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International Consensus Document (ICON): Common Variable Immunodeficiency Disorders

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Abstract

The International Collaboration in Asthma, Allergy and Immunology initiated an international coalition among the American Academy of Allergy, Asthma & Immunology; the European Academy of Allergy and Clinical Immunology; the World Allergy Organization; and the American College of Allergy, Asthma & Immunology on common variable immunodeficiency. An author group was formed and then divided into individual committees. Within the committee, teams of authors were subgrouped to generate content for specific sections of the document. Content was

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derived from literature searches, relevant published guidelines, and clinical experience. After a draft of the document was assembled, it was collectively reviewed and revised by the authors. Where evidence was lacking or conflicting, the information presented represents the consensus expert opinion of the group. The full document was then independently reviewed by 5 international experts in the field, none of whom was among the authors of the original. The comments of these reviewers were incorporated before submission for publication.

DEFINITION

The term “common variable immunodeficiency” (CVID) was coined in 1971 by a World Health Organization committee to separate less well-defined antibody deficiency syndromes from others with a more coherent clinical description and Mendelian inheritance.[1,2] Therefore, the hypogammaglobulinemic syndrome of CVID became a diagnosis of exclusion. Since then, the International Union of Immunological Societies Expert Primary Immunodeficiency Committee redefined the conditions in 2009 as “common variable immunodeficiency disorders”, thus retaining the CVID acronym but emphasizing the heterogeneous nature of these hypogammaglobulinemic states.[3] According to the proposal by the European Society for Immunodeficiencies and the Pan American Group for Immunodeficiency in 1999, CVID was defined as follows:

> CVID is probable in a male or female patient who has a marked decrease of IgG (at least 2 SD below the mean for age) and a marked decrease in at least one of the isotypes IgM or IgA, and fulfills all of the following criteria:
>
> 1. Onset of immunodeficiency at greater than 2 years of age
> 2. Absent isohemagglutinins and/or poor response to vaccines
> 3. Defined causes of hypogammaglobulinemia have been excluded according to a list of differential diagnosis (Table I).
>
> As will be discussed further below, CVID encompasses a group of heterogeneous primary antibody failure syndromes characterized by hypogammaglobulinemia. The number of potential distinct entities within this group is still unknown, and the diagnosis remains one of exclusion. Monogenic forms have been described, but polygenic inheritance is likely in most cases.[4–6] Despite the fact that several monogenic defects underlying apparent CVID have been defined, because of the rarity of each defect and the lack in most cases of significant impact on management, as well as the cost of testing, genetic studies are not considered appropriate for routine use in patients with CVID at this time.

The onset of the varied clinical manifestations and laboratory abnormalities do not necessarily coincide, and may occur at any age from early childhood to old age. Given (1) the broad differential diagnosis of hypogammaglobulinemia (Table I),[7] (2) the challenge of differentiating some of these in early childhood (particularly regarding definitive assessment of vaccine responses), and (3) that CVID is considered a diagnosis of exclusion, it is best not to confer this diagnosis before at least age 4 years.

Antibody production is always disturbed in CVID. This is often the result of B-cell dysfunction, but may also result primarily from impairment of T-cell function and lack of sufficient help for antibody production. Infection susceptibility is mainly to encapsulated extracellular bacteria in the respiratory tract, but there may also occur various other clinical manifestations affecting many organ systems. The phenotype is very broad, ranging from only bacterial infections, to progression from a CVID-like condition to severe disease similar to a combined immunodeficiency, possibly having a different etiology.[8,9] Some patients may also have distinct initial presentations, such as autoimmune disease, granulomatous disease, or enteropathy without recurrent infections (discussed in detail below).[10,11]

The normal range of IgG serum levels varies in different age groups; therefore, it is critical that this be defined according to the age-adjusted reference range for the population. An absolute lower limit value of IgG at 4.5 g/L for adults has been proposed, because nearly 95% of the patients with CVID in a European cohort fulfilled this criterion.[12] However, it is recognized that some patients with CVID have relatively high residual IgG levels (up to 6 g/L) at diagnosis while still showing impaired specific antibody formation.[13] Furthermore, the normal range of IgG levels may also vary according to race or ethnicity.[14] Thus, for practical purposes, the definition of hypogammaglobulinemia depends on the local or regional reference range applicable to the patient. In addition to a low IgG level, IgA or IgM level must be low for a definite diagnosis of CVID.[15] Note that not all clinical immunologists agree regarding these laboratory criteria. Some do not confer a diagnosis of CVID if the IgA level is normal. We publish the less stringent criteria here because it is an accepted standard for many practitioners. It is of critical importance that all immunoglobulin measurements be interpreted according to age-specific normal ranges and that levels be consistently low on repeated measurements at least 3 weeks apart.

Vaccine responses will be discussed later in greater depth. Impairment of IgG vaccine responses is an extremely important element of the definition of CVID. Note that depending on circumstances, some immunologists forego antibody measurement, for example, if the total IgG level is very low (<100 mg/dL) or if the clinical presentation and other laboratory features are highly characteristic; see section on Diagnosis).

Consensus definition of CVID

1. Most patients will have at least 1 of the characteristic clinical manifestations (infection, autoimmunity, lymphoproliferation). However, a diagnosis of CVID may be conferred on asymptomatic individuals who fulfill criteria 2 to 5, especially in familial cases.
2. Hypogammaglobulinemia should be defined according to the age-adjusted reference range for the laboratory in which the measurement is performed. The IgG level must be repeatedly low in at least 2 measurements more than 3 weeks apart in all patients. Repeated measurement may be omitted if the level is very low (<100–300 mg/dL depending on age), other characteristic features are present, and it is considered in the best interest of the patient to initiate therapy with IgG as quickly as possible.

3. IgA or IgM level must also be low. (Note that some experts prefer a more narrow definition requiring low IgA level in all patients.)
4. It is strongly recommended that all patients with an IgG level of more than 100 mg/dL should be studied for responses to T-dependent (TD) and T-independent (TI) antigens, whenever possible. In all patients undergoing such testing, there must be a demonstrable impairment of response to at least 1 type of antigen (TD or TI). At the discretion of the practitioner, specific antibody measurement may be dispensed with if all other criteria are satisfied and if the delay incurred by prevaccination and postvaccination antibody measurement is thought to be deleterious to the patient's health.
5. Other causes of hypogammaglobulinemia must be excluded (Table I).
6. Genetic studies to investigate monogenic forms of CVID or for disease-modifying polymorphisms are not generally required for diagnosis and management in most of the patients, especially those who present with infections only without immune dysregulation, autoimmunity, malignancy, or other complications. In these latter groups of patients, however, single gene defects may be amenable to specific therapies (eg, stem cell therapy) and molecular genetic diagnosis should be considered when possible.

Ameratunga et al[16] have recently proposed a distinct set of diagnostic criteria for CVID. Differences between the criteria of Ameratunga et al[16] and those stated above are summarized in Table II. Although the criteria presented here do not define "possible" or "probable" forms of CVID, we recognize that some patients with a low IgG level and impaired vaccine responses may not fulfill our criteria for CVID (at least at initial evaluation) because IgA or IgM level is not low. This is a form of hypogammaglobulinemia with antibody deficiency that should not be called CVID (it may be called "unspecified IgG deficiency" or "unspecified hypogammaglobulinemia"). Alternatively, IgG and IgA levels may be low, but vaccine responses may appear normal by standard criteria. In all these cases, patients should be assessed repeatedly over time because immunoglobulin levels and antibody function may wane to the point that the above criteria are met and a diagnosis of CVID may be conferred. Regardless of whether there is deterioration over time, many patients with abnormal immunoglobulin levels and/or functional antibody responses not meeting criteria for CVID may have a significant burden of infections and should be assessed for benefit from IgG replacement.

We do not see a benefit to defining possible or probable categories of diagnosis on the basis of laboratory or histopathologic criteria. The requirement for low IgA (or IgM) level provides additional diagnostic specificity. We believe that it is more appropriate to define hypogammaglobulinemia according to regional and ethic laboratory norms rather than using a single numeric criterion across the board.

EPIDEMIOLOGY

Primary immunodeficiency disorders are usually considered to be "rare diseases." However, as a whole, this group of diseases may not be as rare as once thought. Neither the true

incidence nor the true prevalence of primary immunodeficiency is known. Most studies are geographically limited and based on survey data or record review of diagnosed and/or registered cases.[17–21] The number of undiagnosed cases is unknown because a comprehensive population-based screening process for defined primary immunodeficiency has not been developed anywhere in the world.

Almost every primary immunodeficiency registry available for consultation reports a predominance of antibody defects (generally >50%), and in most of them, CVID is the most frequent symptomatic antibody deficiency diagnosed in adulthood.[20,22] IgA deficiency occurs with higher frequency overall, but most patients with IgA deficiency are asymptomatic.[23] Note that in children, specific antibody deficiency is more often diagnosed.[24] In 2007, a Latin American Group for Immunodeficiency registry report revealed that in a total of 3321 patients registered, the most common form of primary immunodeficiency disease was predominantly antibody deficiency (53.2%), with IgA deficiency and CVID reported as the most frequent types.[20] A recent report from the European Society for Immunodeficiencies registry database including 13,708 patients from 41 countries established that CVID represents the most common entity with 2880 patients or 21% of all entries.[18,25] The United States Immunodeficiency Network registry contains 3459 subjects, with 1049 subjects with CVID (30%).[26]

There are no precise data on the prevalence of CVID, but it has been estimated at between 1:100,000 and 1:10,000 of the population.[12] The European Society for Immunodeficiencies registry estimates a total primary immunodeficiency diseases (PIDD) prevalence ranging from 1.3 (Poland) to 5 (France) per 100,000 living persons in European countries.[18,25] The calculated prevalence of CVID in these European countries ranges from 0.07 to 0.98 patients per 100,000 inhabitants. These observed differences between countries are thought to be a consequence of underreporting in those showing the lower rates of prevalence.[18] The reported prevalence in Japan is also within this range (0.25:100,000).[27] Discrepancies between these reports are likely a result of different methodologies and their influences on various forms of ascertainment bias. Additional factors in apparent geographic variance in incidence/prevalence could be due to access to health care, rate at which patients are properly diagnosed, or population genetic differences.

NATURAL HISTORY

Pathogenesis

With the exception of some known monogenic forms of CVID (discussed below), no cause for the immune defect has been found in 98% of the patients with CVID. With the hallmark of hypogammaglobulinemia, the immune defect common to all patients with CVID is loss of B-cell function. This is either intrinsic to B cells, or a result of insufficient help from other cells for antibody production. In particular, there is a reduction in the number and percentage of isotype-switched B cells in a majority (not all)[28,29] and a loss of plasma cells in both bone marrow and mucosal tissues.[30,31] The causes of these abnormalities remain largely obscure.

Patients with CVID have often been stratified on the basis of peripheral blood B- and T-cell phenotype (discussed below) and *in vitro* B-cell function, using a number of stimuli. In most

cases, B cells of some subjects produce normal amounts of immunoglobulin in culture, others produce only IgM, and others are unable to produce any immunoglobulin at all.[32] One recent analysis using flow cytometric phenotyping and measurement of kappa-deleting recombination excision circles (KRECs, see below) distinguished 5 possible subgroups or defects: (1) B-cell production, (2) early peripheral B-cell maturation or survival, (3) B-cell activation and proliferation, (4) germinal center, and (5) postgerminal center.[33] In some patients, calcium flux after activation of the B-cell receptor may be impaired (note that these correspond to low switched memory B cells) with expansion of the $CD21^{low}$ population (see Table III).[34] Others have demonstrated distinct signaling abnormalities in subpopulations with CVID. For example, stimulation of B cells and/or plasmacytoid dendritic cells via Toll-like receptors 7, 8, and 9 is inhibited in some patients; this correlates with lower levels of switched memory B cells.[35]

A relative loss of T-cell function in many subjects has been demonstrated, including a lack of circulating CD4 T cells,[9] and especially, naive CD4 T cells,[36] antigen-specific T cells,[37,38] and impaired proliferation, activation,[39] and secretion of some cytokines (IL-2, IFN-γ, and IL-10)[40,41] with increases in IL-6[42] and perhaps IL-12.[43] More recently, defects in thymic maturation,[44–46] monocyte/dendritic cell defects,[47] and impaired innate immune responses[48] including loss of natural killer cells[49] have also been demonstrated. It is not simple to dissect the primary and secondary changes observed in CVID, especially because the mechanisms are likely to be heterogeneous.

Studies of the bone marrow of patients with CVID show depletion of plasma cells in 94%; the degree of depletion correlates with serum immunoglobulin levels.[30] The presence of aggregates of T cells in the bone marrow correlates with autoimmune cytopenias. In 9 of 25 (36%) patients, a block in the pre-B I-II transition correlated with lower peripheral blood B-cell numbers.

Clinical manifestations

In a recent large (2212 patients) study from Europe, a large proportion (34%) of the patients had disease onset before age 10 years.[50] There was a reported 2:1 male predominance before age 11 years, this was less pronounced up to age 30 years, and there was a slight female predominance (1.3:1) after age 30 years. Mendelian inheritance is relatively infrequent (between 5% and 25%), displaying both autosomal-dominant and autosomal-recessive patterns and depending at least partly on regional genetic factors[11,50,51] In a large American cohort of 248 patients, the age of onset of symptoms was found to be bimodal, with peaks in the first and third decades.[52] However, in a European cohort of 413 patients, the age of onset was found to be a continuous curve, with a mean age of 35.3 years and median of 33 years.[53] The more recent European cohort suggested again a slightly bimodal onset curve similar to the earlier American report.[50] The early peak may reflect the disproportionately higher rate of diagnosis in young males.

There may be significant delay between the onset of symptoms and the establishment of the diagnosis of CVID. In the American cohort, this delay was approximately 5 to 6 years.[52] In an older report of a European cohort, there was a mean diagnostic delay of 7.5 years (median, 5 years; range, 0–61 years)[53] and 8.9 years in an Italian cohort.[11] In a more recent

European report, the delay was approximately 4 to 5 years, overall.[50] In this cohort, there was no reduction in the delay in patients diagnosed after the year 2000 in comparison to those diagnosed before. However, the delay was considerably shorter in those patients with onset of symptoms after age 10 years, in comparison to those who became ill at younger ages (3.1 vs 7.2 years, respectively).

The first literature report of CVID appeared in 1954 and described a 39-year-old woman with agammaglobulinemia who had many of the observed complications of this immune defect, including chronic bronchitis, episodes of bacterial pneumonia, *Haemophilus influenzae* meningitis, chronic diarrhea and malabsorption leading to weight loss, and severe hypocalcemia.[54] Frequent and severe infections are common at the time of diagnosis of CVID. Complications related to immune dysregulation are not present in all patients. Depending on details in how various patient cohorts were studied, approximately 33% to 80% do not develop these complications at all ("infection-only" phenotype), though they may have infection-related structural changes such as bronchiectasis.[8,9,55] The other 20% to 67% of the patients may develop various additional clinical problems including autoimmunity, interstitial lung disease, granulomatous disease, liver disease, gastrointestinal inflammatory disease, lymphoid hyperplasia, and/or cancer or lymphoma. These are all discussed in greater detail below.

There are significant differences in the prevalence of these complications between countries in Europe and in comparison to other large cohorts.[11,53,56,57] With increased reporting of patients with CVID from newly established registries around the world, new patterns of complications of CVID may emerge.

Unusual infections—Recurrent urinary tract or uterine cervical infections due to *Ureaplasma urealyticum* have been described.[58] Arthritides and lung infections may also be caused by *Ureaplasma* or *Mycoplasma* organisms, and these should be considered when other common pathogens are not found.[59–61] Enteroviral infections may cause meningoencephalitis or a dermatomyositis-like syndrome in undiagnosed patients not receiving IgG, or in those who are receiving lower (inadequate) doses (0.1–0.3 g/kg/month).[62] The mortality of this complication is high (50%). The occurrence of other opportunistic infections should raise suspicion for a combined immunodeficiency or diagnosis other than CVID.[9]

Chronic lung disease—Airway inflammation is common in CVID and may progress over time to obstructive or restrictive disease and bronchiectatic changes evident on computed tomography (CT).[11,53,63] Bronchoscopy may be needed to identify pathogenic organisms. Lavage culture may include organisms potentially not susceptible to antibody clearance such as nontypeable *H Influenzae* and/or viruses.[64] *Mycoplasma* and *Ureaplasma* organisms are prominent pathogens for sinopulmonary as well as nonrespiratory infections (see below).[61]

Mediastinal lymphadenopthy is common in CVID. When nodes are large, or coupled with larger or persistent nodules in the lung fields, an open lung biopsy is required to determine whether the lung collections are scars, lymphoid cells, clonal proliferations, granulomatous

infiltrates resembling sarcoidosis, or malignancy. Lymphoid interstitial pneumonia or follicular bronchitis/bronchiolitis may lead to fatigue, cough, shortness of breath, and alveolar damage resulting in reduced gas transfer.[65] On high-resolution chest CT, pulmonary interstitial infiltrates appear as reticulonodular changes, marked linear opacities, fibrosis, and a ground glass appearance.[66]

Although granulomas may be found in many organs in CVID, in the lung, the granulomas are commonly accompanied by lymphoid infiltrations, leading to what has been termed "granulomatous lymphocytic interstitial lung disease."[67,68] In a series, open lung biopsy revealed that 11 of 12 patients with clinical/radiographic diagnosis of granulomatous lymphocytic interstitial lung disease had granulomas and all had follicular bronchiolitis and lymphoid interstitial pneumonitis (J.M. Routes et al., unpublished data, 2015). The granulomas, although not necrotizing, are not perilymphatic as in sarcoidosis. Furthermore, follicular bronchiolitis and lymphoid interstitial pneumonitis are not prominent in sarcoidosis, suggesting that granulomas in the lung represent a different pathophysiology. Other series have shown different combinations of pathologies, suggesting various etiologies depending on the locality or genetic background of the patients.[65,69] The evolution of granulomas or interstitial pneumonitis in CVID is not yet well understood. Early stages may be asymptomatic. It is recommended that patients have a chest CT scan and measurement of gas transfer obtained at some time relatively close to the time of diagnosis to provide a baseline for comparison in the future. Whenever suggestive findings occur, this diagnosis (or other) must be formally established by histopathological analysis. Ongoing inflammation leads to lung damage and diminished survival. Chronic lung disease is a major cause of mortality in CVID.[8,50,70,71]

Diffuse granulomatous disease—Granulomatous disease or atypical sarcoidlike lesions occur in 8% to 22% of the patients with CVID and may be discovered on the basis of various organ biopsies years before the recognition of the immune defect.[68,72–78] Lungs, lymph nodes, and spleen are commonly affected. However, skin, liver, bone marrow, kidney, gastrointestinal tract, eyes, and/or brain may also be involved.[74,79–81] The granulomas in CVID are noncaseating, and microbial associations have not been described. The cause of these tissue collections remains unknown.

In individuals who already carry a diagnosis of CVID, the constellation of symptoms and signs described here is not to be confused with sarcoidosis. However, confusion may occur in patients who have undiagnosed CVID. Hematologic abnormalities such as variable cytopenias (generally nonimmune) are common in sarcoidosis, as is monocytosis. Importantly, *hyper*-gammaglobulinemia is frequently seen in sarcoidosis, and most of the remainder have normal immunoglobulin levels, in contrast to the hypogammaglobulinemia of a patient with CVID. Additional differences between CVID and sarcoidosis include the distribution and size of pulmonary nodules and the very high prevalence of splenomegaly in the former.[82] All patients being evaluated for sarcoidosis should have measurement of serum immunoglobulins.

Autoimmunity—Autoimmunity occurs in approximately 25% to 30% of the patients with CVID.[50,55] Quinti et al[11] described autoimmunity as one of the presenting manifestations of

CVID in 17% of 224 patients, and in 2.3%, autoimmune disease was the only clinical complication at the time of diagnosis of CVID.[10] The most common of these include cytopenias: immune thrombocytopenia purpura (ITP), autoimmune hemolytic anemia (AIHA), or both at the same or different times (Evans syndrome). Autoimmune neutropenia is much less common.[83–85] For unclear reasons, these patients may not have a typical history of recurrent infections and severe cytopenia may be the first manifestation of the immune defect.[8] Patients with CVID with granulomatous disease and evidence of lymphoproliferation are more likely to have had episodes of ITP and/or AIHA.[72,78] In the recent European cohort report, autoimmunity was correlated with enteropathy, granulomatous disease, splenomegaly and splenectomy, low IgA level, and later age of onset.[50] Note that autoimmune manifestations may even occur before the appearance of hypogammaglobulinemia. These patients may appear similar to those with syndromes of immune dysregulation such as autoimmune lymphoproliferative syndrome.[86]

Other autoimmune diseases in patients with CVID include inflammatory bowel disease, seronegative arthritis, pernicious anemia, Sjogren syndrome, uveitis, vasculitis, thyroiditis, alopecia, vitiligo, hepatitis, primary biliary cirrhosis, sicca syndrome, or systemic lupus erythematosus.[10,55,87,88] These do not appear to be linked to the occurrence of cytopenias. Some other common autoimmune conditions, such as insulin-dependent diabetes, psoriasis, celiac disease, hypothyroidism, and seropositive rheumatoid arthritis, do not appear to be increased in CVID.[10,50,88–90]

Gastrointestinal disease—Some form of enteropathy was found in 9% of the patients studied in the recent European report.[50] This was correlated with autoimmunity, splenomegaly, lobectomy, low IgM level, and age of onset. Enteropathy in CVID has a high rate of nonmalignant mortality, possibly due to malabsorption.[53,71] Bacterial, protozoal (mainly *Giardia lamblia*), and viral gastrointestinal infections occur in CVID and often respond to standard medical treatments. Eradication may be difficult for some patients. Even more challenging is a form of chronic small bowel inflammation that occurs in 4% to 12% of the patients, depending on the cohort studied. This is associated with unexplained persistent chronic diarrhea, weight loss, steatorrhea, and malabsorption with loss of both minerals and fatsoluble vitamins.[91–93] Vitamin A deficiency is also important as a cause of night blindness as well as having a negative effect on intrinsic immunoglobulin production.[94] This has been referred to as CVID-associated autoimmune enteropathy. Bacterial overgrowth is common and can lead to bloating and worsening diarrhea.

Although the pathogenesis of AIE is unclear, on biopsy, the mucosa shows villous blunting and crypt distortion with increased lymphocytes (usually CD8 T cells), lymphoid aggregates (lymphoid hyperplasia), and loss of plasma cells.[91,95] Note that lack of plasma cells is a frequent histological feature in CVID.

Some authors conclude that the absence of plasma cells and increased lymphoid hyperplasia reliably distinguish AIE from celiac disease.[92] Others suggest that celiac disease–associated HLA-DQ markers in patients with CVID may help distinguish AIE due to immune dysregulation.[96] That is, if celiac disease markers are absent, a diagnosis of AIE is more likely. Although MHC genetic tests may be helpful, serologic tests (transglutaminase and

other antibodies) usually are not. Mild hepatomegaly with persistently increased liver enzyme levels, including alkaline phosphatase, is frequent in CVID. The most commonly identified cause of liver abnormalities is nodular regenerative hyperplasia.[97–99] Although previously thought to have a relatively benign course, a significant proportion of patients progress to autoimmune hepatitis with typical histopathological changes and/or develop portal hypertension. These patients frequently have hypersplenism with neutropenia and many succumb to infection. Gall bladder disease with cholestasis, primary biliary cirrhosis, and autoimmune or granulomatous hepatitis are also potential causes of liver abnormalities. Hepatitis B and C are uncommon in CVID unless risk factors are present.

Allergic disease—Recent studies of allergic respiratory diseases in CVID have revealed low incidences of allergic asthma, 6.5% of 62 patients as a whole and 22.2% of the 18 patients with a clinical history suggestive of asthma.[100] Likewise, the same group found allergic rhinitis to be equally unusual.[101] Although 82% of the patients had a history of chronic or episodic rhinitis or rhinosinusitis, an allergic cause was confirmed only by detection of specific IgE to aeroallergens in 5.6% of the 72 patients with CVID with a clinical history suggestive of the diagnosis. This is in contrast to patients not having CVID with low or absent IgA levels with or without IgG subclass deficiency in whom allergic diseases, particularly asthma, are more common.[102–104]

Lymphoid hyperplasia—Cervical, mediastinal, and abdominal lymphoid hyperplasia and/or splenomegaly are found in at least 20% of the patients with CVID[105,106]; splenomegaly was reported in 26% of the recent European cohort.[50] Biopsies of lymph nodes usually show atypical lymphoid hyperplasia, reactive lymphoid hyperplasia, or granulomatous inflammation. Lack of plasma cells and the presence of ill-defined germinal centers in lymph nodes and other lymphoid tissues are characteristic.[107] These tissues need to be examined for B- and T-cell clonality, using fluorescence markers, cytogenetics, and/or molecular analysis to rule out lymphoid malignancy. For B-cell infiltrates, examination for EBV-encoded RNAs by in situ hybridization can be performed. Because subjects with CVID can have unusual lymphoid structures with loss of characteristic boundaries, it is important for an experienced pathologist to examine these tissues. However, the presence of clonal lymphocytes is not diagnostic of lymphoma because these can be found in CVID lymphoid tissue showing reactive hyperplasia.[106]

As noted above, an increased spleen size is a common finding in patients with CVID but neither its causes nor its consequences are well understood. Splenomegaly can be massive and yet not cause clinical symptoms. Histological descriptions of spleen abnormalities after splenectomy showed granulomatous lesions, congestive red pulp, follicular hyperplasia, and atrophic germinal centers/white pulp. These abnormalities might contribute to a splenic sequestration as the cause of thrombocytopenias in patients with CVID.[105,106]

Malignancy—Malignancies of all types are increased in patients with CVID compared with the general population, occurring in possibly 6% to 9% of the patients. Most of the literature to date indicates that lymphomas are the most common form of malignancy in CVID. 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.[108] However, suggesting a potential

downward trend of stomach cancer in recent years, there were 3 stomach cancers in 476 patients (0.6%) in contrast to 32 non-Hodgkin lymphomas (6.7%) and 4 cases of Hodgkin disease.[71] In a country where *H pylori* is prevalent, this organism was found in 14 of 34 subjects with gastric symptoms, 1 of whom had gastric cancer.[109] In a large Italian cohort of 353 patients, adenocarcinoma was an initial presentation in 5 (1.4%).[70] A recent report from a large (2,212 patients) European database found solid tumors outnumbering lymphoma at a rate of 5% versus 3%, respectively.[50]

Other complications—Various additional clinical problems may arise in patients with CVID. The relationship of these to the underlying pathophysiology remains unknown. One such potential association is osteoporosis in association with increased bone turnover.[110,111] Hypothyroidism is also occasionally seen, although not with increased frequency compared with the general population.[112]

Laboratory manifestations

Despite the heterogeneity of patients with CVID, large population retrospective studies both in the United States and in Europe have suggested that IgG levels of less than 4.5 g/L are found in most patients with CVID (85%–94%, respectively).[11,52,53] IgM levels are variable. In the series from the United States, approximately 80% of the patients had IgM levels of less than 0.25 g/L, whereas the mean IgM level was 0.4 g/dL in an Italian cohort of 224 patients with CVID. In one study, females with CVID tended to have higher levels of IgM.[71] IgA levels are low or undetectable in CVID, with 70% of the patients demonstrating values of less than 0.1 g/L in the US cohort vs 49% of the patients with IgA levels of less than 0.07 g/L in the European cohort. (As noted in the section on Definition, some experts require that the IgA level be below the age-adjusted normal range for *all* patients given a diagnosis of CVID.) There are several reported cases of patients with selective IgA deficiency with normal IgG level at initial evaluation in whom IgG levels slowly decline until they fulfill laboratory criteria for CVID.[113] Finally, up to 21% of the patients with CVID may have very low levels or absence of all immunoglobulin isotypes at presentation.[29,50]

Specific antibody production may be variable in some patients with CVID. Antigen-specific IgG levels or vaccine responses in patients suspected to have CVID may be within normal limits at initial presentation, but may decrease over time, ultimately becoming consistent with the diagnosis. In a small study of childhood CVID, a large proportion of children (73%) retained normal isohemagglutinin titers and specific antibody responses to protein antigens were protective at the time of diagnosis in 44% to 62%.[114] In contrast, absent responses to pneumococcal polysaccharide antigens was noted in 71% of children, whereas such response was impaired in 21% of children. In a study of 21 adults with CVID and receiving IgG replacement, about half responded to at least 1 of 5 different protein/peptide or conjugate vaccines.[115] Four of 21 responded to more than 1 protein vaccine, and 3 of 17 made some measurable antibody to pneumococcal polysaccharide.

Some patients will have clinical manifestations of CVID, but may not fulfill laboratory criteria because of their IgG or other isotype level being too high, or their vaccine responses appearing to be adequate. These patients must be followed longitudinally. As noted above,

milder laboratory phenotypes such as IgA deficiency or IgG subclass deficiency may evolve over time until laboratory criteria are met and a diagnosis of CVID is appropriate.

Most patients with CVID will have normal levels of total circulating T cells and natural killer cells in peripheral blood.[49,52] However, B-cell numbers are variable. In the 2008 retrospective review of European data comprising mainly adult patients with CVID, 54% of the patients had normal levels (6%–16%) of circulating B cells, 19% had increased levels (>17%), 12% had reduced levels (1%–6%), and 12% had undetectable levels.[53]

Efforts to study patients with CVID have been fraught by the heterogeneous nature of the disorder. Thus, for more than a decade now, efforts have been put forth to systematically classify patients with CVID by using easily accessible standard flow cytometry criteria (Table III).[28,29,116,117] Such immunophenotypic classifications have permitted insights into the pathogenesis of clinical manifestations. Thus, the EUROclass trial was designed to bring consensus among several classification schemes.[29] Based on B-cell immunophenotyping, levels of class-switched memory B cells, defined by the expression of cell surface markers $CD27^{+}IgM^{-}IgD^{-}$, have been found to be associated with splenomegaly, granulomatous disease, possibly chronic lung disease, and autoimmunity. The added value of identification of transitional B cells ($CD38^{hi}IgM^{hi}$) and $CD21^{low}$ B cells also appear to aid in defining subcategories having potential clinical relevance such as lymphadenopathy and splenomegaly, respectively.

Variable dysfunction within the T-cell compartment has been reported in groups of patients with CVID.[36] One study found that CD4 T cells were decreased in 29% of the 473 patients with CVID, while 50% of this cohort demonstrated abnormal proliferative responses to at least 1 mitogen.[71] Reduced numbers of naive T cells are also commonly observed as reported by the French DEFI group of 311 patients with CVID and others.[9,118] This decrease in the naive CD4 population ($CD45RA^{+}CCR7^{+}CD4^{+}$) is most pronounced among those patients who meet criteria for late-onset combined immune deficiency (LOCID, see below). Measurement of T-cell receptor excision circles may distinguish CVID subgroups (see below).

Restricted T-cell receptor repertoires, oligoclonality, increased T-cell apoptosis, and reduced expression of CD40L have been noted in some patients, indicating that T- cell function is not normal in subgroups of patients with CVID.[119–121] Because B cells require help from CD4 T cells for response to (glyco-) protein antigens, T-cell abnormalities may contribute to defective antibody production in patients with CVID. However, in many patients, T cells may be able to undergo activation and terminal differentiation, with ability to generate specificity to cytomegalovirus, EBV, and influenza virus, supporting a potential benefit of influenza subunit vaccination for most patients with CVID.[122]

Dendritic cells and regulatory T cells may also have roles in the pathogenesis of some phenotypes or complications of CVID, such as autoimmune or inflammatory manifestations.[41,123,124] The mechanisms underlying these cellular abnormalities in CVID are yet to be fully elucidated.

In a French cohort of 311 patients with CVID, 9% had either an opportunistic infection, a CD4 T-cell count of less than 200 cells/μL, or both. In this group of patients, intestinal disease, splenomegaly, lymphomas, and granulomas occurred with greater frequency than in the remainder of the cohort.[9] This phenotype was named LOCID and is now classified as a combined immunodeficiency by the International Union of Immunological Societies. It is notable that consanguinity was more common in this group, suggesting possible Mendelian genetic defect(s). This phenotype is very similar to Good syndrome although thymoma, characteristic of Good syndrome, is not seen in LOCID.[125]

GENETICS

CVID is a complex, multifocal disease, the genetic origins of which are beginning to be at least partially understood. Most cases of CVID are sporadic. Approximately 5% to 25% are familial, with an autosomal-dominant pattern of inheritance being more frequently observed.[51,126] Rarely, families exhibiting autosomal-recessive inheritance have been reported.

A number of studies concentrated on CVID/IgAD families revealed several putative susceptibility loci identified within the HLA region on chromosome 6p.[127] Linkage analysis indicated a susceptibility locus termed IGAD1. Other selected HLA-DQ/DR haplotypes conferred either protection or susceptibility to IgAD and CVID. The strong influence of the MHC region has been noted in several other cohorts. In one, most of the patients inherited HLA *DQ2, *DR7, *DR3, *B8, and/or *B44. B44 was present in almost half and was the most common susceptibility allele.[128] Genetic linkage studies in such families have found evidence of causative mutations on chromosome arms 4q[51] and 16q,[129] but disease-associated genes have not been identified.

To date, mutations in various nonredundant genes have been shown to be disease causing in some patients who fulfill criteria for CVID. Some of the clinical and laboratory features of these disorders are summarized in Table IV. However, these disease-causing mutations currently account for only a very small fraction (about 2%) of the population with CVID. Furthermore, many patients with mutations in some of these genes (eg, *CTLA4* and *LRBA*) exhibit combined immunodeficiency with clinical features or laboratory abnormalities not often seen in CVID. These have been segregated in the CVID classification (from those with no known defect) by the International Union of Immunological Societies and are classified as distinct entities on the basis of defined genetic defects.[154]

DNA repair variants may account for some forms of CVID. With inappropriate DNA repair, a predisposition to radiation damage and cancer are plausible outcomes. Subjects with CVID have an increased propensity to cancer, and some appear to have increased cellular radiosensitivity. Genes encoding elements important for DNA mismatch repair have been associated with IgA deficiency and CVID.[155]

Particular polymorphisms in the TACI *(TNFRSF13B)* and *MSH5* genes may affect the phenotype of about 5% to 8% of the patients with CVID, though they are also present in a significant number of healthy individuals (~1%).[154,156] TACI polymorphisms may impair T-

cell independent class-switch recombination because interactions between TACI and its ligands (APRIL [a proliferation-inducing ligand] and BAFF [B cell activating factor]) are important for this process.[157,158] Most individuals with biallelic *TNFRSF13B* polymorphisms develop CVID, whereas those with single-allele mutations or rare variants are at an increased risk for developing CVID and autoimmune phenomena.[159,160] One kindred with a CVID-like phenotype has been found to have mutations in *TNFRSF13C* (BAFFR), with both siblings having reduced IgG and IgM levels but persistently normal IgA levels.[161] A recent report indicates that polymorphisms in this gene are fairly common and may contribute to an altered B-cell response.[162]

Thus far, the defects described have mainly been monogenic, but it is anticipated that many of the genetic causes of CVID yet to be characterized will be polygenic, and modifier genes may play crucial roles in the development of disease. For example, polymorphisms in genes encoding IL-10 and TNF have been associated with granuloma formation.[163] Polymorphisms in genes encoding alpha-1 antitrypsin and mannose-binding lectin may affect the occurrence of bronchiectasis and pulmonary fibrosis.[164,165]

The identification of novel disease-causing genes is further complicated by the fact that the same clinical disorder may be caused by mutations in different genes and that mutations in different locations of the same gene may give rise to completely different primary immunodeficiency disorders.[154] In addition, epigenetic overlay, as illustrated by IgA-deficient discordant monozygotic twins,[166] may be expected to add to the etiological complexity.

The heterogeneous nature of CVID is further confirmed after a genomewide association study identified multiple potential susceptibility loci for CVID.[4] Three hundred and sixty-three patients with CVID were genotyped. Single nucleotide polymorphism (SNP) associations and copy number variations were recognized and distinguished the CVID cases from control subjects. The strongest associations with CVID were found in MHC and disintegrin/metalloproteinase gene loci. There were 16 associated gene duplications/deletions and many (~100) unique intraexonic duplications and deletions. A total of approximately 1,000 composite SNPs predicted the CVID phenotype. SNP analysis revealed genes associated with particular phenotypes, including mitogen-activated protein 3 kinase 7-interacting protein 3 *(MAP3K7IP3)* significantly associated with low IgA level. Genes significantly associated with lymphoma including *PFTK1, HAVCR1*, and *KIAA0834* were also found. The gene *CACNA1C* (calcium channel, voltage-dependent, L type, alpha 1C subunit) was common to both patients with CVID and enteropathy and patients with inflammatory bowel diseases.[167]

Note again that in our current consensus definition of CVID (see item 6), molecular genetic analysis of patients is not a requirement for conferring the diagnosis. However, in light of the possible definitive or supportive therapies (eg, stem cell therapy and cytokine therapies) that may be afforded to patients with specific genetic defects, consideration should be given to pursuing a molecular diagnosis, if possible. This applies especially to patients exhibiting clinical or laboratory features that are unusual in CVID. Assessment of patients' relatives may distinguish familial from sporadic CVID.

DIAGNOSIS

Clinicians must maintain an index of suspicion for antibody deficiency in patients of all ages. Conditions associated with acquired hypogammaglobulinemia should always be considered during the evaluation of a patient with a suspected antibody deficiency. These include drugs (chronic glucocorticosteroid use, antiepileptic drugs, rituximab therapy), malignancies (chronic lymphocytic leukemia, lymphomas), nephrotic syndrome, protein-losing enteropathy, and congenital lymphangiectasias. See Table I for these and a more complete list of diagnoses to be excluded before making a determination of CVID.

Regarding glucorticoid use, daily doses of more than 20 mg for 14 days in individuals (or doses >2 mg/kg in children weighing <10 kg) or lower doses over longer periods (months to years) may lead to hypogammaglobulinemia.[168,169] There is also a possibility that vaccine responses may be impaired when steroids are used in high doses and for prolonged periods. Although hypogammaglobulinemia with systemic steroid use is well documented, impaired vaccine response is more theoretical; there has been little formal prospective assessment of vaccine responses in patients on systemic steroid therapy. One study found no effect on responses to yellow fever vaccine.[170] Chronic inhaled steroids did not impair responses to influenza vaccine in another study.[171]

In light of the definition of CVID discussed above, the minimum laboratory studies that should be performed during evaluation include measurement of serum immunoglobulin levels and vaccine responses to at least 1 T-dependent and 1 T-independent antigen. For maximum diagnostic specificity, flow cytometry analysis of peripheral circulating lymphocytes to delineate T-, B-, and natural killer–cell populations to exclude combined immunodeficiency is essential. Measurement of B-cell subtypes may also be helpful for differentiating CVID from other disorders.

Serum immunoglobulins

Levels of 4 major isotypes—IgG, IgM, IgA, and IgE—should be measured. At birth, IgG levels are high due to transfer of maternal IgG during gestation. Levels fall to a nadir between age 3 and 6 months and then increase steadily thereafter. Thus, age-related local normal ranges must be used. Wherever possible, population-specific ranges should also be applied to account for racial or environmental differences. Normal values are usually reported as 2 SDs above or below the mean or the 5th to 95th percentile intervals. Because the distribution of serum immunoglobulins is nonparametric, percentile criteria for normality may be preferred, but this is not the rule in all laboratories. Regardless, it is important to recognize that 2.5% to 5% of normal subjects may fall below the defined norms for each age group.

It is common to find discrepancies between laboratories. In addition, intercurrent illnesses, fluid shifts, or other processes may affect immunoglobulin levels. Because of such variability, diagnosis merits demonstration of persistently low serum immunoglobulin levels (as discussed previously) before starting IgG therapy. However, IgG therapy should not be unduly delayed if there is reasonable suspicion of the disease based on other features and delay might be harmful to the patient’s health.

Quantitation of IgG subclasses is not relevant to the diagnosis of CVID. Measurement of IgE level is not usually necessary to make a diagnosis of CVID, but an elevated concentration of IgE is unusual in this setting and should prompt consideration of an alternative diagnosis and/or investigation of immune dysregulation. When IgM levels are either normal or elevated in conjunction with low IgG and IgA levels, the clinician should consider one of the hyper-IgM syndromes or defects of class switch recombination before establishing a diagnosis of CVID.

Assessment of vaccine responses

Vaccine responses should be determined in all patients except those who present with very low or undetectable IgG levels. Even with very low IgG levels (100–200 mg/dL), adequate levels of vaccine-specific IgG may be found and could lead one to consider secondary hypogammaglobulinemia or other diagnoses. Of course, this evaluation should always be performed before initiating IgG therapy. Note that some experts do not require measurement of vaccine responses in all patients. For example, in a patient with characteristic clinical features having low IgG and IgA levels and abnormally low memory B cells with severe sinopulmonary infection, the practitioner may choose to forego the month needed to assess vaccine response in favor of immediate initiation of IgG infusions for therapeutic benefit. In other patients, detection of specific antibodies to known/documented previous infections (such as measles and herpes simplex) or previous immunizations may suffice to rule out primary antibody failure. These decisions must be made on a case-by-case basis. The consensus of the authors of this document is that vaccine responses should be measured in all patients except in cases in which the treating physician judges the potential morbidity of delaying IgG therapy to be unacceptable.

The quality of an antibody response is complex and encompasses many different aspects of antibody function including clonal diversity, binding affinity/avidity, opsonizing and neutralizing capacity, and the effective development of immunologic memory capable of eliciting an anamnestic response. In clinical practice, a patient’s ability to mount normal functional antibody responses is assessed by measuring the serum levels of antigen-specific IgG antibody in response to vaccine antigens or documented infection, and should include evaluation of both T-dependent responses (to protein or glycoprotein antigens) and T-independent responses (to polysaccharide antigens).

Common vaccines available in most countries include tetanus and diphtheria toxoids, *Haemophilus influenza* type B, and pneumococcus. The first 3 of these are composed of protein antigens or a polysaccharide antigen coupled to a protein carrier (conjugate vaccine), and measurement of specific IgG levels to these vaccine antigens provides information on T-dependent responses. Pneumococcal vaccines may be either conjugate (eg, Prevnar-13 [United States] or Prevenar-13 [Europe]) or pure polysaccharide (eg, Pneumovax). T-independent responses are evaluated by measurement of the specific IgG response to pure polysaccharide antigens contained within the pneumococcal polysaccharide vaccine. Other vaccines of diagnostic value include those for meningococcus (both protein-conjugate and polysaccharide preparations) and pure polysaccharide salmonella vaccine. Measurement of antibodies for other routine childhood vaccines such as measles, mumps, rubella, polio,

hepatitis B, and varicella may sometimes be helpful. Assessment of responses to pathogens the patient is known to be infected with (eg, herpes simplex virus, cytomegalovirus, and EBV) may also be informative.

The approach to evaluation of functional antibody responses to T-dependent antigens is to first measure serum levels of specific IgG to various vaccines. If antigen-specific antibody levels are low on initial measurement, immunization followed by repeat measurement of specific antibody levels 3 to 6 weeks later (4 weeks is often considered standard) should be performed to assess production of specific antibody. Diphtheria and tetanus toxoid vaccines are the most commonly used vaccines to evaluate T-cell–dependent responses in both children and adults.

Evaluation of functional antibody responses to T-independent antigens requires measurement of postimmunization specific IgG level because high titers of naturally occurring cross-reactive antipolysaccharide antibodies that correlate poorly with functional activity are commonly present in preimmunization sera.[172] The polysaccharide pneumococcal vaccine is the most commonly used vaccine to assess T-independent response and may be used reliably in adults and in children older than 12 months.[173,174] Recent studies demonstrate normal functional antibody responses to Pneumovax in 12-month-old infants, supporting its use in the evaluation of T-independent responses in even younger children.[174,175]

Protective levels of specific IgG to many protein and conjugate vaccine antigens have been established. Common examples include diphtheria and tetanus toxoids (0.15 IU/mL) and *Haemophilus influenzae* type B (HIB) polysaccharide (1 μg/mL). Levels below these thresholds are suggested to indicate impaired specific responses to these antigens, although this has not been formally established. Some patients with CVID receiving tetanus do make a “protective” response (by concentration criteria) but still need replacement immunoglobulin therapy to prevent bacterial infections.[115]

Studies from immunization trials evaluating the efficacy of pneumococcal conjugate vaccines suggest that a titer of 0.35 μg/mL or more is protective against invasive pneumococcal disease (not otitis media, sinusitis, or nasal colonization) in healthy infants.[176] Specific criteria regarding the number or fraction of serotypes to which an individual responds after receiving a conjugate pneumococcal vaccine have not been developed, if serotype-specific assays are used. Specific IgA and IgM antibody responses to pneumococcal capsular polysaccharides are being studied, but these tests are not routinely available in clinical practice. In the future, these specific IgA and IgM responses may provide an additional way to assess antibody responses in patients on IgG therapy and further characterize CVID phenotypes.[115,177]

Criteria for the interpretation of specific antibody responses to pure pneumococcal polysaccharide antigens have been developed. Although the level of protective antibody for an individual serotype may be defined, there is tremendous individual variability in healthy people with respect to the response pattern across serotypes. Following immunization with a pure polysaccharide pneumococcal vaccine, 1.3 μg/mL type-specific IgG is considered

protective against invasive disease for that type.[178] Recently, consensus criteria have been proposed by an expert group regarding the proportion of types to which an individual responds and the change in preimmunization and postimmunization levels.[179] Four response phenotypes are defined (summarized in Table V). Note that these criteria exclude serotypes contained within pneumococcal conjugate vaccines if previously vaccinated with these (within ~5 years) because of the effect of priming. These new criteria have not been formally validated. Many European laboratories use either whole Pneumovax or Typhum Vi vaccines for evaluating polysaccharide responses.[180]

It should also be noted that simply measuring the level of antibody does not give complete information regarding the quality of the immune response. It must be considered that in some individuals, currently available clinical laboratory tests may not always adequately define impairment of antibody production. For example, some individuals with “protective” levels of pathogen-specific IgG antibody may nevertheless not be protected by virtue of producing an antibody with low avidity or low opsonophagocytic activity.[181,182] However, there are currently no accepted clinical criteria regarding normal vaccine response based on measurements other than specific serum IgG antibody concentration.

Measuring titers of isohemagglutinins, naturally occurring antibodies of IgM and IgG isotypes to polysaccharide blood group antigens, may be an alternative clinically relevant analysis to assess T-independent antibody function in young patients, or in those who have already been started on IgG therapy. Rabies or tick-borne encephalitis vaccines may also be useful diagnostically in patients who are already receiving IgG and have not received these vaccines previously.[130] It is also possible to use standard vaccines to assess responsiveness in patients receiving IgG therapy (see section on Laboratory Manifestations above), although interpretation of results must be adjusted.[115] This is not considered a standard practice. Alternative methods using flow cytometric measurement of B-cell activation following immunization are being developed.[183]

MANAGEMENT

Immunoglobulin replacement therapy

IgG can be given by intravenous or subcutaneous route and at varying intervals to suit the patient’s specific needs.[184] Both types of preparations are efficacious, safe for infusion at home, and widely available, being on the World Health Organization Essential Medicines Lists for adults and children. Patients require monitoring of breakthrough bacterial infections and serum trough or steady-state IgG levels because each individual has a unique threshold level of IgG to prevent breakthrough bacterial infections.[8,185,186]

The required IgG dose for an individual patient is unknown, so most national and international guidelines suggest a starting dose of 0.4 to 0.5 g/kg/month for both intravenous immunoglobulin (IVIG) and 0.4 to 0.6 g/kg/month for subcutaneous immunoglobulin (SCIG).[187] If there is preexisting bronchiectasis, there is evidence for using 0.6 g/kg/month.[188] Some practitioners also recommend higher doses (0.6–0.8 g/kg/month) for patients with enteropathy or splenomegaly.[8,189,190] Higher rates of respiratory infection and poorer outcomes are associated with underdosing IgG and vice versa.[50,191,192]

IVIG infusions are usually given at 3- or 4-week intervals. Adverse events tend to be associated with rapid infusion rates, concurrent acute infections, and previously untreated patients, when a significant time has elapsed between infusions (>6 weeks), or when there is a change in product.[193,194]

Typical acute reactions associated with IVIG infusions include headaches, nausea and vomiting, flushing, hives, chills, myalgia, arthralgia, or abdominal and/or back pain; these usually resolve with antihistamine therapy or acetaminophen or nonsteroidal anti-inflammatory drugs and slowing of the infusion rate. Delayed reactions (fatigue, headache, myalgias) can occur up to 72 hours after the infusion. Pretreatment and posttreatment with the same medications can also frequently alleviate these delayed minor adverse events. Moderate acute and delayed adverse effects may require the addition of corticosteroids to preinfusion and postinfusion medications. Severe, life-threatening anaphylactoid reactions are very rare and are treated acutely with epinephrine, antihistamines, and corticosteroids.[194] Occasionally, switching to a different IVIG product may alleviate adverse effects.

Some patients with CVID with absent serum IgA (<7 mg/dL) may develop IgG anti-IgA antibodies. It is possible that high levels of such antibodies may be associated with anaphylactic reactions to IVIG.[23,195,196] However, such reactions are quite rare, and it is *not* routine to study IgA-deficient patients with CVID for the presence of such antibodies before initiating therapy.

SCIG doses in adults vary from 100 to 200 mg/kg/week and dosing intervals from daily to twice weekly, once a week, or every 2 weeks.[197,198] Absorption of IgG administered subcutaneously takes 3 to 7 days.[199,200] Some practitioners prefer to initiate therapy with IVIG until the patient is stable and then transition to SCIG, whereas others initiate SCIG directly. IVIG and SCIG can also be given on the same day, particularly if a loading dose is desired at the same time as training in self-infusion of SCIG. Therapy can also be started with SCIG on a daily basis to provide rapid increases in IgG levels while training parents or patients in administration.[197,200] With weekly SCIG dosing, steady-state IgG levels are reached after approximately 6 months; the steady-state level can be reached more quickly with 5 daily infusions of the weekly dose followed by weekly infusions.[200] It is possible to use SCIG in patients who previously had severe adverse effects with IVIG and in those with high titers of IgG anti-IgA antibodies.[23,195,201] Systemic reactions to SCIG are rare; local tissue reactions are common.[202] However, these decline over time.[203] More recently, it was shown that using a new infusion area (eg, changing from abdomen to thighs) increases the occurrence of local tissue reactions.[204]

SCIG may also be administered with facilitation by hyaluronidase.[205] In this technique, a 10% IgG solution is administered subcutaneously at the same site after infusion of recombinant human hyaluronidase. The enzyme permits infusion and absorption of much larger volumes in comparison to unfacilitated SCIG. Hyaluronidase SCIG is administered according to the same dose regimen as IVIG, the only difference being subcutaneous versus intravenous administration.

IVIG may be administered in a health care facility, by an infusion service in the patient's home, or self-infused by the patient at home after training. SCIG is usually self-infused at home by a patient or parent. Patient acceptance and safety are proven, quality of life is improved, and there may be cost savings with SCIG, as well.[193,206] The push method without a pump has been used for SCIG in Europe for some time because pumps are expensive and cost savings have also been confirmed in Canada.[207] Educational programs in specialist centers, with the stated aims that patients should be able to self-infuse at home and that parents be able to perform infusions with their child, have increased compliance with therapy by patients and parents.[208]

Complications due to transmission of infectious agents, such as hepatitis B or hepatitis C, are now extremely rare.[209] However, it is still important to continue to monitor patients on replacement therapy for transmission of unknown or new pathogenic agents. Measurement of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) should be performed once or twice annually; significant persistent elevation should be investigated. Serum may be stored for retrospective analysis in the event of future suspected disease transmission.

Renal complications have been observed in patients receiving IVIG. Most of these are associated with sucrose-containing products and in patients with preexisting kidney disease.[210] However, renal injury can occur in any patient with any product. Serum blood urea nitrogen (BUN) and/or creatinine should also be monitored regularly in patients receiving IgG therapy. Hemolysis and thromboembolic phenomena are also rare but important complications of IVIG and SCIG therapies. These require regular monitoring of hematologic parameters and vigilance for thrombosis.[211,212]

Immunization

The effectiveness of common vaccines has not been formally evaluated in patients with CVID. Routine boosters of tetanus or diphtheria toxoids or pneumococcus are probably not necessary for individuals receiving IgG replacement therapy because these antibodies are present in high amounts in therapeutic polyclonal IgG.[213] Less commonly used inactivated vaccines do not pose any risk to patients, but efficacy is unknown. Because cellular immunity is thought to be largely intact in many patients with CVID, and inactivated vaccines may induce some cellular immunity, these may be administered according to the individual needs of the patient. In particular, some immunologists recommend routine administration of the inactivated influenza vaccine.[214]

Therapeutic IgG contains significant amounts of neutralizing antibodies to the most commonly used live viral vaccines such as measles, mumps, rubella, polio, and varicella.[215] Thus, most of these vaccines are neutralized and rendered ineffective in patients receiving IgG. Note that some of these vaccines, especially live attenuated polio, may cause disease in patients with CVID if they have not yet been diagnosed or if IgG therapy has not been initiated; only inactivated or subunit vaccines should be given if CVID is suspected. Note also that the amount of antibody against these agents varies from product to product or from lot to lot and that caution regarding exposure is still advisable when patients live in or travel to areas where these diseases are still common.[216] Efficacy and safety of less frequently

used live-agent vaccines have not been studied in patients with CVID, and they are usually considered to be contraindicated. The risk of transmission of routine (and other) live-agent vaccines is usually low, and therapeutic IgG is neutralizing for measles, mumps, rubella (MMR) and varicella vaccines, so they may be used routinely in family members of patients with CVID. Vaccine polio transmission may occur from family contacts, and this does pose a risk to individuals with CVID because replacement IgG therapy may not be protective.[217]

Treatment of complications

Rhinosinusitis—Recurrent infections in the upper respiratory tract result in chronic sinusitis and nasal polyps. Patients with CVID in whom bacterial sinus infections persist after the commencement of adequate replacement immunoglobulin therapy should have sinus imaging and consultation with an otolaryngologist, removal of any polyps, and possible surgical restoration of sinus drainage. Note that a role for functional endoscopic sinus surgery in the management of any antibody deficiency, including CVID, has not been formally evaluated. Routine saline nasal rinses may be used to aid in mucus clearance. In addition, antibiotic prophylaxis may be required for periods of months, or longer.

Regarding antibiotic prophylaxis for chronic or recurrent rhinosinusitis and/or otitis media, no controlled trials have been conducted in antibody-deficient patients. There is no general consensus among practitioners whether intermittent, continuous, or rotating antibiotics provide improved therapy in subjects with CVID. However, many treating physicians with broad experience with immunodeficiency do use antibiotic prophylaxis for those patients with chronic sinus disease.[218] Various agents and regimens may be considered. Suitable drugs include (but are not necessarily limited to) amoxicillin, trimethoprim sulfa, and macrolides. The latter may provide additional anti-inflammatory effects.[219]

Bronchiectasis—A baseline chest CT and lung function tests are essential to identify bronchiectasis or scarring, assess severity, and discover other pathologies (interstitial disease, granulomas).[53,220] Bronchiectasis should be managed with appropriate measures including physiotherapy and sometimes prophylactic antibiotics, depending on the severity.[220] Recent studies in patients with bronchiectasis (excluding cystic fibrosis) suggest that prophylactic use of azithromycin in patients with frequent exacerbations is useful on a trial basis at least.[221,222] Sputum cultures before the institution of azithromycin prophylaxis may be taken to exclude nontuberculous mycobacteria and ascertain sensitivity to azithromycin. Patients may require monitoring for cardiac or hearing problems, and macrolides should be used with caution in patients at risk for prolonged Q-T interval. In extreme bronchiectasis, 7% hypertonic saline in conjunction with pulmonary hygiene has been found to be useful.[223] Aminoglycoside antibiotics delivered via a nebulizer may also be considered (authors' personal observations). Patients may benefit from joint management with a pulmonary specialist.

Unusual infections—*Ureaplasma* or *Mycoplasma* infections should be treated with a macrolide antibiotic to which the organism is sensitive.[58] In the case of urogenital infections, it may often be useful to treat the patient's partner as well. *Mycoplasma* in joints or lungs may require intravenous antibiotics.[58,59] There are no consistently effective

therapies for enteroviral infections causing meningoencephalitis. High-dose IVIG with measurable titer antibody to the infecting serotype may be helpful.[62,224] The survival rate is only 50%. Fortunately, these infections do not appear to occur in patients maintaining relatively high (>800 mg/dL) IgG trough levels. Giardia infections are treated with high-dose tinidazole or metronidazole, with the addition of paromomycin in resistant cases.[225]

Autoimmune cytopenias—For autoimmune cytopenias, steroids in standard doses (1–2 mg/kg daily prednisone equivalent in divided doses) are usually sufficient. Higher doses of IgG (1–2 g/kg/month) can be used to supplement baseline therapy with oral steroids tapered over several weeks or more.[226] Antirhesus antigen globulin may also be effective.[227] Rituximab in standard doses has been successful for both refractory or recurrent ITP and/or AIHA.[228] A repeat course of rituximab was needed in some patients.

Severe infections have occurred in some patients after splenectomy.[52,229] However, this was not observed in all series.[84] Splenectomy has been curative of ITP or AIHA in CVID and may be needed if other therapies fail. Recent reports indicate that splenectomy does not increase mortality in CVID if adequate immunoglobulin replacement is used.[71,230]

Organ-specific autoimmune disorders in patients with CVID are also treated as they would be in otherwise immunocompetent patients.

Granulomatous disease—Treatment of granulomas is empirical.[78,231,232] Corticosteroids, in low doses for long periods to avoid steroid-related complications, have been found to result in short-term resolution in sites that are easily monitored by endoscopy or imaging. Steroid-sparing agents, such as azathioprine, cyclosporine, or other agents, have been tried with varying success. Infliximab has been successful for skin granulomas, but caution is advised in view of the increased risk of pyogenic or mycobacterial infections.[233]

Enteropathy—Biopsies of the intestinal mucosa should be performed in patients with CVID with chronic enteritis. Although the pathology is similar to that of celiac disease, there are histological differences.[92] Unlike celiac disease, the enteropathy more often seen in CVID is not responsive to gluten withdrawal.[75,234] IgG replacement alone does not generally ameliorate gastrointestinal involvement.[235] Agents such as 5-aminosalicylic acid and/or nonabsorbed oral steroids such as budesonide are commonly used.[91] Low-dose corticosteroids such as prednisone can be used in doses of 10 mg/day; however, higher doses can lead to a significant risk of opportunistic 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. Infliximab has also been used with some benefit in severe enteropathy, although its effectiveness may not be long-lasting.[236] Bacterial overgrowth may be ameliorated by broad-spectrum antibiotics (metronidazole or tinidizole or ciprofloxacin). It is important to treat deficiency of fat-soluble vitamins even in those without enteropathy or malabsorption.[93]

Interstitial lung disease—This complication in CVID has a high mortality, so it is important to detect it as early as possible.[53,67] All patients should have at least 1 high-resolution CT scan at diagnosis. Those without evidence of disease may be monitored at

least annually with spirometry. The frequency of follow-up imaging in the absence of functional changes is unclear. Evidence of interstitial or other lung disease should be followed by full pulmonary function testing including diffusion capacity at least annually with imaging according to functional changes.

It is important to define the histopathology of lung disease so that the most potentially effective therapy can be used.[53,67] There are no controlled studies that define optimal therapy, but a combination of azathioprine and rituximab was found to be effective in subjects with granulomatous/lymphocytic infiltrates in a small open-label study.[237] In forms with a prominent T-cell infiltration, corticosteroids, with or without cyclosporine, have been reported to be successful.[238] Anti-TNF antibody therapy has been successfully used in isolated cases of complex interstitial lung disease.[233]

Lymphoproliferation—More than 30% of the patients with CVID have an enlarged spleen, either palpable or on imaging, though symptoms of hypersplenism are often mild. There may be no need to treat these patients on the basis of splenomegaly alone. Likewise, persistent hypertrophy of lymph nodes should result in review of the diagnosis to exclude lymphoma or autoimmune lymphoproliferative syndrome but does not require treatment per se. Corticosteroids usually lead to regression of these phenomena, but they may recur when steroids are tapered. An acute increase in adenopathy or splenomegaly should prompt evaluation for possible malignant transformation.

Lymphoma—Clinicians must maintain a high index of suspicion for lymphoma in patients with CVID. Lymphoma may be difficult to distinguish from polyclonal lymphoid proliferation. Clonal analysis can be misleading because oligoclonal lymphocyte populations have been demonstrated in biopsies irrespective of histology.[106] Treatment follows the current protocols for immunocompetent patients.

Stem cell therapy

Until now, bone marrow transplantation or other forms of hemopoietic stem cell therapy (HSCT) have not been considered to have an important role in the treatment of CVID, and experience has been limited. One study in severely ill patients with complex CVID showed that HSCT can be successful, but there was significant procedure-related mortality in those receiving HSCT equal to that of those remaining on the waiting list.[239] More recently, a retrospective study of 25 patients with CVID receiving HSCT in 14 worldwide centers has been reported.[240] The indication for HSCT was hematologic malignancy in 7 patients; 6 (83%) of these survived. The other 18 patients had 1 or more of the following conditions refractory to conventional therapies: autoimmune cytopenias, respiratory or gastrointestinal infections, interstitial/granulomatous lung disease, and/or autoimmune enteropathy. Only 33% of these patients survived. Of the total 12 surviving patients, half were able to discontinue IgG therapy and the indication for transplantation resolved in 11 (92%). With improved laboratory predictors, it may be possible in the near future to make better prognostic assessments and so transplant those in whom survival is likely to be considerably reduced.

Special considerations

Children—The main goal of therapeutic management in children with CVID is to decrease the morbidity and mortality associated with recurrent infections. The consensus among pediatric immunologists is that close clinical monitoring and appropriate IgG replacement can ultimately extend the life expectancy of these young patients to approach that of the general population. The optimal dose and interval of replacement immunoglobulin needed to achieve this aim is still under investigation.

In a multicenter randomized, double-blind cross-over study of 18 children (and 25 adults) with antibody deficiencies, the patients who received 800 mg/kg IVIG every 4 weeks had significantly reduced number and duration of infections versus those who received 400 mg/kg every 4 weeks.[241] These findings suggest that in children, as in adults, higher doses of IgG replacement therapy result in fewer infections. Similar conclusions were reached in 2 meta-analyses of infection incidence in relation to IVIG and SCIG dosing.[189,190]

Although the general concerns regarding IgG therapy affect adults and children equally, reduced blood volumes and immature renal function places neonates and infants at risk of developing electrolytic imbalances or volume overload. For these patients, selection of IVIG products with a higher protein concentration, low osmolality, and neutral pH constitute the best option.[242] In children, periodic dose adjustments are required during periods of accelerated growth.

Complications in children may be more common than in adult patients with CVID.[243,244] Furthermore, recurrent infections, chronic inflammation, chronic nutritional deficits, and associated gastrointestinal abnormalities may pose threats to optimal growth in children. Bronchial hyperreactivity associated with allergen sensitization may be seen in some children with CVID.[100] Children with asthma who have other features suggestive of CVID should be screened for antibody deficiency. Although CVID is not common in the general population with asthma, other milder forms of antibody deficiency may also require IgG therapy. As in adults, it is also important to distinguish early structural damage and overt bronchiectasis from interstitial lung disease.[245] Many children already have bronchiectasis by the time they are diagnosed with CVID. In a series of 22 children, bronchiectasis was present in 7 cases (age range, 2.5–15 years) and detected before CVID diagnosis in 5 children.[246] Similar findings were observed in another pediatric cohort.[244]

To prevent organ damage, the importance of screening of family members of children with CVID is emphasized in a recent report demonstrating that a considerable proportion displayed either a positive clinical history with symptoms suggestive of primary immunodeficiency or alterations in humoral immunity including CVID.[247]

Pregnancy—Plasma dilution in the third trimester of pregnancy results in a modest reduction in serum IgG trough levels. At the same time, the fetus is receiving maternal IgG via transport across the placenta. It is advisable to increase the replacement IgG dose during this time and for delivery. Authorities differ in their recommendations for dose increase, ranging anywhere from 10% to 50%[248–250] Female patients can be assured that SCIG can be

delivered into the abdominal wall safely during pregnancy. Depending on body mass index, alternative sites may be chosen for comfort.

Travel—Although many Web sites relating to travel medicine propose specific recommendations regarding immunocompromised travelers, these do not necessarily apply to those with primary antibody failure patients receiving adequate IgG replacement therapy. Patients should discuss their plans for travel with their specialist physician or pediatrician well in advance. Avoidance of infectious agents to which patients with CVID are particularly susceptible, such as water-borne Giardia, Campylobacter, and Salmonella, should be avoided by using only clean water and eschewing uncooked food in countries where these pathogens are common. Caution should be advised regarding travel to areas where certain infections (eg, meningococcal meningitis) are endemic and protection by IgG may not be adequate.

Support—The aim of management is to enable patients to live in a near-normal fashion as much as possible, and to take charge of the disease and the treatment. Lifestyle considerations (sleep, exercise, smoking, drug use, etc) must be emphasized regularly. Children should be encouraged to play outdoors with other children, attend school, and participate in sports and other extracurricular activities, especially those that promote aerobic exercise. There may be circumstances in which the frequency of infections or exposure to other irritant agents may render day care (especially in larger group settings) and school attendance problematic for individual patients. Similar considerations apply to certain work occupations and environments for adult patients. Decisions regarding such attendance or work must be made on a case-by-case basis with the participation of all involved. The goal should always be to promote as much social integration as possible.

Participation in support groups (Table VI) provides essential information relating to work, schooling, insurance, and access to medical and expert care. Other patients and families offer perspectives and mutual support not obtainable from medical personnel. Such groups can help with the social, economic, emotional, and psychological issues of chronic disease.

PROGNOSIS

In the first UK Medical Research Council Report in 1979, survival of patients with CVID 12 years after diagnosis was only 30%.[251] By the end of the 1990s, with the advent of high-dose IVIG therapy, survival 20 years after diagnosis was 64% for males and 67% for females, as compared with the expected 92% and 94% population survival, respectively.[52] Since the year 2000, as the standard replacement dose of IgG has steadily increased, more and more patients have had more normal IgG levels for the majority of their lives, leading to an expected survival overall of 58% 45 years after diagnosis.[53,71] In a large Italian cohort, overall survival was 35% at 40 years. However, while no patients with cancer survived beyond 35 years after diagnosis, patients without malignancy had overall survival of 65% at 40 years.[70] Individual prognosis depends on the clinical phenotype of the patient. Those without disease-related complications have an almost normal life expectancy.[12] Patients with unexplained enteropathy, chronic lung disease, polyclonal lymphoproliferation, or cytopenia have reduced survival (see below).[53]

Data obtained in 2 large surveys over a period of 4 decades showed that causes of death included respiratory failure from chronic lung disease accounting for about 35%, lymphomas accounting for 18%, and cancers other than lymphomas 10% to 33%.[70,71] The importance of cancers other than lymphomas as CVID-associated diseases was further underlined by observations that intestinal adenocarcinomas were the first clinical presentation in some and that in about 3% of the patients with CVID more than 1 distinct primary malignancy occurred.

IgG replacement is the standard of care in CVID and significantly reduces infections (see below). However, this therapy does not seem to prevent or treat the poorly understood noninfectious complications that have emerged as the most difficult aspects of patient management.[53,186] Subjects with CVID who have had infections as their only manifestation of immune deficiency do well over time, with survival resembling that of age-matched controls. Long-term follow-up reveals that subjects with CVID with inflammatory complications have increased morbidity and mortality despite IgG replacement therapy.[52,53,71,252]

There are differences among large series reported as to the prognostic value of serum immunoglobulins at presentation. In a cohort of 473 patients followed for 4 decades at Mount Sinai Medical Center (New York, NY), lower baseline levels of serum IgG and higher IgM levels were associated with poor survival.[71] In a retrospective study from Europe, serum immunoglobulin levels did not predict survival.[53] In both cohorts, elevated levels of serum IgM at diagnosis correlated with the later development of lymphoproliferation or lymphoid malignancy.

In the European cohort, low number of B cells at presentation did not predict survival.[53] This is in contrast to the Mount Sinai study in which lower numbers of peripheral B cells continued to be associated with reduced survival, as previously reported.[52,71]

AREAS FOR FURTHER STUDY

Definition

It is evident from this work and other publications[16] that full consensus regarding the definition of CVID does not yet exist. Some groups include clinical criteria in the definition, however, as for other primary immune defects, and considering the diverse manifestations of this disease, we conclude that the diagnosis of CVID should be primarily based on laboratory criteria. It is possible that advances in the areas of biomarkers and genetics (see below) will provide new material for or a new approach to the development of such a consensus.

Biomarkers

In CVID, the immunological and clinical picture might change gradually over time, even in patients receiving treatment. Similarly, the clinical and laboratory presentation at diagnosis might also depend on the time elapsed since the onset of symptoms because additional complications may arise and immunologic alterations may progress after the initial manifestations of the disease.[8] In particular, B-cell function might gradually decrease or

improve over time. This is most clearly seen in most of the patients with transient hypogammaglobulinemia of infancy who normalize IgG values, mostly within 2 to 4 years of age.[253] A minority of these children develop a form of persistent undefined hypogammaglobulinemia that may not meet diagnostic criteria for CVID. As noted above, other forms of antibody deficiency may progress in severity, as illustrated by patients with selective IgA deficiency who ultimately develop CVID over time.[113] Thus, immunological abnormalities, including immunoglobulin levels and antibody responses, should be periodically assessed. The evaluation of the latter criterion in most patients will be performed before IgG replacement therapy and will need to account for the altered vaccination schedule in many countries, including conjugated vaccination against *S pneumoniae* during childhood, which can complicate the evaluation of the polysaccharide response.

The possibility of measuring IgM and IgA antibody responses, instead of specific IgG, would overcome the difficulty of studying vaccine responses in patients who are already on IgG therapy. Antipneumococcal polysaccharide IgM and IgA assays might be useful in the distinction between responders and nonresponders. Such assays could also help stratify patients with CVID with respect to residual B-cell capacity to mount an antibody response and the risk of developing invasive infections. Thus, they might serve as prognostic markers in patients with CVID. Study of mucosal immunity at the tissue level may improve understanding of the immunological abnormalities in patients with CVID. These data might provide additional prognostic markers.

Lymphocyte phenotyping via flow cytometry and other methods will likely continue to reveal finer detail in peripheral blood populations that may have relevance for disease severity, clinical complications, and progression.

TRECs and KRECs as clinical markers for CVID—TRECs and signal joint immunoglobulin KRECs are nuclear episomal DNA by-products of V(D)J recombination during T-cell and B-cell neogenesis. Impairment of T- or B-lymphocyte development leads to a reduction in the proportion of TREC- or KREC-containing T or B cells in the periphery. Real-time PCR-based quantification of TRECs and KRECs is being applied for newborn screening of severe combined immunodeficiency[254] and B-lymphocyte deficiency (agammaglobulinemia).[255] In addition to the newborn screening, it has been reported that TRECs and KRECs can be used as clinical markers for the severity and progression of various primary immunodeficiency diseases.[46]

As discussed above, although CVID is still considered to be a disease with predominant B-cell dysfunction, many individuals also exhibit important abnormalities of T-cell development and function and suffer from complications that may be related to T-cell deficiency, including opportunistic infections, autoimmune diseases, and malignancies.[5,53] It can be challenging to draw the line between T-cell dysfunction in CVID and combined immunodeficiency (CID) “misdiagnosed” as CVID.[5] Therefore, identifying novel markers to better classify CVID and distinguish CID from CVID is desirable (also see the discussion of LOCID above).

Measurement of TRECs and KRECs may provide useful clinical markers to distinguish CID from CVID. In a report, 37 patients with CVID all receiving IgG therapy were analyzed for TRECs and KRECs.[46] Many patients in this study had opportunistic infections, suggesting that CID may often be misdiagnosed as CVID.

On the basis of TREC and KREC copy numbers, patients were classified into 4 groups: A: TREC(+) KREC(+), B: TREC(+) KREC(−), C: TREC(−) KREC(+), and D: TREC(−) KREC(−). Correlation was found with the TREC/KREC-based classification and clinical symptoms in each patient group. The cumulative events of complications (opportunistic infections, autoimmune diseases, and malignancies) per 10 patient-years were highest in group D, followed by group C, group B, and group A. Events in groups D and C were significantly higher than those in group A. TREC/KREC-based classification also correlated with prognosis. One patient in group D died of *Pneumocystis jirovecii* pneumonia, and 2 other patients in the same group received HSCT following complications due to EBV-related lymphoproliferative disorder. In contrast to group D patients, group A patients remained relatively healthy. One possible explanation is that these patients harbor defects only in terminal B-cell differentiation, but not in T cells. In group B patients, autoimmune diseases were often observed, suggesting that the balance between T and B cells is important in the development of autoimmune diseases in CVID.[5] Group C and D patients suffered a high frequency of both opportunistic infections and malignancies, suggesting that these TREC(−) patients have functionally important T-cell deficits. HSCT may be considered as a treatment to “cure” group D patients, as reported in severe CVID/CID cases, because event-free survival is poor.[239]

Genetics

Genetic variation may be further studied in relation to clinical symptoms (ie, infection-predominant, inflammation-predominant, autoimmune-predominant), in relation to disease severity (ie, disease course, treatment efficacy), and in relation to immunological parameters (ie, immunophenotyping and/or function *in vitro/in vivo*).

Complete genome or exome sequencing may be highly informative for elucidating more common disease-causing genetic alterations as well as the assessment of relevant disease-modifying loci or genes. Further large cohort studies using genomic sequencing and other high-throughput methods (assessment of copy number variations and SNPs) applied in international studies with subjects from diverse genetic backgrounds will be needed in the future to illuminate the (possibly) many causes of this disease and possible therapeutic targets.

Management

What is the best practice for following subjects with CVID over time? Because of the heterogeneity of this disease, there are no set rules aside from regularly scheduled follow-ups and periodic monitoring of serum IgG levels. Full chemistry panels and complete blood cell counts are also important to check for problems that can arise over time (see above). Best practice for monitoring subjects for lung disease has been controversial, and there is no current consensus. The significance of possible radiosensitivity needs to be further studied in

CVID.[256] Magnetic resonance imaging may represent a reliable radiation-free technique for diagnosis and follow-up.[257] Further attention must also be paid to early diagnosis of lymphoid and nonlymphoid cancers. Additional prospective data from large cohorts are needed to better define the most efficient and cost-effective strategies.

How it is possible to individualize immunoglobulin replacement in terms of intervals and doses? Health care delivery systems are quickly changing in response to economic pressures and concerns about quality of care. The system of care is itself an important determinant of patient outcomes. Elucidating the effects of the system of care on patient outcomes requires new methodologic approaches to identify what works in which setting and under what conditions. Personalized health research presents further methodologic challenges because emphasis is placed on the individual response rather than on the population.[258]

The Oxford group proposed to increase the immunoglobulin dose by 0.15 g/kg/month when patients present with a serious infection, persistent infection, or 3 or more moderate infections over a year.[188] Other factors contributing to infections may need to be assessed before these increased doses are made permanent for a specific patient. Other options include shortening the interval between IgG doses with or without increase in the cumulative IgG monthly dose.

It may be that replacement therapy in primary immunodeficiencies is not a mere passive transfer of antibodies exclusively to prevent recurrent infections but also has an active role in regulating autoimmune and inflammatory responses through modulating B-cell or other-cell functions.[259] Consequently, we need a better understanding of the biological effects of IgG replacement even if administered at lower doses than usually used for inflammatory disease.

From existing data, it is not possible at the moment to provide clear assessment of the outcome of HSCT as a potentially curative approach in patients with CVID with poor prognosis. Knowing that the supportive care and efficacy of newer antimicrobial drugs will continue to improve clinical outcomes, it has remained difficult to advise patients with CVID to undergo HSCT. Elaboration of prognostic scores and better diagnostic tools (eg, for stromal cell defects) will be of utmost importance for early selection of suitable patients to better inform choices in the future.[239]

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Abbreviations used

AIE	autoimmune enteropathy
AIHA	autoimmune hemolytic anemia
CID	combined immunodeficiency
CT	computed tomography
CVID	common variable immunodeficiency disorders
HSCT	hemopoietic stem cell therapy
ITP	immune thrombocytopenic purpura
IVIG	intravenous immunoglobulin
LOCID	late-onset combined immune deficiency
SCIG	subcutaneous immunoglobulin
SNP	single nucleotide polymorphism
TREC	T-cell receptor excision circle

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TABLE I

Differential diagnosis of hypogammaglobulinemia

Drug induced
Antimalarial agents
Captopril
Carbamazepine
Glucocorticoids
Fenclofenac
Gold salts
Penicillamine
Phenytoin
Sulfasalazine
Anti-CD20 mAbs (rituximab)
Single gene and other defects
Ataxia telangiectasia
Autosomal-recessive forms of SCID and other forms of combined immunodeficiency
Hyper-IgM syndromes
Transcobalamin II deficiency and hypogammaglobulinemia
X-linked agammaglobulinemia
X-linked lymphoproliferative disorder (EBV-associated)
X-linked SCID
Some metabolic disorders
Chromosomal anomalies
Chromosome 18q-syndrome
Monosomy 22
Trisomy 8
Trisomy 21
Infectious diseases
HIV
Congenital infection with rubella virus
Congenital infection with cytomegalovirus
Congenital infection with *Toxoplasma gondii*
EBV
Malignancy
Chronic lymphocytic leukemia
Immunodeficiency with thymoma
Non-Hodgkin lymphoma
Monoclonal gammopathy (mutiple myeloma, Waldenstrom macroglobulinemia)
Other systemic disorders

Immunodeficiency caused by excessive loss of immunoglobulins (nephrosis, severe burns, lymphangiectasia, protein-losing enteropathy)

SCID, Severe combined immunodeficiency

TABLE II

Differences between the definition of CVID ICON vs Ameratunga et al[16]

CVID ICON	Ameratunga et al[16]
The diagnosis is “definite” if all criteria are met.	The diagnosis is “probable” if all criteria are met.
“Probable” or “possible” CVID is not defined.	Both “probable” and “possible” CVID are defined; there is no “definite” CVID.
Serum IgG level must be below local/regional clinical laboratory norms.	Serum IgG must be <5 g/L for all.
IgA or IgM must be low (IgA low preferred).	IgA or IgM may be low, but neither is required to be low.
Impaired vaccine response is required for the diagnosis.	Impaired vaccine response may be supportive of the diagnosis, but is not required.
The diagnosis may be established solely on the basis of laboratory criteria.	Some symptom/clinical manifestation must be present for “probable” CVID.
The diagnosis is not influenced by additional laboratory criteria.	“Probable” CVID may be established with supportive laboratory criteria (low IgG_3, low memory B cells, increased CD21, low B cells, autoantibodies) and genetic alterations (*TACI, BAFFR, MSH5*, and others).
The diagnosis does not depend on histological criteria.	“Probable” CVID may be established with supportive histological criteria (granulomas, lung or gastrointestinal disease).

ICON, International Consensus.

TABLE III

Classification schemes defining subgroups of patients with CVID on the basis of flow cytometric B-cell immunophenotyping [*]

Nearly absent B cells (<1% [†])	Includes all patients with severe defects in B-cell differentiation
Low switched memory B cells (<2%)	Indicates a defective germinal center development similar to
$CD27^{+}IgM^{-}IgD^{-}$	• ICOS deficiency
	• CD40L deficiency
	Increased risk:
	• Splenomegaly
	• Granulomatous disease
Expansion of transitional B cells (>9%) $CD38^{hi}IgM^{hi}$	Associated with lymphadenopathy
Expansion of $CD21^{low}$ B cells (>10%)	Associated with splenomegaly

ICOS, Inducible T cell co-stimulator.

[*] Adapted from Wehr et al.[29]

[†] Expressed as a percentage of total B cells ($CD19^{+}$ or $CD20^{+}$).

TABLE IV

Monogenic CVID-like immunodeficiencies

Gene	Clinical features	Autoimmunity	Laboratory features	References
CD19	Recurrent respiratory infections	No	Low IgG and IgA level, poor PS vaccine response, normal total B cells, low memory B cells	130,131
CD20	Recurrent respiratory infections	No	Low IgG level, poor PS vaccine response, normal total B cells, low switched memory B cells	132
CD21	Recurrent respiratory infections, diarrhea	No	Low IgG level, normal vaccine responses, normal total B cells, low switched memory B cells	133
CD27	EBV-associated LPD, lymphoma, recurrent sinusitis in some	No	Low IgG or IgA level in some, poor vaccine responses, T-cell dysfunction, normal total B cells, absent memory B cells	134,135
CD81	Recurrent respiratory infections, Henoch-Schonlein purpura, glomerulonephritis	ITP	Low IgA level, poor vaccine response, normal total B cells, low memory B cells	136
CTLA4	Autosomal-dominant, respiratory infections, diarrhea, lymphoid organ infiltration	Various	Low IgG and/or IgA levels, poor vaccine response, low total B cells, and low switched memory B cells	137,138
ICOS	Recurrent respiratory, gastrointestinal infections	Present in some	Low IgG and IgA levels (low IgM level in some), poor vaccine response, low total B cells, low memory B cells, poor CD4/CD8 effector T-cell function	139,140
IL21	Recurrent respiratory infections, cryptosporidium, other severe bacterial/viral infections	No	Low IgG level, high IgE level, poor vaccine response, low B cells, low memory B cells, poor T-cell cytokine production, low natural killer–cell cytotoxicity	141,142
IL21R	Recurrent respiratory infections, IBD	IBD	Low IgG level, high IgE level, poor vaccine response, low B cells, low memory B cells, low T-cell antigen response	141,143
LRBA	Recurrent respiratory infections, enteropathy	ITP, AIHA, others	Low IgG, IgA, and IgM levels, poor vaccine responses, low/normal total B cells, low switched memory B cells	144–146
NFKB2	Autosomal-dominant, recurrent respiratory infections, meningococcal meningitis, adrenal insufficiency	ITP	In some: low IgG and/or IgA/IgM levels, poor PS vaccine response, normal total B cells, low switched memory B cells	147,148
PIK3CD	Autosomal-dominant, recurrent respiratory infections, bronchiectasis, severe herpesvirus infections, lymphoma	No	Low IgG level, low IgG_2 level, poor PS vaccine response, variable low T cells and B cells, low switched memory B cells, high transitional B cells	149–151
RAC2	Recurrent respiratory infections, post-strep. GN	Thyroid	Low IgG, IgA, and IgM levels, poor PS vaccine response, low/normal B cells, low naive T cells	152
TWEAK	Autosomal-dominant, recurrent respiratory infections, pneumococcal meningitis, warts	No	Low IgG (or low $IgG_{2/4}$), IgA, and IgM levels, poor vaccine response, low/normal total B cells, low memory B cells	153

IBD, Inflammatory bowel disease; *LPD*, lymphoproliferative disease; *post-strep. GN*, post–streptococcal glomerulonephritis; *PS*, polysaccharide. All are autosomal recessive unless otherwise specified.

TABLE V

Summary of PPV23-deficient response phenotypes

Phenotype*	PPV23 response, age >6 y	PPV23 response, age <6 y	Notes
Severe	<2 protective titers (>1.3 mg/mL)	<2 protective titers (>1.3 mg/mL)	Protective titers present are low
Moderate	<70% of the serotypes are protective (>1.3 mg/mL)	<50% of the serotypes are protective (>1.3 mg/mL)	Protective titers present to >3 serotypes
Mild	Failure to generate protective titers to multiple serotypes or failure of a 2-fold increase in 70% of the serotypes	Failure to generate protective titers to multiple serotypes or failure of a 2-fold increase in 50% of the serotypes	2-Fold increases assume a prevaccination titer of less than cutoff values of 4.4–10.3 μg/mL, depending on serotype
Memory	Loss of response within 6 mo	Loss of response within 6 mo	Adequate initial response to >50% of the serotypes in children aged <6 y and >70% in those aged >6 y

*All phenotypes assume a history of infection. Reproduced from Orange et al[179] with permission.

TABLE VI

Support organizations for patients with immunodeficiency

Organization	Web site address (URL)
The Jeffrey Modell Foundation (JMF)	jmfworld.org
The Immune Deficiency Foundation (IDF)	primaryimmune.org
International Patient Organization for Primary Immunodeficiencies (IPOPI)	ipopi.org
IPOPI provides support for the national patient organizations in each of 50 countries. It will provide contact information for any of the member country organizations upon request.	