Chapter 2
Common Variable Immunodeficiency, Hypogammaglobulinemia, and Specific Antibody Deficiency

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Introduction

Antibody deficiencies are a group of primary immune deficiencies caused by defects in B-cell development, B-cell activation, or antibody synthesis. They account for more than half of all diagnosed cases of primary immune deficiencies [1, 2]. Immune deficiencies that are considered primarily antibody deficiencies include agammaglobulinemia (X-linked and autosomal recessive), combined variable immunodeficiency (CVID), specific antibody deficiency (SAD), unspecified hypogammaglobulinemia, transient hypogammaglobulinemia of infancy, selective IgA deficiency, and immunoglobulin class-switch defects. While IgG subclass deficiency has also been recognized as an antibody deficiency, there is some controversy regarding its significance in the absence of associated functional defects in specific antibody production [3]. The focus of this chapter will be on the diagnosis and management of CVID, SAD, and unspecified hypogammaglobulinemia.

There is uncertainty regarding the exact prevalence of CVID; however, it is agreed that it affects at least one in 30,000 persons worldwide [2]. The prevalence of SAD differs between different populations; it has been found to be present in 6–23% of children with recurrent infections [4–7]. In adults, SAD was diagnosed in 12–24% of patients with chronic rhinosinusitis and 8% of patients with recurrent pneumonia [8]. Females have a higher prevalence of antibody deficiencies as compared with males [1]. Complicating prevalence estimates of these conditions is the concern that primary

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immune deficiencies are likely underdiagnosed [1]. Diagnostic delay also occurs, with multiple studies of patients with CVID demonstrating a mean delay ranging from 5 to 9 years between the onset of symptoms and disease diagnosis [9–12].

Classification schema for antibody deficiencies has evolved over time, beginning in 1966 when Rosen and Janeway grouped them by their mode of inheritance [13]. Currently, there has been a focus on classifying CVID subgroups based on B-cell phenotype via flow cytometry [12].

Antibody deficiencies can have infectious and noninfectious disease presentations. While infectious complications are common in all three diseases discussed in this chapter, noninfectious features are common in CVID and are rare in SAD and hypogammaglobulinemia. Overall, these antibody deficiencies have a good prognosis. Morbidity related to infectious complications has decreased drastically after the introduction of immunoglobulin (Ig) replacement [11]. However, noninfectious complications remain a burden and are the major cause of morbidity and mortality in CVID (Table 2.1). These noninfectious symptoms require close monitoring and a multidisciplinary approach.

Table 2.1 Noninfectious complications of CVID

Pulmonary
Lymphocytic interstitial pneumonitis
Nodular lymphoid hyperplasia
Granulomatous lymphocytic interstitial lung disease (GLILD)
Dermatologic
Psoriasis
Vitiligo
Lichen planus
Alopecia
Gastrointestinal
Atrophic gastritis
Gastric carcinoma
Pernicious anemia
Autoimmune enteropathy
Small bowel villous flattening
Primary biliary cirrhosis
Primary sclerosing cholangitis
Rheumatologic
Lupus
Rheumatoid arthritis
Vasculitis
Hematologic
Immune thrombocytopenia
Hemolytic anemia
Autoimmune neutropenia
Evan's syndrome
Lymphoid
Lymphoid hyperplasia
Splenomegaly
Non-Hodgkin's lymphoma

Case Presentation 1

A 2-year-old male with a history of controlled allergic rhinitis and mild intermittent asthma presented to immunology clinic for the evaluation of frequent infections. He had been suffering from frequent upper respiratory infections, including bilateral otitis media, sinusitis, and pharyngitis. His symptoms started when he was 6 months old, and he required antibiotic courses every 2–4 weeks. He had bilateral tympanostomy tubes placed without improvement in symptoms. He did not have a history of pneumonia or skin infections. On physical exam, he was a well-nourished male with bilateral tympanostomy tubes present, pink nasal mucosa without turbinate swelling, and normal lung exam. There was no lymphadenopathy or organomegaly present. His laboratory evaluation showed normal complete blood count (CBC) with differential. He had a low IgA level (<5 mg/dL) but had normal levels of IgG (850 mg/dL) and IgM (29 mg/dL) for his age. His baseline pneumococcal titers (following primary pneumococcal conjugate vaccine series) showed 4 out of 23 serotypes protective (≥1.3 μg/mL), and he had protective titers against tetanus. He received pneumococcal polysaccharide vaccine, and repeat pneumococcal titers 1 month following vaccination were protective against only 8 out of 23 serotypes. A diagnosis of specific antibody deficiency (SAD) was made. He took trimethoprim-sulfamethoxazole prophylaxis for 3 months, and the frequency of infection improved; however, he continued to have a significant burden from infections. Subsequently, he was started on 0.5 g/kg of intravenous immunoglobulin (IVIG) every 4 weeks with control of infections.

Clinical Presentation

Differentiating frequent infections due to common risk factors such as day-care attendance or passive smoke exposure from primary immune deficiency should be based on a detailed history and physical examination. It is crucial to determine the location, timeline, and severity of the infections. On average, a healthy child will have four to six upper respiratory infections per year, and it is typical for children attending day care to have an increased number of infections [14]. Children with intact immune systems typically handle these infections well, either without antibiotics or with rapid resolution of bacterial infections using appropriate antibiotics.

The clinical presentation of hypogammaglobulinemia and specific antibody deficiency consists mostly of increased frequency and severity of sinopulmonary infections as seen in the case above. In contrast, common variable immune deficiency (CVID) is a clinical disease label that encompasses a heterogeneous group of disease presentations. A substantial subset of patients with CVID have noninfectious complications that drive much of the morbidity and mortality related to the diagnosis, while others may have isolated infectious complications without evidence of

immune dysregulation. Patients with hypogammaglobulinemia and specific antibody deficiency will generally present with mild bacterial infections, including sinusitis, bronchitis, and otitis media. Severe infections such as meningitis, sepsis, osteomyelitis, and skin abscesses are rare in SAD. In contrast, patients with CVID are at higher risk of developing pneumonia and invasive infections such as meningitis and sepsis.

Common respiratory organisms implicated in upper and lower respiratory infections in CVID, SAD, and hypogammaglobulinemia include encapsulated bacteria (e.g., *Haemophilus influenzae*, *Streptococcus pneumoniae*) and atypical bacteria (*Mycoplasma* sp.) [9, 15, 16]. These patients are also at risk for recurrent viral infections with common pathogens such as human rhinovirus [17]. Ten to fifteen percent of patients with CVID may have symptoms consistent with allergic asthma, despite negative specific IgE to common aeroallergens [18].

Patients with antibody deficiencies also have an increased incidence of gastrointestinal infections, sometimes resulting in chronic diarrhea and malabsorption. The most common pathogens include *Giardia* spp., *Campylobacter jejuni*, and *Salmonella* spp. However, *Helicobacter pylori*, *Shigella* spp., *Norovirus*, *and Parechovirus* can also be implicated in these diseases [9]. Rarely, patients with CVID can also have recurrent urinary tract infections with *Ureaplasma* spp. [16, 19].

Physical appearance can provide clues regarding disease syndromes that may be associated with antibody deficiencies. These include Down syndrome, Kabuki syndrome, trichohepatoenteric syndrome, and Wolf-Hirschhorn syndrome [20–23]. Structural abnormalities in the nasal, otic, and respiratory pathways should be assessed on physical exam, as may be underlying causes of recurrent sinusitis, otitis media, or pneumonia. On examination of the lungs, localized inspiratory or expiratory wheezes may reveal bronchial obstruction, while crackles or rhonchi may elucidate lung parenchymal damage. Lymphadenopathy or organomegaly are found in some CVID patients. Imaging should be obtained when the diagnosis of bacterial infection is unclear, when structural abnormalities are suspected, and as baseline evaluation for bronchiectasis or interstitial disease in CVID, but it should be used judiciously as patients with CVID have been found to be radiosensitive [24].

Diagnostic Criteria

CVID is largely a clinical diagnosis, and the diagnostic criteria have varied over time and from different sources. The widely accepted definition of CVID is proposed by the International Consensus Document (ICON). It defines CVID as low IgG (compared to age-specific norms) along with either low IgA or IgM (low IgA preferred), and an impaired vaccine response, with other causes of hypogammaglobulinemia being excluded [25]. Clinical manifestations such as infections or autoimmunity are not required for the diagnosis, though most patients will have at least one characteristic manifestation of CVID at the time of diagnosis.

Low functional antibody response to vaccines has to be present for a patient to be diagnosed with CVID, SAD, or hypogammaglobulinemia. The exception to the rule is when a patient is found to have an extremely low IgG level of <100 to 300 mg/dL in the absence of protein-losing enteropathy. Given such low IgG levels, there is a high likelihood of these patients having a clinically significant antibody deficiency and being at risk of severe invasive infections. It is recommended to start immunoglobulin replacement without waiting for the evaluation of immune response to vaccines when the IgG level is extremely low [26, 27].

Hypogammaglobulinemia diagnoses include both transient hypogammaglobulinemia of infancy (THI) and unspecified hypogammaglobulinemia that can persist through adulthood. Maternal IgG is transferred to infants transplacentally and has a half-life of 21 days [28]. Maternally acquired IgG remains in an infant for the first 3–6 months of their life [29]. In some children, there is delayed antibody production and do not develop a normal humoral immune system until early childhood. Due to this delay, they have recurrent upper respiratory infections in infancy and early childhood. The diagnosis of THI is a diagnosis of exclusion and is made after immunoglobulin levels have normalized. In patients with THI, IgG levels normalize at 27 months of age on average, and all THI patients reach normal levels by 59 months. Those patients that have persistent infections and low immunoglobulins past this age are given alternative diagnoses of CVID or unspecified hypogammaglobulinemia. Generally, patients with THI can produce specific antibodies to antigens; however, some may have a suppressed response until 36–48 months [30]. Hypogammaglobulinemia beyond 60 months of age is termed unspecified hypogammaglobulinemia. For this diagnosis, the patient needs to have increased infections consistent with antibody deficiency, along with low IgG levels (normal IgA and IgM levels) and abnormal vaccine response [31].

A patient with recurrent respiratory infections, normal immunoglobulin levels, and abnormal vaccine response to the unconjugated polysaccharide *Streptococcus pneumoniae* vaccine is diagnosed with SAD. Patients with SAD will have a normal response to protein and protein-conjugated polysaccharide vaccines [27]. SAD is often identified in children and may represent a subtle developmental delay of the humoral immune system. As seen with other humoral immune deficiencies, these patients develop infections sometime after 7–9 months of age, once maternal IgG has been lost by the infant [32]. However, the diagnosis cannot be given to patients younger than two years of age as the immune system is unable to respond to polysaccharide antigens before this age. In a study of pediatric patients with SAD by Wolpert et al., 44% outgrew the immune defect, developing normal antibody responses after an average of 3.1 years [33]. Ruuskanen et al. reported eight of ten children with initial diagnosis of SAD eventually responded to revaccination with pneumococcal vaccine [34]. However, SAD has also been described in adult patients [35].

The presence of low total immunoglobulins but intact functional responses to vaccines is not indicative of a primary immune deficiency, and the immunoglobulin levels should be repeated. These patients should be evaluated for other causes of low immunoglobulins such as medications, AIDS/HIV, protein-losing enteropathy, and

nephrotic syndrome. Stool testing for alpha-1-antitrypsin is used to screen for protein-losing enteropathy, and urinalysis is performed when nephrotic syndrome is suspected. Medications commonly known to lead to hypogammaglobulinemia include, among others, anticonvulsants (carbamazepine, phenytoin, valproic acid), antimalarials, chemotherapeutics (gold salts, thiopurines), and anti-B–cell monoclonal antibodies [25, 36]. RT-PCR should be used to evaluate HIV/AIDS, and referral to hematology should be made when bone marrow failure or B-cell lymphoma are suspected.

Laboratory Findings

Initial evaluation for antibody deficiency includes complete blood count (CBC) with differential to screen for lymphopenia, and serum immunoglobulin IgA, IgM, and IgG concentrations along with measurement of T-cell–dependent and –independent vaccine response. If the patient has lymphopenia on CBC with differential or extremely low total serum immunoglobulins, flow cytometry for lymphocyte subsets should be obtained. As mentioned earlier, to be diagnosed with CVID, patients must present with low IgG concentrations associated with either low IgA or IgM concentration. Patients with nonspecific hypogammaglobulinemia have low IgG concentrations with normal IgA and IgM concentrations, while patients with SAD have normal total immunoglobulin levels. It is critical to compare immunoglobulin concentrations to age-specific norms during evaluation [37]. In the EUROclass trial, 24% of the patients diagnosed with CVID had a low IgA level, and 50% had an undetectable level. Low and undetectable IgM levels were present in 49% and 30% of patients with CVID, respectively [12]. Some patients with CVID may also present with elevated IgM levels, and this may be associated with poorer prognosis. In one series, for every 100 mg/dL increase in IgM concentration, there was 16% and 31% higher risk of developing polyclonal lymphocytic infiltrate and lymphoid malignancy, respectively [38].

Vaccine Response

Vaccines are used to gain insight into the functional capacity of the adaptive immune system. Vaccines containing protein, polysaccharide, and protein-conjugated polysaccharide antigens are used for this evaluation. The humoral immune response to a protein vaccine, such as tetanus or diphtheria, and to a polysaccharide vaccine, such as 23-valent unconjugated pneumococcal polysaccharide vaccine, should be assessed during evaluation for immune deficiency. Protein and protein-conjugated polysaccharide vaccines produce T-cell–dependent antibody responses, while polysaccharide vaccines produce T-cell–independent immune responses, which are weaker and more short-lived.

Protein antigens in protein and protein-conjugated polysaccharide vaccines are presented by dendritic cells to CD4+ T cells via major histocompatibility complex (MHC) class II, leading to helper T-cell activation. These antigens are also recognized by B-cell receptors (BCRs), leading to receptor-mediated endocytosis of the antigen by B cells. These B cells then engage with antigen-specific helper T cells via CD40:CD40L interactions. This T:B cell interaction leads to isotype switching, affinity maturation, and production of memory B cells. Polysaccharides, glycolipids, and nucleic acids cannot be presented to T cells via MHC molecules; hence, T-cell help is not engaged when developing an antibody response to these antigens. These non-protein antigens are multivalent and instead lead to B-cell activation through BCR crosslinking. B-cell activation can be further enhanced by complement proteins and toll-like receptors in this T-cell–independent antibody response, there are low levels of isotype switching: no affinity maturation and limited memory B-cell production [39].

There are two types of pneumococcal vaccines: 23-valent unconjugated pneumococcal polysaccharide vaccine (PPV23) and pneumococcal conjugate vaccine (PCV13). PPV23 formulation contains 23 serotypes of pneumococcal polysaccharide capsule: 1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20, 22F, 23F, and 33F. The PCV13 vaccine includes serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, and 19F. Conventionally, unconjugated polysaccharide vaccines such as PPV23 are reserved for ages 2 and older [40]. However, some data suggest that infants over the age of 6 months can produce an adequate response to polysaccharide antigens [41, 42].

Specific antibody responses are measured 4–8 weeks following vaccination. When using PPV23, specific antibodies to at least six serotypes only present in PPV23 (not common to PCV13) should be checked. There have been controversies surrounding what constitutes an adequate response to PPV23 vaccination. An adequate serotype-specific titer to prevent invasive pneumococcal disease following PPV is considered to be ≥1.3 μg/mL [27]. Most immunocompetent patients will have a twofold increase in antibody titers from baseline in response to vaccination. However, the higher the pre-vaccination titers, the lesser the magnitude of increase after vaccination. Expert opinion suggests that a normal response to PPV23 for children 2–5 years old is conversion of 50% or more serotypes with at least a twofold increase in the titers. For patients ages 6–65 years, a normal response is considered to be conversion of at least 70% of serotypes with at least a twofold increase in the titers [27]. If normal response is not achieved, repeat doses of PPV23 vaccine in close succession are not recommended as it can lead to a diminished response to the vaccine [27].

SAD can be classified into phenotypes based on degree of response to the unconjugated PPV23 vaccine. For patients less than 6 years of age, a response of ≤2 protective antibody titers is considered to be a severe phenotype, <50% of serotypes protective is considered a moderate phenotype, and failure of a twofold increase in 50% of serotypes is considered mild phenotype. For patients over 6 years of age, a response of ≤2 protective titers is considered severe, <70% of serotypes protective is considered moderate, and failure of a twofold increase in 70% of serotypes is considered mild. For all patients, loss of response within 6 months following

vaccination is considered to be a memory-deficient phenotype of specific antibody deficiency [27].

Other vaccines can also be used in the assessment of humoral immune deficiency in place of pneumococcal and tetanus vaccines. *Haemophilus influenzae* type b conjugate, meningococcal conjugate, pneumococcal conjugate, and rabies vaccines can be used to assess T-cell–dependent responses. The coupling of saccharides to proteins converts the polysaccharides to T-cell–dependent antigens, which are capable of eliciting a more robust B-cell immune response. In contrast, unconjugated meningococcal polysaccharide vaccine can be used to assess T-cell–independent responses. Alternatively, isohemagglutinin titer concentrations can also be used to check for IgG and IgM polysaccharide-specific antibody responses [43]. It is also possible to measure antibody function in an opsonophagocytic assay as wells as antibody avidity; however, these tests are not commercially available [44, 45].

Case Presentation 2

A 6-year-old female with a history of asthma and chronic rhinitis developed chronic vomiting, iron deficiency anemia, and hypoalbuminemia. Endoscopy and colonoscopy demonstrated nodularity in the gastric bulb, gastric antrum, esophagus, ileum, and colon. Pathology was significant for multiple lymphoid nodules in the GI tract and eosinophils in the distal esophagus and stomach. She had an infectious history of frequent otitis media, bronchitis, sinusitis, and pneumonia, but never exhibited severe enough infections that warranted hospitalization.

Her CBC with differential was significant only for microcytic anemia. Immunoglobulin levels were IgG 239 (nl 591–1597), IgA 22.6 (nl 52–329), and IgM 38 (nl 28–115). She had protective antibody responses against rubella and tetanus but was not protected against measles, despite being up-to-date on vaccinations. Her baseline pneumococcal titers were 0/23 protective, and her titers 1-month post-PPV23 were again 0/23 protective. Flow cytometry for lymphocyte subsets showed normal numbers of CD4, CD8, CD3, CD19, and NK cells, but B-cell phenotyping revealed low switched memory B cells (1.8%) (Table 2.2). She was diagnosed with CVID and was started on IVIG 0.6 g/kg every 4 weeks, with the improvement of

Table 2.2 B-cell subpopulation surface markers

B-Cell Subpopulation	B-Cell Surface Markers
Mature naïve B cell	CD27−
Activated B cell	$CD21^{lo}CD38^{lo}$
Marginal zone B cell	CD27+ IgM+ IgD+
Switched memory B cell	CD27+ IgG+ IgM− IgD−
Transitional B cell	$CD38^{hi}IgM^{hi}$
Plasmablast	$CD38^{hi}IgM-$
Plasma cell	CD27+, CD138+

Data from [12, 39]

infections. Her gastrointestinal symptoms also improved, with resolution of vomiting, and her laboratory abnormalities including anemia and hypoalbuminemia normalized. Due to clinical improvement in the gastrointestinal symptoms, her family declined further colonoscopy. A commercial genetic testing panel for genes implicated in CVID and CVID-like diseases showed a known pathogenic heterozygous mutation in *TNFRSF13B* (TACI).

Clinical Presentation

Although recurrent or persistent infections are the most common presentation of antibody deficiencies, noninfectious diseases cause a higher morbidity. In the case above, the evaluation of immune deficiency was prompted by nodular lymphoid hyperplasia in the gastrointestinal tract. The patient suffered from sinopulmonary infections as well, but her significant disease burden was resultant of gastrointestinal pathology. Noninfectious complications can include autoimmune, lymphoproliferative, and granulomatous diseases (see Table 2.1). These noninfectious diseases are common in CVID, and though they can also occur in SAD, THI, or hypogammaglobulinemia, these occurrences are relatively rare [46, 47]. Pulmonary, gastrointestinal, or hematologic manifestations are the most common noninfectious complications in CVID. Since these complications might be the presenting symptoms in some cases of CVID, it is essential they are recognized. It has been noted that patients presenting with only autoimmune disorders have a greater delay in the diagnosis of CVID than those presenting with recurrent infections [38].

Respiratory Disease

Thirty percent of patients with CVID suffer from noninfectious respiratory disease. This occurs equally in males and females [48]. Noninfectious pulmonary complications are challenging to treat and persist after the resolution of infections post-initiation of immunoglobulin replacement therapy.

Bronchiectasis occurs in 11% of patients with CVID and is associated with reduced survival. It is thought to be secondary to recurrent lower respiratory tract infections as opposed to immune dysregulation [38, 48]. Recurrent respiratory infections can also lead to restrictive or obstructive pulmonary disease. On computed tomography (CT) scans, patients with CVID can have nodular, reticular, fibrotic, or ground glass changes. These nodules could be scars, lymphoid collections, or granulomatous infiltrates [49].

Granulomatous and lymphocytic interstitial lung disease (GLILD) is a serious pulmonary manifestation of CVID characterized by granulomatous and lymphoproliferative histopathologic patterns. These include noncaseating granulomas, lymphoproliferative interstitial pneumonia, follicular bronchiolitis, and lymphoid

hyperplasia. Patients with GLILD usually present with cough, sputum production, and dyspnea. The pulmonary function test shows a restrictive pattern with decreased CO diffusion capacity. GLILD is also found to be associated with splenomegaly [50]. In a small study of nine patients with GLILD, the human herpesvirus 8 genome was detected in biopsies of 80% of the patients with GLILD versus 5% in the control group [51].

Gastrointestinal Disease

Gastrointestinal complications in CVID can include abnormal liver function tests, chronic gastritis, nodular lymphoid hyperplasia, chronic liver disease, villous atrophy, and inflammatory bowel disease. Chronic gastritis in CVID can be associated with *H. pylori* infection or atrophic gastritis [52, 53]. A T-cell–mediated process is implicated in the pathogenesis of atrophic gastritis in CVID instead of autoantibodies to parietal cells or intrinsic factor [53]. Patients with CVID suffer from enteropathy, which is similar to celiac sprue; however, it is insensitive to gluten withdrawal. These patients have villous atrophy on biopsy, and it is associated with malabsorption, weight loss, diarrhea, hypoalbuminemia, anemia, and low CD4+ T cells [54].

Chronic diarrhea is the most common gastrointestinal manifestation of CVID, and while some cases can be related to infection with *Giardia*, Norovirus, or other pathogens, diarrhea in CVID may also be noninfectious. Findings can include steatorrhea, achlorhydria, pernicious anemia, or small intestinal abnormalities [55]. Eight percent of patients with CVID have intestinal nodular lymphoid hyperplasia [11]. Along with malabsorption, diarrhea, and weight loss, nodular lymphoid hyperplasia is associated with mucosal flattening and can cause intestinal obstruction due to large nodules. The etiology is unknown but is thought to be a compensatory mechanism to the antibody deficiency [52].

Around 40% of the patients with CVID have abnormal liver function tests, with an increased level of alkaline phosphatase being the most common abnormality. Liver pathology in CVID can occur secondary to viral infection, granulomatous infiltrative disease, or nodular regenerative hyperplasia, leading to non-icteric portal hypertension [56]. Some patients with CVID have also been found to have unexplained hepatomegaly [38].

Autoimmune Disease

It has been estimated that 22–29% of the patients with CVID have one or more autoimmune manifestations. The most common manifestations are autoimmune cytopenias [9, 10, 25, 48]. Cytopenias are present in 12–20% of the patients with CVID [12, 38], and idiopathic thrombocytopenia, autoimmune hemolytic anemia, or both (Evan syndrome) are present in 64%, 25%, and 11% of these patients,

respectively. Other autoimmune manifestations include vitiligo, psoriasis, pernicious anemia, atrophic gastritis, hypothyroidism, thyroiditis, seronegative arthritis, antinuclear antibody-positive connective tissue like disease, and diabetes [12]. Some patients with THI have also been noted to exhibit autoimmunity [46].

Lymphoproliferative Disease

Patients with CVID are susceptible to neoplastic and non-neoplastic lymphoproliferative disease. Non-neoplastic lymphoproliferative disease is secondary to polyclonal lymphocytic infiltration in lymph nodes, the spleen, lungs, and gastrointestinal tract but may manifest as unexplained granulomas [38]. Splenomegaly can be present in 40% of patients, while lymphadenopathy is present in 26% of the patients with non-neoplastic lymphoproliferative disease. There is no difference in sex, age at onset, or age at diagnosis in patients with or without splenomegaly or lymphadenopathy [12]. Splenomegaly is associated with many other complications of CVID, including cytopenia, hepatomegaly, granulomas, and solid organ autoimmunity [38]. Granulomatous disease can present in the lungs, bone marrow, spleen, liver, and gastrointestinal tract. It is often associated with an increased incidence of autoimmune disease and is often confused with sarcoidosis [12, 57].

Malignancies

Patients with antibody deficiency have increased incidence of hematologic and solid organ malignancies. Common hematologic malignancies associated with CVID includes non-Hodgkin's lymphoma and lymphoma of mucosal-associated lymphoid tissue. Solid organ tumors can include breast, prostate, ovary, skin, and colon cancers [9]. Non-neoplastic lymphoproliferative disease is a risk factor for developing B-cell malignancies. In 1985, the incidence of stomach cancer in patients with CVID was thought to be 47-fold higher than in the general population [47]. However, recent studies show that the relative risk in patients with CVID is closer to 10-fold greater than in the general population. This risk is independent of pernicious anemia or *H. pylori* infection [58, 59].

Good Syndrome

In the differential diagnosis of CVID and unspecified hypogammaglobulinemia, it is important to recognize a subset of patients with Good syndrome, who have adult-onset hypogammaglobulinemia or agammaglobulinemia associated with thymoma. Along with low IgG levels, it is common for these patients to have low IgA and IgM

levels. These patients present with sinopulmonary infections similar to CVID; however, they are also at risk for opportunistic infections including mucocutaneous candidiasis, severe varicella infection, *Pneumocystis carinii*, cytomegalovirus, and recurrent herpes simplex virus. CT of the chest is required for the diagnosis. Similar to CVID, Good syndrome also presents with noninfectious complications, including autoimmune diseases, which are mostly cytopenias. These patients also suffer from chronic diarrhea of unknown etiology. However, unlike CVID, Good syndrome is not associated with lymphadenopathy or splenomegaly [60, 61].

Laboratory Findings

Flow Cytometry

Flow cytometry for lymphocyte subsets is not part of the typical evaluation of unspecified hypogammaglobulinemia or SAD. However, it is an important tool for CVID subclassification. In patients with CVID, most have B cells within the normal limits. However, <10% of patients diagnosed with CVID can have <1% B cells, and in these patients, evaluation for mutations associated with X-linked or autosomal recessive agammaglobulinemia is essential. While the majority of patients with CVID have a normal number of T cells and NK cells, about 20% of patients do have some degree of CD4 T-lymphopenia, and decreased naïve T-cell subsets have been demonstrated in patients with CVID [9, 12, 62]. Patients with Good syndrome present with absent or very low B cells, low CD4+ T cells, and reduced in vitro T-cell response to mitogens [61]. While patients with SAD and unspecified hypogammaglobulinemia have normal lymphocyte subsets, rarely patients with THI can have low levels of T cells [63].

In recent years, several CVID classification schemes based on B-cell immunophenotyping have emerged. There are six basic populations of circulating B cells: naive B cells (IgM+ IgD+ CD27−), marginal zone-like B cells (IgM+ IgD+ CD27+), switched memory B cells (IgM− IgD− CD27+), transitional B cells ($CD38^{hi}IgM^{hi}$), activated B cells ($CD21^{lo}CD38^{lo}$), and switched plasmablasts ($CD38^{hi}IgM-$) (see Table 2.2). Their role in pathogenesis of CVID has not been defined, but some associations with different phenotypes have been observed. More than 80% of the patients with CVID have a percentage of switched memory B cells below the normal range (nl 6.5–29.2% of total B cells), with 58% of CVID patients having very low switched memory B cells (≤2% of total B cells; smB−). About 15% of the patients had expansion of transitional B cells (≥9% of total B cells; tr^{hi}), and most of these were associated with low marginal zone-like B cells. About 76% of the patients with CVID had increased levels of $CD21^{lo}$ B cells [12].

The EUROclass classification (Fig. 2.1) is the most recent CVID classification schema utilizing B-cell subsets. It incorporates features from previous classifications (Freiburg and Paris) [12, 64, 65], and identified associations between

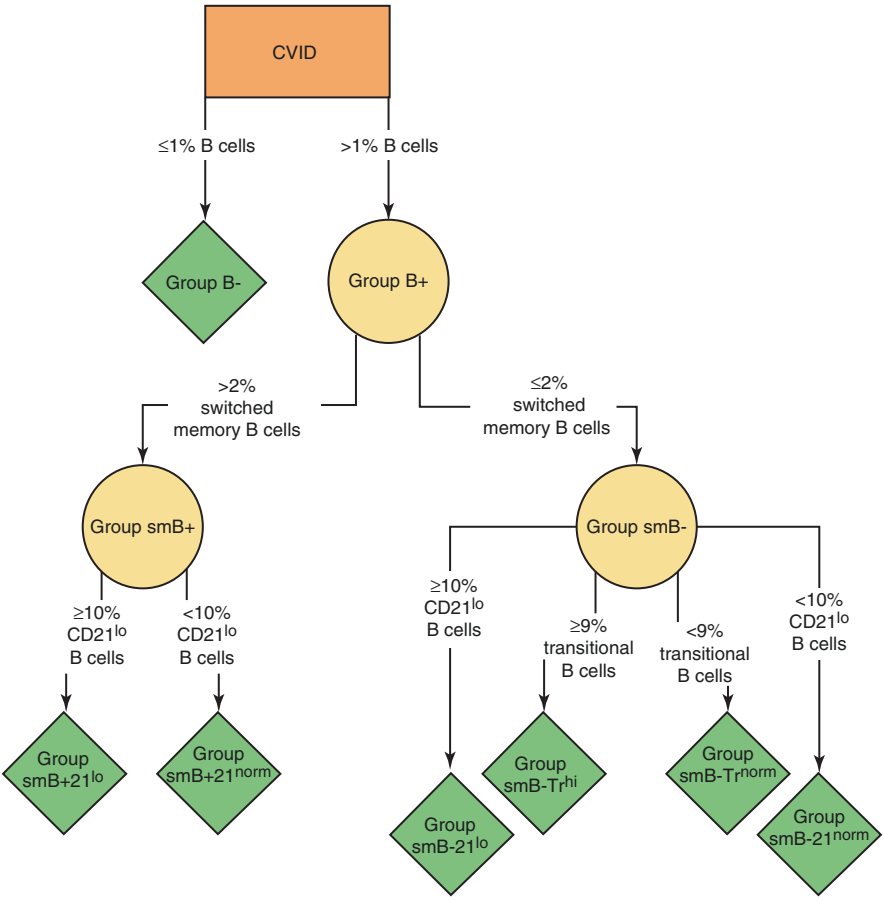

Fig. 2.1 B-cell subsets in CVID. EUROclass classification divides patients into the following subgroups: B- (<1% B-cells), group smB+ 21^{lo} (>2% switched memory B cells and ≥10% $CD21^{lo}$ B cells), smB+ 21^{norm} (>2% switched memory B cells and <10% $CD21^{lo}$ B cells), smB-21^{lo} (≤2% switched memory B cells and ≥10% $CD21^{lo}$ B cells), smB−21^{norm} (≤2% switched memory B cells and <10% $CD21^{lo}$ B-cells), smB-Tr^{hi} (≤2% memory B cells and ≥9% transitional) and smB-Tr^{norm} (≤2% switched memory B cells and <9% transitional) [12]

clinical parameters and various imbalances in B-cell subsets. Incidence of splenomegaly and granulomatous disease was higher in the group of patients with ≤2% switched memory B cells (smB−) versus >2% switched memory B cells (smB+). In the smB− group, splenomegaly and granulomatous diseases were seen in 52% and 17% of patients, respectively. Furthermore, a subgroup of patients with ≥10% B cells with low expression of CD21 activated B cells ($CD21^{lo}$) had increased incidence of splenomegaly, independent of whether they were in the smB− or smB+ group. The incidence of lymphadenopathy was highest (57%) in patients with low switched memory B cells and high transitional B cells (smB−tr^{hi}) [12].

A study by Carsetti et al. compared patients with recurrent pneumonia and bronchiectasis with patients without lung disease and found a lack of IgM memory B cells in patients with recurrent infections. Furthermore, these patients were not able to develop anti-pneumococcal polysaccharide IgM. Evident from this study is that IgM memory B cells are required for immune response to encapsulated bacteria and seem to be decreased in patients with increased infections [66].

Decreased switched memory B cells have been observed in patients with SAD as well [46, 67]. In a study of patients with THI, Moschese et al. found that children with lower IgM levels or switched memory B cells were more likely to have persistence of immune deficiency [46].

Genetic Testing

The majority of patients with CVID have no history of affected family members. However, 10–20% of patients have one or more family members with either CVID or a more subtle antibody deficiency, such as selective IgA deficiency [68]. There are currently no known mutations for SAD or unspecified hypogammaglobulinemia. The genetic cause of CVID is unknown in a majority of cases. However, broader availability of genetic testing has recently led to increasing identification of causative mutations in patients with CVID-like disease. The most common genetic mutation in CVID includes mutation in one of the alleles of *TNFRSF13B*. It has been found to occur in 9–21% of patients with CVID [64, 65]. *TNFRSF13B* encodes TNF receptor superfamily 13B that encodes transmembrane activator and CAML interactor (TACI). TACI is involved in class-switch recombination to IgG and IgA. B-cell activating factor (BAFF) and a proliferating inducing ligand (APRIL), produced by monocytes and dendritic cells, bind to TACI and BAFF-R, leading to isotype switching. Patients with TACI polymorphism have been found to have either IgA deficiency or CVID [64]. After genetic analysis, some patients with symptoms initially attributed to CVID are found to have X-linked agammaglobulinemia, X-linked lymphoproliferative disorder, or immunoglobulin class-switch defects.

Patients with predominantly noninfectious complications may have a genetic defect causing a CVID-like primary immune regulatory disease (PIRD). PIRDs present with immune dysregulation including immune cytopenias, enteropathy or colitis, interstitial lung disease, and nonmalignant lymphoproliferation, mirroring many of the noninfectious complications seen in CVID, and hypogammaglobulinemia is a more variable feature of many of these defects. Heterozygous *CTLA-4* mutations cause a disease of immune dysregulation and infectious susceptibility. CTLA-4 is an inhibitory receptor which competes with the CD28 costimulatory receptor on T cells for the binding of CD80/CD86 on antigen-presenting cells (APC), preventing APC activation of conventional T cells. It is also essential for the function of regulatory T cells [69]. The clinical presentation of CTLA-4 often includes severe autoimmune cytopenias, lymphoproliferation and increased risk of lymphoma, enteropathy or inflammatory bowel disease, GLILD, and recurrent infections, with an immune phenotype that may include hypogammaglobulinemia

and CD4 T-lymphopenia [70]. Homozygous *LRBA* mutations result in a phenotype similar to that of CTLA-4 haploinsufficiency. LRBA is a scaffold protein controlling movement of CTLA-4 from endosomes to the cell membrane of T cells. When LRBA is deficient, CTLA-4 is not adequately expressed on the T-cell membrane [71]. The clinical phenotype of LRBA deficiency is variable but may include hypogammaglobulinemia with recurrent infections, hepatosplenomegaly and lymphoproliferation, immune cytopenias, enteropathy, GLILD, and Type I diabetes [72]. Autosomal dominant gain-of-function mutations in *PIK3CD* and *PIK3R1* are the causes of activated phosphoinositide 3-kinase delta syndrome-1 and -2 (APDS-1 and APDS-2), respectively. APDS-1 and -2 present with variable humoral immune deficiency, respiratory infections often with bronchiectasis, herpes virus infections, splenomegaly and lymphadenopathy with increased risk of lymphomas, nodular lymphoid hyperplasia, and frequent autoimmunity [73]. Numerous other rare genetic mutations associated with CVID are summarized in Table 2.3.

Table 2.3 Genetic mutations in CVID

Gene	Inheritance	Notable features
CVID-causing mutations		
ICOS	AR	Autoimmunity, granulomas
TNFRSF13B (TACI)	AD or AR	Variable clinical expression
TNFRSF13C (BAFF-R)	AR	Variable clinical expression
CD19	AR	Possible glomerulonephritis
CD81	AR	Only one identified patient, glomerulonephritis
CR2 (CD21)	AR	Respiratory tract infections
MS4A1 (CD20)	AR	Respiratory tract infections
TNFSF12 (TWEAK)	AD	Only one patient identified
IKZF1 (IKAROS)	AD	Risk of acute lymphocytic leukemia
IRF2BP2	AD	Autoimmunity, inflammatory disease
NFKB1	AD	Alopecia, immune cytopenias, EBV-induced lymphoproliferation
NFKB2	AD (LOF)	Alopecia, endocrinopathies
Primary immune regulatory diseases		
LRBA	AR	Organomegaly, immune cytopenias, enteropathy, hypogammaglobulinemia, GLILD, Type I diabetes
CTLA4	AD	Severe immune cytopenias, hypogammaglobulinemia, lymphoproliferation and risk of lymphoma, enteropathy/colitis, GLILD
PIK3CD	AD	Respiratory bacterial infections, herpesvirus infections, lymphoproliferation and risk of lymphoma, nodular lymphoid hyperplasia

continued

Table 2.3 (continued)

Gene	Inheritance	Notable features
PIK3R1	AD	Respiratory bacterial infections, herpesvirus infections, lymphoproliferation and risk of lymphoma, nodular lymphoid hyperplasia
IL21	AR	Early-onset inflammatory bowel disease
IL21R	AR	Cholangitis, liver disease, *Cryptosporidium*
PRKCD	AR	Multiple autoimmune conditions, lymphoproliferation, variable immunoglobulin levels
PLCG2	AD	Cold urticaria, granulomatous disease, autoimmunity, hypogammaglobulinemia

Data from [64, 70, 72, 73, 82–90]

Management

Standard of care for treatment of CVID is lifelong routine replacement of immunoglobulin (Ig) via intravenous or subcutaneous routes. Most US and international guidelines recommend a starting dose of 400–500 mg/kg/month for intravenous immunoglobulin (IVIG) or 400–600 mg/kg/month for subcutaneous immunoglobulin (SCIG). In patients with bronchiectasis, dosing at 600 mg/kg/month may give better outcomes. Some experts also recommend higher doses of 600–800 mg/kg/month for patients with enteropathy or splenomegaly. There is recent research supporting the consideration of individualization of the Ig dose, focusing on the incidence of breakthrough infections, rather than a standard IgG trough or weight-based Ig dose [74, 75]. Unfortunately, replacement Ig has not been shown to prevent or treat noninfectious inflammatory complications of CVID such autoimmunity, granulomatous disease, or malignancy.

Treatment with prophylactic antibiotics may be trialed as first-line therapy of specific antibody deficiency or hypogammaglobulinemia, before moving on to Ig replacement therapy. However, in addition to the response to antibiotic prophylaxis, severity of infections should be an important factor in the decision to provide Ig replacement therapy. In patients with SAD, a recent AAAAI Work Group paper recommended the following as indications for Ig therapy: difficult-to-manage recurrent otitis media at risk for permanent hearing loss, bronchiectasis, recurrent infections necessitating IV antibiotics, failed antibiotic prophylaxis, impaired quality of life due to recurrent infections despite antibiotic prophylaxis, and multiple antibiotic hypersensitivities interfering with treatment [76]. Patients with initial poor response to the pneumococcal polysaccharide vaccine may clinically benefit from immunization with the conjugate vaccine, though it does not play a role in the diagnosis of SAD.

Dysregulatory features of CVID are often not responsive to treatment with conventional Ig replacement and represent a major challenge in the treatment of patients with CVID. High-dose IVIG is often successful in treating immune thrombocytopenic purpura associated with CVID, but rituximab (anti-CD20 mAb) is the preferred treatment for CVID-associated autoimmune hemolytic anemia [77]. Rituximab has

been trialed for other lymphoproliferative complications of CVID, with variable results, but rituximab combined with azathioprine has become the standard treatment for GLILD [78]. For several CVID-like PIRDs, targeted treatment with biologic therapies have offered new opportunities for treating the dysregulatory complications that are major features of these diseases.

Prognosis

Specific antibody deficiency and unspecified hypogammaglobulinemia are often not lifelong diagnoses, especially when presentation occurs in childhood. Several groups have observed that young children may outgrow specific antibody deficiency and, therefore, recommended holding immunoglobulin (if started) and revaccinating 6–24 months after the initial diagnosis [33, 79]. However, there are also patients that have been found to progress from these milder humoral defects to a more dramatic CVID phenotype.

The prognosis for patients with CVID has improved dramatically in the last 50 years, and these improvements are felt to be due in large part to increasing standard replacement doses of Ig therapy. In a 1971 report, survival to 12 years after diagnosis only occurred in 30% of patients with hypogammaglobulinemia [80]. Twenty-year survival following diagnosis improved to 64% for males and 67% for females by the late 1990s [9]. In some of the most recent literature, there is an expected survival rate of 58% 45 years after diagnosis [38]. Individual prognosis depends on the clinical phenotype of the patient. Those without noninfectious complications have an almost normal life expectancy. However, patients with enteropathy, chronic lung disease, lymphoproliferation, or cytopenias have reduced survival. In a large Italian cohort, overall survival was 35% at 40 years following diagnosis. While no patients with cancer survived beyond 35 years after diagnosis, patients without malignancy had an overall survival of 65% at 40 years [81].

Clinical Pearls and Pitfalls

- Patients with antibody deficiencies can present with infectious or noninfectious complications. Noninfectious complications occur in a substantial subset of patients with CVID and are rare in SAD and non-specific hypogammaglobulinemia.
- Common sites of infection include the sinopulmonary and gastrointestinal tracts. Bacterial respiratory infections are caused by encapsulated and atypical bacteria, while gastrointestinal infections are most commonly caused by *Giardia* sp., *Campylobacter jejuni*, and *Salmonella* sp.
- Noninfectious complications seen in CVID can include chronic lung disease, gastrointestinal disease, autoimmune disease, and lymphoproliferative disease.

- Diagnosis of antibody deficiencies is based on the clinical picture, immunoglobulin levels, and functional immune response to vaccines.
- In patients with CVID, low levels of class-switched memory B cells are associated with increased incidence of splenomegaly, autoimmunity, and granulomatous disease.
- Initial treatment for SAD and hypogammaglobulinemia includes prophylactic antibiotics before immunoglobulin replacement therapy, while immunoglobulin replacement therapy is the first-line treatment for CVID.
- Recommended starting dose of immunoglobulin replacement is 400–500 mg/kg/month for intravenous immunoglobulin (IVIG) or 400–600 mg/kg/month for subcutaneous immunoglobulin (SCIG). Doses may then be adjusted to minimize significant breakthrough infections.
- Immunoglobulin replacement therapy has improved survival for patients with antibody deficiency. Patients with isolated infectious symptoms have a good prognosis, yet patients with noninfectious complications still experience reduced life expectancy.

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