4.4 Immunodeficiency 337

4.4 Immunodeficiency 337

ESSENTIALS Immunodeficiency is caused by failure of a component of the im- mune system and results in increased susceptibility to infections. The possibility of an underlying immunodeficiency should be considered if a patient has: (1) serious, persistent, unusual, or recurrent infections; (2) failure to thrive in infancy; (3) known family history of immuno- deficiency; (4) unexplained lymphopenia in infancy; (5) combination of clinical features characteristic of a particular immunodeficiency syndrome. The nature of the microbial infection in a particular pa- tient provides a clue to the likely cause of immunodeficiency. Primary immunodeficiency diseases are potentially heritable dis- orders that result in defects in an intrinsic component of the immune system. Increasingly, the alternative term ‘inborn error of immunity’ is preferred to embrace other manifestations of impaired immune func- tion such as autoimmunity, lymphoproliferation and autoinflammation. Secondary immunodeficiencies are caused by conditions that impair the normal function of the immune system and include viral infections, myelomatosis, non-Hodgkin’s lymphoma, severe renal or liver failure, and use of therapeutic agents which impair immunity. Defects in anatomical and physiological barriers to infection These are some the commonest predisposing causes of infection (e.g. obstruction of the biliary tract, urinary tract, or bronchi; presence of foreign bodies or avascular areas). Recurrent infections within the same anatomical locations are a characteristic feature, with typical organisms including pyogenic bacteria such as staphylococci, commensal organ- isms from the skin or intestinal tract, and fungi, especially candida. Combined immunodeficiency (T-cell immunodeficiency) T-cell hypofunction is accompanied by variable degrees of humoral immunodeficiency. In the most severe types a complete block in T-cell development leads to catastrophic failure of the adaptive im- mune system. Clinical features—these include (1) susceptibility to all types of in- fection (especially intracellular pathogens); (2) immune dysregulation; (3) increased risk of neoplasia, especially lymphomatous and/or vir- ally associated; (4) variable primary effects on other components of the immune system +/– extrahaematological manifestations, depending on the molecular defect. Causes—these may be inherited (rare) or acquired. Commonest causes of acquired T-cell deficiency include HIV infection or immunosuppressive therapy. Inherited causes include (1) severe combined immunodeficiency—caused by a variety of molecular de- fects; (2) other conditions including MHC class II deficiency, Wiskott– Aldrich syndrome, LRBA deficiency, hyper IgM syndrome, X-linked lymphoproliferative syndrome, thymic defects, DNA repair defects associated with immunodeficiency, autosomal dominant hyper IgE syndrome. Management—(1) severe inherited T-cell disorders—invariably fatal unless treated with haematopoietic stem cell transplantation or (in a very few instances) with gene therapy; (2) secondary T-cell deficiency—requires supportive therapy with antiviral and antibac- terial chemotherapy agents.

Primary antibody deficiencies Antibody deficiency diseases are characterized by a decrease in the levels of serum immunoglobulins below the fifth centile for age. The reduction may be in all classes of immunoglobulins or a single isotype. Clinical features—typical presentation is with recurrent infec- tions by encapsulated bacteria (e.g. Streptococcus pneumoniae, Haemophilus influenzae type B); most patients suffer from re- peated sinopulmonary infections, eventually resulting in struc- tural lung damage; arthritis occurs in a few patients; diarrhoea and malabsorption may occur in a few patients; due to chronic infec- tion with intestinal pathogens or bacterial overgrowth in the small intestine. Causes—major forms of antibody deficiency include (1) common variable immune deficiency—the commonest primary immuno- deficiency disease; underlying molecular defect usually unknown; clinically defined by susceptibility to infection accompanied by low serum IgG and evidence of impaired specific antibody pro- duction in response to natural microbial exposure or vaccination. (2) X-linked agammaglobulinaemia—caused by a defect in a cyto- plasmic tyrosine kinase that results in the arrest of B-cell maturation; affected boys usually develop recurrent infections typical of antibody deficiency from around 6 months of age. (3) Other conditions—including (a) autosomal recessive antibody deficiencies with B lymphopenia; (b) physiological antibody deficiencies; (c) transient hypogammaglobulinaemia of infancy; (d) selective antibody defi- ciency with normal immunoglobulins; (e) antibody deficiency asso- ciated with thymoma; (f) IgA deficiency; (g) IgG subclass deficiency. 4.4 Immunodeficiency Sophie Hambleton, Sara Marshall, and Dinakantha S. Kumararatne

338 SECTION 4 Immunological mechanisms Management—immunoglobulin replacement therapy through the intravenous (IVIG) or subcutaneous (SCIG) routes is the mainstay of therapy. Diseases of immune dysregulation Complex regulatory mechanisms ensure that innate and adaptive im- mune responses are held in check within the healthy immune system. Haemophagocytic lymphohistiocytosis is a life-threatening systemic illness in which there is excessive but ineffective immune activation. An increasing number of monogenic disorders are being recognized as causing autoimmunity, often in association with lymphoproliferation. Phagocyte deficiencies Clinical features—these typically include repeated visceral abscesses caused by Staphylococcus aureus or some species of Gram-negative bacteria, and invasive fungal infections are a particular risk. Causes—these include (1) neutropenia—the commonest phago- cyte deficiency seen in clinical practice; a neutrophil count less than 0.5 × 109/litre is associated with a high risk of life-threatening bac- terial sepsis; (2) defects in bacterial killing—the best-characterized condition is chronic granulomatous disease (CGD), which is due to faulty postphagocytic activation of the NADPH oxidase complex; (3) defects in leucocyte adhesion and migration. Management—this requires prophylactic antibacterial and antifungal agents, with the aggressive use of antibiotic chemotherapy of infections when they occur. Haemopoietic Stem Cell Transplantation (HSCT) is required for patients with defective leucocyte migration. HSCT is in- creasingly used for CGD, and gene therapy is in development. Introduction The primary function of the immune system is to resist infection; a role in restraining neoplasia is also increasingly recognized. In the well-functioning immune system, these tasks are achieved without inappropriate host-damaging responses. Immunodeficiency dis- orders are typically characterized by an increased susceptibility to infection with or without autoimmunity and/or neoplasia (es- pecially of the haemopoietic system); in certain disorders there is also excessive autoinflammation and/or allergic sensitization. While classically described immunodeficiencies predispose to a broad range of infections, we now recognize more subtle lesions of pathogen-specific immunity that may not be fully penetrant. On a philosophical level, every clinically evident infection results from a pathogen overcoming the

immune defences of the body. However, most patients who suffer an infection do not have an underlying im- munodeficiency, and the infectious episode is due to a shifting of the dynamic balance between the resistance of the host and the viru- lence of the pathogen. The possibility of immunodeficiency should be considered under the following circumstances: • Severe, potentially life-threatening infections—immunodeficient patients may present for the first time with this type of infection • Persistent infection—despite adequate and appropriate therapy • Recurrent infection—assessment of this criterion depends on age and clinical circumstances. For example, six to eight upper respiratory tract infections a year may not be unusual in young children, especially if they have recently joined a playgroup or started school, but such a pattern in adults would need investiga- tion to exclude immunodeficiency • Unusual infection—infections caused by pathogens of low-grade virulence are pathognomonic of immunodeficiency. Examples are Pneumocystis jirovecii pneumonitis, atypical mycobacterial disease, or persistent oral candidiasis in an adult without a predisposing factor • Failure to thrive in infancy—often reflecting an infective enter- opathy; possible associated skin rash, organomegaly, and lymph- adenopathy. Immunodeficiency needs to be considered in the differential diagnosis, ideally as early as possible, since treatment of primary immunodeficiency is most successful if instituted be- fore the onset of significant infections • Known family history of immunodeficiency—especially if pre- senting with repeated or persistent infections • Unexplained lymphopenia in infancy—lymphocyte counts in infancy are significantly higher than in adults (around 6 × 109/ litre in infancy, compared with 1.0–3.0 × 109/litre in adults). Retrospective review of children with severe combined immuno- deficiency (SCID) showed that many had absolute lymphocyte counts below the age-specific normal range at presentation • Combination of clinical features characteristic of a specific im- munodeficiency syndrome—for example, recurrent respiratory infections, eczema, and thrombocytopenia associated with small-sized platelets in a boy raises the possibility of Wiskott–Aldrich syndrome • Susceptibility to infection with otherwise unexplained lymph oproliferation such as lymphadenopathy, hepatosplenomegaly +/– lymphoid hyperplasia of gut or respiratory tract mucosae— sometimes associated with systemic features such as fever and weight loss; progression to lymphoma may occur in some cases • Recurrent sterile fever with other evidence of end-organ inflam- mation such as skin and joint involvement or uveitis—may indicate autoinflammatory disorders such as periodic fever syndromes. • Defects in the immune system can impair immuno-regulatory mechanisms which normally prevent autoimmunity, and hence autoimmunity may be a presenting feature of immunodeficiency— a combination of autoimmunity and susceptibility to infection is particularly suggestive of an underlying immune deficiency The type of microbial pathogen causing infection in a particular pa- tient may be a clue to the likelihood of immunodeficiency and will often indicate the category of immunodeficiency. Classification of immunodeficiency disease Primary immunodeficiency diseases are heritable disorders which result from defects within the immune system. Most primary im- munodeficiency disorders are caused by single-gene defects. Others may represent the end result of an interaction between the geno- type and environmental influences, including infections. Primary immunodeficiencies are rare, although it is difficult to give precise estimates due to the paucity of data, as well as variations between different ethnic groups. On the basis of data from national regis- tries, these diseases are estimated to occur in 1 in 2000 to 1 in 10 000 live births.

 The International Union of Immunological Societies (IUIS) con- venes a committee which meets biannually to review the classifica- tion of primary immunodeficiency diseases. The main categories are: 1. Immunodeficiencies affecting cellular and humoral immunity,

where T-cell function is defective (humoral immunity is often impaired to a variable degree as a consequence of T-cell dysfunction); 2. Combined immunodeficiencies with associated or syndromic features; 3. Predominantly antibody deficiencies, where cell-mediated im- munity is substantially intact; 4. Diseases of immune dysregulation; 5. Congenital defects in phagocyte number, function, or both; 6. Defects of intrinsic or innate immunity; 7. Autoinflammatory disorders; 8. Complement deficiencies; and 9. Phenocopies of primary immunodeficiency are also recognized (e.g. due to anticytokine autoantibodies). Each of these categories of immunodeficiency is characterized by a pattern of infection and associated features, summarized in Table 4.4.1. The main primary immunodeficiency diseases cur- rently identified are summarized in Table 4.4.2. Secondary immunodeficiencies (Table 4.4.3), also known as ac- quired immunodeficiencies, are much more common than primary immune deficiencies. They occur when a previously functioning im- mune system is compromised by external factors. Common causes Table 4.4.1 Immunodeficiency: usual patterns of associated infection and local pattern of associated infections Physiological mechanism Abnormality Organismsa Site: types of infectionb Integumental barrier Burns, eczema, skull fracture, sinus tract Pyogenic and enteric bacteria occasionally fungi, especially candida Recurrent in same location Outflow Obstruction of eustachian tube, urinary tract, or bronchi Pyogenic and enteric bacteria Vascular perfusion Oedema, angiopathy, infarction Microbiological flora Alteration by antibiotic therapy Opportunistic infection, especially candida Phagocyte function Chemotaxis Defects of neutrophil migration, e.g. leucocyte adhesin deficiency Staphylococci, enteric bacteria Skin, any site/localized and systemic Opsonin deficiency (See ‘Humoral systems’) Skin and respiratory tract Phagocytosis Neutropenia Staphylococci, enteric bacteria Pseudomonas species Any site/localized and bacteraemic, stomatitis, perianal excoriation Asplenia Pneumococcus, Haemophilus influenzae type b, (malaria, babesia)c Septicaemia, meningitis, severe wound infection with Capnocytophaga canimorsus following animal bites Killing Intrinsic cellular defects, e.g. chronic granulomatous disease Staphylococci, enteric bacteria Aspergillus, Candida, BCG Skin, lymph node, and visceral abscesses Humoral systems Circulating antibody Hypogammaglobulinaemia Pyogenic bacteria, less commonly enteric bacteria, enteroviruses Upper/lower respiratory tract; gastrointestinal, any site/localized and bacteraemic Complement Congenital deficiency C3, Factor I Pyogenic bacteria, especially pneumococci Bacteraemia, meningitis pyoderma Congenital deficiency C5, C6, C7, C8 Neisseria meningitidis or N. gonorrhoeae Meningitis, pyogenic arthritis C1 inhibitor No specific infection susceptibility Develop angio-oedema C2, C4 No infections or occasionally pneumococcal sepsis Cell-mediated immunity Primary T-lymphocyte defects Viruses, fungi, protozoa, intracellular bacteria; plus infections typical of antibody deficiency Any site/localized and systemic; mucocutaneous candida infections Th-1 cytokine/cytokine receptor defects, e.g. IFNγ receptor, IL-12, IL-12 receptor (see section on innate immunity for comprehensive list) Poorly pathogenic mycobacteria e.g. M. avium, BCG; salmonella Lymph node; bone; disseminated Defects in innate immunity Defects in pattern recognition receptors or relevant downstream signalling pathway Depending on pathway may present with predominant susceptibility to pyogenic, viral, fungal or mycobacterial infection Any site/localized and systemic a Common infecting organisms are emphasized. ‘Pyogenic bacteria’ refers to pneumococci, Streptococcus pyogenes, Haemophilus influenzae, meningococci, and staphylococci. ‘Enteric bacteria’ refers to enterococci and the Gram-negative bacilli common to the intestinal tract, especially Escherichia coli, Pseudomonas, Klebsiella–enterobacter, and proteus species. b Skin infections include furunculosis, subcutaneous abscesses, and cellulitis; respiratory tract infections include recurrent pneumonia, otitis media, and sinusitis. c Potentially fatal infections caused by blood-borne parasites if exposed by travel/residence in endemic area. d Liver, lungs,

lymph nodes, and spleen. Source data from Johnston RB Jr. (1984). Recurrent bacterial infections in children. N Engl J Med, 310, 1237–43, with permission.

340 SECTION 4 Immunological mechanisms Table 4.4.2 Classification of immunodeficiencies based on the International Union of Immunology Societies (IUIS) classification. This table only includes key immunological disorders in each category and does not aim to comprehensive. Readers should refer to latest version of the IUIS classification and online databases (e.g. OMIM) for a comprehensive list Antibody deficiencies Predominantly antibody deficiency diseases Mutated gene/pathogenesis Associated features X-linked agammaglobulinaemia BTK Antibody deficiency and B lymphopenia Autosomal recessive agammaglobulinaemia Mutations in genes for μ heavy chain (IGHM), IgA (CD79A), λ5 surrogate light chain (IGLL1), or BLNK, PIK3R1 Antibody deficiency and B lymphopenia Thymoma with antibody deficiency Unknown Antibody deficiency and B lymphopenia Hyper IgM syndrome (autosomal recessive) UNG or AICDA which encodes for AID or PMS2, resulting in defective mismatch repair Low IgG and IgA, raised IgM Common variable immunodeficiency Unknown in most; TNFRSF13B which encodes for TACI in c.10%, rarely ICOS, CD19, or TNFRSF13C which encodes for BAFFR, CD20, CD81, CD21, TWEAK, NFKB1, NFKB2 Antibody deficiency; may have autoimmunity, lymphoproliferation, systemic granulomata Selective IgA deficiency Most unknown; few due to mutations in TNFRSF13B, which encodes for TACI Most remain healthy; increase in autoimmunity, atopy, coeliac disease IgG subclass deficiency Unknown If associated with selective antibody deficiency may have recurrent sinopulmonary infections Specific antibody deficiency with normal serum immunoglobulins Unknown Deficient antibody responses to some antigens. Antipolysaccharide antibody deficiency may be associated with recurrent sinopulmonary infections IgG2 low plus poor responses to pneumococcal polysaccharide and haemophilus B (activated PI3K-d syndrome) PIK3CD encoding for P110 subunit of PI3K Bronchiectasis, autoimmunity, nodular lymphoproliferation, increased susceptibility to Herpes family viruses (HZV, CMV, EBV), increased incidence of B-cell lymphoma Congenital B lymphocytosis CARD11 gain-of-function mutations Lymphadenopathy, splenomegaly, bacterial and viral infections, chronic EBV infection, autoimmune cytopenias Transient antibody deficiency of infancy Unknown Reduced IgA and IgG; recovery by 3 years of age Cellular and humoral deficiencies Combined T (cellular) and
B-cell (humoral) deficiency Example mutated gene Associated features Severe combined immunodeficiency (SCID) Lymphopenia, low serum Igs, failure to thrive, severe recurrent infections by viruses, bacteria, and parasites; fatal without corrective therapy such as BMT SCID due to failure of cytokine receptor signalling IL2RG (common g-chain), IL7RA, JAK3 T Lymphopenia; B-cell number normal (T-B+ SCID) SCID due to defective VDJ gene recombination RAG 1, RAG2, DCLRE1C (Artemis) T-B-SCID SCID due to defective DNA repair PRKDC (PKcs), NHEJ1 (Cernunnos/XLF), LIG4 Radiosensitivity, microcephaly, and developmental delay SCID due to defective nucleotide salvage ADA T-, NK-, and B-cell lymphopenia (T-B-NK-SCID) SCID due to defective T-cell receptor function CD3D, CD3E, CD3Z, PTPRC (CD45) Normal B cell and NK numbers SCID due to lack of T-cell egress from thymus CORO1A Causes a T-B+NK+ SCID Reticular dysgenesis AK2 Profound neutropenia; sensorineural deafness; early presentation often with overwhelming sepsis in newborn period MHC class II deficiency CIITA, RFXANK, RFX5, RFXAP Lack of MHC class II expression resulting in CD4 lymphopenia and severe failure of T-cell and B-cell function Omenn’s syndrome Hypomorphic mutation of RAG1, RAG2, DCLRE1C (Artemis) or other genes Variant of SCID. Some T cells develop but are oligoclonal. Features include erythroderma, lymphadenopathy, hepatosplenomegaly, eosinophilia. Outcome poor without BMT

4.4 Immunodeficiency 341 Cellular and humoral deficiencies Combined T (cellular) and B-cell (humoral) deficiency Example mutated gene Associated features MHC class I deficiency TAP1, TAP2, or TAPBP (TAP binding protein, tapasin) Lack of MHC class I expression on cells; CD8 lymphopenia; present with bronchiectasis or vasculitis X-linked hyper IgM syndrome CD40LG Lack of CD40-ligand on activated T cells. Failure of Ig class-switching and affinity maturation; low IgG/IgA, raised or normal IgM; may develop neutropenia, autoimmune cytopenias, opportunistic infections, and gastrointestinal and liver pathologies CD40 deficiency (a type of autosomal recessive hyper IgM syndrome) CD40 Lack of CD40 expression on B cells. Other features similar to CD40L deficiency DOCK 8 deficiency DOCK8 Recurrent sinopulmonary infections and cutaneous viral infections (Molluscum contagiosum and HPV); low serum IgM and variable IgG responses MHC class I deficiency TAP1, TAP2, or TAPBP (which encodes for the TAP binding protein tapasin) Lack of MHC class I expression on cells; CD8 lymphopenia; present with bronchiectasis or vasculitis IKBKB deficiency Defects in IKBKB, encoding IkB 2 kinase 2, a component of the NF-kB pathway Normal total T cells; absent regulatory and γδ T cells; impaired TCR activation; normal B cell numbers; impaired B-cell receptor (BCR) activation; hypogammaglobulinaemia; recurrent bacterial, viral, and fungal infections; clinical phenotype of SCID LRBA deficiency Mutations in LRBA (lipopolysaccharide responsive beige-like anchor protein); AR Normal or decreased CD4 numbers; T-cell dysregulation; low or normal numbers of B cells; reduced I IgG and IgA in most; recurrent infections, inflammatory bowel disease; autoimmunity; EBV infections CD27 deficiency Mutations in CD27 (TNFRSF7) required for generation and long-term maintenance of T-cell immunity; AR No memory B cells; low iNKT cells; clinical and immunologic features triggered by EBV infection; HLH; aplastic anaemia; lymphoma; hypogammaglobulinemia CID with syndromes Combined immunodeficiencies with associated or syndromic features Mutated gene/pathogenesis Associated features

1. Congenital thrombocytopenia Wiskott–Aldrich syndrome (WAS) Mutations in WASP; cytoskeletal and immunologic synapse defect affecting haematopoietic stem cell derivatives. XL Progressive decrease, abnormal lymphocyte responses to anti-CD3, normal numbers of B cells, thrombocytopenia with small platelets; eczema; lymphoma; autoimmune; decreased IgM; antibody to polysaccharides particularly decreased; often increased IgA and IgE, disease; IgA nephropathy; bacterial and viral infections. XL thrombocytopenia is a mild form of WAS, and XL neutropenia is caused by missense mutations in the GTPase binding domain of WASP WIP deficiency Mutations in WIPF1; cytoskeletal and immunologic synapse defect affecting haematopoietic stem cell derivatives. AR T cells reduced, defective lymphocyte responses to anti-CD3; recurrent infections; eczema; thrombocytopenia. WAS-like phenotype
2. DNA repair defects (other than those in Table 4.4.1) Ataxia telangiectasia Mutations in ATM; disorder of cell-cycle checkpoint and DNA double-strand break repair; AR T cells progressive decrease, abnormal proliferation to mitogens; often decreased IgA, IgE, and IgG subclasses; increased IgM monomers; antibodies variably decreased; ataxia; telangiectasia; pulmonary infections; lymphoreticular and other malignancies; increased α-fetoprotein and increased radiosensitivity; chromosomal instability Nijmegen breakage syndrome (nibrin); disorder of cell-cycle checkpoint and DNA double- strand break repair Hypomorphic mutations in NBN; AR T cells progressive decrease; often decreased IgA, IgE, and IgG subclasses; increased IgM; antibodies variably decreased; microcephaly; bird-like face; lymphomas; solid tumours; increased radiosensitivity; chromosomal instability

3. Thymic defects with additional congenital anomalies DiGeorge syndromea Contiguous gene deletion in chromosome 22q11.2 or mutation of a gene within this deletion region, TBX1, encoding a transcription factor critical for development of thymus and adjacent embryonic structures; De novo haploinsufficiency (majority) or AD; phenocopies may have other as yet undefined genetic lesions; Decreased or normal; 5% have <1500 CD3 T cells/ul in neonatal period; hypoparathyroidism, conotruncal cardiac malformation, velopalatal insufficiency, abnormal facies, intellectual disability, and other abnormalities Table 4.4.2 Continued (continued)

342 SECTION 4 Immunological mechanisms CID with syndromes Combined immunodeficiencies with associated or syndromic features Mutated gene/pathogenesis Associated features CHARGE syndrome due to CHD7 or SEMA3E defects Variable defects of the thymus and associated T-cell abnormalities, often due to deletions or mutations in transcription regulator CHD7 semaphorin SEMA3E; de novo haploinsufficiency (majority) or AD T cells decreased or normal; response to PHA may be decreased; coloboma, heart anomaly, choanal atresia, mental retardation, genital, and ear anomalies; some are SCID-like and have low TRECs Winged helix deficiency (nude) Defects in forkhead box N1 transcription factor encoded by FOXN1;AR T cells markedly decreased; alopecia; nail dystrophy; severe infections; abnormal thymic epithelium; impaired T-cell maturation 4. Immune-osseous dysplasias Mutations in RMRP (RNase MRP RNA) Involved in processing of mitochondrial RNA and cell- cycle control; AR T cells varies from severely decreased (SCID) to normal; impaired lymphocyte proliferation; immunoglobulins variably decreased; short-limbed dwarfism with metaphyseal dysostosis; sparse hair; bone marrow failure; autoimmunity; susceptibility to lymphoma and other cancers; impaired spermatogenesis; neuronal dysplasia of the intestine 5. Hyper IgE syndromes (HIES); AD-HIES (Job or Buckley syndrome) Dominant-negative heterozygous mutations in signal transducer and activator of transcription STAT3; AD T cells normal overall Th-17 and T-follicular helper cells decreased; B cells normal; reduced switched and nonswitched memory B cells; anti- B cell activation factor (BAFF) expression increased; normal; reduced switched and nonswitched memory B cells; BAFF expression increased 6. Anhidrotic ectodermal dysplasia with immunodeficiency (EDA-ID); (EDA-ID. NEMO/IKBKG deficiency); Mutations of NEMO (IKBKG), a modulator of NF-κB activation; XL T cells normal or decreased; poor cell receptor (CR) activation function; low B memory B cells; decreased; poor specific antibody responses, absent antibody to polysaccharide antigens; anhidrotic ectodermal dysplasia + specific antibody deficiency (lack of Ab response to polysaccharides) + various infections (mycobacteria and pyrogens) EDA-ID IKBA gain-of-function mutation Gain-of-function mutation in NFKBIA, encoding IκBα, a component of the NF-κB pathway; AD Normal total T cells; impaired TCR activation; normal B cell numbers; impaired BCR activation; decreased; poor specific antibody responses, absent antibody to polysaccharide antigens; various infections (bacteria, mycobacteria, viruses, and fungi); colitis, EDA (not in all patients); variable defects of skin, hair, and teeth; T-cell and monocyte dysfunction 7. Calcium channel defects ORAI-I deficiency Mutation in ORAI1, a Ca++ release-activated channel (CRAC) modulatory component; AR T cells normal; defective TCR mediated activation; autoimmunity, anhidrotic ectodermic dysplasia, nonprogressive myopathy STIM1 deficiency Mutations in STIM1, a stromal interaction molecule 1; AR T cells normal; defective TCR mediated activation; autoimmunity, anhidrotic ectodermal dysplasia, nonprogressive myopathy 8. Other defects Immunodeficiency with multiple intestinal atresias Mutation in TTC7A (tetratricopeptide repeat (TPR) domain 7A) protein, of unknown function; AR T cells variable, but sometimes absent; multiple intestinal atresias, often with intrauterine polyhydramnios and early

demise; some with SCID phenotype Purine nucleoside phosphorylase (PNP) deficiency Mutation of PNP leading to absent PNP, T-cell and neurologic defects from elevated toxic metabolites, especially dGTP; AR T cells progressive decrease; immunoglobulins normal or decreased; autoimmune haemolytic anaemia, neurological impairment Idiopathic CD4 cell lymphopenia CD4 lymphopenia of unknown cause Infections typical of T-cell deficiency Defects in immunoregulation Defects in Immune regulation Mutated gene/pathogenesis Associated features

1. Familial hemophagocytic lymphohistiocytosis (FHL) syndromes 1.1. FHL syndromes without hypopigmentation Perforin deficiency (FHL2)
2. Mutations in PRF1; perforin is a major cytolytic protein; AR Decreased to absent NK and cytotoxic T lymphocytes (CTL) activities cytotoxicity; fever, hepatosplenomegaly (HSMG); hemophagocytic lymphohistiocytosis (HLH), cytopenias UNC13D/Munc13-4 deficiency (FHL3) Mutations in UNC13D; required to prime vesicles for fusion; AR Decreased to absent NK and CTL activities cytotoxicity; fever, hepatosplenomegaly (HSMG); hemophagocytic lymphohistiocytosis (HLH); cytopenias Syntaxin 11 deficiency, (FHL4) Mutations in STX11, required for secretory vesicle fusion with the cell membrane; AR Decreased to absent NK and CTL activities cytotoxicity; fever; hepatosplenomegaly (HSMG); hemophagocytic lymphohistiocytosis (HLH); cytopenias STXBP2/Munc18-2 deficiency (FHL5) Mutations in STXBP2, required for secretory vesicle fusion with the cell membrane; AR or AD Decreased to absent NK and CTL activities cytotoxicity; fever, hepatosplenomegaly (HSMG); hemophagocytic lymphohistiocytosis (HLH), cytopenias Table 4.4.2 Continued

4.4 Immunodeficiency 343 Defects in immunoregulation Defects in Immune regulation Mutated gene/pathogenesis Associated features
SH2D1A deficiency (XLP1) Mutations in SH2D1A encoding an adaptor protein regulating intracellular signalling; XL Reduced memory B cells; partially defective NK cell and CTL cytotoxic activity; absent iNKT cells; clinical and immunologic features triggered by EBV infection: HLH, lymphoproliferation, hypogammaglobulinaemia; aplastic anaemia, lymphoma XIAP deficiency (XLP2) Mutations in XIAP/BIRC4 encoding an inhibitor of apoptosis; XL Low iNKT cells; increased T-cell susceptibility to apoptosis to CD95 and enhanced activation-induced cell death (AICD); EBV infection, splenomegaly, lymphoproliferation HLH, colitis, inflammatory bowel disease (IBD), hepatitis 1.2. FHL syndromes with hypopigmentation Chediak–Higashi syndrome Mutations in LYST, impaired lysosomal trafficking; AR Decreased NK and CTL activities (cytotoxicity and/or degranulation); partial albinism, recurrent infections, fever, HSMG, HLH; giant lysosomes, neutropenia, cytopenias, bleeding tendency, progressive neurological dysfunction Griscelli syndrome, type 2 Mutations in RAB27A encoding a GTPase that promotes docking of secretory vesicles to the cell membrane; AR Decreased NK and CTL activities (cytotoxicity and/or degranulation); partial albinism, fever, HSMG, HLH, cytopenias 2. T regulatory cells genetic defects IPEX, immune dysregulation, polyendocrinopathy, enteropathy X-linked Mutations in FOXP3, encoding a T-cell transcription factor; XL Lack of (and/or impaired function of) CD4+ CD25+ FOXP3+ regulatory T cells (Tregs); autoimmune enteropathy, early onset diabetes, thyroiditis haemolytic anaemia, thrombocytopenia, eczema; elevated IgE, IgA CD25 deficiency Mutations in IL2RA, encoding IL-2Rα chain; AR No CD4 + C25+ cells with impaired function of Tregs cells; lymphoproliferation, autoimmunity. Impaired T-cell proliferation CTLA4 deficiency (ALPSV) Mutations in CTLA4, encoding Cytotoxic

T-lymphocyte antigen 4, a protein that negatively regulate T-cell receptor signalling and T-cell activation; AD Impaired function of Treg cells; autoimmune cytopenias; enteropathy; interstitial lung disease; extralymphoid lymphocytic infiltration recurrent infections STAT3 GOF mutations Mutations in STAT3, encoding signal transducer and activator 3; AD Autoimmunity (especially cytopenias, enteropathy, pneumonitis), susceptibility to infection, variable lymphocyte numbers, low IgE; short stature in many 3. Autoimmunity with or without lymphoproliferation APECED (APS-1), autoimmune polyendocrinopathy with candidiasis and ectodermal dystrophy Mutations in AIRE, encoding a transcription regulator needed to establish thymic self- tolerance; AIRE1 serves as checkpoint in the thymus for negative selection of autoreactive T cells and for generation of Tregs Autoimmunity: hypoparathyroidism hypothyroidism, adrenal insufficiency, diabetes, gonadal dysfunction, and other endocrine abnormalities, chronic mucocutaneous candidiasis, dental enamel hypoplasia, alopecia areata; enteropathy, pernicious anaemia, urticaria, pneumonitis Autoimmune lymphoproliferative syndrome (ALPS) ALPS-FAS Germinal mutations in TNFRSF6, encoding CD95/Fas cell surface apoptosis receptor; AD; AR: somatic Increased CD4−CD8−TCRαβ double-negative (DN) T cells; apoptosis defect FAS mediated; splenomegaly, adenopathies, autoimmune cytopenias, increased lymphoma risk; IgG and A normal or increased; elevated FasL and IL-10, vitamin B12 ALPS-FASLG Mutations in TNFSF6, Fas ligand for CD95 apoptosis; AR Increased DN T cells; apoptosis defect FAS mediated; splenomegaly, adenopathies, autoimmune cytopenias, SLE; soluble FasL is not elevated ALPS-caspase 10 Mutations in CASP10, intracellular apoptosis pathway; AD Lymphadenopathy and splenomegally; autoimmune diseases ALPS-caspase 8 Mutations in CASP8, intracellular apoptosis, and activation pathways; AR Slightly increased DN T cells; defective lymphocyte apoptosis and activation; adenopathies, splenomegaly, bacterial and viral infections; hypogammaglobulinemia 4. Immune dysregulation with colitis IL-10 deficiency Mutations in IL10, encoding IL-10; AR No functional IL-10 secretion; IBD; folliculitis, recurrent respiratory diseases; arthritis IL-10Rα deficiency Mutations in IL10RA, encoding IL-10R1; AR IBD; folliculitis; recurrent respiratory diseases; arthritis; lymphoma IL-10Rβ deficiency Mutations in IL10RB, encoding IL-10R2; AR Leukocytes no response to IL-10, IL-22, IL-26, IL-28A, IL-28B, and IL- 29; IBD, folliculitis; recurrent respiratory diseases; arthritis; lymphoma 5. Type 1 interferonopathies Table 4.4.2 Continued (continued)

 Phagocyte functional defects Congenital defects of phagocyte number, function, or both Mutated gene/pathogenesis Associated features

1. Congenital neutropenias See Chapter 22.3.1 on neutropenia See Chapter 22.3.1 on neutropenia
2. Defects of motility Leukocyte adhesion deficiency Type 1 (LAD1) mutation in ITGB2: B chain for adhesion proteins CD18/CD11; AR Neutrophilia, monocytosis; lymphocytosis. Impaired chemotaxis. Delayed cor separation, omphalitis, periodontitis, poor wound healing, pyoderma-like skin ulcers, pyogenic sepsis Leukocyte adhesion deficiency type 2 (LAD2) Mutation in SLC35C1: GDP-fucose transporter; AR Mild LAD type 1 features, plus hh-blood group plus mental and growth retardation Leukocyte adhesion deficiency type 3 (LAD3) Mutation in KINDLIN3: AR LAD type 1 plus bleeding tendency Rac 2 deficiency Mutation in RAC2: regulation of actin cytoskeleton; AD impaired chemotaxis and Superoxide production; poor wound healing, leucocytosis Papillon–Lefèvre syndrome Mutation in CTSC: cathepsin C activation of serine proteases; AR Periodontitis, palmoplantar hyperkeratosis in some patients Shwachman–Diamond syndrome Mutation

in SBDS: defective ribosome synthesis; AR Pancytopenia, exocrine pancreatic insufficiency, chondrodysplasia

3. Defects of respiratory burst X-linked chronic granulomatous disease (CGD) Mutation in CYBB: electron transport protein (gp91phox); XL Killing (faulty O2 production); McLeod phenotype in patients with deletions extending into the contiguous Kell locus; staphylococcal, Gram-negative, and fungal infections Autosomal recessive CGD Mutation in CYBA: electron transport protein (p22phox); AR Killing (faulty O2 production); infections as in X-linked chronic granulomatous disease (XLCGD), autoinflammatory phenotype Autosomal recessive CGD Mutation in NCF1: adapter protein (p47phox); AR Killing (faulty O2 production); infections as in XLCGD, autoinflammatory phenotype Autosomal recessive CGD Mutation in NCF2: activating protein (p67phox); AR Killing (faulty O2 production); infections as in XLCGD, autoinflammatory phenotype Autosomal recessive CGD Mutation in NCF4: activating protein (p40 phox); AR Killing (faulty O2 production); infections as in XLCGD, autoinflammatory phenotype
4. Other defects GATA2 deficiency (mono MAC syndrome) Mutations in GATA2: master transcription factor in haematopoiesis; AD Low monocytes + peripheral dendritic cells; low NK cells; susceptibility to mycobacteria; papilloma viruses, EBV, histoplasmosis; alveolar proteinosis, MDS/AML/CMML Pulmonary alveolar proteinosisa Mutation in CSF2RA; biallelic mutations in pseudoautosomal gene defective GM-CSF signalling; alveolar proteinosis Defects in innate immunity Defects in intrinsic and innate immunity Mutated gene/pathogenesis Associated features
5. Mendelian Susceptibility to Mycobacterial Disease (MSMD) IL-12 and IL-23 receptor β1 chain deficiency Mutation in IL12RB1: IL-12 and IL-23 receptor β1 chain; defective IFN-γ secretion; AR Susceptibility to mycobacteria and salmonella IL-12p40 deficiency Mutation in IL12B: subunit p40 of IL12/IL23; defective IFN-γ secretion; AR Susceptibility to mycobacteria and salmonella IFN-γ receptor 1 deficiency Mutation in IFNGR1:IFN-γR ligand binding chain; defective IFN-γ binding and signalling; AR Susceptibility to mycobacteria, salmonella and viruses IFN-γ receptor 1 deficiency Heterozygous mutation in IFNGR1:IFN-γR ligand binding chain; AD Susceptibility to mycobacteria and salmonella IFN-γ receptor 2 deficiency Mutation in IFNGR2: IFN-γR accessory chain; defective IFN-γ binding and signalling; AR Susceptibility to mycobacteria and salmonella STAT1 deficiency (AD form) Heterozygous mutation in STAT1 (loss of function); defective IFN-γ signalling; AD Susceptibility to mycobacteria and salmonella Table 4.4.2 Continued

4.4 Immunodeficiency 345 Defects in innate immunity Defects in intrinsic and innate immunity Mutated gene/pathogenesis Associated features Macrophage gp91 phox Mutation in CYBB: electron transport protein (gp 91 phox), in macrophages only; intramacrophage killing faulty; XL Isolated susceptibility to mycobacteria IRF8-deficiency (AD form) Mutation in IRF8: IL12 production by CD1c+ myeloid dendritic cells (MDC); AD Defective differentiation of CD1c + MDC subgroup; susceptibility to mycobacteria; leucocytosis Tyk2 deficiency Mutation in TYK2; multiple cytokine signalling defect; AR Susceptibility to intracellular bacteria (mycobacteria, salmonella), fungi, and viruses ISG15 deficiency Mutation in ISG15; AR; defective IFNγ production Susceptibility to mycobacteria (BCG); brain calcification RORC deficiency Mutation in RORC; lack of functional RORγT protein; complete absence of IL-17A/F-producing T cells; defective IFNγ production; AR Mycobacteriosis and candidiasis 2. Epidermodysplasia verruciformis EVER1 deficiency Mutations of TMC6; EVER proteins may be involved in the regulation of cellular zinc homeostasis in lymphocytes;

AR HPV (group B1) infections and cancer of the skin (typical EV) EVER2 deficiency Mutations of TMC8; EVER proteins may be involved in the regulation of cellular zinc homeostasis in lymphocytes; AR HPV (group B1) infections and cancer of the skin (typical EV) 3. WHIM (warts, hypogammaglobulinaemia, infections, myelokathexis) syndrome Gain-of-function mutations of CXCR4, the receptor for CXCL12; AD Warts/human papilloma virus (HPV) infection; neutropenia; reduced B cell number; hypogammaglobulinemia 4. Predisposition to severe viral infection STAT1 deficiency Mutations of STAT1; defective STAT1-dependent IFN-α, and -β response; AR Severe viral infections, mycobacterial infections STAT2 deficiency Mutations of STAT2, defective STAT2-dependent IFN-α, and -β response; AR Severe viral infections (disseminated vaccine-strain measles) IRF7 deficiency Mutation in IRF7, defective IFN-α, and -β and -λ production; AR Severe influenza disease CD16 deficiency Mutation in CD16; deficient spontaneous NK cell cytotoxicity; AR Susceptibility to severe viral infections, inc. HSV, EBV, HPV 5. Herpes simplex encephalitis (incomplete clinical penetrance for all aetiologies listed here) TLR3 deficiency Mutations of TLR3; defective TLR3-dependent IFN-α, -β, and -λ induction in central nervous system (CNS) resident cells and fibroblasts; AD Herpes simplex virus 1 encephalitis (incomplete clinical penetrance for all aetiologies listed here) UNC93B1 deficiency Mutations of UNC93B1; defective UNC-93B- dependent IFN-α, -β, and -λ induction in CNS resident cells and fibroblasts; AR Herpes simplex virus 1 encephalitis TRAF3 deficiency Mutations of TRAF3; defective TRAF3-dependent IFN-α, -β, and -λ induction in CNS resident cells and fibroblasts; AD Herpes simplex virus 1 encephalitis TRIF deficiency Mutations of TRIF, also called TICAM1; defective TRIF-dependent IFN-α, -β, and -λ induction in CNS resident cells and fibroblasts; AD Herpes simplex virus 1 encephalitis TBK1 deficiency Mutations of TBK1; defective TBK1-dependent IFN-α, -β, and -λ induction in CNS resident cells and fibroblasts; AD Herpes simplex virus 1 encephalitis 6. Predisposition to invasive fungal diseases CARD9 deficiency Mutations of CARD9; defective CARD9 signalling pathway; AR Invasive candidiasis infection; deep dermatophytoses Table 4.4.2 Continued (continued)

7. Chronic mucocutaneous candidiasis (CMC) IL-17RA deficiency Mutations in IL17RA; defective IL-17RA signalling pathway; AR CMC; folliculitis Folliculitis 613953 IL-17RC deficiency Mutations in IL17RC; defective IL-17RC signalling pathway; AR CMC IL-17F deficiency Mutations in IL17F; AD CMC; folliculitis STAT1 gain-of-function Gain-of-function mutations in STAT1; gain- of-function STAT1 mutations that impair the development of IL-17-producing T cells; AD CMC; various fungal, bacterial, and viral (HSV) infections; autoimmunity (thyroiditis, diabetes, cytopenia); enteropathy ACT1 deficiency Mutations in ACT1, also called TRAF3IP2; fibroblasts fail to respond to IL-17A and IL-17
F, and their T cells to IL-17E; AR CMC; blepharitis, folliculitis, and macroglossia 8. Toll-like receptor (TLR) signalling pathway deficiency IRAK-4 deficiency Mutations of IRAK4, a component of TLR- and IL- 1R-signalling pathway; AR Bacterial infections (pyogenic) esp. S. pneumoniae, S. aureus, and Gram-negative bacteria; poor acute-phase responses MyD88 deficiency Mutations of MYD88, a component of the TLR and IL-1R signalling pathway; AR Bacterial infections (pyogenic) esp.
S. pneumoniae, S. aureus, and Gram-negative bacteria; poor acute-phase responses 9. Isolated congenital asplenia (ICA) Mutations in RPSA; RPSA encodes ribosomal protein SA, a component of the small subunit of the ribosome; AD Asplenia; bacteraemia (encapsulated bacteria) 10. Trypanosomiasis Mutations in APOL1; AD Trypanosomiasis Phenocopies of PID Genetic defect/presumed pathogenesis Associated features Associated with somatic mutations

Autoimmune lymphoproliferative syndrome (ALPS–SFAS) Somatic mutation in TNFRSF6; defective lymphocyte apoptosis Increased CD4−CD8−double-negative (DN) T α/β cells; increased number of CD5+ B cells, splenomegaly, lymphadenopathy, autoimmune cytopenias RAS-associated autoimmune leukoproliferative disease (RALD) Somatic mutation in KRAS (gain-of-function) Splenomegaly, lymphadenopathy, autoimmune cytopenias, granulocytosis, monocytosis/ALPS-like RAS-associated autoimmune leukoproliferative disease (RALD) Somatic mutation in NRAS (gain-of-function) Splenomegaly, lymphadenopathy, autoantibodies/ALPS-like Cryopyrinopathy, (Muckle-Wells/ CINCA/NOMID-like syndrome) Somatic mutation in NLRP3 Urticaria-like rash, arthropathy, neurological symptoms Associated with autoantibodies Chronic mucocutaneous candidiasis (isolated or with APECED syndrome) Germline mutation in AIRE; autoAb to IL-17 and/ or IL-22 Endocrinopathy, chronic mucocutaneous candidiasis/CMC Adult-onset immunodeficiency AutoAb to IFN-γ Mycobacterial, fungal, salmonella VZV infections/MSMD, or CID Recurrent skin infection AutoAb to IL-6 Staphylococcal infections/STAT3 deficiency Pulmonary alveolar proteinosis AutoAb to GM-CSF Pulmonary alveolar proteinosis, cryptococcal meningitis/CSF2RA deficiency Acquired angioedema AutoAb to CI inhibitor Angioedema/C1 INH deficiency (hereditary angioedema) Atypical haemolytic uremic syndrome AutoAb to complement factor H Atypical haemolytic uremic syndrome; spontaneous activation of the alternative complement pathway Disorders of homeostasis of inflammation (autoinflammatory syndromes) See Chapter 12.12.2 Inherited complement defects See Chapter 4.2 Source data from Picard C, et al. (2018). International Union of Immunological Societies: 2017 Primary Immunodeficiency Diseases Committee Report on Inborn Errors of Immunity. J Clin Immunol, 38, 96–128. Table 4.4.2 Continued

4.4 Immunodeficiency 347 include infections, such as HIV and measles; and cytotoxic and immunosuppressive drugs (including biologic therapies), particularly those used in the management of transplantation, autoimmunity, and cancer. Physiological immune deficiency may occur at the extremes of age. Before investigating for a possible primary immunodeficiency disease, it is essential to consider the history, examination, and other investigations to exclude secondary immunodeficiency states. A stepwise approach to the diagnosis of immunodeficiency is shown in Table 4.4.4. Defects in anatomical or physiological barriers to infection One of the commonest predisposing causes of infection is a de- fect in the anatomical or physiological barriers to infection. Intact epithelial membranes, especially a stratified squamous epithelial surface such as the skin, constitute an extremely effective barrier to infection. Table 4.4.3 Causes of secondary immunodeficiency Causes of secondary immunodeficiency Defect Defects in anatomical and physical barriers to infection (see text for explanation) Various Malignancies of the B-cell system Antibody Myelomatosis Non-Hodgkin’s lymphoma Chronic lymphocytic leukaemia Therapeutic agents Biological agentsa Anti-B cell agents: e.g. rituximab, ibrutinib Antibody Anti-TNF agents Innate immunity and CMI Biologics blocking T-cell costimulation or integrins CMI and/or innate immunity Anticomplement C5 Terminal complement pathway Anticytokines (e.g. anti-IL12; anti-IL-6, anti-IL17, etc.) Innate immunity and CMI Cytotoxic drugs: alkylating agents, cytotoxic antibiotics, antimetabolites, vinca alkaloids, etoposide, etc. Myelosuppression and CMI Immunosuppressive drugs: corticosteroids, calcineurin inhibitors (e.g. ciclosporin), antiproliferative immunosuppressants (azathioprine, mycophenolate) CMI Drugs causing antibody deficiency: gold, penicillamine, sulphasalazine, carbamazepine, valproate, clozapine Antibody Radiotherapy CMI Metabolic/nutritional deficiencies Renal failure CMI and innate immunity Liver failure CMI and innate immunity Protein calorie malnutrition CMI Vitamin A deficiency CMI Zinc deficiency CMI Transcobalamin-II deficiency Antibody Multiorgan failure CMI and innate Increased loss of

immunoglobulin Nephrotic syndrome Protein losing enteropathy Dystrophia myotonica Virus infections HIV CMI Measles CMI congenital rubella Antibody congenital CMV Antibody Age-related prematurity CMI, innate, and antibody extreme old age CMI and innate CMI, cell-mediated immunity. a This is a large and expanding area of therapeutics, therefore review properties of any Biological agent used to treat patient for possible immunosuppressive effect.

348 SECTION 4 Immunological mechanisms Table 4.4.4 Diagnostic algorithm for immunodeficiency disorders Type of immune disorder (IUIS classification) CID CID with associated features Predominantly antibody deficiency Immune dysregulation Phagocyte disorders Disorders of intrinsic/ innate immunity Autoinflammatory disorders Complement disorders Presentation Recurrent/chronic ENT/respiratory infection • • ■ • • Failure to thrive in infancy, diarrhoea, opportunistic infection, eczema ■ • • Recurrent infections with pyogenic bacteria &/or fungi +/- granuloma, gut inflammation • • ■ • • Unusual/unusually severe infections (including opportunistic pathogens) • • • • • Recurrent infections with one type of pathogen or stereotyped inflammatory response • • ■ • • Autoimmunity, chronic inflammation, and/or lymphoproliferation • • ■ • • • Immunodeficiency with associated syndromic features • ■ • •

4.4 Immunodeficiency 349 Diagnostic work up First-line tests All patients: thorough microbiologic evaluation including appropriate search for opportunistic pathogens and coinfection where—may require cross-sectional imaging, bronchoalveolar lavage, tissue biopsy, special culture conditions FBC + differential Lymphocyte subsets inc. naïve T cells, Class-Switched Memory B cells In vitro proliferation to mitogens Serum IgG, A, M, E Vaccine-specific responses Biopsy skin rash in infants for evidence of GVHD Exclude HIV by PCR and serology Consider cardiac review where relevant Serum IgG, A, M, E Isohaemagglutinins Vaccine-specific responses FBC + differential Consider assessing response to booster vaccinations As for CID plus: enumerate Tregs and double-negative T cells vit B12 autoantibody screen including ANA, direct agglutination test thyroid function for HLH, measure ferritin, triglycerides, fibrinogen, soluble CD25 FBC + differential (serially to exclude cyclical neutropenia) Blood film for neutrophil morphology Neutrophil oxidative burst (NBT, DHR) Neutrophil surface phenotype (CD18/11, CD15) FBC + differential Lymphocyte subsets inc. naïve T cells, Class- Switched Memory B cells Serum IgG, A, M, E Vaccine-specific responses Mycobacterial infection: cytokine studies (IL12/IFNg production and response), NOB Fungal susceptibility: anticytokine antibodies, thyroid function Recurrent bacterial sepsis: splenic ultrasound, blood film for Howell- Jolly bodies, complement function, CD62L shedding Viral susceptibility: exclude Combined Immunodeficiency see Chapter 12.12.2 CH50, AP50, C3, C4 Second line tests If abnormal, consider: T-cell receptor repertoire (for T-cell clonality) Tests for materno-fetal engraftment in infants with features of GVHD MHC I and MHC II expression on lymphocytes Metabolic tests re ADA, PNP, TCN2 deficiency FISH/CGH to detect del22q11 If abnormal: Lymphocyte subsets inc. naïve T cells, B-cell phenotyping Special tests depending on clinical context, e.g. in a male, expression of BTK, CD40L, SAP; hair microscopy Assess target organs for damage Consider: tissue biopsy and detailed histology where relevant e.g. gut, skin, lung pulmonary function testing ophthalmologic evaluation endocrine assessment urinary sediment, protein:creatinine ratio specific tests as indicated, e.g. STAT phosphorylation, apoptosis assay, lymphocyte degranulation, perforin expression, anticytokine antibodies Consider: leukocyte subsets with detailed monocyte and dendritic cell phenotyping tissue biopsy and detailed histology where relevant Consult specialist laboratories for appropriate functional testing If only CH50 abnormal, investigate individual elements of classical pathway; if only AP50 abnormal investigate

individual elements of Alt pathway; if both CH50 and AP50 abnormal investigate C3 and terminal pathway. If angioedema/ abdominal pain, and low C4 investigate C1INH; also seek advice of specialist lab All patients: molecular genetic testing (single-gene/panel/open-ended depending on availability and clinical suspicion) ■ - Most frequent diagnosis. • - (very inclusive—see main text for further details of discriminating features of individual immunodeficiency disorders)

350 SECTION 4 Immunological mechanisms The following defects predispose to infection: • Integumentary damage caused by burns, eczema, or trauma (including surgery) • Skull fracture, particularly damage of the cribriform plate, which may result in recurrent episodes of bacterial meningitis • Sinus tracts between deeper tissues and the skin surface • Presence of foreign bodies or avascular areas (e.g. within bone) • Obstruction to the drainage of hollow tubes and viscera (e.g. ob- struction of the biliary tract, urinary tract, or bronchi) • Impaired vascular perfusion of the tissues due to oedema, or angiopathy (including microvascular changes following diabetes mellitus) • Alteration of the normal commensal flora by broad-spectrum antibiotic therapy • Damage from surgical instruments, perfusion lines, and catheters • Damaged tissues such as damaged cardiac valves Infections that recur in the same anatomical site are often due to defective anatomical or physiological barriers and hence should in- duce a diligent search for such factors. Causative organisms are pyo- genic bacteria such as staphylococci, commensal organisms from the skin or intestinal tract, and fungi, especially candida. Primary immune deficiencies—combined immunodeficiency (T-cell immunodeficiency) Primary combined immunodeficiencies are a genetically heteroge- neous group of disorders in which T-cell hypofunction is accom- panied by variable degrees of humoral immunodeficiency. In the most severe type, a complete block in T-cell development leads to catastrophic failure of the adaptive immune system, severe com- bined immunodeficiency (SCID). SCID usually presents in infancy, though with increased application of genomics it is evident that mo- lecular defects usually causing SCID may rarely present in later life. Other disorders may be compatible with preserved T-cell numbers but impaired function, leading to variable degrees of immunodefi- ciency and correspondingly diverse clinical presentations. Figure 4.4.1 summarizes the immunodeficiencies that result from a block in lymphocyte development. Causes of combined immunodeficiency
(T-cell immunodeficiency) These may be primary (congenital; see Table 4.4.2 for list of condi- tions) or secondary (see Table 4.4.3 for list of conditions). Clearly, HIV infection produces secondary T-cell immunodeficiency: the incidence of this disorder varies with geographical location and the presence of risk factors for acquiring HIV infection. Clinical phenotype of patients with T-cell deficiency or combined immunodeficiency The key clinical features of combined immunodeficiency can be summarized as follows: • susceptibility to infection—all pathogen types, but especially intracellular pathogens; opportunistic; severe; refractory/ recurrent (see Table 4.4.1 and Fig. 4.4.1) • immune dysregulation—ranging from Omenn’s syndrome to organ-specific autoimmunity • increased risk of neoplasia—especially lymphomatous and/or vir- ally associated (e.g. human papilloma virus (HPV)-associated car- cinoma, Epstein–Barr virus (EBV)-lymphoproliferative disease) • variable primary effects on other components of the immune system +/– extrahaematological manifestations—depending on the molecular defect The clinical phenotype of patients with impaired T-cell dependent immunity is summarized in Table 4.4.1 and 4.4.4. Major categories of immunodeficiency exhibiting impaired T-cell function are now described. Severe combined immunodeficiency (SCID) This syndrome is characterized by severe failure of adaptive im- mune responses because of a profound block T-cell development. Patients with SCID exhibit a clinical and immunological pheno- type characterized by functional defects in both B and T cells.

These are rare disorders, with an estimated incidence of 1 in 50 000 to 1 in 100 000 live births. Clinical features SCID presents in infancy, with failure to thrive and recurrent, se- vere, potentially life-threatening bacterial, viral, or fungal infections. These infections may be caused by a broad range of common patho- gens, but often include persistent infections by organisms that usu- ally exhibit low-grade virulence (e.g. Candida, cytomegalovirus). Diarrhoea, which is often due to viral infection, is common and associated with failure to thrive. Chronic lung infection may result from respiratory viruses such as respiratory syncytial virus, para- influenza virus, cytomegalovirus, and adenovirus, while interstitial pneumonia caused by Pneumocystis jirovecii is pathognomonic for T-cell deficiency. Other common infections at presentation include oral candidiasis and regional or systemic spread of bacille Calmette- Guérin from the site of neonatal vaccination. Physical signs are chiefly those due to the presence of infection or complications of infection, including failure to thrive. The ab- sence of tonsils or other lymph nodes may be noted, and chest X- ray may reveal the absence of a thymus. A syndrome resembling graft-versus-host disease, with skin rashes, hepatosplenomegaly, and lymphadenopathy, may result from materno-fetal engraftment, transfusion of nonirradiated blood or Omenn’s syndrome (see fol- lowing paragraphs). Immunologically, SCID is characterized by lymphopenia compared to age-related absolute lymphocyte counts, the severe reduction or absence of major lymphocyte subsets, absent in vitro T-cell proliferation to mitogens, and markedly reduced total and specific antibody levels. Immunological and molecular classification Based on the blood lymphocyte phenotype, patients with SCID can be divided into two broad groups (see Fig. 4.4.1): • T–B+ SCID—those who lack T cells but have normal or increased B-cell numbers • T–B– SCID—those who lack both T and B cells Defects in four functionally related genes cause T–B+ SCID. The commonest is X-linked SCID, due to a defective IL2RG gene that

4.4 Immunodeficiency 351

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= HSC CLP PRO NK PRE B1 PRO T im m B im m T PRE B2

PRE T CD4 T CD8 T NK trans B Thymus CD4 T CD8 T NK Blood

=

=

=

AK2 ADA RAG1/2 DCLRE1C LIG4 PRKDC CD3E CD247 IL2RG JAK3 IL7R IL2RG JAK3 BTK, BLNK IGHM CD79A/B IGLL1, TCF3 PIK3R1 CORO1 CD45 ZAP70 TAP1/2 CD45

CIITA RFX etc PNP, CXCR4 PRO B GATA2 CD3D PNP 2° lymphoid tissue naïve mature B MZ B foll B IgM+ plasma cell plasma cell class switched memory B cell BAFFR TWEAK TACI POLE class switch recombination defects: AID UND, PMS2, DNA repair defects MCM4 =

B-cell activation defects: ICOS, CD40, CD40LG, IL21R, CARD11, NIK, NEMO, IKBKB, HOIL1, HOIP, TI RAP, RAK4, MyD88 Fig. 4.4.1 Summary of immunodeficiencies resulting from a block in lymphocyte development. Haematopoietic stem cells differentiate in bone marrow into common lymphocyte precursors, from which NK, T, and B lymphocytes originate. γC, JAK-3, IL-7R deficiencies impair γC-dependent cytokine signalling necessary for T-cell and NK lymphocyte development. RAG1, RAG2, and DCLRE1C (Artemis) gene mutations impair V(D)J recombination of T-cell receptor and

immunoglobulin genes in pro-T and pro-B cells, respectively. HLA class II deficiency impairs development of CD4 T cells. ZAP70 kinase deficiency impairs CD8 T-cell development and leads to the development of nonfunctional CD4 T cells. TAP 1/2 deficiencies impair positive selection of CD8 T cells. μ heavy chain, Igα and β associated subunit, λ5, and BLNK deficiencies prevent the transition from pro-B to pre-B cells. BTK deficiency impairs B-cell development. CD40L, AID (activation-induced cytidine deaminase), and uracil-DNA glycosylase (UNG) deficiencies prevent immunoglobulin class switch recombination. Modified from The Lancet, Vol. 357, Fischer A, Primary immunodeficiency diseases: an experimental model for molecular medicine, Pages 1863–9.

 encodes the signal transducing γ-chain common to the receptors for six cytokines (interleukins 2, 4, 7, 9, 15, and 21). The absence of response to these critically important cytokines explains the broad range of defects in specific B- and T-cell function in these patients. Failure to respond to interleukins 7 and 15 results in the arrest of T and natural killer (NK) cell development at an early stage. Interaction of the common γ-chain with the JAK-3 tyrosine kinase is essential for signal transduction through the aforementioned cytokine recep- tors. Therefore JAK-3 gene mutations result in an autosomal reces- sive form of SCID with a similar phenotype. Mutation of the α-chain of the interleukin 7 receptor (IL7R) is a further cause of T–B+ SCID but in this case NK cell development is preserved. About 50% of patients with T–B– SCID have a mutation in one of the recombinase-activating genes (RAG1 or RAG2). RAG1 and RAG2 are required to initiate the V, D, J gene rearrangements that generate a normal repertoire of T- and B-cell antigen recep- tors. Without RAG1 and RAG2 function, T- and B-cell develop- ment fails, giving rise to T– B– SCID. Hypomorphic mutations of RAG1 or RAG2 can cause the distinct entity Omenn's syndrome (OMIM 603554). In this condition a few T-cell clones develop and undergo secondary expansion in the periphery, leading to pathologic inflammatory infiltration of the skin and viscera, resembling graft-versus-host disease. Although patients with Omenn's syndrome may have lymphocyte counts within the normal range, their T cells are oligoclonal and clinically they are severely immunodeficient. A few patients with T–B– SCID have mutations in genes required for the repair of double-strand breaks generated during VDJ re- combination (DCLRE1C, PRKDC, LIG4). These individuals are also highly radiation-sensitive, which should be taken into account when designing conditioning regimens prior to HSCT. About 15% of cases of SCID are caused by adenosine deaminase (ADA) deficiency, which shows autosomal recessive inheritance. This enzyme is essential for the salvage of nucleotides within lymphoid cells. The lack of ADA results in the accumulation of toxic purine metabolites, and increased rates of lymphocyte death, through mechanisms that are incompletely understood. ADA defi- ciency results in profound lymphopenia with reduced T, B, and NK cells. Rare hypomorphic mutations of adenosine deaminase may cause a milder defect that presents in older patients. Importantly, ADA function can be supplied to deficient individuals in the form of pegylated enzyme replacement therapy as a temporizing measure. This is also one of the few conditions to have been successfully treated by gene therapy with excellent rates of survival and immune reconstitution, even compared with stem cell transplantation. None of these treatments prevents neurodevelopmental effects of ADA deficiency, which is associated with both cognitive and behavioural problems in survivors. Purine nucleoside phosphorylase (PNP) is another enzyme re- quired for purine salvage within lymphocytes. PNP deficiency causes a rare form of SCID which has a milder immunological but typically a more severe neurodevelopmental phenotype than seen in ADA deficiency. PNP deficiency is nevertheless usually fatal in childhood, unless treated with HSCT. A rare group of defects responsible for SCID impairs signal trans- duction

through the T-cell receptors. This includes a defect in the protein tyrosine phosphatase CD45 which perturbs signalling through both T- and B-cell receptors. Mutation of the δ-chain of the CD3 complex also causes SCID while defects in the γ- and ε-chains of CD3 or the TCR-α chain may cause a milder phenotype. A mu- tation of the gene encoding ZAP70 (zeta chain associated protein 70), which interacts with the ζ-chain of CD3, results in severe CD8 lymphopenia and profound immunodeficiency resembling SCID. In this condition, CD4 lymphocyte counts may be normal but their function is also reduced. A mutation of the ORAI1 gene encoding a subunit of the plasma membrane calcium channel CRAC, causes a rare form of SCID due to defective calcium entry into T cells which impairs T-cell function. Recently, a T-B+ NK+ form of SCID has been described in which a failure of T-cell egress from the thymus is caused by a mutation of the gene CORO1A, encoding for the actin regulatory protein coronin 1A. Diagnosis The diagnosis of SCID is readily suspected in infants who fail to thrive and suffer from recurrent severe infections from an early age. The clinical features raising the suspicion of SCID are summar- ized earlier. SCID is a medical emergency, as patients can rapidly succumb to life-threatening infections. Untreated SCID is invari- ably fatal, with most children dying in the first year of life, and the balance succumbing within the second year. Conversely, early stem cell transplantation results in long-term survival in more than 90% of cases. The occurrence of intractable infections prior to transplant is associated with poorer outcome. For the aforementioned reasons, early diagnosis is essential and newborn screening for T lymphopenia has therefore been imple- mented or is planned in several countries. This capitalizes on ex- isting neonatal screening programmes by utilizing portions of the same dried blood spots for testing. Innovatively, the test involves amplification by polymerase chain reaction of T-cell receptor ex- cision circles (TRECs). TRECs are small, circularized fragments of DNA that are generated in the process of TCR gene rearrangement and are normally found in a fraction of circulating T cells. SCID leads to a profound lack of TRECs, although these are also reduced in a variety of other T-lymphopenic states. Babies with low TREC numbers are urgently referred for further assessment including flow cytometric characterization of peripheral lymphocyte subsets. The TREC screening test appears to perform well with high sensitivity and acceptable specificity. A detailed family history should enquire into consanguinity of parents, the occurrence of immunodeficiency in other family mem- bers, and deaths in early infancy within the pedigree. HIV infection may present with a similar clinical picture and needs to be excluded with appropriate tests. Initial tests used in the assessment of an individual with possible SCID are: • blood count and differential count • enumeration of blood lymphocyte populations • measurement of serum immunoglobulins Severe lymphopenia (absolute lymphocyte count <2.5 × 109/ litre in the first year of life) is a characteristic feature seen in over 80% of patients with SCID. Hence SCID needs to be excluded in all infants with a lymphocyte count below the age-related refer- ence range. The second stage is to enumerate blood lymphocyte subsets (T cells, B cells, and NK cells) using flow cytometry. These

 results should be interpreted using age-matched reference ranges. The minimum panel of monoclonal antibodies recommended for lymphocyte phenotype determination is summarized in Table 4.4.5. The lymphocyte phenotypes typically associated with different mo- lecular variants of SCID are summarized in Table 4.4.6. The absence of lymphopenia does not completely rule out SCID. This can occur in SCID patients engrafted with transplacentally ac- quired maternal lymphocytes, in Omenn’s syndrome, or in T-B+ SCID. In patients behaving as SCID despite apparently normal T-cell numbers, a lack of naive T cells, oligoclonality of the T-cell reper- toire, and poor in vitro T-cell proliferation to mitogens help to con- firm a diagnosis of SCID/Omenn’s. These tests are only available in specialized centres. HLA typing of the mother and

baby will help to distinguish maternal engraftment from Omenn's syndrome. Serum immunoglobulin levels are difficult to interpret in young infants. In SCID, IgM and IgA levels are usually low. The level of IgG, which is maternally derived, may be normal in early infancy but progressively declines with time. In Omenn's syndrome, IgE levels may be elevated. SCID is the probable diagnosis in infants who are less than 2 years of age and have (1) an absolute lymphocyte count less than 2.5 × 109/litre; (2) CD3 cells less than 20% of the total lymphocyte count; and (3) proliferative responses to mitogens less than 10% of control values. Maternal engraftment is also an absolute indication of SCID. Once the diagnosis of SCID or Omenn's syndrome is considered likely, additional investigations to identify the molecular phenotype of SCID are important, as these may guide the details of therapy, family counselling, and prenatal diagnosis. Such tests are available through nationally designated laboratory services and include metabolic studies (to identify adenosine deaminase or purine nu- cleoside phosphorylase deficiency), detection of proteins required for lymphocyte function by flow cytometry or Western blotting (e.g. to identify common γ-chain defect), signalling assays (e.g. STAT5 phosphorylation by flow cytometric analysis), and mutation analysis of candidate genes. Management and prognosis Untreated SCID has a fatality rate of 100%. Patients suspected of SCID should be transferred to expert paediatric centres as soon as possible. Immediate management includes protective isolation, prophylaxis for Pneumocystis jirovecii pneumonia, a diligent search for existing infection and its treatment, as well as general supportive care. If infection is suspected but the microbiological diagnosis is uncertain, empirical antimicrobial therapy is usually indicated. Any blood transfusions should be irradiated and from cytomegalovirus- negative donors. Live vaccines are contraindicated. Immunoglobulin replacement should commence without delay. Once a diagnosis of SCID is confirmed, haemopoietic stem cell transplantation (HSCT) from an HLA-identical family donor is gen- erally the treatment of choice. If a tissue-matched family donor is not available, other donor choices include matched unrelated or a T-cell-depleted haplo-identical family donor (typically a parent). In patients with SCID, HSCT can be achieved with little or no im- munosuppressive therapy, although long-term immune reconstitu- tion may depend on myeloid engraftment and hence the degree of myeloablative conditioning. European data to 2005 indicate that 10-year survival after trans- plants from HLA-matched unrelated donors was 66%, while matched sibling donor transplants produced 84% survival. Treatment with HSCT before 3.5 months of age has produced 95% long-term survival. Delay in treatment and (particularly) the occurrence of in- fection impairs outcome. Infection and graft-vs.-host disease are the main short-term complications following stem cell transplantation. Review of European data between 1968 and 2005 indicates the pro- gressive improvement of outcome over time, which is mainly due to better prevention of graft-versus-host disease and the aggressive treatment of infection. Gene therapy for SCID Long-term immune reconstitution is possible following gene therapy in patients with SCID caused by the common γ-chain deficiency or ADA deficiency. This can be achieved by ex vivo gene transfer to haemopoietic stem cells isolated from the patient's bone marrow. Table 4.4.5 Designations of monoclonal antibody combinations recommended for lymphocyte phenotyping Surface antigen recognized by antibody Cells recognized CD3 All T cells CD3+CD4 T helper CD3+CD8 T cytotoxic CD16 and/or CD56 NK cells CD19 or CD20 B cells MHC class II B cells, monocytes, activated T cells MHC class I All nucleated cells CD3+TCRαβ TCRαβ–bearing T cells CD3+TCRγδ TCRγδ-bearing T cells Table 4.4.6 Blood lymphocyte profile in different molecular forms of SCID particularly associated with lymphopenia SCID variant CD3+ CD4+ CD8+ B cells NK cells IL2RG (common γ-chain), JAK3, Low Low Low Normal Low IL7RA, CD3D, CD3E, CD247, PTPRC, CORO1A Low Low Low Normal or high Normal or high RAG 1, RAG2, DCLRE1C (Artemis), PRKDC, LIG4, Cernunnos Low Low Low Low

Normal ADA, AK2 Low Low Low Low Low MHC class II deficiency, LCK, MAGT1, UNC119 Normal Low Normal Normal Normal ZAP-70, MHC I deficiency (TAP1, TAP2, TAPBP, B2M), CD8 Normal Normal Low Normal Normal Omenn syndrome (hypomorphic mutations) Low, normal, or high Variable Variable Usually low Normal

 These gene-reconstituted stem cells are retransfused into the patient, sometimes after mild conditioning. To date, gene therapy has been restricted to patients without an HLA-matched family donor. Unfortunately, several cases of leukaemia occurred among γ- chain deficient patients treated in early trials of gene therapy. In these cases, the retroviral vector had integrated close to the LMO2 proto- oncogene in the leukaemic clone, leading to aberrant transcription and expression of LMO2. While this resulted in temporary discon- tinuation of gene therapy, safer treatment protocols have since been developed and trials continue with improved vectors. Other combined immunodeficiencies (CID) There are forms of combined immunodeficiency in which T-cell de- velopment is preserved to a greater or lesser extent, yet T-cell effector function is impaired. Sometimes this produces a clinical phenotype as severe as SCID—as in the case of deficiencies of CARD11, IKBKB, ZAP70, and MHC class II. However, most non-SCID disorders af- fecting T cells produce an immunodeficiency that is less severe, with onset typically delayed beyond infancy. In clinical practice this often means that patients progressively acquire end-organ damage re- sulting from chronic or recurrent infection and/or autoimmunity. Confident diagnosis of individual disorders in the absence of genetic testing is often difficult unless characteristic associated syn- dromic features are present (for example, skeletal dysplasia, facial dysmorphism, abnormal dentition, and so on). It is beyond the scope of this chapter to detail all forms of CID individually, but some generalizations about clinical behaviour will be made before describing selected illustrative disorders. Susceptibility to viruses is typically milder than in SCID and simple infections including respiratory viruses may be cleared. However, fatal primary infection with common exanthematous viruses (e.g. measles, varicella zoster virus (VZV)) can occur, and viral infections such as rotavirus or norovirus may persist abnormally. Patients com- monly fail to suppress herpes viruses such as CMV, herpes simplex virus (HSV), VZV, and EBV. Certain immunodeficiencies cause a particular predilection to EBV-related lymphoproliferation, notably deficiencies of ITK, MST1, CD27, and CTPS1. EBV may also cause severe infectious mononucleosis or hairy leukoplakia of the tongue (as in HIV-AIDS) in affected individuals. Persistent oral candidiasis in an adult, without predisposing fac- tors like broad-spectrum antibiotic therapy, the wearing of den- tures, or the use of inhaled corticosteroids, and which recurs after antifungal treatment, is highly suspicious of T-cell deficiency. In these patients Candida may affect the oesophagus and trachea as well. Interestingly, invasive candidiasis is not a typical feature of T-cell deficiency whereas invasive infection caused by filamentous fungi (Aspergillus, Mucor) or Cryptococcus can occur in more severe forms of CID, as can interstitial pneumonia caused by Pneumocystis jirovecii. T-cell deficient patients are highly susceptible to de novo infec- tion or reactivation of tuberculosis, which may be disseminated, extrathoracic, or atypical in presentation. In populations with low tuberculosis (TB) prevalence, other poorly pathogenic mycobac- teria may cause opportunistic infection, including Mycobacterium avium intracellulare and Bacille Calmette–Guérin (BCG), which can be life-threatening. Other intracellular bacteria such as Salmonella spp. may also establish persistent infection. Protozoal pathogens including Cryptosporidium and Giardia are on the differential diag- nosis for chronic gastrointestinal symptoms in these patients. Many with CID experience recurrent respiratory tract infections culminating in bronchiectasis, even though total immunoglobulins may be present in normal

quantities. The quality of vaccine-specific responses are often impaired, and susceptibility to pneumococcal disease is often a particular feature. Infection-related malignancies may develop at excessive rate; for example, Epstein–Barr virus-induced non-Hodgkin's lymphoma, HPV-related carcinoma, and Kaposi's sarcoma (in which human herpes virus 8 is the cofactor). In addition, many disorders show an increased tendency towards lymphoma that is independent of EBV. There is an increased incidence of cutaneous malignancies in indi- viduals who are exposed to significant amounts of ultraviolet light (e.g. basal cell carcinoma and squamous cell carcinoma of skin). Skin malignancies are not common in northern latitudes but are typically seen in parts of the world with high year-round sun exposure. Autoimmunity is an increasingly recognized manifestation of combined immunodeficiency, presumably reflecting impaired homeostasis of an immune system that may lack critical regula- tory components. The commonest manifestations are autoimmune cytopenias, particularly thrombocytopenia and autoimmune haemolytic anaemia, but neutropenia is also seen. Certain disorders (Wiskott–Aldrich syndrome, hyper IgE syndrome (STAT3), STAT5b deficiency) are linked to atopic phenomena, especially dermatitis, but also occasionally food allergy (e.g. in DOCK8 deficiency). MHC class II deficiency The lack of expression of MHC class 2 on lymphocytes (MHC class 2 deficiency) leads to a combined immunodeficiency that clinic- ally resembles SCID. Autosomal recessive defects in various genes encoding for components of a transcription complex promoting the transcription of MHC class 2 genes can lead to this condition. CD4 T lymphocytes recognize antigen in the context of MHC class 2 genes expressed by antigen-presenting cells. The absence of MHC class 2 therefore results in a failure of normal CD4 cell development and function. In turn this produces a severe failure of cell-mediated im- munity. The consequent absence of CD4-mediated help for B cells results in defective antibody responses. Wiskott–Aldrich syndrome This X-linked syndrome (OMIM 301000) is characterized by eczema and thrombocytopenic purpura with small, defective platelets and combined immunodeficiency. Patients usually present in infancy with a bleeding tendency, manifesting as petechiae, bruising, pro- longed bleeding from wounds, or bloody diarrhoea. Eczema can vary in severity. Antibody production to bacterial capsular polysacchar- ides is deficient and protein antibodies decline abnormally quickly. Patients therefore commonly develop recurrent sinopulmonary and middle ear infections. Progressive T lymphopenia develops with time, and T cells and NK cells display reduced functional capacity. Hence patients can develop opportunistic infections typical of T-cell deficiency. Autoimmune conditions such as colitis, glomeruloneph- ritis, vasculitis, and autoimmune cytopenias occur in these patients. The risk of malignancies in Wiskott–Aldrich syndrome patients has been estimated at 2% per year. Lymphomas are the most frequent tumours, most of which are induced by Epstein–Barr virus.

4.4 Immunodeficiency 355 The gene that is defective in Wiskott–Aldrich syndrome codes for the Wiskott–Aldrich syndrome protein (WASP), which is a cytoplasmic component that regulates actin polymerization and cytoskeletal reorganization, required for normal platelet and leuko- cyte function. For example, WASP is involved in the formation of immunological synapses between cooperating T cells and antigen- presenting cells. Certain missense mutations of WASP cause X-linked thrombocytopenia or X-linked neutropenia. It is now rec- ognized that female carriers with skewed X-chromosome inactiva- tion can occasionally be symptomatic. The diagnosis of Wiskott–Aldrich syndrome is suspected on identifying thrombocytopenia with small platelets and confirmed in many cases by demonstrating the absence of WASP by Western blotting or flow cytometry. The severity of disease relates loosely to the degree of WASP function, its complete absence being associated with a severe phenotype. In the days before stem cell transplantation,

the outlook for these patients was poor, with a median survival of 5–7 years. HLA-identical sibling-derived HSCT is curative and associated with an approxi- mately 90% 5-year survival. HLA-matched unrelated transplants car- ried out before 5 years of age have a similar success rate. Above this age, individual risk assessment is needed. Immunoglobulin replace- ment therapy and antibiotics are supportive therapies. Splenectomy may help to raise platelet counts but compounds the existing immunocompromise and is associated with increased risk of sepsis both pre- and post-transplant. LRBA deficiency (lipopolysaccharide (LPS) responsive
beige-like anchor protein) LRBA is a member of the BEACH-WD40 protein family and is ex- pressed in tissues including haematopoietic, neural, gastrointes- tinal, and endocrine cells. The repeated WD40 domain, located at the C-terminal of LRBA, is highly conserved and participates in multiple cellular processes, including cytoskeleton assembly, signal transduction, vesicular trafficking, transcriptional regula- tion, chromatin dynamics, and apoptosis. In normal T cells, LRBA colocalizes with CTLA4 within recycling endosomes and the trans- Golgi network The disease phenotype caused by LRBA deficiency comprises a combination of enteropathy, autoimmunity, and immuno-deficiency, as well as lymphoproliferation. The enteropathy includes a spectrum of autoimmune conditions, an inflamma- tory bowel disease-like condition and noninfectious diarrhoea; the autoimmunity phenotype includes autoimmune cytopenias; and the immunodeficiency phenotype includes combined im- munodeficiency (CID) and a common variable immune defi- ciency (CVID)-like disease. Patients with CVID-like disease can develop interstitial lung disease due to dense T-cell infiltrates. A few patients have developed B-cell lymphomas. There is no obvious genotype-phenotype correlation as patients with the same mutation may have different clinical phenotypes or even be asymptomatic. An important function of LRBA is to support the expression of the T-cell costimulatory molecule CTLA-4 (cytotoxic T-lymphocyte antigen-4) by regulating its trafficking to the lysosomal compart- ment. It has therefore been postulated that the clinical manifest- ations of LRBA deficiency are due to underexpression of CTLA-4. This is supported by studies showing that abatacept, a fusion pro- tein that mimics CTLA4 function, is associated with marked clinical improvement. Hyper IgM syndromes During primary antibody responses, B cells initially produce IgM. They later switch to the production of IgG, IgA, and IgE. This pro- cess is called immunoglobulin class switching and is associated with somatic hypermutation of the immunoglobulin variable-region genes resulting in enhancement of antibody affinity for the stimu-lating antigens (affinity maturation). Reflecting the complexity of this process, several different molecular defects can lead to failure of immunoglobulin class switching and affinity maturation, as well as impaired generation of B memory cells. CD40L and CD40 deficiencies One of the key steps in the process of immunoglobulin class switching is the interaction of CD40 on the surface of B cells with the activation-induced CD40 ligand (CD40L) protein on the surface of CD4 lymphocytes. Failure at this point may be caused by muta- tions in the CD40 ligand gene or the CD40 gene, which result in X- linked and autosomal recessive hyper IgM syndromes, respectively. CD40L deficiency can be diagnosed by demonstrating the absence of this protein on the surface of in vitro activated T cells by flow cytometry and confirmed by screening the CD40LG gene for mu- tations. Boys with defects in CD40L suffer from recurrent bacterial infections typical of antibody deficiency. However, they also suffer from opportunistic infections characteristic of T-cell deficiency such as Pneumocystis jirovecii pneumonia (around one-third present this way), cryptosporidiosis, toxoplasmosis, and nontuberculous mycobacterial infection. These opportunistic infections can be ex- plained on the basis that CD40L on activated T cells is also involved in the activation of macrophages and dendritic cells. Many patients with CD40L deficiency develop progressive liver damage (sclerosing cholangitis), probably as a result of cryptosporidial infection of the bile ducts.

Recurrent or persistent neutropenia and thrombocyto- penia occur in over one-half of patients with CD40L deficiency. NEMO deficiency Hypomorphic mutations of the gene encoding the NFκB essen- tial modulator (NEMO, IKBKG), a component of the NFκB acti- vation pathway which is required for the B-cell activation process (including signal transduction following CD40/CD40L interaction), causes a further rare form of X-linked combined immunodeficiency. This may present as hyper IgM syndrome, but there is usually strong clinical evidence of combined immunodeficiency, such as oppor- tunistic infections (pneumocystis, mycobacteria) and sometimes inflammatory bowel disease. Signalling via NF-κB is also essential for ectodermal development and many (but not all) patients with NEMO defects have ectodermal dysplasia characterized by dental hypoplasia, reduced sweating, and hypoplastic hair. Autosomal dominant activating mutations in the related gene NFKBIA can cause a similar phenotype. DNA editing enzyme mutations Defects in the DNA editing enzymes activation-induced cytidine deaminase (AICDA) and uracil-DNA glycosylase (UNG) interfere

 directly with the class-switching process to cause hyper IgM syn- drome and are the only pure B-cell defects currently known to cause hyper IgM syndrome. Homozygous mutation in the PMS2 compo- nent of the DNA mismatch repair machinery was identified as a rare cause of defective immunoglobulin class switching, resulting in low levels of serum IgG and IgA. PI3Kinase δ mutations Recently an activating heterozygous mutation in PI3Kinase δ was found to be responsible for about 10% of cases of hyper IgM syn- drome unexplained by one of the genetic defects just described. Clinically, this is characterized by recurrent respiratory infection with progressive lung damage, susceptibility to B-cell lymphoma, nodular lymphoproliferation, and increased susceptibility to herpes viral infections. Laboratory evaluation reveals IgG2 subclass defi- ciency, normal or modestly elevated serum IgM levels, impaired specific antibody responses to bacterial capsular polysaccharides, and skewing of CD8+ T cells towards differentiation and senes- cence. Heterozygous splicing mutations in the PIK3R1 gene cause a similar syndrome. Immunoglobulin replacement therapy is required for patients with all forms of hyper IgM syndrome. Patients with CD40L defi- ciency require prophylaxis for Pneumocystis jirovecii pneumonia and precautions to prevent cryptosporidial infection, including boiling drinking water. Because of the high risk of developing severe liver disease, haemopoietic stem cell transplantation has been used to treat CD40L deficiency diagnosed in infancy but this practice is by no means universal. X-linked lymphoproliferative syndromes Males with type I X-linked lymphoproliferative disease (XLP1), also called Duncan’s disease, have a mutation in an adaptor pro- tein called SAP (surface lymphocyte activation molecule associated protein). This regulates the activation of T lymphocytes and NK cells, and is particularly important in defence against herpes virus infections. Patients with XLP1 have defective NK and CD8 T-cell cytotoxicity towards Epstein–Barr virus-(EBV-)infected B cells and reduced numbers of certain innate-like T cells known as natural killer T (NKT) cells. The persistence of virally infected cells together with ineffective responses by dysregulated CD8+ T cells drives the immunopathology of this condition. Most patients present with severe infectious mononucleosis with a high mortality (80%), usually caused by a hepatic necrosis induced by activated cytotoxic (CD8) T cells. Other consequences of EBV infec- tion in these patients include haemophagocytic lymphohistiocytosis, aplastic anaemia, the development of B-cell non-Hodgkin’s lymphoma, and/or progressive dysgammaglobulinaemia. The out- look of EBV-infected patients is poor, with most dying in childhood unless treated with stem cell transplantation. Mutations in the gene XIAP which encodes for the protein X-linked inhibitor of apoptosis causes a second form of X- linked lymphoproliferative syndrome. Similar to

XLP1, EBV- triggered haemophagocytic lymphohistiocytosis (HLH), and hypogammaglobulinaemia are major features, but XLP2 is distinguished clinically by frequent splenomegaly, occurrence of colitis, and lack of lymphomatous transformation. Flow cytometric testing can reveal lack of SAP or XIAP expression and has become an important screen in males with severe EBV- related disease. Thymic defects Hemizygous deletion of chromosome 22q11 (del22q11.2) causes a complex syndrome including cardiac malformation, thymic hypoplasia, palatal abnormalities with associated velopharyngeal dysfunction, hypoparathyroidism, and facial dysmorphism, known as DiGeorge syndrome or thymic aplasia (OMIM 188400). 22q deletion has an incidence of about 1 in 2500 live births, but the clinical phenotype is highly variable. Some patients with 22q deletion have normal thymic development (and hence normal T-cell mediated immunity) but have cardiac, pharyngeal, and a var- iety of other defects associated with the velocardiofacial (VCF) or Shprintzen syndrome (OMIM 192430). These abnormalities arise from defective development of the third and fourth branchial arches during fetal development. Only about 20% of those with 22q deletion show evidence of re- duced number and function of T cells. The degree of T lymphopenia is modest in most affected infants, and a near normal repertoire and the function of T cells is acquired by 2 years of age; infections char- acteristic of T-cell deficiency are therefore uncommon. A minority (<1%) exhibit profound T lymphopenia (CD3 count <0.5 × 109/litre) and manifest a SCID-like phenotype, with opportunistic infections (‘complete’ DiGeorge syndrome). Such patients have been treated with HLA-matched stem cell transplants or thymic transplants with variable success. The diagnosis of 22q deletion should be considered in any child with congenital heart disease, velopharyngeal abnormalities, or neo- natal hypocalcaemia. The 22q deletion that is seen in 95% of patients with DiGeorge/velocardiofacial syndrome can be readily detected by cytogenetic studies employing fluorescent in-situ hybridization. In most (96%) affected individuals the 22q deletion is de novo and in the remaining 4% it is inherited from a parent. There is exten- sive phenotypic overlap between 22q11 deletion and CHARGE syndrome, the latter often resulting from heterozygous mutations in CHD7. TBOX 1 (TBX1) is a gene which maps to the centre of the DiGeorge syndrome chromosomal region on 22q11.2. It is one member of the so-called TBOX genes, which are transcription factors involved in the regulation of developmental processes. TBX1 mutations have been identified in patients with the clinical phenotypes that are seen in the del22q11.2 syndrome, including abnormal facies, cardiac de- fects, thymic hypoplasia, velopharyngeal defects, and hypoparathyr- oidism. This suggests that haploinsufficiency of the TBX1 gene may be responsible for significant components of the phenotype of the 22q deletion syndrome. DNA repair defects associated with immunodeficiency Ataxia telangiectasia Cerebellar ataxia, oculocutaneous telangiectasia, growth retard- ation, variable immunodeficiency, and autosomal recessive in- heritance are typical features of ataxia telangiectasia (OMIM 208900). Affected individuals exhibit increased sensitivity to ion- izing radiation and radiomimetic drugs, and 80% of patients show increased susceptibility to malignancy, especially leukaemias and lymphomas. IgA deficiency, with or without IgG subclass

 deficiency, and defective responses to bacterial capsular polysac- charides are common. Patients therefore often develop recurrent sinopulmonary infections. Lymphopenia and impaired T-cell function may also be detected. Chromosomal translocations cor- responding to the locations of immunoglobulin heavy chain and T-cell receptor loci are commonly detected in T cells of ataxia tel- angiectasia patients. The product of the affected gene, ATM, is required for detecting double-stranded breaks in DNA prior to their repair. This explains the radiation sensitivity, abnormal immune cell development and function, and the cytogenic

abnormalities that are frequently detected in ataxia telangiectasia. Some 95% of affected individuals have elevations in serum α-fetoprotein, which is helpful for diagnosis. There is unfortunately no specific treatment for this condition and most patients die by the third decade of lymphoreticular malignancy or complications of neurological disease. Other DNA repair defects associated with immunodeficiency Several other, rare defects in the process of nonhomologous DNA double-strand break repair cause similar syndromes of immuno- deficiency, genetic instability including sensitivity to ionizing ra- diation, and neurodevelopmental delay. The Nijmegen breakage syndrome (OMIM 251260) is caused by mutation of the NBN gene encoding a protein that acts as a substrate for ATM and which is also critical for sensing damage to DNA. Both Nijmegen Breakage Syndrome and DNA-ligase 4 deficiency (OMIM 601837), which also causes defective DNA repair, result in growth retard- ation with disproportionate microcephaly and immunodeficiency. Cernunnos deficiency is a related disorder caused by mutations of NHEJ1. Mutation of the MRE11A gene, which encodes for another component of the DNA damage-sensing machinery, causes a syndrome similar to ataxia telangiectasia (OMIM 604391), but without mutations in the ATM gene. Autosomal dominant hyper IgE syndrome Autosomal dominant hyper IgE syndrome (OMIM 147060) is a condition characterized by recurrent bacterial (S. aureus, Gram- negative bacteria) and fungal infections of skin, lymph nodes, lungs, bones, and joints; dermatitis; facial dysmorphic features; delayed shedding of primary dentition connective tissue defects, especially cardiovascular (aneurysms); and osteopenia. These patients have elevated serum IgE, levels, eosinophilia, and impaired acute-phase responses during infections. Patients with this disorder have heterozygous mutations in the gene encoding the signal transducing protein STAT3. These mutant proteins reduce the DNA binding of the phosphorylated STAT3 dimer in response to interferon-α, IL-10, and IL-6. This results in a combination of functional cytokine defects: reduced response to IL-6 explains the defective acute-phase response, and the defective response to IL-10 explains the overproduction of IgE. STAT3 is es- sential for the generation of T-helper 17 cells, which produce the cytokines IL-17 and IL-22 that are required for the secretion of the bactericidal peptides called β-defensins by epithelial cells of the skin and lungs, as well as for neutrophil mobilization and recruit- ment to the sites of infection. This may in part explain the increased incidence of severe bacterial and fungal sepsis, especially involving the lungs. Primary immune deficiencies— predominantly antibody deficiencies Antibody deficiency diseases are characterized by a decrease in the levels of serum immunoglobulins to below the fifth centile for age. The reduction may be in all classes of immunoglobulins or a single isotype. Clinical features associated with antibody deficiency are summarized in Table 4.4.4. Disorders causing antibody deficiencies Common variable immune deficiency (CVID) Patients with CVID are a heterogenous group, the diagnosis being based on the exclusion of other known causes of antibody deficiency. CVID is the commonest primary immunodeficiency disease with an estimated incidence of 1 in 10 000 to 1 in 50 000. It affects both sexes equally and can present at any age, although the modal presentation is in the second or third decade of life. The underlying molecular defect in most CVID patients is unknown, although the number of single-gene defects identified is increasing with the application of next generation sequencing methodologies (see next), and 10–15% of cases can be attributed to a specific molecular defect involved in B-cell maturation and differentiation. Many cases are sporadic while others are familial, with autosomal recessive or dominant modes of inheritance. There is clinical variation within affected pedigrees, with the phenotype ranging from selective IgA deficiency to CVID. These defects are summarized in Table 4.4.2. Suspected antibody deficiency should be confirmed with: 1. Measurement of serum IgG, IgA, IgE, and IgM (IgG subclasses (see section discussing IgG subclass deficiency, next)) and com- parison with age-specific normal ranges

to determine if these levels are below the fifth centile. 2. Serum protein electrophoresis and, if required, immunofixation for the exclusion of paraproteinaemia, with the possibility of malignancies of the B-cell system (myelomatosis or B-cell non- Hodgkin's lymphoma) excluded by appropriate investigations. 3. Response to immunization with T-cell dependent (tetanus toxoid, haemophilus B conjugate) and T-cell independent (poly- valent Pneumococcal polysaccharide, if >2 years of age) vaccines should be assessed. Diagnosis and differential diagnosis As with other major immunodeficiencies, diagnostic criteria for CVID have been agreed by a consortium of European and American immunologists (Box 4.4.1). The condition is a clinically defined syndrome characterized by susceptibility to infection accompanied by a reduction of serum IgG below the fifth centile for age, and with evidence of impaired specific antibody production in response to natural microbial exposure or vaccination. Serum IgA is reduced in most patients with CVID, while IgM is often but not invariably re- duced. Since CVID is a diagnosis of exclusion, patients with normal or elevated serum IgM should be evaluated for hyper IgM syn- dromes, and X-linked agammaglobulinaemia should be excluded in male patients with antibody deficiency and B lymphopenia. It is also essential to exclude secondary causes of antibody deficiency (Table 4.4.3). The clinical features of antibody deficiency are sum- marized in Box 4.4.2.

 X-linked agammaglobulinaemia This is caused by a defect in a cytoplasmic tyrosine kinase desig- nated Bruton's tyrosine kinase (BTK), which results in the arrest of B-cell maturation at the pre-B-cell stage. As a consequence, there is peripheral B lymphopenia associated with profound antibody de- ficiency. The gene for BTK is encoded on the X chromosome and affected males usually develop recurrent infections typical of anti- body deficiency, commencing at around 6 months of age when ma- ternal immunoglobulin has been catabolized. They may also fail to handle certain viral diseases (notably enteroviral encephalitis) and enteric infections (e.g. giardiasis) for reasons that are incompletely understood. Characteristic diagnostic features include profound reduction of all immunoglobulin isotypes (below the fifth centile for age) and absence of isohaemagglutinins and responses to childhood vaccines. Numbers and function of T lymphocytes are normal. Demonstration of the absence of BTK protein in monocytes or platelets by flow cytometry or Western blotting, or a demonstration of a pathogenic mutation in the BTK gene, confirm the diagnosis but are not essential. Patients with X-linked agammaglobulinaemia do not develop systemic granulomatous disease, as is seen in CVID. In female car- riers the chromosome carrying the BTK mutation is preferentially lyonized during B-cell development. During the characterization of the BTK gene defect it has been recognized that the clinical pheno- type may vary, even within the same family. Some affected males may therefore present at a later age and the condition should be con- sidered in all males with antibody deficiency, especially in the pres- ence of B lymphopenia. The outlook is good provided X-linked agammaglobulinaemia is diagnosed early, before organ damage is evident, and patients are treated with optimum immunoglobulin replacement therapy and antibiotics as required. Autosomal recessive antibody deficiencies with B lymphopenia Seven autosomal recessive gene defects have been identified as resulting in antibody deficiency associated with severe B lymphopenia. These are mutations in the μ heavy chain gene (IGHM), the gene encoding the surrogate light chain which is util- ized by the pre-B-cell receptors (IGLL1), and signalling compo- nents of the B-cell receptor complex, namely Igα and Igβ (CD79A and CD79B, respectively) and the signal transducing/scaffold pro- tein called B-cell linker protein (BLNK). A homozygous truncating variant in the PIK3R1 gene also causes hypogammaglobulinaemia Box 4.4.1 European Society of Immunodeficiency diagnostic criteria for CVID Probable Male or female patient who has a marked decrease of IgG (at least 2 SD

below the mean for age) and a marked decrease in at least one of the isotypes IgM or IgA, and fulfils all of the following criteria: 1 Onset of immunodeficiency at greater than 2 years of age 2 Absent isohaemagglutinins and/or poor response to vaccines 3 Defined causes of hypogammaglobulinemia have been excluded Possible Male or female patient who has a marked decrease (at least 2 SD below the mean for age) in at least one of the major isotypes (IgM, IgG, and IgA) and fulfils all of the following criteria: 1 Onset of immunodeficiency at greater than 2 years of age 2 Absent isohaemagglutinins and/or poor response to vaccines 3 Defined causes of hypogammaglobulinemia have been excluded Box 4.4.2 Clinical features associated with antibody deficiency 1 Recurrent infections caused by encapsulated bacteria, for example Streptococcus pneumoniae or Haemophilus influenzae type B (HIB). Sites involved are the upper and lower respiratory tract, middle ear, meninges, bones, and joints. Most patients with antibody deficiency suffer from repeated sinopulmonary infections which eventually result in structural damage, and bronchiectasis is the most important cause of morbidity in these patients. Nontypeable Haemophilus influenzae commonly cause exacerbations of sinopulmonary infections. Less common respiratory pathogens in patients with antibody deficiency include S. aureus and Gram-negative bacteria such as Pseudomonas spp. Infections by fungi, intracellular bacteria (e.g. mycobacteria) or parasites are not usually a problem in these patients. 2 Viral infections are generally not a problem in pure antibody deficiency diseases, except for the rare occurrence of enteroviral infections. ECHO viruses or Coxsakie viruses can cause meningoencephalitis or dermatomyositis-like conditions. Poliomyelitis associated with oral polio vaccine has been rarely reported in patients with antibody deficiency. 3 Arthritis has been reported in a few patients. This may be septic caused by HIB, S. pneumoniae, or mycoplasma/ureaplasma, or aseptic, re- sembling seronegative rheumatoid arthritis. 4 Diarrhoea and malabsorption may occur due to chronic infection with intestinal pathogens including giardia, campylobacter, salmon- ella, or cryptosporidium, or as a consequence of bacterial overgrowth in the small intestine. Chronic diarrhoea is often associated with a mild colitis and a minority may have Crohn’s-like inflammatory bowel disease with ileitis and occasional strictures. A few patients may have intestinal villous atrophy with a nonspecific inflammatory infiltrate of the mucosa and submucosa, and a minority of these will respond to a gluten-free diet, although antibody-based screening tests for coeliac disease will be negative. In common variable immunodeficiency (CVID) the following features may be seen 5 Intestinal villous atrophy in CVID is often caused by chronic norovirus genotype 2 infection. Patients with antibody deficiency associated with this condition may have nodular submucous lymphoid hyper- plasia throughout the small intestine and occasionally the large intes- tine. This is usually clinically silent, although occasionally these lesions may bleed or cause obstruction. 6 Granulomatous lesions occurring in the lungs giving rise to a sarcoid- like condition with impaired gas transfer and secondary fibrosis. They may also affect other organs such as the liver, spleen, kidneys, or lymph nodes. The aetiology of this condition is unknown. 7 Autoimmune disorders are seen in approximately one-fifth of patients with CVID. These include autoimmune haematological disorders such as haemolytic anaemia, autoimmune thrombocytopenia, and pernicious anaemia, or neurological diseases such as Guillain–Barré syndrome, autoimmune endocrinopathies (e.g. thyroid disease), and (rarely) a lupus-like syndrome. 8 Splenomegaly can be seen in up to 30% of patients with CVID; in many this is due to infiltration with sarcoid-like granulomata. 9 Malignancies: there is an increased incidence of non-Hodgkin’s lymphomas and gastric neoplasms in patients with CVID. The inci- dence of gastric carcinoma may be related to atrophic gastritis and Helicobacter pylori infection.

4.4 Immunodeficiency 359 with severe B lymphopenia. Heterozygous Ikaros deficiency (IKZF1) and autosomal recessive hypomorphic mutations in SLC39A7 (ZIP7) were also recently linked to absent B cells. All these conditions are rare and share many clinical features with X- linked agammaglobulinaemia and CVID. Physiological antibody deficiencies During the last trimester of pregnancy, maternal IgG is actively transported across the placenta to the fetus. At full term, neonates are born with IgG levels approximating to or even higher than the adult normal range. In contrast, preterm babies are relatively IgG deficient at birth, to a degree that correlates with the degree of pre- maturity. Maternally derived immunoglobulins are metabolized after birth and the IgG levels reach a nadir around 4 to 6 months of age. Serum IgG levels begin to rise after this due to increase in synthesis by the neonate, and reach approximately 70% of adult levels by 12 months. During the first 6 months of life, therefore, the neonate is protected by maternally transferred immunoglobulins. Protection by maternal antibody explains why many children with inherited antibody deficiencies do not develop infections until 4 to 6 months of age. Human infants, including preterm babies, have normal antibody responses to protein and protein-polysaccharide conjugate vaccines (e.g. Haemophilus B conjugate vaccine), hence primary immun- ization can start at 2 months of age. In contrast, children less than 2 years of age are unable to produce effective antibody responses to bacterial capsular polysaccharides. Antipolysaccharide antibody responses progressively mature after 2 years of age and it may take up to 5 to 7 years before the responses are quantitatively and qualita- tively equivalent to those of adults. Transient hypogammaglobulinaemia of infancy In some infants there is a delay in the onset of de novo immuno- globulin synthesis and as a result serum IgG levels show a pro- longed trough lasting up to 18 to 36 months of age. These infants can be differentiated from patients with primary antibody defi- ciency by their capacity to respond to immunization with T-cell dependent vaccines (tetanus, Haemophilus b conjugate vaccine) and their ability to produce blood group isohaemagglutinins. No treatment is required if affected infants are asymptomatic, but antibiotic prophylaxis is warranted if there are severe or recurrent bacterial infections. Replacement immunoglobulin is only very rarely required. Although this is a self-limiting disorder, infants should be followed up until immunoglobulin levels are normal to differentiate them from children with primary immunodeficiency disease. Selective antibody deficiency with normal immunoglobulins Some individuals with recurrent respiratory tract infections fail to respond to specific microbial antigens. The most common de- fect is an inability to respond to bacterial capsular polysaccharides that lasts beyond early childhood. Protein antibody responses are characteristically preserved. The prevalence of this condition is not known. Although most such individuals are asymptomatic, some develop recurrent sinopulmonary infections. The diagnosis is established by demonstrating normal IgG and IgM levels, accompanied by a failure to respond to immunization with some antigens, but with normal responses to others. Tetanus and the Haemophilus b (Hib) conjugate vaccine can be used to assess T-cell dependent responses. Measurement of serotype-specific re- sponses to the pneumococcal polysaccharide vaccine (Pneumovax) is used to assess thymus-independent antibody responses. Pneumococcal conjugate vaccine stimulates T-cell dependent anti- body responses. In countries employing routine immunization of infants with the conjugate pneumococcal polysaccharide vaccine, antibody responses to five or more serotypes contained only within the polyvalent pneumococcal polysaccharide vaccine need to be as- sessed. Such serotype-specific pneumococcal antibody assays need to be calibrated with an international reference standard (Food and Drug Administration SF 89) and the patient’s serum preabsorbed with C-polysaccharide shared by all pneumococcal strains and 22F polysaccharide, which is cross-reactive. Interpretation of pneumococcal antibody responses is difficult because of the lack of age-

specific normal ranges. Furthermore, even healthy individuals may show reduced responses to individual serotypes. Pure polysaccharides are poor immunogens in infants less than 2 years of age, but response to at least 50% of the serotypes tested is the norm between 2 and 5 years, while normal adults re- spond to about 70% of the capsular polysaccharides when immun- ized with the pneumococcal polysaccharide vaccine. Haemophilus b and pneumococcal conjugate vaccines are powerful immunogens, and failure to respond to a full course of these vaccines should raise the suspicion of a defect of antibody production. A consensus group in the United States of America has published provisional criteria for interpreting postimmunization responses to pneumococcal polysaccharide vaccines, defining a normal response as achieving an antibody level of at least 1.3 µg/ml against each serotype, or a greater than fourfold increase over baseline values, although the evidence base for such diagnostic consensus criteria are limited. Patients with selective polysaccharide antibody deficiency respond to and may benefit from conjugate vaccines. Antibiotic prophylaxis is sufficient for the management of most infection-prone patients with selective antibody deficiency. A few patients failing these meas- ures may need a trial of immunoglobulin replacement therapy. Antibody deficiency associated with thymoma Antibody deficiency is an uncommon complication of thymoma, known as Good's syndrome. The presenting feature may be oppor- tunistic infections, including recurrent bacterial infections, and autoimmune neutropenia, haemolytic anaemia, and red cell aplasia may occur. Laboratory findings are complete absence of or very low numbers of B cells, and low serum IgG and IgM antibody levels. Plain radiographs may miss a thymoma and a CT scan of the chest may be required. These tumours can be locally invasive and thym- ectomy is recommended, although the immunodeficiency is not re- versed by this procedure. IgA deficiency This condition has an approximate incidence of 1 in 700 in white persons. It is rare in Africans and Japanese. Most individuals remain healthy, but long-term prospective studies indicate that a few de- velop recurrent sinopulmonary infections. Most infection-prone patients have concomitant IgG2 subclass deficiency and a selective inability to respond to pure capsular polysaccharides. IgA deficiency is associated with an increased incidence of atopy, coeliac disease, and a range of autoimmune diseases including

 arthritis, a lupus-like syndrome, autoimmune endocrinopathies, and autoimmune cytopenias. Individuals with complete IgA defi- ciency (serum levels less than 0.07 g/litre) are at risk of developing anti-IgA antibodies on receiving blood products, and such patients are at risk of transfusion reactions following the administration of subsequent blood or its fractions. IgA deficiency can coexist in families with other members affected by CVID. Mutations in TNFRSF13B (which encodes the transmem- brane activator and CAML interactor protein, TACI) can cause IgA deficiency in some family members, while others develop CVID. IgG subclass deficiency Serum IgG is comprised of four subclasses—IgG1, -2, -3, and -4— in order of the relative abundance of these isotypes in the serum. IgG subclass deficiency is diagnosed when there is a reduction in the serum IgG subclass concentration two standard deviations below the normal value for age, despite the total IgG level being normal. CVID is more likely if the total IgG level is reduced. The lack of an internationally accepted reference preparation makes IgG sub- class assays difficult to standardize. Furthermore, there are genetic variations that influence IgG subclass levels among different ethnic groups, and age- and population-related normal bounds are not always available. Functional assessment of antibody production through vaccine challenge is therefore often used to determine the clinical significance of low IgG subclass levels. As with IgA deficiency, many individuals with IgG subclass de- ficiency are asymptomatic, although some are prone to recurrent sinopulmonary and other infections. Most with

sinopulmonary infec- tions exhibit impaired capacity to mount specific antipolysaccharide antibodies against antigens like the pneumococcal capsule. This is most often seen in individuals with IgG2 deficiency, with or without concomitant IgA deficiency. Most infection-prone patients with IgG subclass deficiency can be managed with antibiotic therapy or prophylaxis. Immunoglobulin replacement should be limited to those with recurrent severe sinopulmonary infections despite antibiotic prophylaxis. Such pa- tients usually have specific antibody deficiency, especially to polysac- charides, hence (in the United Kingdom) there is a strong consensus that assessing specific antibodies is useful in determining the clinical significance of IgG subclass deficiency in infection-prone patients. Management of antibody deficiency: Immunoglobulin replacement therapy Immunoglobulin replacement therapy through the intravenous (IVIG) or subcutaneous (SCIG) routes is the mainstay of therapy for antibody deficiency. Different products are licensed for IVIG and SCIG therapy, and these are not interchangeable. IVIG and SCIG have been shown to be equivalent in terms of safety and ef- ficacy. All licensed immunoglobulin products have similar efficacy, safety, and tolerability, hence product selection depends on avail- ability. However, once patients are stabilized on one preparation, this should not be changed except for sound medical reasons. Several methods for delivering immunoglobulin have been de- veloped. Intravenous immunoglobulin is generally administered every 3 weeks. SCIG is traditionally infused once or twice a week, using a small infusion pump. It can also be delivered by adminis- tering a fractionated daily dose by a slow subcutaneous push using a syringe and needle. Recently, an immunoglobulin replacement product, to be used by subcutaneous infusion facilitated by a pre- ceding hyaluronidase infusion, has been licensed. This product enables the whole monthly dose to be infused subcutaneously, al- lowing subcutaneous therapy to be infused at 3–4 weekly intervals. With adequate training and regular supervision, most patients can administer immunoglobulin replacement therapy at home. Current practices of prescreening donors and multiple antiviral steps employed by manufacturers have eliminated the risk of trans- mission of HIV and hepatitis B and C. Rare hepatitis C outbreaks occurred in the 1990s before the current multistage viral inactiva- tion steps were introduced. Creutzfeldt–Jakob disease (classical and new variant) could theoretically by transmitted by immunoglobulin therapy, but the risk has been estimated to be exceedingly low. Adequacy of replacement therapy is judged by clinical well- being (freedom from infections and prevention of their complica- tions) and preinfusion (trough) levels in the middle of the normal range (approximately 8 g/litre). Based on these criteria, replacement therapy needs to be individualized for each patient by altering the dose or frequency of administration. Dosage of immunoglobulin replacement therapy Recent publications have addressed the appropriate dosage of im- munoglobulin replacement therapy in patients with primary anti- body deficiency. One study analysed data from patients with CVID collected over 20 years and showed that the range of trough IgG levels preventing breakthrough infection in individual patients ranged from 5 to 17 g/litre, with the doses of immunoglobulin re- quired to prevent infection ranging from 0.2 to 1.2 g/kg per month. A meta-analysis of published literature provided evidence that the incidence of pneumonia can be progressively reduced by immuno- globulin replacement therapy in patients with primary antibody de- ficiency by achieving higher IgG trough levels. The goal of treatment should therefore be to reduce breakthrough infection rather than to achieve a particular trough IgG level, with individual tailoring of dosage of immunoglobulin replacement therapy. Typical dosage for immunoglobulin replacement therapy are shown in Box 4.4.3. Adverse effects of immunoglobulin replacement therapy About 10% of patients experience mild reactions during or imme- diately after IVIG therapy, including headaches, malaise, backache, nausea, and myalgia. These can usually be overcome by a combin- ation of reducing the infusion rate, antihistamines,

and antipyretics. Anaphylactic reactions requiring cessation of therapy and adren- aline (epinephrine) are rare, but commoner during the first few in- fusions or in the presence of intercurrent infections. These can be almost eliminated by administration of the initial infusion at a slow rate and postponing IVIG therapy until infections have resolved on antibiotic therapy. Rarely, anaphylactic reactions may be due to pa- tients with severe IgA deficiency (serum levels less than 0.07 g/litre) producing anti-IgA antibodies. Box 4.4.3 Dosage of immunoglobulin replacement therapy • IVIG—from 400 to 1200 mg/kg every 4 weeks. • SCIG—from 100 to 300 mg/kg once a week, or half the dose adminis- tered twice a week; alternatively, a fractionated daily dose is delivered by slow subcutaneous push.

4.4 Immunodeficiency 361 Acute kidney injury and thromboembolic disease have also been occasionally reported, especially following high-dose IVIG therapy. Premedication with paracetamol, antihistamines, and/or hydro- cortisone, or changing the immunoglobulin product, often help in patients who develop repeated adverse reactions. Apart from local pain and swelling, adverse reactions are rare with SCIG therapy. Switching to SCIG may be an option for patients who fail to tolerate IVIG. Supplementary management of antibody deficiency Breakthrough infections can occur, even with optimum immuno- globulin replacement therapy. There should be a low threshold for treating infections with antibiotics and recurrent infections, especially when associated with structural lung damage, may re- quire long-term antibiotic prophylaxis. Amoxicillin, co-amoxiclav, clarithromycin, azithromycin, doxicycline, and ciprofloxacin are useful agents for prophylaxis. Postural drainage of lung secretions and appropriate treatment of concomitant bronchial asthma is important. A subset of patients with common variable immunodeficiency (CVID) develops granulomatous and lymphocytic interstitial lung disease (GLILD), a restrictive lung disease associated with early mortality. The optimal therapy for this condition is uncer- tain, but recent small studies have shown improvement with a combination of rituximab (monoclonal antibody to CD20) with azathioprine. Patients with serious lung disease, gastrointestinal disease, or impaired liver function should be managed with multidisciplinary input from relevant organ-based specialists. Patients should be encouraged to join support groups for education and counselling as well as practical help with social problems. Referral for genetic counselling should be considered in patients with a familial disorder or a known gene defect. Prognosis Prospective studies have shown that optimal immunoglobulin re- placement therapy decreases the frequency of infections and re- duces the incidence of sepsis, especially by encapsulated bacteria. Recipients are likely to have a normal lifespan if this is instituted before structural lung damage is established. However, long-term studies in Italy have demonstrated that some patients with X-linked agammaglobulinaemia may continue to develop lung damage des- pite optimum immunoglobulin replacement therapy. The cause for this is unclear. CVID patients with systemic granulomatous disease or interstitial lung disease exhibit reduced survival com- pared to those without these complications. The occurrence of non- Hodgkin’s lymphoma (2–7%) and gastric carcinoma (approximately 1%) reduce survival. Diseases of immune dysregulation Complex regulatory mechanisms ensure that innate and adaptive immune responses are held in check within the healthy immune system. Their importance is revealed by a series of distinct pheno- types in which prominent immune dysregulation predominates over susceptibility to infection. Haemophagocytic lymphohistiocytosis (HLH) HLH describes a life-threatening systemic illness in which exces- sive but ineffective immune activation leads to a stereotyped pat- tern of fever, splenomegaly, and laboratory abnormalities including cytopenias and hyperferritinaemia. The Histiocyte Society has pro- posed a consensus set of diagnostic criteria to assist in the prompt recognition of HLH, which is a medical emergency. Both

congenital (‘primary’) and acquired (‘secondary’) forms are recognized, al- though genetic factors are likely to contribute to both. Familial HLH is a set of autosomal recessive diseases that are as- sociated with a failure of cytotoxicity. The onset may be triggered by infection. Many of the cases are caused by mutations in the perforin gene, the genes Munc13-4 and 18-2, and in syntaxin 11 or its binding protein. Others are associated with partial oculocutaneous albinism (Chédiak–Higashi syndrome, Griscelli syndrome, Hermansky– Pudlak syndrome), but there remain some patients for whom no underlying genetic diagnosis can be found. HLH may also be a presenting feature of other forms of im- munodeficiency, particularly those that predispose to severe EBV infection (XLP1, XIAP deficiency (see section on X-linked lymphoproliferative syndromes); ITK deficiency, CD27 deficiency), but also others such as class II MHC deficiency. Secondary HLH is a macrophage activation syndrome with haemophagocytosis as a result of immunological activation trig- gered by a variety of conditions including infection, rheumatoid dis- orders, malignancies, and metabolic disorders. Familial HLH is fatal without curative therapy. Survival and cure depend on initial and continuation therapy to control HLH followed by early HSCT, preferably while in remission. First-line treatment consists of a regimen containing steroids, ciclosporin, etoposide +/– intrathecal methotrexate. In patients who fail to respond or relapse, salvage therapy may be attempted using T-cell directed biologics. Similar approaches are required for patients with most other forms of immune deficiency presenting as HLH. Patients with secondary HLH may also need active management at first as not all cases resolve spontaneously. Treatment may then need to be adapted depending upon the underlying cause of the disease. Syndromes with autoimmunity Autoimmune lymphoproliferative syndrome (ALPS) An increasing number of monogenic disorders are being rec- ognized as causing autoimmunity, often in association with lymphoproliferation. Nomenclature is somewhat confusing as the term ‘autoimmune lymphoproliferative syndrome’ (ALPS) is re- served for a particular subset of disorders, most of which result from impaired lymphocyte apoptosis. Consensus diagnostic criteria for ALPS require both clinical evidence of lymphoproliferation (spleno- megaly, lymphadenopathy) and an excess of CD4-CD8-TCRαβ+ T lymphocytes. Cytopenias are the commonest manifestation of autoimmunity, but others including a lupus-like picture can be seen. Susceptibility to infection is part of the primary picture in some dis- orders. The most frequent molecular lesion, heterozygous germline mutation of FAS, is incompletely penetrant and there is some evi- dence that a ‘second hit’ is required to produce disease. Nonetheless, a highly significant (up to 250-fold) increase in lymphoma inci- dence has been documented and affects asymptomatic carriers as well as individuals with clinical ALPS. Sirolimus can be an effective

 steroid-sparing agent, while combinations of high-dose IV im- munoglobulin and rituximab may help to relieve cytopenias. Immunodysregulation, polyendocrinopathy, enteropathy, X-linked (IPEX) IPEX is a severe disorder in which the function of regulatory T cells (Treg) is impaired by mutations in FOXP3. This gene encodes a tran- scription factor that is critical to Treg differentiation and activity. Affected boys often present with neonatal diabetes along with ex- tremely severe autoimmune enteropathy, eczema, and a variety of other autoimmune phenomena such as cytopenias. Laboratory evalu- ation may show impaired expression of FOXP3 by cells destined to become Tregs as shown by their high levels of the high affinity IL2 receptor, CD25, and lack of the IL7 receptor, CD127. Other conditions affecting regulatory T cells Other lesions that impair Treg function may produce a similar spec- trum of autoimmunity, albeit the tempo of disease is often slower. Among these are deficiencies of CTLA4 (also known as ALPSV), LRBA and IL2RA, and gain-of-function (GOF) mutations in STAT3.

Conservative management of these disorders using immuno- suppressive medication can be extremely challenging despite the availability of agents such as sirolimus and abatacept/belatacept that target the relevant cells and pathways. Stem cell transplantation has curative potential and has become the treatment of choice for IPEX syndrome, while experience of transplantation for CTLA4 defi- ciency and STAT3 GOF continues to accumulate. Disorders affecting the IL-10 pathway Early onset, severe colitis is the major feature in disorders of the IL10 pathway, including deficiencies of IL-10 itself and either component of the IL10 receptor. Associated features may include recurrent respira- tory infection, arthritis, and lymphoma. The likelihood of a monogenic origin for inflammatory bowel disease is high among children with onset before 5 years of age and special investigations are warranted. Interferonopathies The IUIS classification places type I interferonopathies among the im- mune dysregulatory disorders. These are a heterogenous group of dis- orders characterized by inappropriate activation of type 1 interferon signalling. The phenotypic spectrum is broad, ranging from mild cu- taneous disease to severe neurological disorders, and the determin- ants of this variability are unknown. The predominant pathology is autoinflammatory in nature, with autoimmune overlap in certain types, sometimes amounting to familial lupus. The fundamental problem driving inflammation is usually inappropriate signalling via innate antiviral recognition pathways, often because of a failure to catabolize endogenous nucleic acids. Demonstration of a type I inter- feron stimulated gene signature can be diagnostically helpful in such patients. Although treatment remains challenging at the present time, early results with JAK inhibitors are encouraging. Phagocyte deficiencies Neutropenia The commonest phagocyte deficiency seen in clinical practice is neu- tropenia, which results in increased susceptibility to a broad range of pyogenic organisms and fungi. Commensal organisms including skin and intestinal bacteria often cause septicaemic illnesses in neutropenic patients. Invasive candidiasis and occasionally other fungal infections may also be seen. Neutrophils are particularly im- portant for maintaining the integrity of mucous membranes, hence inflammation of mucous membranes (e.g. ulceration of mouth and perioral tissues and perianal inflammation and excoriation) can be features of neutropenia. A neutrophil count of less than 0.5 × 109/ litre is associated with a high risk of life-threatening bacterial sepsis. Several inherited monogenic defects lead to severe congenital neutropenia as an isolated finding (e.g. ELANE, JAGN1, WAS GOF) or in conjunction with syndromic features (e.g. HAX1, SBDS). It is important to remember that neutropenia can also complicate primary immunodeficiencies of the adaptive im- mune system such as CD40L deficiency or X-linked agamma- globulinaemia. Severe congenital neutropenias may respond to granulocyte-colony-stimulating-factor therapy, but with age comes an increasing risk of myelodysplasia and transformation to acute myeloid leukaemia. Defects in bacterial killing Functional defects of neutrophils are rare. The best-characterized condition is chronic granulomatous disease, with an incidence of about 1 in 100 000 births. Neutrophils and macrophages of these pa- tients show impaired killing of ingested bacteria. This is due to faulty postphagocytic activation of the NADPH oxidase complex, the role of which is to produce superoxide (O_2^-) and generate a milieu within the phagosome that activates bactericidal enzymes cathepsin and elastase. In the X-linked form (75% of all cases) this is due to a de- fect of the 91-kD chain of the cytochrome b (gp91phox), whereas the rarer autosomal recessive form may be either due to deficiency of the 22-kD chain of cytochrome b (p22phox) or cytosolic cofactors called p47phox and p67phox, respectively. Chronic granulomatous disease typically presents with infec- tions in infancy, but inflammatory phenomena may predominate and initial presentation in adulthood is well documented. Patients typically develop infections with S. aureus or Gram-negative bac- teria (Burkholderia cepacia, Salmonella, Serratia, enteric bacteria). Invasive fungal infections (Aspergillus) can be life-threatening. Nocardia

is another pathogen seen in chronic granulomatous dis- ease. Unusual environmental bacteria of low-grade virulence may be isolated from blood and lymph nodes. Characteristic sites of in- fection include skin, lymph node or deep subcutaneous abscesses, or visceral abscesses involving liver, spleen, or lung. Oral and perioral ulceration and gingivitis are common. These patients also develop granulomas in various tissues: granulomatous obstruction of the gastrointestinal tract or the urinary tract may occur, and granuloma- tous infiltration of the lung may rarely be seen. Hepatosplenomegaly due to granulomatous involvement of these organs may also be a feature. Colitis resembling Crohn's disease is seen in approximately 15% of cases. The diagnosis is based on the inability of affected neutrophils to oxidize a dye called nitro blue tetrazolium and change it from yellow to a blue-black colour. Modifications of this principle using newer methods such as the oxidation of the fluorescent dye dihydrorhodamine, which can be detected by flow cytometry, are reliable and sensitive for establishing the diagnosis. Management consists of antimicrobial prophylaxis and prompt diagnosis and treatment of infections. Co-trimoxazole at 5 mg/kg

4.4 Immunodeficiency 363 divided into two doses per day significantly reduces bacterial infec- tions, and daily itraconazole (100 mg/day for patients <50 kg body weight or 200 mg/day for heavier individuals) reduces Aspergillus infections. US studies have shown a reduction in severe infections with prophylactic interferon-γ at 50 μg/m2, three times a week, via subcutaneous injection, but clinical experience is not clear-cut and this practice has not been widely adopted in Europe. Invasive fungal infections are difficult to treat despite the avail- ability of an expanding range of antifungals such as voriconazole and posaconazole. Granulocyte transfusions may be beneficial in those with severe, refractory infections. Steroids may also play a role, particularly for refractory visceral infection such as liver abscess, but also for chronic granulomatous inflammation, but these com- pound the existing immunodeficiency. Stem cell transplantation is becoming the standard of care based on excellent medical outcomes and improved health-related quality of life. Gene therapy has pro- duced temporary physiological and clinical improvement for a few months in a few patients, and clinical trials are ongoing. Defects in leucocyte adhesion and migration To confer protection from infection, circulating leucocytes need to migrate along chemotactic gradients across capillary endothelium into sites of infection. As a prelude to this, Lymphocyte function- associated antigen 1 (LFA1) on leucocytes needs to bind tightly to the ligand intercellular adhesion molecule 1 (ICAM-1) on activated endothelial cells. Leucocyte adhesion deficiency type 1 is caused by deficiency of CD18, which is a subunit component of three leucocyte surface re- ceptors called CD11a/CD18 (LFA1), CD11b/CD18 (complement receptor 3), and CD11c/CD18 (complement receptor 4). In leuco- cyte adhesion deficiency type 2, Sialyl-Lewis X, which is expressed on the surface of leucocytes and acts as the ligand for E selectin expressed on endothelial cells, cannot be synthesized. This is due to autosomal recessive mutation of a GDP-fucose transporter re- sulting in a failure of fucosylation of proteins within the Golgi ap- paratus. Without this interaction the initial adhesion of leucocytes to endothelial cells, a prelude to diapedesis, fails. Leucocyte ad- hesion deficiency types 1 and 2 thus exhibit impaired endothelial adherence, chemotaxis, and diapedesis of neutrophils and other leucocytes, which are held back in the circulation and cannot reach the sites of infection. Patients with leucocyte adhesion deficiency characteristically manifest delayed cord separation and periumbilical sepsis during early infancy. Other features are recurrent pyogenic infections, per- sistent marked leucocytosis (>15 × 109/litre) due to the inability of leucocytes to migrate from the bloodstream into the tissues, and poor wound healing, with the development of pyoderma-like ul- cers that may eventually heal with paper-thin scars. Pus fails to form during infections due to failure of neutrophils to enter sites of infec- tion.

These inherited disorders of neutrophil function are charac- teristically associated with gingivitis and periodontal disease, again indicating the particular importance of normal neutrophil function for the maintenance of a healthy dental/gingival interface. Patients with leucocyte adhesion deficiency type 2 have facial dysmorphism and developmental delay. Diagnosis of these conditions is by flow cytometry of blood leucocytes to detect CD18 or CD15 (Sialyl-Lewis X) deficiency, respectively. In the complete form of leucocyte adhesion deficiency type 1, and in type 2, outcome is poor with early death from sepsis. Rare patients with a partial form of type 1 and a milder phenotype may survive to adulthood. Stem cell transplantation is curative in leucocyte adhesion deficiency type 1 and should be considered early. Oral fucose supplementation can result in clinical improvement in leucocyte adhesion deficiency type 2. For leucocyte adhesion defi- ciency type 3, see Table 4.4.2. For information on rarer primary immunodeficiency diseases with impaired phagocyte function, see the sources listed in the 'Further reading' section. Defects in intrinsic and innate immunity Many disorders are now recognized as predisposing to infec- tions caused by a narrow spectrum of pathogens. Frequently this reflects the nonredundancy of pathogen-specific innate im- mune mechanisms of sensing or antimicrobial activity. These conditions may manifest as susceptibility to invasive infections caused by pyogenic bacteria, predominant susceptibility to viral infection, susceptibility to fungal infections, or susceptibility to mycobacteria. Some of these recently described defects are outlined next. Predominant susceptibility to invasive infections with pyogenic bacteria Innate immune responses to pathogens are initiated by recogni- tion of pathogen associated molecular patterns by cell surface and intracellular 'pattern recognition receptors', for example Toll-like receptors. The interleukin receptor-associated kinase-4 mediates signalling via most Toll-like receptors and members of the IL-1 re- ceptor superfamily. Individuals with homozygous mutations of the IRAK4 gene develop recurrent, life-threatening, pyogenic sepsis. They are especially susceptible to pneumococcal, S. aureus and P. aeruginosa infection. Interestingly, the incidence and severity of infections decreases by adolescence, with improvement in out- come. Mutations in the gene encoding the protein myeloid differen- tiation primary response gene 88 (MYD88), which is also required for signal transduction following Toll receptor engagement, causes a similar clinical syndrome. A combination of antibiotic prophylaxis and immunoglobulin supplementation has been advocated for chil- dren with these disorders. Predominant susceptibility to viral infection UNC93B is a protein of the endoplasmic reticulum involved in the activation of Toll-like receptors. Mutations in UNC93B results in de- fective interferon-α and -β production in response to herpes simplex and other viruses, and patients develop herpes simplex encephalitis between 3 months to 6 years of age. Heterozygous dominant-negative mutations in the gene-encoding Toll receptor 3 (TLR3) have rarely been identified in patients with herpes simplex encephalitis. TLR3 is expressed in the central ner- vous system where it helps to initiate interferon-α and -β responses to viral double-stranded DNA. TRIF, also known as TICAM1, is a Toll/IL1 receptor (TIR) domain-containing adaptor molecule, that specifically interacts with TLR3 and activates nuclear factor kappa-B (NFKB), thus inducing interferon-β production. Cells lacking tumour necrosis

 factor (TNF) receptor-associated factor 3 (TRAF3) are defective in type I interferon responses activated by several different Toll-like re- ceptors. TRIF mutations, as well as autosomal dominant–negative mutations of TRAF3, cause susceptibility to develop herpes simplex encephalitis. TANK-binding kinase 1 (TBK1) is a kinase at the crossroads of multiple type I interferon (IFN)-inducing signalling pathways. Partial TBK1 deficiency caused by heterozygous mutations in this gene also causes increased susceptibility to herpes simplex

encephalitis. Signal transduction via receptors to interferons -γ, -α, and -β in- volves the participation of the signal transducing molecule STAT1. IFNγ-R-mediated signalling results in dimerization of phosphoryl- ated STAT1 molecules, which migrate to the nucleus and induce gene transcription. Signalling via interferon-α and -β receptors involves the formation of a complex between STAT1, STAT2, and a third pro- tein called interferon stimulated gene factor 3-γ (ISGF3-γ). Complete (homozygous) defects of STAT1 result in impaired responses to interferons- γ, -α, and -β, resulting in susceptibility to disseminated mycobacterial infections, as well as severe herpes simplex virus infec- tion. Partial STAT1 deficiency, which interferes with STAT1 dimer- ization required for signal transduction via interferon-γ receptors, produces increased susceptibility to mycobacterial infections alone. In these patients the cellular responses to interferon-α and -β are in- tact, thus preserving antiviral immunity. By contrast, autosomal reces- sive deficiency of STAT2 or IFNAR produces the reciprocal phenotype by selectively impacting innate interferon signalling. Affected patients can suffer dissemination of live attenuated vaccine viruses. Another immunodeficiency characterized by susceptibility to a specific viral infection is the Warts hypogammaglobulinaemia in- fections myelokathexis (WHIM) syndrome (OMIM 193670). This is characterized by severe warts, hypogammaglobulinaemia, and neu- tropenia due to retention of neutrophils in the bone marrow. This is an immunodeficiency caused by a gain-of-function mutation in the gene encoding the CXCR4 chemokine receptor, with the mutant re- ceptors showing increased responsiveness to its ligands and leading to a failure of chemotaxis and leucocyte trafficking. Predominant susceptibility to fungal diseases. Chronic mucocutaneous candidiasis (CMC) is a syndrome consisting of recurrent and/or refractory infections of the skin, nails, and oral and genital mucosa with candida species in the absence of a recog- nized inherited or acquired T-cell immune deficiency. Recognized clinical associations of this condition are summarized in Table 4.4.7. Recent findings have helped to elucidate its pathophysiology and molecular basis. CMC is caused by conditions that result in defi- ciency of IL 17, neutralization of IL-17 by autoantibodies, or lack of response to IL-17. In approximately 50% of patients with isolated or autoimmunity-associated CMC, gain-of-function mutations in the signal transducing molecule STAT1 have been identified. This abnor- mality is associated with secondary inhibition of IL-17 production. Specific susceptibility to candida infection is a feature of another group of patients who may develop invasive candidiasis affecting the brain as well as recurrent mucocutaneous candidiasis. These patients have autosomal recessive mutations in the gene encoding the caspase recruitment domain-containing protein, CARD9, which is required for intracellular signalling downstream of Dectin-1, a pattern recognition receptor for fungal carbohydrates. Activation of this signalling pathway results in the production of proinflammatory cytokines, including IL- 1β, IL-6, and IL-23. CARD9 deficient patients also have reduced IL-17- producing T cells that also contribute to mucosal immunity. Mendelian susceptibility to mycobacterial disease (MSMD) Primary and secondary immunodeficiencies leading to severely impaired T-cell function result in increased susceptibility to myco- bacterial infections, including those caused by poorly patho- genic mycobacteria (nontuberculous mycobacteria) and bacillus Calmette–Guérin (BCG). However, a few individuals are specifically susceptible to mycobacteria, which may occur in a disseminated or fatal form in the absence of other evidence of immune deficiency. This condition has been called Mendelian susceptibility to mycobac- terial disease (OMIM 209950). Causal genetic defects Genetic analyses of affected kindreds have, to date, identified mu- tations in thirteen disease-causing genes, including two X- linked (CYBB and NEMO) and thirteen autosomal (IFNGR1, IFNGR2, STAT1 (LOF), IL12B, IL12RB1, ISG15, IRF8, TYK2, RORC, JAK1 (LOF) , SPPL2a, IL-12RB2 and IL-23R) genes. Mutations in JAK1 and RORC have been described as responsible for syndromic MSMD. MSMD-

causing genes affect IFN-γ dependent immunity, in terms of either IL-12/IL-23/ISG15-dependent induction of IFN-γ or IFN-γ induced down-stream, cellular responses (Fig. 4.4.2). Genetic lesions of dendritic cell development and function also pro- duce prominent mycobacterial susceptibility, although usually this is accompanied by other evidence of immunodeficiency. Several gene defects responsible for Mendelian Susceptibility to Mycobacterial Disease have been documented:
Table 4.4.7 Conditions associated with chronic mucocutaneous candidiasis Clinical condition Pathogenesis of CMC Autoimmune polyendocrinopathy syndrome type 1
due to mutation in AIRE Neutralizing autoantibodies to IL-17 family of cytokines and to IL-22 Thymoma Neutralizing autoantibodies to IL-17 family of cytokines Hyper IgE syndrome (STAT3 mutation) Low TH-17 cells, which produce IL17A and IL22. Hence deficiency of the cytokines IL-17A and IL-22 IL12p40 or IL-12 receptor b1 deficiency Low IL-17A-producing T cells Caspase recruitment domain 9 (CARD9) deficiency Low IL-17A-producing T cells Autosomal recessive IL-17 receptor deficiency Abolishes cellular responses to IL17-A and IL17-F homo- and heterodimers Autosomal dominant IL-17F deficiency Reduced activity of IL-17F homo- and heterodimers resulting in partial IL-17 deficiency CMC with isolated hypothyroidism Activating mutation of STAT1 gene resulting in secondary reduction of IL-17 family of cytokines

4.4 Immunodeficiency 365 Phagocytes/DC ISG15 TH1/NK TNF-α IL-12 IL-23 IL 18-R1 IL 18-R2 IL18 p35 IL 12-Rβ2 IL 12-Rβ1 IL 23R TYK-2 TYK-2 JAK-2 STAT-4 STAT-4 STAT-4 JAK-2 NK / (T) ? TNF-α IFN-γ + + + IL 12-Rβ1 IKK IKK IRF8 (GATA2) TRAF TRAF Y/NEMO y/NEMO α β p40 p40 p19 Mycobacterium CYBB gp91phox GTP MΦ p22 phox P membrane O2 O2– • NADPH NADP p67phox p40 phox Rac Phagosome CYBB Lysosome STAT-1 IL-12 IL-23 IL-18 α β IFN-γ IFN-γR2 IFN-γR1 STAT-1 JAK-1 JAK-2 p47 phox TNFα Granulocytes Type I IFN's ? TLR Fig. 4.4.2 Genetic defects predisposing to MSMD. A highly simplified diagrammatic representation of the key cytokine receptor interactions relevant for immunity against intracellular bacteria, derived from observations in gene knock-out mice. Stimulation of macrophages/dendritic cells by mycobacteria by infection and via Toll receptors results in secretion of IL-12 which acts on antigen stimulated CD4 T cells (which express IL-12 receptors). IL-12 partitions responding CD4 T cells to develop along the Th1 pathway and secrete interferon-γ. Interferon-γ homodimers activate (a) macrophages enhancing their antimicrobial pathways and (b) T cells and NK cells in an autocrine fashion, via IFN-γR1/R2 dimers. Type I cytokine deficient patients indicate the relevance of these pathways for human immunity.

366 SECTION 4 Immunological mechanisms • Recessive null mutations in the gene encoding the interferon- γ receptor (IFN-γR1) chain—these can either abolish receptor expression or their binding of interferon-γ. Dominant IFN- γR1 deficiency is due to the truncation of the intracellular do- main of the receptor chain, resulting in the accumulation of nonfunctional receptors which interfere with the function of the residual normal receptors. Recessive mutations of the gene encoding the IFN-γR2 signalling chain are responsible for com- plete or partial IFN-γR2 deficiency. • Null recessive mutations of the IL-12RBI gene encoding the IL-12 receptor chain, IL-12RβI—these abrogate the cell surface expres- sion of this chain, which is shared by IL-12 and IL-23 receptors, re- sulting in the inability to respond to the cytokines IL-12 and IL-23. Mutation of the IL-12/23 receptor-associated tyrosine kinase, Tyk 2, also results in defective signal transduction via IL-12 receptors. • Inability to produce IL-12 and IL-23, due to deletion within the gene encoding the inducible chain of IL-12 (IL12B) which is shared by IL-12 and IL-23. • Partial or complete defects in the signal transduction molecule STATI, which is required for signalling via the interferon-γ receptor. In addition, acquired

interferon-γ deficiency due to the produc- tion of neutralizing autoantibodies to this cytokine has been identi- fied in patients with disseminated mycobacterial infection. This may also result in infections caused by other intracellular pathogens such as Penicillium marneffei. These defects need to be sought by immunological and molecular methods in patients with refractory or disseminated mycobacterial infections in the absence of an underlying cause such as HIV in- fection, immunosuppressive therapy, or a recognized primary T-cell immunodeficiency.
Clinical features The severity of the clinical phenotype depends on the genotype. Patients with complete IFN-γR1 or R2 deficiencies develop dissem- inated mycobacterial infections caused by BCG or nontuberculous mycobacteria, present in early childhood, and have a high mortality. The lesions in these patients are characteristically multibacillary and associated with impaired granuloma formation. In contrast, partial IFN-γR1 deficiency, complete IL-12B defi- ciency (resulting in IL-12 and IL-23 deficiency), and IL-12/IL-23 re- ceptor deficiency are usually associated with milder mycobacterial infections presenting at a later age. The dominant form of partial STAT1 deficiency, with impaired biological responses to interferon-γ, appears to primarily affect antimycobacterial defences. In contrast, recessive, complete STAT1 deficiency with impaired responses to interferon-γ and type 1 inter- ferons leads to mycobacterial infections and to fatal herpes viral in- fections which present in infancy. In addition to this, extraintestinal or systemic relapsing infections caused by nontyphoid Salmonella species are the most common infection occurring in patients with defects in the IL-12/23 system. X-linked susceptibility to mycobacterial infection can occur due to mutations of the CYBB gene encoding the p91-phox component of the phagocyte oxidase complex. Defective NFκB activation caused by X-linked hypomorphic mu- tations of the NFκB essential modulator gene (IKBKG) compromises the function of Toll-like, IL-1, and tumour necrosis factor α (TNFα) receptors, and also increases susceptibility to severe mycobacterial infections. Patients with inherited defects in the phagocyte NADPH oxidase system are highly susceptible to Salmonella infections but exhibit only slightly increased susceptibility to mycobacteria. Autosomal recessive deficiency of interferon regulatory factor 8 (IRF8) causes a severe immunodeficiency with absent monocytes and dendritic cells, characterized by early onset disseminated BCG infection and a myeloproliferative blood picture. Autosomal dom- inant IRF8 deficiency is associated with more subtle abnormalities of the dendritic cell compartment and mycobacterial susceptibility. Monocytopenia and dendritic cell deficiency, associated with myco- bacterial, viral, and histoplasma infections, as well as susceptibility to pulmonary alveolar proteinosis and myelodysplasia, is caused by heterozygous mutations in the GATA2 gene. RORC deficiency has been identified in patients with susceptibility to both mycobacteria and candida infections. Mycobacterial infections in patients with IL-12B, IL-12B1, and dominant partial IFN-γR deficiency that are refractory to chemo- therapy may respond to interferon-γ supplementation. Interferon-γ is of no use in complete IFNγ-R1 or -R2 deficiency, where the out- come is often poor despite antimycobacterial chemotherapy, and HSCT should be considered at an early age.
Complement deficiencies Defects in the complement pathway resulting in immunodeficiency are described in Chapter 4.2. The role of genomics in primary immunodeficiency The foregoing text has highlighted significant molecular diagnostic challenges arising from the tremendous genetic heterogeneity of primary immunodeficiency, the overlapping and pleiomorphic na- ture of disease presentation, and the existence of contrasting allelic disorders with alternative mutation types. Nonetheless, correct as- certainment of genetic diagnosis can bring significant benefits for patients, based on better knowledge of disease mechanism, natural history, and inheritance model. In turn, these insights inform treat- ment selection, prediction of prognosis, and genetic counselling, respectively. Furthermore, the molecular dissection of primary im- munodeficiency

offers important scientific opportunities for im- proved understanding of the immune system in health and disease, and the potential to develop novel targeted therapies in the context of ‘precision medicine’. In this context, it is not surprising that the primary immuno- deficiency community has been quick to embrace next generation sequencing as both a clinical diagnostic and a research tool. This technology enables massively parallel sequencing of very large num- bers of DNA fragments. These can be derived from an entire genome (‘whole genome sequencing’, WGS) or enriched for regions of interest by hybridization to probes corresponding to particular disease genes (‘targeted panel’) or indeed the entire coding fraction of the genome (‘whole exome sequencing’, WES). Currently available platforms re- quire many overlapping fragments to be sequenced individually but

4.4 Immunodeficiency 367 simultaneously. The individual sequences are then aligned with the reference genome and with each other to stitch together a patchwork covering the entire region of interest. Subsequent bioinformatic ana- lysis is an increasingly streamlined process using open source or proprietary software to implement a series of filtering steps. In the case of rare monogenic disease these are designed to focus attention on the most likely pathogenic variant(s) by eliminating common, silent, or predicted tolerated variants from consideration. Targeted primary immune deficiency panels have been designed and implemented in many diagnostic centres and offer the ability to screen a large number of disease genes in a rapid and efficient fashion. Variants are typically identified with a high degree of confi- dence, although it is still standard practice to confirm medically ac- tionable findings by conventional (dideoxy) sequencing. However, as with any genetic test, the significance of variants within disease genes may not immediately be apparent, particularly in the case of missense mutations, hence laboratories and clinicians must be ready to interrogate pathogenicity further where relevant by pro- tein/functional assays and/or further genetic testing within affected families. Whole exome and whole genome sequencing have powerful po- tential to enable disease gene discovery. Since 2010 these methods have contributed to an explosion of knowledge amounting to more than 50 new primary immune disorder (PID) genes. This rate of gene discovery, while clearly not sustainable indefinitely, none- theless emphasizes the extreme heterogeneity of PID and suggests that comprehensive targeted gene panels are likely to remain unob- tainable for some years to come. WGS offers several other advan- tages including its ‘one size fits all’ applicability to the full range of genetic disorders, improved coverage of disease genes when com- pared with targeted capture approaches, and potential to reveal pathogenic variants within noncoding space. As a result, several healthcare organizations are exploring the clinical diagnostic im- plementation of WGS, and ultimately this may become the inves- tigation of choice for patients who present with severe, unusual, or recurrent infections. FURTHER READING Amaya-Uribe L, et al. (2019). Primary immunodeficiency and auto- immunity: a comprehensive review. J Autoimmun, 99, 52–72. Bonilla FA, et al. (2015). Practice parameter for the diagnosis and management of primary immunodeficiency. J Allergy Clin Immunol, 136, 1186–205, e1–78. Bousfiha A, et al. (2018). The 2017 IUIS Phenotypic Classification for Primary Immunodeficiencies. J Clin Immunol, 38, 129–43. de Vries E (2012). Patient-centred screening for primary immuno- deficiency, a multi-stage diagnostic protocol designed for non-immunologists: 2011 update. Clin Exp Immunol, 167, 108–19. Gennery AR, et al. (2010). Transplantation of hematopoietic stem cells and long-term survival for primary immunodeficiencies in Europe: entering a new century, do we do better? J Allergy Clin Immunol, 126, 602–10.e1. Heimall J (2019). Genetic testing to diagnose primary immunodefi- ciency disorders and to identify targeted therapy. Immunol Allergy Clin North Am, 39, 129–40. Kwan A, Puck JM (2015). History and current status of newborn screening for severe combined immunodeficiency. Semin Perinatol, 39,

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