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Assessment and clinical interpretation of reduced IgG values

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Patients are often referred to immunologists for the evaluation of reduced serum IgG levels. Because antibody deficiencies are the most common of the primary immune defects, examination of humoral immunity in these patients is valuable.^{1,2} This article is the first in a series dealing with the diagnosis of immunodeficiency disorders, with focus on the interpretation of reduced IgG values. The information presented should be interpreted in the clinical context of each patient along with other evaluation measures, such as IgM and IgA levels and functional humoral immunity, discussed in subsequent articles.

VARIABLES AFFECTING MEASUREMENT AND INTERPRETATION

Nephelometry is an automated and rapid method used to measure serum immunoglobulin levels; it relies on the light-scattering properties of antigen-antibody complexes. However, substances other than antigen-antibody complexes in solution can increase background light scatter, leading to incorrect results. Monoclonal immunoglobulins or heterophile antibodies (usually anti-goat immunoglobulins) may elevate levels of detected immunoglobulins.³ Serum samples should ideally be stored at 2°C to 8°C or frozen at –15°C to –20°C if the assay is delayed. However, because immunoglobulins and antibodies are rather resistant to deterioration, these conditions, although desirable, are not mandatory. Correct interpretation of IgG levels relies on reference to age-matched controls (Table 1). An immunoglobulin level within 2 SDs of the mean for age-matched controls is considered normal. In the first year of life, premature infants should be compared with infants of similar gestational age.^{2,5}

INTERPRETATION OF REDUCED IgG LEVELS

Reductions in total IgG levels in adolescents or adults may be classified as mild-moderate (300–600 mg/dL), significant (100–299 mg/dL), or profoundly reduced (<100 mg/dL). In adolescents and adults, a total immunoglobulin (IgG + IgM + IgA) level greater than 600 mg/dL, with confirmed normal antibody responses, probably excludes humoral deficiency. Total immunoglobulin levels of 400 to 600 mg/dL or IgG levels of 200 to 400 mg/dL may contain adequate amounts of antibody; this becomes less likely if total immunoglobulin levels are less than 400 mg/dL or serum IgG levels are less than 200 mg/dL.^{2,6}

IMMUNOLOGIC CONDITIONS WITH REDUCED IgG LEVELS

Hypogammaglobulinemia in infants younger than 2 years may suggest transient hypogammaglobulinemia of infancy. Laboratory findings include IgG levels less than 2 SDs below the mean for age, normal B-lymphocyte numbers, and normal or near normal IgG antibody responses to vaccines. Most infants with transient hypogammaglobulinemia of infancy achieve normal levels of serum IgG by the age of 2 years; however, few continue to have low levels of IgG until 5 or 6 years of age.²

The diagnosis of X-linked agammaglobulinemia or the rarer autosomal recessive form of agammaglobulinemia is usually made in the first few years of life due to family history or recurrent sinopulmonary infections. Laboratory findings include profound hypogammaglobulinemia and extremely low to absent circulating B cells. Serum IgG levels are usually less than 200 mg/dL, and IgM and IgA levels are less than 20 mg/dL. Peripheral blood CD19⁺ B-cell counts are commonly less than 0.1%.^{1,7-9}

Patients with one of the hyper-IgM syndromes, X-linked or autosomal recessive, have a deficiency of IgG and IgA. Laboratory studies show low levels of serum IgG and IgA with normal or elevated levels of IgM, decreased IgG antibody responses, and variable T-cell defects.¹⁰

Serum IgG levels reduced by more than 2 SDs below the mean, accompanied by deficiencies in IgA and/or IgM, suggest common variable immunodeficiency.^{1,7,11} Usually the IgG level is less than 400 mg/dL; 70% of patients will have very low or absent IgA content.¹² Documentation of impaired production of specific antibodies or poor response to vaccines is fundamental for this diagnosis. Peripheral B-cell numbers may be reduced or normal. CD4⁺ T-cell numbers may be reduced, CD8⁺ T-cell numbers may possibly be increased, and reduced T-cell proliferation to mitogens or antigens is common.^{1,11,12}

Goods syndrome is a form of adult-onset hypogammaglobulinemia or near agammaglobulinemia associated with a benign or (less commonly) malignant thymoma. Immunoglobulin levels are variably reduced, and a hallmark of this defect is low to absent levels of B cells. Some patients have CD4⁺ T-cell lymphopenia and reduced T-cell proliferation responses to mitogens. The thymoma may precede the diagnosis of hypogammaglobulinemia, but removal does not seem to forestall or resolve hypogammaglobulinemia.^{1,13}

MEASUREMENT AND INTERPRETATION OF IgG SUBCLASS LEVELS

IgG subclass deficiency is defined as a reduction in 1 or more subclasses of IgG (IgG1 and IgG2 in particular) by more than 2 SDs below the mean for age-matched controls.^{14,15} Deficiencies in IgG1 or IgG2 are more likely to cause low serum IgG levels because these are the major components. IgG1 levels stabilize by the age of 5 years; however, adult levels of IgG2, IgG3, and IgG4 may not be achieved until adolescence.¹⁶ Thus, the interpretation of subclass levels is additionally problematic because levels of each subclass increase at different rates during development. The significance of isolated IgG subclasses is controversial. Laboratories have different age-appropriate reference ranges; aliquots of the same serum may result in different levels from different laboratories.¹⁵ Reduced levels of 1 or more subclasses may be found in healthy individuals, making precise clinical interpretation challenging. If performed, proper evaluation of IgG subclasses should include measurements on 2 separate occasions at least 1 month apart while the patient is free of infections.⁶ Determination of IgG subclasses may be useful in patients with selective IgA deficiency, in which IgG2 deficiency is found in approximately 10% of patients.¹⁵ However, quantitation of IgG subclasses provides insufficient information about antibody function; therefore, specific functional antibody response to proteins and polysaccharide antigens is important. Without clear deficits of functional antibody, IgG subclass deficiency is not likely to be clinically significant.

SECONDARY CAUSES OF HYPOGAMMAGLOBULINEMIA

There are numerous causes of secondary hypogammaglobulinemia, including the effects of selected medications, malnutrition, burns, gastrointestinal loss, nephrotic syndrome, and malignancy (Table 2). Secondary causes can be divided into 2 categories: increased loss or

reduced production. Before a diagnosis of primary immunodeficiency is made, the potential contribution of these factors should be considered.

IMMUNOGLOBULIN REPLACEMENT

There has been no formal algorithm to decide which patients should start immunoglobulin replacement therapy. In this decision process, physicians generally consider clinical history and pertinent physical findings and laboratory variables, including serum immunoglobulin levels, history of infections and concomitant diseases, antibody response to proteins and vaccines, radiographic studies, and pulmonary function tests. Patients with profoundly reduced (<100 mg/dL) or significantly reduced (100–299 mg/dL) IgG levels with clearly impaired antibody response are generally treated with replacement immunoglobulin starting at 100 mg/kg per week given either intravenously or subcutaneously. Prophylactic antibiotics may also be required in some individuals. Individualization of dosage and frequency is based on clinical response and determination of “trough” serum IgG levels. Most prescribing physicians aim to maintain the serum IgG level greater than 600 mg/dL. Higher trough levels (>800 mg/dL) may have the potential to improve pulmonary outcome.¹⁰ Serum IgG levels can be obtained at 4- to 6-month intervals to ensure that adequate trough levels are maintained.¹² In patients with mild-moderate reductions in IgG levels (300–600 mg/dL) and normal antibody responses, immunoglobulin replacement therapy may be withheld if the patient is carefully monitored by a knowledgeable specialist.

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Table 1Concentration of IgG in Relation to Age^a

Age	IgG, mean (range), mg/dL
Cord blood (term)	1,121 (636–1606)
1 mo	503 (251–906)
2 mo	365 (206–601)
3 mo	334 (176–581)
4 mo	343 (196–558)
5 mo	403 (172–814)
6 mo	407 (215–704)
7–9 mo	475 (217–904)
10–12 mo	594 (294–1,069)
1 y	679 (345–1,213)
2 y	685 (424–1,051)
3 y	728 (441–1,135)
4–5 y	780 (463–1,236)
6–8 y	915 (633–1,280)
9–10 y	1,007 (608–1,572)
Adult	994 (639–1,349)

^a Adapted from Jolliff et al.⁴ IgG levels were obtained using rate nephelometry.

Table 2

Secondary Causes of Hypogammaglobulinemia

Cause	IgG	IgA	IgM	Antibody responses	Diagnosis	T cells CD4 ⁺ and CD8 ⁺	B cells
Burns/trauma	↓	Normal	Normal	Normal	Physical examination	Generally normal	Generally normal
Gastrointestinal loss	↓	↓	↓	Normal	Serum albumin; stool alpha-1-trypsin	↓ CD4 ⁺ ; ↓ CD4 ⁺ CD45RA ⁺ in intestinal lymphangiectasia	Normal/↓
Nephrotic syndrome	↓	Normal/↑	Normal/↑	Normal/↓	Urine studies	↓ CD3 ⁺ and CD4 ⁺ cells in corticosteroid-sensitive patients; ↑ CD8 ⁺ , CD16 ⁺ , and CD4 ⁺ CD45RO ⁺ during disease relapse	Generally normal
Malignancy	↓	↓	↓	↓	Peripheral blood lymphoid clonality; examine bone marrow	Normal/↑	Normal/↑
Medications ^a	↓	↓	↓	Normal/↓	Withdraw if possible and retest	Generally normal	Generally normal

Symbols: Downward arrow, decreased; upward arrow, increased.

^aPhenytoin, carbamazepine, antimalarial agents, captopril, glucocorticoids, fenclofenac, gold salts, penicillamine, sulfasalazine, and others.⁷