Common Variable Immunodeficiency: Etiological and Treatment Issues

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Autoimmunity  B cells  Immunodeficiency  Recurrent infections

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

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

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

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

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

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

**Table 2. Secondary causes of IgG deficiency [25]**

<table>
<thead>
<tr>
<th>Conditions</th>
</tr>
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<tbody>
<tr>
<td>Burns</td>
</tr>
<tr>
<td>Protein-losing enteropathies</td>
</tr>
<tr>
<td>Nephrotic range proteinuria</td>
</tr>
<tr>
<td>Malignancy</td>
</tr>
<tr>
<td>HIV-related immunodeficiency</td>
</tr>
<tr>
<td>Other secondary causes of IgG deficiency</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Medications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antihypertensives</td>
</tr>
<tr>
<td>Antimalarials</td>
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<tr>
<td>Antiepileptics</td>
</tr>
<tr>
<td>NSAIDS</td>
</tr>
<tr>
<td>Antirheumatics</td>
</tr>
<tr>
<td>Chelating agents</td>
</tr>
</tbody>
</table>

**Table 3. Established laboratory criteria for the diagnosis of CVID**

<table>
<thead>
<tr>
<th>Ig abnormality</th>
<th>Probability (additional criteria needed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Significant decrease in both IgA and IgG</td>
<td>probable</td>
</tr>
<tr>
<td>Significant decrease in IgM, IgG or IgA</td>
<td>possible</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Additional diagnostic criteria</th>
<th>Diagnostic procedure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immunodeficiency onset &gt;2 years of age</td>
<td>history</td>
</tr>
<tr>
<td>Impaired antibody production to vaccines</td>
<td>diphtheria/tetanus titers pre-/post-vaccine</td>
</tr>
<tr>
<td>Impaired antibody production to polysaccharides</td>
<td>serum isohemagglutinins; pneumococcal titers pre-/post-vaccine</td>
</tr>
</tbody>
</table>
ic the clinical presentation of Ig defects [14]. We also note that patients may present with subtle Ig changes and develop more frank abnormalities during subsequent follow-up [26]. In the case of CVID, reduced IgG levels with normal or slightly reduced IgA levels are typical; if this latter abnormality is isolated, the alternative diagnosis of selective IgA deficiency needs to be considered [14]. Marked IgE level elevation is suggestive of atopic disease or immunodeficiency associated with hyper-IgE syndrome, while the implications of isolated IgM and IgG subclass deficiencies are unclear. Ultimately, immunoglobulin levels alone are insufficient to adequately establish the diagnosis, and inadequate follow-up evaluation may put patients at significant risk of serious consequences with the inappropriate administration of IVIG [27].

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

### CVID Clinical Features

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

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

### Table 4. Conditions potentially mimicking CVID

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

### Table 5. Monogenic diseases indistinguishable from CVID

<table>
<thead>
<tr>
<th>Protein defect</th>
<th>Locus</th>
<th>Inheritance</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICOS</td>
<td>2q33</td>
<td>autosomal recessive</td>
<td>7, 120, 121</td>
</tr>
<tr>
<td>CD19</td>
<td>16p11.2</td>
<td>autosomal recessive</td>
<td>122, 123</td>
</tr>
<tr>
<td>TACI</td>
<td>17p11.2</td>
<td>autosomal dominant or recessive</td>
<td>126–130</td>
</tr>
<tr>
<td>BAFF-R</td>
<td>22q13</td>
<td>autosomal, presumed recessive</td>
<td>139, 143</td>
</tr>
<tr>
<td>MSH5</td>
<td>6p22.1–p21.3</td>
<td>unknown</td>
<td>144</td>
</tr>
</tbody>
</table>
CVID may result in severe bronchiectasis and pulmonary fibrosis [19, 35, 38–48], possibly influenced by mannose-binding lectin polymorphisms [42]. Further, patients with CVID are at risk for granulomatous infiltration and interstitial pneumonia in a pattern termed GLILD (granulomatous/lymphocytic interstitial lung disease) [19, 44, 48–51]. In approximately 20% of patients with CVID, digestive complications are found, with diarrhea of infectious etiology [19] primarily from *Salmonella* and *Campylobacter* species in the minority of cases in which a cause is proven. Cytomegalovirus and *Cryptosporidium* enteritis, while more commonly associated with HIV or cellular immunodeficiencies, have also been observed in CVID [19, 52–54]. When colon history was evaluated in patients with CVID with digestive complaints, 19% had granulomas, while approximately 50% had histological patterns mimicking celiac disease [52]. Similarly, nodular lymphoid hyperplasia and inflammatory bowel disease can be found in about 20 and 30%, respectively, of patients with digestive complaints [19]. The liver may also be affected and while acute hepatitis has been reported following contaminated IVIG, autoimmune liver disease may also occur [19, 55–58]. Indeed, autoimmunity is prominent in CVID [52, 59–61] and 23–50% of patients manifest unclassified autoimmune features [28, 62]. The mechanisms that lead to loss of tolerance in patients with immune deficiency as well as the same genetic issue in autoimmune disease have been recently discussed [62–72]. In patients with X-linked agammaglobulinemia, a non-CVID disorder characterized by an extremely reduced B cell count, the remaining B cells are enriched in autoreactive clones [73]. CVID-associated autoimmune diseases may range across the spectrum of rheumatologic disorders, but granulomatous disease and autoimmune cytopenias are most common [62, 74], with the former potentially impacting survival [49, 75–78]. Nonmalignant lymphoproliferative diseases commonly manifest as lymphadenopathy and splenomegaly, and are not uncommon in CVID, with clustering of B cell subsets determined on flow cytometry [79]. The role of human herpes virus 8 in the etiology of lymphoproliferative disease remains to be determined [80]. Although CVID patients may be expected to have an increased risk of infectious events following pharmacological immunosuppression, the management of autoimmunity in these patients does not differ from non-CVID cases [14, 81, 82]. Lastly, malignancy is not uncommon in patients with CVID, secondary to an increased risk of gastric cancer and non-Hodgkin’s lymphoma [19, 83–85], among others [19, 36, 45, 84–87]. Of note, neoplasia may modify the disease classification since humoral immunodeficiencies with benign or malignant thymoma may manifest as CVID but should be classified as a separate entity [14, 34, 37, 54, 88–91].

### Cell Flow Cytometry Phenotyping in CVID

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

### Monogenic Disorders Mimicking CVID

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

<table>
<thead>
<tr>
<th>Table 6. Euroclass CVID flow-cytometry subclassification</th>
</tr>
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<tbody>
<tr>
<td><strong>A</strong> Type B−: &lt;1% circulating B cells</td>
</tr>
<tr>
<td><strong>B</strong> Type B+: &gt;1% circulating B cells</td>
</tr>
<tr>
<td>1 CD21 low: &gt;10% CD21lo B cells</td>
</tr>
<tr>
<td>(associated with splenomegaly)</td>
</tr>
<tr>
<td>a smB+: &gt;2% CD27+/IgD−/IgM− switched B cells</td>
</tr>
<tr>
<td>b smB−: ≤2% CD27+/IgD−/IgM− switched B cells</td>
</tr>
<tr>
<td>(associated with higher incidence of splenomegaly and granulomatous disease)</td>
</tr>
<tr>
<td>i TrHi: ≥9% CD38hi/IgMhi transitional B cells</td>
</tr>
<tr>
<td>(associated with lymphadenopathy)</td>
</tr>
<tr>
<td>ii TrNorm: &lt;9% CD38hi/IgMhi transitional B cells</td>
</tr>
<tr>
<td>2 CD21 norm: ≤10% CD21lo B cells</td>
</tr>
<tr>
<td>a smB+: &gt;2% CD27+/IgD−/IgM− switched B cells</td>
</tr>
<tr>
<td>(lower incidence of granulomatous disease than other subsets)</td>
</tr>
<tr>
<td>b smB−: ≤2% CD27+/IgD−/IgM− switched B cells</td>
</tr>
<tr>
<td>(associated with higher incidence of splenomegaly and granulomatous disease)</td>
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</tr>
<tr>
<td>ii TrNorm: &lt;9% CD38hi/IgMhi transitional B cells</td>
</tr>
</tbody>
</table>
and warrant further discussion in this article. As an example, X-linked agammaglobulinemia, a disorder leading to profound loss of B cells, may present atypically or later in life [33, 73, 95–107] while CD40 ligand deficiency may present with deceptively unimpressive IgM levels [29]. Similarly, X-linked lymphoproliferative disorders may mimic CVID in men [108–111]. It should be noted that the most recent International Union of Immunological Sciences (IUIS) classification now includes ICOS and CD19 deficiencies as separate entities, while defects in TACI, BAFF-R, and MSH5 remain within the CVID family and are proposed to be susceptibility or disease-modifying defects [37].

**ICOS Deficiency**

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

**CD19 Deficiency**

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

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

**TACI Deficiency**

TACI deficiency is regarded as a B cell limited disorder [112, 126–130] and appears different from other deficiencies in that several distinct TACI mutations were initially reported to be associated with CVID [15, 126–131], while 2 groups later reported a total of 6 TACI mutations resulting in CVID or IgA deficiency. Two of these mutations, specifically S194X and S144X, appeared to have an autosomal recessive mode of inheritance, whereas 2 others (C104R and A181E) were associated with immunoglobulin defects (CVID or IgA deficiency) in a heterozygous state [15, 129] and compound heterozygosity is also reported [127]. The R202H mutation, like C104R and A181E, is also able to induce humoral defects in heterozygous patients [15, 127, 129]. In general terms, the analysis of families with heterozygous mutations demonstrates a variable disease phenotype despite identical genetic defects among family members [130], possibly secondary to unknown additional factors in the heterozygous state [130, 132] or to...
variable functional degrees of the mutated proteins [10]. Nonpathogenetic allelic variations were reported at similar rates in both patients with humoral immunodeficiencies and healthy controls [131, 133]. Lastly, a recent study demonstrated significant associations between CVID and heterozygosity for the CI04R mutation, whereas other mutations were too rare to allow comparisons with sufficient power [128].

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

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

**BAFF Receptor Deficiency**

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

**MSH5 Deficiency**

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

**Management of Patients with CVID**

**Ig Replacement**

The benefit of γ-globulin replacement in ameliorating the symptoms of immunoglobulin deficiencies has been recognized since shortly after World War II [146], and current practice guidelines support the use of subcutaneous or intravenous Ig replacement in patients with the goal of maintaining specific antibody deficiencies; whereas gray areas exist in patients with milder clinical entities such as IgG subclass deficiency, patients fulfilling the case definition of CVID meet the treatment criteria [28, 147]. Whereas subcutaneous or intramuscular injection was the initial mode of administration, intramuscular injection was painful and associated with reduced compliance, and adequate subcutaneous delivery was limited by volume issues [147, 150]. Slow subcutaneous infusions of preparations designed for intramuscular use addressed some of these concerns, but were complicated by long in-
fusion times and were largely abandoned after higher-dose intravenous Ig preparations became available [150–152]. However, a more recent Ig preparation approved specifically for subcutaneous infusion has demonstrated benefits in quality of life measures and has a favorable pharmacokinetic profile with equivalent efficacy to intravenous administration [147, 152–155]. Subcutaneous Ig can be used either as an initial modality of therapy or as a salvage therapy in selected patients who have been unable to tolerate intravenous preparations [152]. There is no consensus on the ideal regimens for Ig replacement in humoral immunodeficiencies [25]. Recommended starting doses for intravenous Ig in humoral immunodeficiencies include a bolus of 1 mg/kg followed by monthly infusions starting at 400 mg/kg, while subcutaneous Ig infusion typically starts at 100–200 mg/kg/week [14, 152]. While the literature describes a minimum serum level of 500 mg/dl and a common trough target of 600 mg/dl in CVID, other studies have suggested a benefit in dosing as high as 800 mg/dl in agammaglobulinemic patients [25, 46, 147]. Extrapolation of these agammaglobulinemia patient data to CVID is not necessarily appropriate, as other reports caution against the utility of dosing to trough levels in disorders such as CVID where some level of endogenous antibody production exists [35, 156]. Some authors recommend consideration of dose adjustments based on clinical response rather than trough levels [156]. Intravenous Ig preparations vary with regard to excipients, fluid loads, and IgA content and are not necessarily interchangeable [25, 157]. Current consensus guidelines recognize immunoglobulin preparations as equally effective, though availability and individual patient characteristics may guide initial choices [14]. The possibility of generating anti-IgA antibodies and subsequent IgA reactions in patients with coexistent IgA deficiency has long been recognized, but may be minimized with the use of low-IgA preparations [147, 158–160]. In selected cases, testing for anti-IgA IgE may be helpful to prevent this risk [147]. Potential indications with regard to specific characteristics of different preparations in given patient populations are listed in table 7 [161]. While the administration of subcutaneous preparations may diminish certain risks associated with the intravenous agents, they require more frequent dosing [147, 152, 156, 161].

### Antibiotics

Although parenteral Ig replacement has been shown to be safe and effective in CVID, infections are not uncommon [19, 35, 82, 148, 157] and the choice of an appropriate antibiotic therapy is indicated in the setting of acute infection. The appropriateness of a continuous rotation of antibiotics is unclear, as there are no data from well-designed studies to address their use [38], but published opinion supports ongoing antibiotic prophylaxis in CVID patients with bronchiectasis or persistent infections [6, 14].

#### Screening for Pulmonary Abnormalities

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

<table>
<thead>
<tr>
<th>Preparation</th>
<th>Excipient/contaminant</th>
<th>Populations at risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gammagard 5%/10%</td>
<td>glucose</td>
<td>diabetics</td>
</tr>
<tr>
<td>Polygam S/D</td>
<td>glucose</td>
<td>diabetics</td>
</tr>
<tr>
<td>IVEEGAM-EN</td>
<td>glucose</td>
<td>diabetics</td>
</tr>
<tr>
<td>Gaminune-N 5%</td>
<td>maltose</td>
<td>diabetics (false meter reading)</td>
</tr>
<tr>
<td>Octagam</td>
<td>maltose</td>
<td>diabetics (false meter reading)</td>
</tr>
<tr>
<td>Gaminune</td>
<td>glycine</td>
<td>glycine metabolic disorders/reactivities</td>
</tr>
<tr>
<td>Gammagard</td>
<td>glycine</td>
<td>glycine metabolic disorders/reactivities</td>
</tr>
<tr>
<td>Polygam S/D</td>
<td>glycine</td>
<td>glycine metabolic disorders/reactivities</td>
</tr>
<tr>
<td>Carimune</td>
<td>IgA</td>
<td>IgA hypersensitivity</td>
</tr>
<tr>
<td>IVEEGAM-EN</td>
<td>IgA</td>
<td>IgA hypersensitivity</td>
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<tr>
<td>Privigen</td>
<td>IgA</td>
<td>IgA hypersensitivity</td>
</tr>
<tr>
<td>Venoglobulin-S</td>
<td>IgA</td>
<td>IgA hypersensitivity</td>
</tr>
<tr>
<td>Gaminune</td>
<td>IgA</td>
<td>IgA hypersensitivity</td>
</tr>
<tr>
<td>Octagam</td>
<td>IgA</td>
<td>IgA hypersensitivity</td>
</tr>
<tr>
<td>Panglobulin</td>
<td>IgA</td>
<td>IgA hypersensitivity</td>
</tr>
<tr>
<td>Privigen</td>
<td>proline</td>
<td>proline metabolic disorders/reactivities</td>
</tr>
<tr>
<td>Carimune</td>
<td>sucrose</td>
<td>renal insufficiency</td>
</tr>
<tr>
<td>Panglobulin</td>
<td>sucrose</td>
<td>renal insufficiency</td>
</tr>
<tr>
<td>Solutions under 10%</td>
<td>dilute fluids</td>
<td>water restriction, infants</td>
</tr>
</tbody>
</table>
of X-ray exposure, some groups have used monitoring with CT scan at intervals of 4–5 years, with interim annual pulmonary function testing [35, 167].

**Screening for Digestive Complications**

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

**Screening for Hematologic Complications**

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

**Screening for Neoplasia**

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

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

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

### Conclusions and Future Directions

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

### Acknowledgments

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Acquired Immunoglobulin Deficiency

Int Arch Allergy Immunol 2009;150:311–324


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Erratum

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