IMMUNODEFICIENCY SYNDROME
TESTING AND TREATMENT
HS-298

APPLICATION STATEMENT

The application of the Clinical Coverage Guideline is subject to the benefit determinations set forth by the Centers for Medicare and Medicaid Services (CMS) National and Local Coverage Determinations and state-specific Medicaid mandates, if any.

DISCLAIMER

The Clinical Coverage Guideline (CCG) is intended to supplement certain standard WellCare benefit plans and aid in administering benefits. Federal and state law, contract language, etc. take precedence over the CCG (e.g., Centers for Medicare and Medicaid Services [CMS] National Coverage Determinations [NCDs], Local Coverage Determinations [LCDs] or other published documents). The terms of a member’s particular Benefit Plan, Evidence of Coverage, Certificate of Coverage, etc., may differ significantly from this Coverage Position. For example, a member’s benefit plan may contain specific exclusions related to the topic addressed in this CCG. Additionally, CCGs relate exclusively to the administration of health benefit plans and are NOT recommendations for treatment, nor should they be used as treatment guidelines. Providers are responsible for the treatment and recommendations provided to the member. The application of the CCG is subject to the benefit determinations set forth by the Centers for Medicare and Medicaid Services (CMS) National and Local Coverage Determinations and state-specific Medicaid mandates, if any. All links are current at time of approval by the Medical Policy Committee (MPC) and are subject to change prior to the annual review date. Lines of business (LOB) are subject to change without notice; current LOBs can be found at www.wellcare.com. All guidelines can be found at this site as well but selecting the Provider tab, then “Tools” and “Clinical Guidelines”.

BACKGROUND

The immune system protects the body from harmful substances called antigens. Examples of antigens include bacteria, viruses, toxins, cancer cells, and foreign blood or tissues from another person or species. When the immune system detects an antigen, it responds by producing proteins called antibodies that destroy the harmful substances. The immune system response also involves a process called phagocytosis. During this process, certain white blood cells swallow and destroy bacteria and other foreign substances. Proteins called complement help with this process. Immunodeficiency disorders may affect any part of the immune system. Most often, these conditions occur when special white blood cells called T or B lymphocytes (or both) do not function normally or the
body does not produce enough antibodies.  

Inherited immunodeficiency disorders that affect B cells include hypogammaglobulinemia (which usually leads to respiratory and gastrointestinal infections) and agammaglobulinemia (which results in severe infections early in life, and is often deadly). Inherited immunodeficiency disorders that affect T cells may cause repeated Candida (yeast) infections. Inherited combined immunodeficiency affects both T cells and B cells. It may be deadly within the first year of life if it isn't treated early. People are said to be immunosuppressed when they have an immunodeficiency disorder due to medicines that weaken the immune system (such as corticosteroids). Immunosuppression is also a common side effect of chemotherapy given to treat cancer.  

Acquired immunodeficiency may be a complication of diseases such as HIV infection and malnutrition (especially if the person does not eat enough protein). Many cancers may also cause immunodeficiency.  

People who have had their spleen removed have an acquired immunodeficiency, and are at higher risk for infection by certain bacteria that the spleen would normally help fight. Those with diabetes are also at higher risk.  

As people age, the immune system becomes less effective. Immune system tissues (especially lymphoid tissue such as the thymus) shrink, and the number and activity of white blood cells drop. The following conditions and diseases can lead to an immunodeficiency disorder:  

- Ataxia-telangiectasia  
- Complement deficiencies  
- DiGeorge syndrome  
- Hypogammaglobulinemia  
- Job syndrome  
- Leukocyte adhesion defects  
- Bruton disease  
- Wiscott-Aldrich syndrome  

**Exams and Tests**  

Testing for immunodeficiency disorder may be ordered when an individual has:  

- Infections that keep coming back or do not go away  
- Severe infection from bacteria or other infectious agents that do not usually cause severe infection  
- Other signs may include:  
  - Poor response to treatment for infections  
  - Delayed or incomplete recovery from illness  
  - Certain types of cancers (such as Kaposi’s sarcoma or non-Hodgkin lymphoma)  
  - Opportunistic infections (including some forms of pneumonia or repeated yeast infections)  

The following screening diagnostic tests may be recommended to screen for immunodeficiency syndromes when the following systems show symptoms:  

- **Upper Respiratory Tract.** Serum immunoglobulin levels, antibody titers to protein and polysaccharide vaccines; isohemagglutinins; CH50  
- **Lower Respiratory Tract.** Serum immunoglobulin levels, antibody titers to protein and polysaccharide vaccines; isohemagglutinins; CH50; WBC with manual differential to count neutrophils, lymphocytes and platelets; Respiratory Burst Assay  
- **Skin, internal organs.** Respiratory Burst Assay/CD11/CD18 Assay  
- **Blood or Central Nervous System.** Serum immunoglobulin levels, antibody titers to protein and polysaccharide vaccines; CH50
Tests used to help diagnose an immunodeficiency disorder may include:

- Complement levels in the blood, or other tests to measure substances released by the immune system
- HIV test
- Immunoglobulin levels in the blood
- Protein electrophoresis (blood or urine)
- T (thymus derived) lymphocyte count
- White blood cell count

_Treatment_ ¹

For individuals that develop an infection, aggressive treatment may involve long-term use of antibiotic or antifungal medications and preventive (prophylactic) treatments.

Interferon is used to treat viral infections and some types of cancer. It is an immunostimulant drug, a medicine that makes the immune system work better.

Individuals with HIV or AIDS may take combinations of drugs to reduce the amount of HIV in their immune systems and improve their immunity.

Individuals who are going to have a planned splenectomy should be vaccinated two weeks before the surgery against bacteria such as Streptococcus pneumonia and Haemophilus influenzae.

Bone marrow transplants may be used to treat certain immunodeficiency conditions.

Passive immunity (receiving antibodies produced by another person or animal) may sometimes be recommended to prevent illness after you have been exposed to certain bacteria or viruses.

**POSITION STATEMENT**

Applicable To:

- ☑ Medicaid
- ☑ Medicare

Testing for a primary immunodeficiency is considered medically necessary when the:

- Member has recurrent infections or there is an unusual or persistent infection; OR
- Member has/had a usually mild childhood disease which has worsened or has become life-threatening; OR
- Member’s blood cell counts are low or persistently high.

In addition, see specific criteria below:

**Antibody Production Defects**

Infections and conditions include:

- Recurrent sinopulmonary infections
  - Pneumonia with fever
  - Sinusitis documented by X-ray or Computerized tomography (CT) scan
  - Otitis media (frequent ear infections are seen in normal children, an evaluation may still be indicated for individuals on a case by case basis.)
- Meningitis and/or sepsis (blood stream infection)
- Gastrointestinal infections
- Cutaneous (skin) infections

Symptoms / indicators for testing for antibody production defects include:
- Absence or reduced size of tonsils and lymph nodes in X-linked agammaglobulinemia and in X-linked Hyper IgM syndrome; OR
- Enlarged lymph nodes and splenomegaly in CVID and autosomal recessive Hyper IgM syndrome; OR
- Scarred tympanic membranes; OR
- Unusual skin changes such as, complete absence of eyebrows and hair, severe eczema resistant to treatment, mouth thrush resistant to treatment after 4 months of age, candida skin infections, petechiae, vitiligo, recurrent or persistent warts or severe molluscum contagiosum; OR
- Rales and rhonchi in lungs, clubbing of the fingers.

Useful diagnostic screening tests include:

- Complete blood count and manual differential
- Quantitative serum immunoglobulin (IgG, IgA, IgM and IgE) levels
- Measurement of specific antibodies to vaccines

Monitoring IG therapy in antibody deficient patients includes:

- **Frequency of testing for trough levels.** Monitor IgG levels at least once a year (more often if the patient is having infections) or just before the next infusion. Be aware that gastrointestinal tract infection with the parasite Giardia lamblia or other enteropathies can cause enteric loss of IgG leading to unexpectedly low IgG levels. Generally, once the optimal dose of immune globulin has been established in a patient, monthly monitoring of the IgG level is not indicated unless there is protein loss through the GI or urinary tracts.
- **For patients on long-term follow up of patients on IG therapy.** Evaluations regarding hepatitis A, B, and C by PCR (polymerase chain reaction) screening may be indicated.
- **Adverse event monitoring on IG therapy.** Creatinine level and liver function tests (every 6-12 months).

In addition, cancer screening may be indicated on a periodic basis, as it is for individuals with intact immune systems. Some subgroups of those with a primary immunodeficiency disease, such as patients with CVID, particularly those with chronic lymphadenopathy may merit baseline complete pulmonary function studies, CT, MRI and/or PET scans and more intensive screening. Lymphoma evaluation is the same as for those without hypogammaglobulinemia. Useful diagnostic screening tests for malignancy include determination of uric acid, LDH (lactic dehydrogenase) and ESR (erythrocyte sedimentation rate).

### Cellular or Combined Defects

Infections and conditions include:

- Severe Combined Immunodeficiency (“Bubble Boy” Disease, SCID)
- DiGeorge Syndrome also known as 22q11 Deletion Syndrome (Thymic aplasia)
- Ataxia Telangiectasia (AT)
- Wiskott-Aldrich Syndrome (WAS)

Symptoms / indicators for testing for cellular or combined defects include any of the following:

- Appear ill
- Have facial dysmophia (DiGeorge syndrome) or ectodermal dysplasia (NEMO or “NF-kappa B Essential Modulator”)
- Failure to thrive (e.g., weight is a more important determinant than length)
- Have congenital heart disease (heart murmur at birth, cyanosis, DiGeorge syndrome)
- Have skin changes
  - Severe diaper rash or oral candidiasis (thrush)
  - Eczema (as in Wiskott-Aldrich syndrome or Graft versus Host Disease [GVHD])
  - A red rash as in GVHD, Omenn’s syndrome or atypical complete DiGeorge syndrome
Phagocytic Cell Immune Defects

Infections and conditions include:
- Leukocyte Adhesion Defect (LAD)
- Chronic Granulomatous Disease (CGD)
- Chediak Higashi Syndrome (CHS)
- Cyclic Neutropenia Kostman Disease

Signs of defects in the phagocytic cells are manifest in many organ systems. The onset of symptoms is usually in infancy or early childhood. Symptoms / indicators for testing for phagocytic cell immune defects include any of the following:

- **Skin.** Abscesses (boils) (seen in Chronic granulomatous disease [CGD] and the Hyper IgE syndrome) and/or cellulitis (inflammation of the skin)
- **Lymph nodes.** May be swollen and contain pus in CGD patients
- **Leukocyte adhesion deficiency (LAD).** May be delayed shedding of the umbilical cord or infection of the cord base (omphalitis) and cellulitis but no abscesses.
- **Osteomyelitis.** An infection of bone seen frequently in patients with chronic granulomatous disease (CGD).
- **Hepatic Abscess.** Liver abscesses may also be seen in CGD.
- **Lungs.** Aspergillus (mold) lung disease is insidious and common in patients with CGD. Abscesses and other infections may occur due to pathogens that do not result in abscesses in normal hosts.
- **Gastrointestinal tract outlet and/or urinary tract.** Obstruction resulting in abdominal or back pain is often seen in CGD, as is constipation.
- **Mouth (gingivitis).** Gum inflammation, mouth ulcers.
- **Unexplained fever without identifiable cause.**
- **Malaise and fatigue.**
- **Albinism** may be seen in Chediak Higashi syndrome.

Defects in phagocytic cells can be due to an insufficient number of such cells, an inability of the cells to get to an infected area, or to an inability to kill ingested bacteria or fungi normally. Useful diagnostic screening tests include:

A white blood cell count with a manual differential should be obtained to determine whether the patient has a low absolute lymphocyte count (i.e. is lymphopenic). Age-appropriate normal values must be considered. The following levels are considered low, according to age:

- **< 2055/μL** Birth
- **< 4000/μL** 5-6 Months Up to Age 1
- **< 1000/μL** Adult
A complete blood count and differential are needed to determine whether phagocytic cells (neutrophils) are present in normal number. In the case of cyclic neutropenia, the test (absolute neutrophil count or ANC) has to be repeated sequentially (e.g. 2 times per week for 1 month).

A test for CD11/CD18 expression on white cells is needed to exclude LAD.

A Respiratory Burst Assay (the replacement for the NBT assay) should be performed to determine if phagocytic cells can produce oxygen radicals needed to kill bacteria and fungi. Neutrophils from patients with CGD do not produce these oxygen radicals.

As is the case in CGD, patients with the Hyper IgE syndrome also present with abscesses (boils) although they have a normal number of neutrophils and a normal Respiratory Burst Assay result. Thus, a serum IgE level should be measured in patients with recurrent abscesses to make certain that the Hyper IgE syndrome is not the underlying cause.

Complement Defects

Infections and conditions include:

- C1 Esterase Inhibitor Deficiency (Hereditary Angioedema)
- Complement Component Deficiencies (e.g. C1, C2, C3, C4, C5, C6, C7, etc.)

Symptoms / indicators for testing for complement defects include any of the following:

- C1, C4 or C2 deficiencies may present with recurrent pneumococcal disease, i.e. otitis, pneumonia or bacteremia. There can also be concomitant antibody deficiency due to poor antigen uptake by dendritic cells, which normally interact with antigen-antibody complexes bearing complement components. System lupus erythematosus is much more common than infections as a manifestation of early complement component deficiencies.
- C3 deficiency is very rare, but is characterized by recurrent serious bacterial infections, such as pneumonia or bacteremia, and development of membranoproliferative glomerulonephritis.
- Systemic Neisserial infections in children and adolescents suggest C5-7 deficiencies:

Useful diagnostic screening tests for a diagnosis of CH50 and AH50 include:

- In the work up for complement deficiency, the CH50 is an excellent screening test, but the blood needs to be handled carefully—see below. Alternative Pathway defects can be screened for with the AH50 test. Identification of the particular component that is missing will require studies in a research or specialized laboratory.
- For diagnosis, proper specimen collection of blood samples is very important. Complement is very heat labile. In general, if the CH50 is undetectable, the patient likely has a deficiency in a complement component, however, if the CH50 is just low, it is more likely that the specimen was not handled properly or that the patient has an autoimmune disease.

Monitoring includes:

- Prophylactic antibiotics may be appropriate for deficiencies of any of the components of the complement cascade. Meningococcal vaccine and/or antibiotic prophylaxis may be helpful for any person diagnosed with a C5 through C9 deficiency.
- All complement deficient patients should receive immunization with Prevnar® or Pneumovax or both for pneumococcal infection prevention. Early recognition of fevers and prompt evaluation (including blood cultures) is very important.
- Complications of complement deficiency include autoimmune disease, especially systemic lupus erythematosus, lupus-like syndromes, glomerulonephritis, and infections.
- Mannose binding lectin, a protein of the innate immune system, is involved in opsonisation and
phagocytosis of micro-organisms. Most of those with the Mannose Binding Lectin defect are healthy except for skin infections, but some resemble patients with early complement component defects. In the setting of recurrent infection with suspected mannose binding lectin deficiency, a specialty laboratory (not a commercial one) must diagnose this defect.

**CODING**

**Covered CPT Codes**

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<td>82785</td>
<td>Gammaglobulin (immunoglobulin); IgE</td>
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<td>Blood count; manual cell count (erythrocyte, leukocyte, or platelet) each</td>
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<td>86003</td>
<td>Allergen specific IgE; quantitative or semiquantitative, each allergen</td>
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**Covered ICD-10 CM - Diagnosis Codes**

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<td>A09</td>
<td>Infectious gastroenteritis and colitis, unspecified</td>
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L08.89 Other specified local infections of the skin and subcutaneous tissue
L92.8 Other granulomatous disorders of the skin and subcutaneous tissue
L98.0 Pyogenic granuloma
L08.89 Other specified local infections of the skin and subcutaneous tissue
L08.9 Local infection of the skin and subcutaneous tissue, unspecified
L22 Diaper dermatitis
P28.2 Cyanotic attacks of newborn
R19.7 Diarrhea, unspecified
R23.3 Spontaneous ecchymoses
R50.9 Fever, unspecified
R62.51 Failure to thrive (child)
R68.3 Clubbing of fingers

Coding information is provided for informational purposes only. The inclusion or omission of a CPT, HCPCS, or ICD-10 code does not imply member coverage or provider reimbursement. Consult the member's benefits that are in place at time of service to determine coverage (or non-coverage) as well as applicable federal / state laws.

REFERENCES

MEDICAL POLICY COMMITTEE HISTORY AND REVISIONS

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