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# IgG Subclass Deficiency

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**Abstract:** Immunoglobulin G subclass deficiency has been diagnosed in 25% of patients presenting with recurrent infections. Similar to other primary immunodeficiencies, it is commonly overlooked or misdiagnosed. The diagnosis includes documentation of a decreased level of one or more subclasses in conjunction with an inadequate response to a vaccine challenge. Understanding the specific actions of the four subclasses allows the clinician to direct the evaluation and define a treatment program. Several subclass deficiencies are also associated with other disease states. Diagnosis of this entity will limit patient morbidity and allow for more rapid identification of other potentially life-altering illnesses.

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## Introduction

Patients with recurrent or refractory infections present a diagnostic and therapeutic challenge. While the differential diagnosis is extensive, several primary immunodeficiency states need to be considered. Among these are common variable immune deficiency (CVID), specific antibody deficiency (SAD), and immunoglobulin G (IgG) subclass deficiency (Table 1). These entities may be very similar in clinical presentation but can be differentiated by IgG quantitative and subclass evaluation. IgG subclass deficiency has been documented in approximately 25% of patients presenting with recurrent infections [1]. This article will review the clinical presentation of IgG subclass deficiency, as well as the approach to diagnosis and therapeutic options.

**Table 1: Primary** Immunodeficiency

| | CVID | SAD | IgG1 | IgG2 | IgG3 | IgG4 |
|---|---|---|---|---|---|---|
| IgG total | Low | Normal | Normal | Normal | Normal | Normal |
| IgA total | Low | Normal | Normal | +/– | Normal | +/– |
| Sinopulmonary infections | + | + | + | + | + | + |
| Response to polysaccharide vaccine | Abnl | Abnl | Abnl | Abnl | +/– | +/– |
| Response to protein vaccine | Abnl | Normal | +/– | +/– | +/– | +/– |

Abnl, abnormal; CVID, common variable immune deficiency; IgA, immunoglobulin A; IgG, immunoglobulin G; SAD, specific antibody deficiency; +, common; +/–, variable.

## Definition

To identify a patient as having an IgG subclass deficiency, two parameters must be present. First, one or more IgG subclasses must be decreased. Secondly, the total IgG concentration must be normal. The finding of decreased subclass deficiencies does not necessarily correlate with a clinically significant disorder. To qualify for this diagnosis, a patient must have recurrent infections plus an inadequate response to a vaccine challenge.

## Review of IgG Subclasses

Four IgG subclasses have been identified. It is important to recognize other disease entities that have been reported with individual or multiple subclass deficiencies. This may serve to identify occult immunodeficiencies, decreasing the time to diagnosis.

IgG1: This antibody comprises over 60% of total IgG. Deficiencies in IgG1 are commonly found in patients with diffuse hypogammaglobulinemia, necessitating an evaluation for CVID. Since a patient must have a normal total IgG to be diagnosed with a subclass deficiency, an isolated IgG1 deficiency is rare.

IgG2: A deficiency of IgG2 is more commonly identified in children and may occur as an individual deficiency or one associated with IgG4. In one study, 17% of pediatric patients with immunodeficiency disorders were diagnosed with IgG2 deficiency [2]. The natural course of this deficiency was delineated by Wolpert et al, who evaluated 120 children over 2 years of age. After 3 years of evaluation, over 85% of patients had normal immunoglobulin levels as well as a normal response to a polysaccharide vaccine challenge [3].

This is the principal subclass for responses to polysaccharide antigens. Subsequently, patients with IgG2 deficiency are at increased risk of infection with encapsulated organisms such as *Streptococcus pneumoniae*, *Haemophilus influenzae* type b (Hib), and *Neisseria meningitidis*.

As documented below, numerous diseases have been associated with an IgG2 deficiency [4].

IgG3: A deficiency of IgG3 is more common in adults and may occur in combination with IgG1. This antibody is responsible for protection against *Moraxella catarrhalis* and, to a large extent, *Streptococcus pyogenes*. The latter is secondary to IgG3 activity against the M component of group A streptococcus. This antibody participates to a greater extent with immunologic responses to proteins. Accordingly, patients with an isolated IgG3 deficiency may have a normal response to a polysaccharide vaccine challenge [4,5].

IgG4: A deficiency of IgG4 is not uncommon, but most patients are asymptomatic, making diagnosis difficult. While IgG4 may be an isolated finding, it is commonly associated with IgG2 with or without an IgA deficiency. As is seen with IgG2, IgG4 deficiency is associated with many other disease states.

The differentiation of IgG subclass deficiency from other immunodeficiency states is summarized in Table 1.

## Associated Disease States

As stated previously, recurrent sinopulmonary infections are the most common presentation for a patient with IgG subclass deficiencies. Other disease states, however, may be present and may provide clues to the underlying immunodeficiency. Ataxia telangiectasia, interferon gamma deficiency, growth hormone deficiency, chronic mucocutaneous candidiasis, and allergic colitis have been associated with IgG2 and IgG4 deficiencies. Bronchospastic illness, chronic bronchitis, and recurrent lymphocytic meningitis have been associated with IgG3 deficiency [6,7].

## Differential Diagnosis

Secondary hypogammaglobulinemia is the most pertinent consideration in patients being evaluated for IgG subclass deficiency. This can result from either increased protein losses or a decreased production of immunoglobulin. Losses may occur through either the kidney (nephrotic syndrome) or gastrointestinal tract (protein-losing enteropathies). Production may be decreased due to any of the following factors:

- Malignancy, such as chronic lymphocytic leukemia or lymphoma.
- Infections, including Epstein–Barr virus, cytomegalovirus, HIV, or any other disease entity that suppresses bone marrow function.
- Medications, particularly glucocorticoids, phenytoin, carbamazepine, and sulfasalazine.

## Clinical Evaluation

Clinical evaluation requires a 4-step process. Initially, an extensive history and physical exam must be performed to identify clues to any of the above diseases. In patients with recurrent sinusitis, imaging of the sinuses may be appropriate to eliminate anatomic obstructions as the etiology. If such an obstruction is identified, referral to an ear, nose, and throat surgeon may be appropriate. Laboratory evaluation should include complete blood cell count, chemistry profile, HIV when appropriate, quantitative immunoglobulins, IgE, and IgG subsets.

The next step is to measure the patient's ability to generate a protective antibody to a vaccine challenge. In general, a response to both protein and polysaccharide vaccines should be assessed. Polysaccharide capabilities can be assessed by analyzing a response to the pneumococcal 23 valent vaccine. Protective levels from invasive disease are 1.3 mcg/mL. The ability to generate an antibody to a protein-based challenge can be assessed by evaluating levels of diphtheria, tetanus, or *H. influenzae* vaccine. Protective levels are >0.01 IU/mL for diphtheria, >0.1 IU/mL for tetanus, and >1 mcg/mL for Hib. If baseline titres are below the level of protection, a repeat dose should be given and levels reassessed in approximately 1 month. At least 70% of titres should be at or above the minimum protective level.

As is commonplace in medicine, despite an aggressive evaluation, the diagnosis of IgG subclass deficiency may be uncertain. In this case, it may also be appropriate to consult with an immunologist to review the data and verify the therapeutic approach.

## Therapy

Once the diagnosis has been established, a multi-pronged approach is indicated. Initially, any active infection should be adequately treated with appropriate antibiotics. Subsequently, the patient should be vaccinated for protection from the most likely pathogens. If the patient has poor responses to polysaccharide vaccines, a pneumococcal and Hib conjugate vaccine should be administered, and has been shown to be protective [8,9].

Prophylactic antibiotics may be indicated for patients with recurrent infections [3]. While many patients are adequately managed with this intervention, some will experience refractory or multiple recurrent infections, necessitating a more aggressive approach.

Intravenous immune globulin (IVIG) therapy may be utilized for these patients and has been shown to be successful in decreasing the number of yearly infections [10]. This therapy should be reserved for patients with documented impaired responses to polysaccharide and/or protein vaccines.

The initial IVIG dose is 400 mg/kg, administered every 4 weeks. The dose can be increased to 600 mg/kg and the interval shortened to 3 weeks if a less than optimal response is experienced. Regardless, patients should receive therapy for 6–12 months and be reevaluated for persistent immunoglobulin deficiencies [3].

## Summary

Immunoglobulin G subclass deficiency is a primary immunodeficiency that presents in a similar fashion to CVID and SAD. It is critical to consider this diagnosis when evaluating patients with recurrent infections. Therapy with IVIG has been successful in limiting infections, but should be reserved for patients with an inability to generate antibodies to polysaccharide or protein vaccines.

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