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# An Update on the Treatment of Pediatric Autoimmune Encephalitis


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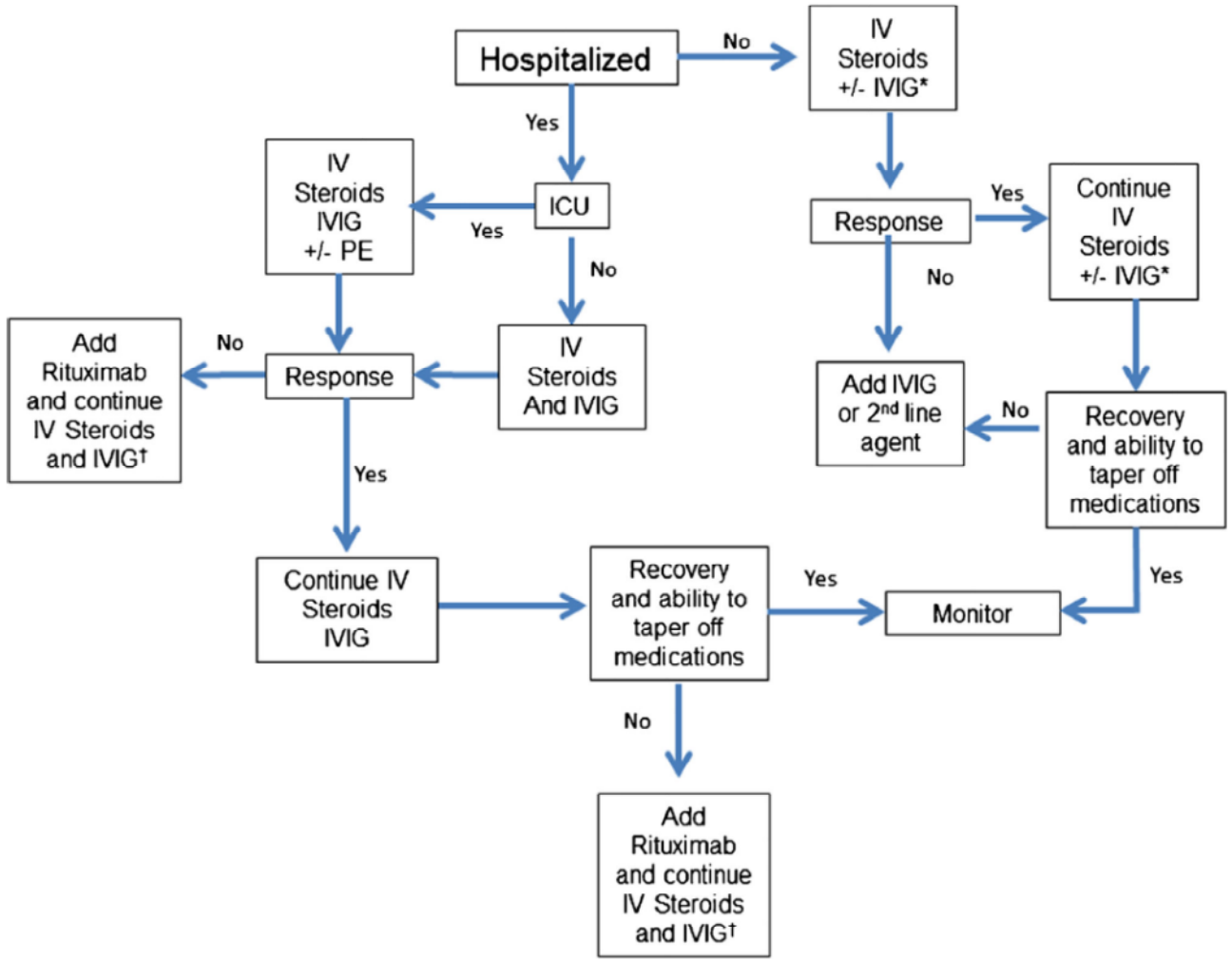
# Probable Autoimmune Encephalitis




PE=Plasma exchange IV steroids=IV methylprednisolone or dexamethasone.
2nd line agents include rituximab, mycophenolate mofetil, azathioprine
*Depending on severity and results of evaluation consider IV steroids alone vs adding IVIG. Recommend 3-6 months of sustained treatment before tapering.
†Continue first line therapy with IVIG and IV steroids while giving time for second line therapy to take effect, then slowly taper off to ensure no recurrence of symptoms.

### *Immune therapy versus no immune therapy*

Results in the reviewed articles suggest that the use of immune therapy is associated with a better outcome. In particular, within the non-paraneoplastic group in the cohort described by Irani and colleagues, those patients administered no immune therapy did significantly worse than those who were treated ($p < 0.0001$).[28] In the large case series by Titulaer,[29] 29% of the 29 patients who received no surgery and no immune therapy had a poor outcome (mRS 3–6) as opposed to 21.3% of the total cohort ($n = 501$). Moreover, the use of immune therapy in the initial episode of encephalitis was associated with a lower frequency of relapses ($p = 0.038$).[29]

### *Timing of immune therapy*

Several observations in the reviewed articles also suggest that early commencement of immune therapy favors a better neurological outcome. In particular, improvement of mRS score was associated with early (<40 days) administration of immune therapies in non-paraneoplastic patients ($p < 0.0001$).[28] Similarly, early treatment was a predictor of good outcome (mRS 0–2) ($p < 0.0001$) in the cohort described by Titulaer.

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# Clinical Management of Pediatric Acute-Onset Neuropsychiatric Syndrome: Part II—Use of Immunomodulatory Therapies

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Table 1. General Strategies for Management of Pediatric Acute-Onset Neuropsychiatric Syndrome Based on Disease Trajectory

| *Disease trajectory* | *Recommendations* |
|---|---|
| **New-onset or acute flare** | (1) Work-up infections and other causes of acute neuropsychiatric deteriorations per guidelines[a] (Van Mater 2014; Chang et al. 2015; Graus et al. 2016; Cooperstock et al. 2017; Dale et al. 2017).<br>(2) Refer for CBT and provide other supportive therapies (Thienemann et al. 2017).<br>(3) Consider early use of corticosteroids (oral bursts or IV pulses) to abort or shorten flares (Tables 2 and 3).<br>(4) Consider high-dose IVIG or other immunomodulatory therapies in moderate-to-severe cases (Tables 2 and 4). |
| **Relapsing-remitting** | (1)–(4) as above.<br>(5) Evaluate for possibility of recurrent infections/exposures triggering flares.<br>(a) If GAS infection is a frequent trigger for relapses, evaluate/treat close contacts and consider prophylaxis according to guidelines (Cooperstock et al. 2017).<br>(b) Keep in mind that most flares are viral triggers. See (2)–(4) above for treatment of each flare.<br>(c) Evaluate immune system competency: pursue immunodeficiency work-up if patient has recurrent sinopulmonary disease or fevers per guidelines (Chang et al. 2015). If immunodeficiency is present, IVIG may reduce the number and severity of intercurrent infections (Cooperstock et al. 2017). |
| **Chronic-static or chronic-progressive**<br><br>*Initial therapy is proposed in the box to the right. Patients with chronic-static or progressive disease may respond to corticosteroids or other induction immunotherapies but then relapse if therapy is stopped. Some patients need repeated doses of steroids and/or other immunotherapies (IVIG or other steroid-sparing agent).* | (1)–(4) as mentioned.<br>(5) Pursue immunomodulatory therapies according to symptom categories below:<br>Mild-to-moderate neuropsychiatric symptoms:<br>NSAIDs (Table 3).<br>Oral corticosteroid burst (Table 3) to see whether baseline improves.<br>Caution: use of combination NSAIDs+corticosteroids may result in gastritis; but these medications can be used safely in tandem.<br>Mild-to-moderate neuropsychiatric symptoms with no response to NSAIDs and/or short burst of corticosteroids:<br>(Repeat) oral prednisone ± prolonged taper (Table 3).<br>Pulse corticosteroids (oral dexamethasone or IV methylprednisolone) (Table 3).<br>Moderate-to-severe neuropsychiatric symptoms:<br>Oral prednisone±taper or pulse corticosteroids (Table 3).<br>High-dose IVIG or other induction steroid-sparing agent (Table 4).<br>Severe-to-extreme neuropsychiatric symptoms:<br>Refer to subspecialists for further evaluation for AE, NPSLE, CNS vasculitis, and consideration of using established (published and institutionally based) treatment protocols.<br>Consider high-dose IV corticosteroids and/or other immunotherapies (Tables 3 and 4).<br>Refractory disease course (i.e., psychiatric symptoms not responsive to initial immunomodulatory approaches already mentioned and no improvement in neurological signs):<br>Refer to subspecialist for consideration of additional agents[b] and/or combination therapy (up to four immunomodulatory therapies are used simultaneously to treat inflammatory brain diseases; that is, corticosteroids+TPE+IVIG+rituximab).<br>Consider possibility of injured neurocircuitry and need for shifting to primary rehabilitation mode. |

Table 4. Corticosteroid-Sparing Agents (Therapies Used in Conjunction with Steroids or to Replace Corticosteroids) That Have Been Used in Pediatric Acute-Onset Neuropsychiatric Syndrome/Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal infection

| | *IVIG* | *TPE* | *Rituximab or MMF*[a] |
|---|---|---|---|
| **New onset.** | One to six monthly courses of IVIG in moderate-to-severe disease or in severe-to-extreme if TPE not available. | Use in severe-to-extreme cases if patient has life-threatening disease. | Patient has moderate-to-extreme impairment.<br>and<br>patient has proven (documented by mental health professional) responsiveness to corticosteroids, IVIG, or TPE.<br>and<br>patient has evidence of inflammation/autoimmunity and objective signs of organic brain disease. |
| **Relapsing-remitting course.** | Consider repeated dosing of IVIG if patient meets criteria for an immunodeficiency syndrome. | Not indicated unless patient is in a severe-to-extreme flare. | Consider use if patient has a deteriorating baseline (i.e., each flare leaves the patient with permanent deficits) or frequent relapses.<br>and<br>patient has proven responsiveness to corticosteroids, IVIG, or TPE.<br>and<br>patient has evidence of inflammation/autoimmunity and objective signs of organic brain disease. |
| **Very delayed care, chronic-static, or chronic-progressive course.** | Trial of IVIG. If patient responds, then symptoms recrudesce then patient is deemed immune therapy responsive, thus consider (A), (B), or (C).<br>(A) Monthly IVIG until patient is no longer having period of improvement after IVIG and recrudescence as IVIG effect wanes.<br>(B) Rituximab, MMF, etc.<br>(C) (A)+(B). | Response to TPE may be transient. Consider introduction of rituximab or MMF if there is evidence of autoimmunity. | Patient has moderate-to-extreme impairment.<br>and<br>patient has proven responsiveness to corticosteroids, IVIG, or TPE.<br>and<br>patient has evidence of inflammation/autoimmunity and objective signs of organic brain disease. |

# UNITED HEALTHCARE


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**Medical Benefit Drug Policy**

## IMMUNE GLOBULIN (IVIG AND SCIG)

**Policy Number**: 2020D0035AA

**Effective Date**: February 1, 2020

# Autoimmune encephalitis does not appear at all, other than one type, Rasmussen syndrome.

**Immune globulin is unproven and not medically necessary for:**

Opsoclonus myoclonus
Paraneoplastic cerebellar degeneration, sensory neuropathy, or encephalopathy
Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS)
POEMS syndrome
Postinfectious cerebellar ataxia
Postoperative sepsis
Pseudomembranous colitis
Rheumatic fever, acute

# **AETNA,** PARENTERAL IMMUNOGLOBULINS GUIDELINES 01/02/2020

Again, the word of autoimmune encephalitis does not appear other than Rasmussen Encephalitis

Moreover, they include limbic encephalitis, and major subtype of autoimmune encephalitis under

| |
|---|
| **Aetna considers IVIG therapy experimental and investigational for any of the following conditions (in alphabetical order):** |
| |

# Aetna considers IVIG therapy experimental and investigational for any of the following conditions (in alphabetical order):

Health conditions in Alphabetical order

- **Acquired factor VIII inhibitors**
- **Acquired von Willebrand's disease**
- **Acute lymphocytic leukemia**
- **Acute lymphoblastic leukemia**
- **Acute myeloid leukemia**
- **Acute optic neuritis**
- **Adrenoleukodystrophy**
- **Alpha-1 antitrypsin deficiency**
- **Alzheimer’s disease**
- **Amyotrophic lateral sclerosis**
- **Angioedema**
- **Anti-myelin-associated glycoprotein neuropathy**
- **Anti-synthetase syndrome**
- **Antiphospholipid syndrome**
- **Aplastic anemia**
- **Asthma**
- **Asymptomatic kidney transplant recipients with donor specific antibodies**
- **Attention deficit hyperactivity disorder**
- **Autism**
- **Autoimmune autonomic ganglionopathy**
- **Autoimmune autonomic neuropathy**
- **Autoimmune bullous skin diseases**
- **Autoimmune chronic urticaria**
- **Autoimmune encephalopathy**
- **Autoimmune epilepsy**
- **Autoimmune inner ear disease**
- Hand-foot-mouth disease
- Hashimoto's encephalopathy
- Hemolytic transfusion reaction
- Hemolytic-uremic syndrome
- Hemophagocytic syndrome (e.g., hemophagocytic lymphohistiocytosis)
- Henoch-Schonlein purpura
- Hereditary motor and sensory neuropathy (including Charcot Marie Tooth)
- HTLV-1 associated myelopathy
- Hunter syndrome (mucopolysaccharidosis type II)
- Idiopathic chronic serositis
- Idiopathic environmental illness and multiple chemical sensitivity syndrome
- Idiopathic lumbosacral plexopathy
- Idiopathic progressive neuropathy
- Idiopathic pulmonary fibrosis
- Immune reconstitution inflammatory syndrome
- Implantation rash/rash after embryo transfer
- Inclusion body myositis
- Infertility
- Interstitial lung disease
- Intractable seizures
- Isaacs syndrome
- Isoimmune hemolytic disease
- Juvenile systemic sclerosis
- Landau-Kleffner syndrome
- Langerhans cell histiocytosis
- Paraneoplastic cerebellar degeneration
- Paraneoplastic syndromes other than neuroblastoma
- Paraproteinemic neuropathy (IgM variant
- Parkinson’s disease
- Parsonage-Turner syndrome (brachial neuritis)
- Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infection (PANDAS)
- Pediatric infection-triggered autoimmune neuropsychiatric disorders (PITAND)
- Plasmacytoma, postural tachycardia syndrome (POTS)
- POEMS syndrome footnotes for acronym of POEMS syndrome**
- Polyarteritis nodosa
- Polyneuritis cranialis
- Pre-thymectomy

However, surprise, surprise!

According to AETNA
Opsoclonus-myoclonus - considered medically necessary for treatment of either of the following:

- Paraneoplastic opsoclonus-myoclonus-ataxia associated with neuroblastoma.
- Refractory opsoclonus-myoclonus, as last-resort treatment.

AETNA considers Acute Disseminated Encephalomyelitis - considered medically necessary for acute disseminated encephalomyelitis in members who have had an insufficient response to intravenous corticosteroid treatment. United healthcare does not even mention this diagnosis.

Drug and Biologic Coverage Policy

Effective Date ..... 1/1/2020
Next Review Date… ..... 1/1/2021
Coverage Policy Number ..... 5026

# Immune Globulin

**When coverage is available and medically necessary, the dosage, frequency, duration of therapy, and site of care should be reasonable, clinically appropriate, and supported by evidence-based literature and adjusted based upon severity, alternative available treatments, and previous response to therapy.**

**Intravenous Immune Globulin (IVIG) or Subcutaneous Immune Globulin (SCIG) is considered experimental, investigational or unproven for ANY other use including the following (this list may not be all inclusive):**

- Hashimoto encephalopathy
- Inclusion body myositis (IBM)
- Lyme neuropathy
- Neonatal sepsis
- Pediatric acute-onset neuropsychiatric syndrome (PANS) and Pediatric autoimmune neuropsychiatric disorder associated with group A streptococci (PANDAS)
- Primary progressive multiple sclerosis (MS) and secondary progressive MS, acute MS exacerbations, or clinically isolated syndrome
- Recurrent pregnancy loss

# Again, the word of autoimmune encephalitis does not appear other than Rasmussen Encephalitis.

However, CIGNA will pay for opsoclonus myoclonus

| | |
|---|---|
| **Opsoclonus-Myoclonus-Ataxia Syndrome** | Treatment when there is a documented diagnosis. |

And this is the explanation

**Opsoclonus-Myoclonus-Ataxia Syndrome**

There are no randomized, controlled clinical trials evaluating the use of IVIG in opsoclonus-myoclonus-ataxia syndrome. Support for use is derived from case reports and case series, as well as expert opinion. (Feasby, 2007; Gorman, 2010)

# But when it comes to PANDAS this is what CIGNA has to say:

Pediatric Acute-onset Neuropsychiatric Syndrome (PANS) is a clinical diagnosis given to children who have a sudden onset of neuropsychiatric symptoms including obsessions, compulsions, or food restriction. Streptococcal infections cause exacerbation of symptoms in some children with obsessive-compulsive and tic disorders, possibly as an autoimmune response. This syndrome is referred to as Pediatric Autoimmune Neuropsychiatric Disorder Associated with Streptococcal infection (PANDAS). According to the PANS Research Consortium (PRC) immunomodulatory task force, treatment protocols must include immunological interventions for PANS cases in which the symptoms appear as neuroinflammation or postinfectious autoimmunity, as seen in the PANDAS subgroup. (Frankovich, 2017) However, most of the information about PANS/PANDAS has been obtained by studying individuals with long-standing obsessive-compulsive disorder (OCD) or tic disorder in research centers. The treatment guidelines in the review article cited are based on the expertise of healthcare professionals and scientists treating individuals with PANS. Randomized, controlled clinical trial studies are needed before immunological interventions become a standard of therapy.

Some of the insurance companies make claims such as “the results of the use of IVIG in PANDAS and PANS are inconclusive”, and that “more comprehensive studies are necessary”. Obviously, they do not tell you who is going to fund such studies, and until such funding is found, they intend to keep the money in the pocket and let the children suffer and families disintegrate.

For example, this is what CIGNA says about Hashimoto encephalopathy

Hashimoto encephalopathy (HE) is an uncommon autoimmune syndrome associated with neuropsychiatric manifestations responsive to steroid treatment. Until randomized, controlled clinical trials evaluating the use of IVIG in HE are completed and IVIG becomes a standard of care, its' use is considered experimental, investigational and unproven.

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# POLICY Document for Intravenous Immune Globulin (IVIG)

## I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

A. FDA-Approved Indications
1. Primary immunodeficiency
2. Idiopathic thrombocytopenic purpura (ITP)
3. Chronic inflammatory demyelinating polyneuropathy
4. Multifocal motor neuropathy
5. Kawasaki syndrome
6. B-cell chronic lymphocytic leukemia (CLL)

B. Compendial Uses
1. Prophylaxis of bacterial infections in pediatric human immunodeficiency virus (HIV) infection
2. Prophylaxis of bacterial infections in bone marrow transplant (BMT)/hematopoietic stem cell transplant (HSCT) recipients
3. Dermatomyositis
4. Polymyositis
5. Myasthenia gravis
6. Guillain-Barre syndrome
7. Lambert-Eaton myasthenic syndrome
8. Fetal/neonatal alloimmune thrombocytopenia
9. Parvovirus B19-induced pure red cell aplasia
10. Stiff-person syndrome

All other indications are considered experimental/investigational and are not a covered benefit.

# FDA indication cannot serve as a basis for decision about the use of the medication.

## INDICATIONS AND USAGE

GAMUNEX-C is an immune globulin injection (human), 10% liquid indicated for treatment of:

- Primary Humoral Immunodeficiency (PI) in patients 2 years of age and older (1.1)
- Idiopathic Thrombocytopenic Purpura (ITP) (1.2)
- Chronic Inflammatory Demyelinating Polyneuropathy (CIDP) (1.3)

IVIG has no patented. It is produced from plasma for from blood banks. It is already in use. Drug companies are never going to perform studies for new indication for IVIG.