International Archives of
Allergy and
Immunology

Common Variable Immunodeficiency: Etiological and Treatment Issues

Sean Deane   Carlo Selmi   Stanley M. Naguwa   Suzanne S. Teuber
M. Eric Gershwin

Division of Rheumatology, Allergy and Clinical Immunology, University of California at Davis School of Medicine,
Davis, Calif., USA

Abstract
One of the great advances in clinical medicine was the recognition of the pleomorphism of the immune response and the multiple afferent and efferent limbs of antigen processing and responsiveness. A significant contribution to this understanding was derived from studies of human immunodeficiency states, including both inherited and acquired syndromes. Amongst these syndromes, one of the most common, and least understood, is common variable immune deficiency (CVID). CVID is a syndrome that leads to a reduction in serum immunoglobulins and complications including recurrent infections. Management includes immunoglobulin replacement therapy; however, patients with CVID are at risk for complications of exogenous immunoglobulin administration as well as CVID-associated diseases such as autoimmune processes and malignancies. To assess the current state of knowledge in the field, we performed a literature review of a total of 753 publications covering the period of 1968 until 2008. From this list, 189 publications were selected for discussion. In this review, we demonstrate that while the molecular basis of CVID in many cases remains incompletely understood, significant strides have been made and it is now clear that there is involvement of several pathways of immune activation, with contributions from both T and B cells. Furthermore, despite the current gaps in our knowledge of the molecular pathogenesis of the syndrome, there have been dramatic advances in management that have led to improved survival and significantly reduced morbidity in affected patients.

Copyright © 2009 S. Karger AG, Basel

Introduction

To coin a name for something requires some understanding of the entity. In naming common variable immunodeficiency (CVID) in 1973, immunologists perhaps did more to acknowledge what we do not know [1]. Despite remaining a rare disorder, CVID is the second most frequent syndrome causing primary immunodeficiency [2] and its pathogenesis remains poorly understood [3]. Over the past few years, moreover, the role of T cell defects has been established beside the well-defined changes in B cells [4–11]. We will, herein, focus on the clinical features of CVID in the molecular age and discuss the emerging view of CVID as a spectrum of diseases with divergent molecular defects, the new diagnostic workup guidelines for patients suspected of having CVID, and current treatment options.

Correspondence to: Prof. Merrill Eric Gershwin
Division of Rheumatology, Allergy and Clinical Immunology
University of California at Davis School of Medicine
451 E Health Sciences Drive, GBSF, Suite 6510, Davis, CA 95616 (USA)
Tel. +1 530 752 2884, Fax +1 530 752 4669, E-Mail megershwin@ucdavis.edu

Table 1. Suggested tests for the screening of suspect primary immunodeficiencies

Complete blood count with manual differential
Comprehensive metabolic panel (including glucose and lipid markers)
Serum calcium
Urinalysis (with urine protein electrophoresis if proteinuria is found)
Quantitative IgM, IgG, IgA and IgE
HIV serology
Additional tests (in selected cases)
Sweat chloride
Quantitative flow cytometry for B and T cell subsets and NK cells
Complement CH50, AH50

Table 2. Secondary causes of IgG deficiency [25]

Conditions	
Burns	
Protein-losing enteropathies	
Nephrotic range proteinuria	
Malignancy	
Medications	
Antihypertensives	captopril [28]
Antimalarials	chloroquine primaquine [28]
Antiepileptics	carbamazepine [28] phenytoin [2, 28]
NSAIDS	fenclofenac [28] sulfasalazine [28]
Antirheumatics	gold salts [2, 28]
Chelating agents	penicillamine [2, 28]

Table 3. Established laboratory criteria for the diagnosis of CVID

Ig abnormality	Probability (additional criteria needed)
Significant decrease in *both* IgA *and* IgG	probable
Significant decrease in IgM, IgG *or* IgA	possible
Additional diagnostic criteria	**Diagnostic procedure**
Immunodeficiency onset >2 years of age	history
Impaired antibody production to vaccines	diphtheria/tetanus titers pre-/post-vaccine
Impaired antibody production to polysaccharides	serum isohemagglutinins; pneumococcal titers pre-/post-vaccine

The Challenge of CVID Diagnosis and Epidemiology

CVID affects males and females equally, with a prevalence estimated to be between 5 and 100 per million [12, 13]. It is second only to selective IgA deficiency among humoral immunodeficiencies [14–17]. As a comparison, HIV-related immunodeficiency currently affects over 1 in 200 [18]. One major issue in CVID epidemiology is related to the diagnostic delay. Indeed, the heterogeneity of CVID presentation shares the common trait of recurrent respiratory infections which are managed by primary care physicians until the frequency increases or a sentinel event occurs, prompting further investigation [2, 9, 19–21]. Accordingly, diagnostic delays are not uncommon, with a time period from the onset of earliest symptoms estimated at 5–6 years in the USA and 4 years in Europe [19, 22], but available data vary widely. In a single-center study, approximately one quarter of patients were not diagnosed for over a decade [23]. These observations clearly support the critical role of a high index of clinical suspicion in the evaluation for CVID, while the proposed scoring systems are helpful tools once a case is suspected [20, 21, 24].

Once a case is suspected, the evaluation begins with a detailed patient history for risk factors related to secondary causes of immune suppression, such as drugs or malignancies. When the presentation is consistent with a humoral immunodeficiency, the initial evaluation is followed by appropriate laboratory screening (table 1). When immunoglobulin (Ig) levels are reduced, further evaluation is indicated to rule out secondary causes of hypogammaglobulinemia (table 2) [14, 25], while normal Ig levels should prompt evaluation for alternative immune defects, such as complement deficiencies, that may mim-

Table 4. Conditions potentially mimicking CVID

Disease	Gene or protein defect
Hyper-IgM	
Type I	CD40L [101, 171–175]
Type II	AICDA/AID [101, 176, 177]
Type III	CD40 [178]
Type IV	Unknown [29, 179]
Type V	Ung [101, 180]
X-linked Hyper-IgM with ectodermal dysplasia	NEMO [101, 181]
X-linked agammaglobulinemia	BTK [146, 182–184]
X-linked lymphoproliferative disease	SH2D1A, XIAP [30, 32, 108–111, 185–187]

Table 5. Monogenic diseases indistinguishable from CVID

Protein defect	Locus	Inheritance	Ref.
ICOS	2q33	autosomal recessive	7, 120, 121
CD19	16p11.2	autosomal recessive	122, 123
TACI	17p11.2	autosomal dominant or recessive	126–130
BAFF-R	22q13	autosomal, presumed recessive	139, 143
MSH5	6p22.1–p21.3	unknown	144

ic the clinical presentation of Ig defects [14]. We also note that patients may present with subtle Ig changes and develop more frank abnormalities during subsequent follow-up [26]. In the case of CVID, reduced IgG levels with normal or slightly reduced IgA levels are typical; if this latter abnormality is isolated, the alternative diagnosis of selective IgA deficiency needs to be considered [14]. Marked IgE level elevation is suggestive of atopic disease or immunodeficiency associated with hyper-IgE syndrome, while the implications of isolated IgM and IgG subclass deficiencies are unclear. Ultimately, immunoglobulin levels alone are insufficient to adequately establish the diagnosis, and inadequate follow-up evaluation may put patients at significant risk of serious consequences with the inappropriate administration of IVIG [27].

Criteria for a possible or probable CVID diagnosis were established by international consensus statements and require the demonstration, when possible, of impaired specific antibody production (table 3) [28]. Within these criteria, once CVID is suspected, current practice guidelines recommend the exclusion of disorders possibly mimicking CVID (table 4) and considering genotyping for known monogenic causes of immunodeficiency (table 5) [14, 29]. However, whether definitive genetic laboratory investigation should be encouraged remains a matter of controversy [30–33].

CVID Clinical Features

In contrast to most primary immunodeficiencies, CVID may manifest in childhood but is frequently not diagnosed until the early adult years [19, 28, 34–36]. As illustrated in table 3, the current CVID case definition requires an age at diagnosis older than 2 years and the demonstration of impaired specific immunity, along with the exclusion of known genetic causes of the CVID phenotype [14, 28]. In patients who fulfill the CVID criteria and in whom specific monogenic defects are found, the diagnosis of CVID should be revised [13, 37].

Sinopulmonary infections are the most common clinical sign of the CVID spectrum [14] and nearly all patients have recurrent sinusitis, otitis, and bronchitis, with pneumonia found in two thirds of cases in one series in the USA [19]. A British study reported that 75% and 90% of CVID cases manifested upper and lower respiratory complaints, respectively [34]. The predominance of lower respiratory infections was also confirmed in a Dutch series [36]. While encapsulated organisms such as *Streptococcus pneumoniae* or atypicals such as *Mycobacteria* are the most commonly identified pathogens, patients may also present with infections typically associated with T cell defects such as *Pneumocystis jiroveci* [14, 19]. As might be expected, it has long been recognized that chronic inflammation and recurrent infections associated with

Table 6. Euroclass CVID flow-cytometry subclassification

A	Type B–: <1% circulating B cells

B Type B+: >1% circulating B cells
1 CD21 low: >10% CD21lo B cells
   (associated with splenomegaly)
   a smB+: >2% CD27+/IgD–/IgM– switched B cells
   b smB–: ≤2% CD27+/IgD–/IgM– switched B cells
      (associated with higher incidence of splenomegaly and
      granulomatous disease)
      i   TrHi: ≥9% CD38hi/IgMhi transitional B cells
          (associated with lymphadenopathy)
      ii TrNorm: <9% CD38hi/IgMhi transitional B cells
2 CD21 norm: ≤10% CD21lo B cells
   a smB+: >2% CD27+/IgD–/IgM– switched B cells (lower
      incidence of granulomatous disease than other subsets)
   b smB–: ≤2% CD27+/IgD–/IgM– switched B cells
      (associated with higher incidence of splenomegaly and
      granulomatous disease)
      i   TrHi: ≥9% CD38hi/IgMhi transitional B cells
          (associated with lymphadenopathy)
      ii TrNorm: <9% CD38hi/IgMhi transitional B cells

CVID may result in severe bronchiectasis and pulmonary fibrosis [19, 35, 38–48], possibly influenced by mannose-binding lectin polymorphisms [42]. Further, patients with CVID are at risk for granulomatous infiltration and interstitial pneumonia in a pattern termed GLILD (granulomatous/lymphocytic interstitial lung disease) [19, 44, 48–51]. In approximately 20% of patients with CVID, digestive complications are found, with diarrhea of infectious etiology [19] primarily from *Salmonella* and *Campylobacter* species in the minority of cases in which a cause is proven. Cytomegalovirus and *Cryptosporidium* enteritis, while more commonly associated with HIV or cellular immunodeficiencies, have also been observed in CVID [19, 52–54]. When colon histology was evaluated in patients with CVID with digestive complaints, 19% had granulomas, while approximately 50% had histological patterns mimicking celiac disease [52]. Similarly, nodular lymphoid hyperplasia and inflammatory bowel disease can be found in about 20 and 30%, respectively, of patients with digestive complaints [19]. The liver may also be affected and while acute hepatitis has been reported following contaminated IVIG, autoimmune liver disease may also occur [19, 55–58]. Indeed, autoimmunity is prominent in CVID [52, 59–61] and 23–50% of patients manifest unclassified autoimmune features [28, 62]. The mechanisms that lead to loss of tolerance in patients with immune deficiency as well as the same generic issue in autoimmune disease have been recently discussed [62–

72]. In patients with X-linked agammaglobulinemia, a non-CVID disorder characterized by an extremely reduced B cell count, the remaining B cells are enriched in autoreactive clones [73]. CVID-associated autoimmune diseases may range across the spectrum of rheumatologic disorders, but granulomatous disease and autoimmune cytopenias are most common [62, 74], with the former potentially impacting survival [49, 75–78]. Nonmalignant lymphoproliferative diseases commonly manifest as lymphadenopathy and splenomegaly, and are not uncommon in CVID, with clustering of B cell subsets determined on flow cytometry [79]. The role of human herpes virus 8 in the etiology of lymphoproliferative disease remains to be determined [80]. Although CVID patients may be expected to have an increased risk of infectious events following pharmacological immunosuppression, the management of autoimmunity in these patients does not differ from non-CVID cases [14, 81, 82]. Lastly, malignancy is not uncommon in patients with CVID, secondary to an increased risk of gastric cancer and non-Hodgkin's lymphoma [19, 83–85], among others [19, 36, 45, 84–87]. Of note, neoplasia may modify the disease classification since humoral immunodeficiencies with benign or malignant thymoma may manifest as CVID but should be classified as a separate entity [14, 34, 37, 54, 88–91].

Cell Flow Cytometry Phenotyping in CVID

Beginning in 2002, efforts to subclassify CVID based on B cell characteristics were proposed by separate groups in Freiburg and Paris [92, 93]. Both criteria included analysis of CD27+ B cell subsets, while the Paris protocol additionally included evaluation of total CD27+ B cells and the Freiburg protocol added the evaluation of CD21 expression [92–94]. The 2 guidelines have now been unified in the Euroclass consensus classification (table 6) which first separates the small group of CVID patients with essentially no circulating B cells from the remainder of the population. This classification facilitates prediction of which patients are at higher risk for lymphoproliferation and granulomatous disease, which may be clinically useful to guide evaluation and management decisions.

Monogenic Disorders Mimicking CVID

As previously discussed, defined genetic disorders (table 5) which are clinically different from CVID may manifest in individual patients with a similar phenotype

and warrant further discussion in this article. As an example, X-linked agammaglobulinemia, a disorder leading to profound loss of B cells, may present atypically or later in life [33, 73, 95–107] while CD40 ligand deficiency may present with deceptively unimpressive IgM levels [29]. Similarly, X-linked lymphoproliferative disorders may mimic CVID in men [108–111]. It should be noted that the most recent International Union of Immunological Sciences (IUIS) classification now includes ICOS and CD19 deficiencies as separate entities, while defects in TACI, BAFF-R, and MSH5 remain within the CVID family and are proposed to be susceptibility or disease-modifying defects [37].

ICOS Deficiency

ICOS deficiency, albeit the first discovered monogenic cause of CVID, was identified at a molecular level only in 2003 [7, 10], as a 1,815 bp defect leading to a frameshift mutation and the lack of ICOS expression on the T cell membrane [112, 113]. ICOS expression is limited to activated T cells, confirming that although CVID manifests more commonly as a defect in humoral immunity, the underlying defect may affect other cell populations [8, 113–116]. ICOS is a member of the CD28 family of molecules, which includes other costimulatory proteins such as CTLA-4 and CD28 [112, 117]. The monomeric receptor ICOS-L is constitutively expressed on antigen presenting cells [112, 118] but its genetic polymorphisms are not associated with CVID [119, 120]. ICOS signaling is implicated in GM-CSF, TNF-α and IFN-γ production, as well as induction of IL-4, IL-5, IL-6 and IL-17 [112, 121]. It has particular relevance to CVID in the superinduction of IL-10, with subsequent IL-10-mediated differentiation of B cells to plasma cells and memory B cells [117]. In most ICOS deficiency cases, the clinical symptoms of CVID manifest at adult age [121]. With the notable exception of a minority of patients who develop early symptoms, children have deceptively normal numbers of circulating B cells that subsequently decline to extremely low levels in adulthood [121]. Abnormalities in CD27+ switched memory B cells and a reduction in IgM memory B cells are common, along with autoimmune disorders, lymphoid hyperplasia and splenomegaly [121].

CD19 Deficiency

CD19 deficiency-related CVID was first identified in 2006 in a patient from Turkey and 3 siblings from Colombia. Further investigations revealed novel mutations in an additional patient from Japan [122, 123]. The 4 gene defects identified thus far result in a truncated protein with loss of the C-terminal signaling region [122, 123]. In homozygous or compound heterozygous subjects, CD19 expression on B cells was either absent or greatly reduced, whereas CD20 expression was unaffected. As somewhat expected, heterozygous carriers of the mutations were clinically normal but had intermediate levels of CD19 expression [123]. CD19 comprises 1 subunit of a 4-protein coreceptor complex that also includes CD21, CD81 and CD225 [112, 123, 124]. The subunits of the coreceptor complex lower the activation threshold for B-cell receptor signaling upon binding antigen complexed to C3d [112, 124, 125]. While CD21 serves as the extracellular receptor portion of the coreceptor complex, intracellular signaling is mediated by CD19 [112, 124]. Abrogation of the CD19-mediated signaling in CD19 deficiency results in diminished calcium flux upon stimulation of the B cell receptor, variably reduced capacity for affinity maturation upon vaccine rechallenge, reduced CD27+ memory B cells, and variably reduced capacity for B cell proliferation in vitro [122, 123].

The clinical presentation of CD19 deficiency is variable, with 1 patient reported to have recurrent infections starting within the first year of life and recurrent infections appearing prior to reaching adulthood in all cases [122, 123]. Whereas gastrointestinal complaints were prominent in several patients and each of them suffered from recurrent respiratory infections, associations with autoimmune diseases are less clear [122, 123].

TACI Deficiency

TACI deficiency is regarded as a B cell limited disorder [112, 126–130] and appears different from other deficiencies in that several distinct TACI mutations were initially reported to be associated with CVID [15, 126–131], while 2 groups later reported a total of 6 TACI mutations resulting in CVID or IgA deficiency. Two of these mutations, specifically S194X and S144X, appeared to have an autosomal recessive mode of inheritance, whereas 2 others (C104R and A181E) were associated with immunoglobulin defects (CVID or IgA deficiency) in a heterozygous state [15, 129] and compound heterozygosity is also reported [127]. The R202H mutation, like C104R and A181E, is also able to induce humoral defects in heterozygous patients [15, 127, 129]. In general terms, the analysis of families with heterozygous mutations demonstrates a variable disease phenotype despite identical genetic defects among family members [130], possibly secondary to unknown additional factors in the heterozygous state [130, 132] or to

variable functional degrees of the mutated proteins [10]. Nonpathogenetic allelic variations were reported at similar rates in both patients with humoral immunodeficiencies and healthy controls [131, 133]. Lastly, a recent study demonstrated significant associations between CVID and heterozygosity for the C104R mutation, whereas other mutations were too rare to allow comparisons with sufficient power [128].

TACI and its binding partners APRIL and BAFF are members of the TNF-like family of proteins [113, 134] with TACI and APRIL-mediated signaling possibly also involving heparin sulfate proteoglycans [135]. While found in all B cells, TACI expression is prominent in marginal zone and transitional B cells and is induced by antibodies specific for CD40 or membrane-bound IgM [112, 113], and its expression in macrophages appears to be involved in cell survival [136]. TACI-mediated signaling has a dual role as both an agonist and an antagonist for B cell response [136–138] and has been implicated in the generation of T cell independent responses, IgA class switching and B cell negative regulation [112].

The clinical phenotype of TACI deficiency is heterogeneous, with some patients manifesting CVID, others IgA deficiency and others without overt disease [113, 126, 129–131] despite TACI mutations [131]. Transition between these stages is also possible and the follow-up of the subjects identified in the earliest genetic report demonstrated that patients presenting with IgA deficiency later progressed to CVID [126]. Autoimmune comorbidities can be observed in at least a quarter of patients, while more than a third develop lymphoproliferative disease and nearly all have recurrent infections [128]. B cell numbers in TACI deficiency are also variable and CD19+/IgM+/CD27+ transitional B cells may be normal, while CD19+/IgM–/CD27+ switched memory B cells are consistently reduced [10].

BAFF Receptor Deficiency

The monogenic CVID related to BAFF receptor deficiency is secondary to a homozygous 24-bp deletion identified for the first time in a 60-year-old man without a known family history of immunodeficiency [139, 140]. The BAFF receptor is a member of the TNF-receptor like superfamily that is primarily expressed on B cells [13, 141] and appears to be highly specific for BAFF [140–142] to ultimately enhance B cell survival [134]. In humans, available data on the resulting phenotype of BAFF receptor deficiency are scanty and limited to recurrent respiratory infections, including fungal infections [139, 143].

MSH5 Deficiency

MSH5 deficiency was recently identified and included in the updated IUIS classification for CVID [37, 144]. The MSH5 gene encodes a single member of a group of 5 mammalian mismatch repair genes implicated in class switch recombination and cell meoisis [144, 145]. Each member acts as a heterodimer stage and binds to DNA repair or recombination sites [144]. Given the observed defect in class-switched B cells in CVID patients and findings of defective class switch recombination in knock-out animal models, members of this group of proteins represent ideal candidates for pathogenic mutations in CVID. In humans, the MSH5 gene product is expressed in tonsillar lymphoid tissue and shows enhanced expression in CD77+ germinal center B cells. From a genetic standpoint, when patients of European descent with CVID and IgA deficiency were compared with healthy controls, MSH5 polymorphisms were significantly associated with both conditions and mechanistic studies concluded that these contributed to abnormalities in IgS joint regions and defective binding to protein heterodimerization partners. The heterozygous state for the observed polymorphisms, on the other hand, were not observed to have defects in IgA production, thus suggesting that the observed MSH5 defects likely predispose to CVID and IgA deficiency but are not sufficient to independently cause their onset.

Management of Patients with CVID

Ig Replacement

The benefit of γ-globulin replacement in ameliorating the symptoms of immunoglobulin deficiencies has been recognized since shortly after World War II [146], and current practice guidelines support the use of subcutaneous or intravenous Ig replacement in patients with CVID [6, 14, 19, 147–149]. Ig replacement therapy should be initiated in patients with recurrent infections who demonstrate specific antibody deficiencies; whereas gray areas exist in patients with milder clinical entities such as IgG subclass deficiency, those patients fulfilling the case definition of CVID meet the treatment criteria [28, 147]. Whereas subcutaneous or intramuscular injection was the initial mode of administration, intramuscular injection was painful and associated with reduced compliance, and adequate subcutaneous delivery was limited by volume issues [147, 150]. Slow subcutaneous infusions of preparations designed for intramuscular use addressed some of these concerns, but were complicated by long in-

fusion times and were largely abandoned after higher-dose intravenous Ig preparations became available [150–152]. However, a more recent Ig preparation approved specifically for subcutaneous infusion has demonstrated benefits in quality of life measures and has a favorable pharmacokinetic profile with equivalent efficacy to intravenous administration [147, 152–155]. Subcutaneous Ig can be used either as an initial modality of therapy or as a salvage therapy in selected patients who have been unable to tolerate intravenous preparations [152]. There is no consensus on the ideal regimens for Ig replacement in humoral immunodeficiencies [25]. Recommended starting doses for intravenous Ig in humoral immunodeficiencies include a bolus of 1 mg/kg followed by monthly infusions starting at 400 mg/kg, while subcutaneous Ig infusion typically starts at 100–200 mg/kg/week [14, 152]. While the literature describes a minimum serum level of 500 mg/dl and a common trough target of 600 mg/dl in CVID, other studies have suggested a benefit in dosing as high as 800 mg/dl in agammaglobulinemic patients [25, 46, 147]. Extrapolation of these agammaglobulinemia patient data to CVID is not necessarily appropriate, as other reports caution against the utility of dosing to trough levels in disorders such as CVID where some level of endogenous antibody production exists [35, 156]. Some authors recommend consideration of dose adjustments based on clinical response rather than trough levels [156]. Intravenous Ig preparations vary with regard to excipients, fluid loads, and IgA content and are not necessarily interchangeable [25, 157]. Current consensus guidelines recognize immunoglobulin preparations as equally effective, though availability and individual patient characteristics may guide initial choices [14]. The possibility of generating anti-IgA antibodies and subsequent IgA reactions in patients with coexistent IgA deficiency has long been recognized, but may be minimized with the use of low-IgA preparations [147, 158–160]. In selected cases, testing for anti-IgA IgE may be helpful to prevent this risk [147]. Potential indications with regard to specific characteristics of different preparations in given patient populations are listed in table 7 [161]. While the administration of subcutaneous preparations may diminish certain risks associated with the intravenous agents, they require more frequent dosing [147, 152, 156, 161].

Antibiotics

Although parenteral Ig replacement has been shown to be safe and effective in CVID, infections are not uncommon [19, 35, 82, 148, 157] and the choice of an appropriate antibiotic therapy is indicated in the setting of

Table 7. Selected IVIG preparations and considerations for specific patient populations [14, 147, 156, 188]

Preparation	Excipient/contaminant	Populations at risk
Gammagard 5%/10%	glucose	diabetics
Polygam S/D	glucose	diabetics
IVEEGAM-EN	glucose	diabetics
Gaminune-N 5%	maltose	diabetics (false meter reading)
Octagam	maltose	diabetics (false meter reading)
Gamunex	glycine	glycine metabolic disorders/reactivities
Gammagard	glycine	glycine metabolic disorders/reactivities
Polygam S/D	glycine	glycine metabolic disorders/reactivities
Carimune	IgA	IgA hypersensitivity
IVEEGAM-EN	IgA	IgA hypersensitivity
Privigen	IgA	IgA hypersensitivity
Venoglobulin-S	IgA	IgA hypersensitivity
Gamunex	IgA	IgA hypersensitivity
Octagam	IgA	IgA hypersensitivity
Panglobulin	IgA	IgA hypersensitivity
Privigen	proline	proline metabolic disorders/reactivities
Carimune	sucrose	renal insufficiency
Panglobulin	sucrose	renal insufficiency
Solutions under 10%	dilute fluids	water restriction, infants

acute infection. The appropriateness of a continuous rotation of antibiotics is unclear, as there are no data from well-designed studies to address their use [38], but published opinion supports ongoing antibiotic prophylaxis in CVID patients with bronchiectasis or persistent infections [6, 14].

Screening for Pulmonary Abnormalities

The recommended schedule of tests for patients with CVID is illustrated in table 8. First-line screening studies such as chest X-ray and pulmonary function tests fail to identify a significant number of patients that have granulomatous and interstitial disease or structural changes on CT scans [41, 44, 48]. Current practice parameters and published opinions support the use of an initial chest CT at the time of diagnosis of CVID, with some authors recommending the routine use of periodic CT as often as every 12–24 months to evaluate for the development or progression of pulmonary complications [9, 41, 157, 162]. However, there have been increasing concerns of the iatrogenic cancer risk with the rising use of CT in both adult and pediatric patients, and CVID patients may be at higher risk for radiosensitivity [163–166]. Given the risks

Table 8. Recommended monitoring and procedure regimen in patients with CVID

Procedure	Interval
Chest CT [167]	diagnosis and every 5 years
Esophagogastroduodenoscopy [35, 167]	diagnosis, consider every 2 years
H. pylori stool antigen [167]	annually
Abdominal ultrasound [35, 167]	annually
Pulmonary function test [14, 167]	annually
Liver enzymes [14]	every 3–6 months
Serum chemistries [14]	every 3–6 months
IgG levels (children) [14]	every 3–6 months
IgG levels (adults) [14]	every 3–6 months
Office evaluation by clinical immunologist [14]	every 6–12 months
Inactivated influenza vaccination [14]	yearly
Inactivated/killed vaccines [14]	per general population guidelines
Live virus vaccines [14]	contraindicated
Complete blood count [35, 189]	consider every 3–6 months

of X-ray exposure, some groups have used monitoring with CT scan at intervals of 4–5 years, with interim annual pulmonary function testing [35, 167].

Screening for Digestive Complications

The modality and frequency of radiographic and endoscopic screening for gastrointestinal disease in CVID has not been addressed in the most recent practice parameter from the Joint Council of Allergy, Asthma, and Immunology. When a defined protocol for gastrointestinal screening included biannual endoscopy and yearly ultrasound, the prevalence of gastrointestinal manifestations increased over time despite the use of IVIG [35]. Other centers currently use endoscopy at the time of diagnosis, yearly *Helicobacter pylori* screening, and follow-up endoscopy as indicated [167].

Screening for Hematologic Complications

Practice guidelines currently do not address the recommended frequency of screening for hematologic complications of CVID. Intervals of 3–6 months are recommended for monitoring of patients on IVIG treatment and may guide practical considerations in determining the frequency of hematologic laboratory monitoring [35].

Screening for Neoplasia

Patients with CVID are at higher risk for malignancy. Although some types of cancers might be detected earlier using CVID-specific screening procedures for complications, age-adjusted cancer screening programs as recommended for the general public apply also to CVID [82].

Conclusions and Future Directions

Recent advances in molecular diagnostics have expanded our understanding of the wide spectrum of CVID and highlighted the concept of the disorder being a syndrome with multiple putative causes. While the availability of Ig replacement has greatly improved the outcome for patients, this approach neither cures nor eliminates disease associated with the syndrome. The care of CVID patients still requires lifelong clinical vigilance and appropriate management of complications of both the disorder and the treatments chosen. The recently established registries – USIDnet in the United States, ESID in Europe and RAPID in Asia – will enable further characterization of the clinical and molecular pathogenesis of CVID, improving our understanding of the mechanisms of immunity as they further the cause of caring for our patients by allowing the collection of significant series of patients with similar clinical features [168–170].

References

1 Cooper MD, Faulk WP, Fudenberg HH, Good RA, Hitzig W, Kunkel H, Rosen FS, Seligmann M, Soothill J, Wedgwood RJ: Classification of primary immunodeficiencies. N Engl J Med 1973;288:966–967.

2 Spickett GP, Farrant J, North ME, Zhang JG, Morgan L, Webster AD: Common variable immunodeficiency: how many diseases? Immunol Today 1997;18:325–328.

3 Janeway CA, Apt L, Gitlin D: Agammaglobulinemia. Trans Assoc Am Physicians 1953; 66:200–202.

4 Primary immunodeficiency diseases. Report of an IUIS Scientific Committee. International Union of Immunological Societies. Clin Exp Immunol 1999;118(suppl 1):1–28.

5 Boncristiano M, Majolini MB, D'Elios MM, Pacini S, Valensin S, Ulivieri C, Amedei A, Falini B, Del Prete G, Telford JL, Baldari CT: Defective recruitment and activation of ZAP-70 in common variable immunodeficiency patients with T cell defects. Eur J Immunol 2000;30:2632–2638.

6 Buckley RH: Pulmonary complications of primary immunodeficiencies. Paediatr Respir Rev 2004;5(suppl A):S225–S233.

7 Grimbacher B, Hutloff A, Schlesier M, Glocker E, Warnatz K, Drager R, Eibel H, Fischer B, Schaffer AA, Mages HW, Kroczek RA, Peter HH: Homozygous loss of ICOS is associated with adult-onset common variable immunodeficiency. Nat Immunol 2003; 4:261–268.

8 Jaffe JS, Eisenstein E, Sneller MC, Strober W: T-cell abnormalities in common variable immunodeficiency. Pediatr Res 1993;33: S24–S27; discussion S27–S28.

9 Morimoto Y, Routes JM: Immunodeficiency overview. Prim Care 2008;35:159–173, viii.

10 Salzer U, Grimbacher B: Monogenetic defects in common variable immunodeficiency: what can we learn about terminal B cell differentiation? Curr Opin Rheumatol 2006; 18:377–382.

11 Sneller MC, Strober W, Eisenstein E, Jaffe JS, Cunningham-Rundles C: NIH conference: new insights into common variable immunodeficiency. Ann Intern Med 1993;118: 720–730.

12 Di Renzo M, Pasqui AL, Auteri A: Common variable immunodeficiency: a review. Clin Exp Med 2004;3:211–217.

13 Schaffer AA, Salzer U, Hammarstrom L, Grimbacher B: Deconstructing common variable immunodeficiency by genetic analysis. Curr Opin Genet Dev 2007;17:201–212.

14 Bonilla FA, Bernstein IL, Khan DA, Ballas ZK, Chinen J, Frank MM, Kobrynski LJ, Levinson AI, Mazer B, Nelson RP Jr., Orange JS, Routes JM, Shearer WT, Sorensen RU: Practice parameter for the diagnosis and management of primary immunodeficiency. Ann Allergy Asthma Immunol 2005;94:S1–S63.

15 Castigli E, Geha RS: TACI, isotype switching, CVID and IgAD. Immunol Res 2007;38: 102–111.

16 Cunningham-Rundles C: Clinical and immunologic studies of common variable immunodeficiency. Curr Opin Pediatr 1994;6: 676–681.

17 Hammarstrom L, Vorechovsky I, Webster D: Selective IgA deficiency (SIgAD) and common variable immunodeficiency (CVID). Clin Exp Immunol 2000;120:225–231.

18 Centers for Disease Control and Prevention: HIV prevalence estimates: United States, 2006. MMWR Morb Mortal Wkly Rep 2008; 57:1073–1076.

19 Cunningham-Rundles C, Bodian C: Common variable immunodeficiency: clinical and immunological features of 248 patients. Clin Immunol 1999;92:34–48.

20 Mehra A, Sidi P, Doucette J, Estrella L, Rouvelas H, Cunningham-Rundles C: Subspecialty evaluation of chronically ill hospitalized patients with suspected immune defects. Ann Allergy Asthma Immunol 2007; 99:143–150.

21 Yarmohammadi H, Estrella L, Doucette J, Cunningham-Rundles C: Recognizing primary immune deficiency in clinical practice. Clin Vaccine Immunol 2006;13:329–332.

22 Eades-Perner AM, Gathmann B, Knerr V, Guzman D, Veit D, Kindle G, Grimbacher B: The European internet-based patient and research database for primary immunodeficiencies: results 2004–2006. Clin Exp Immunol 2007;147:306–312.

23 De Santis W, Esposito A, Conti V, Fantauzzi A, Guerra A, Mezzaroma I, Aiuti F: Health care and infective aspects in patients affected by common variable immunodeficiency assisted in the Lazio Regional Authority Reference Centre for Primary Immunodeficiencies (in Italian). Infez Med 2006;14:13–23.

24 Cunningham-Rundles C, Sidi P, Estrella L, Doucette J: Identifying undiagnosed primary immunodeficiency diseases in minority subjects by using computer sorting of diagnosis codes. J Allergy Clin Immunol 2004; 113:747–755.

25 Agarwal S, Cunningham-Rundles C: Assessment and clinical interpretation of reduced IgG values. Ann Allergy Asthma Immunol 2007;99:281–283.

26 Mrusek S, Marx A, Kummerle-Deschner J, Tzaribachev N, Enders A, Riede UN, Warnatz K, Dannecker GE, Ehl S: Development of granulomatous common variable immunodeficiency subsequent to infection with *Toxoplasma gondii*. Clin Exp Immunol 2004; 137:578–583.

27 Buckley RH: Primary immunodeficiency or not? Making the correct diagnosis. J Allergy Clin Immunol 2006;117:756–758.

28 Conley ME, Notarangelo LD, Etzioni A: Diagnostic criteria for primary immunodeficiencies: representing PAGID (Pan-American Group for Immunodeficiency) and ESID (European Society for Immunodeficiencies). Clin Immunol 1999;93:190–197.

29 Buckley RH: Primary Immunodeficiency Diseases; A. W. Burks, B. W., R. S., et al. ATS/AAAAI 2008 Pulmonary And Allergy Fellows Symposia. Toronto, 2008, 189–240.

30 Eastwood D, Gilmour KC, Nistala K, Meaney C, Chapel H, Sherrell Z, Webster AD, Davies EG, Jones A, Gaspar HB: Prevalence of SAP gene defects in male patients diagnosed with common variable immunodeficiency. Clin Exp Immunol 2004;137:584–588.

31 Goldacker S, Warnatz K: Tackling the heterogeneity of CVID. Curr Opin Allergy Clin Immunol 2005;5:504–509.

32 Salzer U, Hagena T, Webster DB, Grimbacher B: Sequence analysis of BIRC4/XIAP in male patients with common variable immunodeficiency. Int Arch Allergy Immunol 2008;147:147–151.

33 Weston SA, Prasad ML, Mullighan CG, Chapel H, Benson EM: Assessment of male CVID patients for mutations in the Btk gene: how many have been misdiagnosed? Clin Exp Immunol 2001;124:465–469.

34 Hermaszewski RA, Webster AD: Primary hypogammaglobulinaemia: a survey of clinical manifestations and complications. Q J Med 1993;86:31–42.

35 Quinti I, Soresina A, Spadaro G, Martino S, Donnanno S, Agostini C, Claudio P, Franco D, Maria Pesce A, Borghese F, Guerra A, Rondelli R, Plebani A: Long-term follow-up and outcome of a large cohort of patients with common variable immunodeficiency. J Clin Immunol 2007;27:308–316.

36 Van der Hilst JC, Smits BW, van der Meer JW: Hypogammaglobulinaemia: cumulative experience in 49 patients in a tertiary care institution. Neth J Med 2002;60:140–147.

37 Geha RS, Notarangelo LD, Casanova JL, Chapel H, Conley ME, Fischer A, Hammarstrom L, Nonoyama S, Ochs HD, Puck JM, Roifman C, Seger R, Wedgwood J: Primary immunodeficiency diseases: an update from the International Union of Immunological Societies Primary Immunodeficiency Diseases Classification Committee. J Allergy Clin Immunol 2007;120:776–794.

38 Busse PJ, Farzan S, Cunningham-Rundles C: Pulmonary complications of common variable immunodeficiency. Ann Allergy Asthma Immunol 2007;98:1–8; quiz 8–11, 43.

39 Curtin JJ, Webster AD, Farrant J, Katz D: Bronchiectasis in hypogammaglobulinaemia: a computed tomography assessment. Clin Radiol 1991;44:82–84.

40 Hermans PE, Diaz-Buxo JA, Stobo JD: Idiopathic late-onset immunoglobulin deficiency: clinical observations in 50 patients. Am J Med 1976;61:221–237.

41 Kainulainen L, Varpula M, Liippo K, Svedstrom E, Nikoskelainen J, Ruuskanen O: Pulmonary abnormalities in patients with primary hypogammaglobulinemia. J Allergy Clin Immunol 1999;104:1031–1036.

42 Litzman J, Freiberger T, Grimbacher B, Gathmann B, Salzer U, Pavlik T, Vlcek J, Postranecka V, Travnickova Z, Thon V: Mannose-binding lectin gene polymorphic variants predispose to the development of bronchopulmonary complications but have no influence on other clinical and laboratory symptoms or signs of common variable immunodeficiency. Clin Exp Immunol 2008; 153:324–330.

43 Martinez Garcia MA, de Rojas MD, Nauffal Manzur MD, Munoz Pamplona MP, Compte Torrero L, Macian V, Perpina Tordera M: Respiratory disorders in common variable immunodeficiency. Respir Med 2001;95:191–195.

44 Obregon RG, Lynch DA, Kaske T, Newell JD Jr., Kirkpatrick CH: Radiologic findings of adult primary immunodeficiency disorders: contribution of CT. Chest 1994;106:490–495.

45 Ogershok PR, Hogan MB, Welch JE, Corder WT, Wilson NW: Spectrum of illness in pediatric common variable immunodeficiency. Ann Allergy Asthma Immunol 2006;97:653–656.

46 Quartier P, Debre M, De Blic J, de Sauverzac R, Sayegh N, Jabado N, Haddad E, Blanche S, Casanova JL, Smith CI, Le Deist F, de Saint Basile G, Fischer A: Early and prolonged intravenous immunoglobulin replacement therapy in childhood agammaglobulinemia: a retrospective survey of 31 patients. J Pediatr 1999;134:589–596.

47 Sweinberg SK, Wodell RA, Grodofsky MP, Greene JM, Conley ME: Retrospective analysis of the incidence of pulmonary disease in hypogammaglobulinemia. J Allergy Clin Immunol 1991;88:96–104.

48 Tanaka N, Kim JS, Bates CA, Brown KK, Cool CD, Newell JD, Lynch DA: Lung diseases in patients with common variable immunodeficiency: chest radiographic, and computed tomographic findings. J Comput Assist Tomogr 2006;30:828–838.

49 Bates CA, Ellison MC, Lynch DA, Cool CD, Brown KK, Routes JM: Granulomatous-lymphocytic lung disease shortens survival in common variable immunodeficiency. J Allergy Clin Immunol 2004;114:415–421.

50 Dibbern DA Jr., Claman HN, Dreskin SC: Dyspnea and pulmonary infiltrates in a 53-year-old woman with common variable immunodeficiency. Ann Allergy Asthma Immunol 2001;87:18–21.

51 Morimoto Y, Routes JM: Granulomatous disease in common variable immunodeficiency. Curr Allergy Asthma Rep 2005;5:370–375.

52 Daniels JA, Lederman HM, Maitra A, Montgomery EA: Gastrointestinal tract pathology in patients with common variable immunodeficiency (CVID): a clinicopathologic study and review. Am J Surg Pathol 2007;31:1800–1812.

53 Stack E, Washington K, Avant GR, Eisen GM: Cytomegalovirus enteritis in common variable immunodeficiency. South Med J 2004;97:96–101.

54 Tarr PE, Sneller MC, Mechanic LJ, Economides A, Eger CM, Strober W, Cunningham-Rundles C, Lucey DR: Infections in patients with immunodeficiency with thymoma (Good syndrome): report of 5 cases and review of the literature. Medicine (Baltimore) 2001;80:123–133.

55 Bjorkander J, Cunningham-Rundles C, Lundin P, Olsson R, Soderstrom R, Hanson LA: Intravenous immunoglobulin prophylaxis causing liver damage in 16 of 77 patients with hypogammaglobulinemia or IgG subclass deficiency. Am J Med 1988;84:107–111.

56 Fukushima K, Ueno Y, Kanegane H, Yamagiwa Y, Inoue J, Kido O, Nagasaki F, Kogure T, Kakazu E, Nakagome Y, Matsuda Y, Obara N, Kimura O, Shimosegawa T: A case of severe recurrent hepatitis with common variable immunodeficiency. Hepatol Res 2008;38:415–420.

57 Razvi S, Schneider L, Jonas MM, Cunningham-Rundles C: Outcome of intravenous immunoglobulin-transmitted hepatitis C virus infection in primary immunodeficiency. Clin Immunol 2001;101:284–288.

58 Thatayatikom A, Thatayatikom S, White AJ: Infliximab treatment for severe granulomatous disease in common variable immunodeficiency: a case report and review of the literature. Ann Allergy Asthma Immunol 2005;95:293–300.

59 Brandt D, Gershwin ME: Common variable immune deficiency and autoimmunity. Autoimmun Rev 2006;5:465–470.

60 Iyengar SR, Blackburn BG, Lewis DB: Severe hypogammaglobulinemia and absent B cells in an adult patient: a case report. J Allergy Clin Immunol 2007;119(suppl 1):S256.

61 Jerschow E, De Vos GS, Hudes G, Rubinstein A, Lipsitz EC, Rosenstreich D: A case of common variable immunodeficiency syndrome associated with Takayasu arteritis. Ann Allergy Asthma Immunol 2007;98:196–199.

62 Cunningham-Rundles C: Hematologic complications of primary immune deficiencies. Blood Rev 2002;16:61–64.

63 Chen X, Jensen PE: MHC class II antigen presentation and immunological abnormalities due to deficiency of MHC class II and its associated genes. Exp Mol Pathol 2008;85:40–44.

64 Ehlers M, Ravetch JV: Opposing effects of Toll-like receptor stimulation induce autoimmunity or tolerance. Trends Immunol 2007;28:74–79.

65 Harrison LC, Honeyman MC, Morahan G, Wentworth JM, Elkassaby S, Colman PG, Fourlanos S: Type 1 diabetes: lessons for other autoimmune diseases? J Autoimmun 2008;31:306–310.

66 Hogan TV, Ang DK, Gleeson PA, van Driel IR: Extrathymic mechanisms of T cell tolerance: Lessons from autoimmune gastritis. J Autoimmun 2008;31:268–273.

67 Jordan MA, Baxter AG: The genetics of immunoregulatory T cells. J Autoimmun 2008; 31:237–244.

68 Lan RY, Mackay IR, Gershwin ME: Regulatory T cells in the prevention of mucosal inflammatory diseases: patrolling the border. J Autoimmun 2007;29:272–280.

69 Morahan G, Peeva V, Mehta M, Williams R: Systems genetics can provide new insights into immune regulation and autoimmunity. J Autoimmun 2008;31:233–236.

70 Ryan KR, Patel SD, Stephens LA, Anderton SM: Death, adaptation and regulation: the three pillars of immune tolerance restrict the risk of autoimmune disease caused by molecular mimicry. J Autoimmun 2007;29:262–271.

71 Pai S, Thomas R: Immune deficiency or hyperactivity-Nf-kappab illuminates autoimmunity. J Autoimmun 2008;31:245–251.

72 Poletaev AB, Stepanyuk VL, Gershwin ME: Integrating immunity: the immunculus and self-reactivity. J Autoimmun 2008;30:68–73.

73 Ng YS, Wardemann H, Chelnis J, Cunningham-Rundles C, Meffre E: Bruton's tyrosine kinase is essential for human B cell tolerance. J Exp Med 2004;200:927–934.

74 Michel M, Chanet V, Galicier L, Ruivard M, Levy Y, Hermine O, Oksenhendler E, Schaeffer A, Bierling P, Godeau B: Autoimmune thrombocytopenic purpura and common variable immunodeficiency: analysis of 21 cases and review of the literature. Medicine (Baltimore) 2004;83:254–263.

75 Arnold DF, Wiggins J, Cunningham-Rundles C, Misbah SA, Chapel HM: Granulomatous disease: distinguishing primary antibody disease from sarcoidosis. Clin Immunol 2008;128:18–22.

76 Sutor G, Fabel H: Sarcoidosis and common variable immunodeficiency: a case of a malignant course of sarcoidosis in conjunction with severe impairment of the cellular and humoral immune system. Respiration 2000; 67:204–208.

77 Wang J, Cunningham-Rundles C: Treatment and outcome of autoimmune hematologic disease in common variable immunodeficiency (CVID). J Autoimmun 2005;25:57–62.

78 Wang J, Rodriguez-Davalos M, Levi G, Sauter B, Gondolesi GE, Cunningham-Rundles C: Common variable immunodeficiency presenting with a large abdominal mass. J Allergy Clin Immunol 2005;115:1318–1320.

79 Wehr C, Kivioja T, Schmitt C, Ferry B, Witte T, Eren E, Vlkova M, Hernandez M, Detkova D, Bos PR, Poerksen G, von Bernuth H, Baumann U, Goldacker S, Gutenberger S, Schlesier M, Bergeron-van der Cruyssen F, Le Garff M, Debre P, Jacobs R, Jones J, Bateman E, Litzman J, van Hagen PM, Plebani A, Schmidt RE, Thon V, Quinti I, Espanol T, Webster AD, Chapel H, Vihinen M, Oksenhendler E, Peter HH, Warnatz K: The EUROclass trial: defining subgroups in common variable immunodeficiency. Blood 2008;111:77–85.

80 Wheat WH, Cool CD, Morimoto Y, Rai PR, Kirkpatrick CH, Lindenbaum BA, Bates CA, Ellison MC, Serls AE, Brown KK, Routes JM: Possible role of human herpesvirus 8 in the lymphoproliferative disorders in common variable immunodeficiency. J Exp Med 2005; 202:479–484.

81 Cunningham-Rundles C, Routes JM, Hostoffer R, Sullivan KE: Uncommon conundrum in common variable immunodeficiency. Clin Immunol 2005;116:208–210.

82 Park MA, Li JT, Hagan JB, Maddox DE, Abraham RS: Common variable immunodeficiency: a new look at an old disease. Lancet 2008;372:489–502.

83 Cunningham-Rundles C, Cooper DL, Duffy TP, Strauchen J: Lymphomas of mucosal-associated lymphoid tissue in common variable immunodeficiency. Am J Hematol 2002; 69:171–178.

84 Cunningham-Rundles C, Siegal FP, Cunningham-Rundles S, Lieberman P: Incidence of cancer in 98 patients with common varied immunodeficiency. J Clin Immunol 1987;7: 294–299.

85 Kinlen LJ, Webster AD, Bird AG, Haile R, Peto J, Soothill JF, Thompson RA: Prospective study of cancer in patients with hypogammaglobulinaemia. Lancet 1985;1:263–266.

86 Mellemkjaer L, Hammarstrom L, Andersen V, Yuen J, Heilmann C, Barington T, Bjorkander J, Olsen JH: Cancer risk among patients with IgA deficiency or common variable immunodeficiency and their relatives: a combined Danish and Swedish study. Clin Exp Immunol 2002;130:495–500.

87 Zenone T, Souquet PJ, Cunningham-Rundles C, Bernard JP: Hodgkin's disease associated with IgA and IgG subclass deficiency. J Intern Med 1996;240:99–102.

88 Agarwal S, Cunningham-Rundles C: Thymoma and immunodeficiency (Good syndrome): a report of 2 unusual cases and review of the literature. Ann Allergy Asthma Immunol 2007;98:185–190.

89 Di Renzo M, Pasqui AL, Bruni F, Voltolini L, Gotti G, Auteri A: Hypogammaglobulinemia and thymoma (Good's syndrome): a case report and a literature review (in Italian). Ann Ital Med Int 2005;20:58–61.

90 Di Renzo M, Pasqui AL, Voltolini L, Gotti G, Pompella G, Auteri A: Myelodysplasia and Good syndrome: a case report. Clin Exp Med 2008;8:171–173.

91 Hon C, Chui WH, Cheng LC, Shek TW, Jones BM, Au WY: Thymoma associated with keratoconjunctivitis, lichen planus, hypogammaglobinemia, and absent circulating B cells. J Clin Oncol 2006;24:2960–2961.

92 Piqueras B, Lavenu-Bombled C, Galicier L, Bergeron-van der Cruyssen F, Mouthon L, Chevret S, Debre P, Schmitt C, Oksenhendler E: Common variable immunodeficiency patient classification based on impaired B cell memory differentiation correlates with clinical aspects. J Clin Immunol 2003;23:385–400.

93 Warnatz K, Denz A, Drager R, Braun M, Groth C, Wolff-Vorbeck G, Eibel H, Schlesier M, Peter HH: Severe deficiency of switched memory B cells (CD27(+)IgM(–)IgD(–)) in subgroups of patients with common variable immunodeficiency: a new approach to classify a heterogeneous disease. Blood 2002;99:1544–1551.

94 Berglund LJ, Wong SW, Fulcher DA: B-cell maturation defects in common variable immunodeficiency and association with clinical features. Pathology 2008;40:288–294.

95 Bulley SR, Zhang J, Kwong S, Roifman C: Newly diagnosed X-linked agammaglobulinemia (XLA), bruton's tyrosine kinase (Btk) mutation, in a 39 year-old male. J Allergy Clin Immunol 2002;109:S188.

96 Hashimoto S, Miyawaki T, Futatani T, Kanegane H, Usui K, Nukiwa T, Namiuchi S, Matsushita M, Yamadori T, Suemura M, Kishimoto T, Tsukada S: Atypical X-linked agammaglobulinemia diagnosed in three adults. Intern Med 1999;38:722–725.

97 Kanegane H, Futatani T, Wang Y, Nomura K, Shinozaki K, Matsukura H, Kubota T, Tsukada S, Miyawaki T: Clinical and mutational characteristics of X-linked agammaglobulinemia and its carrier identified by flow cytometric assessment combined with genetic analysis. J Allergy Clin Immunol 2001;108: 1012–1020.

98 Kanegane H, Tsukada S, Iwata T, Futatani T, Nomura K, Yamamoto J, Yoshida T, Agematsu K, Komiyama A, Miyawaki T: Detection of Bruton's tyrosine kinase mutations in hypogammaglobulinaemic males registered as common variable immunodeficiency (CVID) in the Japanese Immunodeficiency Registry. Clin Exp Immunol 2000;120:512–517.

99 Kornfeld SJ, Haire RN, Strong SJ, Tang H, Sung SS, Fu SM, Litman GW: A novel mutation (Cys145→Stop) in Bruton's tyrosine kinase is associated with newly diagnosed X-linked agammaglobulinemia in a 51-year-old male. Mol Med 1996;2:619–623.

100 Lee WI, Huang JL, Kuo ML, Lin SJ, Chen LC, Chen MT, Jaing TH: Analysis of genetic defects in patients with the common variable immunodeficiency phenotype in a single Taiwanese tertiary care hospital. Ann Allergy Asthma Immunol 2007;99:433–442.

101 Lee WI, Torgerson TR, Schumacher MJ, Yel L, Zhu Q, Ochs HD: Molecular analysis of a large cohort of patients with the hyper immunoglobulin M (IgM) syndrome. Blood 2005;105:1881–1890.

102 Lin MT, Chien YH, Shyur SD, Huang LH, Chiang YC, Wen DC, Liang PH, Yang HC: De novo mutation in the BTK gene of atypical X-linked agammaglobulinemia in a patient with recurrent pyoderma. Ann Allergy Asthma Immunol 2006;96:744–748.

103 Mitsui T, Tsukamoto N, Kanegane H, Agematsu K, Sekigami T, Irisawa H, Saitoh T, Uchiumi H, Handa H, Matsushima T, Karasawa M, Murakami T, Miyawaki T, Nojima Y: X-linked agammaglobulinemia diagnosed in adulthood: a case report. Int J Hematol 2006;84:154–157.

104 Noordzij JG, de Bruin-Versteeg S, Hartwig NG, Weemaes CM, Gerritsen EJ, Bernatowska E, van Lierde S, de Groot R, van Dongen JJ: XLA patients with BTK splice-site mutations produce low levels of wild-type BTK transcripts. J Clin Immunol 2002;22:306–318.

105 Sigmon JR, Kasasbeh E, Krishnaswamy G: X-linked agammaglobulinemia diagnosed late in life: case report and review of the literature. Clin Mol Allergy 2008;6:5.

106 Stewart DM, Tian L, Nelson DL: A case of X-linked agammaglobulinemia diagnosed in adulthood. Clin Immunol 2001;99:94–99.

107 Usui K, Sasahara Y, Tazawa R, Hagiwara K, Tsukada S, Miyawaki T, Tsuchiya S, Nukiwa T: Recurrent pneumonia with mild hypogammaglobulinemia diagnosed as X-linked agammaglobulinemia in adults. Respir Res 2001;2:188–192.

108 Aghamohammadi A, Kanegane H, Moein M, Farhoudi A, Pourpak Z, Movahedi M, Gharagozlou M, Zargar AA, Miyawaki T: Identification of an SH2D1A mutation in a hypogammaglobulinemic male patient with a diagnosis of common variable immunodeficiency. Int J Hematol 2003;78:45–47.

109 Morra M, Silander O, Calpe S, Choi M, Oettgen H, Myers L, Etzioni A, Buckley R, Terhorst C: Alterations of the X-linked lymphoproliferative disease gene SH2D1A in common variable immunodeficiency syndrome. Blood 2001;98:1321–1325.

110 Nistala K, Gilmour KC, Cranston T, Davies EG, Goldblatt D, Gaspar HB, Jones AM: X-linked lymphoproliferative disease: three atypical cases. Clin Exp Immunol 2001; 126:126–130.

111 Soresina A, Lougaris V, Giliani S, Cardinale F, Armenio L, Cattalini M, Notarangelo LD, Plebani A: Mutations of the X-linked lymphoproliferative disease gene SH2D1A mimicking common variable immunodeficiency. Eur J Pediatr 2002;161:656–659.

112 Bacchelli C, Buckridge S, Thrasher AJ, Gaspar HB: Translational mini-review series on immunodeficiency: molecular defects in common variable immunodeficiency. Clin Exp Immunol 2007;149:401–409.

113 Salzer U, Grimbacher B: Common variable immunodeficiency: the power of co-stimulation. Semin Immunol 2006;18:337–346.

114 Fischer MB, Hauber I, Vogel E, Wolf HM, Mannhalter JW, Eibl MM: Defective interleukin-2 and interferon-gamma gene expression in response to antigen in a subgroup of patients with common variable immunodeficiency. J Allergy Clin Immunol 1993;92:340–352.

115 Holm AM, Sivertsen EA, Tunheim SH, Haug T, Bjerkeli V, Yndestad A, Aukrust P, Froland SS: Gene expression analysis of peripheral T cells in a subgroup of common variable immunodeficiency shows predominance of CCR7(–) effector-memory T cells. Clin Exp Immunol 2004;138:278–289.

116 North ME, Webster AD, Farrant J: Defects in proliferative responses of T cells from patients with common variable immunodeficiency on direct activation of protein kinase C. Clin Exp Immunol 1991;85:198–201.

117 Hutloff A, Dittrich AM, Beier KC, Eljaschewitsch B, Kraft R, Anagnostopoulos I, Kroczek RA: ICOS is an inducible T-cell costimulator structurally and functionally related to CD28. Nature 1999;397:263–266.

118 Carreno BM, Collins M: The B7 family of ligands and its receptors: new pathways for costimulation and inhibition of immune responses. Annu Rev Immunol 2002;20:29–53.

119 Ohm-Laursen L, Schjebel L, Jacobsen K, Permin H, Svejgaard A, Barington T: Normal ICOS, ICOSL and AID alleles in Danish patients with common variable immunodeficiency. Scand J Immunol 2005;61:566–574.

120 Salzer U, Maul-Pavicic A, Cunningham-Rundles C, Urschel S, Belohradsky BH, Litzman J, Holm A, Franco JL, Plebani A, Hammarstrom L, Skrabl A, Schwinger W, Grimbacher B: ICOS deficiency in patients with common variable immunodeficiency. Clin Immunol 2004;113:234–240.

121 Warnatz K, Bossaller L, Salzer U, Skrabl-Baumgartner A, Schwinger W, van der Burg M, van Dongen JJ, Orlowska-Volk M, Knoth R, Durandy A, Draeger R, Schlesier M, Peter HH, Grimbacher B: Human ICOS deficiency abrogates the germinal center reaction and provides a monogenic model for common variable immunodeficiency. Blood 2006;107:3045–3052.

122 Kanegane H, Agematsu K, Futatani T, Sira MM, Suga K, Sekiguchi T, van Zelm MC, Miyawaki T: Novel mutations in a Japanese patient with CD19 deficiency. Genes Immun 2007;8:663–670.

123 van Zelm MC, Reisli I, van der Burg M, Castano D, van Noesel CJ, van Tol MJ, Woellner C, Grimbacher B, Patino PJ, van Dongen JJ, Franco JL: An antibody-deficiency syndrome due to mutations in the CD19 gene. N Engl J Med 2006;354:1901–1912.

124 Fearon DT, Carroll MC: Regulation of B lymphocyte responses to foreign and self-antigens by the CD19/CD21 complex. Annu Rev Immunol 2000;18:393–422.

125 Carter RH, Fearon DT: CD19: lowering the threshold for antigen receptor stimulation of B lymphocytes. Science 1992;256:105–107.

126 Castigli E, Wilson S, Garibyan L, Rachid R, Bonilla F, Schneider L, Morra M, Curran J, Geha R: Reexamining the role of TACI coding variants in common variable immunodeficiency and selective IgA deficiency. Nat Genet 2007;39:430–431.

127 Castigli E, Wilson SA, Garibyan L, Rachid R, Bonilla F, Schneider L, Geha RS: TACI is mutant in common variable immunodeficiency and IgA deficiency. Nat Genet 2005;37:829–834.

128 Salzer U, Bacchelli C, Buckridge S, Pan-Hammarstrom Q, Jennings S, Lougaris V, Bergbreiter A, Hagena T, Birmelin J, Plebani A, Webster AD, Peter HH, Suez D, Chapel H, McLean-Tooke A, Spickett GP, Anover-Sombke S, Ochs HD, Urschel S, Belohradsky BH, Ugrinovic S, Kumararatne DS, Lawrence TC, Holm AM, Franco JL, Schulze I, Schneider P, Gertz EM, Schaffer AA, Hammarstrom L, Thrasher AJ, Gaspar HB, Grimbacher B: Relevance of biallelic versus monoallelic TNFRSF13B mutations in distinguishing disease-causing from risk-increasing TNFRSF13B variants in antibody deficiency syndromes. Blood 2009;113:1967–1976.

129 Salzer U, Chapel HM, Webster AD, Pan-Hammarstrom Q, Schmitt-Graeff A, Schlesier M, Peter HH, Rockstroh JK, Schneider P, Schaffer AA, Hammarstrom L, Grimbacher B: Mutations in TNFRSF13B encoding TACI are associated with common variable immunodeficiency in humans. Nat Genet 2005;37:820–828.

130 Zhang L, Radigan L, Salzer U, Behrens TW, Grimbacher B, Diaz G, Bussel J, Cunningham-Rundles C: Transmembrane activator and calcium-modulating cyclophilin ligand interactor mutations in common variable immunodeficiency: clinical and immunologic outcomes in heterozygotes. J Allergy Clin Immunol 2007;120:1178–1185.

131 Pan-Hammarstrom Q, Salzer U, Du L, Bjorkander J, Cunningham-Rundles C, Nelson DL, Bacchelli C, Gaspar HB, Offer S, Behrens TW, Grimbacher B, Hammarstrom L: Reexamining the role of TACI coding variants in common variable immunodeficiency and selective IgA deficiency. Nat Genet 2007;39:429–430.

132 Rachid R, Castigli E, Geha RS, Bonilla FA: TACI mutation in common variable immunodeficiency and IgA deficiency. Curr Allergy Asthma Rep 2006;6:357–362.

133 Jin R, Kaneko H, Suzuki H, Arai T, Teramoto T, Fukao T, Kondo N: Age-related changes in BAFF and APRIL profiles and upregulation of BAFF and APRIL expression in patients with primary antibody deficiency. Int J Mol Med 2008;21:233–238.

134 Mackay F, Schneider P, Rennert P, Browning J: BAFF and APRIL: a tutorial on B cell survival. Annu Rev Immunol 2003;21:231–264.

135 Sakurai D, Hase H, Kanno Y, Kojima H, Okumura K, Kobata T: TACI regulates IgA production by APRIL in collaboration with HSPG. Blood 2007;109:2961–2967.

136 Mackay F, Schneider P: TACI, an enigmatic BAFF/APRIL receptor, with new unappreciated biochemical and biological properties. Cytokine Growth Factor Rev 2008;19:263–276.

137 Salzer U, Grimbacher B: TACItly changing tunes: farewell to a yin and yang of BAFF receptor and TACI in humoral immunity? New genetic defects in common variable immunodeficiency. Curr Opin Allergy Clin Immunol 2005;5:496–503.

138 Salzer U, Jennings S, Grimbacher B: To switch or not to switch – the opposing roles of TACI in terminal B cell differentiation. Eur J Immunol 2007;37:17–20.

139 Grimbacher B, Salzer U, Franco JL, Warnatz K: The genetics of hypogammaglobulinemia. Inmunología 2005;24:384–386.

140 Losi CG, Silini A, Fiorini C, Soresina A, Meini A, Ferrari S, Notarangelo LD, Lougaris V, Plebani A: Mutational analysis of human BAFF receptor TNFRSF13C (BAFF-R) in patients with common variable immunodeficiency. J Clin Immunol 2005;25:496–502.

141 Ng LG, Sutherland AP, Newton R, Qian F, Cachero TG, Scott ML, Thompson JS, Wheway J, Chtanova T, Groom J, Sutton IJ, Xin C, Tangye SG, Kalled SL, Mackay F, Mackay CR: B cell-activating factor belonging to the TNF family (BAFF)-R is the principal BAFF receptor facilitating BAFF costimulation of circulating T and B cells. J Immunol 2004;173:807–817.

142 Castigli E, Wilson SA, Scott S, Dedeoglu F, Xu S, Lam KP, Bram RJ, Jabara H, Geha RS: TACI and BAFF-R mediate isotype switching in B cells. J Exp Med 2005;201:35–39.

143 Warnatz K, Salzer U, Gutenberger S, Schlesier M, Grimbacher B, Peter HH, Eibel H: Finally found: human BAFF-R deficiency causes hypogammaglobulinemia. Clin Immunol 2005;115:S20.

144 Sekine H, Ferreira RC, Pan-Hammarstrom Q, Graham RR, Ziemba B, de Vries SS, Liu J, Hippen K, Koeuth T, Ortmann W, Iwahori A, Elliott MK, Offer S, Skon C, Du L, Novitzke J, Lee AT, Zhao N, Tompkins JD, Altshuler D, Gregersen PK, Cunningham-Rundles C, Harris RS, Her J, Nelson DL, Hammarstrom L, Gilkeson GS, Behrens TW: Role for Msh5 in the regulation of Ig class switch recombination. Proc Natl Acad Sci USA 2007;104:7193–7198.

145 Wu X, Tsai CY, Patam MB, Zan H, Chen JP, Lipkin SM, Casali P: A role for the MutL mismatch repair Mlh3 protein in immunoglobulin class switch DNA recombination and somatic hypermutation. J Immunol 2006;176:5426–5437.

146 Bruton OC: Agammaglobulinemia. Pediatrics 1952;9:722–728.

147 Berger M: Principles of and advances in immunoglobulin replacement therapy for primary immunodeficiency. Immunol Allergy Clin North Am 2008;28:413–437.

148 Busse PJ, Razvi S, Cunningham-Rundles C: Efficacy of intravenous immunoglobulin in the prevention of pneumonia in patients with common variable immunodeficiency. J Allergy Clin Immunol 2002;109:1001–1004.

149 Garcia-Lloret M, McGhee S, Chatila TA: Immunoglobulin replacement therapy in children. Immunol Allergy Clin North Am 2008;28:833–849.

150 Berger M: Subcutaneous immunoglobulin replacement in primary immunodeficiencies. Clin Immunol 2004;112:1–7.

151 Berger M, Cupps TR, Fauci AS: Immunoglobulin replacement therapy by slow subcutaneous infusion. Ann Intern Med 1980;93:55–56.

152 Moore ML, Quinn JM: Subcutaneous immunoglobulin replacement therapy for primary antibody deficiency: advancements into the 21st century. Ann Allergy Asthma Immunol 2008;101:114–121; quiz 122–113, 178.

153 Gardulf A, Borte M, Ochs HD, Nicolay U: Prognostic factors for health-related quality of life in adults and children with primary antibody deficiencies receiving SCIG home therapy. Clin Immunol 2008;126:81–88.

154 Gardulf A, Nicolay U: Replacement IgG therapy and self-therapy at home improve the health-related quality of life in patients with primary antibody deficiencies. Curr Opin Allergy Clin Immunol 2006;6:434–442.

155 Gardulf A, Nicolay U, Math D, Asensio O, Bernatowska E, Bock A, Costa-Carvalho BT, Granert C, Haag S, Hernandez D, Kiessling P, Kus J, Matamoros N, Niehues T, Schmidt S, Schulze I, Borte M: Children and adults with primary antibody deficiencies gain quality of life by subcutaneous IgG self-infusions at home. J Allergy Clin Immunol 2004;114:936–942.

156 Orange JS, Hossny EM, Weiler CR, Ballow M, Berger M, Bonilla FA, Buckley R, Chinen J, El-Gamal Y, Mazer BD, Nelson RP Jr., Patel DD, Secord E, Sorensen RU, Wasserman RL, Cunningham-Rundles C: Use of intravenous immunoglobulin in human disease: a review of evidence by members of the Primary Immunodeficiency Committee of the American Academy of Allergy, Asthma and Immunology. J Allergy Clin Immunol 2006;117:S525–S553.

157 Gelfand EW, Goldsmith J, Lederman HM: Primary humoral immunodeficiency: optimizing IgG replacement therapy. Clin Focus Prim Immune Defic 2003;11:1–15.

158 Burks AW, Sampson HA, Buckley RH: Anaphylactic reactions after gamma globulin administration in patients with hypogammaglobulinemia: detection of IgE antibodies to IgA. N Engl J Med 1986;314:560–564.

159 Cunningham-Rundles C, Wong S, Bjorkander J, Hanson LA: Use of an IgA-depleted intravenous immunoglobulin in a patient with an anti-IgA antibody. Clin Immunol Immunopathol 1986;38:141–149.

160 Cunningham-Rundles C, Zhou Z, Mankarious S, Courter S: Long-term use of IgA-depleted intravenous immunoglobulin in immunodeficient subjects with anti-IgA antibodies. J Clin Immunol 1993;13:272–278.

161 Orange J: The nuts and bolts of immunoglobulin administration. Am Coll Allergy, Asthma Immunol Sci Meet, Seattle, 2008, pp 405–412.

162 Bates CA, Brown K, Routes J: Pulmonary disease associated with common variable immunodeficiency. J Allergy Clin Immunol 2002;109:S188.

163 FDA public health notification: reducing radiation risk from computed tomography for pediatric and small adult patients. Pediatr Radiol 2002;32:314–316.

164 Brenner D, Elliston C, Hall E, Berdon W: Estimated risks of radiation-induced fatal cancer from pediatric CT. AJR Am J Roentgenol 2001;176:289–296.

165 Brenner DJ, Hall EJ: Computed tomography: an increasing source of radiation exposure. N Engl J Med 2007;357:2277–2284.

166 Vorechovsky I, Scott D, Haeney MR, Webster DA: Chromosomal radiosensitivity in common variable immune deficiency. Mutat Res 1993;290:255–264.

167 Yong PFK, Tarzi M, Chua I, Grimbacher B, Chee R: Common variable immunodeficiency: an update on etiology and management. Immunol Allergy Clin North Am 2008;28:367–386.

168 Guzman D, Veit D, Knerr V, Kindle G, Gathmann B, Eades-Perner AM, Grimbacher B: The ESID Online Database network. Bioinformatics 2007;23:654–655.

169 Keerthikumar S, Raju R, Kandasamy K, Hijikata A, Ramabadran S, Balakrishnan L, Ahmed M, Rani S, Selvan LD, Somanathan DS, Ray S, Bhattacharjee M, Gollapudi S, Ramachandra YL, Bhadra S, Bhattacharyya C, Imai K, Nonoyama S, Kanegane H, Miyawaki T, Pandey A, Ohara O, Mohan S: RAPID: Resource of Asian Primary Immunodeficiency Diseases. Nucleic Acids Res 2008;37:D863–D867.

170 Ochs H, Cunningham Rundles C: US Immunodeficiency Network. www.usidnet.org/index.cfm.

171 Allen RC, Armitage RJ, Conley ME, et al: CD40 ligand gene defects responsible for X-linked hyper-IgM syndrome. Science 1993;259:990–993.

172 Aruffo A, Farrington M, Hollenbaugh D, et al: The CD40 ligand, gp39, is defective in activated T cells from patients with X-linked hyper-IgM syndrome. Cell 1993;72:291–300.

173 DiSanto JP, Bonnefoy JY, Gauchat JF, Fischer A, de Saint Basile G: CD40 ligand mutations in x-linked immunodeficiency with hyper-IgM. Nature 1993;361:541–543.

174 Farrington M, Grosmaire LS, Nonoyama S, Fischer SH, Hollenbaugh D, Ledbetter JA, Noelle RJ, Aruffo A, Ochs HD: CD40 ligand expression is defective in a subset of patients with common variable immunodeficiency. Proc Natl Acad Sci USA 1994;91:1099–1103.

175 Korthauer U, Graf D, Mages HW, Briere F, Padayachee M, Malcolm S, Ugazio AG, Notarangelo LD, Levinsky RJ, Kroczek RA: Defective expression of T-cell CD40 ligand causes X-linked immunodeficiency with hyper-IgM. Nature 1993;361:539–541.

176 Minegishi Y, Lavoie A, Cunningham-Rundles C, Bedard PM, Hebert J, Cote L, Dan K, Sedlak D, Buckley RH, Fischer A, Durandy A, Conley ME: Mutations in activation-induced cytidine deaminase in patients with hyper IgM syndrome. Clin Immunol 2000;97:203–210.

177 Revy P, Muto T, Levy Y, Geissmann F, Plebani A, Sanal O, Catalan N, Forveille M, Dufourcq-Labelouse R, Gennery A, Tezcan I, Ersoy F, Kayserili H, Ugazio AG, Brousse N, Muramatsu M, Notarangelo LD, Kinoshita K, Honjo T, Fischer A, Durandy A: Activation-induced cytidine deaminase (AID) deficiency causes the autosomal recessive form of the Hyper-IgM syndrome (HIGM2). Cell 2000;102:565–575.

178 Ferrari S, Giliani S, Insalaco A, Al-Ghonaium A, Soresina AR, Loubser M, Avanzini MA, Marconi M, Badolato R, Ugazio AG, Levy Y, Catalan N, Durandy A, Tbakhi A, Notarangelo LD, Plebani A: Mutations of CD40 gene cause an autosomal recessive form of immunodeficiency with hyper IgM. Proc Natl Acad Sci USA 2001;98: 12614–12619.

179 Imai K, Catalan N, Plebani A, Marodi L, Sanal O, Kumaki S, Nagendran V, Wood P, Glastre C, Sarrot-Reynauld F, Hermine O, Forveille M, Revy P, Fischer A, Durandy A: Hyper-IgM syndrome type 4 with a B lymphocyte-intrinsic selective deficiency in Ig class-switch recombination. J Clin Invest 2003;112:136–142.

180 Imai K, Slupphaug G, Lee WI, Revy P, Nonoyama S, Catalan N, Yel L, Forveille M, Kavli B, Krokan HE, Ochs HD, Fischer A, Durandy A: Human uracil-DNA glycosylase deficiency associated with profoundly impaired immunoglobulin class-switch recombination. Nat Immunol 2003;4:1023–1028.

181 Jain A, Ma CA, Liu S, Brown M, Cohen J, Strober W: Specific missense mutations in NEMO result in hyper-IgM syndrome with hypohydrotic ectodermal dysplasia. Nat Immunol 2001;2:223–228.

182 Saffran DC, Parolini O, Fitch-Hilgenberg ME, Rawlings DJ, Afar DE, Witte ON, Conley ME: Brief report: a point mutation in the SH2 domain of Bruton's tyrosine kinase in atypical X-linked agammaglobulinemia. N Engl J Med 1994;330:1488–1491.

183 Tsukada S, Saffran DC, Rawlings DJ, et al: Deficient expression of a B cell cytoplasmic tyrosine kinase in human X-linked agammaglobulinemia. Cell 1993;72:279–290.

184 Vetrie D, Vorechovsky I, Sideras P, et al: The gene involved in X-linked agammaglobulinaemia is a member of the src family of protein-tyrosine kinases. Nature 1993;361: 226–233.

185 Coffey AJ, Brooksbank RA, Brandau O, Oohashi T, Howell GR, Bye JM, Cahn AP, Durham J, Heath P, Wray P, Pavitt R, Wilkinson J, Leversha M, Huckle E, Shaw-Smith CJ, Dunham A, Rhodes S, Schuster V, Porta G, Yin L, Serafini P, Sylla B, Zollo M, Franco B, Bolino A, Seri M, Lanyi A, Davis JR, Webster D, Harris A, Lenoir G, de St Basile G, Jones A, Behloradsky BH, Achatz H, Murken J, Fassler R, Sumegi J, Romeo G, Vaudin M, Ross MT, Meindl A, Bentley DR: Host response to EBV infection in X-linked lymphoproliferative disease results from mutations in an SH2-domain encoding gene. Nat Genet 1998;20:129–135.

186 Rigaud S, Fondaneche MC, Lambert N, Pasquier B, Mateo V, Soulas P, Galicier L, Le Deist F, Rieux-Laucat F, Revy P, Fischer A, de Saint Basile G, Latour S: XIAP deficiency in humans causes an X-linked lymphoproliferative syndrome. Nature 2006; 444:110–114.

187 Sayos J, Wu C, Morra M, Wang N, Zhang X, Allen D, van Schaik S, Notarangelo L, Geha R, Roncarolo MG, Oettgen H, De Vries JE, Aversa G, Terhorst C: The X-linked lymphoproliferative-disease gene product SAP regulates signals induced through the co-receptor SLAM. Nature 1998;395:462–469.

188 Zhang R, Szerlip HM: Reemergence of sucrose nephropathy: acute renal failure caused by high-dose intravenous immune globulin therapy. South Med J 2000;93: 901–904.

189 Sewell WA, Buckland M, Jolles SR: Therapeutic strategies in common variable immunodeficiency. Drugs 2003;63:1359–1371.

Erratum

In the article 'Common Variable Immunodeficiency: Etiological and Treatment Considerations' (Int Arch Allergy Immunol 2009; 150: 311–324), the line 'Recommended starting doses for intravenous Ig in humoral immunodeficiencies include a bolus of 1 mg/kg followed by monthly infusions …' should read as follows: 'Recommended starting doses for intravenous Ig in humoral immunodeficiencies include a bolus of 1 g/kg (where agammaglobulinemia or severe hypogammaglobulinemia is present) followed by monthly infusions …'.