How I treat common variable immune deficiency

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Common variable immunodeficiency is a rare immune deficiency, characterized by low levels of serum immunoglobulin G, A, and/or M with loss of antibody production. The diagnosis is most commonly made in adults between the ages of 20 and 40 years, but both children and older adults can be found to have this immune defect. The range of clinical manifestations is broad, including acute and chronic infections, inflammatory and autoimmune disease, and an increased incidence of cancer and lymphoma. For all these reasons, the disease phenotype is both heterogeneous and complex. Contributing to the complexity is that patient cohorts are generally small, criteria used for diagnosis vary, and the doses of replacement immune globulin differ. In addition, routines for monitoring patients over the years and protocols for the use of other biologic agents for complications have not been clarified or standardized. In the past few years, data from large patient registries have revealed that both selected laboratory markers and clinical phenotyping may aid in dissecting groups of subjects into biologically relevant categories. This review presents my approach to the diagnosis and treatment of patients with common variable immunodeficiency, with suggestions for the use of laboratory biomarkers and means of monitoring patients. (*Blood*. 2010;116(1): 7-15)

Introduction

Common variable immunodeficiency (CVID) is the most common clinically important primary immune deficiency disease because of its prevalence, estimated to be between 1 in 25 000 to 50 000 white patients, complications, hospitalizations, and requirement for lifelong replacement immunoglobulin (Ig) therapy.[1,2] Unlike many genetic immune defects, most subjects diagnosed with CVID are adults between the ages of 20 and 40 years, although many are found outside this age range. Although the syndrome was first described more than 50 years ago,[3] the diagnosis is still commonly delayed by 6 to 8 years, even after the onset of characteristic symptoms. A number of reports[1,4-8] of cohorts of subjects with CVID have appeared. In appropriate doses, Ig replacement reduces the incidence of acute bacterial infections; however, Ig does not address the more problematic of complications that have now emerged as the foremost concerns, including chronic lung disease, systemic granulomatous disease, autoimmunity, lymphoid hyperplasia and infiltrative disease, gastrointestinal disease, and the development of cancer. These complications now appear to be the major cause of morbidity and death in patients with CVID.[1,9] This review is intended as a personal summary of how I assess patients at the outset and an outline for how one may monitor and treat some of these challenging complications.

Diagnosis of CVID

The diagnosis of CVID (International Classification of Diseases code 279.06) is often misused. It is defined as a genetic immune defect characterized by significantly decreased levels of immunoglobulin G (IgG), immunoglobulin A (IgA), and/or immunoglobulin M (IgM) with poor or absent antibody production, with exclusion of genetic or other causes of hypogammaglobulinemia.[1,2,9,10] On the basis of the standard definition, antibody deficiency with normal Ig levels, or IgG deficiency alone, would not qualify for the diagnosis of CVID. Because CVID is not always easily discerned from transient hypogammaglobulinemia of infancy, a general consensus is that this diagnosis should not be applied until after a patient reaches the age of 4. This allows time for the immune system to mature, and if necessary, for one to consider the possibility of other genetic primary immune defects. However, the published criteria still leave open rather wide boundaries. First laboratory standards for normal ranges differ; in addition, the use of the 95% percentile for Ig allows 2.5% of normal subjects to fall below the normal range.

Sometimes forgotten, the additional necessary criteria for CVID also include a proven lack of specific IgG antibody production, which is usually demonstrated by lack of IgG responses (not attaining laboratory-defined protective levels) to 2 or more protein vaccines, such as tetanus or diphtheria toxoids, Hemophilus conjugate, measles, mumps, and rubella vaccines, and also by a lack of response to pneumococcal polysaccharide vaccines. Other options for protein antigens include hepatitis A or B vaccines or varicella, either after vaccination or disease exposure. Examining blood for pertinent isohemagglutins is another a common means of testing (mostly) IgM anticarbohydrate antibody production in older children and adults.

Although extensive antibody testing is not as important for subjects with very low serum IgG (potentially $\leq$150 mg/dL), those with greater levels of serum IgG (450-600 mg/dL), and especially those with only minimally reduced serum IgA, require more extensive evaluation. It is more likely that these subjects have preservation of IgG antibody production and are therefore less likely to benefit from Ig therapy. A suggested template for such analyses is given in Table 1. Demonstration of persistence of IgG antibody at 6 months after vaccination can be important to prove sustained antibody production in some cases. The many reasons for a very thorough evaluation before the diagnosis of CVID include the fact that the diagnosis of CVID has an impact on short- and

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Table 1. Suggested template evaluation to verify lack of IgG antibody

Serum IgG < 150 mg/dL	Repeat serum immune globulins for verification; no antibody testing required
Serum IgG between 150 and 250 mg/dL	Repeat serum immune globulins for verification; Consider testing antibodies to tetanus and diphtheria or other protein based vaccines; optional, non conjugated pneumococcal vaccine and test 4 weeks after vaccination.
Serum IgG between 250 and 450 mg/dL	Repeat serum immune globulins for verification. Test antibodies to tetanus and diphtheria or other protein-based vaccines; also nonconjugated pneumococcal vaccine and test 4 weeks after vaccination.
Serum IgG between 450 and 600 mg/dL	Repeat serum immune globulins for verification. Test antibodies to tetanus and diphtheria and also other protein-based vaccines (measles mumps rubella, H zoster) also nonconjugated pneumococcal vaccine and test 4 weeks after vaccination

IgG indicates immunoglobulin.

long-term insurance coverage, influences the outcome of all subsequent medical encounters, and may alter school and job choices and other life decisions, such as family planning and travel. In addition, if replacement Ig therapy is initiated without a compete evaluation and the use of this therapy is later questioned, it must be stopped for approximately 5 months before such an evaluation can be performed.

Ig replacement

The primary treatment of CVID is replacement of antibody, achieved by either an intravenous or subcutaneous route of Ig, usually in doses of 400 to 600 mg/kg body weight per month.[11] This dose is usually divided into once or twice a week, or every 2 weeks (for the subcutaneous route) or every 3 or 4 weeks (for the intravenous route). The original calculation for the half-life of IgG of 21 days was determined on the basis of iodinated IgG protein,[12] but current intravenous Igs have half-lives closer to 30 days,[13-16] suggesting that original estimations might be inaccurate because of protein modification. However, the half-life in individual patients may vary considerably for not entirely clear reasons. Administered IgG in CVID subjects with chronic lung or gastrointestinal disease appears to have a shorter half-life. In addition, biologic variations in the abundance of the neonatal Fc receptor[17] might have an impact on IgG turnover.

The goal of Ig therapy is to prevent infections; however, the target trough serum IgG to attain varies depending on the baseline level of IgG. For a subject with a baseline serum IgG of less than 100 mg/dL, a suggested trough level would be at least 600 mg/dL, but for a subject with an initial IgG of 300 mg/dL with no functional antibody, the required trough level might be 900 mg/dL to supply the minimum "normal" level of functional Ig. Ig is often given in the home. Both intravenous and subcutaneous methods provide both safe and effective replacement strategies[11,18,19]; convenience to the patient can best guide these choices. In our practice, most of our patients are given 400 mg/dL intravenously once per month; 10% to 15% receive subcutaneous treatment in prorated doses given more frequently. Attention is given to those patients with lung disease or previous autoimmunity to ensure that more-than-adequate "trough" levels are maintained.

By definition, most patients with CVID have little or no serum IgA; although anti-IgA antibodies have been reported,[20] these are quite rare, and from a pragmatic point of view, the determination of whether IgG anti-IgA is present is not clinically important. I am opposed to the use of indwelling ports because they mark patients as medically impaired, provide known risks of infection, and in any case, need replacement with time. Poor intravenous access can be addressed by use of the subcutaneous route, with the physician dividing the required monthly dose into biweekly or weekly doses. On stable doses of replacement Ig, patients receiving Ig therapy can be adequately followed, with their trough serum IgG levels measured at 6- to 12-month intervals.

Table 2. Summary of complications and incidence*

	Numbers	Percentage
Infections	428	90
Autoimmunity	97	25
Lung impairment	88	24
Gastrointestinal disease	51	14
Malabsorption	31	5
Lymphoid malignancy	36	10
Previous splenectomy	31	8
Granulomatous disease	31	8
Other cancers	21	6

*On the basis of on a cohort of 476 subjects.

Complications and management

The commonest clinical history in CVID includes frequent infections in most but not all subjects. The respiratory tract is most commonly involved, occurring in up to 73% of patients, with pneumonia attributable to *Streptococcus pneumonia*, *Haemophilus influenzae*, or mycoplasma species appearing as the most prevalent condition before diagnosis.[5,6,8,21] Severe bacterial infections, such as empyema, sepsis, meningitis, or osteomyelitis, often with the same organisms, are less common but are noted in all series. In our current cohort, 90% of 476 subjects have had 1 or more of these infectious complications. However, subjects with CVID have other less well-understood inflammatory, autoimmune, or neoplastic conditions, as outlined for our cohort, in Table 2. Although the incidence of these complications appears to vary in different countries,[1] they appear in all cohorts so far examined. The ramifications and treatment of these complications are described in the subsections to follow.

Chronic lung disease

Although pneumonia is clearly much less common after adequate Ig replacement is initiated,[22] continued respiratory tract disease even after treatment is instituted can lead to obstructive, restrictive, bronchiectatic changes in some cases.[8] Parenchymal and interstitial changes include nodules on high-resolution computed tomography scans, reticular changes, fibrosis, and/or ground glass appearance. For larger or persistent nodules, a biopsy may be required to

determine whether these are scars, lymphoid collections of possibly clonal cells, or granulomatous infiltrates. Continued lung damage can lead to substantial morbidity, in the more severe cases, necessitating continuous oxygen treatment and/or heart or lung transplantation.[10] It is unclear whether such a downward spiral is caused by previous lung damage that is difficult to reverse, continued low-grade infections that are not adequately addressed by replacement Ig, ongoing inflammatory changes caused by immune dysregulation, or a combination of all of these factors. The microbiology of the lungs may also include organisms potentially not susceptible to antibody clearance, including the most prevalent organism, nontypeable *H influenzae*, and/or viruses.[23] Greater doses of Ig (600 mg/kg/month) may help to prevent infections and possibly chronic lung disease,[24,25] but no controlled trials have been conducted to select which patients would benefit and what doses of Ig would be needed. In my view, for continued lung disease, daily antibiotic prophylaxis (trimethoprim sulfa, or possibly better, macrolides, which provide substantial anti-inflammatory effects[26]) provide more benefit than much greater doses of Ig therapy. Although the rotation of antibiotics to discourage resistant organisms often is used in immune-competent patients with chronic lung disease, I have not found it necessary to rotate antibiotics in CVID; resistant organisms can be treated if they arise.

Granulomatous/lymphoid infiltrative disease

Localized or systemic granulomatous disease, sometimes erroneously called "sarcoidosis," occurs in 8% to 22% of subjects with CVID.[10,27-32] The granulomatous changes may be diagnosed years before the recognition of hypogammaglobulinemia and may in these cases delay the recognition of the immune defect because the diagnosis of sarcoidosis is assumed to be established. Lungs, lymph nodes, and spleen are the more commonly affected sites, although the skin, liver, bone marrow, kidney, gastrointestinal tract, and brain may be involved.[27,33-35] The granuloma in CVID are variously well-formed, noncaseating, and may contain nonnecrotizing epithelioid and giant cells. Although organisms are sought, these are very rarely found. In our series of 37 patients, 8.1% of our CVID subjects, the median age at diagnosis of CVID was 26 years (range, 2-59 years). A total of 14 patients had granulomas 1 to 18 years before they were diagnosed CVID; in 6 the detection of granulomas coincided with this diagnosis; for 17, granulomas were documented later. A total of 54% had lung granulomas, 43% in lymph nodes and 32% in liver.[31] For unclear reasons, subjects with granulomatous disease also are at much greater risk for autoimmune disease (almost always immune thrombocytopenia or autoimmune hemolytic anemia) than CVID subjects who do not have this pathology; for example, 54% of our patients with known granulomatous disease have had autoimmune disease. As described in "Survival, clinical phenotypes, and biomarkers," these subjects also are almost always those who have very few circulating, isotype-switched memory B cells.[36] In some of these patients, an intense lymphoid infiltration accompanies the granulomas in lungs, leading to what has been termed "granulomatous lymphocytic interstitial lung disease,"[29,37] the presence of which is prognostic of a poor outcome.[37]

The authors of a recent study reported a median survival of 13.7 years in CVID patients with granulomatous/lymphoid interstitial infiltrates, compared with 28.8 years in those without this complication.[29] Human herpesvirus 8 has been proposed to play a role of in the development of granulomatous disease in CVID,[38] but this is still to be confirmed. No case-control studies have been performed to define the most effective treatment of granulomatous disease in CVID. Oral steroids in doses of 10 mg a day or 20 mg every other day may preserve lung or liver function; however, one should realize that this use presents a risk for infections and other undesirable side effects. For long-term therapy, I prescribe 200 to 400 mg a day (range, 3.5-6.5 mg/kg) of hydroxycloroquine on the basis of its mechanistic roles in reducing Toll-like receptor responses, antigen presentation, and its use in autoimmunity and sarcoidosis.[39,40] For pulmonary granuloma, twice daily inhaled beclomethasone is also prescribed.

Greater doses of intravenous immunoglobulin have been found in one instance to aid in controlling lymphoid interstitial disease and granuloma,[41,42] but this does not appear to be a universal experience. Some years ago, Aukrust et al[43] showed that some patients with CVID had elevated serum levels of tumor necrosis factor alpha (TNF-alpha) and soluble TNF receptors. Later, Mullighan et al[28] reported granuloma in 20 of 90 patients with CVID (22%); 8 of these had an unusual TNF-alpha allele (TNF +488A), but TNF-alpha production or levels were not actually examined. On this basis, and suggestive earlier work in sarcoidosis, TNF-alpha inhibitors (infliximab or etanercept) have been used in subjects with CVID with granuloma, with benefit in some cases[35,44,45]; however, no controlled trials have been performed. I have had limited experience using TNF inhibitors for granulomatous disease; in 2 cases (both with granuloma in lung) it was not helpful, but both patients had substantial lung defects.

Lymphoid infiltrates in the lung leading to lymphoid interstitial pneumonia or follicular bronchitis/bronchiolitis without granuloma are equally challenging because they lead to cough, shortness of breath, alveolar damage, and ultimately, the need for oxygen therapy. Because of scarring and the predominance of T cells in the lung infiltrate (as shown in Figure 1), cyclosporine also has been used with benefit (125 mg a day; serum level 76 ng/mL).[46] We have used cyclosporine in 2 subjects, with some stabilization of lung function for 4 years, but both patients succumbed to respiratory insufficiency, complicated by fatal acute hemolytic anemia in one of these subjects.[31]

Autoimmunity

Other complications resulting from immune dysregulation in CVID include autoimmune disease in up to 25%, mostly immune thrombocytopenia purpura (ITP), autoimmune hemolytic anemia (AIHA), or both (Evans syndrome) or more rarely, autoimmune neutropenia (Table 3).[47,48] CVID subjects with ITP or Evans syndrome tend to be younger than those who developed AIHA.[49] This group of subjects are also likely to have very few isotype switched memory B cells in peripheral blood.[36] As we have found that more episodes of recurrent episodes of ITP and/or AIHA occur before replacement Ig treatment is started than afterward, Ig in these doses may exert a protective effect.[49] Greater doses of Ig (1 g/kg body weight) given weekly for a short time can be used to supplement baseline therapy if autoimmune disease persists. Intravenous steroids (1 g of methylprednisolone) followed by moderate doses of oral steroids tapered over several weeks or more will also often resolve ITP or AIHA. More recently, we have used rituximab in standard doses, for more refractory or recurrent ITP and/or AIHA with success in 11 patients with CVID. Splenectomy is to be avoided in CVID because severe infections have occurred, as we and other have shown,[5,50] although this is not found in all series.[48] Other autoimmune diseases also occur in CVID, including pernicious anemia, rheumatoid arthritis, Sjögren syndrome, vasculitis, thyroiditis, alopecia, vitiligo, hepatitis, primary biliary cirrhosis,

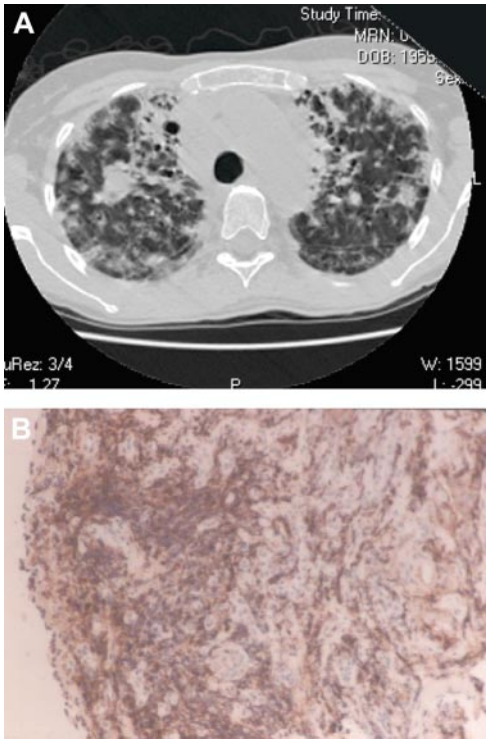

Figure 1. Lymphocytic pulmonary infiltrates. (A) A 40-year-old woman with gradually worsening severe lung disease. Computed tomography of the chest revealed massive infiltrates composed of lymphocytic collections and fibrotic scars. (B) On biopsy, the infiltrating T cells in the lung, obliterating normal architecture, were revealed as $CD4^+$ by the brownish monoclonal peroxidase conjugated monoclonal anti-$CD4^-$ staining pattern (magnification ×25).

uveitis, sicca syndrome, and systemic lupus erythematosus; the treatment for these is standard therapy.

Cancer, lymphoid hyperplasia, splenomegaly, and lymphoma

The incidence of malignancy appears overall increased in CVID, occurring in up to 15% of subjects. In a 1985 study of 220 patients, a 5-fold increase in cancer was found mostly attributable to excesses of stomach cancer (47-fold) and non-Hodgkin lymphoma (30-fold).[51] For 176 subjects in a European study, the observed to expected ratio for lymphoma in CVID was 12.1 and for stomach cancer was 10.3.[52] Zullo et al[53] found *Helicobacter pylori* in 14 of 34 subjects with gastric symptoms, one of whom had gastric cancer, suggesting a potentially causative role. However, suggesting a potential downward trend of this cancer, in our current cohort of 476 patients, there have been 3 stomach cancers (0.6%) in contrast to 32 non-Hodgkin lymphomas (6.7%) and 4 cases of Hodgkin disease (Table 4).

Cervical, mediastinal, and abdominal lymphoid hyperplasia and enlarged spleen are found in at least 20% of CVID subjects.

Table 3. Hematologic autoimmunity*

Condition	Number	Percentage
Thrombocytopenia	44	9.0
Evans syndrome	11	2.3
Acute hemolytic anemia	8	2.0
Anti-IgA antibodies	6	1.0
Neutropenia	2	0.4
Pernicious anemia	2	0.4

IgA indicates immunoglobulin A.
*On the basis of a cohort of 476 subjects.

Table 4. Cancer in CVID*

Type	Number	Percentage†
Non-Hodgkin lymphoma	32	6.7
Other cancers*	20	4.0
Hodgkin disease	4	0.8
Waldenström macroglobulinemia	1	0.2
Aplastic anemia	2	0.2

*On the basis of 476 subjects.
†Other cancers: breast, 6; colon, 3; gastric, 3; mouth, 2; melanoma, 2; lung, 1; skin, 1; ovary, 1; and vagina, 1.

Lymphoid infiltrates occur in lung or other organs such as the liver or kidneys. Biopsies of lymph nodes usually show atypical lymphoid hyperplasia, reactive lymphoid hyperplasia, or granulomatous inflammation. In most cases no specific treatment is required unless pulmonary involvement or other organ involvement impairs functions. Splenomegaly can massive and yet not cause clinical symptoms. It is not my practice to suggest or endorse splenectomy for any reason unless there is marked hypersplenism, uncontrollable autoimmunity, or a real possibility of lymphoma. When there is doubt about the nature of an infiltrate, nodule, or enlarged node, I request a biopsy and histologic staining, in addition to studies that use a standard panel of monoclonal markers appropriate for lymphoma. Enlarged lymph nodes usually show atypical or reactive hyperplasia, with or without preservation of germinal center boundaries; granulomatous infiltrations are found in some.[54] There is a typical lack of plasma cells in lymph nodes or other lymphoid tissues in CVID.[55] We also save tissue for Epstein-Barr–encoded RNAs by in situ hybridization, cytogenetics, and studies of B- and T-cell clonality by molecular analysis. However, the presence of clonal lymphocytes is not diagnostic because they can be found in biopsy results that demonstrate reactive hyperplasia but no evidence of lymphoma.[56,57]

When lymphomas appear in CVID, they are usually extranodal, B cell in type, and, unlike lymphomas in other congenital immune defects, are more common in subjects in the 4th to 7th decade of life and usually negative for Epstein-Barr virus.[5,47,58] The median age at diagnosis of CVID in our cohort was 44 years; the median age at death of lymphoma was 59 years. Lymphoproliferative disease was diagnosed mostly the 5th decade, but the range was between age 13 and 88 years. In our experience, female patients appear more likely to develop lymphoma than male patients; of our current group of patients with lymphoid malignancies, 72% are women. A number of cases of marginal zone (mucosa-associated lymphoid tissue) lymphomas have been reported,[59] in some cases related to *H pylori*.[60] Lymphoma may be more likely to arise in subjects with preexisting polyclonal lymphoproliferation, as shown for 10 cases in 334 CVID subjects extracted from the previously established European Society for Immune Deficiency Registry.[1,61,62] In this study, a greater baseline serum IgM in CVID was correlated with both lymphoid hyperplasia and lymphoma.[1] The lymphomas in CVID appear to respond to standard chemotherapy and rituximab protocols. However, it should be noted that 2 female patients with mucosa-associated lymphoid tissue lymphomas (diagnosed 2 to 8 years previously) that we follow are entirely stable and have not yet been treated.

Gastrointestinal disease

The main gastrointestinal manifestation of CVID is transient or persistent diarrhea, found in 21% to 57% of subjects.[63-65] When a cause is identified, *Giardia lamblia* is the most common organism;

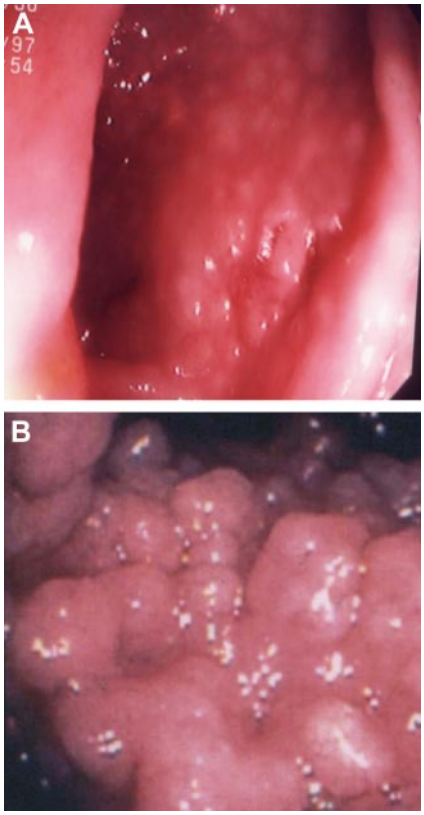

Figure 2. Gastrointestinal lymphoid nodules. (A) A 50-year-old woman who had a history of a duodenal ulcer, now resolved. She had a repeat gastroscopy for symptoms of gastritis; *H pylori* was not found. The mucosa of the stomach folds of this female patient contained numerous lymphoid follicles. (B) The jejunum of a 28-year-old male patient containing massive nodules of lymphoid hyperplasia; he had experienced a 20-lb weight loss.

treatment with metronidazole is generally effective but may require several courses. Other pathogens can also be identified, including *Cryptosporidium parvum*, cytomegalovirus, *Salmonella* species, *Clostridium difficile*, and *Campylobacter jejuni*.[66] *H pylori* infection has been associated with gastritis.[53] Aside from bacterial and parasitic infections, inflammatory bowel disease remains a significant problem in 19% to 32% of patients.[6,65] Dissecting infectious from inflammatory disease is not always simple; both can lead to chronic even severe diarrhea, characterized by weight loss, steatorrhea, and malabsorption.[5]

On biopsy, the gastrointestinal mucosa contains excess intraepithelial lymphocytes, villous blunting, lymphoid aggregates, granulomas, crypt distortion, and as noted previously, a characteristic lack of plasma cells.[64,65] Another common feature is villous flattening in the small intestine suggesting celiac sprue. However, we have not found wheat withdrawal to be beneficial, and instead it leads to additional weight loss. In the worst cases, significant loss of essential nutrients (eg, calcium, zinc, and vitamins A, E, and D) leads to bone loss and neurologic deficits, which are not easily reversed.[67] Nodular lymphoid hyperplasia (containing an expanded number of B cells but no plasma cells) is common and may be observed on endoscopy in any area of the gastrointestinal tract; when massive, this can lead to both severe chronic diarrhea and weight loss (Figure 2). Initial treatment is determined on the basis of culture results, biopsy findings, and usually includes antibiotics, restoration of nutrients, and rehydration.

The management of inflammatory bowel disease in CVID is the same as for immunocompetent patients, including antibiotics, such as metronidazole or tinidizole or ciprofloxacin, 5-aminosalicylic acid and/or nonabsorbed oral steroids, such as budesonide. Low-dose corticosteroids such as prednisone can be used in doses of 10 mg/day; however, greater doses can lead to a significant risk of infections. Immunomodulators, such as azathioprine or 6-mercaptopurine, can be used safely because the doses used (as for Crohn disease) are low and do not appear to affect standard T- and B-cell function tests.[66] Infliximab has also been used with some benefit in severe enteropathy.[68]

Excluding hepatitis C virus or any other persistent virus, liver disease, including primary biliary cirrhosis and what appears to be autoimmune hepatitis, also occurs in CVID. This leads to persistently increased liver enzyme levels; 43% of 1 cohort had abnormal liver function tests, predominantly increased alkaline phosphatase. Nodular regenerative hyperplasia leading to portal hypertension and cholestasis is a complication increasingly recognized in CVID; it was found in 14 of 40 subjects in a cohort of subjects who had these abnormalities in liver function tests.[69,70]

Organ and stem cell transplantation in CVID

There are a few reports of liver and lung transplant in CVID, with at least short-term survival but overall variable outcome.[71-73] What has not been clarified is with what complications and at what stage, stem cell or bone marrow transplantation, should be considered in CVID. This question is most likely to arise when severe immune compromise has been already documented and T-cell immunity is impaired. These cases resemble a form of combined immune deficiency, and hypomorphic defects of genes known to cause SCID (adenosine deaminase, Artemis or RAG1 or RAG2, and likely others[74-76]) should be sought. Unfortunately, there is little if any published information on stem cell transplant in well-described CVID patients.

Genetics

Only some of the genetics leading to the CVID phenotype have been clarified. These include several very rare recessive mutations: in the T cell, inducible costimulatory, (ICOS) in one kindred,[77] mutations in CD19 in a few unrelated families,[78,79] B-cell activating factor (BAFF) receptor in 2 siblings,[80] and CD20 and CD81 in 1 patient each.[81,82] Because these events are very rare occurrences and not found in general populations of patients, requesting these genetic tests in a workup is not recommended. More promising, but from a research point of view, has been work that identified mutations in transmembrane activator and calcium-modulating cyclophilin ligand interactor (TNFRSF13B) in approximately 8% of patients.[83-85] Two of these, an extracellular mutation, C104R, and a transmembrane mutation, A181E, account for most of these. C104R leads to a disruption of a region important for binding the ligand BAFF and another soluble ligand, a proliferation-inducing ligand (APRIL); the transmembrane or intracytoplasmic mutations are presumed to lead to impaired BAFF and APRIL signaling. In all studied populations, heterozygous are far more common than homozygous mutations, and we and others have found that these are associated with both autoimmunity and lymphoid hyperplasia. Whether this is attributable to the generation of abnormal signals or haploinsufficiency has not been clarified.[86,87] However, because the same mutations are routinely found in normal family members and sometimes in normal blood donors, testing for transmembrane activator and calcium-modulating cyclophilin ligand interactor

Table 5. Suggested monitoring for patients with CVID*

Patients	Type	Interval
All	Interval history, physical examination, height and weight	12 months
	Complete blood counts: Hgb, Hct, white blood cells and differential, platelets, and chemistry panel, including liver and kidney functions; albumin	12 months
	serum IgG*	6-12 months or with weight gain, pregnancy
	Chest x-ray	Referral
	Spirometry	12 months
With lung disease	High-resolution chest computed tomography	3-4 years or after change of therapy
	Complete lung functions with carbon monoxide diffusion	12 months
With gastrointestinal complications	Upper and/or lower endoscopy	Intervals as required for optimum treatment
With evidence of malabsorption, including loss of height (women in particular)	Bone density, evaluation of nutrients	As dictated by the therapy used

CVID indicates common variable immune deficiency; Hct, hematocrit; Hgb, hemoglobin; IgA, immunoglobulin A; IgG, immunoglobulin G; and IgM; immunoglobulin M.
*Consider adding also serum IgA or IgM if there is a question about the stability of the diagnosis or onset of other complications.

mutations in patients is neither diagnostic of CVID nor predictive of immune deficiency in the future. For this reason, I do not recommend it for either of these purposes.

Survival, clinical phenotypes, and biomarkers

In an earlier report on CVID, 56 (23%) of 248 of subjects died during a follow-up period of 1 to 20 years (mean, 7.5 years). Compared with age-matched control patients, the survival was significantly reduced, with male subjects at 64% compared with 92% for control subjects and 67% for female subjects, with control subjects expecting 94% survival for the same periods of time.[5] These outcomes were similar to a report of 240 patients in the United Kingdom,[4] in which during a 25-year period, 30% of subjects died.[5] The main causes of death in both studies included chronic respiratory tract insufficiency, destructive granulomatous organ involvement, liver disease, malnutrition attributable to gastrointestinal pathology, uncontrolled autoimmune disease, and lymphoma.[1,9]

In more recent years the overall survival of subjects with CVID appears improved, very likely because of the now-standard doses of replacement Ig. Of the 334 CVID subjects collected from the European Society for Immune Deficiency Registry, 51 subjects (15%) died during a longer mean follow-up period (22.5 years). However, other factors appear important in survival as revealed by examination of these data. Although approximately one-half of the patients had infections as the only manifestation, others with one or more of the other complications outlined previously (autoimmunity, gastrointestinal disease, lymphoid hyperplasia, splenomegaly, granulomatous disease, cancer, or non-Hodgkin lymphoma) had diminished survival.[1] Although a very low initial serum IgG level might be the most logical predictor for complications, there was no association found between the level of the serum IgG level at diagnosis and severe infections (including pneumonia), a greater incidence of lung disease, or increased mortality. Strangely, neither age at onset of symptoms, age at diagnosis, or length of diagnostic delay was related to increased mortality.

These registry data illustrate the need for additional biologically relevant biomarkers to guide both evaluation and treatment in CVID. Previous studies showed that poorer T-cell functions, reduced lymphocyte counts, very low numbers of B cells, and reduced numbers of both $CD4^+$ T cells and $CD45RA^+CCR7^+CD4^+$T cells[88] are associated with both opportunistic infections and reduced survival.[5,10,88] More recently, the authors of other studies[89-92] have suggested that the numbers and phenotypes of peripheral blood B cells are useful biomarkers. $CD27^+$ B cells but especially IgD-$CD27^+$ isotype-switched memory B are decreased, and both we and others[93,94] found that CVID subjects with the fewest switched memory B cells produce less IgG antibody after vaccine challenge. In our studies, less than 0.5% isotype-switched memory B cells is very significantly associated with autoimmunity, granulomatous disease, hypersplenism, and lymphoid hyperplasia. We also found that female patients with CVID have significantly more IgM^+CD27^+ memory cells and IgD^-CD27^+ cells than male patients, which suggests to us interesting difference between sexes in CVID.[36] We have not been able to verify that CVID patients who have significantly lower numbers of circulating IgM^+CD27^+ memory B cells are more likely to develop chronic lung disease as previously suggested.[95,96] Other suggested markers include reduced Tregs,[97] very low $CD21^+$ B cells,[92] and high levels serum BAFF and APRIL,[98] which might be associated with selected clinical conditions such as autoimmunity and lymphoid hyperplasia.

Monitoring patients over time

Most patients with CVID carry out all normal activities; many are treated on home care programs for years. Although these improvements represent ongoing advances in medical care, regularly scheduled and careful follow-up is still mandatory because new problems may arise or evolve over time. Stable patients must be seen at least yearly intervals, and those with the aforementioned complications at shorter intervals, such as 3 to 6 months. Table 5 outlines a suggested template for monitoring patients. Routines to monitor subjects for and with lung disease have been controversial, and there is no current consensus. Chest x-rays are not as revealing as HRCT, so it is reasonable to obtain these at baseline referral. However, radiosensitivity has been demonstrated in CVID,[99,100] and for a younger subject, yearly or examinations every 2 years, especially in concert with other x-ray procedures, could lead to excessive radiation exposure over time.[101] For more frequent follow-up of patients with chronic cough and/or known lung damage, I prefer complete lung functions, including carbon monoxide diffusion as a means of assessing lung damage at shorter intervals, with possible HRCT at 3- to 4-year intervals or at less frequent intervals to monitor changes in therapy. Monitoring for autoimmunity is not required because routine blood counts and general medical oversight will reveal characteristic symptoms. Gastrointestinal diseases will be similarly evident, with patient

complaints of diarrhea and, often, weight loss, occurring. Loss of height may reflect loss of bone density, which is especially prevalent in women with CVID with any degree of deficiency or calcium loss; treatment requires reconstitution with vitamin D, calcium, and other standard therapies. Routine endoscopy is not required, although patients with suggestive gastrointestinal symptoms should have appropriate upper and/or lower endoscopy with examination for *H pylori* or other mucosal changes.

The issue of enlarged lymph nodes is always troublesome. When new nodes appear and persist, biopsy may be required; however, in most cases, lymphomas are extra nodal and appear in unusual locations such as lung or mucosal associated tissues and are thus not amenable to any standard follow-up measures. In my experience, bone marrow examinations to seek lymphoma also have not been positive, except in the most advanced cases, where the diagnosis was already known.

Conclusions

During the past 3 decades, the outlook for patients with CVID has greatly improved because of standard Ig replacement therapy and more effective antibiotic coverage. Although it is disturbing to note that even in the most recent surveys the diagnosis is still delayed 6 to 8 years after the first characteristic symptoms, most patients now go to school or work and are not significantly disabled. Perhaps because infections are not as prominent, morbidities globally ascribed to inflammation or immune dysregulation have become the areas of main medical concern. From the research point of view, CVID represents a promising model to better understand mediators of immune function and inflammation as well as the still relatively uncharted genetics of antibody production.

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Authorship

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References

1. Chapel H, Lucas M, Lee M, et al. Common variable immunodeficiency disorders: division into distinct clinical phenotypes. *Blood*. 2008;112(2):277-286.
2. Notarangelo LD, Fischer A, Geha RS, et al. Primary immunodeficiencies: 2009 update. *J Allergy Clin Immunol*. 2009;124(6):1161-1178.
3. Janeway CA, Apt L, Gitlin D. Agammaglobulinemia. *Trans Assoc Am Phys*. 1953;66:200-202.
4. Hermaszewski RA, Webster AD. Primary hypogammaglobulinaemia: a survey of clinical manifestations and complications. *Q J Med*. 1993;86(1):31-42.
5. Cunningham-Rundles C, Bodian C. Common variable immunodeficiency: clinical and immunological features of 248 patients. *Clin Immunol*. 1999;92(1):34-48.
6. Kainulainen L, Nikoskelainen J, Ruuskanen O. Diagnostic findings in 95 finnish patients with common variable immunodeficiency. *J Clin Immunol*. 2001;21(2):145-149.
7. 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(3):140-147.
8. Quinti I, Soresina A, Spadaro G, et al. Long-term follow-up and outcome of a large cohort of patients with common variable immunodeficiency. *J Clin Immunol*. 2007;27(3):308-316.
9. Chapel H, Cunningham-Rundles C. Update in understanding common variable immunodeficiency disorders (CVIDs) and the management of patients with these conditions. *Br J Haematol*. 2009;145(6):709-727.
10. Cunningham-Rundles C. Common variable immunodeficiency. *Curr Allergy Asthma Rep*. 2001;1(5):421-429.
11. Orange JS, Hossny EM, Weiler CR, et al. 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(4 suppl):S525-S553.
12. Waldmann TA, Strober W. Metabolism of immunoglobulins. *Prog Allergy*. 1969;13:1-110.
13. Berger M. A multicenter, prospective, open label, historically controlled clinical trial to evaluate efficacy and safety in primary immunodeficiency diseases (PID) patients of Flebogamma 5% DIF, the next generation of Flebogamma. *J Clin Immunol*. 2007;27(6):628-633.
14. Ballow M, Berger M, Bonilla FA, et al. Pharmacokinetics and tolerability of a new intravenous immunoglobulin preparation, IGIV-C, 10% (Gamunex, 10%). *Vox Sang*. 2003;84(3):202-210.
15. Ochs HD, Pinciaro PJ. Octagam 5%, an intravenous IgG product, is efficacious and well tolerated in subjects with primary immunodeficiency diseases. *J Clin Immunol*. 2004;24(3):309-314.
16. Berger M, Cunningham-Rundles C, Bonilla FA, et al. Carimune NF liquid is a safe and effective immunoglobulin replacement therapy in patients with primary immunodeficiency diseases. *J Clin Immunol*. 2007;27(5):503-509.
17. Sachs UJ, Socher I, Braeunlich CG, Kroll H, Bein G, Santoso S. A variable number of tandem repeats polymorphism influences the transcriptional activity of the neonatal Fc receptor alpha-chain promoter. *Immunology*. 2006;119(1):83-89.
18. Gardulf A, Andersen V, Bjorkander J, et al. Subcutaneous immunoglobulin replacement in patients with primary antibody deficiencies: safety and costs. *Lancet*. 1995;345(8946):365-369.
19. Berger M. Subcutaneous administration of IgG. *Immunol Allergy Clin North Am*. 2008;28(4):779-802, viii.
20. Björkander J, Hammarstrom L, Smith CI, Buckley RH, Cunningham-Rundles C, Hanson LA. Immunoglobulin prophylaxis in patients with antibody deficiency syndromes and anti-IgA antibodies. *J Clin Immunol*. 1987;7(1):8-15.
21. Touw CM, van de Ven AA, de Jong PA, et al. Detection of pulmonary complications in common variable immunodeficiency [published online ahead of print November 13, 2009]. *Pediatr Allergy Immunol*. doi:10.1111/j.1399-3038.2009.00963.x.
22. 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(6):1001-1004.
23. Kainulainen L, Nikoskelainen J, Vuorinen T, Tevola K, Liippo K, Ruuskanen O. Viruses and bacteria in bronchial samples from patients with primary hypogammaglobulinemia. *Am J Respir Crit Care Med*. 1999;159(4 Pt 1):1199-1204.
24. Roifman CM, Levison H, Gelfand EW. High-dose versus low-dose intravenous immunoglobulin in hypogammaglobulinaemia and chronic lung disease. *Lancet*. 1987;1(8541):1075-1077.
25. Eijkhout HW, van Der Meer JW, Kallenberg CG, et al. The effect of two different dosages of intravenous immunoglobulin on the incidence of recurrent infections in patients with primary hypogammaglobulinemia. A randomized, double-blind, multicenter crossover trial. *Ann Intern Med*. 2001;135(3):165-174.
26. López-Boado YS, Rubin BK. Macrolides as immunomodulatory medications for the therapy of chronic lung diseases. *Curr Opin Pharmacol*. 2008;8(3):286-291.
27. Fasano MB, Sullivan KE, Sarpong SB, et al. Sarcoidosis and common variable immunodeficiency. Report of 8 cases and review of the literature. *Medicine (Baltimore)*. 1996;75(5):251-261.
28. Mullighan CG, Fanning GC, Chapel HM, Welsh KI. TNF and lymphotoxin-alpha polymorphisms associated with common variable immunodeficiency: role in the pathogenesis of granulomatous disease. *J Immunol*. 1997;159(12):6236-6241.
29. Morimoto Y, Routes JM. Granulomatous disease in common variable immunodeficiency. *Curr Allergy Asthma Rep*. 2005;5(5):370-375.

30. Knight AK, Cunningham-Rundles C. Inflammatory and autoimmune complications of common variable immune deficiency. *Autoimmun Rev*. 2006; 5(2):156-159.
31. Ardeniz O, Cunningham-Rundles C. Granulomatous disease in common variable immunodeficiency. *Clin Immunol*. 2009;133(2):198-207.
32. Park JH, Levinson AI. Granulomatous-lymphocytic interstitial lung disease (GLILD) in common variable immunodeficiency (CVID). *Clin Immunol*. 2010;134(2):97-103.
33. Misbah SA, Spickett GP, Esiri MM, et al. Recurrent intra-cranial granulomata presenting as space-occupying lesions in a patient with common variable immunodeficiency. *Postgrad Med J*. 1992;68(799):359-362.
34. Mechanic LJ, Dikman S, Cunningham-Rundles C. Granulomatous disease in common variable immunodeficiency. *Ann Intern Med*. 1997;127(8 Pt 1):613-617.
35. Lin JH, Liebhaber M, Roberts RL, Dyer Z, Stiehm ER. Etanercept treatment of cutaneous granulomas in common variable immunodeficiency. *J Allergy Clin Immunol*. 2006;117(4):878-882.
36. Sánchez-Ramón S, Radigan L, Yu JE, Bard S, Cunningham-Rundles C. Memory B cells in common variable immunodeficiency: clinical associations and sex differences. *Clin Immunol*. 2008; 128(3):314-321.
37. 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(2):415-421.
38. Wheat WH, Cool CD, Morimoto Y, et al. Possible role of human herpesvirus 8 in the lymphoproliferative disorders in common variable immunodeficiency. *J Exp Med*. 2005;202(4):479-484.
39. Fazzi P. Pharmacotherapeutic management of pulmonary sarcoidosis. *Am J Respir Med*. 2003; 2(4):311-320.
40. Kyburz D, Brentano F, Gay S. Mode of action of hydroxychloroquine in RA-evidence of an inhibitory effect on toll-like receptor signaling. *Nat Clin Pract Rheumatol*. 2006;2(9):458-459.
41. Popa V. Lymphocytic interstitial pneumonia of common variable immunodeficiency. *Ann Allergy*. 1988;60(3):203-206.
42. de Gracia J, Vendrell M, Alvarez A, et al. Immunoglobulin therapy to control lung damage in patients with common variable immunodeficiency. *Int Immunopharmacol*. 2004;4(6):745-753.
43. Aukrust P, Lien E, Kristoffersen AK, et al. Persistent activation of the tumor necrosis factor system in a subgroup of patients with common variable immunodeficiency–possible immunologic and clinical consequences. *Blood*. 1996;87(2):674-681.
44. 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(3):293-300.
45. Hatab AZ, Ballas ZK. Caseating granulomatous disease in common variable immunodeficiency treated with infliximab. *J Allergy Clin Immunol*. 2005;116(5):1161-1162.
46. Davies CW, Juniper MC, Gray W, Gleeson FV, Chapel HM, Davies RJ. Lymphoid interstitial pneumonitis associated with common variable hypogammaglobulinaemia treated with cyclosporin A. *Thorax*. 2000;55(1):88-90.
47. Cunningham-Rundles C. Hematologic complications of primary immune deficiencies. *Blood Rev*. 2002;16(1):61-64.
48. Michel M, Chanet V, Galicier L, et al. Autoimmune thrombocytopenic purpura and common variable immunodeficiency: analysis of 21 cases and review of the literature. *Medicine (Baltimore)*. 2004; 83(4):254-263.
49. Wang J, Cunningham-Rundles C. Treatment and outcome of autoimmune hematologic disease in common variable immunodeficiency (CVID). *J Autoimmun*. 2005;25(1):57-62.
50. Seve P, Bourdillon L, Sarrot-Reynauld F, et al. Autoimmune hemolytic anemia and common variable immunodeficiency: a case-control study of 18 patients. *Medicine (Baltimore)*. 2008;87(3): 177-184.
51. Kinlen LJ, Webster AD, Bird AG, et al. Prospective study of cancer in patients with hypogammaglobulinaemia. *Lancet*. 1985;1(8423):263-266.
52. Mellemkjaer L, Hammarstrom L, Andersen V, et al. 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(3):495-500.
53. Zullo A, Romiti A, Rinaldi V, et al. Gastric pathology in patients with common variable immunodeficiency. *Gut*. 1999;45(1):77-81.
54. Sander CA, Medeiros LJ, Weiss LM, Yano T, Sneller MC, Jaffe ES. Lymphoproliferative lesions in patients with common variable immunodeficiency syndrome. *Am J Surg Pathol*. 1992; 16(12):1170-1182.
55. Taubenheim N, von Hornung M, Durandy A, et al. Defined blocks in terminal plasma cell differentiation of common variable immunodeficiency patients. *J Immunol*. 2005;175(8):5498-5503.
56. Gompels MM, Hodges E, Lock RJ, et al. Lymphoproliferative disease in antibody deficiency: a multi-centre study. *Clin Exp Immunol*. 2003;134(2):314-320.
57. Elenitoba-Johnson KS, Jaffe ES. Lymphoproliferative disorders associated with congenital immunodeficiencies. *Semin Diagn Pathol*. 1997; 14(1):35-47.
58. 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(4):294-299.
59. Cunningham-Rundles C, Cooper DL, Duffy TP, Strauchen J. Lymphomas of mucosal-associated lymphoid tissue in common variable immunodeficiency. *Am J Hematol*. 2002;69(3):171-178.
60. Desar IM, Keuter M, Raemaekers JM, Jansen JB, van Krieken JH, van der Meer JW. Extranodal marginal zone (MALT) lymphoma in common variable immunodeficiency. *Neth J Med*. 2006; 64(5):136-140.
61. Eades-Perner AM, Gathmann B, Knerr V, et al. The European internet-based patient and research database for primary immunodeficiencies: results 2004-2006. *Clin Exp Immunol*. 2007;147(2):306-312.
62. Gathmann B, Grimbacher B, Beaute J, et al. The European internet-based patient and research database for primary immunodeficiencies: results 2006-2008. *Clin Exp Immunol*. 2009;157(suppl 1):3-11.
63. Washington K, Stenzel TT, Buckley RH, Gottfried MR. Gastrointestinal pathology in patients with common variable immunodeficiency and X-linked agammaglobulinemia. *Am J Surg Pathol*. 1996;20(10):1240-1252.
64. 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(12):1800-1812.
65. Agarwal S, Mayer L. Pathogenesis and treatment of gastrointestinal disease in antibody deficiency syndromes. *J Allergy Clin Immunol*. 2009;124(4): 658-664.
66. Agarwal S, Mayer L. Gastrointestinal manifestations in primary immune disorders. *Inflamm Bowel Dis*. 2010;16(4):703-711.
67. Aslam A, Misbah SA, Talbot K, Chapel H. Vitamin E deficiency induced neurological disease in common variable immunodeficiency: two cases and a review of the literature of vitamin E deficiency. *Clin Immunol*. 2004;112(1):24-29.
68. Chua I, Standish R, Lear S, et al. Anti-tumour necrosis factor-alpha therapy for severe enteropathy in patients with common variable immunodeficiency (CVID). *Clin Exp Immunol*. 2007;150(2): 306-311.
69. Ward C, Lucas M, Piris J, Collier J, Chapel H. Abnormal liver function in common variable immunodeficiency disorders due to nodular regenerative hyperplasia. *Clin Exp Immunol*. 2008;153(3): 331-337.
70. Malamut G, Ziol M, Suarez F, et al. Nodular regenerative hyperplasia: the main liver disease in patients with primary hypogammaglobulinemia and hepatic abnormalities. *J Hepatol*. 2008;48(1): 74-82.
71. Bethune CA, Spickett GP. Common variable immunodeficiency: an update on therapeutic approaches. *BioDrugs*. 2000;13(4):243-253.
72. Burton CM, Milman N, Andersen CB, Marquart H, Iversen M. Common variable immune deficiency and lung transplantation. *Scand J Infect Dis*. 2007;39(4):362-367.
73. Reyes J, Todo S, Green M, et al. Graft-versus-host disease after liver and small bowel transplantation in a child. *Clin Transplant*. 1997;11(5 Pt 1):345-348.
74. Shovlin CL, Simmonds HA, Fairbanks LD, et al. Adult onset immunodeficiency caused by inherited adenosine deaminase deficiency. *J Immunol*. 1994;153(5):2331-2339.
75. Moshous D, Pannetier C, Chasseval Rd R, et al. Partial T and B lymphocyte immunodeficiency and predisposition to lymphoma in patients with hypomorphic mutations in Artemis. *J Clin Invest*. 2003;111(3):381-377.
76. Schuetz C, Huck K, Gudowius S, et al. An immunodeficiency disease with RAG mutations and granulomas. *N Engl J Med*. 2008;358(19):2030-2038.
77. Grimbacher B, Hutloff A, Schlesier M, et al. Homozygous loss of ICOS is associated with adult-onset common variable immunodeficiency. *Nat Immunol*. 2003;4(3):261-268.
78. van Zelm MC, Reisli I, van der Burg M, et al. An antibody-deficiency syndrome due to mutations in the CD19 gene. *N Engl J Med*. 2006;354(18): 1901-1912.
79. Kanegane H, Agematsu K, Futatani T, et al. Novel mutations in a Japanese patient with CD19 deficiency. *Genes Immun*. 2007;8(8):663-670.
80. Warnatz K, Salzer U, Rizzi M, et al. B-cell activating factor receptor deficiency is associated with an adult-onset antibody deficiency syndrome in humans. *Proc Natl Acad Sci U S A*. 2009;106(33): 13945-1350.
81. Kuijpers TW, Bende RJ, Baars PA, et al. CD20 deficiency in humans results in impaired T-cell–independent antibody responses. *J Clin Invest*. 2010;120(1):214-222
82. van Zelm MC, Smet J, Adams B, et al. Cd81 gene defect in humans disrupts CD19 complex formation and leads to antibody deficiency. *J Clin Invest*. 2010;120(4):1265-1274.
83. Salzer U, Chapel HM, Webster AD, et al. Mutations in TNFRSF13B encoding TACI are associated with common variable immunodeficiency in humans. *Nat Genet*. 2005;37(8):820-828.
84. Pan-Hammarström Q, Salzer U, Du L, et al. Reexamining the role of TACI coding variants in common variable immunodeficiency and selective IgA deficiency. *Nat Genet*. 2007;39(4):429-430.
85. Castigli E, Wilson SA, Garibyan L, et al. TACI is mutant in common variable immunodeficiency and IgA deficiency. *Nat Genet*. 2005;37(8):829-834.
86. Zhang L, Radigan L, Salzer U, et al. 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(5):1178-1185.

87. Salzer U, Bacchelli C, Buckridge S, et al. Relevance of biallelic versus monoallelic TNFRSF13B mutations in distinguishing disease-causing from risk-increasing TNFRSF13B variants in antibody deficiency syndromes. *Blood*. 2009;113(9):1967-1976.
88. Malphettes M, Gerard L, Carmagnat M, et al. Late-onset combined immune deficiency: a subset of common variable immunodeficiency with severe T-cell defect. *Clin Infect Dis*. 2009;49(9):1329-1338.
89. Agematsu K, Futatani T, Hokibara S, et al. Absence of memory B cells in patients with common variable immunodeficiency. *Clin Immunol*. 2002;103(1):34-42.
90. Warnatz K, Denz A, Drager R, et al. 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(5):1544-1551.
91. Piqueras B, Lavenu-Bombled C, Galicier L, et al. Common variable immunodeficiency patient classification based on impaired B-cell memory differentiation correlates with clinical aspects. *J Clin Immunol*. 2003;23(5):385-400.
92. Wehr C, Kivioja T, Schmitt C, et al. The EUROclass trial: defining subgroups in common variable immunodeficiency. *Blood*. 2008;111(1):77-85.
93. Ko J, Radigan L, Cunningham-Rundles C. Immune competence and switched memory B cells in common variable immunodeficiency. *Clin Immunol*. 2005;116(1):37-41.
94. Alachkar H, Taubenheim N, Haeney MR, Durandy A, Arkwright PD. Memory switched B-cell percentage and not serum immunoglobulin concentration is associated with clinical complications in children and adults with specific antibody deficiency and common variable immunodeficiency. *Clin Immunol*. 2006;120(3):310-318.
95. Carsetti R, Rosado MM, Donnanno S, et al. The loss of IgM memory B cells correlates with clinical disease in common variable immunodeficiency. *J Allergy Clin Immunol*. 2005;115(2):412-417.
96. Detková D, de Gracia J, Lopes-da-Silva S, et al. Common variable immunodeficiency: association between memory B cells and lung diseases. *Chest*. 2007;131(6):1883-1889.
97. Melo KM, Carvalho KI, Bruno FR, et al. A decreased frequency of regulatory T cells in patients with common variable immunodeficiency. *PLoS ONE*. 2009;4(7):e6269.
98. Knight AK, Radigan L, Marron T, Langs A, Zhang L, Cunningham-Rundles C. High serum levels of BAFF, APRIL, and TACI in common variable immunodeficiency. *Clin Immunol*. 2007;124(2):182-189.
99. Palanduz S, Palanduz A, Yalcin I, et al. In vitro chromosomal radiosensitivity in common variable immune deficiency. *Clin Immunol Immunopathol*. 1998;86(2):180-182.
100. Vorechovský I, Scott D, Haeney MR, Webster DA. Chromosomal radiosensitivity in common variable immune deficiency. *Mutat Res*. 1993;290(2):255-264.
101. Fazel R, Krumholz HM, Wang Y, et al. Exposure to low-dose ionizing radiation from medical imaging procedures. *N Engl J Med*. 2009;361(9):849-857.