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Humoral Immunodeficiency in Adults: Common Variable Immunodeficiency, IgG Subclass Deficiency, and Specific Antibody Deficiency: A Comprehensive Clinical Review

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Abstract: Humoral immunodeficiencies, particularly common variable immunodeficiency, IgG subclass deficiency, and specific antibody deficiency, represent the most clinically significant primary antibody disorders encountered in adult practice. Common variable immunodeficiency is the most prevalent, characterized by reduced serum immunoglobulin G together with decreased IgA and/or IgM, poor vaccine responses, and the absence of other defined immunodeficiency states. IgG subclass deficiency accounts for approximately 25% of patients presenting with recurrent infections. It is characterized by normal total IgG with decreased levels of one or more IgG subclasses, and impaired vaccine responses. Specific antibody deficiency, previously known as selective antibody deficiency with normal immunoglobulins, is characterized by normal immunoglobulin and IgG subclass levels but an abnormal response to polysaccharide antigens, and is estimated to be the eighth most common primary immunodeficiency. All three conditions present with recurrent sinopulmonary infections and share overlapping clinical features, yet they differ fundamentally in diagnostic criteria, pathophysiology, and therapeutic approach. This comprehensive review synthesizes the clinical features, diagnostic workup, differential diagnosis, and evidence-based management of common variable immunodeficiency, IgG subclass deficiency, and specific antibody deficiency, providing clinicians with a practical framework for the evaluation and treatment of humoral immune defects.

Keywords: common variable immunodeficiency; IgG subclass deficiency; specific antibody deficiency; hypogammaglobulinemia; primary immunodeficiency; polysaccharide antigens

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Introduction

Primary immunodeficiencies are common and frequently go undiagnosed for prolonged periods of time in both children and adults. These delays may result in significant morbidity and possibly mortality. As an example, bronchiectasis is an overlooked presenting manifestation with an incidence as high as 30% in patients with primary antibody deficiencies [1,2]. Clinical suspicion is the key to more timely diagnosis and therapy.

Humoral immunodeficiencies constitute the most common category of primary immunodeficiency disorders and are primarily characterized by defective antibody production. Among these, common variable immunodeficiency (CVID), IgG subclass deficiency, and specific antibody deficiency (SAD) are the most clinically relevant entities in adult medicine.

CVID represents a heterogeneous group of disorders unified by impaired immunoglobulin production, with an estimated prevalence of 1 in 25,000 to 1 in 50,000 individuals [3,4]. Despite being one of the more common primary immunodeficiencies, the average time from symptom onset to diagnosis is 4 to 9 years, reflecting the protean nature of its clinical manifestations and the frequent misattribution of symptoms to other conditions [5].

IgG subclass deficiency is similarly underrecognized. In a study of pediatric patients with immunodeficiency disorders, 17% were diagnosed with IgG2 deficiency, and IgG subclass deficiency overall accounts for approximately 25% of patients presenting with recurrent infections [6,7]. Unlike CVID, IgG subclass deficiency is defined by normal total IgG with decreased levels of one or more subclasses, combined with an inadequate vaccine response [3,8].

SAD represents another frequently overlooked primary immunodeficiency. The diagnosis of SAD requires normal immunoglobulin and IgG subclass levels, with the only immunologic deficiency being an abnormal response to polysaccharide antigens. The incidence of SAD in adults with recurrent infections has been reported to range from 8 to 40% [9,10]. In a recent study by Stabler et al., 39.8% of adults with recurrent or severe infections were diagnosed with an immunodeficiency, and 78.7% of these were diagnosed with SAD [11].

This review provides a clinically oriented synthesis of CVID, IgG subclass deficiency, and SAD, equipping the practicing infectious disease clinician with a unified framework for diagnosis and management.

Part I: Common Variable Immunodeficiency

Definition and Epidemiology

CVID is formally defined as a collection of clinical syndromes characterized by: (1) reduced serum concentrations of IgG in combination with either low IgA, IgM, or both; (2) poor or absent response to immunizations; and (3) the absence of another identified immunodeficiency state that would better account for the hypogammaglobulinemia [4]. The diagnosis is typically made after the age of two years, with bimodal peaks of onset in childhood (ages 5–10) and young adulthood (ages 20–40) [3].

Clinical Presentations of CVID (Table 1)

Recurrent Infections

Recurrent infections are the most common presenting feature of CVID, reported in over 94% of patients [3]. Sinopulmonary infections predominate, with pneumonia occurring in approximately 75% of affected individuals. The responsible organisms typically include encapsulated bacteria such as *Streptococcus pneumoniae* and *Haemophilus influenzae*, as well as *Mycoplasma* species and *Pneumocystis jirovecii*. Gastrointestinal infections are also common and may involve

Campylobacter, *Salmonella*, and chronic parasitic infections including giardiasis, cryptosporidiosis, and norovirus [3,5].

Table 1: Clinical manifestations of CVID.

Category	Key Features	Notes
Recurrent Infections (>94%)	Sinopulmonary (pneumonia ~75%), GI (Campylobacter, Giardia, Norovirus)	Encapsulated bacteria, Mycoplasma, PJP
Chronic Lung Disease (30–50%)	Bronchiectasis (~50%), ILD/GLILD	Restrictive or obstructive pattern
GI Abnormalities (10–20%)	IBD-like, sprue-like, protein-losing enteropathy	Nodular lymphoid hyperplasia, GI lymphoma
Granulomatous Disease	Lymph nodes, liver, spleen, eyes, skin	Often confused with sarcoidosis
Autoimmune Disease	ITP, RA, pernicious anemia, Hashimotos	Vitiligo
Malignancy	Non-Hodgkin lymphoma	Requires long-term surveillance

Chronic Lung Disease

Chronic lung disease is present in 30–50% of patients at the time of CVID diagnosis, underscoring the significant diagnostic delay [7]. Bronchiectasis occurs in approximately 50% of CVID patients and is more prevalent among older individuals [5,7]. Interstitial lung disease (ILD), including the granulomatous–lymphocytic interstitial lung disease (GLILD) variant, tends to present more frequently in younger patients. Pulmonary function testing may reveal either restrictive or obstructive patterns depending on the predominant pathology [5].

Gastrointestinal Abnormalities

Gastrointestinal manifestations affect 10–20% of CVID patients and can mimic a variety of other conditions [3]. These include inflammatory bowel disease-like presentations, protein-losing enteropathy, a sprue-like illness characterized by flat villi (often without anti-tissue transglutaminase antibodies), nodular lymphoid hyperplasia of the small intestine, and gastrointestinal lymphoma [5].

Other Associations

Extrapulmonary granulomatous disease may involve the lymph nodes, liver, spleen, eyes, intestines, and skin, and are frequently confused with sarcoidosis. A key differentiating feature is the presence of hypogammaglobulinemia, which is not characteristic of sarcoidosis [5]. Other notable associations include allergic asthma with a paradoxically low IgE level, cholestatic hepatitis, and a range of autoimmune conditions including immune thrombocytopenic purpura (ITP), rheumatoid arthritis (RA), pernicious anemia, Hashimotos thyroiditis, and vitiligo [3,5]. Additionally, patients with CVID carry an increased risk of non-Hodgkin lymphoma [8].

Part II: IgG Subclass Deficiency

Definition and Clinical Significance

IgG subclass deficiency is a commonly overlooked primary immunodeficiency defined by two required criteria: (1) one or more IgG subclasses below the normal reference range, and (2) an inadequate response to vaccine challenge. Critically, the total IgG concentration must be normal; if total IgG is low, the diagnosis shifts toward CVID [4,12]. Decreased subclass levels alone do not confirm a clinically significant disorder; recurrent infections plus inadequate vaccine response are required. IgG subclass deficiency accounts for approximately 25% of patients presenting with recurrent infections [6].

IgG Subclass Characteristics

The characteristics of IgG subclass deficiencies are summarized below (Table 2).

Table 2: IgG subclass characteristics and clinical associations.

Subclass	% Total IgG	Key Antigens	Infection Risk	Associations
IgG1	>60%	Protein	Evaluate for CVID if low	Rarely isolated
IgG2	~20%	Polysaccharide	*S. pneumoniae*, *H. influenzae*, *N. meningitidis*	AT, IFN-γ deficiency
IgG3	~8%	Protein (M protein)	*M. catarrhalis*, *S. pyogenes*	Chronic bronchitis, bronchospasm
IgG4	~4%	Variable	Often asymptomatic	Often with IgG2 ± IgA deficiency

IgG1 Deficiency

IgG1 constitutes greater than 60% of the total IgG. Isolated IgG1 deficiency is rare because significant reduction typically lowers the total IgG, at which point CVID should be evaluated [12,13].

IgG2 Deficiency

IgG2 represents approximately 20% of the total IgG and is the principal subclass mediating responses to polysaccharide antigens. IgG2 deficiency is more common in children, but in a longitudinal study of 120 children, over 85% had normalized immunoglobulin levels and polysaccharide vaccine responses after 3 years of follow-up [7,13]. Among pediatric patients with immunodeficiency disorders, 17% are diagnosed with IgG2 deficiency [7]. Patients with IgG2 deficiency are at increased risk for infections with encapsulated organisms including *Streptococcus pneumoniae*, *Haemophilus influenzae* type b, and *Neisseria meningitidis*. Associated disease states include ataxia telangiectasia (AT), interferon gamma deficiency, growth hormone deficiency, chronic mucocutaneous candidiasis, and allergic colitis [12,13].

IgG3 Deficiency

IgG3 comprises approximately 8% of the total IgG and is more commonly deficient in adults. It may co-occur with IgG1 deficiency. IgG3 provides protection against *Moraxella catarrhalis* and *Streptococcus pyogenes* via anti-M protein activity and responds primarily to protein antigens. Isolated IgG3 deficiency may therefore show a normal polysaccharide vaccine response [14,15]. Associations include bronchospastic illness, chronic bronchitis, and recurrent lymphocytic meningitis [14].

IgG4 Deficiency

IgG4 constitutes approximately 4% of the total IgG. IgG4 deficiency is not uncommon, but most patients are asymptomatic, making diagnosis challenging. It is commonly associated with IgG2 deficiency with or without concurrent IgA deficiency. Linked disease states are similar to those of IgG2 deficiency, including ataxia telangiectasia, interferon gamma deficiency, growth hormone deficiency, chronic mucocutaneous candidiasis, and allergic colitis [12,13].

Part III: Specific Antibody Deficiency

Definition and Clinical Significance

SAD, previously known as selective antibody deficiency with normal immunoglobulins, represents an important but frequently overlooked primary immunodeficiency. By definition, this diagnosis requires levels of both quantitative immunoglobulins and IgG subsets to be normal [16], as well as a normal response to protein-based and conjugate vaccinations. The only immunologic deficiency in patients with SAD is an abnormal response to polysaccharide antigens, as found in the PPV23 (23-valent pneumococcal polysaccharide vaccine) [9,16].

Clinical Presentations

Recurrent upper respiratory tract infections (URIs) and/or lower respiratory tract infections (LRIs), particularly chronic sinusitis, are the most common clinical presentations of SAD [9]. A more severe and potentially life-threatening presentation is invasive infection with encapsulated organisms such as *Streptococcus pneumoniae*, *Haemophilus influenzae*, or *Neisseria* species. Bronchitis, otitis media, and pneumonia may also be presenting manifestations [10].

Incidence and Epidemiology

The incidence of SAD in adults with recurrent infections has been widely debated in the literature, ranging from 8 to 40% [9,10]. Recently, Stabler et al. studied 118 patients between the ages of 18 and 65 with one of three presentations: (1) two benign URIs or LRIs for at least two years, (2) one severe URI or LRI requiring intravenous antibiotics or hospital admission, or (3) at least one invasive infection (such as meningitis, bacteremia, or arthritis) due to an encapsulated organism [10]. Patients were excluded if they had underlying diseases that could potentially preclude appropriate response to polysaccharide antigens (HIV, diabetes, neutropenia, sickle cell disease, intravenous drug use, splenectomy, or other immunocompromising conditions). In this cohort, 47 patients (39.8%) were diagnosed with immunodeficiency, and 37 (78.7%) of these were diagnosed with SAD [11].

Part IV: Comparative Diagnostic Framework

Distinguishing CVID, IgG Subclass Deficiency, and Specific Antibody Deficiency

Critical clinical skill is differentiating among the primary humoral immunodeficiencies (Table 3). In CVID, total IgG is low along with IgA and/or IgM, and abnormal responses to both polysaccharide and protein vaccines occur [4]. In IgG subclass deficiency, total IgG is normal while one or more subclasses are decreased, with variable responses to polysaccharide and protein vaccines depending on the specific subclass involved [12]. SAD is characterized by normal total IgG and normal subclass levels but an abnormal polysaccharide vaccine response with normal protein vaccine responses [13,16].

Table 3: Comparison of primary humoral immunodeficiencies.

Feature	CVID	SAD	IgG1 Def.	IgG2 Def. ^	IgG3 Def.
Total IgG	Low	Normal	Normal	Normal	Normal
IgA *	Low	Normal	Normal	±	Normal
IgG Subclasses	Variable	Normal	Low IgG1	Low IgG2	Low IgG3
Sinopulmonary Infections	+	+	+	+	+
Polysaccharide Response	Abnormal	Abnormal	Abnormal	Abnormal	±
Protein Vaccine Response	Abnormal	Normal	±	±	±

+ = common; ± = variable; * IgM may also be low; ^ IgG4 deficiency similar to IgG2.

Differential Diagnosis: Excluding Secondary Causes

For CVID, IgG subclass deficiency, and SAD, secondary causes of hypogammaglobulinemia must be systematically excluded before a primary diagnosis is established [4]. Decreased immunoglobulin production may result from medications (glucocorticoids, rituximab, phenytoin, carbamazepine, sulfasalazine), malignancies (chronic lymphocytic leukemia, lymphoma, multiple myeloma), and infections (EBV, CMV, HIV, bone marrow-suppressive infections) [4,12,17].

The differential diagnosis of polysaccharide nonresponse includes [9,11,16]:

- **IgG subclass deficiency:** Most antibodies against bacterial polysaccharides are of the IgG2 subset
- **CVID:** URI, LRI, and gastrointestinal infections with hypogammaglobulinemia
- **Ataxia telangiectasia:** Usually pediatric with neurologic abnormalities, URI, and skin rash
- **Hyper IgE syndrome:** Characteristic facial anomalies and eczema
- **HIV infection:** Decreased polysaccharide response with CD4 suppression
- **Asplenia:** Invasive infections with encapsulated organisms
- **Lymphocytic malignancies:** CLL with hypogammaglobulinemia; lymphoma with immunoglobulin-depleting therapy

Increased immunoglobulin losses occur in protein-losing enteropathies, nephrotic syndrome, and extensive burns [4]. A thorough medication history and evaluation for underlying malignancy are essential components of the diagnostic workup.

Part V: Unified Diagnostic Approach

Clinical suspicion is the single most important factor in the timely diagnosis of humoral immunodeficiency. Given the heterogeneity of presentations, clinicians should maintain a high index of suspicion in patients presenting with:

- Recurrent sinopulmonary or gastrointestinal infections
- Unexplained bronchiectasis
- Extrapulmonary granulomas resembling sarcoidosis (particularly with hypogammaglobulinemia)
- Allergic asthma with a low IgE level
- Chronic giardiasis or cryptosporidiosis
- Autoimmune disease in the context of recurrent infections [4,5]

Systematic 4-Step Clinical Evaluation

Step 1: History and Physical Examination. A thorough history targeting recurrent infections, associated diseases, and family history of immunodeficiency is essential. Sinus imaging should be obtained if recurrent sinusitis is present to rule out anatomic abnormalities [9,12].
Step 2: Laboratory Evaluation. Initial studies should include a complete blood count, comprehensive metabolic panel, HIV testing, quantitative immunoglobulins (IgG, IgA, IgM), IgE, and IgG subsets (1–4). These form the basis for distinguishing CVID (low total IgG) from IgG subclass deficiency (normal total IgG, low subclass) from SAD (normal total IgG and normal subclasses) [4,12,16].
Step 3: Vaccine Challenge. This is a critical component of the evaluation for all three conditions. Baseline antibody titers to both polysaccharide (pneumococcus) and protein antigens (tetanus, diphtheria, H. influenzae) should be obtained, followed by administration of:

- The 23-valent pneumococcal polysaccharide vaccine (PPSV23) to assess T-cell-independent responses
- Protein-based vaccines including tetanus toxoid and diphtheria for T-cell-dependent responses

Titers are rechecked approximately one month after vaccination. At least 70% of titers should reach protective levels to constitute an adequate response (Table 4). For pneumococcal antibodies, protective levels from invasive disease equate to 1.3 mcg/mL. If baseline levels are greater than 1.3 mcg/mL, a two-fold increase in titers is considered a normal response [4,10,18,19]. Low baseline titers have been found to be predictive of SAD [20].

Table 4: Vaccine challenge: protective antibody levels.

Vaccine/Antigen	Type	Protective Level
Pneumococcal (PPSV23)	Polysaccharide	$\geqslant$1.3 mcg/mL
Diphtheria	Protein	>0.01 IU/mL
Tetanus	Protein	>0.1 IU/mL
H. influenzae (Hib)	Protein (conjugate)	>1 mcg/mL

Part VI: Therapeutic Management (Table 5)

Management of CVID

Intravenous immunoglobulin (IVIG) replacement therapy is the cornerstone of CVID management. Multiple studies have demonstrated that IVIG significantly decreases the incidence of infections, reduces the frequency of pneumonia and hospitalizations by more than 50%, and may slow the progression of chronic lung disease [8,21]. The standard initial dose is 400–600 mg/kg administered intravenously every 3 to 4 weeks. Trough IgG levels should be measured at approximately 6 months to guide dose adjustments, with the therapeutic goal of achieving a trough level greater than 50% of the lower limit of the normal reference range [4,21]. Higher dosing regimens (600 mg/kg) may be indicated in patients with continued infections despite standard dosing, established chronic lung disease, protein-losing enteropathy, or during the third trimester of pregnancy [21].

Supportive measures include:

- Prompt and aggressive treatment of acute infections.
- Pulmonary rehabilitation for patients with established lung disease.
- Gastroenterology referral for significant gastrointestinal involvement.
- Surveillance for autoimmune and lymphoproliferative complications.
- Appropriate vaccination strategies for household contacts [4,8].

Table 5: IVIG dosing recommendations.

Parameter	CVID	IgG Subclass Def.	SAD	Notes
Standard Dose	400–600 mg/kg q3–4 weeks	400 mg/kg q4 weeks	400 mg/kg q4 weeks	First-line for CVID; third-line for subclass deficiency and SAD
Dose Escalation	600 mg/kg	600 mg/kg q3 weeks	Variable	For suboptimal response
Trough Monitoring	At 6 months; goal > 50% LLN	Reassess at 6–12 months	Reassess at 6–12 months	May discontinue if subclass normalizes
Special Situations	600 mg/kg in pregnancy (3rd trimester)	Conjugate vaccines if poor polysaccharide response	Conjugate vaccines preferred	

Management of IgG Subclass Deficiency: A Stepwise Approach

Unlike CVID, where IVIG is first line, the management of IgG subclass deficiency follows a stepwise escalation:

First Line: Treat and Vaccinate. Active infections should be treated with appropriate antibiotics. Patients should be vaccinated against likely pathogens. If poor polysaccharide response is documented, conjugate vaccines (Pneumococcal conjugate vaccine, Hib) should be used instead of polysaccharide vaccines [10,18].

Second Line: Prophylactic Antibiotics. For patients with recurrent infections despite vaccination, prophylactic antibiotics should be considered [12]. Prophylactic antibiotics, however, may induce multidrug-resistant organisms, making future therapeutic interventions more difficult.

Third Line: IVIG Therapy. IVIG is reserved for patients with refractory or recurrent infections despite the above measures, with documented impaired vaccine responses. The initial dose is 400 mg/kg every 4 weeks, with escalation to 600 mg/kg every 3 weeks if response is suboptimal. Treatment duration is typically 6–12 months, after which reassessment for persistent immunoglobulin deficiencies is performed. IVIG has been shown to significantly decrease the number of yearly infections [22].

Management of Specific Antibody Deficiency

The therapeutic approach to SAD follows a similar stepwise algorithm [10,17,23]:

Initial Management: Therapeutic antibiotics should be used to aggressively treat acute infections. Once the patient has responded, vaccination with conjugate or protein-based vaccines directed against encapsulated pathogens should be administered to optimize protection.

Prophylactic Antibiotics: A trial of prophylactic antibiotics may be indicated and has been shown to be effective at decreasing the number of clinical infections [17].

IVIG Therapy: An alternative approach is the use of intravenous immunoglobulin (IVIG) at a monthly dose of 400 mg/kg. Establishing realistic clinical expectations at the initiation of therapy is important since occasional infections may still occur despite IVIG therapy. A more realistic outcome is a decrease in the number of infections and courses of antibiotics over time. The duration of therapy is poorly defined but should proceed for at least 6–12 months [10]. At that time, the intervention should be re-evaluated including the efficacy of therapy, patient adverse reactions and compliance, and financial considerations.

Summary

CVID, IgG subclass deficiency, and specific antibody deficiency are the most clinically relevant primary humoral immunodeficiencies in adult practice. They present similarly with recurrent sinopulmonary infections, yet they differ in fundamental ways [3–5,12,16]:

- CVID is characterized by low total IgG with impaired polysaccharide and protein vaccine responses.
- IgG subclass deficiency features normal total IgG with selective subclass reductions and variable vaccine response patterns.
- SAD presents with normal total IgG and normal IgG subclasses but selectively impaired polysaccharide vaccine responses.

A high index of clinical suspicion is essential for all three conditions.

The diagnostic workup for all three conditions requires quantitative immunoglobulin and IgG subclass measurement, vaccine challenge assessment, and systematic exclusion of secondary causes. IVIG replacement therapy is the cornerstone of CVID management. Early recognition and appropriate management of these conditions significantly reduce infection rates, limit end-organ damage, and improve long-term outcomes [8,21–23].

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