

The Variable in Common Variable Immunodeficiency: A Disease of Complex Phenotypes

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List of Design Committee Members: Stephen Jolles, FRCP, FRCPath, PhD

Activity Objectives

1. To understand the genes currently known to cause a common variable immunodeficiency (CVID) phenotype.
2. To understand the clinical phenotypes of CVID.
3. To understand the available biomarkers that may aid risk stratification in CVID.
4. To understand advances in imaging and treatment of chest disease in CVID.

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Common variable immunodeficiency (CVID) is the most common and clinically most important severe primary antibody deficiency and is characterized by low levels of IgG, IgA, and/or IgM, with a failure to produce specific antibodies. This diagnostic category represents a heterogeneous group of disorders, which present not only with acute and chronic infections but also with a range of inflammatory and autoimmune disorders as well as an increased incidence of

lymphoma and other malignancies. Patients can now be categorized into distinct clinical phenotypes based on analysis of large cohort studies and be further stratified by immunologic laboratory testing. The biologic importance of this categorization is made clear by the 11-fold increase in mortality if even one of these phenotypes (cytopenias, lymphoproliferation, or enteropathy) is present. Limited progress in defining the underlying molecular causes has been made with known causative single gene defects accounting for only 3% of cases, and, for this and the reasons mentioned above, CVID remains resolute in its variability. This review provides a practical approach to risk stratification of these complex phenotypes by using current clinical categories and laboratory biomarkers. The effects of infection as well as inflammatory and autoimmune complications on different organ systems are discussed alongside strategies to reduce diagnostic delay. Recent developments in diagnostics and therapy are also explored. © 2013 American Academy of Allergy, Asthma & Immunology (*J Allergy Clin Immunol Pract* 2013;1:545-56)

Key words: Common variable immunodeficiency; Antibody deficiency; Primary immunodeficiency; Biomarker; Immunoglobulin

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Abbreviations used

ADAM-A disintegrin and metalloproteinase
 APRIL-A proliferation inducing ligand
 BAFFR-B-cell activating factor receptor
 CRP-C reactive protein
 CVID-Common variable immunodeficiency
 GLILD-Granulomatous lymphocytic interstitial lung disease
 HRCT-High-resolution computed tomography
 ICOS-Inducible costimulator
 KREC- κ -deleting recombination excision circles
 LFT-Liver function test
 LIP-Lymphocytic interstitial pneumonia
 LRBA-Lipopolysaccharide responsive beige-like anchor protein
 MBL-Mannan binding lectin
 mRNA-Messenger RNA
 NOD2-Nucleotide binding oligomerization domain containing protein 2
 PAD-Primary antibody deficiency
 TACI-Transmembrane activator and calcium-modulator and cyclophilin-ligand interactor
 TPN-Total parenteral nutrition
 TREC-T-cell receptor excision circle
 VNTR-Variable number tandem repeat

antibodies. CVID is by far the most frequent diagnosis within the category of primary antibody deficiencies and accounts for the majority (57%) of symptomatic primary immunodeficiency on the European Society for Immunodeficiencies registry (www.esid.org). CVID is an important diagnosis not only because of its prevalence (1 in 25,000-50,000) but also because of the frequent requirement for medical attention and intervention. The morbidity and the need for health resources is exacerbated by a diagnostic delay of, on average, between 6 and 7 years before appropriate treatment is started.¹ In contrast to many other primary immunodeficiency diseases, patients with CVID may be diagnosed at almost any age, with the majority being recognized between 20 and 40 years of age.¹ This has implications for the methodology and timing of screening approaches aimed at reducing diagnostic delay.

The protean manifestations of CVID are reflected in the number of specialties to which these patients may present, and this alongside the wide variation of the noninfectious complications may result in a delay in recognition of the underlying diagnosis. The diagnosis of CVID in the very young is more problematic because it must be differentiated from transient hypogammaglobulinemia of infancy, and this is only possible with the passage of time and in practice when children are older than 4 years of age.² Advances in genetic tools have allowed the identification of the individual genes for the majority of the well-defined immunodeficiencies over the past 2 decades. There have been remarkable advances in our understanding of the molecular basis of severe combined immunodeficiencies³ and mendelian susceptibility to mycobacterial disease.⁴ In antibody deficiency, mutations in genes that comprise 90% of early B-cell defects have been identified, and, similarly, in the hyper-IgM syndromes, known genes now account for approximately 70% to 80% of patients.

Following on from the discovery of the association of particular MHC haplotypes with CVID in the 1990s,⁵ progress has been painfully slow; however, there now is a small list of monogenic disorders with a CVID-like phenotype, which

include ICOS (inducible costimulator),⁶ CD19,⁷ BAFFR (B-cell activating factor receptor),⁸ CD20,⁹ CD21,¹⁰ CD81,¹¹ and LRBA (lipopolysaccharide responsive beige-like anchor protein).¹² In addition, TACI (transmembrane activator and calcium-modulator and cyclophilin ligand interactor),^{13,14} is believed to be a disease-associated rather than disease-causing gene. Up to now, unravelling the bulk of the molecular causes of CVID has remained elusive, with the exception of TACI (which is found in 8%-10% of patients with CVID and 1% or more of healthy controls), the remaining genes account for fewer than 3% of patients with CVID.¹⁵ It is well recognized that, in primary immunodeficiency, there may be considerable clinical heterogeneity even in patients with the same defined mutation. But CVID is yet more complex because not only are the mutations not known, neither are the number of distinct disorders or the key environmental modifiers for this mixed group of single gene and polygenic disorders.

THE DIAGNOSIS OF CVID

Clinically, the majority of patients with CVID present with recurrent sinopulmonary bacterial infections¹⁶ and reduced serum levels of IgG, IgA, and/or IgM, with reduced or absent specific-antibody production after test vaccination.¹⁷ The diagnostic criteria for CVID illustrate some of the difficulties faced when there is considerable heterogeneity within a diagnostic category. The criteria¹⁸ are: a male or female patient with a marked decrease in IgG (at least 2 SDs below the mean for age) and at least one of the IgA or IgM isotypes; onset of immunodeficiency at more than 2 years of age; the absence of iso-hemagglutinins and/or poor responses to vaccines; and that other defined causes of hypogammaglobulinemia have been excluded.

The diagnosis, therefore, is one of exclusion, there is no clear cutoff for immunoglobulin levels, and "poor" responses to vaccines do not specify what constitutes an adequate response, nor do the diagnostic criteria differentiate between responses to conjugated, T-dependent vaccines, such as those for tetanus, hemophilus, and pneumococcus (Mentorix [GlaxoSmithKline, Uxbridge, UK], Prevenar 13 [Pfizer, Sandwich, UK]), and unconjugated polysaccharide T-independent vaccines (Pneumovax II [Sanofi Pasteur MSD Limited, Maidenhead, UK]) or their durability.

The *condicio sine qua non* to make the diagnosis is a low IgG, and although levels at approximately 4 SDs below the mean at less than 4 g/L in adults are more convincing than levels just below the lower limit of normal of 6 g/L, it remains important to assess responses to vaccination before commencing immunoglobulin replacement therapy. This introduces a delay of 3-4 weeks to await the post-vaccination responses, but patients may be treated with prophylactic antibiotics during this period both to offer some protection but also to reduce any chronic lung or sinus infection ahead of immunoglobulin if it is initiated.

Diagnostic delay

Early diagnosis and optimal management are likely to result in improved clinical and quality-of-life outcomes for patients with CVID. Reducing diagnostic delay, therefore, is crucial, and approaches include improved education and awareness, particularly regarding the adult onset and variable noninfectious presentations, of clinicians in both primary and secondary care. Unfortunately, the very successful newborn screening for severe combined immunodeficiency that looks for TREC (T-cell receptor excision circles) in DNA extracted from Guthrie spots,¹⁹

when extended to B-cell KREC (κ -deleting recombination excision circles)²⁰ will not detect CVID due to the adult onset and presence of B cells in the majority of patients. Guthrie spots are also unsuitable for the detection of IgA deficiency as a marker in neonates because the IgA is of both fetal and maternal origin.²¹ A number of UK centers have started to use calculated globulin (total protein – albumin), which is a component of liver function testing (LFT) as a screen for antibody deficiency. LFTs are performed in very high numbers (just under 2 million/yr for a population of 3.6 million in Wales) and are inexpensive because the inclusion of total protein (if not already included) within the LFT test set costs 7 pence or 11 US cents. By using appropriately established method-dependent cutoff values, it has been possible to detect antibody deficiencies, and patients with CVID found by using this approach have commenced immunoglobulin replacement. By using the bromocresol green methodology for the measurement of albumin,²² we found a cutoff value of <18 g/L for calculated globulin defines a population in which 89% have an IgG level of <6 g/L (unpublished data, 2013). Immunology laboratories also have opportunistically detected cases of antibody deficiency by cascade testing for immunoglobulins when there is a very low background in ELISAs used for IgA-based celiac disease testing, such as the tissue transglutaminase assay²³ and also when there is a very low IgE <2 IU/mL.²⁴ Clinical approaches to screening also have involved the use of the “10 warning signs” of primary immunodeficiency and the use of computer sorting of diagnostic codes.²⁵ A study into the clinical features that identify children with immunodeficiency found that, of the 10 warning signs, the strongest predictors were family history, intravenous antibiotics for sepsis (neutrophil defects), and failure to thrive (T-cell defects), whereas, for B-cell defects, the only predictor was family history of immune deficiency.²⁶

Baseline investigations and monitoring

The varied presentations of CVID are reflected in the diverse routes of referral to immunology from clinicians in respiratory medicine, gastroenterology, hematology, Ear Nose and Throat (ENT), medicine, general practice, rheumatology, and others. Diagnostic testing may have already been taken place, but it is important that, once the patient is referred, initial blood tests are performed centrally in an accredited laboratory, because ongoing monitoring will be referenced to this baseline. Once the diagnosis of CVID is made, there are a number of tests important for the initial workup before commencing immunoglobulin replacement therapy. Baseline testing includes a complete blood cell count; hematinics; a peripheral lymphoma panel; biochemistry renal; LFTs; bone profile; C-reactive protein; immunoglobulins; serum and urine electrophoresis; specific antibodies to tetanus, hemophilus, and pneumococcus; lymphocyte phenotypes with EUROclass B-cell panel and naive T cells; and MBL (mannan binding lectin) (this is not intended to be an exhaustive list of tests and reflects the author's practice). Lung function measurement is performed by using spirometry every 6 months, and extended testing, including gas exchange annually, with chest high-resolution computed topography (HRCT) at entry into the cohort and thereafter as clinically indicated. In stable patients, repeated HRCT is not routine at intervals of less than 5 years. Patients are reviewed on a 6-monthly basis in the clinic if well, by both the immunology specialist nurses and the medical team, and monitoring takes place both at these appointments as well as through

send-in monitoring for trough IgG levels, LFTs, and C reactive protein (CRP) every 3 to 4 months. The immunology specialist nurses initially perform annual home visits for those patients infusing immunoglobulin at home followed by two yearly visits if stable, and emergency appointment slots are available if needed. Further investigations of the lungs, gut, autoimmunity, lymphoproliferation, or other systems are driven by the presentation, existing disease, and ongoing evaluation. It is expected that details of practice will vary among centers and countries.

CLINICAL PHENOTYPES AND BIOMARKERS

Mortality in CVID was reported in the 1990s at 23% (56/248) during a follow-up of 1-20 years (mean, 7.5 years),²⁷ alongside reduced survival versus with age-matched controls for the same period, of 64% versus 92% for male patients and 67% versus 94% for female patients. About the same time, figures from the United Kingdom were similar with a 30% mortality in a cohort of 240 patients followed up for 25 years.²⁸ Over time, there has been a clear improvement in survival of patients with CVID shown in European figures from the European Society for Immunodeficiencies registry, in which 15% of patients (51/334) died over a longer mean follow-up period of 22.5 years.¹ That having been said, the overall survival of both male and female patients with CVID remains considerably lower than that of age-matched controls.²⁹

The major reason to subdivide CVID into clinical phenotypes is to better predict disease course and complications, thus improving management in the absence of defined genetic diagnoses for this group of disorders. In addition clear and stable clinical phenotypes allow comparison of more homogenous groups of patients within studies. Clinical phenotypes have been described after analysis of large CVID cohorts³⁰ and further refined into 4 phenotypes³¹:

1. No other disease-related complications (infections only)
2. Cytopenias (thrombocytopenia, autoimmune hemolytic anemia, and/or neutropenia)
3. Polyclonal lymphoproliferation (granuloma, lymphocytic interstitial pneumonia, persistent unexplained lymphadenopathy)
4. Unexplained enteropathy

It is clear that the phenotypes define significant differences in biology as the presence of one or more noninfectious complications is associated with an almost 11-fold increase in mortality during follow-up.^{29,30} Patients with no other disease-related complications had a long-term survival of 95% versus 42% in those with noninfectious complications.²⁹ The phenotypes appeared distinct in patients from 2 European and 1 American cohort, with 89% to 94% fitting into a single phenotype.³¹ The proportions of the phenotypes (Figure 1) and the effects on survival were most marked for enteropathy, followed by lymphoproliferation and cytopenias.³¹ An analysis of geographically distinct cohorts shows wide variation with, for example, Swedish patients having much lower prevalence of lymphoproliferative complications, 12%, than those in the Czech Republic, at 54%.³⁰ These differences are likely to reflect the effects of distinct genetic backgrounds on the expression of the phenotypes, although differences in the care of these different groups, for example, intensity of prophylactic antibiotic use, must also be considered.

When autoimmune manifestations were separated into cytopenias and organ-specific autoimmunity, it was found that only

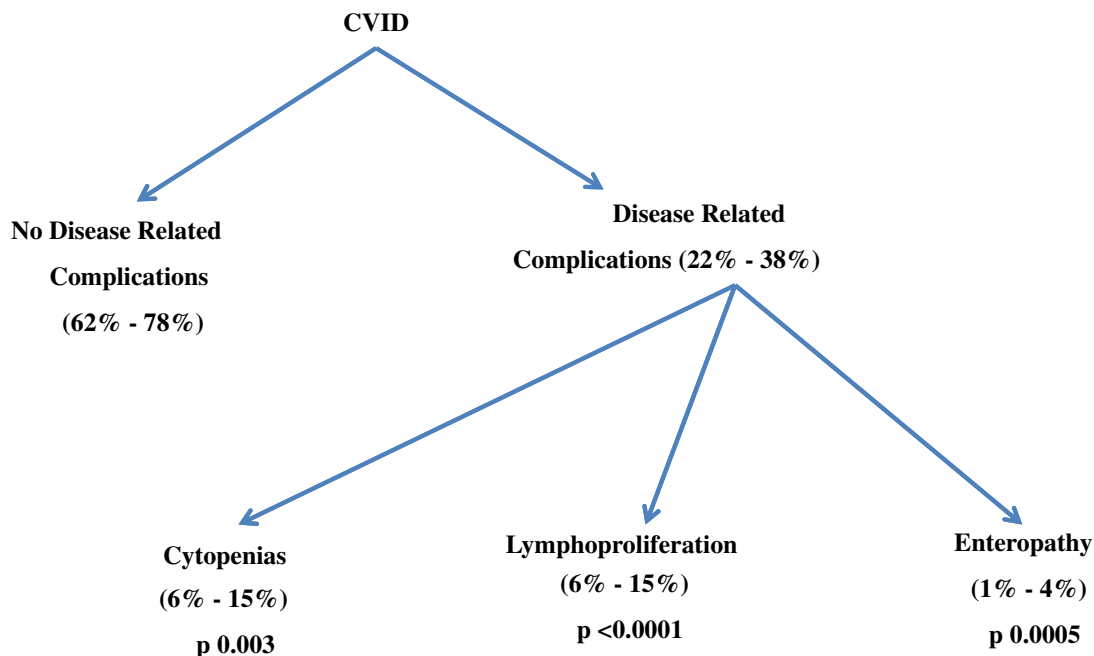


FIGURE 1. Clinical phenotypes in CVID. The clinical phenotypes in CVID are shown with the ranges of percentages of patients with each phenotype in an analysis of a total of 848 patients from 3 large cohorts.³¹ These represent the improved, better-defined categories and will exclude some patients who are counted as having complications in other studies. The *P* values that relate to the risk of reduced survival for each phenotype are also shown. A small number of patients had more than one phenotype and are not shown.

cytopenias were associated with reduced survival,³¹ and, in another large study, no decrease in survival was noted with autoimmunity.²⁹ The lymphoproliferative expansion of cells into the tissues manifests as noncaseating granulomas in 8% to 22% of patients, predominantly in the lungs, lymph nodes, liver, and spleen but also in other sites, including the brain.^{29,32} The finding of granulomas often predates the diagnosis of CVID and may then be mistakenly diagnosed as sarcoidosis.³³ Splenomegaly can be massive in CVID, sometimes necessitating splenectomy for cytopenias or pain, and a recent retrospective study of 45 cases of splenectomy in CVID offers reassurance that this was an effective treatment in 75% of patients and did not result in increased mortality.³⁴ It is likely that rituximab therapy for cytopenias may reduce the need for splenectomy. Therapy of the lymphoproliferative and inflammatory complications, particularly as they affect the lungs, gut, and liver, is a challenging balancing act because immunosuppressive treatments are needed to minimize inflammatory damage in the setting of immunodeficiency. It also should be noted that lymphoproliferation, at least in part, can be a response to infection and that optimization of therapy with pulmonary hygiene, prophylactic antibiotics, early and quick attention to common infection, and appropriate adjustment of immunoglobulin replacement may be of some benefit.

Laboratory testing such as the EUROClass B-cell flow cytometric classification system³⁵ has developed the key pathogenic observation of a severe reduction in class-switched memory B cells (SmB⁺ defined as <2% IgD⁺IgM⁺CD27⁺ of CD19⁺ B cells) in the majority of patients with CVID as a clinically correlated biomarker. The reduction in class-switched memory B cells suggests impaired germinal center function, which is

a requirement for T-dependent antibody formation.³⁶ However, reduced class-switched memory is not specific for CVID and is also found in a range of primary immunodeficiencies, including X-linked hyper-IgM syndrome,³⁷ Wiskott Aldrich syndrome,³⁸ X-linked lymphoproliferative disease,³⁹ idiopathic CD4 lymphopenia,⁴⁰ and chronic granulomatous disease.⁴¹ In CVID, the SmB⁺ phenotype was associated with a higher risk of splenomegaly and granulomatous disease. An expansion of transitional B cells (Tr^{hi} >9% CD38^{hi}IgM^{hi}) in SmB⁺ patients is linked to lymphadenopathy and expansions of CD21^{low} B cells higher than 10% of B cells is linked to splenomegaly. One of the characteristic features of CVID is the impaired terminal differentiation of B-cell memory and very low numbers of plasma cells in the bone marrow, lymph nodes, and gut.^{15,42-45} In patients with BAFRR deficiency, there is an increase in transitional B cells (>20%), which may offer a clue toward this diagnosis.⁸ Investigation of the T-cell compartment demonstrates reduced naive CD4 T cells and significant associations between this parameter and class-switched memory B cells.⁴⁶ In an analysis of the French DEFI cohort, a subset of patients with late onset combined immunodeficiency who were defined as having an opportunistic infection and a CD4 T-cell count of <200 × 10⁶ cells/L had a higher frequency of splenomegaly, granulomas, enteropathy, and lymphoma.⁴⁷ A summary of selected biomarkers used in CVID is shown in Table I.

The heterogeneity of CVID defined by clinical phenotypes and biomarkers has been further supported by a large genome-wide association study, which identified a strong association with the MHC as well as associations with ADAM (disintegrin and metalloproteinase) genes. Copy number variation analysis defined a range of novel disease-associated deletions and

TABLE I. Summary of biomarkers in CVID

	Comment	Reference nos.
Clinical biomarkers		
Earlier age at diagnosis or symptom onset	Reduced survival	29, 30
Lymphoma (not other cancers)	Reduced survival	29
Liver disease and/or hepatitis	Reduced survival	29
Chronic lung disease (structural and functional)	Reduced survival	29
Cytopenias	Reduced survival (although autoimmunity did not associate with reduced survival in all studies)	29, 31
Lymphoproliferation	Reduced survival	29, 31
Enteropathy and/or gastrointestinal disease and/or malabsorption	Reduced survival	29, 30
Organ-specific autoimmunity	Not associated with reduced survival	29, 31
Splenectomy	Not associated with increased infection or reduced survival	29, 34
Bronchiectasis alone	Not associated with reduced survival	29
Serum biomarkers		
IgG	Complex interpretation, low initial IgG correlates with lower SmB ⁺ , reduced survival, and chronic lung disease but increasing initial IgG is associated with cytopenia and reduced IgG replacement efficiency	29, 31, 57, 71, 100, 101
IgA	Increased IgA correlates with a greater likelihood of no disease related complications and lower risk of lymphoproliferation	29-31, 57, 71
IgM	Increased IgM associates with hepatomegaly, reduced survival, and lymphoma	29-31
β-2 microglobulin (>3 mg/mL) (sIL-2R is a similar marker)	Elevated levels correlate with splenomegaly, LIP, granuloma, and nodular regenerative hyperplasia	30, 31
Albumin	High levels of albumin correlate with improved efficiency of IgG replacement	100
MBL and IgA	The combination of a low serum IgA level and serum MBL was associated with the presence of bronchiectasis and lower lung function and with worsening of HRCT abnormalities	57, 107
Elevated BAFFR and APRIL	Possible association with autoimmunity and lymphoid hyperplasia	108
B-cell biomarkers		
Low SmB ⁺ <2% IgD ⁺ IgM ⁺ CD27 ⁺ of CD19 ⁺ B cells	Associated with a higher risk of splenomegaly and granulomatous disease, although not specific for CVID	35
Expansion of transitional B cells (Tr ^{hi} >9% CD38 ^{hi} IgM ^{hi})	Linked to lymphadenopathy in the SmB ⁺ group	35
CD21 ^{low} B cells (>10% of B cells)	Linked to splenomegaly and granulomatous disease	35
Reduced or absent B cell numbers	Reduced survival and increased risk of chronic lung disease and non-lymphomatous cancers	29, 31
T-cell biomarkers		
Reduced naive CD4 T cells	Correlation with SmB ⁺ , cytopenias, and lymphoproliferation	46, 109
CD4 T cells <200 × 10 ⁶ cells/L	Linked to a higher frequency of splenomegaly, granulomas, enteropathy, and lymphoma and SmB ⁺ , and increased CD4 numbers correlate with decreased risk of hepatomegaly	31, 47
Reduced regulatory T cells	Associated with autoimmunity, splenomegaly, and granulomas	110-113
Molecular biomarkers		
TACI mutations	Associated with autoimmunity and lymphoid hyperplasia	1
Telomeres	Telomere-dependent replicative senescence contributes to the immune dysfunction in patients with expanded numbers of CD21 ^{low} B cells, which is associated with lymphoproliferation and autoimmunity	114
FcRn VNTR polymorphism	Higher IgG efficiency in patients homozygous for the VNTR 3/3 polymorphism of the neonatal Fc receptor	100
FcRn expression (mRNA level)	Lower levels correlated with generalized bronchiectasis and fibrosis	101
MBL polymorphisms with low MBL level	Association with early disease onset and autoimmunity	115
TNFα+488A allele	Association with granulomatous disease	116
1858T allele of PTPN22	Associated with autoimmunity in PAD	117

PAD, Primary antibody deficiency.

Note. Selected reported biomarkers are categorized into clinical, serum, B-cell, T-cell, and molecular groups, and their association or consequence are described. These represent information from a number of studies and show that some markers, for example, IgA, are associated with both greater likelihood of complications at low levels or protection from complications at higher levels. Immunoglobulin levels must be interpreted in the light of age-related reference ranges.

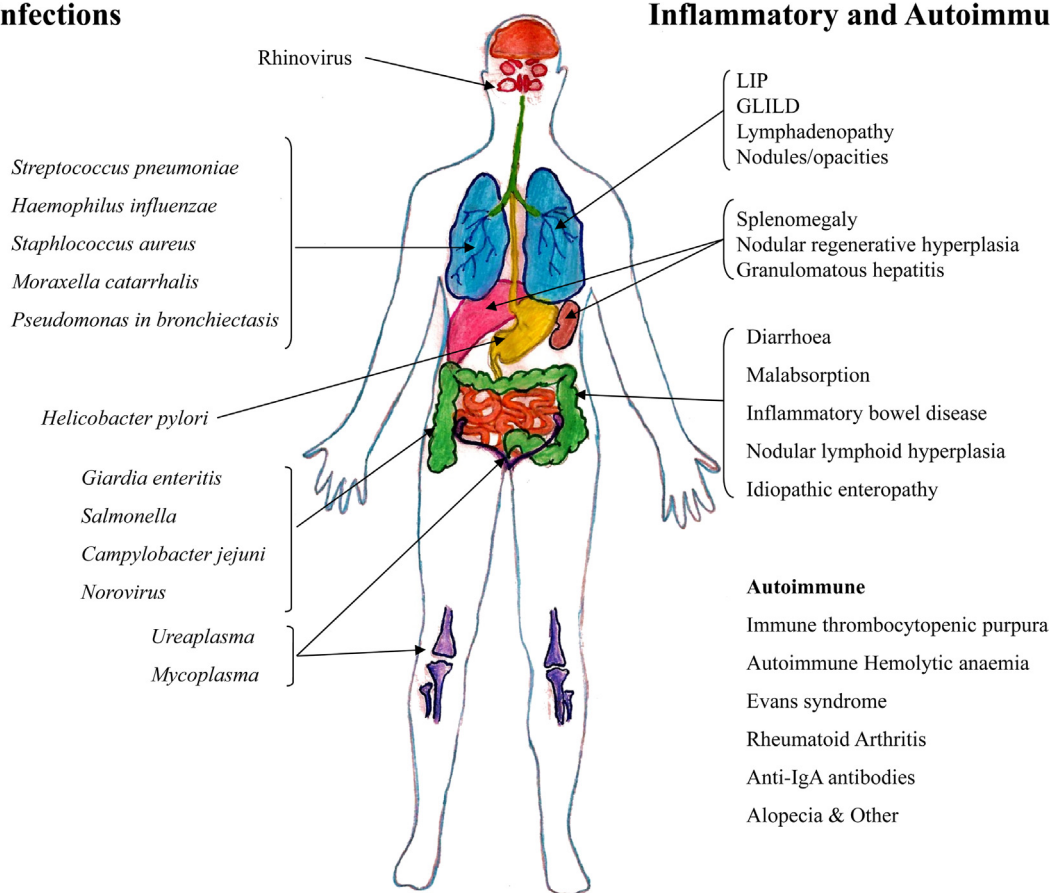
Infections**Inflammatory and Autoimmune**

FIGURE 2. Infections and autoimmune and/or inflammatory complications in CVID. The predominant organisms and sites of infection are shown on the left, with the inflammatory and autoimmune complications on the right. Other autoimmune complications include neutropenia, vitiligo, Sjögren syndrome/Sicca syndrome, autoimmune thyroiditis, diabetes mellitus, multiple sclerosis, pernicious anemia, systemic lupus erythematosus, antiphospholipid syndrome, uveitis, juvenile rheumatoid arthritis, lichen planus, vasculitis, and psoriasis.¹⁰⁶ (Drawn by Pippa Jolles.) LIP, Lymphocytic interstitial pneumonia; GLILD, granulomatous lymphocytic interstitial lung disease.

duplications, including duplication of ORC4L (origin of recognition complex 4L) in 15 cases, and the 1000 most significant single nucleotide polymorphisms (SNPs) were strongly predictive of CVID phenotype.⁴⁸ Interestingly, several patients with 22q11.2 syndrome, which is known to be associated with antibody deficiency,⁴⁹ were discovered within the CVID group.

LUNG DISEASE IN CVID

In evaluating the lungs of patients with CVID, the challenge lies in determining the degree of impairment due to infection versus that due to inflammation seemingly unrelated to infection. Recurrent bacterial infections occur in 90% of patients with CVID and with the lungs and sinuses being most frequently affected in 73%;¹ the types of pathogen and inflammatory manifestations encountered are shown in Figure 2. Prevention and treatment of infections is a major component of the care of patients with CVID and, in particular, the optimal management of chest and sinus infections is critical. Although there is no doubt that careful adjustment of immunoglobulin based on clinical response and better antibiotics, including more aggressive use of prophylactic antibiotics, has made a major difference for serious infections, such as pneumonia, other acute, chronic, and

underdiagnosed infections^{50,51} that result in inflammation, continue to cause morbidity and mortality. The continued high level of respiratory tract infections in contrast to the reduction in pneumonias over time in data from 2 cohorts is shown in Figure 3. Although there is no doubt that radiologically documented pneumonia is an important and concrete measure in clinical trials and cohort studies, it may represent “too high a bar” and lack sensitivity as a realistic overall respiratory outcome measure for several reasons. Pneumonia has become much less frequent as immunoglobulin trough levels have increased, patients are often provided with a rescue home treatment plan and antibiotics for early use in the event of a respiratory tract infection, and most of these infections will not be documented either microbiologically (even if this is encouraged) or radiologically. With increased centralization of specialist services, patients are less likely to be seen at the center for episodes of infection given the greater travel distances. Documentation, therefore, is retrospective and relies on a careful history of the infection frequency, site, severity, information on sputum production change in volume and color, and the use and duration of antibiotics.

The use of imaging such as HRCT, however, plays an important role, and reporting should aim to define the earliest

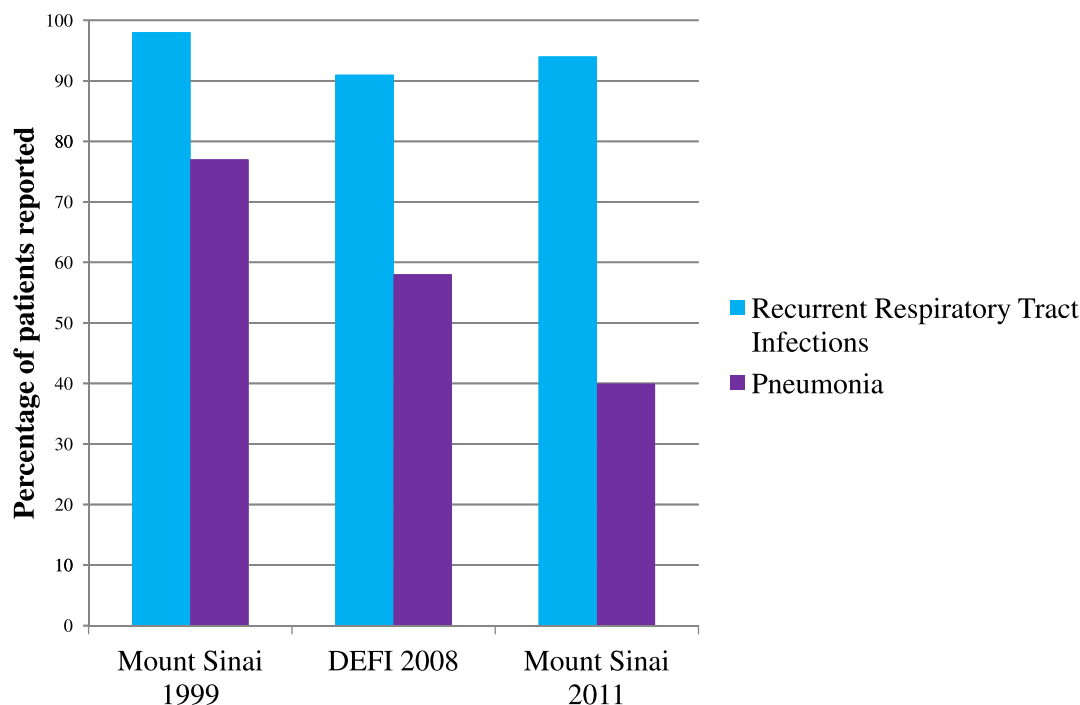


FIGURE 3. A decline in pneumonia in CVID. A combined analysis of data on the percentage of patients who experience pneumonia and recurrent respiratory tract infections is shown in 3 large series of patients in CVID in 1999, 2008, and 2011 (2 from the same cohort in the United States 12 years apart, 248 and 252 patients, and one from a French cohort of 473 patients). While accepting the potential difficulties in the interpretation of combined data from several sources, there is a decline in the percentage of patient's with pneumonia over time, perhaps representing a change in immunoglobulin dosing or greater use of prophylactic antibiotics. In contrast, the percentage of patients with recurrent respiratory tract infections has remained high, at more than 90% in all of the studies. This term will include infections of the sinuses, throat, and upper and lower respiratory tract, which do not fulfill criteria for pneumonia.

stages of airway injury, such as air-trapping, bronchial-wall thickening, mucous plugging, and atelectasis, so that intervention can be optimized to reduce damage, which leads ultimately to progressive and irreversible lung disease. Once bronchiectasis, which occurs predominantly in the lower and middle lobes in CVID, is established, management is of chronic pulmonary sepsis and for limitation of further scarring.⁵²⁻⁵⁵ Results of several studies have shown a decline in lung function over time, which has been associated with lower immunoglobulin dose,⁵⁶ IgG trough <5 g/L, low IgA, and low MBL levels.⁵⁷ Reduced class-switched memory B-cell numbers are also associated with a higher frequency of patients with bronchiectasis, reduced spirometry, and chronic noninfectious diarrhea.⁵⁸

Interstitial lung disease in antibody deficiency is challenging to manage and presents with a wide radiologic and pathologic spectrum of findings.⁵⁹ On radiologic examination, the most common findings are nodular densities, linear and/or irregular opacities, consolidation, ground glass, honeycombing, and emphysema.⁶⁰ Histologically, granulomatous lung disease, lymphocytic interstitial pneumonia, nonspecific interstitial pneumonia, and organizing pneumonia⁶¹ are all described, and patterns can overlap.⁵⁵

In CVID granulomatous and lymphoproliferative (lymphocytic interstitial pneumonia, follicular bronchiolitis, and lymphoid hyperplasia) patterns may coexist and have been grouped together under the term granulomatous lymphocytic interstitial lung disease (GLILD).^{62,63} The improved recognition and better definition of the different forms of interstitial lung

disease in CVID will be important because therapeutic strategies combining rituximab and azathioprine used in a small somewhat heterogeneous number of patients with granulomatous lymphocytic interstitial lung disease has shown promising early results.⁶⁴ This being said, further studies are needed to define the radiologic, histologic, and cellular findings that best identify those most likely to respond to treatment approaches that target B cells.

The cause of respiratory symptoms and deteriorating lung function in CVID may thus be due to interstitial lung disease rather than to recurrent infections and associated bronchiectasis, which emphasizes the importance of HRCT in the assessment of these patients. There has been a reluctance to overexpose patients to x-rays based on reports of radiosensitivity in CVID⁶⁵⁻⁶⁷; however, improved safety and similar sensitivity may be possible by using magnetic resonance imaging when more frequent imaging is needed.⁶⁸ In addition, there are important ongoing initiatives in the standardization of HRCT assessment for antibody deficiency (<http://www.chest-ct-group.eu>) and prospective analysis of HRCT of the chest for patients with CVID across time in ongoing studies.

GUT DISEASE IN CVID

The manifestations of gut disease in CVID fall into 3 main groups: those due to infection, those due to inflammation or autoimmunity, and malignancies that affect the gut. It may be very difficult to separate fully the effects of infection and

inflammation that can result in malabsorption⁶⁹ as well as the loss of replaced immunoglobulin. Interactions between the gut microbiome and the mucosal immune system⁷⁰ are likely to be significantly influenced by the variable degree of impairment observed in both cellular and humoral immunity in CVID (including mucosal IgA).⁷¹ It has been long recognized that defects in antibody production can result in prolonged polio virus shedding⁷²⁻⁷⁴ from the gut, but the effects of CVID, and, indeed, the use of frequent or prophylactic antibiotics on the interface with the microbiome have not been fully elucidated, and further studies in this area are required.

The main gastrointestinal symptom encountered in CVID is a transient or persistent diarrhea, which occurs in between 21% and 57% of patients,⁷⁵⁻⁷⁷ and it is important to rule out infections, which include *Giardia lamblia*, *Salmonella* species, *Campylobacter jejuni*, and cytomegalovirus.⁷⁸ Testing for *Clostridium difficile* toxin should be undertaken, particularly if frequent or prophylactic antibiotics have been used. Inflammatory complications of CVID in the gut affect 19% to 32% of patients,^{78,79} with macroscopic features, including lymphoid follicles and nodular lymphoid hyperplasia often seen at endoscopy. Microscopic findings on small intestinal biopsy frequently show villous flattening and atrophy, which may be suggestive of celiac disease; however, features that differentiate CVID from celiac disease are a profound depletion of plasma cells and follicular lymphoid hyperplasia.⁸⁰ Exclusion of gluten tends to result in temporary and partial rather than long-lasting benefit. In addition, granulomas, crypt distortion, lymphoid aggregates, and inflammatory infiltrates are observed. The lymphoid aggregates contain B cells, with a striking reduction in plasma cells.^{75,76} The frequency of mutations in *NOD2*, a gene linked to Crohn's disease, early onset sarcoidosis, and Blau syndrome, when studied in patients with CVID and with granulomas, did not show an increase over controls.⁸¹

If pathogens are indentified,⁸² then appropriate antibiotics are required. For inflammatory changes, therapies similar to those used in Crohn's disease and ulcerative colitis in patients who are immunocompetent may be helpful. These include corticosteroids such as prednisolone or those with a high first-pass hepatic metabolism (budesonide, fluticasone), aminosaliclates, immunosuppressive agents, and biologic therapies, such as anti-TNF- α .⁸³ Treatment remains challenging, with often partial rather than complete responses,⁸⁴ and, given the presence of B cells in the lymphoid follicles and granulomas, it is interesting to consider whether there may be a role for agents such as rituximab in therapy of some aspects of CVID gut inflammation.

Liver disease and abnormal liver function tests occur in 10% of patients, and histology most frequently shows nodular regenerative hyperplasia or granulomatous hepatitis.^{16,85,86} Autoimmune complications that affect the gut in CVID include pernicious anemia, primary biliary cirrhosis, hepatitis, and cirrhosis of unknown origin, which makes checking for the development of portal hypertension and varices in this setting vital.²⁹

It is always essential to examine the oral cavity. A painful glossitis is shown in Figure 4, which was negative for microbiology but further testing showed vitamin B₁₂ deficiency, and the glossitis resolved on B₁₂ replacement. This highlights the need to be aware of and actively screen for the potential development of vitamin deficiencies in CVID due either to autoimmune (pernicious anemia) or inflammatory complications that affect the gut. Patients have been described with neurologic complications due to

vitamin E deficiency⁶⁹ as well as deficiency of vitamin A, which has been shown to influence B cells acting through Toll-like receptors.^{87,88}

The presence of chronic *Norovirus* infection associated with enteropathy and villous atrophy in patients with CVID⁸⁹ is increasingly recognized. The clinical impact appears to vary but can be severe, and patients may present with vomiting, nausea, profuse diarrhea, profound weight loss requiring total parenteral nutrition (TPN), and electrolyte disturbances extreme enough to cause hypocalcemic tetany (unpublished data, 2013). Treatment to achieve viral clearance is challenging, and the implications for other patients with CVID as well as the wider community are not yet clear.

MALIGNANCY

There is an increase in malignancy in CVID in general, with the most frequently reported being lymphoid malignancy at 8.2% in a recent large series.²⁹ Lymphomas were B cell in origin, with non-Hodgkin lymphoma accounting for almost 60% and diffuse large B cell, Hodgkin, and mucosa-associated lymphoid tissue lymphoma making up the majority of the remainder. There appears to have been a reduction in the frequency of gastric carcinoma over time,¹ potentially due to an effect on *Helicobacter pylori*⁹⁰ through increased use of antibiotics. Despite this, and independent of the risk of pernicious anemia, patients with CVID have a 10-fold increased risk of gastric cancer.⁹¹ Breast cancer is now the most common non-lymphoid malignancy in CVID, and there is a lower incidence of oral, esophageal, and colonic cancers.²⁹

IMMUNOGLOBULIN THERAPY

Immunoglobulin replacement remains the mainstay of treatment for CVID, and there has been an increase in both the dose of immunoglobulin (g/kg/mo) used to treat, and the target trough level (IgG) used to monitor replacement adequacy. This gradual dose increase from studies of the late 1980s⁹² is supported by some more recent analyses of dose and clinical outcome for intravenous and subcutaneous immunoglobulin.^{93,94} It is worth being aware of the implications in terms of immunomodulation that dose increases may have, in addition to improved levels of pathogen protection. There is now a greater range of immunoglobulin treatment options for patients, which comprise intravenous immunoglobulin, subcutaneous immunoglobulin weekly or biweekly, facilitated subcutaneous immunoglobulin, and rapid push,^{93,95-97} made possible by improvements in immunoglobulin manufacturing, which have resulted in more concentrated products, faster infusion rates for IVIg, and, for facilitated subcutaneous immunoglobulin, the development of rhuPH20 (recombinant human hyaluronidase).^{97,98}

The pharmacokinetics based on a 2-compartment model of distribution into the vascular and extravascular space for the different routes and regimens is very different. The importance of the saturable FcRn (neonatal Fc receptor) in binding and salvaging IgG from degradation⁹⁹ is underlined by the findings of reduced immunoglobulin replacement efficiency with higher baseline IgG levels and higher efficiency in patients homozygous for the VNTR (variable number tandem repeat) 3/3 FcRn polymorphism.¹⁰⁰ It also has been shown that there are lower levels of FcRn mRNA in patients with bronchiectasis than those without bronchiectasis,¹⁰¹ which suggests a potential mechanism



FIGURE 4. Glossitis due to vitamin B₁₂ deficiency and vitiligo in CVID. This patient with CVID presented with a painful glossitis and no bacterial or fungal pathogens were identified; however, he was found to have a vitamin B₁₂ deficiency, and the glossitis resolved on replacement. The cutaneous depigmentation of vitiligo around the eyes is less obvious but emphasizes the need to look for other autoimmune disorders if one is diagnosed.

for the higher doses needed in this patient group.¹⁰² The role of IgA (the most abundant class of immunoglobulin in the body) in immune exclusion by blocking adherence and penetration of pathogens and maintenance of homeostasis at mucosal sites¹⁰³ is reinforced by its observed protective effects from the development of complications of CVID.²⁹⁻³¹

As practice has evolved, a minimum trough IgG of 7 g/L is often the aim, if there is no structural lung disease or if other complications and infections are controlled. If there is evidence of lung disease or if infections are not sufficiently controlled, a minimum trough of 9 g/L is targeted with a low threshold for prophylactic antibiotics, in particular, macrolides. The mean trough level in the cohort in Cardiff is between 9-10 g/L, the majority of patients receive subcutaneous immunoglobulin, and, in those on intravenous immunoglobulin, almost none have a cycle duration longer than 3 weeks. Individualized dosing based on the clinical response and infection frequency will remain critical, as shown by Bonagura et al¹⁰⁴ who described different biologic immunoglobulin trough levels (rather than a common trough level) required to keep each patient infection free.

SUMMARY AND FUTURE DIRECTIONS

Recent longitudinal cohort studies have helped better define biologically relevant clinical phenotypes in CVID.^{29,30} The presence of any of these noninfective complications is associated with decreased survival, with the strongest association for

enteropathy followed by lymphoproliferation and then cytopenias. Laboratory biomarkers also stratify risk for complications and reduced survival (low B-cell numbers, reduced class-switched memory B cells, and higher IgM), whereas fewer complications and longer survival are predicted by others (higher IgA and IgG, normal numbers of B cells and class-switched memory B cells). Lung disease and cancer, followed by liver disease, continue to be the leading causes of death and morbidity in CVID.²⁹ Delay in diagnosis and pre-existing structural lung disease with impaired lung structure or function are risk factors for further progression of lung disease, and, this may occur, despite adequate levels of immunoglobulin replacement and the reduction in the occurrence of pneumonia. Progress toward a molecular understanding of CVID has been slow, and, although a small number of single gene disorders have been discovered, these do not explain the majority of CVID cases.

There have been significant advances therapeutically in immunoglobulin replacement,⁹⁵⁻⁹⁸ improved antibiotics, and promising studies using rituximab and azathioprine for granulomatous lymphocytic interstitial lung disease.⁶⁴ Exposure to radiation may also be reduced in the future, with increasing evidence for the utility of magnetic resonance imaging in lung imaging,⁶⁸ and this may be particularly important for children as well as adults who require regular scans to identify subclinical changes and monitor existing lung damage to allow earlier and focused interventions.

In the future a combination of careful clinical and immunologic characterization with improved definition of infections feeding into large databases alongside next-generation sequencing with whole exome and/or genome approaches is likely to advance our understanding of this heterogeneous set of disorders. Analysis of recent evidence suggests a role for heterozygous missense mutations in protein kinase C- β as a critical determinant of antipolysaccharide antibody formation in mice,¹⁰⁵ and future studies will need to focus on the role of protein kinase C- β mutations in human antibody production. Studies into mucosal interactions with the gut microbiome,⁷⁰ subclinical infections,⁵¹ the role of bone marrow transplantation, improved biomarkers, better treatment regimens for inflammatory complications, and a refined definition for CVID will all aid management.

At the present time, however, CVID remains variable and complex and, despite the availability of improved genetic tools to unravel this condition, we must not imagine that molecular diagnoses will be an end to the story but rather the beginning of another. This will enable a better understanding of the biology of each of the newly defined disorders and how this knowledge can improve and individualize patient care.

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