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Common Variable Immunodeficiency

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Synonyms and related keywords: CVID, late-onset hypogammaglobulinemia, adult-onset hypogammaglobulinemia, acquired immunodeficiency

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Background: Common variable immunodeficiency (CVID) is the most prevalent of the primary immunodeficiency diseases. CVID is a heterogeneous group of immunologic disorders of unknown etiology, characterized by impaired antibody responses. Patients with CVID have marked reduction in serum levels of both immunoglobulin G (IgG) and immunoglobulin A (IgA); about half of these patients also have reduced immunoglobulin M (IgM). Diagnosis is based on exclusion of known causes of humoral immune system defects. Most patients with CVID present as sporadic cases, although reports exist of familial cases with various inheritance modes, including autosomal dominant with variable penetrance, autosomal recessive, or X-linked.

Pathophysiology: The common immunologic defect in patients with CVID is defective antibody formation. As would be expected in a heterogeneous group of diseases, many different immune system defects have been reported in this group of patients.

B-cell defect

The basic and common immunologic defect in CVID is a failure of B-lymphocyte differentiation into plasma cells that produce the various immunoglobulin (Ig) isotypes.

Earlier studies suggested a B-lymphocyte defect as a cause of CVID in a small group of patients. B lymphocytes from these patients failed to differentiate into Ig-producing cells when stimulated with pokeweed mitogen (PWM) in vitro, even when cocultured with normal T cells, and they were also L-selectin negative. These studies described failure of B-cell differentiation because of altered B-cell surface-molecule expression.

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Other studies have observed a lack of protein kinase C activation and translocation to the plasma membrane when B cells of patients with CVID were stimulated with phorbol ester or anti- μ antibody. B-cell lines from a subset of patients with CVID showed absent IgG and IgA production and increased spontaneous apoptosis that was associated with increased expression of CD95 (APO-1/Fas). A subset of patients with CVID showed impaired B-cell signal transduction cascade associated with abnormalities in protein tyrosine phosphorylation. Another subset exhibited chromosomal radiosensitivity, presumably due to impaired ability to repair DNA. Some patients with CVID have mutations interfering with the regulation of the expression of Ig genes; others have somatic hypermutation in B cells. These abnormalities possibly contribute to an already compromised B-cell maturation system.

T-cell defect

An overwhelming body of literature suggests that most patients with CVID have intact B lymphocytes of immature phenotype. CVID B cells can secrete immunoglobulins (Ig), although often limited to IgM, if given the appropriate in vitro stimulation. Ig secretion has been induced from CVID B cells using B-cell mitogens with soluble T-cell factors, monoclonal B-cell differentiation factors, Epstein-Barr virus (EBV), anti-CD40 plus interleukin (IL)-4 and IL-10. CD40 ligand (CD154) is expressed by activated CD4+ cells and is pivotal in inducing B-cell proliferation and differentiation.

Approximately 40% of patients with CVID have low expression of CD40 ligand on activated T cells. At least 30% of patients have lymphopenia due to the low number of CD4+ subsets. These patients also show decreased in vitro production of interleukin (IL)-2 when their peripheral blood mononuclear cells are stimulated in vitro. Decreased IL-2 production after T-cell receptor stimulation is correlated with diminished CD40 ligand expression.

T cells of patients with CVID show low frequency of antigen-specific precursor T cells following immunization with the neoantigens, keyhole-limpet hemocyanin, and dinitrophenol (DNP)-Ficoll. Many patients with CVID have a defect in CD4+ T-cell priming to antigens, as measured by the number of circulating responsive CD4+ T cells following immunization. Many patients have a reduction in CD4+ CD45RA+ ("unprimed") T cells, suggesting activation of T cells. Others have reported that most patients with CVID show increased production of interferon gamma by circulating CD8+ subsets, increased numbers of DR+/CD4+ T cells with upregulated Fas expression and an increased rate of apoptosis. The abnormality appears to reside in CD4+ T cells and can be overcome by stimulating T cells with phorbol myristate acetate (PMA) and ionomycin, an alternative T-cell activation pathway. This is consistent with defective signal transduction.

Increased endogenous cyclic adenosine monophosphate (cAMP) levels in T cells from patients with CVID are associated with increased activation of protein kinase A type I (PKAI) in T cells and with decreased proliferative response to anti-CD3 stimulation. A selective antagonist of PKAI induces a significant increase in anti-CD3-stimulated proliferative responses, particularly in CD4+ lymphocytes. Approximately 25-30% of patients with CVID have increased numbers of CD8+ lymphocytes, normal or decreased CD4+, and reduced CD4/CD8 ratios (<1). This increase in CD8+ T cells has been observed most often in patients with splenomegaly and bronchiectasis. These cells coexpress human leukocyte antigen (HLA)-DR and IL-2 receptors, suggesting in vitro activation.

Approximately 60% of patients with CVID have diminished proliferative responses to T-cell receptor stimulation and decreased induction of gene expression for IL-2, IL-4, IL-5, and interferon gamma. T-cell receptors show no evident abnormality; T-cell receptor gene analyses indicate normal heterogeneity of gene rearrangements. Tumor necrosis factor (TNF) production from T cells and monocytes is increased in a subgroup of patients with granulomas. Standard tests to assess T-cell function, including in vitro proliferation in response to mitogens, antigens, and allogeneic cells, are subnormal in as many as 50% of patients with CVID, with a small subgroup of patients having very low responses. These results support the hypothesis that most patients with CVID have antibody deficiency secondary to abnormalities in T-cell signaling and defective T- and B-cell interactions.

The recovery of Ig production (mostly IgG and IgM) transiently or permanently following Human Immunodeficiency Virus (HIV) or Hepatitis Virus C (HVC) infection has been reported in patients with CVID. These cases indicate that CVID is associated with potentially reversible defects in immunoregulatory factors and intact B-cell systems.

Frequency:

- **In the US:** Estimated incidence of CVID is 1 case per 10,000-50,000 population.
- **Internationally:** Incidence is similar to that in the United States.

Mortality/Morbidity: The prognosis for patients with CVID is reasonably good if they do not have bronchiectasis and chronic lung damage or severe autoimmune disease or malignancy.

- The survival rate 20 years after diagnosis of CVID is 64% for males and 67% for females,

compared to the expected 92% population survival rate for males and 94% for females.

- In one large series, the most frequent cause of death was lymphoma. Other causes of death relate to cor pulmonale from chronic pulmonary infection, liver failure caused by viral or autoimmune hepatitis, respiratory insufficiency associated with malnutrition, inflammatory bowel disease with malnutrition, and other viral infections.
- Parameters associated with mortality in this report were lower levels of serum IgG, poorer T-cell responses to phytohemagglutinin, and a lower percentage of peripheral B cells.

Race: CVID has been reported in many different races.

Sex: CVID affects males and females equally.

Age: Although the usual age at presentation, according to some reports, is in the second or third decades of life, other reports described the onset of clinical disease as early as the first decade of life, with peaks of onset in children aged 1-5 years and in persons aged 16-20 years. Likewise, age of diagnosis demonstrated bimodal peaks at 6-10 years and 26-30 years. More than two thirds of the patients were adults who were older than 21 years when the diagnosis was first made.

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History: Clinical manifestations of CVID include recurrent infections, autoimmune disease, lymphoid hyperplasia, granulomatous diseases, and malignancy.

- Recurrent infections
 - Recurrent pyogenic infections of upper and lower respiratory tracts are the main clinical manifestations of CVID. Symptoms may appear during childhood or, more often, after puberty. Bronchiectasis may develop if optimal therapy is delayed. *Haemophilus influenzae*, *Moraxella catarrhalis*, *Streptococcus pneumoniae*, and *Staphylococcus aureus* are the organisms most commonly involved.
 - A few patients with CVID present with unusual organisms, such as *Pneumocystis carinii*, mycobacteria, or various fungi. *Mycoplasma pneumoniae* infections in the urinary tract, joints, and deep abscesses have been reported.
 - Persistent diarrhea and malabsorption caused by *Giardia lamblia* also have been reported in patients with CVID. GI symptoms disappeared after *G lamblia* was eradicated with metronidazole.
 - Severe and recurrent infections with herpes simplex are common, and herpes zoster eventually developed in as many as 20% of patients with CVID.
 - Some patients may develop unusual enteroviral infections with a chronic meningoencephalitis and a dermatomyositislike illness. Presenting symptoms are either acute or insidious, with signs of encephalitis, seizures, headache, sensory motor disturbances, and personality changes.
 - Vaccine-associated paralytic poliomyelitis (VAPP) in a patient with CVID has been reported; this patient developed paralytic poliomyelitis 7 years after the last administration of trivalent oral poliovirus vaccine.
- Autoimmune diseases and CVID
 - In contrast to X-linked agammaglobulinemia (XLA), CVID is associated with a high frequency of autoimmune and granulomatous diseases.
 - Some patients develop rheumatoid arthritis, hemolytic anemia, thrombocytopenia, neutropenia, thyroid abnormalities, vitiligo, or keratoconjunctivitis sicca.
 - Approximately 20% of these patients have a severe gastroenteropathy with severe malabsorption resembling celiac sprue, nodular lymphoid hyperplasia, and chronic inflammatory bowel disease such as ulcerative colitis and Crohn disease.
 - A small number of patients develop achlorhydria and pernicious anemia, autoimmune hepatitis, primary biliary cirrhosis, alopecia totalis, hyperthyroidism, vasculitis, and lymphoid interstitial pneumonia.

- Although regular Ig therapy reduces susceptibility to *Giardia* species and *Campylobacter enteritis*, it does not prevent autoimmune mucosal inflammation. Ig replacement therapy does not affect the clinical course of inflammatory bowel disease.
- Lymphoid hyperplasia and granulomatous diseases
 - Atypical lymphoid hyperplasia due to clonal expansion of B or T lymphocytes has been reported in as many as one third of patients with CVID. Extranodal sites, such as the lungs, GI tract, skin, spleen, liver, and parotid gland, may be involved by these lymphoproliferative processes. Lymph nodes show a reactive follicular hyperplasia, atypical hyperplasia, or granulomatous inflammation. Nodular lymphoid hyperplasia in the GI tract with clonal rearrangement of the Ig heavy chain gene or clonal T-cell receptor (TCR) gene rearrangement has been described in otherwise benign cases of lymphoid proliferation in patients with CVID.
 - Granulomas have been reported in approximately 5-10% of patients with CVID. These patients were more likely to have deficient T-cell proliferation to mitogens and antigens. Published studies have reported 22 patients with CVID and sarcoidosis. Granulomas are indistinguishable from those of classic sarcoidosis and are found in the lung, liver, spleen, and conjunctivae. These patients were more likely to have increased frequencies of infections, hepatosplenomegaly, iridocyclitis, autoimmune hemolytic anemia, or immune thrombocytopenic purpura.
- Increased risk of developing malignant neoplasms
 - Patients with CVID have a high risk of developing malignant neoplasms, such as non-Hodgkin lymphoma, GI carcinoma, or malignant lymphoma. Most of these are of the B-cell immunophenotype and frequently are associated with EBV.
 - Lymphoma occurs 300 times more frequently in women with CVID than in affected men. Malignant lymphomas in patients with CVID occur most frequently in the fifth to seventh decade and not in childhood. These malignant lymphomas usually are extranodal and histologically are intermediate- to high-grade non-Hodgkin lymphomas. Most of these lymphomas are of the B-cell immunophenotype and may be associated with EBV. Patients with CVID also are at risk for gastric carcinoma 47 times higher than normal. Other malignancies include colon cancer, breast cancer, gastric cancer, prostate cancer, ovarian cancer, oral cancer, and melanoma.

Physical: In contrast to patients with X-linked agammaglobulinemia, many patients with CVID have generalized lymphadenopathy and splenomegaly. Other positive physical examination findings depend on their clinical presentation and organ involvement (see [History](#)). Young children with CVID may present with failure-to-thrive (FTT) based on frequent infection and increased energy expenditure. FTT may occur secondary to malabsorption syndrome associated with infection, inflammatory bowel disease, or spruelike illness.

Causes: This disorder probably has a variety of causes, and a single etiology is unlikely. The search for gene(s) that underlie CVID has been difficult, partly because of the heterogeneity of CVID.

- A common genetic basis for CVID and selective IgA deficiency (sIgAD) has been suspected because these disorders occur in first-degree relatives of patients. Families of both types of patients have high incidences of abnormal Ig concentrations, autoantibodies, autoimmune diseases, and malignancies. Familial occurrences of sIgAD and CVID have been observed in approximately 20% of cases, including reported cases of sIgAD developing into CVID with time and occasionally vice versa, which suggests these conditions are linked closely and can be progressive or reversible. Deficits in IgG subclasses, most commonly IgG2 and IgG4, are observed in 20-30% of patients with sIgAD.
- Studies of families with multiple cases of sIgAD and CVID have shown that susceptibility to CVID or IgA deficiency may be linked to specific alleles of class II and class III genes of the major histocompatibility complex (MHC). A high incidence of deletion of the C4A gene and rare alleles of the C2 gene in the class III MHC region has been reported in patients with sIgAD or CVID. These findings indicate that susceptibility gene(s) may be present in this region on chromosome 6.
- Recently, multiple allelic deoxyribonucleic acid (DNA) and protein markers were used to examine the extended HLA-DR3, HLA-B8, and HLA-A1 haplotypes in a large American family with several members affected with sIgAD/CVID. This examination identified a susceptibility locus in the class III region within a fragment that contains 21 known genes, including the genes for TNF- α , lymphotoxin (LT)- α , and LT- β . This area, the so-called class IV region, contains a heavy concentration of genes that may play important roles in stress, inflammation, or infection. Others reported that certain MHC haplotypes, which were found in abnormally high frequency in

immunodeficient patients, also were found in normal members of the pedigree. These findings suggest that the presence of these MHC haplotypes alone is not sufficient for expression of the defects.

- CVID and sIgAD have been associated with antirheumatic or antiepileptic drugs. Drug-associated CVID or sIgAD suggests that a pathogenetic process may involve common key steps in individuals with the permissive genetic background.

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Other Problems to be Considered:

Agammaglobulinemia, Bruton agammaglobulinemia, or X-linked agammaglobulinemia

X-linked agammaglobulinemia (XLA) is inherited as an X-linked recessive trait. The genetic defects are mutations in cytoplasmic tyrosine kinase (currently known as Bruton tyrosine kinase [Btk]). Patients with XLA present with agammaglobulinemia affecting all immunoglobulin classes, absent B cells, and paucity of lymphoid tissue. Some patients with CVID have low numbers or undetectable peripheral B cells. These patients, especially males, may have atypical XLA and should be studied for mutations of the *Btk* gene. Female patients with agammaglobulinemia and undetectable peripheral B cells may have phenotypic X-linked agammaglobulinemia. Some female patients with agammaglobulinemia were found to have mutations in the μ heavy-chain gene or $\lambda 5$ gene.

X-linked immunodeficiency with hyper IgM

The genetic basis of X-linked immunodeficiency with hyper IgM (X-HIM) is defects in the gene encoding the CD40 ligand on T cells. CD40L normally binds to CD40 on B cells; therefore, its deficiency results in the failure of B cells to undergo class switching. Not all X-HIM patients have increased levels of IgM, but all have low levels of IgG and IgA. Recently, female patients with hyper IgM syndrome have been reported, and approximately 30% of all HIM patients are females.

Protein-losing enteropathy

Diminished Ig levels may be caused by loss and decreased synthesis. An indirect indication of loss may be obtained by measuring serum albumin, which usually is lost concomitantly through the GI or renal tracts.

Malignancies

Children with neuroblastoma or acute lymphoblastic leukemia may be hypogammaglobulinemic. In adults, hypogammaglobulinemia may be associated with benign thymoma or chronic lymphocytic leukemia.

Transient hypogammaglobulinemia of infancy

Patients with transient hypogammaglobulinemia of infancy (THI) have abnormal delay in the onset of immunoglobulin synthesis during infancy. Normal infants have physiologic hypogammaglobulinemia when aged 2-4 months. This "physiologic" hypogammaglobulinemia may extend into the second or third year of life in THI. Often, these patients have normal IgM and can synthesize antibodies to human type A and B erythrocytes and to protein antigens (eg, diphtheria and tetanus toxoids) by the time the infant is aged 8-11 months, long before their immunoglobulin concentrations become normal. This is a self-limited condition, with recovery during age 18-36 months. IVIG therapy usually is not indicated in this condition.

Severe combined immunodeficiency (SCID)

SCID typically presents during early infancy, with unusually severe common viral, fungal, and bacterial respiratory infections, although opportunistic pathogens may be the initial manifestation. Often infants

with SCID have lymphopenia and panhypogammaglobulinemia. Commonly, infants with SCID also have unique dermatitis or an eczematous rash.

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Lab Studies:

- CVID diagnosis is based on defective functional antibody formation, usually accompanied by decreased (not absent) serum IgG and IgA levels, generally (not invariably) decreased serum IgM, and exclusion of other known causes of antibody deficiency.
- Serum Ig levels are consistently depressed, but they are generally higher in patients with CVID than in patients with XLA. Interpretation of results must consider the marked variations in normal Ig levels that accompany aging; always use age-related normal values for comparison. Normal values should be provided by the laboratory. Serum immunoglobulins commonly are measured by radial immunodiffusion or immunoturbidimetric methods. Electrophoresis and immunoelectrophoresis are not satisfactory techniques for the quantification of immunoglobulins.
 - IgG subclass determination is of limited value in assessing patients with clinical immunodeficiency because functional antibody deficiency may be present despite normal IgG subclass levels. Conversely, deficient levels of a single subclass of IgG may be found in individuals who have effective specific antibody production and are clinically normal.
 - Diminished immunoglobulin levels may be caused by loss and decreased synthesis. An indirect indication of loss may be obtained by measuring serum albumin or α -1-antitrypsin, which usually is lost concomitantly through gastrointestinal or renal tracts.
- Functional antibody production: Assessment of the ability to produce functional antibodies can be obtained by measuring antibody responses to natural antigens or those antigens to which the population commonly is exposed. This assessment also can be done by measuring antibody responses following active immunization with protein or polysaccharide antigens.
 - Antibodies to natural antigens: Isohemagglutinins are IgM antibodies to ABO blood group antigens that are polysaccharide. All individuals, except the 3% of the population who have blood group AB, develop isohemagglutinin titers during the first year of life; therefore, normal infants aged up to 8-10 months and people with the AB blood group lack significant isohemagglutinins.
 - Antibody response to protein antigens
 - In children who have completed immunizations with diphtheria, pertussis, and tetanus (DPT) or Hib-conjugated vaccines: Antibody response to protein antigens can be tested in adults and older children previously immunized with childhood vaccinations by measuring IgG antibodies to tetanus or diphtheria toxoid, and *H influenzae* type b (Hib) polysaccharide antigen. Approximately 80% of children have detectable antibodies to these antigens after 3 immunizations during their first year of life. If the child's antibody level is low, administer 1 booster injection, then measure for antibodies 4 weeks later.
 - For nonimmunized children, recommended doses of diphtheria-tetanus (DT) or Hib-conjugate vaccines may be administered. Draw blood 4 weeks after the last immunization and determine IgG antibodies. Alternatively, administer 3 doses of killed poliomyelitis vaccine (1.0 mL IM at 2-wk intervals); take a blood sample 4 weeks after the last injection and determine antibody level (usually by virus neutralization).
 - Antibody responses to polysaccharide antigens: Antibody responses to polysaccharide antigens depend less on T cells, and they are poor immunogens in children younger than 2 years. Assessment of responses to polysaccharide antigens is important in patients older than 18-24 months because these responses may be deficient in some patients who can respond normally to protein antigens. Pneumococcal (unconjugated) or meningococcal vaccines are commercially available polysaccharide antigens. Protein conjugated pneumococcal vaccine will elicit antibody responses that are T-cell dependent. Therefore, antibody responses should be measured to polysaccharide antigens that are not present in the protein-conjugated pneumococcal vaccine. Alternatively antibody response to typhoid-Vi antigen can be measured following typhoid vaccine administration.
 - Hepatitis B is not a reliable antigen for testing immune competence because of the high frequency of nonresponders in the population, particularly in persons older than 40 years. Bacteriophage PhiX174 (a bacterial virus noninfective in humans) has been shown to be a potent, safe, and useful antigen; it allows measurement of antigen clearance and primary and secondary immune responses. Bacteriophage fX174 is not commercially available, and only a few research laboratories have used it for human in vivo testing.
- In vivo measurement of T-cell mediated immune function
 - In vivo T-cell function can be measured by skin testing for delayed cutaneous hypersensitivity (DHS). The prototype is the tuberculin skin test.

- DHS is a localized immunological skin response and is dependent on functional thymus-derived T lymphocytes. Frequently used antigens are mumps (1 mg/mL), trichophyton (1:30), purified protein derivative (PPD) (2-10 IU), *Candida* (1:100 dilution, or 1:10 if negative with 1:100), or tetanus fluid toxoid (1:100). Several antigens must be used for DCH testing. Perform the tests by intradermal injection of 0.1 mL of antigen. Read results in 48-72 hours for the maximal diameter of induration. This test must be carried out by intradermal injection of antigens.
- Erythema is not an indication of positive DCH. A positive DCH is informative, while a negative DCH test may be difficult to interpret. This is because DCH is influenced by age, steroid therapy, severe illness, previous exposure to testing antigens, concurrent stress, and recent immunization.
- Enumerate circulating T and B lymphocytes
 - This is achieved by immunofluorescent staining of lymphocytes with monoclonal antibodies. Commonly used antibodies are CD19 and CD20 (for B cells), CD3 (for T cells), CD4 (for subsets of helper T cells), and CD8 (for T-suppressor lymphocytes). However, CD3 and CD8 also are expressed on natural killer (NK) cells. Monoclonal antibodies against CD16, CD56, and CD57, even though they are not lineage specific, may be useful for enumeration of NK cells to distinguish these cells from T cells.
 - Some patients with CVID have low numbers or undetectable peripheral B cells. These patients, especially males, may have atypical XLA and should be studied for mutations of the *Btk* gene. Female patients with agammaglobulinemia and undetectable peripheral B cells may have phenotypic X-linked agammaglobulinemia. Some female patients with agammaglobulinemia were found to have mutations in the μ heavy-chain gene or $\lambda 5$ gene.
- In vitro activation of lymphocytes: To test functional integrity of lymphocytes in a patient, lymphocytes can be isolated and stimulated with variety of agents in vitro.
 - Lymphocytes can be activated in vitro by the followings.
 - Mitogens, such as phytohemagglutinin (PHA) or concanavalin A (Con A), stimulate T cell proliferation. Pokeweed mitogen (PWM) stimulates T and B cell proliferation.
 - Antigens, such as PPD, *Candida*, streptokinase, and tetanus toxoid, can activate lymphocytes if the patient has had a prior encounter with the antigen or with superantigens, such as toxic shock syndrome toxin (TSST).
 - Allogeneic cells stimulate T cell proliferation in mixed lymphocyte culture.
 - Lymphocytes can be activated in vitro by antibodies to T-cell surface molecules involved in signal transduction, such as to CD3, CD2, CD28, and CD43.
 - T-lymphocyte activation can be assessed directly by the following:
 - Assess the expression of activation antigens on T cells, such as CD69, IL-2 receptor α (CD25), transferrin receptors (CD71), and MHC class II molecules (HLA-DR). Detection of activation markers by immunofluorescent or immunohistochemical staining can provide rapid results.
 - Measure blastogenesis and/or proliferation of cells. The blastogenic response to soluble PHA or Con A requires presence of monocytes for stimulation of T cells. PWM stimulates a response to T cells and B cells, although T cells must be present for the B cells to be stimulated. The mixed lymphocyte reaction (MLR) results from T-cell reactivity to MHC antigens displayed on B cells and monocytes. (Note that when normal irradiated or mitomycin C-treated lymphocytes are the stimulators of an MLC, the normal T cells in the culture may secrete factors that induce blastogenesis in the patient's lymphocytes. Therefore, using B-cell lines or T-cell depleted normal cells as the stimulators is preferable. Following in vitro stimulation of B cells with B-cell activators, culture supernatant can be tested for secreted Ig.)
 - Measure the release of cytokines or mediators, such as IL-2, IL-4, IL-5, IL-6, interferon- γ , and TNF, in the culture supernatant.
 - Measure the secretion of immunoglobulin in the culture supernatant.
- Complete blood count and test for autoantibodies: Anemia may be secondary to autoantibodies, severe lymphopenia may raise suspicions that a patient has SCID or other primary T-cell defects, small platelets in an infant boy suggest Wiskott-Aldrich syndrome, and neutropenia or thrombocytopenia may occur secondary to autoantibodies. A variety of organ-specific autoantibody production has been reported in patients with CVID. Tests for autoantibody production should correlate to the patient's presenting symptoms and organ involvement.

Imaging Studies:

- High-resolution computed tomography (CT) of the chest may be more sensitive in monitoring of pulmonary abnormalities in these patients than chest radiographs or pulmonary function tests.

Other Tests:

- Studies for infectious agents: Make every effort to diagnose infections and identify infectious agents. The diagnosis of infection is complex and beyond the scope of this chapter.
- Pulmonary function test: All patients who are able to perform forced expiratory maneuvers, usually those older than 6 years, should have periodic monitoring of pulmonary function.

Procedures:

- Bronchoscopy or endoscopy may be necessary for diagnosis of specific lesions or infectious process.

Histologic Findings:

- Lymph node biopsy: Typical histologic findings of lymph nodes from patients with CVID are reactive follicular hyperplasia, atypical hyperplasia, or granulomatous inflammation.
- Intestinal biopsy: Histology of intestine may demonstrate villous atrophy or infection with cryptosporidia or *Giardia lamblia*. Presence or absence of plasma cells in the submucosal tissue can be examined by hematoxylin and eosin (H and E) stain, and immunohistologic stain may be informative. Lymphoid cells are found in intestinal submucosa of normal infants older than 15-20 days.

Staging: Malignancies complicating CVID are staged by conventional guidelines for immunocompetent patients.

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Medical Care: Ig replacement therapy has decreased the frequency of life-threatening infections in these patients significantly. If replacement therapy is started early, and if appropriate amounts are given with sufficient frequency, the cycle of recurrent infections and progressive lung damage can be arrested. Currently available intravenous Ig (IVIG) products in the United States are derived from pooled human plasma. The manufacturing processes include cold ethanol fractionation of Ig and viral inactivation steps.

- In most clinics, Ig replacement is administered intravenously on a regular basis. Tailor dose and frequency to the Ig trough levels and to clinical symptoms.
 - Measure serum IgG before each infusion and adjust the dose of IVIG accordingly. Maintain trough serum IgG concentrations at 400-500 mg/dL in adults, a value close to the lower limit of normal. For most patients, a dose of 400-600 mg/kg every 3-4 weeks suffices to reduce frequency of infection.
 - Some patients with chronic lung disease require up to 600-800 mg/kg per month. The half-life of IgG is highly variable among patients with CVID, but it usually is longer than 18-23 days in healthy individuals. Once established on a regular regime, IVIG can be administered at home.
- Subcutaneous infusion of Ig (SCIG) is an alternative method for patients with difficult venous access. SCIG, at a dose of 160 mg/kg per week, can raise the level of IgG comparable with those obtained with IVIG at a dose of 400-600 mg/kg per month.
 - The SCIG is well accepted by patients and is mostly done at home; furthermore, the risk of infusion reactions is even less than that for IV infusions. SCIG was well tolerated in patients who had a history of severe reactions to IVIG infusions with the same product.
 - SCIG therapy has not been widely accepted in the United States because of the limitation in volume of Ig administration and the increased frequency of infusions, especially for older children. Intramuscular immunoglobulin for intramuscular use (16.5%) is used in Europe to reduce volume of SC injection. However, IMIG is in short supply in the United States and contains thimerosal, a mercury preservative. Therefore, it is recommended to use preservative-free IVIG (10%) preparation by clysis. Stiehm et al reported minimal local and systemic effects using 3 different brands of 10% IVIG for SC infusion without discernible differences.
 - Another concern is potential transmission of blood-borne pathogens. Concentrated IM preparations that have not undergone viral inactivation steps are used for SCIG therapy. With development of a specific virus-inactivated SCIG preparation, this method may be used more widely.
- Adverse reactions to IVIG include nonanaphylactic reactions, anaphylactic reactions, and transmission of infectious agents.
 - Nonanaphylactic reactions
 - These are the most common reactions to IVIG and manifest by backache, nausea, chills, low-grade temperature, or vomiting within the first 30 minutes of infusion. Headache, chills, fever, myalgia, and fatigue may begin at the end of the infusion and continue for several hours. Slowing the infusion rate or interrupting the infusion for a few minutes can prevent most of these reactions. Febrile or phlogistic reactions are thought to be secondary to immune aggregates that fix complement, either IgG aggregates or IgG-antigen, complexes.
 - These reactions tend to occur more frequently in patients with severe hypogammaglobulinemia, particularly at the

initiation of treatment, and in those with intercurrent infections or bronchiectasis.

- These symptoms may be treated with acetaminophen, diphenhydramine, and/or hydrocortisone. To minimize the risk of these reactions, treat or eradicate preexisting infection before administering IVIG for the first time or after a hiatus in therapy. Initiate therapy with one-half the calculated dose of IVIG and then repeat the dose 2 weeks later before going to a 3- to 4-week schedule. Alternatively, premedication with antipyretics, diphenhydramine, and/or corticosteroids may be given.

○ Anaphylactic reactions

- True anaphylactic reactions to IVIG are rare. Patients who have sIgAD or CVID with undetectable IgA may develop IgE antibodies against IgA, following exposure to serum IgA. These patients may develop anaphylactic reactions during subsequent IVIG administrations. Exercise caution during IVIG administration to patients with CVID, particularly those with no detectable IgA.
- Reactions caused by fluid volume, salt, or protein overload may be problematic for patients with cardiovascular limitations, particularly at higher doses. Closely monitor these patients during and after infusions, administer diuretics if necessary.

○ Transmission of infectious agents

- In 1993 and 1994, transmission of hepatitis C virus was reported in recipients of 1 of 2 IVIG products that did not undergo viral inactivation steps during manufacturing. All IVIG products currently marketed in the United States now undergo viral inactivation steps using cold ethanol fractionation and additional viral inactivations steps such as pasteurization or solvent/detergent treatment. No case of HIV infection has resulted from treatment with IVIG because retroviruses are inactivated by the cold ethanol precipitation. Additional viral inactivation steps used by different manufacturers include treatment with organic solvents and detergents, pasteurization, and storage at low pH.
- Acute and chronic renal failure has been reported, most often in patients with preexisting renal disease who received sucrose-containing IVIG solutions. Other rare reactions to IVIG include aseptic meningitis, lymphocytic pleural effusion, thromboembolism, and coagulopathy.

- Most CVID patients with sinopulmonary disease without severe bronchiectasis do well once they are placed on regular IVIG therapy. However, silent progression of bronchiectasis was reported in a small number of patients while receiving adequate IVIG replacement therapy.
- Most patients with CVID and arthritis report reduced arthritic symptoms once they are placed on regular IVIG replacement therapy.
- Gastrointestinal diseases associated with CVID, with a few cases of ulcerative colitis, did not benefit from regular infusion (even high dose) of IVIG.
- However, in some patients with severe autoimmune process, steroids or other immunosuppressive drugs may be needed. Use these drugs with caution and only in patients who have autoimmune disorders that cause significant clinical disease. In general, a short course of steroid therapy is well tolerated. Use of cyclosporin A with favorable outcome in a patient with CVID and lymphoid interstitial pneumonitis has been reported. Successful treatment of autoimmune thrombocytopenia and neutropenia using anti-CD20 monoclonal antibody administration was reported.
- An experimental preparation of IL-2 conjugated with polyethylene glycol (PEG) was administered to a select group of patients with CVID because of the observation that lymphocytes from a subgroup of patients with CVID, when activated in vitro, produce markedly decreased amounts of IL-2. After several months of therapy, a significant increase was noted in in vitro Ig production by patients' B lymphocytes, in vitro IL-2 production, and serum antibodies. Long-term outcomes of this therapy remain to be seen.
- Specific therapy directed to involved organs should be based on clinical manifestations and nature of the disease (ie, CVID patients with chronic lung disease frequently manifest airway obstructive disease indistinguishable from asthma. These patients may require inhaled corticosteroids and other long-term asthma medications along with PRN albuterol therapy.
- Infections should be treated early with full doses of antimicrobial agents. Whenever possible, narrow-spectrum drugs should be used on the basis of microbial sensitivity testing. Prophylactic antibiotics should be avoided because they increase the hazard of infection with fungi or other resistant organisms. Antiviral agents may be useful in some patients with persistent or severe viral infections.

Surgical Care: Often, patients with CVID need a surgical procedure for treatment of complications (eg, endoscopic sinus surgery for chronic sinusitis. Some patients required splenectomy secondary to severe autoimmune thrombocytopenia or hemolytic anemia. Postoperative complications include sepsis and fistula. Rapidly enlarging lymph nodes should be biopsied to rule out infection or malignancy.

Consultations: CVID patients with multiple organ system involvement may benefit from a multidisciplinary team of consultants.

Diet: CVID patients with chronic lung disease may require a high-calorie diet supplementation because of high-energy expenditure. Patients with chronic enteropathy may require an elemental diet.

Activity: Regular physical activity is encouraged.

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Replacement therapy with IVIG in patients with primary immune deficiencies

The overall consensus among clinical immunologists is that a dose of IVIG of 400-600 mg/kg/mo or a dose that maintains trough serum IgG levels greater than 500 mg/dL is desirable. Patients (X-linked agammaglobulinemia) with meningoencephalitis require much higher doses (1 g/kg) and perhaps intrathecal therapy. Measurement of preinfusion (trough) serum IgG levels every 3 months until a steady state is achieved and then every 6 months if the patient is stable may be helpful in adjusting the dose of IVIG to achieve adequate serum levels. For persons who have a high catabolism of infused IgG, more frequent infusions (eg, q2-3wk) of smaller doses may maintain the serum level in the reference range. The rate of elimination of IgG may be higher during a period of active infection; measuring serum IgG levels and adjusting to higher dosages or shorter intervals may be required.

For replacement therapy for patients with primary immune deficiency, all brands of IVIG are probably equivalent, although there are differences in viral inactivation processes (eg, solvent detergent versus pasteurization and liquid versus lyophilized). The choice of brands may be dependent on the hospital or home care formulary and the local availability and cost. The dose, manufacturer, and lot number should be recorded for each infusion in order to review for adverse events or other consequences. Recording all side effects that occur during the infusion is crucial. Monitoring liver and renal function test results periodically, approximately 3-4 times yearly, is also recommended. The FDA recommends that for patients at risk for renal failure (eg, those with preexisting renal insufficiency, diabetes, volume depletion, sepsis, paraproteinemia, those older than 65 y, and those who use nephrotoxic drugs), recommended doses should not be exceeded and infusion rates and concentrations should be the minimum levels that are practicable.

The initial treatment should be administered under the close supervision of experienced personnel. The risk of adverse reactions in the initial treatments is high, especially in patients with infections and those who form immune complexes. In patients with active infection, infusion rates may need to be slower and the dose halved (ie, 200-300 mg/kg), with the remaining dose given the next day to achieve a full dose. Treatment should not be discontinued. After achieving normal serum IgG levels, adverse reactions are uncommon unless patients have active infections.

With the new generation of IVIG products, adverse effects are much reduced. Adverse effects include tachycardia, chest tightness, back pain, arthralgia, myalgia, hypertension or hypotension, headache, pruritus, rash, and low-grade fever. More serious reactions are dyspnea, nausea, vomiting, circulatory collapse, and loss of consciousness. Patients with more profound immunodeficiency or patients with active infections have more severe reactions.

Anticomplementary activity of IgG aggregates in the IVIG and the formation of immune complexes are thought to be related to the adverse reactions. The formation of oligomeric or polymeric IgG complexes that interact with Fc receptors and trigger the release of inflammatory mediators is another cause. Most adverse reactions are rate related. Slowing the infusion rate or discontinuing therapy until symptoms subside may diminish the reaction. Pretreatment with ibuprofen (5-10 mg/kg q6-8h), acetaminophen (15 mg/kg/dose), diphenhydramine (1 mg/kg/dose), and/or hydrocortisone (6 mg/kg/dose, maximum 100 mg) 1 hour before the infusion may prevent adverse reactions. In some patients with a history of severe side effects, analgesics and antihistamines may be repeated.

Acute renal failure is a rare but significant complication of IVIG treatment. Reports suggest that IVIG products using sucrose as a stabilizer may be associated with a greater risk for this renal complication. Acute tubular necrosis, vacuolar degeneration, and osmotic nephrosis are suggestive of osmotic injury to the proximal renal tubules. The infusion rate for sucrose-containing IVIG should not exceed 3 mg sucrose/kg/min. Risk factors for this adverse reaction include preexisting renal insufficiency, diabetes mellitus, dehydration, age older than 65 years, sepsis, paraproteinemia, and concomitant use of nephrotoxic agents. For patients at increased

risk, monitoring blood urea nitrogen and creatinine before starting the treatment and prior to each infusion is necessary. If renal function deteriorates, the product should be discontinued.

IgE antibodies to IgA have been reported to cause severe transfusion reactions in IgA-deficient patients. There are a few reports of true anaphylaxis in patients with selective IgA deficiency and common variable immunodeficiency who developed IgE antibodies to IgA after treatment with immunoglobulin. In actual experience, however, this is very rare. In addition, this is not a problem for patients with X-linked agammaglobulinemia (Bruton disease) or severe combined immunodeficiency (SCID). Caution should be exercised in those IgA deficient patients (<7 mg/dL) who need IVIG because of IgG subclass deficiencies. IVIG preparations with very low concentrations of contaminating IgA are advised (see Table 1).

Table 1. Immune Globulin, Intravenous

Brand (Manufacturer)	Manufacturing Process	PH	Additives	Parenteral Form and Final Concentrations	IgA Content mcg/mL
Gammagard S/D (Baxter Bioscience)	Cohn-Oncley cold ethanol fractionation, followed by ultracentrifugation and ion exchange chromatography; solvent detergent treated	6.8	5% solution: 0.3% albumin, 2.25% glycine, 2% glucose	Lyophilized powder 5%, 10%	1.6 (5% solution)
Gamimune N (Bayer)	Cold ethanol fractionation, diafiltration and ultrafiltration; solvent detergent treated	4-4.5	5% solution: 9-11% maltose 10% solution: 0.16-0.24M glycine	Sterile solution 5%, 10%	270
Gammar-P IV (Aventis)	Heat treated pasteurization	6.8	5% solution: 5% sucrose, 3% albumin, 0.5% NaCl	Lyophilized powder 5%	<20
Iveegam EN (Baxter Bioscience)	Cohn fraction II/III; DEAA Sephadex adsorption; PEG precipitation	7	5% solution: 5% glucose, 0.3% NaCl	Lyophilized powder 5%	<10
Polygam S/D (Baxter Bioscience for the American Red Cross)	Cohn-Oncley cold ethanol fractionation, followed by ultracentrifugation and ion exchange chromatography; solvent detergent treated	6.8	5% solution: 0.3% albumin, 2.25% glycine, 2% glucose	Lyophilized powder 5%, 10%	<1.6 (5% solution)

Panglobulin (Swiss Red Cross for the American Red Cross)	Cold alcohol fractionation, filtration	6.6	Per gram of IgG: 1.67 g sucrose, <20 mg NaCl	Lyophilized powder 3%, 6%, 9%, 12%	720
Sandoglobulin (Swiss Red Cross for Novartis)	Cold alcohol fractionation, filtration	6.6	Per gram of IgG: 1.67 g sucrose, <20 mg NaCl	Lyophilized powder 3%, 6%, 9%, 12%	720
Venoglobulin-S (Alpha Therapeutics)	Cohn-Oncley cold ethanol fractionation, followed by PEG fractionation and ion exchange chromatography; solvent detergent treated	5.2-5.8	5% solution: 5% sorbitol, 0.13% albumin 10% solution: 5% sorbitol, 0.26% albumin	Sterile solution 5%, 10%	11-14

†IVIg products containing sucrose are more often associated with renal dysfunction, acute renal failure, and osmotic nephrosis, particularly with preexisting risk factors (eg, history of renal insufficiency, diabetes mellitus, age >65 y, dehydration, sepsis, paraproteinemia, nephrotoxic drugs).

Contents of table adapted from:

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Further Inpatient Care:

- Inpatient care may be necessary for any serious clinical conditions associated with CVID.

Complications:

- See [History](#) for a discussion of complications.

Prognosis:

- The prognosis for patients with CVID is reasonably good unless severe autoimmune disease or malignancy develops, and if IVIG replacement therapy is started early before severe lung damage takes place (see [Mortality/Morbidity](#)).

Patient Education:

- The effort to educate patients and families regarding early signs of infection should be ongoing. The approach in identifying infectious agents and specific antimicrobial therapy needs to be aggressive. The Immune Deficiency Foundation (40 W Chesapeake Avenue, Suite 308, Towson, MD 21204; phone: 800-296-4433; web site: <http://www.primaryimmune.org>) provides information for laypersons and health care providers.

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Medical/Legal Pitfalls:

- Failure to measure ability to produce functional antibodies
- Administration of live viral vaccine, such as oral polio or MMR vaccine
- Failure to recognize and properly treat concurrent autoimmune process or malignancy

Special Concerns:

- Pregnant CVID patients with chronic lung disease and compromised pulmonary function may experience further compromise in pulmonary function, especially in the third trimester. Newborn infants of CVID patients usually are born with a normal IgG level as long as the mother receives adequate IVIG replacement therapy during pregnancy. IgG is actively transported across the placenta during the third trimester.

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NOTE:

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