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Review article

Common variable immunodeficiency

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Common variable immunodeficiency (CVID) refers to a heterogeneous immunodeficiency syndrome characterized by hypogammaglobulinemia, recurrent bacterial infections and a variety of immunological abnormalities. Affected persons are prone to recurrent bacterial infections, especially involving the upper and lower respiratory tracts. In addition, patients exhibit increased susceptibility to a protean array of autoimmune, gastrointestinal, neoplastic, and inflammatory disorders[1, 2].

Epidemiology

Although CVID is a rare condition, it is probably the most common symptomatic primary immunodeficiency syndrome encountered by the allergy/immunology and pulmonary specialist [1]. Its prevalence ranges from 1:25.000 among Caucasians to 1:100.000 in the Japanese population, and affects men and women equally[3].

The majority of patients exhibit symptoms either in childhood or late-adolescence and present mainly with sinopulmonary infections[4]. However, in some patients, the disease does not become clinically apparent until the second or third decade of life, frequently with some delay between initial onset of recurrent infections and the establishment of the diagnosis[5].

Genetics

In some cases, family members of CVID patients may have selective IgA deficiency (sIgAD), and cases of sIgDA may gradually progress to CVID, leading to the hypothesis that these humoral immunodeficiencies may be genetically related[6]. First-degree relatives of CVID patients are at risk to develop CVID/sIgAD. Most of the CVID families show an autosomal dominant trait, while only about 20% of these familial cases are autosomal recessive[7, 8]. Various groups have made association between sIgAD & CVID and major histocompatibility complex (MHC) Class II/III. The +448 polymorphism of the TNF-α gene has been associated with granulomatous form of CVID[9]. A large microsatellite linkage study of 101 multiple case families with sIgAD and CVID demonstrated a strong susceptibility locus (IGAD1) lying in the telomeric part of the Class II region or the centromeric part of the MHC Class II region of chromosome 6[10, 11].

Recent evidence suggests a role for the inducible co-stimulatory molecule (ICOS), a member of the CD28/CTLA4 family. ICOS is expressed on activated T cells, its ligand (B7H) is expressed on B cells and non-immune cells following inflammatory stimuli. ICOS has a role in T-cell activation and proliferation as well as humoral immunity; it is critical for CD40-mediated antibody class switching[12-14]. Grimbacher and associates[15] demonstrated ICOS deficiency on activated T cells, as a mongenic cause for CVID, in two families with autosomal recessive trait. In addition, mutations in a gene called TACI (transmembrane activator and calcium-modulator and cyclophilin ligand interactor) were found in 5-10% of CVID cases. TACI is a TNF-like receptor that is selectively expressed on B cells and induces T cell-independent immunoglobulin class switch recombination when it interacts with other ligands on B cells like APRIL (a proliferative-inducing ligand)[16]. The discovery of ICOS and TACI mutations in a subset of patients with CVID points to problems in co-stimulation in CVID.

Immunological features

B- cell abnormalities

The hallmark of CVID is hypogammaglobulinemia and impaired specific antibody production[17]. In patients with CVID, IgG levels are reduced to greater than 2 SDs below the mean. Most patients have low levels of IgA, and many have reduced IgM levels. Some authorities recommend that low serum IgA must be included in the diagnostic criteria for CVID[4,18-20]. Documenting impaired production of specific antibodies (isohem-agglutinins and /or poor response to one or more vaccines) is essential for diagnosis. Numbers of B cells in the peripheral blood may be normal or reduced; approximately 13% of patients will have a B-cell count of less than 3% among peripheral blood lymphocytes[4, 21].

T-cell abnormalities

Although CVID is classified as a form of predominantly humoral immunodeficiency, T-cell abnormalities are common[22,23]. These include

reduction in peripheral T-cell populations, as well as functional defects such as reduced in vitro proliferative responses, defects in cytokine production (reduced IL-2,4 and 9 ; increased IL-12, TNF-α and IFN-γ), decreased T-helper cell (CD4) count and in particular CD45-RA number as well as defects in T-cell function, abnormalities in T-cell signaling, diminished expression of the co-stimulatory molecule CD40L, and increased suppressor T-cell number[24].

Some CVID patients exhibit an abnormally low CD4/CD8 ratio that, in most cases, is caused by both an increase in the absolute number of CD8+ T cells that co-express CD57 and a decrease in the absolute number of CD4+ T cells. The expanded population of CD8+ CD57+ T cells in these patients has functional properties that are characteristic of activated cytotoxic T lymphocytes[24]. Expansion of CD8+CD57+ T cells has also been observed in a number of other clinical conditions including cytomegalovirus infection, acute Epstein-Barr virus infection and HIV infection. The origin and functional significance of the expanded population of CD8 T cells in this subgroup of CVID patients is unclear. These CD8+ cells are capable of suppressing B cell immunoglobulin secretion in vitro[1]. However, most patients with this phenotype also exhibit in vitro B cell abnormalities suggesting that T cell suppression is not the primary cause of hypogammablobulinemia. Clinically, this subgroup of patients may exhibit a higher frequency of splenomegaly and granulomatous inflammation[26].

Whether not any of the above T cell abnormalities are responsible for abnormal in vivo antibody secretion in CVID, they emphasize that CVID is not merely a syndrome of defective immunoglobulin secretion; rather, it represents a generalized state of immune dysregulation characterized by functional abnormalities of both T and B cells. Clinically, this is reflected in the susceptibility of these patients to a variety of conditions not easily explained on the basis of isolated humoral immune defect[1].

Moreover, the recovery of Ig production (mostly IgG and IgM) transiently or permanently following human immunodeficiency virus (HIV) infection[27] and hepatitis C virus (HCV) infection[28] has been reported in patients with CVID. These cases indicate that CVID is associated with potentially reversible defects in immunoregulatory factors and intact B-cell systems.

Diagnosis

CVID is a diagnosis of exclusion. Therefore, any other cause of hypogammaglobulinemia needs to be ruled out. Among those, the most important conditions are listed in table 1.

Clinical manifestations of CVID include recurrent infections, autoimmune disease, lymphoid hyperplasia, granulomatous diseases, and malignancy.

Recurrent infections

Recurrent pyogenic infections of upper and lower respiratory tract are the main clinical manifestations of CVID[3,29-31]. Symptoms may appear during childhood or, more often, after puberty[21]. Bronchiectasis may develop if optimal therapy is delayed[32-34]. *Haemophilus influenzae*, *Moraxella catarrhalis*, *Streptococcus pneumoniae*, and *Staphylococcus aureus* are the organisms most commonly involved. A few patients with CVID present with unusual organisms, such as *Pneumocystis carinii*, mycobacteria, or various fungi. *Mycoplasma pneumoniae* infections in the urinary tract, joints, and deep abscesses have been reported[4]. Persistent diarrhea and malabsorption caused by *Giardia lamblia* also have been reported in patients with CVID[30].

Meanwhile, patients with CVID tolerate viral infections normally, but some exceptions exist. Severe and recurrent infections with herpes simplex are common, and herpes zoster eventually developed in as many as 20% of patients with CVID[32]. In addition, several cases of severe infections caused by cytomegalovirus have been reported in CVID patients[35]. Some patients may develop unusual enteroviral infections with a chronic meningoencephalitis and a dermato-myositis-like illness. Presenting symptoms are either acute or insidious, with signs of encephalitis, seizures, headache, sensory motor disturbances, and personality changes[29]. The most common enteroviral pathogens are echoviruses, especially echovirus-11. The diagnosis can be made by culture or polymerase chain reaction amplification (PCR) of cerebrospinal fluid. High-dose IVIG or intrathecal immunoglobulin has been reported to be of benefit to some patients; however, this syndrome is progressive and fatal[36].

Autoimmune diseases and CVID

Approximately 20% of CVID patients will develop one or more autoimmune disease[20] indicating that CVID is a disease of abnormal immune regulation as well as immunodeficiency. The most common autoimmune diseases are autoimmune (Coombs positive) hemolytic anemia and immune thrombocytopenia. Neutopenia is also seen in a significant number of patients with CVID and in

some cases antigranulocyte antibodies have been demonstrated. Paradoxically, these patients are unable to mount an antibody response to infecting microorganisms but retain the ability to produce autoantibodies against red blood cells, platelets and granulocytes[1]. A variety of other autoimmune conditions have been associated with CVID. These include rheumatoid arthritis, systemic lupus erythematosus, polymyositis, vasculitis, autoimmune thyroid disease, Adddison disease, diabetes mellitus, biliary cirrhosis, Gillian-Barre syndrome, alopacia totalis and sicca syndrome. Females with CVID are more prone to develop these conditions[4].

Gastrointestinal disease

Patients with CVID suffer from a variety of infectious and non-infectious gastrointestinal diseases. As many as 60% of untreated CVID patients will develop diarrhea. Giardia lamblia is the most common infectious cause. The diarrhea may be quite severe or prolonged, but usually respond to therapy with metronidazole. Other infectious causes of diarrhea include bacterial pathogens commonly associated with diarrhea such as Salmonella, Shigella, Yersinia and Campylobacter species[30,37]. Approximately 20% of these patients have a severe gastroenteropathy with severe malabsorption resembling celiac sprue, nodular lymphoid hyperplasia, and chronic inflammatory bowel disease such as ulcerative colitis and Crohn's disease[1]. Although regular Ig therapy reduces susceptibility to Giardia and Campylobacter enteritis, it does not prevent autoimmune mucosal inflammation since Ig replacement therapy does not affect the clinical course of inflammatory bowel disease[38].

Meanwhile, a small number of patients develop achlorhydria and pernicious anemia, autoimmune hepatitis and primary biliary cirrhosis[1].

Lymphoid hyperplasia and granulomatous diseases

Approximately 30% of patients with CVID will have splenomegaly, diffuse lymphadenopathy, or both[1,3]. Other sites, such as the lungs (lymphoid interstitial pneumonitis), GI tract, skin, spleen, liver, and parotid gland, may be involved by these lymphoproliferative processes[34,39]. Lymph nodes show reactive follicular hyperplasia, atypical hyperplasia, or non- casiating granulomatous inflammation resembling sarcoidosis[40]. Nodular lymphoid hyperplasia in the GI tract has also been described in patients with CVID[1]. Granulomas have been reported in approximately 5-10% of patients with CVID[41]. In the lungs, these granulomas are indistinguishable from those of classic sarcoidosis[40].

Increased risk of malignant neoplasms

Patients with CVID have a high risk of developing malignant neoplasms, such as non-Hodgkin lymphoma, GI carcinoma, or malignant lymphoma. Most of these are of the B-cell immunophenotype and frequently are associated with EBV[40].

Lymphoma occurs 300 times more frequently in women with CVID than in affected men. Malignant lymphomas in patients with CVID occur most frequently in the fifth to seventh decade and not in childhood. These malignant lymphomas usually are extranodal and histologically are intermediate- to high-grade non-Hodgkin lymphomas. Most of these lymphomas are of the B-cell immunophenotype and may be associated with EBV[42]. Patients with CVID also are at risk for gastric carcinoma 47 times higher than normal. Other malignancies include colon cancer, breast cancer, gastric cancer, prostate cancer, ovarian cancer, oral cancer, and melanoma[1].

Diagnostic considerations

The diagnosis of CVID should be suspected in any patient with recurrent bacterial infections of the upper and lower respiratory tract[40]. In contrast to primary combined immunodeficiency disorders and HIV disease, children with CVID may not present with failure to thrive[42]. Before commencing laboratory studies to evaluate for possible humoral immunodeficiency, a careful medical history should be obtained, with attention to the basis on which prior infections were diagnosed. In addition, family history should be obtained and a careful physical examination performed. Other conditions, such as allergies, anatomic abnormalities of the respiratory tract, ciliarry dysmotility syndrome, cyctic fibrosis, and complement deficiency should be considered in the differential diagnosis[1].

Laboratory evaluation of the humoral immune system includes measuring of serum IgM, IgG, IgA and IgG subclasses, and comparing the values obtained with age-standardized reference ranges [6]. It is also important to determine the ability to mount an antibody response to specific antigen, by measuring titers against microorganisms to which natural or vaccine exposure is common, such as tetanus, diphtheria, and rubella. Isohemagglutinin can provide a measure of the capacity to mount a specific IgM response in patients older than 1 year with appropriate ABO blood types. Immunization with tetanus toxoid and polyvalent pneumococcal vaccine may be used to evaluate functional antibody responses to protein and polysaccharide

antigens respectively. A 4-fold rise in anti-tetanus titers 3 to 4 weeks after immunization is considered normal, and at least a 2-fold rise in titers against most pneumococcal serotypes examined is considered a normal response in children older than 2 years[1,23].

Various attempts have been made to subclassify CVID based on antibody production in culture systems[44] or clinical and laboratory features[45], but these are not in routine clinical use. A more recent method, currently in development for subdividing CVID, which correlates well with the groups of Bryant et al[44] and clinical categories, is the Freiburg classification[46]. This uses flow cytometric analysis of CD19 gated B cells (excluding those CVID patients with low B cell numbers or granulomatous complications) to define CVID Group I with a severe deficiency of switched memory B cells. Group I is further subdivided into Ia with elevated immature B cells, which is associated with splenomegaly and autoimmune cytopenias, and Ib with normal numbers of immature B cells (figure 1). This system is likely to be applied more widely as it is much simpler to perform than previous systems but needs validation across other patients' cohorts.

Differential diagnosis

The differential diagnosis of CVID includes other causes of hypogammaglobulineia listed in table 1. The family history and the age of onset of symptoms are important, because patients presenting after 15 years are unlikely to have one of the known single gene primary immunodeficiencies. Various single gene disorders causing hypo-immunoglobulinemia should be excluded, including 'leaky' severe combined immunodeficiency (SCID), which can rarely present after childhood[47]. Male patients with low numbers of circulating B cells should be screened for X- linked agammaglobulinemia (XLA), and other autosomal recessive causes of agammaglobulinemia considered in females[43]. Also, males with X-linked hyper IgM or X-linked lymphoproliferative syndrome may be confused with CVID, since the former may have normal serum IgM levels[48].

There is no confusion with secondary hypogammaglobulinemia, in which IgA levels are usually moderately low. Nevertheless, routine screening for nephrotic syndrome, chronic lymphocytic leukemia (CLL) and myeloma should not be forgotten. Protein loosing enteropathy with low immunoglobulins can be confusing, but is usually obvious when serum IgG fails to rise on immunoglobulin therapy[8].

Hypogammaglobulinemia can also be induced by a variety of drugs listed in table 1. However, the deficiency is apparently reversible after cessation of therapy, although full recovery may take months or even years[1].

Therapy

Immunoglobulin replacement therapy

The mainstay of therapy in CVID remains replacement IVIG therapy, which has replaced intramuscular immunoglobulin as there are fewer side effects and a greater amount can be infused[49-51]. Patients with CVID showed a reduction in the infection rate after the administration of regular IVIG[50]. The optimal trough level required to prevent infection in CVID has not been established, however, a dose of 200-400 mg/kg of IVIG given every 2-4 weeks would be sufficient. Early diagnosis is important so that IVIG replacement therapy can be commenced before the onset of irreversible organ damage[51].

Subcutaneous immunoglobulin (SCIG) therapy has become increasingly popular particularly in children and patients with poor venous access. SCIG is given more frequently (2 to 3 times a week), however, in terms of efficacy both SCIG and IVIG were found to be equally effective[52,53].

In order to improve and standardize the care and monitoring of patients with CVID receiving IVIG, Sewell and associates[38] proposed a useful form of guidelines listed in table 2.

Antibacterials

The other mainstay of therapy in CVID is antibacterials, which are used as treatment for breakthrough infections, as prophylaxis in patients with recurrent infections despite adequate doses of IVIG therapy and in suppurative lung disease[54,55]. Optimum prophylactic antibacterial therapy in patients with CVID remains to be determined; although numerous regimens are used clinically on a purely empirical basis[38].

Corticosteroids

Despite CVID is an immunodeficiency, there are some occasions when immunosuppression with corticosteroids is required, for example to control CVID associated granulomatous conditions and inflammatory bowel disease. This therapy carries the potential risk of precipitating overwhelming infection[38].

Corticosteroids may also be used in the treatment of CVID associated immune thrombocytopenia (ITP);

however, other modalities of therapy such as high dose IVIG, anti-Rhesus D antibodies or anti-B-cell therapy with rituximab may be considered. Rituximab, an anti-CD20 monoclonal antibody, is an attractive therapy since any subsequent lowering of Ig production is unlikely to be of concern in view of ongoing IVIG replacement; however, it has not been shown to be universally successful in chronic ITP[57, 58].

Surgery

In special conditions such as bronchiectasis, surgery may be indicated to remove localized area of diseased lungs. Also, splenectomy may be indicated to treat thrombocytopenia or granulomatous disease[38].

Immunomodulatory agents

I. Cytokines

T cells from patients with CVID have numerous functional defects including low production of IL-2. Patients with CVID when treated with weekly subcutaneous human recombinant IL-2 conjugated to polyethylene glycol (PEG-IL-2), showed enhanced T cell proliferation, boosted B cell differentiation factor (BCDF) secretion and B cells responsive to signals after 12 weeks of therapy[59]. These data suggest some potential benefit from this form of therapy, but further work on longer and larger studies are required for validation of such therapy.

IL-10 plus anti-CD40 *in vitro* can enhance IgG and IgA production by B cells from patients with CVID[60]. This effect has not been established *in vivo* in CVID patients. However, therapy with IL-10 is an area of active research in Crohn's disease[61] that may also have important implications for treatment of patients with CVID[38].

II. Vitamin A and analogues

In addition to its antioxidant effect, vitamin A has an immunoregulatory effect in patients with immunodeficiency including an influence on cytokine production (TNF-α, IL-2 and IL-4) and lymphocyte growth and function[62]. Decreased serum vitamin A levels in CVID patients has been reported[62]. Reichenbach and associates[63] reported a significant increase in serum IgA and IL-10 together with a remarkable decrease in serum TNF-α and neoptrin levels after the administration of vitamin A at a dose of 6500 IU for 12 weeks in 10 CVID patients.

III. Cimetidine and ketoprofen

Both cimetidine (histamine receptor type-2 [H2] antagonist) and ketoprofin (cyclooxygenase inhibitor) have mild immunoregulatory properties, mainly enhancing cell mediated immunity by increasing proliferative responses to mitogens and antigens and inhibiting T cell suppression. However, studies concerning their efficacy as immunomodulators in vivo remain to be proven[38].

Vaccination in CVID

The use of live vaccines in CVID is contraindicated in view of the possibility of prolonged excretion of a virus such as polio, which may then have the opportunity to revert back to virulence[1]. CVID patients may fail to eliminate attenuated live poliovirus, and should be immunized with killed rather than live polio vaccine[64]. Vaccine-associated paralytic poliomyelitis (VAPP) in a patient with CVID has been reported; this patient developed paralytic poliomyelitis 7 years after the last administration of trivalent oral poliovirus vaccine[64]. Even the use of killed vaccines is probably ineffective in view of reduction in antibody, memory B cells and T cell responses. However, it has been argued that despite a poor antibody response, T cell responses may be partially intact and, therefore, there may be merit in vaccinating to elicit the cell-mediated response[1].

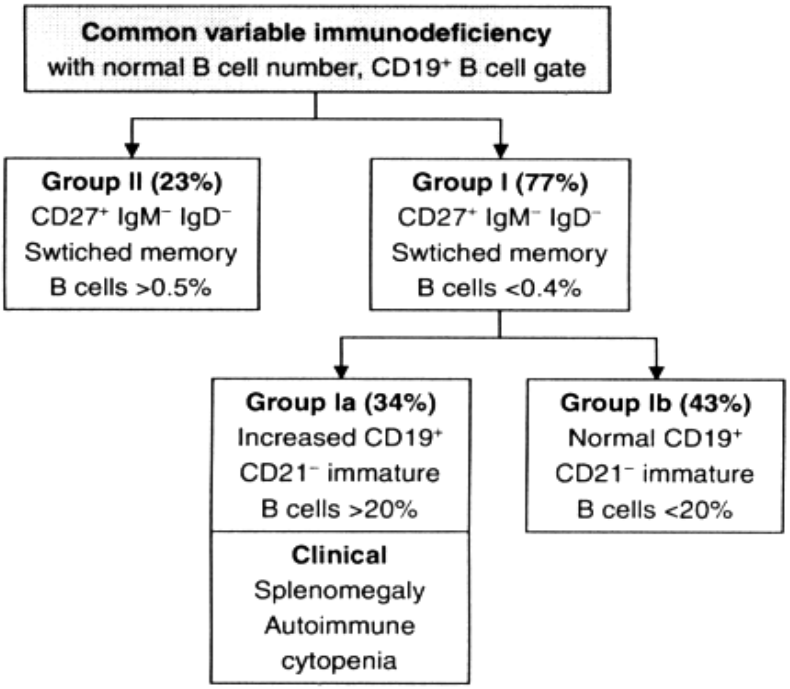

Figure 1. Freiburg classification of common variable immunodeficiency (CVID)[46].
This shows the flow cytometric classification of CVID patients with normal B cell numbers. Patients with granulomatous complications have been excluded. The classification correlates well with the previous functional categories of Bryant et al [44]. Group I includes previous categories A and B and Group II contains category C. Early evidence also suggests that Groups II and Ib may retain limited vaccination responses, while Group Ia is associated with splenomegaly and autoimmune cytopenias. It is not clear if the splenomegaly is granulomatous in nature. Quoted from Sewell and associates[38].

Table 1. Causes of hypogammaglobulinemia**.**

Drug induced	Cytotoxic drugs[1] Anti-B cell antibodies[1] Gold[1] High dose corticosteroids[1] Sulfasalazine[1] Chloroquine[1] Penicillamine[1]	Hydantoin[1] Carbamazepine[1] Zonisamide[2] Valproate[3] Captopril[3] Fenclofenac[3] 1 may affect IgG &IgA 2 may affect IgG2&IgA 3 may affect IgA
Primary immunodeficiency with predominantly antibody deficiency	X- linked agammaglobulinemia (XLA) Autosomal recessive agammaglobulinemia Common variable immunodeficiency (CVID) Ig heavy-chain gene deletions κ Chain deficiency IgG subclass deficiency severe combined immunodeficiency (SCID), leaky type X-linked lymphoproliferative syndrome X-linked hyper IgM syndrome Non X-linked hyper IgM syndrome Transient hypogammaglobulinemia of infancy Inducible co-stimulator (ICOS) deficiency Caspase 8 deficiency	
Chromosomal anomalies	Chromosome 18q- Syndrome Monosomy 22	Trisomy 8 Trisomy 21
Infectious diseases	Human immunodeficiency virus (HIV) (primary in children) Congenital infection with rubella Congenital infection with cytomegalovirus (CMV) Congenital infection with Toxoplasma gondii Epstein-Barr Virus (EBV) (± underlying genetic susceptibility)	
Hematologic malignancies	Chronic lymphocytic leukemia (CLL) Immunodeficiency with thymoma (Good syndrome) Non Hodgkin's lymphoma (NHL). Other B-cell malignancy	
Losses	Gastrointestinal Renal Skin	Severe diarrhea Malabsorption Protein loosing enteropathy Lymphangiectasis Nephrotic syndrome Severe burns

Quoted from Sneller[1], Chapel[2], Notarangelo et al[48].

Table 2. Monitoring guidelines in common variable immunodeficiency (CVID)

Diagnosis	Hypogammaglobulinemia with onset greater than 2 years of age in the absence of known diseases or drugs causing antibody deficiency. Absent isohaemagglutinins and /or poor response to vaccines (no live vaccines). Excluding XLPS, XLA, AID, X-HIM, leaky SCID and deficiency of μ-chain, λ5, Igα chain, BLNK.
Baseline tests	FBC Liver function tests (ALP, ALT, bilirubin plus HBsAg and HCV PCR if indicated) Renal function tests including urinalysis Lung function tests Chest radiograph Circulating lymphocyte subsets (T, B, NK numbers) Circulating immunoglobulins, serum and urine electrophoresis If IgG >3g/L perform IgG subclasses, tetanus, Hib and pneumococcal Ab titers and other vaccinations/infections as appropriate Anti-IgA antibodies (if IgA is low/absent) CT scan of lungs (if respiratory symptoms or signs are present) Sputum culture (if productive cough) Store serum sample at –70°C
Treatment	IVIG or SCIG to maintain trough level at 5-8 g/L Assessment for home therapy training program Prompt treatment of infections and management of septic complications
Genetic counseling	Record pedigree Explain inheritance patterns of CVID and provide patient handout Identify any affected relatives and advise patient how to proceed Give patient details of the primary immunodeficiency association and primary antibody deficiency booklet
Outpatient monitoring	Outpatient visit every 6-12 months (or depending on clinical situation) Monitor infection frequency, complications of treatment and disease and overall health Four monthly liver function tests and trough IgG levels and CRP FBC 6-12 monthly (haematinics iron, TIBC, ferritin, B12 and folate as required) Annual circulating lymphocyte phenotypes Lung function tests annually: spirometry & lung volumes (imaging if indicated) Sputum culture (if productive cough).

Ab: antibody; AID: activation-induced cytidine deaminase; ALP: alkaline phosphatase; ALT: alanine amino-transaminase; BLNK: B-cell linker; CRP: C-reactive protein; CT: computed tomography; FBC: full blood count; HBsAg: hepatitis B surface antigen; HCV: hepatitis C virus; Hib: Haemophilus influenzae type b; IVIG: intravenous immunoglobulin; NK: natural killer cells; PCR: polymerase chain reaction; SCID: severe combined immunodeficiency; SCIG: subcutaneous immunoglobulin; TIBC: total iron binding capacity; X-HIM: X-linked hyper IgM syndrome; XLA: X-linked agammaglobulinemia; XLPS: X-linked lymphoproliferative syndrome. Quoted from Sewell and associates[38].

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