

How I treat common variable immune deficiency

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Abstract:

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

Introduction:

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

Diagnosis of CVID: The diagnosis of common variable immune deficiency (CVID, International Classification of Diseases code, ICD 279.06) is often misused. It is defined as a genetic immune defect characterized by significantly decreased levels of IgG, IgA and/or IgM with poor or absent antibody production, with exclusion of genetic or other causes of hypogammaglobulinemia(1, 2, 9, 10). Based on the standard definition, antibody deficiency with normal immune globulin levels, or IgG deficiency alone, would not qualify for the diagnosis of CVID. As CVID is not always easily discerned from transient hypogammaglobulinemia of infancy, a general

consensus is that this diagnosis should not be applied until after the age of 4. This allows time for the immune system to mature, and if necessary, to consider the possibility of other genetic primary immune defects. However, the published criteria still leave open rather wide boundaries. First laboratory standards for normal ranges differ; in addition, using the 95% percentile for immune globulins, allow 2.5% of normal subjects to fall below the normal range. Sometimes forgotten, the additional necessary criteria for CVID also include a proven lack of specific IgG antibody production. This is usually demonstrated by lack of IgG responses (not attaining laboratory-defined protective levels) to two or more protein vaccines such as tetanus or diphtheria toxoids, Haemophilus conjugate, measles, mumps and rubella vaccines, and also by lack of response to pneumococcal polysaccharide vaccines. Other options for protein antigens include hepatitis A or B vaccines or varicella, either after vaccination or disease exposure. Examining blood for pertinent isohemagglutinins, is another a common means of testing (mostly) IgM anti-carbohydrate antibody production in older children and adults. While extensive antibody testing is not as important for subjects with very low serum IgG (potentially 150 mg/dl or less), those with higher levels of serum IgG (450-600mg/dl) and especially those with only minimally reduced serum IgA, require more extensive evaluation. It is more likely that these subjects have preservation of IgG antibody production and are therefore less likely to benefit from Ig therapy. A suggested template for such analyses is given on Table 1. Demonstration of persistence of IgG antibody at 6 months after vaccination can be important to prove sustained antibody production in some cases. The many reasons for a very thorough evaluation before diagnosing CVID, include the facts that the diagnosis of CVID impacts short and long term insurance coverage, influences the outcome of all subsequent medical encounters, and may alter school and job choices and other life decisions, i.e. family planning and travel. In addition, if replacement Ig therapy is initiated without a complete evaluation and the use of this therapy is later questioned, it must be stopped for about 5 months before such an evaluation can be performed.

Immune globulin replacement: The primary treatment of CVID is replacement of antibody, achieved by either intravenous (IV) or subcutaneous (SQ) route of immune globulin (Ig), usually in doses of 400 to 600 mg/kg body weight a month (11). This dose is usually divided into once or twice a week, or every 2 weeks (for SQ) or every 3 or 4 weeks (IV.) The original calculation for the half-life of IgG of 21 days was based on iodinated IgG protein(12), but current IV Igs have a half lives closer to 30 days(13) (14-16) suggesting that original estimations might be inaccurate due to protein modification. However, the half-life in individual patients may vary considerably for not entirely clear reasons. Administered IgG in CVID subjects with chronic lung or gastrointestinal disease appears to have a shorter half-life. In addition, biologic variations in the abundance of the neonatal Fc receptor(17) might impact IgG turnover.

The goal of Ig therapy is to prevent infections, however, the target trough serum IgG to attain, varies depending on the baseline level of IgG. For a subject with a baseline serum IgG of less than 100 mg/dl, a suggested trough level would be at least 600 mg/dl, but for a subject with an initial IgG of 300 mg/dl with no functional antibody, the required trough level might be 900 mg/dl to supply the minimum “normal” level of functional Ig. Immune globulin is often given in the home. Both IV and SQ methods provide both safe and effective replacement(18) (19) (11); convenience to the patient can best guide these choices. In our practice, the majority of our patients are given 400 mg/dl IV once per month; 10 to 15% are using SQ treatment in pro-rated doses given more frequently. Attention is given to those with lung disease or previous autoimmunity to be sure that more than adequate “trough” levels are maintained. By definition, most patients with CVID have little or no serum IgA; while anti-IgA antibodies have been reported(20), these are quite rare, and from a pragmatic point of view, determining if IgG anti-IgA is present is not clinically important. I am opposed to the use of indwelling ports as these mark

patients as medically impaired, provide known risks of infection, and in any case, need replacing with time. Poor IV access can be addressed using the SQ route, dividing the required monthly dose into biweekly, or weekly doses. On stable doses of replacement Ig, patients on Ig therapy can be adequately followed, measuring trough serum IgG levels at 6 to 12-month intervals.

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

Chronic Lung Disease: While pneumonia is clearly much less common after adequate Ig replacement is initiated(22), continued respiratory tract disease even after treatment is instituted, can lead to obstructive, restrictive, bronchiectatic changes in some cases (8). Parenchymal and interstitial changes include nodules on high resolution CT (HRCT) scans, reticular changes, fibrosis and/or ground glass appearance. For larger or persistent nodules, biopsy may be require to determine if these are scars, lymphoid collections of possibly clonal cells or granulomatous infiltrates. Continued lung damage can lead to substantial morbidity, in the more severe cases, necessitating continuous oxygen treatment and/or heart or lung transplantation

(10). It is unclear whether such a downward spiral is due to previous lung damage that is difficult to reverse, continued low-grade infections that are not adequately addressed by replacement Ig, ongoing inflammatory changes due to immune dysregulation, or a combination of all of these factors. The microbiology of the lungs may also include organisms potentially not susceptible to antibody clearance, including the most prevalent organism, non-typeable *H. Influenzae*, and/or viruses(23). Higher doses of Ig (600 mg/kg/month) may help to prevent infections and possibly chronic lung disease(24, 25) but no controlled trials have been conducted to select which patients would benefit, and what doses of Ig would be needed. In my view, for continued lung disease, daily antibiotic prophylaxis (trimethoprim sulfa, or possibly better, macrolides, which provide substantial anti-inflammatory effects(26)) provide more benefit than much higher doses of Ig therapy. While rotating antibiotics to discourage resistant organisms are often used in immune competent individuals with chronic lung disease, I have not found it necessary to rotate antibiotics in CVID; resistant organism can be treated if they arise.

Granulomatous/ lymphoid infiltrative disease: Localized or systemic granulomatous disease, sometimes erroneously called “sarcoidosis,” occurs in between 8 to 22% of subjects with CVID (10, 27-32) The granulomatous changes may be diagnosed years prior to the recognition of hypogammaglobulinemia and may in these cases delay the recognition of the immune defect because the diagnosis of sarcoidosis is assumed to be established. Lungs, lymph nodes and spleen are the more commonly affected sites, although the skin, liver, bone marrow, kidney, gastrointestinal tract and brain may be involved (27, 33-35). The granuloma in CVID are variously well-formed, non caseating, and may contain contain non-necrotizing epithelioid and giant cells. While organisms are sought, these are very rarely found. In our series of 37 patients, 8.1% of our CVID subjects, the median age at diagnosis of CVID was 26 (2 - 59). 14 had granulomas 1 - 18 years before diagnosis of CVID; in 6 the detection of granulomas coincided with this

diagnosis; for 17, granulomas were documented later. 54% had lung granulomas, 43% in lymph nodes and 32% in liver (31). For unclear reasons, subjects with granulomatous disease are also much greater risk for autoimmune disease (almost always immune thrombocytopenia or autoimmune hemolytic anemia) than CVID subjects who do not have this pathology; for example, 54% of our patients with known granulomatous disease have had autoimmune disease. As described below, these subjects are also almost always those who have very few circulating, isotype switched memory B cells (36). In some of these patients, an intense lymphoid infiltration accompanies the granulomas in lungs, leading to what has been termed “granulomatous lymphocytic interstitial lung disease,” (29, 37) the presence of which is prognostic of a poor outcome (37). A recent study reported a median survival of 13.7 years in CVID patients with granulomatous/lymphoid interstitial infiltrates, as compared to 28.8 years in those without this complication (29). HHV8 has been proposed to play a role of in the development of granulomatous disease in CVID (38) but this is still to be confirmed. No case control studies have been performed to define the most effective treatment of granulomatous disease in CVID. Oral steroids in doses of 10mg a day or 20mg every other day may preserve lung or liver function, realizing that this presents a risk for infections and other undesirable side effects. For long term therapy, I prescribe 200-400 mg a day (or range 3.5 to 6.5 mg/kg) of hydroxychloroquine, based on its mechanistic roles in reducing toll like receptor responses, antigen presentation, and its use in autoimmunity and sarcoidosis (39, 40). For pulmonary granuloma, twice daily-inhaled beclomethasone is also prescribed. Higher doses of IVIG have been found in one instance to aid in controlling lymphoid interstitial disease and granuloma (41, 42) but this does not seem to be a universal experience. Some years ago, work showed that some CVID patients had elevated serum levels of TNF-alpha and soluble TNF receptors(43). Later, Mullighan reported granuloma in 20 of 90 patients with CVID (22%); 8 of these had an unusual TNF-alpha allele (TNF +488A)(28), but TNF- alpha production or levels were not actually examined. On this basis,

and suggestive earlier work in sarcoidosis, TNF-alpha inhibitors (infliximab or etanercept) have been used in subjects with CVID with granuloma, with benefit in some cases (35, 44, 45); however, no controlled trials have been performed. I have had limited experience using TNF inhibitors for granulomatous disease; in 2 cases (both with granuloma in lung) it was not helpful but both patients had substantial lung defects.)

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

Autoimmunity: Other complications resulting from immune dysregulation in CVID include autoimmune disease in up to 25%, mostly immune thrombocytopenia purpura (ITP), autoimmune hemolytic anemia (AIHA) or both (Evans syndrome) or more rarely, autoimmune neutropenia (47, 48). (**Table 3**) CVID subjects with ITP or Evans syndrome tend to be younger than those who developed AIHA (49). This group of subjects are also likely to have very few isotype switched memory B cells in peripheral blood (36). As we have found that more episodes of recurrent episodes of ITP and/or AIHA occur before replacement Ig treatment is started than afterward, Ig in these doses may exert a protective effect (49). Higher doses of Ig (1g/kg body weight) given weekly for a short time can be used to supplement baseline therapy if autoimmune disease persists. Intravenous steroids (1 gram methylprednisolone) followed by moderate doses of oral steroids tapered over several weeks or more, will also often resolve ITP or AIHA. More recently, we

have used rituximab in standard doses, for more refractory or recurrent ITP and/or AIHA with success in 11 patients with CVID (unpublished). Splenectomy is to be avoided in CVID as severe infections have occurred, as we and other have shown(5, 50), although this is not found in all series(48). Other autoimmune diseases also occur in CVID, including pernicious anemia, rheumatoid arthritis, Sjogren's syndrome, vasculitis, thyroiditis, alopecia, vitiligo, hepatitis, primary biliary cirrhosis, uveitis, sicca syndrome and systemic lupus erythematosus; the treatment for these is standard therapy.

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

Cervical, mediastinal and abdominal lymphoid hyperplasia and enlarged spleen are found in at least 20% of CVID subjects. Lymphoid infiltrates occur lung or other organs such as the liver or kidneys. Biopsies of lymph nodes usually show atypical lymphoid hyperplasia, reactive lymphoid hyperplasia, or granulomatous inflammation. In most cases no specific treatment is required unless pulmonary involvement or other organ involvement impairs functions. Splenomegaly can massive and yet not cause clinical symptoms. It is not my practice to suggest or endorse splenectomy for any reason unless there is marked hypersplenism, uncontrollable autoimmunity, or a real possibility of

lymphoma. When there is doubt about the nature of an infiltrate, nodule, or enlarged node, I request biopsy and histologic staining, also studies using a standard panel of monoclonal markers appropriate for lymphoma. Enlarged lymph nodes usually show atypical or reactive hyperplasia, with or without preservation of germinal center boundaries; granulomatous infiltrations are found in some(54). There is a typical lack of plasma cells in lymph nodes or other lymphoid tissues in CVID (55). We also save tissue for Epstein-Barr encoded RNAs (EBER) by *in situ* hybridization, cytogenetics and studies of B and T cell clonality by molecular analysis. However, the presence of clonal lymphocytes is not diagnostic as these can be found in biopsies showing reactive hyperplasia but no evidence of lymphoma (56, 57).

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

Gastrointestinal Disease: The main gastrointestinal manifestation of CVID is transient or persistent diarrhea, found in 21- 57% of subjects (63-65). When a cause is identified, *G lamblia* is the commonest organism; treatment with metronidazole is generally effective but may require several courses. Other pathogens can also be identified, including *Cryptosporidium parvum*, cytomegalovirus, *Salmonella* species, *Clostridium difficile*, and *Campylobacter jejuni*(66) . *Helicobacter pylori* infection has been associated with gastritis(53). Aside from bacterial and parasitic infections, inflammatory bowel disease remains a significant problem in 19%-32% (6, 65). Dissecting infectious from inflammatory disease is not always simple; both can lead to chronic even severe diarrhea, characterized by weight loss, steatorrhea and malabsorption(5). On biopsy, the gastrointestinal mucosa contains excess intraepithelial lymphocytes, villous blunting, lymphoid aggregates, granulomas, crypt distortion, and as noted above, a characteristic lack of plasma cells(64, 65). Another common feature is villous flattening in the small intestine, suggesting celiac sprue. However we have not found wheat withdrawal to be beneficial and instead leads to additional weight loss. In the worst cases, significant loss of essential nutrients (e.g. calcium, zinc, and vitamins A, E and D) leads to bone loss and neurological deficits, which are not easily reversed(67). Nodular lymphoid hyperplasia (containing an expanded number of B cells but no plasma cells) is common, may be observed on endoscopy in any area of the GI tract; when massive, this can lead to both severe chronic diarrhea and weight loss (**Figure 2**). Initial treatment is based on culture results, biopsy findings, and usually includes antibiotics, restoration of nutrients and rehydration.

The management of inflammatory bowel disease in CVID is the same as for immunocompetent patients, including antibiotics, such as metronidazole or tinidazole or ciprofloxacin, 5-aminosalicylic acid and/or non-absorbed oral steroids such as budesonide. 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 infections. Immunomodulators, such as azathioprine or 6-mercaptopurine, can be used safely as the doses used (as for Crohn's disease) are low and do not appear to affect standard T- and B-cell function tests (66). Infliximab has also been used with some benefit in severe enteropathy (68).

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

Organ and Stem cell Transplantation in CVID: There are a few reports of liver and lung transplant in CVID, with at least short term survival but overall variable outcome (71, 72) (73). What has not been clarified, is with what complications and at what stage, stem cell or bone marrow transplantation should be considered in CVID. This question is most likely to arise when severe immune compromise has been already documented and T cell immunity is impaired. These cases resemble a form of combined immune deficiency, and hypomorphic defects of genes known to cause SCID (adenosine deaminase, Artemis or RAG1 or RAG2, and likely others (74-76)) should be sought. Unfortunately, here is little if any published information on stem cell transplant in well-described CVID patients.

Genetics: Only some of the genetics leading to the CVID phenotype have been clarified. These include several very rare recessive mutations: in the T cell inducible co-stimulatory, ICOS in one kindred(77), mutations in CD19 in a few unrelated families(78),(79) BAFF receptor in two siblings(80), CD20 and

CD81 in one patient each (81, 82). As these are very rare events and not found in general populations of patients, requesting these genetic tests in a workup is not recommended. More promising, but from a research point of view, has been work that identified mutations in transmembrane activator and calcium-modulating cyclophilin ligand interactor (TACI, TNFRSF13B) in about 8% patients(83-85). Two of these, an extracellular mutation C104R and a transmembrane mutation, A181E account for most of these. C104R leads to a disruption of a region important for binding the ligands, B cell activating factor (BAFF) and another soluble ligand, a proliferation inducing ligand (APRIL); the transmembrane or intra-cytoplasmic mutations are presumed to lead to impaired BAFF and APRIL signaling. In all studied populations, heterozygous are far commoner than homozygous mutations and we and others have found that these are associated with both autoimmunity and lymphoid hyperplasia. Whether this is due to the generation of abnormal signals or haplo-insufficiency, has not been clarified (86, 87). However, since the same mutations are routinely found in normal family members and sometimes in normal blood donors, testing for TACI mutations in patients is neither diagnostic of CVID nor predictive of immune deficiency in the future. For this reason, I do not recommended it for either of these purposes.

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

In more recent years the overall survival of subjects with CVID appears improved, very likely due to the now standard doses of replacement Ig. Of the 334 CVID subjects collected from the ESID Registry, 51 subjects (15%) died over a longer mean follow-up period (22.5 years.) However, other factors appear important in survival as revealed by examination of these data. While about half of the patients had infections as the only manifestation, others with one or more of the other complications outlined above (autoimmunity, gastrointestinal disease, lymphoid hyperplasia, splenomegaly, granulomatous disease, cancer or non-Hodgkin's lymphoma) had diminished survival(1). While a very low initial serum IgG level might be the most logical predictor for complications, there was no association found between the level of the serum IgG level at diagnosis and severe infections (including pneumonia), a higher incidence of lung disease, or increased mortality. Strangely, neither age at onset of symptoms, age at diagnosis, nor length of diagnostic delay was related to increased mortality.

These registry data illustrate the need for additional biologically relevant biomarkers to guide both evaluation and treatment in CVID. Previous studies showed that poorer T cell functions, reduced lymphocyte counts, very low numbers of B cells, and reduced numbers of both CD4+ T cells, and CD45RA+CCR7+CD4+T(88) cells are associated with both opportunistic infections and reduced survival (10) (5, 88). More recently, other studies have suggested that the numbers and phenotypes of peripheral blood B cells are useful biomarkers. CD27⁺ B cells but especially IgD-CD27⁺ isotype-switched memory B are decreased(89) (90, 91) (92), and both we and others found that CVID subjects with the fewest switched memory B cells produce less IgG antibody after vaccine challenge(93) (94). In our studies, <0.5% isotype-switched memory B cells is very significantly associated with autoimmunity, granulomatous disease, hypersplenism, and lymphoid hyperplasia. We also found that females with CVID have significantly more IgM+CD27⁺ memory

cells and IgD-CD27⁺ cells than males, which suggests to us interesting difference between sexes in CVID(36). We have not been able to verify that CVID patients who have significantly lower numbers of circulating IgM+CD27+ memory B cells are more likely to develop chronic lung disease as previously suggested (95) (96). Other suggested markers include reduced Tregs(97), very low CD21+ B cells (92) and high levels serum BAFF and APRIL (98) which might be associated with selected clinical conditions such as autoimmunity and lymphoid hyperplasia.

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

with vitamin D, calcium and other standard therapies. Routine endoscopy is not required although patients with suggestive gastrointestinal symptoms should have appropriate upper and/or lower endoscopy with examination for *H Pylori* or other mucosal changes.

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

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

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Authorship:

Charlotte Cunningham-Rundles wrote this manuscript.

Conflict of Interest Disclosure:

Baxter Healthcare supports an ongoing research study at Mount Sinai, on the demographics of immune deficiency in New York State, using de-identified data and ICD coding.

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Table 1 Suggested template evaluation to verify lack of IgG antibody

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

Table 2 Summary of Complications and Incidence*

	Numbers	Perce
Infections	428	90
Autoimmunity	97	25
Lung Impairment	88	24
Gastrointestinal disease	51	14
Malabsorption	31	5
Lymphoid malignancy	36	10
Previous Splenectomy	31	8
Granulomatous disease	31	8
Other Cancers	21	6

- Based on a cohort of 476 subjects

Table 3 Hematologic Autoimmunity*

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

- Based on a cohort of 476 subjects

Table 4: Cancer in CVID*

Kind	Number	Percent#
Non Hodgkin's Lymphoma	32	6.7
Other cancers*	20	4.0
Hodgkin's disease	4	0.8
Waldenstrom's macroglobulinemia	1	0.2
Aplastic anemia	2	0.2

* based on 476 subjects

other cancers: breast 6; colon 3, gastric 3; mouth 2; melanoma 2; lung 1; skin 1; ovary 1; vagina 1.

Table 5: Suggested monitoring for patients with CVID*

Patients	Type	Interval
All	Interval history, Physical examination height and weight	12 months
	Complete blood counts: Hgb, Hct, white blood cells and differential, platelets, and chemistry panel including liver and kidney functions; albumin	12 months
	Serum IgG*	6 to 12 months or with weight gain, pregnancy
	Chest X ray	Referral
	Spirometry	12 months
With lung disease	High Resolution Chest CT	3 – 4 years or after change of therapy
	Complete lung functions with CO diffusion	12 months
With gastrointestinal complications	Upper and/or lower Endoscopy	Intervals as required for optimum treatment
With evidence of malabsorption including loss of height; women in particular	Bone density, evaluation of nutrients	As dictated by the therapy used

* consider adding also serum IgA or IgM if there is a question about the stability of the diagnosis or onset of other complications.

Figure legends:

Figure 1a: This is a 40 year old woman with gradually worsening severe lung disease. CT of the chest revealed massive infiltrates composed of lymphocytic collections and fibrotic scars.

Figure 1b: On biopsy, the infiltrating T cells in the lung, obliterating normal architecture, were revealed as CD4+ by the brownish monoclonal peroxidase conjugated monoclonal anti-CD4- staining pattern. (25x magnification)

Figure 2a: This is a 50 year old woman who had a history of a duodenal ulcer, now resolved. She had a repeat gastroscopy for symptoms of gastritis; *H Pylori* was not found. The mucosa of the stomach folds of this female patient contained numerous lymphoid follicles.

Figure 2b: The jejunum of this 28 year old male patient contained massive nodules of lymphoid hyperplasia; he had experienced 20 lb weight loss.

Figure 1 a

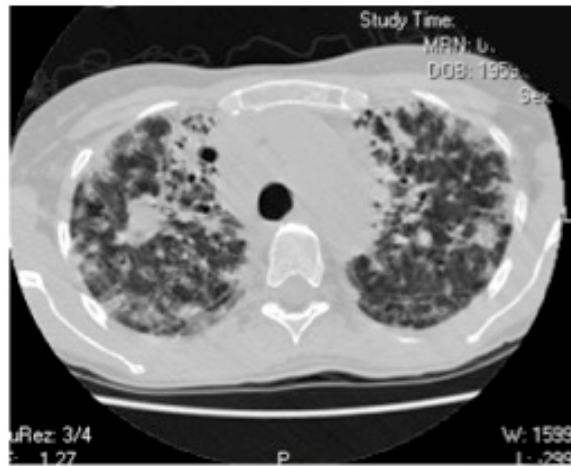


Figure 1 b

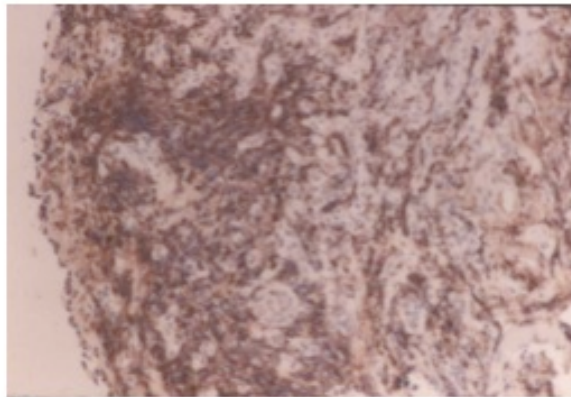


Figure 2a

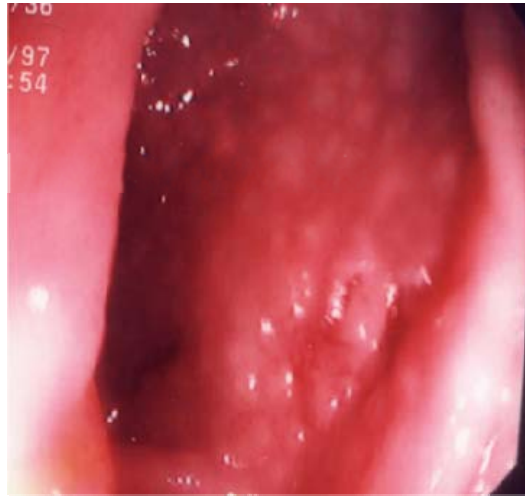


Figure 2b

