Model Coverage Policy for Immunoglobulin Replacement Therapy for Primary and Secondary Immunodeficiency Diseases with Impaired Antibody Response

The following model guideline for insurer coverage policies is presented by the Immune Deficiency Foundation (IDF) as an aid for insurers in preparing their guidelines for immunoglobulin (Ig) replacement therapy for primary immunodeficiency diseases (PI) and secondary immunodeficiencies with impaired antibody responses. This model guideline is based on the current standards of care as set forward by the professional societies most concerned with the diagnosis and care of PI in the Eight Guiding Principles for Effective Use of IVIG for Patients with Primary Immunodeficiency by the American Academy of Allergy, Asthma and Immunology (AAAAI)\(^1\) the Practice Parameter For The Diagnosis And Management of Primary Immunodeficiency by the AAAAI with the American College of Allergy, Asthma and Immunology (ACAAI),\(^2\) and Guidelines for the Use of Immunoglobulin Therapy by the AAAAI.\(^3\) (see reference list).

These standards for immunoglobulin replacement therapy for patients with primary immunodeficiency are summarized below:

- The specific criteria by medical condition as listed below are met.
- The dosage, frequency, site of administration and duration of therapy are reasonable, clinically appropriate, and supported by evidence-based literature as defined by the Guidelines for the Use of Immunoglobulin Therapy.\(^3\)
- The choice of product and route of administration, e.g. intravenous or subcutaneous should be determined by the prescribing physician in consultation with the patient, based on his/her individual needs.
- Because there are substantial differences in tolerability between the different IgG therapies in individual patients, an inappropriate, poorly tolerated product can cause medical complications, impact patient quality of life, and drive behaviors that can result in poor therapeutic compliance and poor health outcomes.
- Switching patients from a well-tolerated IgG product to a different product should be undertaken only after careful consideration of risks and benefits by both the patient and the prescribing physician.
- If a genetic or definitive diagnosis that includes impairment of antibody responses is established, it is not in the best interest of the patient to interrupt immunoglobulin therapy to re-establish a need for continued therapy.
Insurers must cover intravenous immunoglobulin (IVIG) or subcutaneous immunoglobulin (SCIG) as medically necessary for any of the conditions listed below:

**Immunodeficiency with predominately antibody defects, unspecified – ICD-10 D80.9/D80.8**
(including but not limited to Common Variable Immune Deficiency [CVID])

**Major Criteria for Use:**

- **Recurrent Infections**
  - History of infections requiring multiple courses of antibiotic therapy.
  - Evidence of management of underlying conditions such as asthma or allergic rhinitis that may predispose to recurrent infections where applicable.

  The prerequisite for a prior history of recurrent infections should not be required for patients with a confirmed diagnosis of the most profound antibody deficiency disorders or combined immunodeficiencies. Vaccine challenge to demonstrate inability to produce a protective antibody response is not required in these subjects because (i) the lack of serum immunoglobulins precludes such a response, and (ii) the delay in IgG replacement required for testing poses a significant risk of developing severe or life-threatening infections.

- **Immunologic Evaluation**
  - Immune evaluation including documented serum IgG below the reference range for the age of the patient, using the testing laboratory’s reported reference ranges.

- **Impaired Antibody Response (as demonstrated by either of the following):**
  - Lack of protective antibody titers to protein antigens (examples include tetanus toxoid and/or diphtheria toxoid) measured before and at least 4-6 weeks after immunization or proven natural infection.

  OR,

  - Inadequate responsiveness at 4-6 weeks following administration of a polysaccharide vaccine including non-conjugated pneumococcal polysaccharide vaccine (Pneumovax 23), or to S. typhim Vi vaccine.

**Additional Specific Primary Immunodeficiency Disorders Requiring Ig Replacement Therapy:**

The following is a list of primary immunodeficiency disorders associated with a significant defect in the ability to produce protective levels of IgG antibodies in response to a protein and/or polysaccharide vaccine challenge. The list is not inclusive of all disorders or patients who may require therapy. The lack of protective antibody production to antigen challenge is the single most appropriate test in the determination of the need for IgG replacement therapy, irrespective of the levels of each individual immunoglobulin class found in the blood or secretions. Some diagnoses below can be confirmed through genetic testing; and should a gene mutation known to cause a specific clinical phenotype be identified, the AAAAI recommends treatment without the need to demonstrate the incidence of infection or the failure to respond to vaccination.
Partial list of Primary Immunodeficiencies, or Inborn Errors of Immunity, with assigned ICD-10 codes

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>ICD10 Codes</th>
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<tbody>
<tr>
<td>• Agammaglobulinemia (X-linked - BTK)</td>
<td>D80.0</td>
</tr>
<tr>
<td>o Autosomal recessive (AR)</td>
<td></td>
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<tr>
<td>• Wiskott-Aldrich syndrome (WAS)</td>
<td>D82.0</td>
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<tr>
<td>• Hyper IgM syndrome (X-linked) CD40L deficiency</td>
<td>D80.5</td>
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<tr>
<td>o Autosomal recessive</td>
<td></td>
</tr>
<tr>
<td>• DiGeorge syndrome (DGS)</td>
<td>D82.1</td>
</tr>
<tr>
<td>• Ataxia telangiectasia (AT)</td>
<td>G11.3/Q87.19</td>
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<tr>
<td>• Severe combined immunodeficiency (SCID)</td>
<td></td>
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<tr>
<td>o X-Linked (normal, elevated or low B-cell number)</td>
<td>D81.2</td>
</tr>
<tr>
<td>o Autosomal recessive (many individual genes)</td>
<td>D81.1</td>
</tr>
<tr>
<td>o Adenosine deaminase deficiency</td>
<td>D81.31</td>
</tr>
<tr>
<td>• Hyper immunoglobulin E syndrome (HIES)</td>
<td>AD STAT3</td>
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<tr>
<td></td>
<td>D82.4</td>
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<tr>
<td></td>
<td>AR DOCK8</td>
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<tr>
<td></td>
<td>D81.9</td>
</tr>
<tr>
<td>• Immunodeficiency, centromeric instability, facial anomalies (ICF)</td>
<td>D81.9</td>
</tr>
<tr>
<td>• Thymoma with immunodeficiency</td>
<td>D15</td>
</tr>
<tr>
<td>• Common variable immunodeficiency with predominant immunoregulatory T-cell disorders</td>
<td>D83.1</td>
</tr>
<tr>
<td>• Common variable immunodeficiency (CVID)</td>
<td>D83.0/D83.1, D83.2, D83.9</td>
</tr>
<tr>
<td>• WHIM (warts, hypogammaglobulinemia, infection, Myelokathexis (syndrome)</td>
<td>D70.8</td>
</tr>
<tr>
<td>• Immunodeficiency with hereditary defective response to Epstein-Barr virus</td>
<td>D82.3</td>
</tr>
</tbody>
</table>
The International Union of Immunological Societies (IUIS) expert committee has recently updated the classification of Primary Immunodeficiency Diseases, also known as Inborn Errors of Immunity. The application of next-generation sequencing continues to expedite the identification of novel gene defects and broaden the immunological and clinical phenotypes of conditions arising from known gene defects.\(^4\)

**IgG Subclass deficiency (D80.3) and Specific Antibody Deficiency (SAD) (D80.6)**

The following two PI are disorders that are characterized by normal total serum IgG levels and yet may fail to respond normally to protein or polysaccharide vaccine challenge.

**IgG Subclass Deficiency**

Criteria for Use - All of the following are met:

- **Recurrent Infection**
  - History of multiple infections, many of which require antibiotic therapy.
  - Evidence of management of underlying conditions such as asthma or allergic rhinitis that may predispose to recurrent infections where applicable.

- **Immunologic evaluation including** documented normal total serum IgG with one or more subclasses, excluding isolated subclass IgG4, below the lower limits of normal for age of the laboratory’s reported value on at least two occasions.

- **Impaired Antibody Response** - Inadequate responsiveness at 4-6 weeks to vaccination with tetanus/diphtheria toxoids and/or a non-conjugated pneumococcal polysaccharide vaccine.

**Specific Antibody Deficiency (SAD)**

Criteria for Use - All of the following are met:

- **Recurrent Infection (ALL of the following):**
  - History of infections requiring multiple courses of antibiotic therapy
  - Evidence of management of underlying conditions such as asthma or allergic rhinitis that may predispose to recurrent infections where applicable

- **Immunologic evaluation including** documented normal serum IgG, IgA and IgM for age

- **Impaired Antibody Response** – Inadequate responsiveness at 4-6 weeks to vaccination with tetanus/diphtheria toxoids and/or a non-conjugated pneumococcal polysaccharide vaccine or the Salmonella Vi Typhum polysaccharide vaccine

**Secondary Immunodeficiencies with impaired antibody response**\(^5\)

**Criteria for Use of Ig Replacement**

- **Recurrent Infection:**
  - History of infections requiring antibiotic therapy.

- **Immunologic Evaluation**
Immune evaluation including documented serum IgG below the reference range for the age of the patient, using the testing laboratory’s reported reference ranges that often is also complimented by evaluation for circulating B cells in cases where prior history includes the use of B cell directed agents (e.g. Rituxan, CD19 CAR-T cell therapy) to treat an underlying immune dysregulation or malignant condition

- Impaired Antibody Response (as demonstrated by either of the following):
  - Lack of protective antibody titers to protein antigens (examples include tetanus toxoid and/or diphtheria toxoid) measured before and at least 4-6 weeks after immunization or proven natural infection.
  - Inadequate responsive 4-6 weeks following administration of a polysaccharide vaccine including non-conjugated pneumococcal polysaccharide vaccine (Pneumovax 23), or S. typhim Vi (parenteral) vaccine.

Although diagnostic and therapeutic guidelines such as those presented above are critically important in assuring that all but the most unusual cases of PI will receive appropriate therapy with parenteral immunoglobulin, it is impossible to prepare guidelines that will cover every situation. It is important to remember that in the relatively brief time since the human genome project was completed, the known number of recognized primary immunodeficiency diseases (Inborn Errors of Immunity) has more than doubled. Therefore, it is essential that the insurance industry retain some flexibility so that those individuals with documented serious or recurrent infections who do not necessarily match the guidance outlined here can still gain access to at least a trial period of six months of immunoglobulin replacement therapy to determine if their increased susceptibility to infection can be controlled with treatment.

1 Standards of Care documents published by the AAAAI:
   - Eight Guiding Principles for Effective Use of IVIG for Patients with Primary Immunodeficiency
   - Guidelines for the Site of Care for Administration of IGIV Therapy


2 Francisco A. Bonilla, MD, PhD, et.al., Practice parameter for the diagnosis and management of primary immunodeficiency. Journal Allergy and Clinical Immunology, 2015; 136, Pages 1186–1205.e78.

3 Perez EE, Orange JS, Bonilla FA, Chinen J, Chinn IK, Dorsey M et al. Update on Use of Immune Globulin (IG) in Human Disease: A review of evidence by members of the primary immunodeficiency committee of the American Academy of Allergy, Asthma and Immunology. Journal Allergy and Clinical Immunology 2017; 139(3): S1-46.


5 Ballow M and Fleisher TA Secondary Immunodeficiency induced by biologic therapies. UpToDate. Updated May 2021
APPENDIX

Model Coverage Policy for Ig Replacement Therapy for PID with Impaired Antibody Response

General considerations regarding immunoglobulin replacement for PI

Given that spontaneous remissions are extremely rare for these genetic disorders, it is inappropriate to require frequently repeated re-authorizations to continue with immunoglobulin replacement for a life-long condition like PI. In addition, many of the antibody deficiency disorders are not correctly identified until the patients have experienced repeated infections over prolonged periods of time resulting in significant end organ, pulmonary damage (e.g., bronchiectasis) which is irreversible when IgG replacement is finally instituted. For example, patient surveys conducted by the IDF have repeatedly shown that for the most common antibody deficiency disorder in adults, common variable immunodeficiency (CVID), the mean time between the onset of infections and the establishment of a correct diagnosis and starting Ig replacement is about 7-9 years. In this situation, improvement in pulmonary status may not be possible and slowing of progressive pulmonary deterioration may be all we can hope to accomplish by aggressive IgG replacement.

The clinical response to IgG (Ig) replacement is quite variable and each patient needs to be evaluated as an individual because the response to a particular Ig regimen will differ from patient to patient (Lucas et al 2010; Bonagura et al 2008). The same IgG dose given to two similarly sized patients with PI can result in two different peak and trough IgG levels. Similarly, a given dose and trough level could be highly effective in one patient and only marginally effective in another patient with apparently very similar characteristics and disease patterns.

At present, it is not possible to predict which patients are going to require which doses and trough or steady state serum levels of IgG to have the lowest possible incidence of infections. Titration of IgG replacement below the low end of the traditional starting dosage range (400-600 mg/kg) in order to determine the minimum dose and frequency to achieve sustained clinical effect is inappropriate because it will require the patient to experience worsening of their clinical status and potentially even a fatal bacterial infection. Importantly, a recent meta-analysis (Orange JS et. al.) of 17 phase III clinical trials of IVIG administration in PI patients evaluated the IVIG dosage and IgG trough level, and correlated the data with the incidence of pneumonia. In aggregate, the data showed that for every 100 mg/kg Ig dose increase, a 121 mg/dl serum IgG trough increase could be expected. What was surprising, however, was that for every 100 mg/dl trough increment, a 27% decrease in pneumonia incidence was identified. The analysis further indicated that the mean incidence of pneumonia at the 500 mg/dl trough level was 4 fold higher than that observed amongst those treated to achieve trough levels of 1000 mg/dl. Importantly, the pneumonia incidence in these PI patients was not predicted to reach zero at the highest trough levels available from the data set (1000 mg/dl).
Special circumstances regarding immunization with Prevnar and Pneumovax pneumococcal vaccines

- Bacterial polysaccharides induce a T-cell independent type II humoral immune response. Active immunization of adults and children >2 years is performed with a non-conjugated pneumococcal polysaccharide vaccine to assess the antibody response. It is particularly important that antibodies to all 23 serotypes of pneumococci (Pneumovax) be routinely measured to permit the best possible picture of the patient’s antibody response profile since specific serotypes overlap between Prevnar and Pneumovax (see below).

- Individuals with Selective Antibody Deficiency, IgG subclass deficiency and some other disorders of antibody production may produce protective levels of antibody following immunization with the conjugated pneumococcal polysaccharide vaccine (Prevnar) while being poorly responsive to a non-conjugated pneumococcal polysaccharide vaccine. Prevnar is a protein conjugated polysaccharide vaccine and as such, responses are T cell dependent, a characteristic of protein vaccines like tetanus or diphtheria rather than of a purified polysaccharide vaccine like Pneumovax. Therefore, in the evaluation of polysaccharide vaccine responsiveness in someone who has also received one of the Prevnar vaccines, it is essential to only consider responses to the pneumococcal serotypes that are present in Pneumovax but absent in Prevnar. Prevnar 13 shares 12 serotypes with Pneumovax and therefore only 11 of the Pneumovax serotypes are used in evaluating native polysaccharide responsiveness.

  - Pneumovax 23 contains a total of 23 serotypes, namely 1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20, 22F, 23F, and 33F. These 23 serotypes were included because, as a group, they account for approximately 90% of invasive pneumococcal infections. The serotypes in red and indicated by a bold typeface are exclusive to Pneumovax.

  - Prevnar 13 vaccine contains serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 10A, 18C, 19A, 19F, and 23F. These serotypes are the most common cause of invasive pneumococcal disease in children.

  - Hib vaccine for *Haemophilus influenza* type b is also a protein conjugated vaccine and therefore it is not an appropriate vaccine for measuring the anti-polysaccharide antibody response.

- If the patient has been given a vaccine (polysaccharide) within the past 1 year and had not responded to the vaccine, there is no need to administer another vaccine dose to test the patient’s immune response. This is also contrary to the CDC recommendations for immunization to polysaccharide vaccines within a certain time period in that it may impose state of partial tolerance.

References:
Francisco A. Bonilla, MD, PhD, et.al., Practice parameter for the diagnosis and management of primary immunodeficiency. *Journal Allergy and Clinical Immunology*, 2015; 136, Pages 1186–1205.e78.


Elena Perez et al. Update on Use of Immune Globulin (IG) in Human Disease: A review of evidence by members of the primary immunodeficiency committee of the American Academy of Allergy, Asthma and Immunology. Journal Allergy and Clinical Immunology 2017; 139(3): S1-46.


Additional Standards of Care documents published by the AAAAI
  o Eight Guiding Principles for Effective Use of IVIG for Patients with Primary Immunodeficiency
  o Guidelines for the Site of Care for Administration of IGIV Therapy

**Normal levels of immunoglobulins with impaired specific-antibody production [selective antibody deficiency (SAD)]**

**Statements from Selected References:**

**Excerpt of AAAAI guidelines** regarding **Selective Antibody Deficiency (SAD)** published in:
- Elena Perez et al. Update on Use of Immune Globulin (IG) in Human Disease: A review of evidence by members of the Primary Immunodeficiency Committee of the American Academy of Allergy, Asthma and Immunology. Journal Allergy and Clinical Immunology 2017; 139(3): S1-46.

Patients with normal total IgG levels but impaired production of specific antibodies, including those with isolated deficient responses to numerous polysaccharide antigens following vaccination, can present a diagnostic challenge. Immunoglobulin replacement therapy should be provided when there is well-documented severe polysaccharide non-responsiveness and evidence of recurrent infections with a proven requirement for antibiotic therapy.

A protective concentration of polysaccharide antibodies is considered to be ≥1.3 μg/mL, and conversion of an antibody level from non-protective to protective. If the baseline serotype specific antibody level is already at ≥ 1.3 mcg/ml, then an adequate response is a two-fold increase. A normal antibody response to polysaccharide antigens is defined differently according to age: In children ages 2-5 years, responsiveness to ≥50% of the serotypes tested was considered a normal response; In those 6 to 65 years, responsiveness to ≥70% of serotypes tested was considered a normal response.


**NOTE:** A working group of the AAAAI suggests that a normal response to a non-conjugated pneumococcal polysaccharide vaccine challenge should be the production of protective titers of anti-pneumococcal antibodies to at least 70% of the 23 serotypes present in the vaccine in patients over the age of 6. However, in the experience of many clinical immunologists, a normal vaccine response for an individual consists of producing protective titers of antibodies to at least 50% of the serotypes present in the vaccine. Repeated cultures of the upper airways of an encapsulated bacteria such as *H. influenza* or pneumococcus might be an indication of an underlying humoral immune deficiency. It is worth considering an evaluation or referral by a clinician who is experienced in the management of primary antibody immune deficiency.

The FDA recently approved the 20 valent conjugate pneumococcal vaccine that will make it difficult to use the unconjugated pneumococcal vaccine (Pneumovax) to assess a polysaccharide antibody response to evaluate a person for an antibody immune deficiency such as SAD. The Salmonella Vi Typhim vaccine (Sanofi Pasteur SA, Lyon, France, supplied in 0.5-ml single injection syringes containing 0.25% phenol as a preservative), is a pure polysaccharide vaccine that is a neoantigen for most people in the US may be very helpful in evaluating these individuals. Since this antibody is not present in commercial preparations of immune globulin (IVIG or SCIG), antibodies to this vaccine can be measured in patients while on replacement Ig therapy.


Antibody testing is available by contacting the MEDICAL COLLEGE OF WISCONSIN ALLERGY IMMUNOLOGY DIAGNOSTIC LAB CENTER at phone 414-955-4931 or by FAX 414-955-6487.

Four phenotypes of selective antibody deficiency were recently defined: memory, mild, moderate, and severe. Any of these phenotypes may warrant antibiotic prophylaxis, immunoglobulin replacement, or both, depending on the clinical situation.

Patients with the memory phenotype are characterized as able to mount adequate concentrations against polysaccharide antigen but in whom the response wanes within 6 months.
While antibiotic prophylaxis may represent a first-line intervention in these patients, the severity of infection and/or the efficacy of antibiotic prophylaxis should be the driving force behind any decision to provide immunoglobulin replacement therapy. Further evidence of infection, including abnormal findings on sinus and lung imaging, complete blood count, C-reactive protein, and erythrocyte sedimentation rate can additionally support the need for immunoglobulin supplementation in these patients. In this setting, immunoglobulin therapy is appropriate in, but not limited to, patients with difficult-to-manage recurrent otitis media at risk for permanent hearing loss, chronic or recurrent sinusitis, bronchiectasis, recurrent infections necessitating IV antibiotics, failed antibiotic prophylaxis, impaired quality of life due to recurrent infections despite antibiotic prophylaxis, or multiple antibiotic hypersensitivities that interfere with treatment.

When the severity of infections, frequency of infections, level of impairment, or inefficacy of antibiotic prophylaxis warrants the use of immunoglobulin in this form of antibody deficiency, patients and/or their caregivers should be informed that the treatment may be stopped after a period of time (preferably in the spring in temperate regions) and that the immune response will be reevaluated at least 4-6 months after the discontinuation of immunoglobulin.


While some patients, usually children, show improved responses to antigen challenge (typically with pneumococcal polysaccharide vaccine) after treatment with immunoglobulin for 6-24 months and improve clinically, others require restarting the immunoglobulin therapy because of a recurrence of infections.


One or two cessations of therapy are likely to identify whether a patient’s defect in antibody specificity was transient. Repeated multiple cessations of therapy to affect this determination are not useful and can potentially harm the patient.