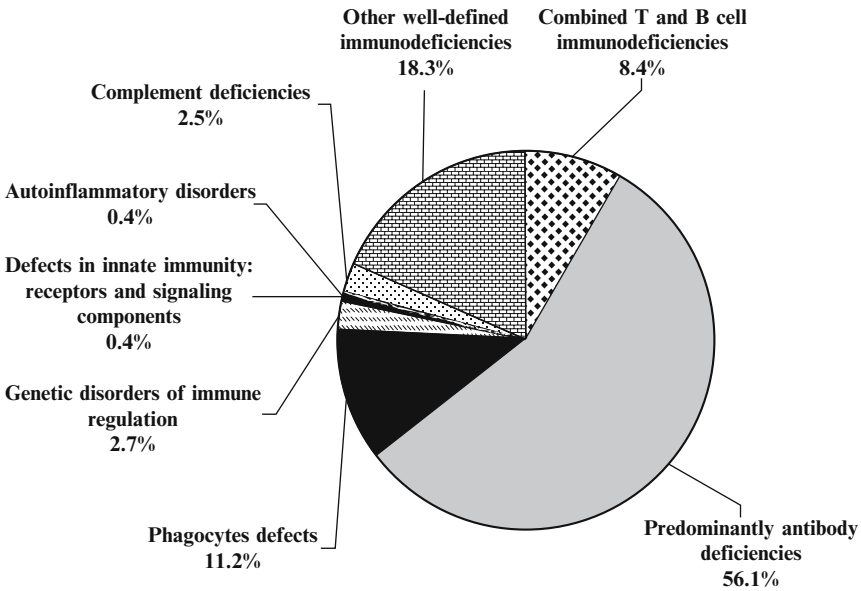

Fig. 1.1 Relative frequencies of primary immunodeficiency diseases; extracted from data of four major registries of ESID, LAGID, Australia and New Zealand, and Iran

general clinical and immunologic features of disease entities arising "primarily" from dysfunction of the immune system. This classification may be cumbersome in other contexts, for example, developing a differential diagnosis based on particular clinical or immunologic features. Other systems have been proposed or formulated with these kinds of considerations in mind [33].

1.2.2 Genetic Defects

More than a hundred distinct genes have been associated with clinical immunodeficiency (Tables 1.1–1.8). This number is even larger when one takes into consideration the many genetically-determined syndromes in which some fraction of individuals have been found to have a degree of immune compromise or infection susceptibility (see Chap. 10 for more details). As can be readily seen (and not surprisingly) by surveying the genes listed in Tables 1.1–1.8, immunodeficiency may arise from disruption of a wide range of biochemical functions, including transcription factors, cytokines and their receptors, cell surface and cytoplasmic signaling mediators, cell cycle regulators, DNA modifying enzymes, intracellular chaperones and transport proteins, and a variety of other specialized enzymatic functions. One may broadly generalize that perhaps more than half of these molecular species are active principally or predominantly in blood cells, lymphocytes and leukocytes in particular, although that relative restriction clearly does not apply in many instances.

Clearly, having a molecular genetic focus adds precision to a diagnosis, although there are important practical caveats to the use of such information, some of which will be introduced here. In addition, at least half of the patients with recurrent infections, or "clinical immunodeficiency", have syndromes whose molecular genetic basis is unknown.

The ability to assign genes and molecular functions to an observable characteristic leads to the concept of genotype–phenotype correlation. Common examples include the genetic basis of traits such as eye color or ABO blood group. This also applies in a general way to disease associations, for example, mutations of *BTK* lead to XLA (see Sect. 3.2 for more details) while mutations of *WAS* lead to WAS (see Sect. 9.4 for more details). However, the concept may also be applied in a more detailed way. Within a group of individuals having any specific immunodeficiency diagnosis, one may distinguish a spectrum of clinical phenotypes. This may relate to the degree of frequency or severity of infections ("severity" of the immunodeficiency), or to the expression of other associated features of the disease such as autoimmunity or malignancy. Thus, one may ask: does the identification of a particular genetic change affecting even submolecular functions (ligand binding, association with signaling intermediates or chaperones, enzymatic activity, cellular transport, etc.)

permit one to predict the severity of the immunodeficiency, the occurrence of autoimmunity or malignancy, etc? In some cases, "yes", although there are many important exceptions making generalization difficult. In some instances, identical mutations may lead to a severe phenotype in one individual, and may be mild, or may not even be expressed at all, in another. For example, some entirely well people have been found incidentally to have mutations of *BTK*, while siblings carrying the same mutation have classic clinical XLA [32, 117] (see Sect. 3.2 for more details). Does an individual who is completely well and who has a "deleterious" mutation of *BTK* have XLA? The answer is not a simple one, because we do not know if it is possible for any such individual to be "completely healthy" with a "normal" lifespan.

It is axiomatic that many (all?) gene products, as well as the environment, interact to determine phenotype. Thus, the clinical and immunologic heterogeneity that we observe with identical genotypes is due to the influence of these interactions. Given the possibility of molecular diagnosis, and the heterogeneity of expression of genotypes, then all syndromes defined solely by clinical and immunologic criteria should be considered diagnoses of exclusion [24]. CVID (see Sect. 3.3 for more details) is a useful illustration of this point. CVID is defined primarily by recurrent infections with hypogammaglobulinemia and impaired antibody response to natural and/or intentional immune challenge [49]. Several genetic lesions have been identified in individuals "diagnosed" with CVID, including *BTK* [110], *SH2D1A* (mutated in X-linked lymphoproliferative syndrome: XLP) [146], *ICOS* (inducible T cell costimulator) [85], *CD19* [206], and possibly *TNFRSF13B* (TACI) [35]. The particular natural history associated with each of these mutations is distinct, so it is most beneficial for patients to know their molecular diagnosis whenever possible. This also creates opportunities for more informed genetic counseling. Note that the principal presenting phenotype associated with XLP (see Sect. 5.4 for more details) is fulminant infectious mononucleosis. This is a good example of how an environmental factor (Epstein-Barr virus infection) may interact with a gene defect *(SH2D1A)* to affect the clinical presentation.

Some individuals expressing mild or variant forms of immunodeficiency have a reversion of a deleterious mutation. These patients are mosaics, they have abnormal mutant cells and another population of cells with normal or near-normal function that have arisen from a precursor that has repaired the defect, either from a second "corrective" mutation, or possibly gene conversion. This has been found in rare cases of adenosine deaminase deficiency [102], X-linked SCID [190], WAS [13], and leukocyte adhesion deficiency (LAD) type I [204].

Some X-linked immunodeficiencies occasionally appear to defy the rules of genetics by affecting females. This apparent aberrant X-linked dominant expression may arise through extreme non-random X chromosome inactivation. In most females, roughly half of all somatic cells will inactivate one X chromosome, and half inactivate the other. In some individuals, 95–100% of cells will all have inactivated the same X chromosome. If the remaining active X carries a mutation causing immunodeficiency, that disease will manifest. This occurrence has been observed with CGD [9], WAS [11, 132], XLA [201], and X-linked Ig class switch recombination (CSR) deficiency [52].

1.2.3 Pathophysiology

The infection susceptibility and other clinical features of a given immunodeficiency arise from the absence or altered function of one or more gene products. All of the details of these aspects of each disorder depend on the biochemical roles of these gene products and the cells or tissues in which they are expressed. As discussed above, the products of interacting genes and their polymorphisms and environmental factors also play a role. For most immunodeficiencies, we still have very much to learn regarding all the biochemical, cellular, organic, and systemic consequences of a particular defect. The majority of the genetically defined immunodeficiencies will be discussed in the remainder of this book. Here, we give a few examples of an interesting phenomenon in immunodeficiency: syndromes having identical or very similar clinical and immunologic phenotypes may arise from disrupted function of molecular entities that interact with one another to subserve a single biochemical function or pathway.

XLA was one of the first immunodeficiencies to be defined at the molecular level [42]. The BTK tyrosine kinase is critical for transducing a signal from the B cell surface immunoglobulin receptor (Fig. 1.2). In the pre B cell, this receptor consists of an immunoglobulin μ heavy chain, the heterodimeric surrogate light chain containing lambda 5 (λ5) and VpreB, and the signal transducers Ig alpha (Igα), and Ig beta (Igβ). Within the cytoplasm, BTK interacts with other kinases, and with so-called scaffold or adaptor proteins that serve to juxtapose other signaling intermediates, permitting activation to proceed downstream

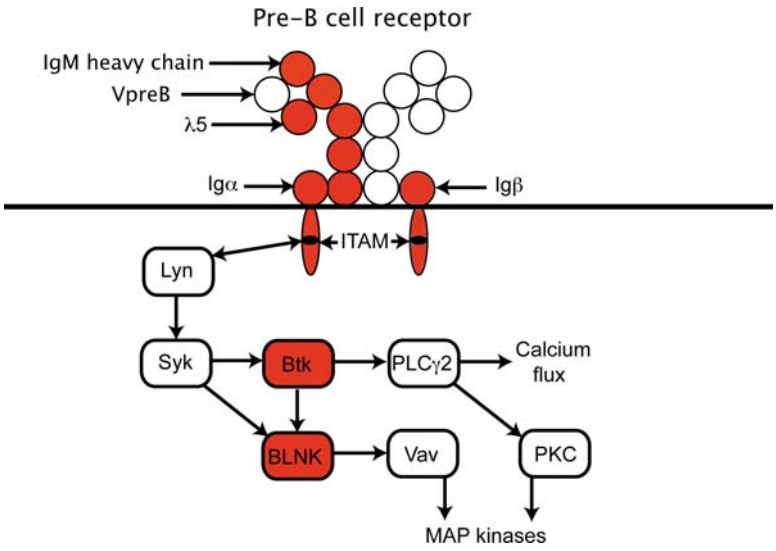

Fig. 1.2 This is a highly simplified diagram summarizing the relationships of several molecules whose absence is associated with agammaglobulinemia. All of the defects indicated here in *red* affect signaling through the pre-B cell receptor and block B cell development at the pre-B cell stage in the bone marrow. The pre-B cell receptor itself is made up of an IgM heavy chain, the surrogate light chain heterodimer of λ5 and VpreB, and the signal transducers Igα and Igβ, which bear the immunoreceptor tyrosine-based activation motifs (*ITAMs*). The ITAMs are phosphorylated by Lyn, a Src family tyrosine kinase, while Syk is the prototype of the tyrosine kinase family that bears the same name. Btk is a member of the Tec family of tyrosine kinases. B cell linker protein (*BLNK*) is a scaffold or adaptor protein, while Vav is a guanine nucleotide exchange factor for downstream GTPases. *PLCγ2* phospholipase C γ2, *PKC* protein kinase C

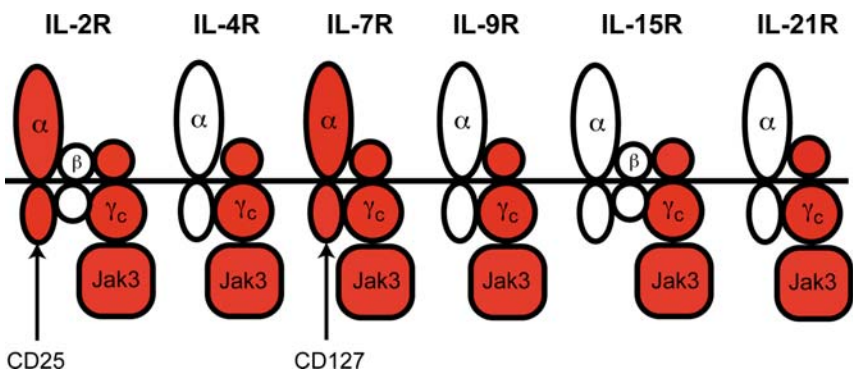

Fig. 1.3 The cytokine receptor common γ chain (γ_c) is a signal transducing component of the six cytokine receptors shown. In every case, its immediate downstream partner is the Jak3 tyrosine kinase. Absence of function of either of these molecules leads to severe combined immune deficiency (SCID) with similar phenotypes. Four of these receptors have only two components, a ligand-biding α chain and γ_c. Two (*IL-2R* and *IL-15R*) have an additional β chain. *IL-2* is a critical autocrine mediator of T cell activation and proliferation and mutations of the IL-2R α chain lead to SCID. *IL-7* is required for early T cell development, and mutations of IL-7R α have also been associated with SCID

along the molecular pathway. One of these is B cell linker protein (BLNK). To date, 4 of these 6 interacting molecules have been associated with autosomal forms of agammaglobulinemia that are indistinguishable from XLA in their clinical and laboratory characteristics; these are IgM heavy chain, λ5, Igα, and BTK [42] (see Sect. 3.2 for more details).

X-linked SCID is the result of a defect in the cytokine receptor common gamma chain (γ_c, Fig. 1.3) [72]. This molecule is a signal transducing component of the multimeric receptors for 6 different cytokines: interleukins-2, -4, -7, -9, -15, and -21. γ_c signals through the kinase JAK3. Mutation of the *JAK3* gene results in a very similar form of SCID with autosomal recessive inheritance [167]. Mutations in the genes encoding the ligand binding chains of the receptors for IL-2 and IL-7 also lead to forms of SCID [79, 179]. Severe combined immunodeficiency is the subject of the Chap. 2.

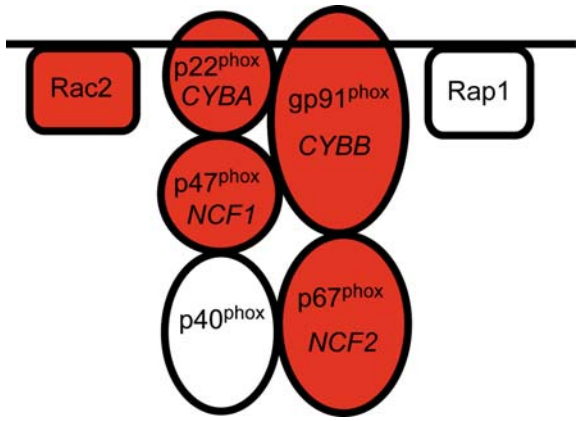

Fig. 1.4 The phagocyte oxidase complex is an electron transporter that is required for effective intracellular killing in the phagolysosomes of neutrophils and macrophages. This enzyme is comprised of five distinct subunits. Absence of four of these (shaded *red*) have been associated with chronic granulomatous disease (CGD). The *gp91^{phox}* (also called cytochrome b558 β, gene *CYBB*) is encoded by a gene on the X-chromosome, the other subunits are encoded by autosomal genes (*p22^{phox}* = cytochrome b558 α, gene *CYBA; p47^{phox}* = neutrophil cytosolic factor 1, gene *NCF1; p67^{phox}* = neutrophil cytosolic factor 2, gene *NCF2*). A neutrophil defect similar to CGD is also associated with mutations of the gene encoding the GTPase *Rac2*

Mutations in genes encoding distinct components of multimeric enzymes may also lead to similar disease phenotypes. CGD results from absent function of the phagocyte oxidase complex (Fig. 1.4) [217]. This complex has five subunits of which the gp91^{phox} subunit is encoded by a gene on the X chromosome. The other four subunits, are all encoded by autosomal genes. A mutation of gp91^{phox} or of three of the other four subunits leads to CGD, although the phenotype of the X-linked form tends to be more severe. CGD and other phagocytes defects are the subjects of Chap. 4.

1.3 Clinical Manifestations

1.3.1 Infections

Recurrent infections, or infection with an opportunistic organism, are the most commonly recognized associations with PID. Several groups have exploited this feature in an effort to develop criteria for an immunologic referral [50, 222, 224]. Most algorithms which have been designed to ascertain patients with PID revolve around a constellation of findings related to infections. These algorithms represent an important starting point for clinicians, but they have not yet been shown to have the sensitivity or specificity required for wide use. A typical algorithm assigns scores according to hospitalizations for infection or some combination of infections and autoimmune disease. These can be fairly sensitive for patients with humoral immunodeficiencies because their most common presenting features are recurrent infections and autoimmunity. In a cohort of patients with repeated hospitalization for infection, approximately 30% were found to have PID, and the majority of these had a defect in antibody production or function [50]. An algorithm was also developed for outpatient evaluations [224]. Scores were assigned to various infection categories and common autoimmune hematologic findings. Patients with PID had higher scores on average according to this schema than patients who did not appear to have an immunodeficiency; however, overlap was significant. Again, the majority of patients ascertained by this algorithm had defects in antibody production, although T cell defects and neutrophil defects were also seen.

Humoral immunodeficiencies are often said to be associated with recurrent respiratory tract infections and retrospective surveys of patients bear this out [43, 49, 62, 67, 218]. Nevertheless, there are no clear criteria for which patients should be evaluated for PID. Evaluation of all children with recurrent otitis media would not be practical or cost effective given the high frequency in the general population. Other types of infections may be more strongly associated with immunodeficiency. In a tertiary care referral center, chronic sinusitis patients were comprehensively evaluated for an immunodeficiency. CVID was identified in 10% and IgA deficiency was identified in 7% [39]. Recurrent pneumonia also appears to have a positive predictive value in children [163]. In a large tertiary care referral center, nearly all patients with recurrent pneumonia were found to have some underlying abnormality to explain their infections. Immunodeficiency was identified in 10% of patients. Similarly, in adult patients with bronchiectasis, an immunodeficiency was identified in 8% of patients [164]. Therefore, in some clinical settings, infections seem to be sufficiently associated with immunodeficiency such that screening tests may be warranted.

Recurrent abscesses also trigger concern regarding an immunodeficiency [217]. Recurrent cutaneous abscesses have become increasingly frequent in

the general population [75, 106, 111]. These are often thought to be a hallmark of innate immune disorders such as Hyper IgE syndrome (HIES) and CGD [84, 145, 147, 184]. There are few prospective data, but the prevalence of immunodeficiency in a population with recurrent cutaneous abscesses must be low. Cutaneous abscesses with unusual organisms or deep abscesses may represent infections with a greater association with immunodeficiencies.

To identify patients who would benefit from an immunological evaluation, it is also helpful to understand the pattern of infections seen in normal children. Children in the toddler age range typically develop one upper respiratory tract infection per month [178]. The frequency tends to be higher in children in a day care setting, as is true for gastrointestinal infections [92, 93]. There have also been studies suggesting that socioeconomic factors can contribute to the pattern of recurrent respiratory tract infections [150, 188]. In one provocative study, one third of 8-month-old children examined as part of a nutrition study were found on examination to have otitis media [139]. The pattern of infection among adults is also changing. It is no longer abnormal for adults and children to develop recurrent staphylococcal infections [75, 106, 111]. Sinus infections are also common in the general population, although in populations with chronic or recurrent disease the frequency of immunodeficiency appears to be approximately 20% [39, 207]. These studies focused on the sickest patients at tertiary care centers and it seems likely that the frequency of immunodeficiency is lower in patients with recurrent sinusitis in the general population [47].

There are limited data prospectively evaluating specific infections as predictive of immunodeficiency. Table 1.10 describes specific infections which are characteristic of immunodeficiencies. Meningococcal infections have long been recognized as being associated with complement defects although rare cases of antibody disorders have also been described [121]. An excellent prospective study from the Netherlands included 189 patients with meningococcal meningitis [199]. The overall prevalence of complement deficiencies in this cohort was 18%. Complement deficiencies were more common in patients infected with unusual serogroups (X, Y, W135, or ungroupable strains) and less common in patients infected with serogroups A or C (45% vs 3%). The majority of complement defects were found to involve properdin or C8. These data are concordant with previous studies of complement deficiencies and meningococcal meningitis [64, 124], although other studies have suggested a much lower risk of complement deficiency in unselected patients with meningococcal meningitis [103].

Another common bacterial infection, *Streptococcus pneumoniae*, is infrequently a predictor of immunodeficiency in general. Pneumococcal vaccine failure and infection with a vaccine-preventable strain might suggest a defect in humoral immunity. After the initial reports of IRAK4 deficiency associated with invasive *Streptococcus pneumoniae* infections [169], a survey of patients revealed that this was not frequently associated with IRAK4 deficiency [101]. All patients with IRAK4 deficiency had recurrent pyogenic infections at a young age and blunted inflammatory responses were common [208]. Thus, invasive streptococcal infections alone are not strongly predictive of IRAK4 deficiency, although in combination with either blunted inflammatory responses or additional invasive pyogenic infections, the disorder should be considered [120].

There are important negative data as well. Invasive group A streptococcal infections were not associated with any cases of immunodeficiency during an outbreak in Sweden [104]. Bacterial meningitis in general was not predictive of complement deficiency [65]. Finally, a single episode of pneumonia was not found to be associated with immunodeficiency [40, 87].

1.3.2 Autoimmunity

Autoimmunity is surprisingly common in patients with PID (Table 1.11). Autoimmune cytopenias are common in both patients with IgA deficiency as well as patients with CVID [48]. ITP precedes the diagnosis of CVID in approximately 10% of the adult patients [210]. Arthritis is also common in patients with IgA deficiency and CVID [49, 118, 128]. Autoimmune gastrointestinal disorders such as inflammatory bowel disease are also seen in these two patients with CVID. Autoimmunity is much less common in XLA suggesting it is not the defect in host defense that predisposes to autoimmunity but rather the dysregulated responses [218]. Consistent with this is the finding that X-linked Ig CSR deficiency is associated with arthritis in approximately 10% of the patients, sclerosing cholangitis in 10–20% of patients and autoimmune cytopenias less frequently [126, 219]. The autosomal recessive form due to defects in activation-induced cytidine deaminase (AID) is more strongly associated with autoimmunity and nearly a third of patients have overt autoimmune disease [173] (see Chap. 3 for more details).

Table 1.10 Infections suggestive of specific immunodeficiencies

Infection	Associated immunodeficiencies	Notes	References
Bacteria			
Burkholderia cepacia	Chronic granulomatous disease (CGD)	Second most frequent cause of death in CGD. Other Burkholderia *sp* seen	[217]
Mycoplasma/ Ureaplasma	Antibody deficiencies	Often found as osteomyelitis or arthritis	[189, 218]
Neisseria meningitidis	Deficiencies of alternative or terminal complement pathways components	Found more frequently in patients with unusual serotypes or recurrent disease	[69, 70]
Nocardia *sp*	Chronic granulomatous disease		[58]
Pseudomonas aeruginosa	Neutropenia		[87]
Salmonella *sp*	Chronic granulomatous disease	Usually invasive infections with Salmonella *sp* of low pathogenicity	[134, 217]
	Macrophage activation disorders		
Serratia marcesens	Chronic granulomatous disease	Excluding urinary tract infections	[217]
Staphylococcus aureus (severe)	Chronic granulomatous disease Hyper IgE syndrome	Visceral infection more suggestive	[84, 217]
Streptococcal sepsis	IRAK4 deficiency NEMO deficiency	IRAK4 deficiency is associated with blunted manifestations of sepsis	[71, 120, 169, 208]
	MyD88 deficiency		
	Asplenia		
	Complement deficiencies		
	Antibody deficiencies		
Atypical mycobacteria	Macrophage activation disorders Chronic granulomatous disease	Excluding isolated cervical adenopathy	[71, 217]
Viruses			
Cytomegalovirus (CMV)/Epstein-Barr virus (EBV)	X-lined lymphoproliferative disease (XLP)	XLP and FHL are usually associated with hemophagocytosis.	[29, 107, 205]
	Familial hemophagocytic lymphohistiocytosis (FHL)		
	Serious T cell deficiencies		
Herpes simplex virus (HSV)	UNC-93B and TLR3 deficiencies (STAT1, Caspase 8, and NEMO deficiencies)	Herpes encephalitis seen as isolated finding with UNC-93B and TLR3 deficiencies (STAT1, caspase 10, Wiskott-Aldrich syndrome and NEMO are also associated with herpes but these defects are usually associated with other infections)	[34, 61, 157, 211, 226]
Influenza (severe)	TLR3 deficiency	Found in one of three patients with influenza encephalitis	[99]
JC virus	Ig CSR deficiencies	Progressive multifocal leucoencephalopathy (PML)	[12, 91]
	Hyper IgE syndrome		
HHV8	Severe T cell deficiencies Wiskott–Aldrich syndrome		[3, 105, 168]
Varicella	Most significant T and NK cell deficiencies	Can be overwhelming or recurrent	[127]
Papilloma virus	Warts, hypogammaglobulinemia infections, myelokathexis syndrome		[56, 161, 198]
	Epidermodysplasia verruciformis		
Severe infection with common respiratory viruses	Severe combined immunodeficiency Other serious T cell deficiencies		[30]

(continued)

Table 1.10 (continued)

Infection	Associated immunodeficiencies	Notes	References
Fungi			
Aspergillus	Chronic granulomatous disease		[217]
Candida	Chronic granulomatous disease		[6, 57, 217]
	Autoimmune polyendocrinopathy with candidiasis and ectodermal dystrophy		
Histoplasmosis	Macrophage activation deficiencies	Disseminated, invasive	[225]
Low pathogenicity fungi	Chronic granulomatous disease		[217]
Parasite			
Cryptosporidia	Ig CSR deficiencies	Ascending cholangitis	[95]
Giardia	Antibody deficiencies		[97, 195]
Pneumocystis jiroveci	Severe T cell deficiencies NEMO deficiency		[18, 55, 140]
Toxoplasmosis	Severe T cell deficiencies Ig CSR deficiencies		[195, 196]

Table 1.11 Autoimmune disorders commonly associated with classical immunodeficiencies

Disorder	Immunodeficiencies associated	Notes
Idiopathic thrombocytopenic purpura	IgA deficiency Common variable immunodeficiency Chronic granulomatous disease Di George syndrome Wiskott–Aldrich syndrome	
Autoimmune hemolytic anemia	IgA deficiency Common variable immunodeficiency Chronic granulomatous disease Di-George Syndrome MHC class II deficiency Purine nucleoside phosphorylase deficiency Wiskott–Aldrich syndrome	
Systemic lupus erythematosus	Complement deficiencies Chronic granulomatous disease (CGD) IgA deficiency	Early classical complement component deficiencies. Lupus in CGD is more likely to be discoid than systemic
Juvenile arthritis	IgA deficiency Di-George Syndrome Wiskott–Aldrich syndrome X-linked agammaglobulinemia (XLA) Ig CSR deficiencies	Arthritis in XLA is often infectious
Sclerosing cholangitis	Ig CSR deficiencies	Often associated with cryptosporidium
Vasculitis	Wiskott–Aldrich syndrome (WAS) X-lined lymphoproliferative disease (XLP)	WAS is associated with Henoch Schonlein purpura. XLP is associated with an aggressive lymphoid vasculitis

Neutrophil disorders in general have a low association with autoimmune disorders, but CGD and carriers of the X-linked form of CGD have a markedly increased susceptibility to discoid lupus and systemic lupus erythematosus [217]. Leukocyte adhesion deficiency can be associated with colitis, but this is typically infectious and not autoimmune (see Chap. 4 for more details). Similarly, macrophage activation disorders such as IFN-γ receptor 1, IFN-γ receptor 2, IL-12/IL-23 receptor β1 chain, and IL-12p40 deficiencies, have a minimal association with autoimmunity. The exception is NEMO (NF-kappa-B essential modulator) deficiency (X-linked anhidrotic ectodermal dysplasia with immunodeficiency) where inflammatory bowel disease is common [149, 158] (see Chap. 6 for more details).

Complement deficiencies were one of the earliest recognized associations of immunodeficiency and autoimmunity. These associations are unusually specific. Early classical component deficiencies are specifically associated with systemic lupus erythematosus (SLE) [5, 181]. The association ranges from nearly all of the C1q or C1r/s deficient patients to approximately 25% of C2 deficient patients [137, 209]. The reason for the specific association with SLE relates to the twin roles of complement in the clearance of apoptotic cells and in B cell tolerance. Deficiencies of complement regulatory proteins are also associated with autoimmune disease and here too the association is extremely specific. Factor H, Factor I, and MCP (membrane cofactor protein) deficiencies are strongly associated with atypical hemolytic uremic syndrome [82]. The term atypical refers to hemolytic uremic syndrome without the typical diarrheal prodrome. It is extremely important to recognize patients with deficiencies of complement regulatory proteins as the untreated disease has a very high mortality rate. Additional defects in related regulatory components have also been described recently. Interestingly, milder defects in factor H have been associated with macular degeneration in adults and the mechanism of disease in both macular degeneration and hemolytic uremic syndrome relates to the role of Factor H in the protection of endothelial cells [90, 113] (see Chap. 8 for more details).

Other well-defined immunodeficiencies tend to have a strong association with autoimmunity. WAS is associated with vasculitis, arthritis, autoimmune cytopenias and Henoch Schonlein purpura [44, 197]. Autoimmune disease confers a poor prognosis in these patients for unknown reasons [60]. Di George syndrome or Di George syndrome is also associated with autoimmune disease in approximately 10% of the patients [108]. Juvenile arthritis, autoimmune cytopenias and autoimmune thyroid disease are the most common conditions associated with Di-George syndrome. Ataxia-telangiectasia is seldom associated with overt autoimmune disease but is frequently associated with autoantibody production [154] (see Chap. 9 for more details).

In the classic immunodeficiencies described above, the autoimmune disease can be a significant management issue; however, it is infrequently the phenotype leading to diagnosis. There are a series of immunodeficiencies for which the autoimmune manifestations are typically the first and most significant finding (Table 1.12). These disorders affect lymphocyte regulation. As T cells develop in the thymus, they undergo positive selection of T cells bearing self reactive T cell receptors. They also undergo negative selection to remove strongly self-reactive T cells. Negative selection relies on the expression of self-antigens on thymic medullary epithelium. Regulation of certain organ-specific self-antigens is regulated by the transcription factor AIRE [10]. Defects in this transcription factor lead to compromised negative selection and are associated with the syndrome, APECED (autoimmune polyendocrinopathy with candidiasis and ectodermal dystrophy). The classical presentation of patients includes invasive candidal infections in infancy and the accrual of autoimmune endocrine disorders with age [6]. Autoimmune adrenal dysfunction, autoimmune parathyroid dysfunction, and autoimmune thyroid dysfunction are common, and autoimmune hepatitis and autoimmune hemolytic anemia are also seen. Significant subsets of patients have only the autoimmune manifestations and the susceptibility to candida is not apparent [166].

Another disorder in which the autoimmune manifestations dominate the clinical picture is called IPEX (immunodysregulation, polyendocrinopathy, enteropathy, X-linked) [19]. The most common clinical features are infantile onset enteropathy with villous atrophy, infantile onset diabetes mellitus, and eczema [19, 215]. The severe form is rapidly fatal in the absence of immunosuppressive therapy often due to sepsis with enteric organisms or dehydration. IPEX is due to another defect in a transcription factor, FoxP3. This transcription factor is required for classical thymic-derived regulatory T cell development. These cells are critical for the prevention of autoimmune disease. When regulatory T cells fail to develop, inflammation develops unchecked at multiple sites. Enteropathy and diabetes are the most prominent clinical features, but autopsy results have demonstrated T cell infiltrates in many organs [96].

Table 1.12 Immunodeficiencies where autoimmune manifestations predominate

Immunodeficiency	Common autoimmune manifestations	Immunodeficiency characteristics and notes
Autoimmune lymphoproliferative syndrome	Autoimmune hemolytic anemia Idiopathic thrombocytopenic purpura Autoimmune neutropenia Glomerulonephritis Primary biliary cirrhosis	Host defense is generally intact. Patients with caspase 8 deficiency have herpetic infections. Lifetime risk of lymphoma increased
Autoimmune polyendocrinopathy with candidiasis and ectodermal dystrophy	Hypoparathyroidism Hypoadrenalism Diabetes mellitus Hypothyroidism Ovarian failure Vitiligo Autoimmune hepatitis	Susceptibility to candida is not understood. Other infections are not often seen. Autoimmune manifestations typically appear in the first decade of life and accumulate with age
Immunodysregulation, polyendocrinopathy, enteropathy, X- linked	Autoimmune enteropathy Diabetes mellitus Hemolytic anemia Hypothyroidism Eczema	Infections can be severe and reflect a compromised gut integrity. Hypogammaglobulinemia has been seen

Another defect in lymphocyte regulation reflects disordered cell death rather than disordered development. ALPS (autoimmune lymphoproliferative syndrome) is due to a collection of molecular defects which all lead to compromised activation induced cell death [73, 74]. This pathway is critical for the downregulation of an ongoing immune response. T cells sensitized by IL-2 from the activated T cells express Fas, a cell surface trimer which induces cell death or apoptosis. Defects in Fas, Fas ligand, NRAS or in downstream caspases all lead to lymphoproliferation with hepatosplenomegaly, adenopathy and autoimmune cytopenias. These patients also have a predisposition to lymphoma [171] (see Chap. 5 for more details).

1.3.3 Malignancies

Malignancies are thought to be increased in all populations of immunodeficient patients with significant T cell or NK cell compromise. There are few studies addressing this important complication. Certain populations have a known association with malignancy such as ALPS, CVID, Ig CSR deficiencies, XLP, and all the syndromes associated with defective DNA repair [31, 95, 116, 171, 172, 212]. Malignancy is infrequently the presenting manifestation of the disorder, although it has been described as an isolated finding in certain kindreds with XLP. A family history of malignancy can also be a helpful finding in patients with suspected DNA repair defects such as A-T or Nijmegen breakage syndrome, because heterozygous carriers may also have an increased risk of malignancy [202].

1.3.4 Other Manifestations

Primary immunodeficiency diseases are not often apparent by casual inspection. Certain patients may have dysmorphic features and in some cases there can be unique physical findings. Absent tonsils and adenoids are typically seen in patients with XLA or patients who have a T cell deficiency such that germinal centers cannot form, as the germinal centers constitute the mass of the secondary lymphoid structures [122]. Signs of infection may be seen in patients with chronic infections and atopy is increased in immunodeficient patients in general and signs of atopy may be seen on physical examination.

In addition to features directly associated with the immunodeficiency, there can be some unique physical features. Dysmorphic features are subtle in Di George syndrome "chromosome 22q11.2 deletion syndrome" but a conotruncal cardiac anomaly and/or hypocalcemia

in infancy are strongly suggestive features [81]. More substantial dysmorphic features are seen in chromosome 18q- minus syndrome [41]. Microcephaly can be seen in Di George syndrome with some frequency and is also a feature of Nijmegen breakage syndrome, Cernunnos deficiency, DNA Ligase IV deficiency, Høyeraal-Hreidarsson syndrome and Seckel syndrome [27, 116, 223]. Other facial features which can be diagnostically helpful are conical teeth found in NEMO deficiency, coloboma seen in CHARGE syndrome (Coloboma, Heart defects, Atresia of the choanae, Retardation of growth and development, Genital and urinary abnormalities, Ear abnormalities and/or hearing loss), the trapezoidal philtrum of Kabuki syndrome, and the coarse and asymmetrical facies of autosomal dominant HIES.

Skeletal manifestations are not uncommonly associated with PID. ADA deficiency is associated with metaphyseal dysplasia, and the scapular blunting can be helpful when seen on chest X-ray. Metaphyseal dysplasia is also seen in Schwachman–Diamond syndrome. Cartilage hair hypoplasia is associated with short-limbed dwarfism that is apparent from birth [135, 136]. Spondyloepiphyseal dysplasia is seen in Schimke's immuno-osseous dysplasia and is also usually apparent from birth [51]. Bone fragility and delayed shedding of the primary teeth are seen in HIES [84].

Cutaneous phenotypes are seen with some immunodeficiencies. Pigmentary dilution is seen in Chediak Higashi syndrome, Griscelli syndrome, and Hermansky–Pudlak syndrome. Absent hair is seen in the Nude form of SCID and bamboo hair is seen in Netherton syndrome. Papillon–Lefèvre syndrome is associated with early loss of teeth and palmoplantar hyperkeratosis. Dyskeratosis congenita is associated with telangiectasias and hyperpigmentation of the skin which increases with age.

The diagnosis of PID often rests on the identification of critical diagnostic laboratory features. Physical findings and historical features are often helpful in guiding the appropriate evaluation of the patient.

1.4 Diagnosis

1.4.1 Warning Signs and Symptoms

First and foremost, infections are the hallmark of immunodeficiency [192]. This should always be kept in mind. However, other symptoms may be more prominent at first, and this can be misleading. Widely varying events, such as failure-to-thrive in children, weight loss in adults, intractable diarrhea, autoimmune manifestations, and granulomatous diseases (see Sect. 1.3 for more details); all these and many more can point to immunodeficiency, but may not.

Young children suffer regularly from infections [139], and even in older children and adults, infections are not uncommon. It is of course impossible, and also unnecessary, to screen every patient with an infection for primary immunodeficiency. Only when the clinical presentation differs from the usually encountered pattern should the physician be alerted to possible immunodeficiency. This is the case when infections recur more frequently than expected, especially when these infections are bacterial in origin. Physicians should also be alerted by infections that present atypically, infections that are unusually severe or chronic, infections that are caused by an unexpected or opportunistic pathogen, or infections that fail regular treatment [192]. However, when infections recur at the same anatomical site, an anatomical defect may be the underlying problem, and this should be investigated first. Periodic fever syndromes can be another pitfall: it can be difficult to distinguish the recurrent episodes of fever from recurrent infections. A thorough investigation for the causative organism – which in the case of periodic fever will not be found – can help to make the distinction [130]. This will also help in case a primary immunodeficiency is indeed present, because the underlying immunodeficiency generally determines which types of pathogen are found [192]. Opsonization with specific antibody and complement and subsequent elimination by phagocytosis is needed for clearance of extracellular encapsulated bacteria that cause sinopulmonary infections. Thus, these infections will continue to recur in agammaglobulinemia, specific antibody deficiency, complement deficiency, neutropenia, and defects in granulocyte function. Local phagocytosis is important for clearance of fungi and bacteria on the skin and mucosal surfaces. If this is impaired, as in neutropenia and defects in granulocyte function, pyogenic skin infections with potential systemic spread occur, as well as, e.g., candidiasis and pulmonary aspergillosis. Intracellular and slow-growing pathogens are eliminated by activated T lymphocytes in interaction with macrophages. Viruses, parasites, mycobacteria, and opportunistic bacteria may therefore cause problems in case of T cell deficiency, SCID, or impaired interaction between T lymphocytes and macrophages (see also Table 1.10). Time is also a distinguishing factor when assessing the possibility of an immunodeficiency. In the first months of life, maternal immunoglobulin will mask

antibody deficiency in a child, but not a deficiency of T lymphocytes. So a child with SCID will mostly start to have problems related to the T lymphocyte deficiency. A child with agammaglobulinemia generally starts to have recurrent infections in the second part of the first year of life, when maternal antibodies are waning. But if the immunodeficiency develops later in life, as in CVID, the infections will also start later.

Besides infections, there are many other signs and symptoms that can point to immunodeficiency. They may be a complication of the repeated infections, or be entirely unrelated to them. Unusual complications of vaccination, unexplained bronchiectasis, absence of immunological tissues, difficult-to-treat obstructive lung disease, abnormal hair, delayed shedding of the umbilical cord or the primary teeth, eczema, and many more, may be symptoms of immunodeficiency.

It is of paramount importance to thoroughly explore the family history. A good family history may reveal consanguinity in the parents, unexplained early infant deaths in the family, or familial occurrence of similar symptoms. This is important for the prompt recognition of genetic disorders. Several affected siblings in the same family point to autosomal recessive inheritance, whereas transmission from parent to child fits autosomal dominant inheritance. Male patients with a disease that is transmitted along the female line, on the other hand, is suggestive for an X-linked recessive disorder. However, many mutations may be new and the family history is not necessarily positive, even if a genetic defect is present.

All in all, it is not an easy task to efficiently identify PID within the large pool of potential cases. Especially for non-immunologists, it works best to rely on pattern recognition of clinical presentations of patients. The better the knowledge about what is normal, the easier it becomes to identify abnormal patterns. Then, by focusing on the characteristic clinical presentations of PID, the attending physician can be guided to the right laboratory tests.

1.4.2 Diagnostic Approach

Primary immunodeficiency diseases generally present with one of eight characteristic clinical presentations (Table 1.13) [53]. So, once such a clinical presentation is encountered, primary immunodeficiency is a possibility that should be explored further. This does not necessarily mean immunological tests have to be performed. In patients with recurrent ear, nose, throat (ENT) and airway infections, other non-immunological problems like bronchial hyperreactivity, allergy and asthma occur much more frequently and should be investigated first. On the other hand, only a few children with failure to thrive will have PID, but delay in diagnosis and treatment will greatly impair their survival, and immunological tests have to be performed at an early stage. In general, severe defects should be ruled out (or identified) promptly with widely available screening tests, whereas less severe forms of PID can safely be identified later. The advice of an immunologist can be very useful during this diagnostic process.

Table 1.13 The eight characteristic clinical presentations of PID [53]

1	Recurrent ENT (ear, nose, throat) and airway infections
2	Failure to thrive from early infancy
3	Recurrent pyogenic infections
4	Unusual infections or unusually severe course of infections
5	Recurrent infections with the same type of pathogen
6	Autoimmune or chronic inflammatory disease and/or lymphoproliferation
7	Characteristic combinations of clinical features in eponymous syndromes
8	Angioedema

It is not necessary to fully understand the underlying immunological mechanisms to be able to use the different clinical presentations for reliable early suspicion of potential PID. Practice parameters can be used to link the clinical presentation to the right set of laboratory tests. The European Society for Immunodeficiencies (ESID) has published a multistage diagnostic protocol that was especially designed for use by non-immunologists [53]. The American Academy, American College and Joint Council of Allergy, Asthma and Immunology practice parameter for the diagnosis and management of primary immunodeficiency offers diagnostic guidelines for immunologists with extensive decision trees [22]. A simplified version can be found in Table 1.14. From the eight characteristic clinical presentations of immunodeficiency in column 1 of this table, the user is guided through the first essential steps in the diagnostic work-up in column 2 with the aid of screening tests that ensure identification of severe defects in an early phase in column 3. If a diagnosis of severe immunodeficiency is made, further identification of the defect is illustrated in columns 4 and 5. If no diagnosis is found in the first screening and problems persist, columns 4 and 5 enable further

Table 1.14 From clinical presentation to laboratory tests [53]

Clinical presentation	First step in the diagnostic process	Screening laboratory tests[a]	Next steps in the diagnostic process[b]	More elaborate laboratory tests [a,b,c]
Recurrent ENT and airway infections	Rule out severe antibody deficiency and neutropenia	IgG, IgA and IgM. Blood count and differential (platelet volume, absolute lymphocyte count, neutrophil and eosinophil counts)	Identify milder forms of antibody deficiency and complement defects	IgG-subclasses. CH_{50} and AP_{50} MBL. Specific antibody responses to tetanus and unconjugated pneumococcal vaccine. M-proteins. Lymphocyte subpopulations. Lymphocyte proliferation tests. CD40/CD40L after stimulation. ANA. Specific complement components
Failure to thrive from early infancy and Unusual infections or unusually severe course of infections	Rule out severe combined immunodeficiency and acquired immunodeficiency syndrome (AIDS)	Blood count and differential (platelet volume, absolute lymphocyte count, neutrophil and eosinophil counts). IgG, IgA and IgM. Lymphocyte subpopulations. Tests for HIV	Identify the different forms of (severe) combined immunodeficiency	Extended protocol for lymphocyte subpopulations. Lymphocyte proliferation tests. CD40/CD40L after stimulation. IL12, IL12-receptor, IFN-γ-receptor, STAT1. IκBα. If no agammaglobulinemia: IgG-subclasses, booster responses, M-proteins. Tests for chimerism. In vitro cytokine production. In vivo tests of T lymphocyte function. Analysis of bone marrow, lymph node biopsy. NK cell cytotoxicity. Uric acid, ADA, PNP, α-fetoprotein, X-ray of long bones if short stature or disproportional growth, thymus size (chest X-ray, ultrasound), chromosomal analysis, radiosensitivity tests, 22q11 analysis, clonality studies (Vβ-gene usage)
Recurrent pyogenic infections	Identify neutropenia, and – if present – its cause	Blood count and differential (platelet volume, absolute lymphocyte count, neutrophil and eosinophil counts)	Identify defects in phagocyte function	Phagocyte function tests. Repeated blood count and differential for cyclic neutropenia. Autoantibodies, ANA, C3/C4, RF, ANCA, Coombs, IgG, IgA and IgM. Analysis of bone marrow (morphology, chromosomes, culture), mobilization tests (GCSF, prednisone), pancreatic function tests. Metabolic tests. IgD. IgE. Hair evaluation. CD11/18 and sLeX expression (flowcytometry, in case of neutrophilia)
Recurrent infections with the same type of pathogen	Consider PID	–	Dependent on type of pathogen: (a) Intracellular bacteria; (b) Meningococci; (c) Candida; (d) Encapsulated bacteria; (e) Viruses	(a) IL12, IL12-receptor, IFN-γ-receptor, STAT1. (b) CH_{50} and AP_{50}. (c) Rows 1 and 2. (d) Row 1; splenic ultrasound. (e) Row 2

(continued)

Table 1.14 (continued)

Clinical presentation	First step in the diagnostic process	Screening laboratory tests[a]	Next steps in the diagnostic process[b]	More elaborate laboratory tests [a,b,c]
Autoimmune or chronic inflammatory disease and/or lymphoproliferation	Consider PID	Immunoglobulins. CH50. Blood count and differential (platelet volume, absolute lymphocyte count, neutrophil and eosinophil counts). Lymphocyte subpopulations. Acute phase proteins during fever. Organ-specific autoantibody screen	Identify specific PID syndrome	Dependent on particular PID
Characteristic combinations of clinical features in eponymous syndromes	Consider PID	Dependent on particular syndrome (see Chap. 10 for more details)	Identify specific PID syndrome	Dependent on particular PID. Chromosomal analysis. α-fetoprotein. 22q11 analysis
Angioedema	Consider specific complement deficiency	–	Identify specific complement deficiency	C1-inhibitor. C4 during an attack

[a]Use age-matched reference values for the interpretation of laboratory tests
[b]Consult an immunologist, not all tests mentioned need necessarily be done!
[c]Perform genetic characterisation of the defect if possible

elaborate tests to characterize milder defects. Not all tests in column 5 need necessarily be done. If in doubt, consult an immunologist!

Recurrent ENT (ear, nose, throat) and airway infections. Recurrent ENT and airway infections are normal in young children, especially in case of passive smoking and day care attendance. Only when their frequency is out of the ordinary, or if the child is unable to lead a life like its peers, is it necessary to look for an underlying cause. Older children and adults can suffer from the occasional ENT or airway infection, but in them, recurrent infections should be considered abnormal. Non-immunological underlying causes such as mucosal swelling caused by allergy and/or bronchial hyperreactivity or anatomical obstruction caused by adenoidal hypertrophy in a young child are frequent. Sometimes gastroesophageal reflux or iron deficiency play a role in children. Infrequently, a more severe problem like bronchopulmonary dysplasia, cystic fibrosis, a foreign body, a congenital anomaly, ciliary dyskinesia or α1-antitrypsin deficiency is present. These generally present in childhood. Only seldom will a PID-like antibody deficiency, complement deficiency, neutropenia or phagocyte function deficiency be present. IgA deficiency, IgG subclass deficiency, and specific antibody deficiency are the most frequently encountered PID, but their clinical relevance is often unclear. In young children, this may be temporary, but in older children and adults this is seldom the case. They may even be a sign of developing CVID, resulting in profound hypogammaglobulinemia in the following years. So, if problems persist, it is essential to repeat the immunological investigations.

Failure to thrive from early infancy. Failure to thrive, often combined with intractable diarrhea, can have many causes. One of them is SCID, which nowadays can have a good prognosis if hematopoietic stem cell transplantation is performed in time. Therefore, prompt investigation of T lymphocyte number and function are of paramount importance in children presenting with failure to thrive. The lymphopenia can most typically be detected in a routine leukocyte differential count.

Recurrent pyogenic infections. Superficial pyogenic infections can be expected on damaged skin, as in eczema or burns, and are not related to immunodeficiency. Deep-seated pyogenic infections, especially in combination with granulomatous inflammation and poor wound healing, point to phagocytes defects. This is mostly due to neutropenia, which is often iatrogenic (chemotherapy and other drugs). Sometimes a true phagocyte function defect such as CGD is present.

Unusual infections or unusually severe course of infections. Unusual infections or an unusually severe course of an infection should always trigger the physician to consider possible immunodeficiency. However, an uncommon presentation of a common disease is much more frequent than an uncommon disease like PID. In spite of that, screening investigations should be done, because early recognition of immunodeficiency prevents sequelae and thereby improves the patient's prognosis.

Recurrent infections with the same type of pathogen. Without an anatomical defect, increased exposure, or inadequate treatment, recurrent infections with the same type of pathogen can be caused by immunodeficiency, even if the patient is otherwise healthy. Generally, only one specific pathway is then affected, but the resulting infection can be life threatening. Recently, several defects have been described, and more can be expected [33].

Autoimmune or chronic inflammatory disease and/or lymphoproliferation. Generally, autoimmunity, chronic inflammation, and lymphoproliferation are not associated with an immunodeficiency. This is possible, however, especially but not exclusively if recurrent infections occur. CVID, complement deficiency, and T lymphocyte deficiency can be complicated by these phenomena. In certain diseases, autoimmunity (APECED, IPEX) or lymphoproliferation (XLP) are core symptoms. Therefore, immunodeficiency should be kept in mind in atypical cases.

Characteristic combinations of clinical features in eponymous syndromes. Many eponymous syndromes are associated with immunodeficiency [142, 143]. These can be of varying severity. Mostly, the immunodeficiency is not the presenting symptom in these patients.

Angioedema. Classical hereditary angioedema occurs after a trigger-like stress or an infection activates the complement system in people who lack the C1 inhibitor. It is often not recognized, especially if the swelling occurs in an internal organ, leading to unnecessary treatment (e.g., exploratory laparotomy). The differential diagnosis includes allergy, malignancy, and autoimmunity.

1.4.3 Laboratory Tests

Laboratory tests that are useful for the identification of PID are listed in Table 1.14. With a limited set of tests that is available in most hospitals, a first screen for PID can be reliably performed (column 3 of Table 1.14). Neutropenia and lymphopenia can be easily identified by a blood count and differential. Serum levels of IgG, IgA, and IgM can show a hypogammaglobulinemia,

and CH_{50} and $AP(AH)_{50}$ can identify most complement defects. T lymphocytes with CD4+ helper and CD8+ cytotoxic subsets, B lymphocytes and natural killer (NK) cells can be determined by flow cytometry. Absolute counts and age-related reference values are needed for accurate interpretation of the results; relative counts can lead to misinterpretations [54]. This is sufficient for identification of most patients with SCID, agammaglobulinemia, neutropenia and complement deficiencies. Serology is usually sufficient to identify an HIV infection, but in young children with possible perinatal exposure, or in those suspected to have a deficiency of humoral immunity, viral load should be determined because antibodies can be maternal in origin, or may not be present.

More elaborate tests (column 5 of Table 1.14) can be performed in immunological laboratories; their results are generally more difficult to interpret. IgG subclass deficiencies as well as mannan-binding lectin (MBL) deficiency are found more often in patients with recurrent infections, but can be asymptomatic. Specific antibody responses to protein (tetanus) or polysaccharide (pneumococci) antigens can be diminished or absent despite normal immunoglobulin serum levels. This can be found in isolation, or be part of a more severe defect such as common variable immunodeficiency. Lymphocyte proliferation tests can be performed with mitogens that stimulate lymphocytes non-specifically, or with stimulators that selectively activate calcium entry into the cell (for example), or antigens that must be recognized by the T cell receptor. Advanced immunophenotyping can help to elucidate which parts of the immune system are disturbed. Random migration, chemotaxis, adherence, phagocytosis, and intracellular microbial killing by phagocytes can be measured in specialised laboratories by conventional methods or flow cytometry. Superoxide generation can be measured by the nitroblue tetrazolium (NBT) dye reduction test, a chemiluminescence assay, or by dihydrorhodamine (DHR) oxidation.

1.5 Management

1.5.1 General Considerations

Since primary immunodeficiency diseases represent a vast array of defects that differentially impair host defenses, there would ideally be an equally vast number of therapeutic options to specifically address each of the deficiencies in these individual conditions. Unfortunately this is not the case, and there are a limited, but expanding, number of therapeutic modalities and management strategies available to patients. In some instances, the available treatments are quite appropriate for closing the gap in host defense created by a given PID, while in others the treatments fall unacceptably short, and patients suffer excessive morbidities and even premature death. There is high quality scientific evidence supporting some of the specific therapeutic interventions applied to particular PID. However, in many, the evidence is extrapolated from other PID-specific data, data from other medical conditions affecting immunologic function, or even consensus among experts caring for patients with PID. Here, general concepts in therapy for PID are introduced so that many of the disease-specific details provided elsewhere throughout this volume can be placed within a broader context.

Primary immunodeficiency disease results in an ineffective balance between the patient and environment. Thus, interventions to bias this balance toward host defense and away from pathogen success should be considered a general goal. In some instances of PID, specific holes in host defense can be filled through therapeutic intervention, while in others treatments are more directed at globally reducing susceptibility to infection. It can be critical to the well-being of the patient to strike this balance perfectly, while maintaining the general health of the patient and their family. As the variety of treatments and management options available to patients affected by the different diagnoses is often specific to a particular diagnosis, this section is focused only upon more general concepts of the expert care of PID patients. Essential general issues in the care of PID patients that can help create an effective structure to prevent and contend with disease morbidity include educating the patient about their diagnosis, insuring general health maintenance, and providing continuity in subspecialty care.

A definite priority for the clinical immunologist is to serve as teacher and educator for patients affected by these relatively rare diseases. If a patient is unable to comprehend the challenges they face from their environment, it is unlikely that they will be able to successfully navigate them. In most cases, this involves some general introduction to the immune system, how it functions to facilitate host defense, the specific component or components that are defective in the given patient's disease, and what strategies are best to close the gap in immunity created by the deficiency. Often this information is overwhelming and needs to be reit-

erated and provided in multiple formats over time. In this regard, there are a number of resources available to the physician including a number from patient organizations such as the Jeffrey Modell Foundation (JMF), the International Patient Organization for Primary Immunodeficiencies (IPOPI) and the Immune Deficiency Foundation (IDF). In particular, the latter organization has a patient and family handbook covering both general and disease specific topics. It is available in print and as a free download from the IDF website (http://www.primaryimmune.org/pubs/book_pats/book_pats.htm). Similarly, the virtual book *Living with Primary Immunodeficiencies* is available for free download from the IPOPI website (http://www.ipopi.org/publications/living-with-pid/). Another source that can be useful for explaining the immune system and its defects to children affected by PID are a number of superb children's-style books, such as the independently published *Cell Wars* [16], the *Our Immune System* pamphlet available through the IDF website (http://www.primaryimmune.org/pubs/book_immunesys/book_immunesys.htm) and the *Play Your Best Defense* picture book available from the JMF. Collaborating with the patient and their family to understand the intricacies of the immunodeficiency can lead to an important and effective therapeutic alliance.

Another important part of managing PID patients is to insure adequate basic health maintenance. General guidelines for the health maintenance for children and adolescents as well as those for adults promoted by organizations such as the American Academy of Pediatrics, the American College of Physicians, and the American Academy of Family Physicians are an important baseline and should be respected. It is unfortunate that the highly complex PID patient can sometimes overwhelm a primary care provider resulting in primary care being shifted to the subspecialist. There are many disadvantages to this paradigm. It can be very useful for the patient to have a strong primary care provider who is informed by the subspecialist regarding the intricacies of the PID diagnosis. These providers are routinely considering age-specific guidelines for general health maintenance and likely have practices equipped to provide such care. Specific additions and modifications to such general guidelines, however, need to be introduced for the different PID diagnoses. Thus, an active dialogue between the subspecialist and the primary physician regarding these alterations as indicated for the patient's diagnosis are invaluable. There are a number of resources available to a subspecialist to facilitate their effort in educating a primary care physician regarding the patient's diagnosis and requirements for care. These include a number of excellent reviews by clinical immunologists in the generalist medical literature [14, 28, 45], as well as the educational materials of the IDF specifically tailored to generalist physicians (http://www.primaryimmune.org/pubs/book_phys/book_phys.htm).

Finally, providing continuity in subspecialist care is a critical part of the comprehensive care and presumed well-being of a PID patient. Despite this seemingly obvious conclusion, there are few data demonstrating the effectiveness of regular subspecialist care, or demonstrating an effective frequency of patient visits. Guidelines have been created [22] and in many cases are disease-specific. Ideally, the subspecialist will actively contribute to the health maintenance of the patient and help guide the patient, family, generalist and other health care providers along a course that will be mindful of the pitfalls inherent to a given PID. Extensive familiarity with the most recent disease-specific literature will enable the subspecialist to recommend and provide the most current and effective therapies for the patient. Although it is difficult to define exactly how often a PID patient should be evaluated by a subspecialist, it is important for the subspecialist to be considered more than a diagnostician and to participate in the formation and execution of ongoing care plans for PID patients.

1.5.2 Vaccination

Vaccines are an essential part of health maintenance for the general population and are required by law in many countries. In general, widespread vaccination programs only stand to benefit patients with PID. These programs reduce the burden of and exposure to diseases that present significant risks to PID patients suffering from ineffective defenses against them. A notable exception is certain live viral vaccinations that have the potential to infect PID patients during a period of viral shedding in the otherwise healthy vaccinee. One for which specific guidance exists and has gained increasing publicity in recent years is small pox (Variola) vaccination. Here according to the Centers for Disease Control and Prevention (CDC), the household contacts of immunodeficient individuals are not to be vaccinated [213]. Furthermore, casual contacts of vaccinated individuals are not to include immunodeficient individuals until the vaccination lesion has fully scabbed.

In terms of the direct vaccination of PID patients, immunizations have the potential to be helpful or harmful depending upon the vaccine and specific

disease of the patient. In general, killed or subunit vaccines are safe for PID patients although they may be ineffective. Live vaccines can be useful, but must be carefully considered as they have the potential to cause disease in their own right in some PID patients. There are cases documented across the range of live vaccines [78, 100]. In this light, the advisory committee on Immunizations Practices (ACIP) of the US CDC (http://www.cdc.gov/vaccines/recs/acip/) has included a number of recommendations specific to patients with immunodeficiency. This broadly covers the avoidance of live viral vaccination for patients with significant immunodeficiency. More specifically, patients with T cell deficiency or combined PID should be considered at relative risk for vaccine complications, and the degree of immunodeficiency needs be carefully evaluated prior to clearing a patient for immunization. There are a number of disease-specific recommendations that exist based upon scientific studies [15, 148, 165] and which should be considered in individual cases. It is also essential that the subspecialist communicates a very clear plan to the primary care provider so that an at-risk patient is not incidentally immunized in the routine process of health maintenance. Important vaccines presenting risk to PID patients that should be carefully considered include measles, mumps, rubella, varicella, rotavirus, poliovirus, BCG, intranasal influenza, yellow fever, and variola.

Although the use of live viral vaccines can potentially be harmful, the use of non-live vaccines may have the potential to provide some prophylactic or even therapeutic efficacy. An important example is influenza. The injectable killed influenza vaccine may have limited effectiveness in PID patients, but may provide some important protection against this very common infection. This may be especially relevant as the antigenic drift and shift inherent to influenza means that neutralizing antibodies against the season's influenza virus may be absent from the plasma pool used for antibody replacement therapy. For this reason, annual non-live influenza vaccination is a consideration for PID patients. One vaccine indication that is often overlooked is the use of pneumococcal polysaccharide vaccine for PID patients who are not receiving immunoglobulin replacement therapy. In particular, the ACIP states, "Persons who have conditions associated with decreased immunologic function that increase the risk for severe pneumococcal disease or its complications should be vaccinated". Improving the range and quantity of anti-pneumococcal polysaccharide antibodies may help reduce the incidence of pneumococcal infection in PID patients. Given that this is a significant morbidity in patients with even mild humoral immune defects, it is important recommendation to consider. A listing of recommended vaccines according to specific category of PID is available from the ACIP and is a reasonable starting point in considering this practice (http://www.cdc.gov/vaccines/pubs/pinkbook/downloads/appendices/A/immuno-table.pdf).

One final concern is vaccination for individuals who are on, or who have been on, immunoglobulin therapy. As a general rule, patients on immunoglobulin replacement therapy do not need to receive immunizations. The live viral vaccines in particular, are actually neutralized by exogenous antibody. There may be utility however, to still providing non-live influenza vaccination as discussed above. It is also important to consider when to reimmunize a patient after they have received immunoglobulin. Here, specific recommendations vary according to country but include waiting as long as 11 months (in the US) before administering a live viral vaccine. A study of measles vaccine efficacy in patients treated with intravenous immunoglobulin (IVIG) for Kawasaki Disease is useful in that it demonstrated the return of protective responses in all patients by 9 months after treatment [144].

1.5.3 Antibiotics

Antibiotics are essential to the survival of most PID patients and have in many cases allowed patients to survive to the point of receiving a diagnosis. Appropriately diagnosing infection in as timely a fashion as possible and then treating with appropriate antibiotics is fundamental. For this reason, it is critical that the subspecialist be familiar with the range of infectious susceptibilities inherent to a particular PID as well as the most appropriate diagnostic approaches to these infections. These individual topics are covered throughout this volume in detail.

In addition to antibiotics used for the specific therapy of clinically apparent infections, there is an important and frequently underappreciated role for prophylactic antibiotics in PID patients. In some PID, the use of antibiotics prophylactically is very clear and is based upon evidence derived from placebo-controlled trials, such as in CGD [76, 138]. In other PID, however, the use of antibiotic prophylaxis is based only upon data extrapolated from other conditions

[216], anecdotal experience [59], and/or expert recommendations [22]. This said, a majority of subspecialist immunologists use prophylaxis for at least some PID patients [156]. A majority also uses it for at least some PID patients as adjunct therapy to IVIG. Better high-quality data regarding the efficacy of prophylactic antibiotics for PID is most certainly needed, but at present should be considered an option for patients who are experiencing frequent infection that requires repeated use of treatment-dose antibiotics. It should also be considered for patients who are at extreme risk for particular type of infections, or severe infections. An example would be *Mycobacterium avium* prophylaxis for patients with NEMO deficiency [160].

1.5.4 Immunoglobulin Replacement Therapy

Immunoglobulin (Ig) replacement therapy is a mainstay for PID patients who do not have the ability to generate or maintain effective antibody responses. In this regard, it represents one of the truly immediate life-altering interventions that can be offered to appropriate patients with PID. In fact, when patients with antibody deficiencies are treated with Ig, their infection frequency can be reduced to that of baseline populations [186]. Specific details regarding the therapeutic use of Ig in PID will be provided in Chap. 11, but it is important to raise a few general considerations at this point.

It is important to use Ig replacement therapy for PID diagnoses that are characterized by an inability to produce antibody, produce specific antibody, or maintain specific antibody. These include XLA, Ig CSR deficiencies, CVID, and specific antibody deficiency. There are other diagnoses, however, in which anecdotal experience supports the use of Ig therapy, but it is unclear if it represents the best evidenced-based practice. In some, this is due to the ambiguity of the diagnosis and in others, the limited experience in treating the diagnosis, or the efficacy of available alternative treatments. There are several guidelines available, which can help navigate the evidence underlying the different indications for Ig therapy [22, 131, 159, 191].

Once a decision has been made to provide Ig replacement therapy, there are a number of options regarding its administration that can affect clinical outcome. These options should be considered and decisions made in accordance with best evidence and patient characteristics. One is the route of therapy, which can be either intravenous (IVIG) or subcutaneous (SCIG). There are important considerations relative to each, but they should at least be considered therapeutically equivalent [20, 38]. Other important variables include the dose of Ig, frequency of Ig, residual trough level (especially in diagnoses characterized by hypogammaglobulinemia or agammaglobulinemia), and management of infusion-associated adverse events. Again, many of these variables will be discussed later, but they are also specifically considered according to evidence elsewhere [17, 159].

1.5.5 Transplantation

Some of the more severe PID that weaken host defense outside the B cell system cannot be effectively treated using only antibiotics and other relatively conservative measures. In these diseases, the patients affected by them are expected to die prematurely if only these therapeutic strategies are employed. Fortunately hematopoietic stem cell (HSC) transplantation (HSCT) has emerged over recent decades as a very viable and effective option for many of these patients [153]. A clear example is SCID, which is uniformly fatal without this intervention [30]. Other PID can also be treated with HSCT, some more successfully than others. These include Ig CSR deficiencies, NEMO deficiency, familial hemophagocytic lymphohistiocytosis (FHL), IPEX, WAS, CGD, and LAD, among others. The specifics, merits and outcomes of HSCT for these diseases are the subject of numerous reviews and primary articles and will also be covered elsewhere in this volume. It is important, however, to mention a few general considerations.

Unfortunately there is no PID in which HSCT is 100% successful, and therefore the risk-benefit relation for the particular patient must be carefully considered. In some situations, it is very clear that nearly any risk must be accepted to provide HSCT for the patient, such as for a classic SCID. In others, however, particular variables should be weighed before proceeding to transplant. These include suitability of a donor, health of the patient and, in some cases, support available to the patient. In terms of donor suitability, there are some diseases that appear to be much more effectively treated through the use of an HLA-identical related donor. In others, there is more flexibility, and a matched unrelated donor or haploidentical donor can be quite effective. These decisions may impact the conditioning regimen selected for the patient and therefore have the potential to affect the transplantation

experience and long-term consequences. In some patients, cord blood-sourced HSCT can be highly effective [187], while in others bone marrow-sourced HSCT is preferred. There are important attributes of each of these options, including potentially different HSC/Kg dose, incidence of graft failure, incidence of graft versus host disease and time to engraftment, that need to be evaluated for each patient. Although the science of transplantation has advanced remarkably in recent years, HSCT does create a disease state in and of itself and the decision to transplant needs be evaluated very carefully. As a result, HSCT is best performed in centers with expertise and preferably in centers with expertise in PID and, better still, for the specific disease being treated.

1.5.6 Gene Therapy

Despite advances that have at times predominated the popular media, gene therapy for PID is still a field in its infancy [21]. Immunologic deficiencies are superb candidates for gene therapy because the HSC can be removed and manipulated in vitro and then carry the therapeutic gene through successive cell divisions and differentiation. Some of the PID are ideally suited as the deficiency of the causative gene results in a selective disadvantage of the affected immune cells. In other words, if the normal gene can be replaced, even into a subset of cells, they will have a superior proliferative or survival capacity and be able to fill the space in the immune system that was otherwise void or occupied by weaker disadvantaged cells. A clear example is lymphocytopenic SCID, in which lymphocytes fail to proliferate. Here, provision of the normal gene into patient HSCs can provide them with the ability to proliferate and fill otherwise unoccupied space. This approach has been successful in patients with X-linked SCID due to *IL2RG* mutation [88]. The limitation in this setting, and a true challenge to gene therapy, has been in developing and using optimal and controllable gene vector systems. In the *IL2RG* patients, a subset developed hematopoietic malignancy that was believed to be due to insertion of the gene therapy vector near the *LMO2* oncogene, thus promoting abnormal growth of the gene transduced cells containing this insertion event [89]. Although this has been debated [221], it is believed that the vector system is to blame [170]. Gene therapy success has also been reported for CGD, but unexpected and preferential insertion of the vector was prerequisite for success [162]. This result helped reconcile the success in CGD, as the defective phagocytes typically do not have a survival disadvantage as demonstrated by carrier females. Thus, the selective immunologic pressure to provide an advantage to gene-transduced cells was now introduced through vector-induced enhanced transcription of specific genes.

Despite these initial successes and increased understanding, it is commonly held that more elegant gene therapy vector systems are needed to provide additional assurance and control over this very promising means of treating PID [36]. Future objectives may include the ability to specifically control an integration site for a gene therapy vector, selectively destroy cells containing the vector (in the case of abnormal expansion), and exogenously control the expression of the transduced gene.

1.5.7 Adjunct Therapies

The health of PID patients can also be improved by a number of more indirect interventions that are believed to provide slight benefits. Again in most cases, these have not been directly studied in the context of PID and are based upon data extrapolated from other conditions affecting immunologic function, or from the opinion and consensus of expert immunologists. In general, these measures are believed to help reduce the susceptibility to infection or improve host defense. Although they may not be perceived as substantial interventions, they can be considered as part of a holistic approach to a PID patient. Firstly, it is important to effectively manage co-morbidities or unrelated conditions that increase the susceptibility to infection that a given patient may have. These include allergic rhinosinusitis, asthma, gastroesophageal reflux and challenges presented by sinus anatomy. In patients without PID, effective management of these diagnoses can be associated with beneficial outcomes.

In PID patients, one often-discussed intervention is hygiene. In some cases, there is a very clear rationale for hygiene, such as excluding mold sources from the environment of CGD patients. In others, however, a rationale for hygiene is based upon studies of hygiene interventions in otherwise healthy individuals, such as the use of regular hand washing or alcohol-based hand gels [214]. Also in this category, it can be useful to discuss nasal/sinus irrigation with saline as this has been demonstrated to have effectiveness in patients with chronic sinusitis, presumably through removing

irritants, bacteria, and debris [174]. At a minimum, discussing reasonable hygiene interventions with a PID patient may have benefit and may prevent them from inappropriately diverting their focus from more effective measures. In particular, having a discussion about the social and developmental merits of participation in school is important, as the immunologic benefit of avoiding school is almost never warranted.

It is also relevant to discuss the use of botanicals and other remedies aimed at reducing the incidence of infection and or improving immunity. In the United States, the sale of botanicals represents a multibillion dollar industry and one not subject to the same evidence-based and marketing controls as standard pharmaceuticals. Since many of these formulations are marketed directly to patients, it is important to have a working knowledge of some of the more common preparations and to be prepared to hold a discussion about the benefits and risks of such remedies. It is also important to advise patients in protecting their financial resources when considering therapies promising great return based upon scarce or no evidence. With this said, some of these therapies are perhaps useful. One worthy of mention is the use of lactobacillus. The use of lactobacillus has been shown to reduce the incidence of infectious diarrhea as well as upper respiratory infection in susceptible non-PID populations [175, 183]. Caution needs be advised regarding the very wide range of lactobacillus preparations available, some of which are associated with significant financial costs.

A final very important consideration is the psychosocial well-being of the PID patient. Psychosocial stress is well documented to adversely affect immune function [228], and PID patients can only benefit from minimizing this impact. A variety of measures are worth consideration including psychosocial therapy, massage therapy and even acupuncture in the appropriate setting. The onus of a life-long chronic illness is tremendous, and being faced with the uncertainty of infectious susceptibility can truly take its toll. It is critical therefore to recognize this, acknowledge it to both patient and family, and provide the patient with the best available resources. Many are available through the national and international patient organizations representing PID, the IDF, JMF and IPOPI. Others are available through local or disease specific groups. In addition, local resources for patients with chronic diseases may be very effective and useful for PID patients, and the subspecialist needs to become familiar with the availability of resources in a given region. Although there are an array of appropriate options, these need to be matched to the individual patient, and discussing these issues should be viewed as a requirement in PID patient care to optimize outcome.

References

1. Abedi MR, Morgan G, Goii H, Paganelli R, Matamoros N, Hammarström L (2000) Report from the ESID Registry of Primary Immunodeficiencies, Accessed Jul 2000, at: http://www.esid.org
2. Abuzakouk M, Feighery C (2005) Primary immunodeficiency disorders in the Republic of Ireland: first report of the national registry in children and adults. J Clin Immunol 25:73–77
3. Agarwal S, Cunningham-Rundles C (2007) Thymoma and immunodeficiency (Good syndrome): a report of 2 unusual cases and review of the literature. Ann Allergy Asthma Immunol 98:185–190
4. Aghamohammadi A, Moein M, Farhoudi A, Pourpak Z, Rezaei N, Abolmaali K, Movahedi M, Gharagozlou M, Ghazi BM, Mahmoudi M, Mansouri D, Arshi S, Trash NJ, Akbari H, Sherkat R, Hosayni RF, Hashemzadeh A, Mohammadzadeh I, Amin R, Kashef S, Alborzi A, Karimi A, Khazaei H (2002) Primary immunodeficiency in Iran: first report of the National Registry of PID in Children and Adults. J Clin Immunol 22:375–380
5. Agnello V (1986) Lupus diseases associated with hereditary and acquired deficiencies of complement. Springer Semin Immunopathol 9:161–178
6. Ahonen P, Myllarniemi S, Sipila I, Perheentupa J (1990) Clinical variation of autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED) in a series of 68 patients. N Engl J Med 322:1829–1836
7. al-Attas RA, Rahi AH (1998) Primary antibody deficiency in Arabs: first report from eastern Saudi Arabia. J Clin Immunol 18:368–371
8. Al-Herz W (2008) Primary Immunodeficiency Disorders in Kuwait: First Report from Kuwait National Primary Immunodeficiency Registry (2004–2006). J Clin Immunol 28:186–193
9. Anderson-Cohen M, Holland SM, Kuhns DB, Fleisher TA, Ding L, Brenner S, Malech HL, Roesler J (2003) Severe phenotype of chronic granulomatous disease presenting in a female with a de novo mutation in gp91-phox and a non familial, extremely skewed X chromosome inactivation. Clin Immunol 109:308–317
10. Anderson MS, Venanzi ES, Klein L, Chen Z, Berzins SP, Turley SJ, von Boehmer H, Bronson R, Dierich A, Benoist C, Mathis D (2002) Projection of an immunological self shadow within the thymus by the aire protein.[comment]. Science. Online 298:1395–1401
11. Andrews PA, Koffman CG (1998) Outcome of renal transplantation in Wiskott-Aldrich syndrome [letter]. Nephrol Dial Transplant 13:524–525
12. Angelini L, Pietrogrande MC, Delle Piane MR, Zibordi F, Cinque P, Maccagnano C, Vago L (2001) Progressive multifocal leukoencephalopathy in a child with hyper-immunoglobulin E recurrent infection syndrome and review of the literature. Neuropediatrics 32:250–255

13. Ariga T, Kondoh T, Yamaguchi K, Yamada M, Sasaki S, Nelson DL, Ikeda H, Kobayashi K, Moriuchi H, Sakiyama Y (2001) Spontaneous in vivo reversion of an inherited mutation in the Wiskott-Aldrich syndrome. J Immunol 166:5245–5249
14. Azar AE, Ballas ZK (2007) Evaluation of the adult with suspected immunodeficiency. Am J Med 120:764–768
15. Azzari C, Gambineri E, Resti M, Moriondo M, Betti L, Saldias LR, AM GG, Vierucci A (2005) Safety and immunogenicity of measles-mumps-rubella vaccine in children with congenital immunodeficiency (DiGeorge syndrome). Vaccine 23:1668–1671
16. Balkwill F (1990) Cell Wars. Lerner Publishing, Minneapolis
17. Ballow M (2007) Safety of IGIV therapy and infusion-related adverse events. Immunol Res 38:122–132
18. BenMustapha-Darghouth I, Trabelsi S, Largueche B, Bejaoui M, Dellagi K, Barbouche MR (2007) [Prevalence of Pneumocystis jiroveci pneumonia in Tunisian primary immunodeficient patients]. Arch Pediatr 14:20–23
19. Bennett CL, Christie J, Ramsdell F, Brunkow ME, Ferguson PJ, Whitesell L, Kelly TE, Saulsbury FT, Chance PF, Ochs HD (2001) The immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome (IPEX) is caused by mutations of FOXP3. Nat Genet 27:20–21
20. Berger M (2004) Subcutaneous immunoglobulin replacement in primary immunodeficiencies. Clin Immunol 112:1–7
21. Blaese RM (2007) What is the status of gene therapy for primary immunodeficiency? Immunol Res 38:274–284
22. Bonilla FA, Bernstein IL, Khan DA, Ballas ZK, Chinen J, Frank MM, Kobrynski LJ, Levinson AI, Mazer B, Nelson RP, Jr., Orange JS, Routes JM, Shearer WT, Sorensen RU (2005) Practice parameter for the diagnosis and management of primary immunodeficiency. Ann Allergy Asthma Immunol 94:S1–63
23. Bonilla FA, Geha RS (2003) 12. Primary immunodeficiency diseases. J Allergy Clin Immunol 111:S571–581
24. Bonilla FA, Geha RS (2005) Are you immunodeficient? J Allergy Clin Immunol 116:423–425
25. Boyle JM, Buckley RH (2007) Population prevalence of diagnosed primary immunodeficiency diseases in the United States. J Clin Immunol 27:497–502
26. Bruton OC (1952) Agammaglobulinemia. Pediatrics 9:722–728
27. Buck D, Malivert L, de Chasseval R, Barraud A, Fondaneche MC, Sanal O, Plebani A, Stephan JL, Hufnagel M, le Deist F, Fischer A, Durandy A, de Villartay JP, Revy P (2006) Cernunnos, a novel nonhomologous end-joining factor, is mutated in human immunodeficiency with microcephaly. Cell 124:287–299
28. Buckley RH (2004) Pulmonary complications of primary immunodeficiencies. Paediatr Respir Rev 5 Suppl A:S225–233
29. Buckley RH, Schiff RI, Schiff SE, Markert ML, Williams LW, Harville TO, Roberts JL, Puck JM (1997) Human severe combined immunodeficiency: genetic, phenotypic, and functional diversity in one hundred eight infants. J Pediatr 130:378–387
30. Buckley RH, Schiff SE, Schiff RI, Markert L, Williams LW, Roberts JL, Myers LA, Ward FE (1999) Hematopoietic stem-cell transplantation for the treatment of severe combined immunodeficiency. N Engl J Med 340:508–516
31. Bundey S (1994) Clinical and genetic features of ataxia-telangiectasia. Int J Radiat Biol 66:S23-S29
32. Bykowsky MJ, Haire RN, Ohta Y, Tang H, Sung SS, Veksler ES, Greene JM, Fu SM, Litman GW, Sullivan KE (1996) Discordant phenotype in siblings with X-linked agammaglobulinemia. Am J Hum Genet 58:477–483
33. Casanova JL, Fieschi C, Bustamante J, Reichenbach J, Remus N, von Bernuth H, Picard C (2005) From idiopathic infectious diseases to novel primary immunodeficiencies. J Allergy Clin Immunol 116:426–430
34. Casrouge A, Zhang SY, Eidenschenk C, Jouanguy E, Puel A, Yang K, Alcais A, Picard C, Mahfoufi N, Nicolas N, Lorenzo L, Plancoulaine S, Senechal B, Geissmann F, Tabeta K, Hoebe K, Du X, Miller RL, Heron B, Mignot C, de Villemeur TB, Lebon P, Dulac O, Rozenberg F, Beutler B, Tardieu M, Abel L, Casanova JL (2006) Herpes simplex virus encephalitis in human UNC-93B deficiency. Science 314:308–312
35. Castigli E, Wilson S, Garibyan L, Rachid R, Bonilla F, Schneider L, Morra M, Curran J, Geha R (2007) Reexamining the role of TACI coding variants in common variable immunodeficiency and selective IgA deficiency. Nat Genet 39:430–431
36. Cavazzana-Calvo M, Fischer A (2007) Gene therapy for severe combined immunodeficiency: are we there yet? J Clin Invest 117:1456–1465
37. Champi C (2002) Primary immunodeficiency disorders in children: prompt diagnosis can lead to lifesaving treatment. J Pediatr Health Care 16:16–21
38. Chapel HM, Spickett GP, Ericson D, Engl W, Eibl MM, Bjorkander J (2000) The comparison of the efficacy and safety of intravenous versus subcutaneous immunoglobulin replacement therapy. J Clin Immunol 20:94–100
39. Chee L, Graham SM, Carothers DG, Ballas ZK (2001) Immune dysfunction in refractory sinusitis in a tertiary care setting. Laryngoscope 111:233–235
40. Clark JE, Hammal D, Hampton F, Spencer D, Parker L (2007) Epidemiology of community-acquired pneumonia in children seen in hospital. Epidemiol Infect 135:262–269
41. Cody JD, Ghidoni PD, DuPont BR, Hale DE, Hilsenbeck SG, Stratton RF, Hoffman DS, Muller S, Schaub RL, Leach RJ, Kaye CI (1999) Congenital anomalies and anthropometry of 42 individuals with deletions of chromosome 18q. Am J Med Genet 85:455–462
42. Conley ME, Broides A, Hernandez-Trujillo V, Howard V, Kanegane H, Miyawaki T, Shurtleff SA (2005) Genetic analysis of patients with defects in early B cell development. Immunol Rev 203:216–234
43. Conley ME, Howard V (2002) Clinical findings leading to the diagnosis of X-linked agammaglobulinemia. J Pediatr 141:566–571
44. Conley ME, Saragoussi D, Notarangelo L, Etzioni A, Casanova JL (2003) An international study examining therapeutic options used in treatment of Wiskott-Aldrich syndrome. Clin Immunol 109:272–277
45. Cooper MA, Pommering TL, Koranyi K (2003) Primary immunodeficiencies. Am Fam Physician 68:2001–2008
46. Cooper MD, Lanier LL, Conley ME, Puck JM (2003) Immunodeficiency disorders. Hematol Am Soc Hematol Educ Program:314–330
47. Costa Carvalho BT, Nagao AT, Arslanian C, Carneiro Sampaio MM, Naspitz CK, Sorensen RU, Leiva L, Sole D

(2005) Immunological evaluation of allergic respiratory children with recurrent sinusitis. Pediatr Allergy Immunol 16:534–538
48. Cunningham-Rundles C (2002) Hematologic complications of primary immune deficiencies. Blood Rev 16:61–64
49. Cunningham-Rundles C, Bodian C (1999) Common variable immunodeficiency: Clinical and immunological features of 248 patients. Clin Immunol 92:34–48
50. Cunningham-Rundles C, Sidi P, Estrella L, Doucette J (2004) Identifying undiagnosed primary immunodeficiency diseases in minority subjects by using computer sorting of diagnosis codes. J Allergy Clin Immunol 113:747–755
51. de Jong M, van Wijk JA, van der Hulst JP, Ludwig M, Bokenkamp A (2005) [Schimke's immuno-osseous dysplasia as an explanation for the rare combination of disproportionately short stature and the nephrotic syndrome]. Ned Tijdschr Geneeskd 149:2178–2182
52. de Saint Basile G, Tabone MD, Durandy A, Phan F, Fischer A, Le Deist F (1999) CD40 ligand expression deficiency in a female carrier of the X-linked hyper-IgM syndrome as a result of X chromosome lyonization. Eur J Immunol 29:367–373
53. de Vries E (2006) Patient-centred screening for primary immunodeficiency: a multi-stage diagnostic protocol designed for non-immunologists. Clin Exp Immunol 145:204–214
54. de Vries E, de Bruin-Versteeg S, Comans-Bitter WM, de Groot R, Boerma GJ, Lotgering FK, van Dongen JJ (1999) Correction for erythroid cell contamination in microassay for immunophenotyping of neonatal lymphocytes. Arch Dis Child Fetal Neonatal Ed 80:F226–229
55. Deerojanawong J, Chang AB, Eng PA, Robertson CF, Kemp AS (1997) Pulmonary diseases in children with severe combined immune deficiency and DiGeorge syndrome. Pediatr Pulmonol 24:324–330
56. Diaz GA, Gulino AV (2005) WHIM syndrome: a defect in CXCR4 signaling. Curr Allergy Asthma Rep 5:350–355
57. Dominguez M, Crushell E, Ilmarinen T, McGovern E, Collins S, Chang B, Fleming P, Irvine AD, Brosnahan D, Ulmanen I, Murphy N, Costigan C (2006) Autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED) in the Irish population. J Pediatr Endocrinol Metab 19:1343–1352
58. Dorman SE, Guide SV, Conville PS, DeCarlo ES, Malech HL, Gallin JI, Witebsky FG, Holland SM (2002) Nocardia infection in chronic granulomatous disease. Clin Infect Dis 35:390–394
59. Dorsey MJ, Orange JS (2006) Impaired specific antibody response and increased B cell population in transient hypogammaglobulinemia of infancy. Ann Allergy Asthma Immunol 97:590–595
60. Dupuis-Girod S, Medioni J, Haddad E, Quartier P, Cavazzana-Calvo M, Le Deist F, de Saint Basile G, Delaunay J, Schwarz K, Casanova JL, Blanche S, Fischer A (2003) Autoimmunity in Wiskott-Aldrich syndrome: risk factors, clinical features, and outcome in a single-center cohort of 55 patients. Pediatrics 111:e622–627
61. Dupuis S, Jouanguy E, Al-Hajjar S, Fieschi C, Al-Mohsen IZ, Al-Jumaah S, Yang K, Chapgier A, Eidenschenk C, Eid P, Al Ghonaium A, Tufenkeji H, Frayha H, Al-Gazlan S, Al-Rayes H, Schreiber RD, Gresser I, Casanova JL (2003) Impaired response to interferon-alpha/beta and lethal viral disease in human STAT1 deficiency. Nat Genet 33:388–391
62. Durandy A, Peron S, Fischer A (2006) Hyper-IgM syndromes. Curr Opin Rheumatol 18:369–376
63. Eades-Perner AM, Gathmann B, Knerr V, Guzman D, Veit D, Kindle G, Grimbacher B (2007) The European internet-based patient and research database for primary immunodeficiencies: results 2004–06. Clin Exp Immunol 147:306–312
64. Ellison RT, Kohler PH, Curd JG, Judson FN, Reller LB (1983) Prevalence of congenital and aquired complement deficiency in patients with sporadic meningococcal disease. N Engl J Med 308:913–916
65. Ernst T, Spath PJ, Aebi C, Schaad UB, Bianchetti MG (1997) Screening for complement deficiency in bacterial meningitis. Acta Paediatr 86:1009–1010
66. ESID (2008) European Society for Immunodeficiencies Registry, Accessed May 2008, at: http://www.esid.org/statistics.php
67. Etzioni A, Ochs HD (2004) The hyper IgM syndrome – an evolving story. Pediatr Res 56:519–525
68. Fasth A (1982) Primary immunodeficiency disorders in Sweden: cases among children, 1974–1979. J Clin Immunol 2:86–92
69. Figueroa J, Andreoni J, Densen P, Fredrikson GN, Truedsson L, Sjoholm AG (1993) Complement deficiency states and meningococcal disease. New procedure for the detection of complement deficiency by ELISA. Analysis of activation pathways and circumvention of rheumatoid factor influence. Immunol Res 12:295–311
70. Figueroa JE, Densen P (1991) Infectious diseases associated with complement deficiencies. Clin Microbiol Rev 4:359–395
71. Filipe-Santos O, Bustamante J, Chapgier A, Vogt G, de Beaucoudrey L, Feinberg J, Jouanguy E, Boisson-Dupuis S, Fieschi C, Picard C, Casanova JL (2006) Inborn errors of IL-12/23- and IFN-gamma-mediated immunity: molecular, cellular, and clinical features. Semin Immunol 18:347–361
72. Fischer A, Le Deist F, Hacein-Bey-Abina S, Andre-Schmutz I, Basile Gde S, de Villartay JP, Cavazzana-Calvo M (2005) Severe combined immunodeficiency. A model disease for molecular immunology and therapy. Immunol Rev 203:98–109
73. Fischer A, Rieux-Laucat F, Le Deist F (2000) Autoimmune lymphoproliferative syndromes (ALPS): models for the study of peripheral tolerance. Rev Immunogenet 2:52–60
74. Fisher GH, Rosenberg FJ, Straus SE, Dale JK, Middleton LA, Lin AY, Strober W, Lenardo MJ, Puck JM (1995) Dominant interfering Fas gene mutations impair apoptosis in a human autoimmune lymphoproliferative syndrome. Cell 81:935–946
75. Frederiksen MS, Espersen F, Frimodt-Moller N, Jensen AG, Larsen AR, Pallesen LV, Skov R, Westh H, Skinhoj P, Benfield T (2007) Changing epidemiology of pediatric Staphylococcus aureus bacteremia in Denmark from 1971 through 2000. Pediatr Infect Dis J 26:398–405
76. Gallin JI, Alling DW, Malech HL, Wesley R, Koziol D, Marciano B, Eisenstein EM, Turner ML, DeCarlo ES, Starling JM, Holland SM (2003) Itraconazole to prevent fungal infections in chronic granulomatous disease. N Engl J Med 348:2416–2422
77. Geha RS, Notarangelo L, Casanova JL, Chapel H, Fischer A, Hammarstrom L, Nonoyama S, Ochs H, Puck J, Roifman

C, Seger R, Wedgwood J (2007) Primary immunodeficiency diseases: an update the International Union of Immunological Societies Primary Immunodeficiency Diseases Classification Committee. J Allergy Clin Immunol 120:776–794
78. Gershon AA (2003) Varicella vaccine: rare serious problems–but the benefits still outweigh the risks. J Infect Dis 188:945–947
79. Giliani S, Mori L, de Saint Basile G, Le Deist F, Rodriguez-Perez C, Forino C, Mazzolari E, Dupuis S, Elhasid R, Kessel A, Galambrun C, Gil J, Fischer A, Etzioni A, Notarangelo LD (2005) Interleukin-7 receptor alpha (IL-7Ralpha) deficiency: cellular and molecular bases. Analysis of clinical, immunological, and molecular features in 16 novel patients. Immunol Rev 203:110–126
80. Glanzmann E, Riniker P (1950) Essentielle lymphocytophthise. Ein neues Krankheitsbild aus der Sauglingspathologie. Ann Paediatr (Basel) 175:1–32
81. Goldberg R, Marion R, Morderon W, Wiznia A, Shprintzen RJ (1985) Phenotypic overlap between cardio-velo-facial syndrome (VCF) and the DiGeorge sequence (DGS). Am J Hum Genet 37:A54
82. Goodship TH (2006) Atypical HUS and complement dysregulation. J Am Soc Nephrol 17:1775–1776
83. Gooi HC (1993) Primary immunodeficiency register, United Kingdom: update 1992. Immunodeficiency 4:191–192
84. Grimbacher B, Holland S, Gallin JI, Greenberg F, Hill S, Malech HL, Miller JA, O'Connell AC, Dent B, Puck JM (1999) Hyper-IgE syndrome with recurrent infections-an autosomal dominant multisystem disorder. N Engl J Med 340:692–702
85. Grimbacher B, Hutloff A, Schlesier M, Glocker E, Warnatz K, Drager R, Eibel H, Fischer B, Schaffer AA, Mages HW, Kroczek RA, Peter HH (2003) Homozygous loss of ICOS is associated with adult-onset common variable immunodeficiency. Nat Immunol 4:261–268
86. Grumach AS, Duarte AJ, Bellinati-Pires R, Pastorino AC, Jacob CM, Diogo CL, Condino-Neto A, Kirschfink M, Carneiro-Sampaio MM (1997) Brazilian report on primary immunodeficiencies in children: 166 cases studied over a follow-up time of 15 years. J Clin Immunol 17:340–345
87. Gutierrez F, Masia M, Rodriguez JC, Mirete C, Soldan B, Padilla S, Hernandez I, De Ory F, Royo G, Hidalgo AM (2005) Epidemiology of community-acquired pneumonia in adult patients at the dawn of the 21st century: a prospective study on the Mediterranean coast of Spain. Clin Microbiol Infect 11:788–800
88. Hacein-Bey-Abina S, Le Deist F, Carlier F, Bouneaud C, Hue C, De Villartay JP, Thrasher AJ, Wulffraat N, Sorensen R, Dupuis-Girod S, Fischer A, Davies EG, Kuis W, Leiva L, Cavazzana-Calvo M (2002) Sustained correction of X-linked severe combined immunodeficiency by ex vivo gene therapy. N Engl J Med 346:1185–1193
89. Hacein-Bey-Abina S, Von Kalle C, Schmidt M, McCormack MP, Wulffraat N, Leboulch P, Lim A, Osborne CS, Pawliuk R, Morillon E, Sorensen R, Forster A, Fraser P, Cohen JI, de Saint Basile G, Alexander I, Wintergerst U, Frebourg T, Aurias A, Stoppa-Lyonnet D, Romana S, Radford-Weiss I, Gross F, Valensi F, Delabesse E, Macintyre E, Sigaux F, Soulier J, Leiva LE, Wissler M, Prinz C, Rabbitts TH, Le Deist F, Fischer A, Cavazzana-Calvo M (2003) LMO2-associated clonal T cell proliferation in two patients after gene therapy for SCID-X1. Science 302:415–419
90. Hageman GS, Anderson DH, Johnson LV, Hancox LS, Taiber AJ, Hardisty LI, Hageman JL, Stockman HA, Borchardt JD, Gehrs KM, Smith RJ, Silvestri G, Russell SR, Klaver CC, Barbazetto I, Chang S, Yannuzzi LA, Barile GR, Merriam JC, Smith RT, Olsh AK, Bergeron J, Zernant J, Merriam JE, Gold B, Dean M, Allikmets R (2005) A common haplotype in the complement regulatory gene factor H (HF1/CFH) predisposes individuals to age-related macular degeneration. Proc Natl Acad Sci USA 102:7227–7232
91. Han GP, Miura K, Ide Y, Tsutsui Y (2005) Genetic analysis of JC virus and BK virus from a patient with progressive multifocal leukoencephalopathy with hyper IgM syndrome. J Med Virol 76:398–405
92. Hardy AM, Lairson DR, Morrow AL (1994) Costs associated with gastrointestinal-tract illness among children attending day-care centers in Houston, Texas. Pediatrics 94:1091–1093
93. Haskins R (1989) Acute illness in day care: how much does it cost? Bull NY Acad Med 65:319–343
94. Hayakawa H, Kobayashi N, Yata J (1986) Primary immunodeficiency diseases and malignancy in Japan. Jpn J Cancer Res 77:74–79
95. Hayward AR, Levy J, Facchetti F, Notarangelo L, Ochs HD, Etzioni A, Bonnefoy JY, Cosyns M, Weinberg A (1997) Cholangiopathy and tumors of the pancreas, liver, and biliary tree in boys with X-linked immunodeficiency with hyper-IgM. J Immunol 158:977–983
96. Heltzer ML, Choi JK, Ochs HD, Sullivan KE, Torgerson TR, Ernst LM (2007) A potential screening tool for IPEX syndrome. Pediatr Dev Pathol 10:98–105
97. Herbst EW, Armbruster M, Rump JA, Buscher HP, Peter HH (1994) Intestinal B cell defects in common variable immunodeficiency. Clin Exp Immunol 95:215–221
98. Hermaszewski RA, Webster AD (1993) Primary hypogammaglobulinemia: a survey of clinical manifestations and complications. Q J Med 86:31–42
99. Hidaka F, Matsuo S, Muta T, Takeshige K, Mizukami T, Nunoi H (2006) A missense mutation of the Toll-like receptor 3 gene in a patient with influenza-associated encephalopathy. Clin Immunol 119:188–194
100. Hidalgo S, Garcia Erro M, Cisterna D, Freire MC (2003) Paralytic poliomyelitis caused by a vaccine-derived polio virus in an antibody-deficient Argentinean child. Pediatr Infect Dis J 22:570–572
101. Hirschfeld AF, Bettinger JA, Victor RE, Davidson DJ, Currie AJ, Ansermino JM, Scheifele DW, Orange JS, Turvey SE (2007) Prevalence of Toll-like receptor signalling defects in apparently healthy children who developed invasive pneumococcal infection. Clin Immunol 122:271–278
102. Hirschhorn R, Yang DR, Puck JM, Huie ML, Jiang CK, Kurlandsky LE (1996) Spontaneous in vivo reversion to normal of an inherited mutation in a patient with adenosine deaminase deficiency. Nat Genet 13:290–295
103. Hoare S, El-Shazali O, Clark JE, Fay A, Cant AJ (2002) Investigation for complement deficiency following meningococcal disease. Arch Dis Child 86:215–217
104. Holm SE, Norrby A, Bergholm AM, Norgren M (1992) Aspects of pathogenesis of serious group A streptococcal infections in Sweden, 1988–1989. J Infect Dis 166:31–37
105. Inhoff O, Doerries K, Doerries R, Scharf J, Groden C, Goerdt S, Schadendorf D (2007) Disseminated cutaneous

Kaposi sarcoma and progressive multifocal leukoencephalopathy in a patient with idiopathic CD4 + T lymphocytopenia. Arch Dermatol 143:673–675
106. Jacobsson G, Dashti S, Wahlberg T, Andersson R (2007) The epidemiology of and risk factors for invasive Staphylococcus aureus infections in western Sweden. Scand J Infect Dis 39:6–13
107. Janka GE (2007) Familial and acquired hemophagocytic lymphohistiocytosis. Eur J Pediatr 166:95–109
108. Jawad AF, McDonald-Mcginn DM, Zackai E, Sullivan KE (2001) Immunologic features of chromosome 22q11.2 deletion syndrome (DiGeorge syndrome/velocardiofacial syndrome). J Pediatr 139:715–723
109. JMF (2008) Primary immunodeficiency resource center. Global survey results, Jeffrey Modell diagnostic and referral centers, Accessed Jun 2008, at: http://www.info4pi.org
110. Kanegane H, Tsukada S, Iwata T, Futatani T, Nomura K, Yamamoto J, Yoshida T, Agematsu K, Komiyama A, Miyawaki T (2000) Detection of Bruton's tyrosine kinase mutations in hypogammaglobulinaemic males registered as common variable immunodeficiency (CVID) in the Japanese Immunodeficiency Registry. Clin Exp Immunol 120:512–517
111. Kerttula AM, Lyytikainen O, Karden-Lilja M, Ibrahem S, Salmenlinna S, Virolainen A, Vuopio-Varkila J (2007) Nationwide trends in molecular epidemiology of methicillin-resistant Staphylococcus aureus, Finland, 1997–2004. BMC Infect Dis 7:94
112. Kirkpatrick P, Riminton S (2007) Primary immunodeficiency diseases in australia and new zealand. J Clin Immunol 27:517–524
113. Klein RJ, Zeiss C, Chew EY, Tsai JY, Sackler RS, Haynes C, Henning AK, SanGiovanni JP, Mane SM, Mayne ST, Bracken MB, Ferris FL, Ott J, Barnstable C, Hoh J (2005) Complement factor H polymorphism in age-related macular degeneration. Science 308:385–389
114. Klemperer MR, Woodworth HC, Rosen FS, Austen KF (1966) Hereditary deficiency of the second component of complement (C 2) in man. J Clin Invest 45:880–890
115. Knerr V, Grimbacher B (2007) Primary immunodeficiency registries. Curr Opin Allergy Clin Immunol 7:475–480
116. Kondratenko I, Paschenko O, Polyakov A, Bologov A (2007) Nijmegen breakage syndrome. Adv Exp Med Biol 601:61–67
117. Kornfeld SJ, Kratz J, Haire RN, Litman GW, Good RA (1995) X-linked agammaglobulinemia presenting as transient hypogammaglobulinemia of infancy. J Allergy Clin Immunol 95:915–917
118. Koskinen S (1996) Long-term follow-up of health in blood donors with primary selective IgA deficiency. J Clin Immunol 16:165–170
119. Kostmann R (1956) Infantile genetic agranulocytosis: a new recessive lethal disease in man. Acta Paediatr Scand 45:1–78
120. Ku CL, Picard C, Erdos M, Jeurissen A, Bustamante J, Puel A, von Bernuth H, Filipe-Santos O, Chang HH, Lawrence T, Raes M, Marodi L, Bossuyt X, Casanova JL (2007) IRAK4 and NEMO mutations in otherwise healthy children with recurrent invasive pneumococcal disease. J Med Genet 44:16–23
121. Lear S, Eren E, Findlow J, Borrow R, Webster D, Jolles S (2006) Meningococcal meningitis in two patients with primary antibody deficiency treated with replacement intravenous immunoglobulin. J Clin Pathol 59:1191–1193
122. Lederman HM, Winkelstein JA (1985) X-linked agammaglobulinemia: an analysis of 96 patients. Medicine (Baltimore) 64:145–156
123. Lee WI, Kuo ML, Huang JL, Lin SJ, Wu CJ (2005) Distribution and clinical aspects of primary immunodeficiencies in a Taiwan pediatric tertiary hospital during a 20-year period. J Clin Immunol 25:162–173
124. Leggiadro RJ, Winkelstein JA (1987) Prevalence of complement deficiencies in children with systemic meningococcal infections. Pediatr Infect Dis J 6:75–76
125. Leiva LE, Zelazco M, Oleastro M, Carneiro-Sampaio M, Condino-Neto A, Costa-Carvalho BT, Grumach AS, Quezada A, Patino P, Franco JL, Porras O, Rodriguez FJ, Espinosa-Rosales FJ, Espinosa-Padilla SE, Almillategui D, Martinez C, Tafur JR, Valentin M, Benarroch L, Barroso R, Sorensen RU (2007) Primary immunodeficiency diseases in Latin America: the second report of the LAGID registry. J Clin Immunol 27:101–108
126. Levy J, Espanol-Boren T, Thomas C, Fischer A, Tovo P, Bordigoni P, Resnick I, Fasth A, Baer M, Gomez L, Sanders EA, Tabone MD, Plantaz D, Etzioni A, Monafo V, Abinun M, Hammarstrom L, Abrahamsen T, Jones A, Finn A, Klemola T, DeVries E, Sanal O, Peitsch MC, Notarangelo LD (1997) Clinical spectrum of X-linked hyper-IgM syndrome. J Pediatr 131:47–54
127. Levy O, Orange JS, Hibberd P, Steinberg S, LaRussa P, Weinberg A, Wilson SB, Shaulov A, Fleisher G, Geha RS, Bonilla FA, Exley M (2003) Disseminated varicella infection due to the vaccine strain of varicella-zoster virus, in a patient with a novel deficiency in natural killer T cells. J Infect Dis 188:948–953
128. Liblau RS, Bach JF (1992) Selective IgA deficiency and autoimmunity. Int Arch Allergy Immunol 99:16–27
129. Lim DL, Thong BY, Ho SY, Shek LP, Lou J, Leong KP, Chng HH, Lee BW (2003) Primary immunodeficiency diseases in Singapore – the last 11 years. Singapore Med J 44:579–586
130. Long SS (2005) Distinguishing among prolonged, recurrent, and periodic fever syndromes: approach of a pediatric infectious diseases subspecialist. Pediatr Clin North Am 52:811–835, vii
131. Looney RJ, Huggins J (2006) Use of intravenous immunoglobulin G (IVIG). Best Pract Res Clin Haematol 19:3–25
132. Lutskiy MI, Sasahara Y, Kenney DM, Rosen FS, Remold-O'Donnell E (2002) Wiskott-Aldrich syndrome in a female. Blood 100:2763–2768
133. Luzi G, Businco L, Aiuti F (1983) Primary immunodeficiency syndromes in Italy: a report of the national register in children and adults. J Clin Immunol 3:316–320
134. MacLennan C, Fieschi C, Lammas DA, Picard C, Dorman SE, Sanal O, MacLennan JM, Holland SM, Ottenhoff TH, Casanova JL, Kumararatne DS (2004) Interleukin (IL)-12 and IL-23 are key cytokines for immunity against Salmonella in humans. J Infect Dis 190:1755–1757
135. Makitie O, Pukkala E, Kaitila I (2001) Increased mortality in cartilage-hair hypoplasia. Arch Dis Child 84:65–67
136. Makitie O, Sulisalo T, de la Chapelle A, Kaitila I (1995) Cartilage-hair hypoplasia. J Med Genet 32:39–43

137. Manderson AP, Botto M, Walport MJ (2004) The role of complement in the development of systemic lupus erythematosus. Annu Rev Immunol 22:431–456
138. Margolis DM, Melnick DA, Alling DW, Gallin JI (1990) Trimethoprim-sulfamethoxazole prophylaxis in the management of chronic granulomatous disease. J Infect Dis 162:723–726
139. Midgley EJ, Dewey C, Pryce K, Maw AR (2000) The frequency of otitis media with effusion in British preschool children: a guide for treatment. ALSPAC Study Team. Clin Otolaryngol Allied Sci 25:485–491
140. Mikaelsson L, Jacobsson G, Andersson R (2006) Pneumocystis pneumonia–a retrospective study 1991–2001 in Gothenburg, Sweden. J Infect 53:260–265
141. Mila Llambi J, Etxagibel Galdos A, Matamoros Flori N (2001) [The Spanish Registry of Primary Immunodeficiencies (REDIP)]. Allergol Immunopathol (Madr) 29:122–125
142. Ming JE, Stiehm ER, Graham JM, Jr. (1999) Syndromes associated with immunodeficiency. Adv Pediatr 46:271–351
143. Ming JE, Stiehm ER, Graham JM, Jr. (2003) Syndromic immunodeficiencies: genetic syndromes associated with immune abnormalities. Crit Rev Clin Lab Sci 40:587–642
144. Miura M, Katada Y, Ishihara J (2004) Time interval of measles vaccination in patients with Kawasaki disease treated with additional intravenous immune globulin. Eur J Pediatr 163:25–29
145. Moin M, Farhoudi A, Movahedi M, Rezaei N, Pourpak Z, Yeganeh M, Gharagozlou M, Mirsaeid Ghazi B, Arshi S, Mansouri D, Sherkat R, Kashef S, Mahmoudi M, Nabavi M, Aghamohammadi A (2006) The clinical and laboratory survey of Iranian patients with hyper-IgE syndrome. Scand J Infect Dis 38:898–903
146. Morra M, Silander O, Calpe S, Choi M, Oettgen H, Myers L, Etzioni A, Buckley R, Terhorst C (2001) Alterations of the X-linked lymphoproliferative disease gene SH2D1A in common variable immunodeficiency syndrome. Blood 98:1321–1325
147. Movahedi M, Aghamohammadi A, Rezaei N, Shahnavaz N, Jandaghi AB, Farhoudi A, Pourpak Z, Moin M, Gharagozlou M, Mansouri D (2004) Chronic granulomatous disease: a clinical survey of 41 patients from the Iranian primary immunodeficiency registry. Int Arch Allergy Immunol 134:253–259
148. Moylett EH, Wasan AN, Noroski LM, Shearer WT (2004) Live viral vaccines in patients with partial DiGeorge syndrome: clinical experience and cellular immunity. Clin Immunol 112:106–112
149. Nenci A, Becker C, Wullaert A, Gareus R, van Loo G, Danese S, Huth M, Nikolaev A, Neufert C, Madison B, Gumucio D, Neurath MF, Pasparakis M (2007) Epithelial NEMO links innate immunity to chronic intestinal inflammation. Nature 446:557–561
150. North Stone K, Fleming P, Golding J (2000) Sociodemographic associations with digit and pacifier sucking at 15 months of age and possible associations with infant infection. The ALSPAC Study Team. Avon Longitudinal Study of Pregnancy and Childhood. Early Hum Dev 60:137–148
151. Notarangelo L, Casanova JL, Conley ME, Chapel H, Fischer A, Puck J, Roifman C, Seger R, Geha RS (2006) Primary immunodeficiency diseases: an update from the International Union of Immunological Societies Primary Immunodeficiency Diseases Classification Committee Meeting in Budapest, 2005. J Allergy Clin Immunol 117:883–896
152. Notarangelo L, Casanova JL, Fischer A, Puck J, Rosen F, Seger R, Geha R (2004) Primary immunodeficiency diseases: an update. J Allergy Clin Immunol 114:677–687
153. Notarangelo LD, Forino C, Mazzolari E (2006) Stem cell transplantation in primary immunodeficiencies. Curr Opin Allergy Clin Immunol 6:443–448
154. Nowak-Wegrzyn A, Crawford TO, Winkelstein JA, Carson KA, Lederman HM (2004) Immunodeficiency and infections in ataxia-telangiectasia. J Pediatr 144:505–511
155. Ochs HD, Smith CIE, Puck JM (2006) Primary immunodeficiency diseases. A molecular and genetic approach, 2 edn. Oxford University Press, New York
156. Orange JS, Boyle J (2007) Specialist pysician perspectives on primary immunodeficiency diseases: a 2006 survey of the AAAAI membership. J Allergy Clin Immunol 119:S71
157. Orange JS, Brodeur SR, Jain A, Bonilla FA, Schneider LC, Kretschmer R, Nurko S, Rasmussen WL, Kohler JR, Gellis SE, Ferguson BM, Strominger JL, Zonana J, Ramesh N, Ballas ZK, Geha RS (2002) Deficient natural killer cell cytotoxicity in patients with IKK-gamma/NEMO mutations. J Clin Invest 109:1501–1509
158. Orange JS, Geha RS (2003) Finding NEMO: genetic disorders of NF-[kappa]B activation. J Clin Invest 112:983–985
159. Orange JS, Hossny EM, Weiler CR, Ballow M, Berger M, Bonilla FA, Buckley R, Chinen J, El-Gamal Y, Mazer BD, Nelson RP, Jr., Patel DD, Secord E, Sorensen RU, Wasserman RL, Cunningham-Rundles C (2006) Use of intravenous immunoglobulin in human disease: a review of evidence by members of the Primary Immunodeficiency Committee of the American Academy of Allergy, Asthma and Immunology. J Allergy Clin Immunol 117:S525–553
160. Orange JS, Jain A, Ballas ZK, Schneider LC, Geha RS, Bonilla FA (2004) The presentation and natural history of immunodeficiency caused by nuclear factor kappaB essential modulator mutation. J Allergy Clin Immunol 113:725–733
161. Orth G (2006) Genetics of epidermodysplasia verruciformis: Insights into host defense against papillomaviruses. Semin Immunol 18:362–374
162. Ott MG, Schmidt M, Schwarzwaelder K, Stein S, Siler U, Koehl U, Glimm H, Kuhlcke K, Schilz A, Kunkel H, Naundorf S, Brinkmann A, Deichmann A, Fischer M, Ball C, Pilz I, Dunbar C, Du Y, Jenkins NA, Copeland NG, Luthi U, Hassan M, Thrasher AJ, Hoelzer D, von Kalle C, Seger R, Grez M (2006) Correction of X-linked chronic granulomatous disease by gene therapy, augmented by insertional activation of MDS1-EVI1, PRDM16 or SETBP1. Nat Med 12:401–409
163. Owayed AF, Campbell DM, Wang EE (2000) Underlying causes of recurrent pneumonia in children. Arch Pediatr Adolesc Med 154:190–194
164. Pasteur MC, Helliwell SM, Houghton SJ, Webb SC, Foweraker JE, Coulden RA, Flower CD, Bilton D, Keogan MT (2000) An investigation into causative

factors in patients with bronchiectasis. Am J Respir Crit Care Med 162:1277–1284
165. Perez EE, Bokszczanin A, McDonald-McGinn D, Zackai EH, Sullivan KE (2003) Safety of live viral vaccines in patients with chromosome 22q11.2 deletion syndrome (DiGeorge syndrome/velocardiofacial syndrome). Pediatrics 112:e325
166. Perheentupa J (2002) APS-I/APECED: the clinical disease and therapy. Endocrinol Metab Clin North Am 31:295–320, vi
167. Pesu M, Candotti F, Husa M, Hofmann SR, Notarangelo LD, O'Shea JJ (2005) Jak3, severe combined immunodeficiency, and a new class of immunosuppressive drugs. Immunol Rev 203:127–142
168. Picard C, Mellouli F, Duprez R, Chedeville G, Neven B, Fraitag S, Delaunay J, Le Deist F, Fischer A, Blanche S, Bodemer C, Gessain A, Casanova JL, Bejaoui M (2006) Kaposi's sarcoma in a child with Wiskott-Aldrich syndrome. Eur J Pediatr 165:453–457
169. Picard C, Puel A, Bonnet M, Ku CL, Bustamante J, Yang K, Soudais C, Dupuis S, Feinberg J, Fieschi C, Elbim C, Hitchcock R, Lammas D, Davies G, Al-Ghonaium A, Al-Rayes H, Al-Jumaah S, Al-Hajjar S, Al-Mohsen IZ, Frayha HH, Rucker R, Hawn TR, Aderem A, Tufenkeji H, Haraguchi S, Day NK, Good RA, Gougerot-Pocidalo MA, Ozinsky A, Casanova JL (2003) Pyogenic bacterial infections in humans with IRAK-4 deficiency. Science 299:2076–2079
170. Pike-Overzet K, de Ridder D, Weerkamp F, Baert MR, Verstegen MM, Brugman MH, Howe SJ, Reinders MJ, Thrasher AJ, Wagemaker G, van Dongen JJ, Staal FJ (2006) Gene therapy: is IL2RG oncogenic in T cell development? Nature 443:E5; discussion E6–7
171. Poppema S, Maggio E, van den Berg A (2004) Development of lymphoma in Autoimmune Lymphoproliferative Syndrome (ALPS) and its relationship to Fas gene mutations. Leuk Lymphoma 45:423–431
172. Purtilo DT (1991) X-linked lymphoproliferative disease (XLP) as a model of Epstein-Barr virus-induced immunopathology. Springer Semin Immunopathol 13:181–197
173. Quartier P, Bustamante J, Sanal O, Plebani A, Debre M, Deville A, Litzman J, Levy J, Fermand JP, Lane P, Horneff G, Aksu G, Yalcin I, Davies G, Tezcan I, Ersoy F, Catalan N, Imai K, Fischer A, Durandy A (2004) Clinical, immunologic and genetic analysis of 29 patients with autosomal recessive hyper-IgM syndrome due to Activation-Induced Cytidine Deaminase deficiency. Clin Immunol 110:22–29
174. Rabago D, Pasic T, Zgierska A, Mundt M, Barrett B, Maberry R (2005) The efficacy of hypertonic saline nasal irrigation for chronic sinonasal symptoms. Otolaryngol Head Neck Surg 133:3–8
175. Reid G, Jass J, Sebulsky MT, McCormick JK (2003) Potential uses of probiotics in clinical practice. Clin Microbiol Rev 16:658–672
176. Rezaei N, Aghamohammadi A, Moin M, Pourpak Z, Movahedi M, Gharagozlou M, Atarod L, Ghazi BM, Isaeian A, Mahmoudi M, Abolmaali K, Mansouri D, Arshi S, Tarash NJ, Sherkat R, Akbari H, Amin R, Alborzi A, Kashef S, Farid R, Mohammadzadeh I, Shabestari MS, Nabavi M, Farhoudi A (2006) Frequency and clinical manifestations of patients with primary immunodeficiency disorders in Iran: update from the Iranian Primary Immunodeficiency Registry. J Clin Immunol 26:519–532
177. Rezaei N, Pourpak Z, Aghamohammadi A, Farhoudi A, Movahedi M, Gharagozlou M, Mirsaeid Ghazi B, Atarod L, Abolmaali K, Mahmoudi M, Mansouri D, Arshi S, Tarash NJ, Sherkat R, Amin R, Kashef S, Hosseini RF, Mohammadzadeh I, Shabestari MS, Nabavi M, Moin M (2006) Consanguinity in primary immunodeficiency disorders; the report from Iranian Primary Immunodeficiency Registry. Am J Reprod Immunol 56:145–151
178. Roberts L, Smith W, Jorm L, Patel M, Douglas RM, McGilchrist C (2000) Effect of infection control measures on the frequency of upper respiratory infection in child care: a randomized, controlled trial. Pediatrics 105:738–742
179. Roifman CM (2000) Human IL-2 receptor alpha chain deficiency. Pediatr Res 48:6–11
180. Rosen FS, Cooper MD, Wedgwood RJ (1995) The primary immunodeficiencies. N Engl J Med 333:431–440
181. Rynes RI (1982) Inherited complement deficiency states and SLE. Clin Rheum Dis 8:29–47
182. Ryser O, Morell A, Hitzig WH (1988) Primary immunodeficiencies in Switzerland: first report of the national registry in adults and children. J Clin Immunol 8:479–485
183. Schrezenmeir J, Heller K, McCue M, Llamas C, Lam W, Burow H, Kindling-Rohracker M, Fischer W, Sengespeik HC, Comer GM, Alarcon P (2004) Benefits of oral supplementation with and without synbiotics in young children with acute bacterial infections. Clin Pediatr (Phila) 43:239–249
184. Segal BH, Leto TL, Gallin JI, Malech HL, Holland SM (2000) Genetic, biochemical, and clinical features of chronic granulomatous disease. Medicine 79:170–200
185. Shabestari MS, Maljaei SH, Baradaran R, Barzegar M, Hashemi F, Mesri A, Rezaei N (2007) Distribution of primary immunodeficiency diseases in the turk ethnic group, living in the northwestern iran. J Clin Immunol 27:510–516
186. Skull S, Kemp A (1996) Treatment of hypogammaglobulinemia with intravenous immunoglobulin, 1973–93. Arch Dis Child 74:527–530
187. Slatter MA, Gennery AR (2006) Umbilical cord stem cell transplantation for primary immunodeficiencies. Expert Opin Biol Ther 6:555–565
188. Somech R, Tal G, Gilad E, Mandelberg A, Tal A, Dalal I (2006) Epidemiologic, socioeconomic, and clinical factors associated with severity of respiratory syncytial virus infection in previously healthy infants. Clin Pediatr (Phila) 45:621–627
189. Sordet C, Cantagrel A, Schaeverbeke T, Sibilia J (2005) Bone and joint disease associated with primary immune deficiencies. Joint Bone Spine 72:503–514
190. Stephan V, Wahn V, Le Deist F, Dirksen U, Broker B, Muller-Fleckenstein I, Horneff G, Schroten H, Fischer A, de Saint Basile G (1996) Atypical X-linked severe combined immunodeficiency due to possible spontaneous reversion of the genetic defect in T cells. N Engl J Med 335:1563–1567
191. Stiehm ER (1997) Human intravenous immunoglobulin in primary and secondary antibody deficiencies. Pediatr Infect Dis J 16:696–707

192. Stiehm ER, Chin TW, Haas A, Peerless AG (1986) Infectious complications of the primary immunodeficiencies. Clin Immunol Immunopathol 40:69–86
193. Stiehm ER, Ochs HD, Winkelstein JA (2004) Immunodeficiency disorders in infants and children, 5 edn. Elsevier Saunders, Philadelphia
194. Stray-Pedersen A, Abrahamsen TG, Froland SS (2000) Primary immunodeficiency diseases in Norway. J Clin Immunol 20:477–485
195. Subauste CS (2006) Primary immunodeficiencies and susceptibility to parasitic infections. Parasite Immunol 28:567–575
196. Subauste CS, Wessendarp M (2006) CD40 restrains in vivo growth of Toxoplasma gondii independently of gamma interferon. Infect Immun 74:1573–1579
197. Sullivan KE, Mullen CA, Blaese RM, Winkelstein JA (1994) A multiinstitutional survey of the Wiskott-Aldrich syndrome. J Pediatr 125:876–885
198. Sun XK, Chen JF, Xu AE (2005) A homozygous nonsense mutation in the EVER2 gene leads to epidermodysplasia verruciformis. Clin Exp Dermatol 30:573–574
199. Swart AG, Fijen CA, te Bulte MT, Daha MR, Dankert J, Kuijper EJ (1993) Complement deficiencies and meningococcal disease in The Netherlands. Ned Tijdschr Geneeskd 137:1147–1152
200. Syllaba L, Henner K (1926) Contribution a l'independence de l'athetose double idiopathique et congenitale: atteinte familiale, syndrome dystrophique, signe du reseau vasculaire conjonctival, integrite psychique. Rev Neurol (Paris) 1:541–562
201. Takada H, Kanegane H, Nomura A, Yamamoto K, Ihara K, Takahashi Y, Tsukada S, Miyawaki T, Hara T (2004) Female agammaglobulinemia due to the Bruton tyrosine kinase deficiency caused by extremely skewed X-chromosome inactivation. Blood 103:185–187
202. Taylor AM (1992) Ataxia-telangiectasia genes and predisposition to leukemia, lymphoma and breast cancer. Br J Cancer 66:5–9
203. Thorpe ES, Handley HE (1929) Chronic tetany and chronic mycelial stomatitis in a child aged four and one-half years. Am J Dis Child 38:328–338
204. Tone Y, Wada T, Shibata F, Toma T, Hashida Y, Kasahara Y, Koizumi S, Yachie A (2007) Somatic revertant mosaicism in a patient with leukocyte adhesion deficiency type 1. Blood 109:1182–1184
205. Ueda I, Ishii E, Morimoto A, Ohga S, Sako M, Imashuku S (2006) Correlation between phenotypic heterogeneity and gene mutational characteristics in familial hemophagocytic lymphohistiocytosis (FHL). Pediatr Blood Cancer 46:482–488
206. van Zelm MC, Reisli I, van der Burg M, Castano D, van Noesel CJ, van Tol MJ, Woellner C, Grimbacher B, Patino PJ, van Dongen JJ, Franco JL (2006) An antibody-deficiency syndrome due to mutations in the CD19 gene. N Engl J Med 354:1901–1912
207. Vanlerberghe L, Joniau S, Jorissen M (2006) The prevalence of humoral immunodeficiency in refractory rhinosinusitis: a retrospective analysis. B-Ent 2:161–166
208. von Bernuth H, Puel A, Ku CL, Yang K, Bustamante J, Chang HH, Picard C, Casanova JL (2005) Septicemia without sepsis: inherited disorders of nuclear factor-kappa B-mediated inflammation. Clin Infect Dis 41 Suppl 7:S436–439
209. Walport MJ (2002) Complement and systemic lupus erythematosus. Arthritis Res 4 Suppl 3:S279–293
210. Wang J, Cunningham-Rundles C (2005) Treatment and outcome of autoimmune hematologic disease in common variable immunodeficiency (CVID). J Autoimmun 25:57–62
211. Wang J, Zheng L, Lobito A, Chan FK, Dale J, Sneller M, Yao X, Puck JM, Straus SE, Lenardo MJ (1999) Inherited human Caspase 10 mutations underlie defective lymphocyte and dendritic cell apoptosis in autoimmune lymphoproliferative syndrome type II. Cell 98:47–58
212. Weemaes CMR, Hustinx TWJ, Scheres JMJC, Van Munster PJJ, Bakkeren JAJM, Taalman RDFM (1981) A new chromosomal instability disorder: the Nijmegen breakage syndrome. Acta Paediatr Scand 70:557–564
213. Wharton M, Strikas RA, Harpaz R, Rotz LD, Schwartz B, Casey CG, Pearson ML, Anderson LJ (2003) Recommendations for using smallpox vaccine in a pre-event vaccination program. Supplemental recommendations of the Advisory Committee on Immunization Practices (ACIP) and the Healthcare Infection Control Practices Advisory Committee (HICPAC). MMWR Recomm Rep 52:1–16
214. White C, Kolble R, Carlson R, Lipson N, Dolan M, Ali Y, Cline M (2003) The effect of hand hygiene on illness rate among students in university residence halls. Am J Infect Control 31:364–370
215. Wildin RS, Smyk-Pearson S, Filipovich AH (2002) Clinical and molecular features of the immunodysregulation, polyendocrinopathy, enteropathy, X linked (IPEX) syndrome. J Med Genet 39:537–545
216. Williams RL, Chalmers TC, Stange KC, Chalmers FT, Bowlin SJ (1993) Use of antibiotics in preventing recurrent acute otitis media and in treating otitis media with effusion. A meta-analytic attempt to resolve the brouhaha. Jama 270:1344–1351
217. Winkelstein JA, Marino MC, Johnston RB, Boyle J, Curnutte J, Gallin JI, Malech HL, Holland SM, Ochs H, Quie P, Buckley RH, Foster CB, Chanock SJ, Dickler H (2000) Chronic granulomatous disease. Report on a national registry of 368 patients. Medicine 79:155–169
218. Winkelstein JA, Marino MC, Lederman HM, Jones SM, Sullivan K, Burks AW, Conley ME, Cunningham-Rundles C, Ochs HD (2006) X-linked agammaglobulinemia: report on a United States registry of 201 patients. Medicine (Baltimore) 85:193–202
219. Winkelstein JA, Marino MC, Ochs H, Fuleihan R, Scholl PR, Geha R, Stiehm ER, Conley ME (2003) The X-linked hyper-IgM syndrome: clinical and immunologic features of 79 patients. Medicine (Baltimore) 82:373–384
220. Wiskott A (1937) Familiarer, angeborener Morbus Werihofii? Aschr Kinderheilk 68:212–216
221. Woods NB, Bottero V, Schmidt M, von Kalle C, Verma IM (2006) Gene therapy: therapeutic gene causing lymphoma. Nature 440:1123
222. Woroniecka M, Ballow M (2000) Office evaluation of children with recurrent infection. Pediatr Clin North Am 47:1211–1224
223. Yaghmai R, Kimyai-Asadi A, Rostamiani K, Heiss NS, Poustka A, Eyaid W, Bodurtha J, Nousari HC, Hamosh A, Metzenberg A (2000) Overlap of dyskeratosis congenita

with the Hoyeraal-Hreidarsson syndrome. J Pediatr 136:390–393
224. Yarmohammadi H, Estrella L, Doucette J, Cunningham-Rundles C (2006) Recognizing primary immune deficiency in clinical practice. Clin Vaccine Immunol 13:329–332
225. Zerbe CS, Holland SM (2005) Disseminated histoplasmosis in persons with interferon-gamma receptor 1 deficiency. Clin Infect Dis 41:e38–41
226. Zhang SY, Jouanguy E, Ugolini S, Smahi A, Elain G, Romero P, Segal D, Sancho-Shimizu V, Lorenzo L, Puel A, Picard C, Chapgier A, Plancoulaine S, Titeux M, Cognet C, von Bernuth H, Ku CL, Casrouge A, Zhang XX, Barreiro L, Leonard J, Hamilton C, Lebon P, Heron B, Vallee L, Quintana-Murci L, Hovnanian A, Rozenberg F, Vivier E, Geissmann F, Tardieu M, Abel L, Casanova JL (2007) TLR3 deficiency in patients with herpes simplex encephalitis. Science 317:1522–1527
227. Zorrilla EP, Luborsky L, McKay JR, Rosenthal R, Houldin A, Tax A, McCorkle R, Seligman DA, Schmidt K (2001) The relationship of depression and stressors to immunological assays: a meta-analytic review. Brain Behav Immun 15:199–226