Written testimony by Dr. Yuval Shafrir.

I'm a pediatric neurologist. I treat several patients with pandas.

The testimony I gave in the committee on February 6, happened to follow a testimony related to a bill that is supposed to protect diabetic patients from the unbelievable and unjustifiable increase in insulin price. The representatives (lobbyists) of the insurance industry responded by blaming the drug companies in price gouging.

In the testimonies presented to the committee of parents, siblings, and patients with pandas, even worse picture was presented, of extreme level of suffering to families, along with financial ruin, taking second mortgages, selling homes, breaking pensions. Obviously, the number of children of pandas is minuscule compared to insulin-dependent diabetics.

In my testimony, I clearly showed that the claim of the insurance companies that this is somehow "an experimental", "unproven" or "not indicated" is completely misleading.

PANDAS is one of a group of brain conditions called "autoimmune encephalopathies". It is probably the "hottest" subject in neurology today. These are group of conditions in which the brain is attacked by the patient's own antibodies. The range of clinical expression of those condition is very wide, starting with life-threatening severe autoimmune encephalitis with patients with constant seizures, coma and severe behavioral changes all the way to dementia and epilepsy. The reason for the intense interest in the subject is the fact that it opened the door for treatment for these conditions which were previously untreatable, frequently leading to severe disability and even death. There is a standard treatment for thess conditions, based on escalating stages of treatment using steroids, IVIG, as well as rituximab and cytotoxic medications such as cyclophosphamide.

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An Update on the Treatment of Pediatric Autoimmune Encephalitis

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As I've shown in my testimony, all the insurance companies IVIG guidelines that I reviewed (United healthcare, CIGNA, Aetna, and CareFirst; see attachments) do not even mention autoimmune encephalopathies, in spite of the fact that there is at least three or four articles on the subject in every leading neurology journal.

I also showed how the guidelines of the insurance companies are contradicting each other, and the notion that only conditions which was subject to control studies will be treated. I brought a specific example of a very rare autoimmune encephalopathy called ops across mitral syndrome which is approved by some insurance companies, not approved by others (were talking about horrible extremely disabling condition of children between the age of one and three for which IVIG is part of the start of treatment recommended by all the experts in the field, no controlled study is feasible, and denying the treatment is an unimaginable moral infarction). There are no controlled studies of this condition, as specifically specified by the insurance companies guidelines.

This is United healthcare:

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

However,

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.

According to CIGNA

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

although the guidelines state:

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)

obviously, exactly the same is true for pandas. The experts' opinion on pandas is much more substantial, and recommended by larger group of experts from the top medical institutions in this country, or recommending the use of IVIG as part of the staged treatment for pandas.

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

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Finally, I clearly showed that the FDA approval for IVIG is very limited. Most of the conditions that are treated (and mostly approved by the insurance companies) are not in the list of the FDA approved indications. Moreover, no pharmaceutical company is going to fund any control studies for the different indications for several reasons:

- There are already well-established guideline offered by group of professionals
- those studies are very expensive
- In many of the conditions, it will be completely unethical to give the patients placebo (especially when by a lot of other medications given together with the IVIG to prevent side effects).
- The drug companies have no interest in performing controlled studies for new indications when IVIG is used already for those indications.
- There is no patent on IVIG. It is prepared from human blood donated to blood banks.

The people who wrote the guidelines for the IVIG use by the different insurance companies, which I reviewed, know very well that randomized controlled studies for the treatment of these conditions are extremely unlikely to be performed. They still, again and again, state that

manifestations responsive to steroid treatment. Until randomized, controlled clinical trials evaluating the use of VIG in HE are completed and IVIG becomes a standard of care, its' use is considered experimental, nvestigational and unproven.

(Cigna on Hashimoto's encephalopathy)

and this is what CIGNA has to say about pandas (CIGNA is the only insurance company was guideline even relate to the above-mentioned guidelines):

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.

I have submitted the very detailed article with a guidelines of treating pandas, including when and how to use IVIG. The insurance company simply ignore this recommendations.

Are they transferring the responsibility for performing such controlled studies (probably unethical in the first place in a severe condition like pandas) to the federal government? To other authorities but they fail to mention? I hope that the federal government spends its resources to stop the coronavirus epidemic, and simply require that the insurance companies will keep their promised coverage of medical conditions for which they are supposed to help.

Special attention should be given to the letter to the committee submitted by Mr. Robert R. Neall, the Secretary of Maryland Department of Health in opposition to the suggested bill. He states that the state Medicaid program does not cover experimental treatments. He defines IVIG for pandas is an experimental treatment. Even the majority of the insurance companies are not making such a claim. What is extremely disturbing in this letter is the fact that the secretary seems to claim to possess some medical knowledge that he clearly does not have, in defining certain treatments is experimental. He does not specify from where this knowledge is derived. If employees of the department of health had unofficial consultations with some healthcare professionals which are not identified the letter, it clearly violates the families of these desperate patients of the right to fair hearing, as those unidentified healthcare professionals should have appeared in the committee and make their points publicly. If, on the other hand, the statement about "experimental treatment" is made without consultation with healthcare professionals, it is completely invalid, the secretary has no qualification to make such a statement. As I showed above, the statement is also false.

I believe that the unfortunate children with this condition in the families deserve the protection of their collected representatives from the greed driven arbitrariness of the insurance companies. At this point, you're the only people who can provide such protection. It is important to remember that even delay in the treatment in other types of autoimmune encephalitis was shown to be associated with poor prognosis. Time is running short for those families.

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An Update on the Treatment of Pediatric Autoimmune Encephalitis

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Abstract

Purpose of review—Autoimmune encephalitis (AE) is an increasingly recognized etiology for neuropsychiatric deficits that are highly responsive to immunotherapy. As a result, rheumatologists are often called upon to help with the diagnosis and treatment of these conditions. The purpose of this review is to provide an update on the pharmacologic treatment of AE.

Recent findings—To date, there are no prospective randomized placebo-controlled trials to guide treatment recommendations for AE. First-line therapies include corticosteroids, intravenous immunoglobulin, and plasma exchange. Second-line therapies include rituximab and cyclophosphamide (CYC), as well as mycophenolate mofetil and azathioprine. For patients refractory to both first- and second-line therapy, there is emerging evidence for the interleukin-6 (IL-6) inhibitor tocilizumab, the proteasome inhibitor bortezomib, and low-dose IL-2. Early treatment initiation and treatment escalation in patients with refractory disease improve outcomes. Given the delayed time between dosing and treatment effects of second-line agents, continuing first-line treatment until the patients shows improvement is recommended.

Summary—Although AE can present with dramatic, life-threatening neuropsychiatric deficits, the potential for recovery with prompt treatment is remarkable. First- and second-line therapies for AE lead to clinical improvement in the majority of patients, including full recoveries in many. Early treatment and escalation to second-line therapy in those with refractory disease improves patient outcomes. Novel treatments including IL-6 blockade and proteasome inhibitors have shown promising results in patients with refractory disease.

Keywords

Autoimmune encephalitis; Treatment; Review; Pediatric; Children

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Conflict of Interest Cory Stingl declares that he has no conflict of interest. Kathleen Cardinale declares that she has no conflict of interest. Heather Van Mater declares that he has no conflict of interest.

Compliance with Ethical Standards

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

Introduction

Autoimmune encephalitis (AE) is an increasingly recognized etiology of acute neuropsychiatric decline in adults and children. The clinical manifestations of AE are broad and include seizures, movement disorders, behavior and mood changes, psychosis, memory/cognitive impairment, autonomic dysfunction, and altered level of consciousness [1–3]. Recently proposed diagnostic criteria provide a framework for making a diagnosis of AE [4]. However, the substantial variability in presenting symptoms, severity, and progression of disease both within and across subtypes of AE, along with the lack of clear treatment recommendations, complicates management. Currently, there are no randomized trials for the treatment of AE and evidence for treatment comes primarily from case reports and cohort studies.

AE starts as an immune response triggered by infection, neoplasm, or unknown genetic and environmental triggers, which ultimately results in an autoimmune process targeting the brain [2, 5]. The immune reaction can be cell mediated, antibody mediated, or both, resulting in a spectrum of neurologic and psychiatric manifestations. While historically considered a paraneoplastic condition primarily in adults, the discovery of anti-neuronal antibodies targeting cell surface receptors has changed the framework and therapeutic approach of AE. Paraneoplastic AE results from neuronal injury and death due to T cell-mediated immunity [6]. The associated autoantibodies are not directly pathogenic and there is minimal reversibility with immunotherapy. In contrast, antibodies that target cell surface receptors are themselves pathogenic. They bind receptors and directly alter neuronal function without causing neuronal death [1, 7]. As a result, these conditions are remarkably sensitive to immunotherapy. It is important to note, however, that a chronically inflamed brain is more likely to sustain injury and long-term damage, highlighting the importance of early treatment and prompt escalation of therapy if children are not responding to initial treatment [8, 9].

Recently published diagnostic criteria for adult AE emphasize recognition of probable AE and initiation of treatment early to maximize potential recovery [4]. It is agreed in both adult and pediatric literature that patients treated early have improved outcomes. While work to modify and validate these diagnostic classifications for pediatric patients is currently in progress, the conceptual framework of these criteria is helpful to guide when to initiate treatment. A diagnosis of possible AE is made when patients present with acute to subacute onset (rapid progression of less than 3 months) of working memory deficits, altered mental status, or psychiatric symptoms, with at least one additional defined abnormality on evaluation (Table 1). Subsequent diagnostic criteria are presented for the various AE subtypes, including definite limbic encephalitis, acute disseminated encephalomyelitis, anti-NMDA receptor encephalitis, Hashimoto’s encephalopathy, and autoantibody-negative but probable AE [4]. While there is significant overlap in the presentations of adults and children, there are also important differences. Pediatric specific diagnostic criteria are currently in development to account for these differences.

Currently, there are no prospective trials for immunomodulatory treatments for AE. The majority of the evidence for treatment comes from a few larger retrospective observational

cohort studies and numerous small case series and case reports [10]. The first neuronal surface autoantibody reported was anti-N-Methyl-D-aspartate (NMDA) and it is currently the most prevalent in children [11]. As a result, the most robust data for clinical findings and treatment recommendations for AE in children are from patients with anti-NMDA receptor (NMDAR) encephalitis. The principles of treatment of NMDAR encephalitis are considered by experts in the field to apply more generally to other forms of AE as well. The general framework for treatment may be divided into first-line, second-line, and maintenance therapy [12]. First-line therapies include steroids, intravenous immunoglobulin, and plasma exchange, all of which have a rapid onset of action and relatively low associated risks. If patients respond promptly to these therapies, the use of prolonged immunosuppressant therapy, or second-line agents, is not necessarily needed. However, if patients are not showing improvement or are worsening, escalation to second-line therapy is warranted. Second-line therapy, including rituximab and cyclophosphamide, are considered higher risk medications given their longer duration of action and increased immunosuppressive nature. The timing of when to escalate is not established. For those requiring inpatient care, many escalate to second-line therapy if the child is not improving within 10–14 days of initiating first-line therapy [13]. The data for those managed in the outpatient setting is less clear and likely varies depending on physician assessment of symptom severity and AE subtype. Our standard practice is to give at least 1 to 2 months to assess response to first-line therapy, escalating sooner if the patient worsens.

Children with refractory disease may benefit from more novel treatments as well. Expert opinion in both adults and children is that treatment should be initiated once a diagnosis of AE is suspected, as autoantibody testing can take weeks to result, and many patients who meet the clinical criteria for AE will not have a detectable known anti-neuronal antibody. Given diagnostic criteria for adult anti-neuronal antibody-negative AE was just recently proposed and no pediatric criteria exist, the percentage of children with seronegative disease is unknown. In our clinical experience, up to a quarter of the children we care for have antibody-negative disease. While the identification of novel surface anti-neuronal antibodies continues to expand, the absence of an autoantibody should not dissuade treatment of children who meet the clinical diagnosis of AE [2, 11].The purpose of this review is to report current treatments for pediatric AE. We will highlight the stepwise approach to immunotherapy (Fig. 1) currently used in practice with a focus on both the physiologic and practical rationale for selecting various treatment options.

Treatment

First-line

The preponderance of studies to date demonstrates the efficacy of corticosteroids and IVIG, which are widely considered first-line medications for the treatment of suspected AE. Plasma exchange is also considered first-line therapy, though many in pediatrics reserve it for those with more severe disease, such as those requiring ICU level care [12]. Compared with other agents discussed in this paper, first-line therapies generally have a shorter latency to effect, proving them more useful in the immediate setting. These medications are often administered concurrently with or shortly after a thorough workup of the patient once AE is

suspected, as patients treated earlier in the course of their disease had improved outcomes compared to those treated later [9]. New recommendations encourage the initiation of first-line therapy once criteria for probable AE are met, prior to detection of a specific anti-neuronal antibody [4]. These first-line therapies (Table 2) are broad in their mechanisms of action and can therefore be utilized empirically. To illustrate this point, children with antibody-negative AE have similar response to first-line therapies compared with those who have a confirmed autoantibody [14]. Even children with a “missed” diagnosis who have had symptoms for months to years can show dramatic responses to immunotherapy. Therefore, regardless of antibody status or duration of symptoms, once a diagnosis of possible or definite AE is made, initiating therapy as soon as possible is indicated. While not discussed in detail in this paper, tumor removal in anti-NMDAR encephalitis and paraneoplastic diseases is an essential component of treatment [1, 14–16].

Steroids

Intravenous corticosteroids have long been the mainstay of first-line treatment in patients with acute exacerbation of a variety of autoimmune diseases. They have numerous effects on the immune system, including reduced leukocyte trafficking into tissues, reduced production of inflammatory cytokines, inhibition of interleukin-2, and T cell depletion. They are useful for CNS-involving disease because they have good penetration into the brain and modulate the blood-brain barrier. However, their use for AE is largely based on retrospective case reports in adult patients or extrapolated from data for other neurologic autoimmune diseases. Steroids do appear to increase the likelihood of good outcomes in patients across the spectrum of AE [1, 17, 18].

While corticosteroid regimens vary by provider, we generally start with intravenous(IV) methylprednisolone at 30 mg/kg (maximum dose of 1000 mg) once daily for 3 to 5 days. Dosing can be repeated depending on response and results of initial evaluation. There are no clear guidelines on how frequently to give repeat dosing. Our practice varies by severity of disease and response to steroids. We consider standard dosing of one infusion every 4 weeks for 3 months in the outpatient setting, but will commonly use dosing every 2 weeks or weekly in those with more severe disease, such as those requiring ICU-level care. We typically avoid oral steroid tapers as we find fewer side effects with intermittent IV dosing compared to prolonged oral steroid use, with reduced complications from mood/behavior changes, sleep disturbances, hypertension, hyperglycemia, and weight gain. If a patient has a good response to steroids but is unable to tolerate decreased dosing or extended dosing intervals, this indicates a more prolonged, ongoing inflammatory state that warrants an additional agent. However, we recommend additive therapy, such that additional agents are combined with continued steroids until the disease becomes well controlled. Only once the patient has demonstrated stability will we decrease the dose of steroids or space the infusions.

Some patients appear to improve with an initial course of IV corticosteroids (3–5 days in a row) but relapse quickly, making it difficult to ascertain whether they were truly steroid responsive. In patients with either antibody-positive or antibody-negative disease where the risks vs benefits of escalating immunotherapy are questioned, it is reasonable to stack steroid

doses, giving weekly infusions (one dose weekly) for 4 weeks to establish if they have clinical improvement. A similar approach has been used in autoimmune epilepsy to help establish reversibility with immunotherapy prior to escalating immunotherapy [19]. In addition, we have used dexamethasone with good effect in rare cases when patients with severe disease have minimal response to IV methylprednisolone [20, 21].

IVIG

Intravenous immunoglobulin (IVIG) is commonly given in conjunction with IV corticosteroids in the acute treatment of AE, although there are reports of its use alone. Its mechanism of action in suppressing the autoimmune response is broad, impacting both innate and adaptive immunity. This includes increasing B cell apoptosis and decreasing B cell proliferation, inhibiting complement activation, neutralizing cytokines, inhibiting dendritic cell differentiation, modulating regulatory T cells, and improving clearance of the pathogenic antibody by saturation of the FcRn receptor [22]. There are randomized trials showing evidence of efficacy of IVIG in non-encephalitic inflammatory neurologic diseases [23]. However, its use for AE is based on case reports and retrospective case series. Several retrospective studies in children specifically have shown improvement in functional outcome with the use of IVIG [2, 14, 24]. A randomized trial in children with encephalitis comparing IVIG with placebo is now ongoing [25].

While many providers report the administration of 2 g/kg IVIG divided over the course of 5 days, we have found that our pediatric patients tolerate a condensed 2-day administration quite well. The optimal dosing of IVIG for AE is not known; however, data from Kawasaki disease suggests higher dose IVIG given over a shorter duration is maximally effective at reducing inflammation quickly. Given the risks of infusion reactions, aseptic meningitis, and other complications of high dose IVIG, induction with 2 g/kg is usually given over 2 days, with monthly maintenance infusions of 1 g/kg over 1 day. Similar to IV steroids, if a patient is unable to taper off IVIG ± steroids by 6 months from initiation, or relapses during this time, we will add an additional disease-modifying agent.

Plasma exchange/plasmapheresis

Plasma exchange (PE), which involves removal and replacement of host plasma with human albumin or fresh frozen plasma, can be an effective adjunctive therapy in combination with steroids and/or IVIG. It is rarely used as monotherapy, but rather in those patients who have responded incompletely to steroids or IVIG and remain hospitalized [13]. Several retrospective studies have shown that PE plus steroids provides significant improvement in modified Rankin scores (mRS) compared with steroids alone [1, 26]. One prospective case control study showed improvement in mRS score (irrespective of prior immunotherapy) with both PE. PE appeared more effective for patients with cell surface autoantibodies (NMDA, LGI1, CASPR, mGluR5) compared with intracellular (Hu, GAD) antigens, consistent with the differences in disease pathogenesis previously discussed. Additionally, greater efficacy was seen in younger patients [27]. However, PE is associated with more adverse events compared with the aforementioned therapies and is therefore not favored as first-line [12]. The most common complications include infection, hypotension, and electrolyte imbalances

due to fluid shifts. Additionally, PE is more invasive as it necessitates a central catheter in children, and generally requires at least five sessions to sufficiently remove the offending antibodies. Protocols differ by institution with some receiving daily PE and others spaced to 2–3 per week. One must also be mindful of using PE shortly after IVIG or rituximab, as it will effectively remove these therapeutic antibodies. Studies have demonstrated significant clearance of rituximab if given within 3 days prior to plasmapheresis [28]. Our protocol is to give at least 5 days between rituximab infusion and the next cycle of plasmapheresis and to give IVIG once PE is complete, bridging with IV steroids after each PE cycle.

While there are a handful of prospective studies and small randomized trials demonstrating the efficacy of PE in adults with AE, studies in children are lacking. Because of this and the potential complications, we rarely utilize PE unless the child is severely affected in an ICU setting (due to seizures, dysautonomia, or coma), and steroids and IVIG have not been effective.

Second-line

Second-line therapy classically consists of rituximab and cyclophosphamide (CYC), though oral anti-metabolite agents such as mycophenolate mofetil (MMF) and azathioprine (AZA) may also be considered. In surveys of neurologists and rheumatologists, European providers were more likely to treat with oral anti-metabolites than their US counterparts [13]. Current expert opinion is to start second-line therapy in hospitalized patients if they are not showing signs of improvement within 10–14 days of first-line therapy [11]. While it is important to give adequate time for first-line therapy to take effect, one must not delay escalation of therapy if the patient is not improving. Significantly more patients with NMDAR encephalitis had a good outcome when treated early compared to those with delayed escalation of therapy [8, 29].

Given that AE is classically considered an antibody-mediated disease, we will first review antibody production. B cells are essential to antibody production through their differentiation into short lived plasma cells, or plasmablasts, and long-lived plasma cells. Plasmablasts are active, rapidly cycling cells which are the source of early antibody production and may be the primary cell type responsible for autoantibody production. This finding helps explain the rapid decline in autoantibody titers compared to overall immunoglobulin levels or protective anti-microbial antibodies with medications that target plasmablasts over long-lived plasma cells, such as rituximab. Ongoing autoantibody production in chronic autoimmune diseases requires continual development of plasmablasts from B cells, or their progression into long-lived plasma cells [30]. Long-lived plasma cells develop under the influence of follicular T helper cells in germinal centers [31]. While plasmablasts are rapidly cycling cells, plasma cells are post-mitotic, having silenced their cell cycle programming. They are therefore not susceptible to medications targeting the cell cycle/proliferation. Though these plasma cells have the potential to be long-lived antibody producers, their survival appears to depend on their microenvironment and continued stimulation from cytokines and other factors, including interleukin 6 (IL-6) and tumor necrosis factor (TNF). If the antibody is primarily produced by plasmablasts, one would expect more susceptibility to medications that target cell division. However, long-lived

plasma cells will not be as susceptible to these treatments and may preferentially respond to medications targeting cytokines or factors necessary to maintain plasma cell longevity.

Rituximab

Rituximab is a monoclonal, chimeric anti-CD20 antibody which acts to deplete B cells and CD20 expressing plasmablasts through both cell-meditated and complement-mediated cytotoxicity. It is important to note that rituximab does not target plasma cells. Though rituximab is classically considered a B cell treatment, ongoing studies have demonstrated more broad anti-inflammatory effects. Rituximab depletes B cells, preventing their development into antibody-producing plasma cells, and directly depletes plasmablasts [32]. In addition, it reduces production of cytokines that stimulate plasma cells and pro-inflammatory CD4 and CD8 T cell responses [33].

Rituximab can be used alone or in combination with CYC for those who require second-line treatment. A large survey of adult neurologists, pediatric neurologists, and pediatric rheumatologists revealed that the majority agreed with the choice of rituximab alone as second-line treatment (60% of US responses vs 53% of other countries) [13]. Studies in both adults and children demonstrate the efficacy of rituximab [20, 34–36]. Several large cohort studies of pediatric patients with NMDAR encephalitis have highlighted that over half of children will require second-line therapy with rituximab chosen most often. Overall outcomes even in children requiring second-line treatments are excellent with the majority having minimal residual disease [3]. The largest cohort study of NMDAR encephalitis to date demonstrated that patients who received second-line therapy with rituximab ± CYC had improved outcomes compared to those who did not [2]. While treatment with rituximab has been suggested to reduce relapse risk, there is insufficient data to make this assessment currently [36].

Common protocols include either weekly dosing for 4 weeks at 375 mg/m^2 per dose, or 750 mg/m2 for two doses 2 weeks apart, with a maximum of 1000 mg per dose in both protocols. We prefer to use the latter in our practice. We also recommend continuing first-line therapy while waiting for the immunomodulatory effects of rituximab which typically takes several weeks to months to take effect. The ideal dosing of rituximab has not been determined. One small study of 10 patients with NMDAR encephalitis used low dose rituximab (100 mg IV weekly for 4 weeks), resulting in 30% of their patients with a full recovery, 5 with partial response and 1 who failed to improve [37]. While peripheral depletion of B cells is seen at lower doses, higher doses and serum levels are needed for depletion in extravascular sites [38]. Additionally, higher doses are associated with higher CNS concentrations, though the ideal dosing and necessary CNS concentration for efficacy are not known. Given the limited CNS bioavailability of rituximab, if the patient has significant intrathecal antibody production and fails to respond to treatment, other agents should be considered.

The safety of rituximab in pediatric neurologic disease was reviewed in a study of 144 children with a variety of autoimmune neurologic diseases, including 39 children with NMDAR encephalitis. Rituximab was found to be well tolerated overall. Infusion reactions

occurred in 12% but responded to treatment with anti-histamines and steroids. Only one patient was unable to tolerate re-dosing of rituximab. Eight percent of children developed serious infections that were at least in part attributed to rituximab, and only one patient had neutropenia [8]. Progressive multifocal leukoencephalopathy has not been reported in the NMDAR encephalitis literature in the > 130 patients treated with rituximab alone or in combination with other immunomodulatory agents [8, 10]. Similar rates of side effects to rituximab have been reported in pediatric cohorts with NMDAR encephalitis [3]. Additionally, rituximab has been used safely in children with post-herpes simplex NMDAR encephalitis [39]. Monitoring of blood counts, lymphocyte panel, and immunoglobulins is necessary as children can develop cytopenias, persistent B cell depletion, and prolonged hypogammaglobulinemia.

Cyclophosphamide

CYC is classified as an alkylating agent with antimitotic and antireplicative effects through inhibition of DNA synthesis [40, 41]. CYC has broad effects on the immune system, suppressing cell-mediated and humoral immunity through its actions on T cells and B cells, but may be less efficacious with long-lived plasma cells [42]. CYC has an advantage in CNS autoimmunity due to its bioavailability within the CNS. Consequently, it may induce local immunomodulation and immunosuppression even after the formation of lymphatic tissues in the CNS, stabilizing the disease and preventing further progression. Evidence of the direct intrathecal and intracerebral actions of CYC on compartmentalized immune cells was provided in studies of both multiple sclerosis and in anti-glutamic acid decarboxylase (GAD) antibody associated epilepsy. In GAD-associated refractory status epilepticus, treatment with CYC resulted in cessation of seizures and intrathecal production of anti-GAD antibody [43].

CYC has been reported as part of the treatment armamentarium for anti-NMDAR encephalitis for a decade [12, 44] and more recently for AE in general [45]. There are no clinical trials supporting the use of CYC in AE or defining optimal dosing recommendations. Though CYC is clearly considered a second-line therapy, it is used less frequently than rituximab in pediatric AE due to its side effect profile [13]. In our practice, we reserve CYC for refractory disease. Duration of therapy varies from two doses in conjunction with rituximab, to more chronic therapy from 3 to 24 months depending on severity and response to treatment. There are numerous potential severe adverse effects including infertility, infection, and malignancy that likely explain the preference for other immunomodulatory therapy.

Mycophenolate mofetil and azathioprine

Though rituximab and CYC are the most frequently used second-line agents, oral agents (MMF or AZA) may have utility as well. Their use is more prevalent in Europe compared to the USA (15 vs 5%), but there are inadequate data to make conclusions about their efficacy in AE [10, 13, 36, 46]. In our experience, these medications can be helpful for patients who have had significant benefits from first-line therapy but are unable to taper IV steroids and/or IVIG without relapse. Conceptually, they are beneficial in antibody-negative disease where

the role of antibodies vs cellular immunity is less clear. We preferentially utilize MMF based on its apparent efficacy over AZA in primary CNS vasculitis [47]. However, in patients who have been unable to tolerate MMF, we have seen good response to AZA as well, with both enabling a taper off IVIG and steroids. Additionally, we have used these agents in patients who respond well to rituximab, but have early B cell repopulation, as a strategy to provide added coverage.

Tocilizumab

There are also several novel medications for the treatment of refractory AE. Interleukin-6 (IL-6) is a pro-inflammatory cytokine with pleotrophic effects on a broad range of cells including neutrophils, T cells, B cells, and plasma cells [48]. IL-6 is a key mediator in plasmablast and plasma cell survival. Plasmablasts produce high levels of IL-6, which is essential for inducing follicular T helper cells. These in turn are essential for production of long-lived plasma cells. IL-6 is therefore a key cytokine for the differentiation and survival of plasma cells [49]. Tocilizumab, an IL-6 inhibitor, was found to be effective for the treatment of refractory neuromyelitis optica spectrum disorder (NMOSD), and a trial is in progress [50–52]. A retrospective cohort study in patients meeting criteria for probable AE who failed to respond to first-line therapy plus at least 4 weeks of rituximab compared treatment with tocilizumab (8 mg/kg IV monthly) vs repeat rituximab dosing vs no additional treatment. At all time points, the tocilizumab group had significantly more patients with a mRS of ≤ 2 than the other two groups. By month 2 of tocilizumab treatment, 60% of patients had a mRS of ≤ 2, which was similar to the last follow-up time point in the tocilizumab group and significantly improved compared to the rituximab group at 2 months (19.4%) and last follow-up (22%) [53]. We have seen remarkable responses in three children with prolonged disease refractory to steroids, IVIG, rituximab, and anti-metabolites, and promising results in two others after 1 month. Tocilizumab has been shown to be well tolerated in children, though adverse effects include infusion reactions, infections, neutropenia, transaminitis, and gastrointestinal perforations. Monitoring of cell counts, liver enzymes, and lipids is important to prevent toxicity.

Bortezomib

The ubiquitin-proteasome system is important for maintenance of cellular homeostasis by controlling intracellular protein degradation. Proteasome inhibitors have a broad range of effects on many cells in the immune system but are particularly potent against plasma cells [54]. Several proteasome inhibitors are approved, but to date, only bortezomib has been used to treat AE refractory to first- and second-line therapy. Two case reports have demonstrated improvements with bortezomib in patients with severe NMDA encephalitis [55, 56]. A separate case series of five patients with NMDA encephalitis treated with between one and six doses of bortezomib demonstrated responses from mild improvement in neurocognitive deficits to complete clinical remission. A partial list of the adverse effects of bortezomib includes infections, gastrointestinal intolerance, peripheral neuropathies, and cytopenias [57].

Interleukin-2

Low doses of interleukin-2 (IL-2) preferentially activate T regulatory cells whereas high doses preferentially activate CD8+ effector T cells [58]. There is growing interest in using low-dose IL-2 to treat a wide range of autoimmune diseases including AE [59–61]. Ten patients were treated with low-dose IL-2 due to treatment-refractory AE [62]. After four treatment cycles, symptoms improved in 60% and no patients worsened. Adverse effects included eosinophilia, subclinical hyperthyroidism, neutropenia, GI intolerance, and flu-like symptoms [62].

Adjunct therapy

In addition to immunotherapy, ongoing symptomatic treatment with anti-epileptic drugs (AEDs) and psychiatric medications are often necessary to maximize functionality and minimize suffering. Benzodiazepines, often at high doses, are frequently used early in the course of disease for agitation, seizures, and catatonia. Catatonia is a prominent feature in many children with AE and differentiating it from psychosis and avoiding antipsychotic medications in those cases can avoid precipitating neuroleptic malignant syndrome [1, 63, 64]. In our experience, with careful assessment to differentiate catatonia from psychosis, antipsychotics can be used safely and effectively to manage psychosis in AE patients, especially once immunotherapy has been initiated [65]. Recovery is often protracted and adjusting to both transient and permanent deficits can be challenging. Being proactive with physical, occupational, and speech therapy along with mental health services can greatly improve patient outcomes and re-entry into their communities.

Conclusion

There is growing evidence to support first- and second-line therapies for AE but prospective, randomized, placebo-controlled studies are lacking. Corticosteroids, IVIG, and plasma exchange are considered first-line therapies. If there is no improvement within 10–14 days of first-line therapy initiation, escalation to a second-line therapy of rituximab or CYC should not be delayed. First-line therapy should be continued when escalating to a second-line therapy. Current practice for pediatric patients shows a preference for rituximab over CYC due to a better side effect profile. There is growing evidence for novel agents including tocilizumab and bortezomib for treatment-refractory disease.

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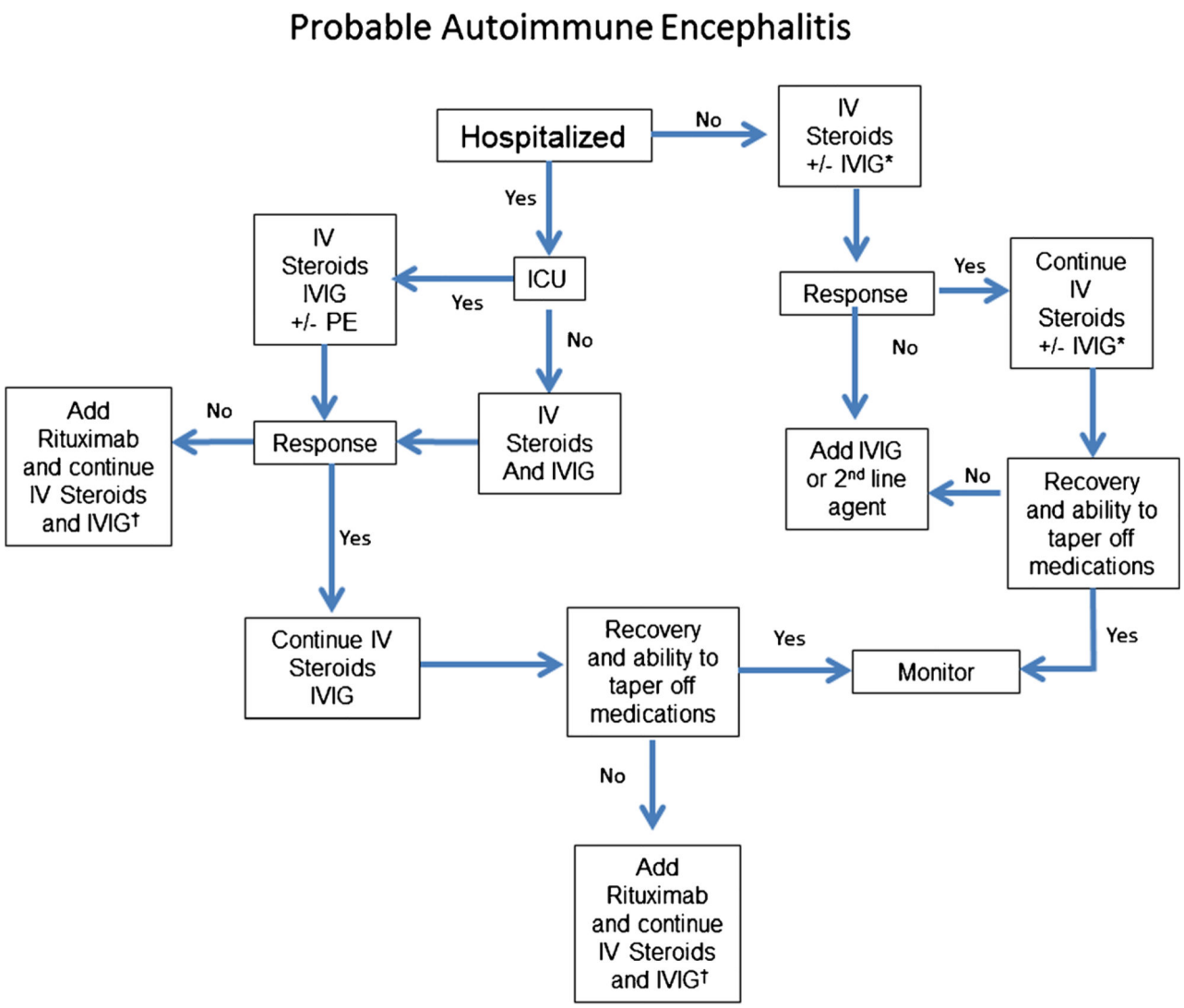

PE=Plasma exchange IV steroids=IV methylprednisolone or dexamethasone.
2nd line agents include rituximab, mycophenolate mofetil, azathioprine
*Depending on severity and results of evaluation consider IV steroids alone vs adding IVIG. Recommend 3-6 months of sustained treatment before tapering.
†Continue 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.

Fig. 1.

Probable autoimmune encephalitis. PE = Plasma exchange, IV steroids = IV methylprednisolone or dexamethasone. Second-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.

Table 1

Possible autoimmune encephalitis diagnostic criteria

Requires all three of the following:

1 Acute[a] to subacute onset of deficits in working memory (short-term memory loss), altered mental status or psychiatric symptoms

2 At least one of the following:

- New focal central nervous system finding
- Seizures (not explained by previously known seizure disorder)
- CSF WBC count > 5 cells/mm^3
- MRI suggestive of encephalitis

3 Exclusion of alternative cause

[a]Modified as pediatric patients often present with an acute presentation

Table 2

Treatment regimens for autoimmune encephalitis in children

Therapy	Initial dosing	Subsequent dosing	Lab monitoring
First line			
Corticosteroids	Methylprednisolone 30 mg/kg (max 1000 mg) daily × 3 to 5 days OR Dexamethasone 5 mg/kg IV (max 200 mg) once	30 mg/kg (max 1000 mg) once monthly (may consider more frequent dosing in severe disease) Dexamethasone 5 mg/kg IV (max 200 mg) once monthly	None none
IVIG	2 mg/kg divided over two days	1 g/kg once monthly	IgA prior to initiation (optional)
Plasmapheresis OR plasma exchange	5–7 exchanges over 5 days to 14 days (recommended). Replacement fluid: albumin OR FFP	Not established	ionized calcium, ferritin
Second line			
Rituximab	750 mg/m^2 (max 1000 mg) for two doses 14 days apart OR 375 mg/m2 once weekly × 4 weeks	750 mg/m^2 (max 1000 mg) OR 375 mg/m^2 every 24 weeks. Note: can decrease interval if relapse or CD20 repopulation prior to 24 week. If requiring more than once every 16 weeks dosing consider novel therapies or CYC	Prior to Initiation: CBC/D, ALT, AST, CD20 count, immunoglobulins, BHCG, PPD Quarterly: CBC/D, immunoglobulins, +/− CD20 count starting 3–4 months following infusion and prior to next infusion, BHCG
Cyclophosphamide	750 mg/m^2 (max 1000 mg) once with pre-hydration	1000 mg/m^2 (max 1500 mg) once monthly for 3–6 months depending on severity of disease and response to therapy	Prior to Initiation: CBC/D, ALT, AST, BUN, Cr, BHCG During infusion: urine SG and blood Day 7–10: CBC/D
Oral adjunct therapies			
Mycophenolate mofetil	300 mg/m^2 every 12 h with titration up over one month to goal dose 600 mg/m^2 (titration to improve GI tolerance)	600 mg/m^2 every 12 h (max 1500 mg every 12 h)	Prior to Initiation: CBC/D, ALT, AST, BHCG Quarterly: CBC/D, ALT, AST, BHCG, mycophenolic acid level
Azathioprine	0.5–1.0 mg/kg once daily titrate after 1 month	2.0–2.5 mg/kg max 150 mg once daily	Prior to Initiation: CBC/D, ALT, AST, BUN, Cr TPMT enzyme level and activity During titration: CBC/D, ALT, AST, BUN, Cr every 2 weeks until at stable dose Quarterly: CBC/D, ALT, AST, BUN, Cr
Novel therapies			
Tocilizumab	8–12 mg/kg IV (max 800 mg) once	8–12 mg/kg IV (max 800 mg) once monthly	Prior to Initiation-CBC/D, ALT, AST, BHCG, cholesterol One month then quarterly: CBC/D, ALT, AST, BHCG Semiannually: Cholesterol
Bortezomib	No standardized dosing in children	See initial dosing regimen	CBC/D, AST, ALT, BHCG, CXR, periodic PFTs
Low-dose IL-2	1.5 million IU[a] SQ once daily × 5 days	3 million IU[a] SQ once daily × 5 days at weeks 3, 6, and 9	CBC/D, electrolytes, BUN, Cr, AST, ALT, CXR, TSH, periodic PFTs

[a]Body surface area or weight-based dosing not reported

BHCG beta-HCG, *BUN* blood urea nitrogen, *CBC/D* complete blood count with differential, *Cr* creatinine, *CXR* chest x-ray, *FFP* fresh frozen plasma, *PFTs* pulmonary function tests, *PPD* purified protein derivated for tuberculosis, *SG* specific gravity, *TPMT* thiopurine methyltransferase, *TSH* thyroid stimulating hormone

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

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Abstract

Introduction: Pediatric Acute-onset Neuropsychiatric Syndrome (PANS) is a clinically heterogeneous disorder with a number of different etiologies and disease mechanisms. Inflammatory and postinfectious autoimmune presentations of PANS occur frequently, with some clinical series documenting immune abnormalities in 75%–80% of patients. Thus, comprehensive treatment protocols must include immunological interventions, but their use should be reserved only for PANS cases in which the symptoms represent underlying neuroinflammation or postinfectious autoimmunity, as seen in the PANDAS subgroup (Pediatric Autoimmune Neuropsychiatric Disorders associated with Streptococcal infections).

Methods: The PANS Research Consortium (PRC) immunomodulatory task force is comprised of immunologists, rheumatologists, neurologists, infectious disease experts, general pediatricians, psychiatrists, nurse practitioners, and basic scientists with expertise in neuroimmunology and PANS-related animal models. Preliminary treatment guidelines were created in the Spring of 2014 at the National Institute of Health and refined over the ensuing 2 years over conference calls and a shared web-based document. Seven pediatric mental health practitioners, with expertise in diagnosing and monitoring patients with

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PANS, were consulted to create categories in disease severity and critically review final recommendations. All authors played a role in creating these guidelines. The views of all authors were incorporated and all authors gave final approval of these guidelines.
Results: Separate guidelines were created for the use of immunomodulatory therapies in PANS patients with (1) mild, (2) moderate-to-severe, and (3) extreme/life-threatening severity. For mildly impairing PANS, the most appropriate therapy may be ''tincture of time'' combined with cognitive behavioral therapy and other supportive therapies. If symptoms persist, nonsteroidal anti-inflammatory drugs and/or short oral corticosteroid bursts are recommended. For moderate-to-severe PANS, oral or intravenous corticosteroids may be sufficient. However, intravenous immunoglobulin (IVIG) is often the preferred treatment for these patients by most PRC members. For more severe or chronic presentations, prolonged corticosteroid courses (with taper) or repeated high-dose corticosteroids may be indicated. For PANS with extreme and life-threatening impairment, therapeutic plasma exchange is the first-line therapy given either alone or in combination with IVIG, high-dose intravenous corticosteroids, and/or rituximab.
Conclusions: These recommendations will help guide the use of anti-inflammatory and immunomodulatory therapy in the treatment of PANS.

Keywords: corticosteroids, IVIG, NSAIDs, PANDAS, PANS, plasmapheresis

Introduction

The diagnosis of Pediatric Acute-onset Neuropsychiatric Syndrome (PANS) is made based on an unusually abrupt onset of obsessive-compulsive (OC) symptoms and/or restricted eating behaviors with at least two comorbid symptoms, including anxiety, emotional lability and/or depression, irritability/oppositionality/aggression, behavior regression, deterioration in school performance, sensory or motor abnormalities, and somatic symptoms. By definition, PANS is a diagnosis of exclusion, so it is only made in the absence of evidence for other neurological or psychiatric conditions (Swedo et al. 2012). Although a comprehensive diagnostic evaluation should yield a clinical diagnosis, options for treatment are more complex, as PANS is a syndromic illness in which the psychiatric and behavioral abnormalities represent a ''final common pathway'' for a number of disparate disorders with varied etiologies and disease mechanisms (Swedo et al. 2012; Chang et al. 2015). Despite the heterogeneity of PANS' presentations, neuroinflammation is postulated to play a role in the etiopathogenesis for the majority of PANS cases with some case series documenting immune abnormalities in >80% of PANS patients (Frankovich et al. 2015a; Murphy et al. 2015; Swedo et al. 2015). Although not all patients with PANS require immunomodulatory therapies, immunomodulatory interventions are an important consideration in the treatment of acute-onset neuropsychiatric symptoms. When indicated, they should be used in conjunction with other therapies. Conventional psychiatric and behavioral interventions provide direct symptomatic relief and are the mainstay of treatment for the behavioral manifestations of PANS (Thienemann et al. 2017). Targeted antimicrobial therapy also may be useful for children when bacterial infectious triggers have been identified (Cooperstock et al. 2017).

For most autoimmune/inflammatory disorders, the clinical presentation and observed disease course guide treatment choices for each individual patient. The same is true for PANS, which has variable presentations and clinical trajectories. Treatment should be individualized to address the patient's primary symptoms, impairments, and clinical course. Patients with PANS may present with a new-onset or acute flare and follow a relapsing-remitting, chronic-static, or chronic-progressive course. PANS cases with a new-onset or acute flare and documented infectious trigger, such as the subset of cases meeting criteria for Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal infection (PANDAS), (Swedo et al. 1998) are comparable to Sydenham's chorea (SC). In SC, interventions are targeted toward elimination of the infectious trigger, termination of the post-infectious inflammatory brain process, and prevention of future relapses. PANS cases that follow a relapsing-remitting course may be comparable to other episodic disorders such as multiple sclerosis (MS), Behçet's disease, and asthma (in the opinion of the authors); as in these disorders, treatment focuses on amelioration of the current episode and prevention of future recurrences. The authors believe that PANS patients presenting with severe symptoms and a chronic-static or chronic-progressive course require consideration of more intensive immunomodulatory approaches like those used for neuropsychiatric systemic lupus erythematosus (NPSLE), central nervous system (CNS) vasculitis, autoimmune encephalitis (AE), chronic-progressive MS, chronic-progressive Behçet's disease, and other persistent neuroinflammatory disorders. In these chronic illnesses, as in PANS, infections and other environmental triggers are thought to play a role in provoking an inflammatory brain response, which evolves into a chronic or progressive neuroimmune disorder (Duzova and Bakkaloglu 2008; Costa-Reis et al. 2013; Van Mater 2014; Graus et al. 2016).

In most of the aforementioned inflammatory brain diseases, diagnosis requires evidence for inflammation (peripheral or central). In the case of seronegative AE, evidence of inflammation is typically nonspecific as cerebrospinal fluid (CSF) biomarkers are lacking. Traditional measures of brain inflammation (CSF pleocytosis, protein, and oligoclonal bands) are thought to have limited sensitivity (Dale et al. 2017) and these ''false negatives'' complicate diagnostic evaluations and treatment decisions. Despite these limitations, it is important to look for such biomarkers, as their presence confirms the presence of CNS inflammation. Additional support for organic cause of the child's mental health deterioration comes from abnormalities of electroencephalography, polysomnography (PSG), and brain imaging studies (magnetic resonance imaging [MRI] with and without contrast). Finally, findings on the physical examination or results of laboratory studies often reveal evidence of systemic inflammation and/or postinfectious autoimmunity—which may support the use of anti-inflammatory and immunomodulatory interventions.

The empiric literature for treatment of PANS is scant, but extensive clinical experience with >1000 patients (cumulative total evaluated by PANS Research Consortium [PRC] clinicians) provides strong anecdotal evidence to support the use of anti-inflammatory

and immunomodulatory therapies in PANS. Significant progress in reducing symptom severity and improving functioning can be accomplished even before evidence emerges from clinical trials, as has been shown for other inflammatory disorders including juvenile idiopathic arthritis, NPSLE (neuropsychiatric lupus), CNS vasculitis, AE, and chronic-progressive Behçet's disease (Hashkes and Laxer 2005; Pohl and Benseler 2013; Van Mater 2014). The immunomodulatory recommendations listed hereunder for severe-to-extreme PANS and chronic-progressive PANS are in accord with management strategies used in other pediatric inflammatory brain disorders (Duzova and Bakkaloglu 2008; Pohl and Benseler 2013; Titulaer et al. 2013; Bale 2015; Dale et al. 2017). Particularly apt are the general ''principles'' of treatment of AE: (1) Patients given immunotherapy do better and relapse less frequently than patients given no treatment. (2) Patients given early treatment do better than patients treated late. (3) When patients fail first-line therapy, second-line therapy improves outcomes and reduces relapses (Nosadini et al. 2015). These ''tenets'' generally hold true for all autoimmune diseases.

Given the limited precision with which PANS/PANDAS can be diagnosed, and the rudimentary understanding of the pathogenesis, any treatment guidelines cannot be definitive. In this article, we acknowledge these limitations while offering guidelines, developed in the context of current knowledge, to aid care-providers in making treatment decisions.

Rationale for Using Immunomodulatory Therapy in PANS

Accumulating evidence supports conceptualizing PANS as an immune-mediated brain disease, akin to SC and PANDAS, involving the caudate, putamen, and other basal ganglia structures. Data supporting this model come from epidemiological, clinical, paraclinical, translational, and basic science investigations of PANDAS and SC. In both PANS and PANDAS, clinical evaluations (Frankovich et al. 2015a; Murphy et al. 2015) and research data (Hornig 2013; Hornig and Lipkin 2013; Cutforth et al. 2016) suggest that immune dysfunction may occur at multiple levels: local (targeted) dysfunction relating to cross-reactive antibodies that recognize specific CNS antigens; regional dysfunction relating to inflammation within neuronal tissues or vasculature of the basal ganglia; and systemic abnormalities of cytokine and chemokine production, with resultant disruption of the blood–brain barrier (BBB) and CNS functions (Williams and Swedo 2015). Animal models of PANDAS and SC point to an essential role of the adaptive immune response (autoantibodies and Th17 cells) as possible contributors to disease pathogenesis and neurovascular damage (Hoffman et al. 2004; Yaddanapudi et al. 2010; Brimberg et al. 2012; Cox et al. 2013; Lotan et al. 2014; Cutforth et al. 2016; Dileepan et al. 2016).

Evidence for group A *Streptococcus* (GAS)-specific cross-reactive antibodies having affinity for neuronal components (including receptors) in the basal ganglia has been demonstrated in human and animal studies (Husby et al. 1976; Kirvan et al. 2003, 2006a, 2006b, 2007; Hoffman et al. 2004; Yaddanapudi et al. 2010; Brimberg et al. 2012; Lotan et al. 2014). Sera and immunoglobulin G (IgG) from SC and PANDAS patients known to bind to components of the GAS cell wall have also been shown to cross-react with components of neurons in the basal ganglia caudate, putamen, and internal segment of the globus pallidus (Kirvan et al. 2006b). Antineuronal IgG antibodies binding to multiple targets, including lysoganglioside, tubulin, and dopamine receptors, have been reported to be elevated in patients with SC and PANDAS compared to controls (Kirvan et al. 2003, 2006a, 2006b, 2007; Cox et al. 2013, 2015). Targeting of such antibodies to dopaminergic neurons in the substantia nigra and ventral tegmental area in the basal ganglia (as well as other cortical neurons) was confirmed in transgenic mice expressing a chimeric antineuronal autoantibody containing $V_H \pm V_L$ regions cloned from a patient with SC (Cox et al. 2013).

Binding of cross-reactive antibodies to neuronal cells can activate intracellular signaling pathways, thereby affecting neuronal function. Addition of serum samples from patients with SC or OC and tic disorders to cultured human neuronal cells activated the enzyme calcium calmodulin-dependent protein kinase II (CAMKII) to levels significantly more than both basal cellular levels and levels induced with serum from controls (Cox et al. 2015; Singer et al. 2015). The antineuronal IgGs have the potential to affect neuronal function, as shown by their induction of increased tyrosine hydroxylase (the rate-limiting enzyme in dopamine synthesis) expression in rat brains and increased dopamine release in cultured human neuronal cells (Kirvan et al. 2006a).

Further supporting a role for the adaptive immune response in disease pathogenesis, cross-reactive antibody levels have been found to correlate with disease activity in humans and to directly induce behavioral changes in rodent models. Among SC and PANDAS patients, serum concentrations of cross-reactive antineuronal autoantibodies reacting to lysoganglioside, tubulin, and dopamine receptors (D1 and D2) are increased during acute flares and decreased during periods of symptom remission (Kirvan et al. 2003, 2006a, 2006b, 2007; Brimberg et al. 2012). Rodents peripherally immunized with inactivated GAS antigen, along with agents that help to breach the BBB, demonstrate a range of cognitive and behavioral disturbances including anxiety, repetitive behaviors and others in parallel with production of cross-reactive antibodies (Hoffman et al. 2004; Brimberg et al. 2012). Furthermore, passive transfer of these GAS-induced cross-reactive antibodies, through infusion into the basal ganglia of rats or by transfer into the peripheral circulation of mice, resulted in antibody binding to brain targets and produced stereotypies and abnormal behaviors reminiscent of the human disease (Yaddanapudi et al. 2010; Lotan et al. 2014).

In contrast to the aforementioned mouse models, which used killed GAS or GAS components, a novel mouse model used multiple intranasal infections with live GAS. The investigators found that four intranasal GAS infections generated GAS-specific Th17 cells that migrated from the nasal-associated lymphoid tissue (the equivalent tissue to human adenoids) into the brain through the olfactory sensory axons. The entry of Th17 cells into the brain was associated with neurovascular damage, including BBB breakdown, neuroinflammation (activation of microglia), and synaptic pathology (loss of excitatory synaptic proteins essential for neurotransmission). This group simultaneously reported that GAS-specific Th17 cells were also present in human tonsils. In this novel mouse model, as previously described in SC, there is evidence of increased levels of cytokines that promote both Th17 responses (interleukin-6 and transforming growth factor beta) and antibody production (Dileepan et al. 2016).

In humans with PANDAS, evidence for regional brain abnormalities comes from neuropsychological evaluations, PSG, and neuroimaging studies demonstrating striatal dysfunction during symptom exacerbations (Williams and Swedo 2015). For example, systematic neuropsychological testing reveals specific deficits of executive function and visuospatial skills, which have been previously shown to reflect basal ganglia dysfunction (Casey et al.

1994a, 1994b; Hirschtritt et al. 2009; Lewin et al. 2011). PSG evaluation found abnormalities of sleep architecture and the pathological presence of movements during rapid eye movement sleep in 13 of 15 (87%) PANS patients, which provides direct evidence of neurological disruption (Gaughan et al. 2016). Volumetric MRI analyses of 34 children with PANDAS showed specific increases in the volume of the caudate, putamen, and globus pallidus during acute illness when compared with 82 age-/sex-matched controls (Giedd et al. 2000). Successful treatment with therapeutic plasma exchange (TPE) correlated with normalization of caudate size in one such case (Giedd et al. 1996). Most recently, Chugani and colleagues used positron emission tomography (PET) and the radiopharmaceutical 11C-[R]-PK11195, which binds to activated microglia in the brain, to study 17 children with PANDAS during acute illness. More microglial activation was demonstrated in actively ill PANDAS patients and Tourette syndrome (TS) patients compared with controls. This microglial activation was present in the bilateral caudate and lentiform nuclei in patients with PANDAS and only the caudate in patients with TS. The abnormalities improved in four of five PANDAS subjects treated with intravenous immunoglobulin (IVIG). In the remaining PANDAS case, the initial higher neuroinflammation indications resolved after further IVIG treatment (Kumar et al. 2015).

Further evidence (although indirect) to support immune dysfunction in PANS comes from the high frequency of immune-based conditions (including autoimmune/inflammatory conditions) in patients and their first degree family members (Frankovich et al. 2015a; Murphy et al. 2015). Approximately 71% of patients' families had one or more first degree relatives with autoimmune/inflammatory disorders (Frankovich et al. 2015a). Further indirect evidence that inflammation can contribute to OC symptoms comes from the frequent association of obsessive-compulsive disorder (OCD) and other neuropsychiatric symptoms in systemic autoimmune diseases like NPSLE, wherein neuropsychiatric symptoms wax and wane in conjunction with systemic inflammation (Slattery et al. 2004; Magro-Checa et al. 2016). Compelling indirect evidence of the link between maternal autoimmunity and tics comes from studies of male offspring with TS and of children with OCD and tics (Murphy et al. 2010; Dalsgaard et al. 2015).

Support for immunomodulation in PANDAS comes from observed benefits of immunomodulatory therapy, with improvements after treatment of PANDAS with IVIG or TPE similar to those reported for SC, Guillain–Barre syndrome, and antibody-mediated AE (Garvey et al. 2005; Dalmau et al. 2011; Hughes et al. 2014). IVIG has been shown to have benefits for each of these disorders, although dosing regimens vary and the mechanism of benefit is unknown (Wong and White 2016). A double-blind, placebo-controlled investigation showed that IVIG and TPE were both effective in reducing OC symptoms in PANDAS patients (by 45% and 58%, respectively), whereas a placebo infusion had no discernable effect (Perlmutter et al. 1999). The results of the trial were sufficiently robust to convince the American Society of Apheresis to include TPE as a Category I, first-line treatment option for PANDAS, as well as for SC (Weinstein 2008). Subsequent to the controlled trial, several case reports and two case series provide additional support for the therapeutic benefits of TPE and IVIG (Giedd et al. 1996; Tucker et al. 1996; Elia et al. 2005; Garvey et al. 2005; Hachiya et al. 2013; Frankovich et al. 2015b; Gerardi et al. 2015; Kovacevic et al. 2015; Latimer et al. 2015). In contrast, non-PANDAS OCD (Nicolson et al. 2000) and tic disorders (Hoekstra et al. 2004) fail to benefit from TPE and IVIG, respectively.

Although the use of IVIG in the treatment of PANS/PANDAS has received considerable attention in the past decade, no additional placebo-controlled trials were published until this past year (Williams et al. 2016). This trial, conducted jointly between National Institute of Mental Health (NIMH) and the Yale Child Study Center, enrolled rigorously screened subjects and randomized them to receive either IVIG ($n = 17$) or placebo ($n = 18$) in a double-blind study. At 6 weeks, the mean decrease in OCD severity was greater in the IVIG cohort than in placebo, but this difference did not reach statistical significance. Subjects who did not meet ''Responder'' status in the trial at the 6-week evaluation interval were offered an open-label IVIG infusion. OCD severity scores for those receiving open-label IVIG (regardless of whether they had received a placebo or blinded IVIG infusion) decreased roughly 50% in 6 weeks. Because these improvements were noteworthy only during the open-label phase of the trial, it is not possible to determine how much of this response is because of a positive psychological effect of receiving treatment rather than from the IVIG itself. A number of unanticipated events (multiple subjects acquired new GAS infections during the trial), as well as the study design issues, may have decreased the effect size of the trial. In particular, participants may have over-reported symptom severity in the double-blind portion of the study to increase the possibility of getting open-label IVIG at 6 weeks. Resolution of the conflicting results of the two controlled trials of IVIG will require additional data from carefully controlled clinical trials.

Methods

The PRC immunomodulatory task force (ITF) is comprised of immunologists, rheumatologists, neurologists, infectious disease experts, general pediatricians, psychiatrists, nurse practitioners, and basic scientists with expertise in neuroimmunology and PANS-related animal models. The purpose of PRC-ITF was to develop treatment guidelines for the use of anti-inflammatory and immunomodulatory therapies to treat patients with PANS and PANDAS. Preliminary guidelines were created in the Spring of 2014 at the NIMH. Treatment guidelines were refined over the ensuing 2 years over numerous conference calls. These guidelines are based on the expert opinions and clinical experiences of the members of the PRC-ITF and psychiatrists who participated in this process. The article was collaboratively shared and edited as a web-based document wherein all authors incorporated their opinions and experience in using these immunomodulatory therapies to treat patients with PANS. Seven pediatric mental health practitioners (primarily psychiatrists), with expertise in diagnosing and monitoring patients with PANS, were consulted to create categories in disease severity and to critically review final guidelines. All authors played a role in creating and/or forming these guidelines and were also given the opportunity to provide anonymous feedback. The views of all authors were incorporated into the article and all authors gave final approval of these guidelines.

Use of Immune Therapies for PANS

Immunomodulatory treatment for PANS/PANDAS requires an individually tailored approach, with the intensity of the therapeutic intervention matched to the severity of the child's symptoms and disease trajectory. To reflect this, we have organized guidelines to address treatment of mild, moderate-to-severe, and extreme/life-threatening clinical presentations. We have made additional recommendations based on disease trajectory, as patients with a single disease episode and relapsing-remitting disease are treated

differently from those with long-standing chronic-static or chronic-progressive course. Table 1 provides an overview of treatment approaches used for PANS based on disease trajectory.

We want to highlight the importance of mental health providers in both the initial evaluation and ongoing assessments of patients with PANS, as these careful assessments of diseases severity, trajectory, and illness course are needed by the medical team to tailor immunomodulatory treatments.

Before initiating immunotherapy, we recommend that clinicians pursue a complete inflammatory brain disease work-up based on published guidelines for AE, CNS vasculitis, NPSLE, acute disseminated encephalomyelitis (ADEM), and Behçet's disease (Van Mater 2014;

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). (2) Refer for CBT and provide other supportive therapies (Thienemann et al. 2017). (3) Consider early use of corticosteroids (oral bursts or IV pulses) to abort or shorten flares (Tables 2 and 3). (4) Consider high-dose IVIG or other immunomodulatory therapies in moderate-to-severe cases (Tables 2 and 4).
Relapsing-remitting	(1)–(4) as above. (5) Evaluate for possibility of recurrent infections/exposures triggering flares. (a) If GAS infection is a frequent trigger for relapses, evaluate/treat close contacts and consider prophylaxis according to guidelines (Cooperstock et al. 2017). (b) Keep in mind that most flares are viral triggers. See (2)–(4) above for treatment of each flare. (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 *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. (5) Pursue immunomodulatory therapies according to symptom categories below: Mild-to-moderate neuropsychiatric symptoms: NSAIDs (Table 3). Oral corticosteroid burst (Table 3) to see whether baseline improves. Caution: use of combination NSAIDs+corticosteroids may result in gastritis; but these medications can be used safely in tandem. Mild-to-moderate neuropsychiatric symptoms with no response to NSAIDs and/or short burst of corticosteroids: (Repeat) oral prednisone ± prolonged taper (Table 3). Pulse corticosteroids (oral dexamethasone or IV methylprednisolone) (Table 3). Moderate-to-severe neuropsychiatric symptoms: Oral prednisone±taper or pulse corticosteroids (Table 3). High-dose IVIG or other induction steroid-sparing agent (Table 4). Severe-to-extreme neuropsychiatric symptoms: Refer to subspecialists for further evaluation for AE, NPSLE, CNS vasculitis, and consideration of using established (published and institutionally based) treatment protocols. Consider high-dose IV corticosteroids and/or other immunotherapies (Tables 3 and 4). Refractory disease course (i.e., psychiatric symptoms not responsive to initial immunomodulatory approaches already mentioned and no improvement in neurological signs): 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). Consider possibility of injured neurocircuitry and need for shifting to primary rehabilitation mode.

[a]If the patient meets criteria for another brain inflammatory disease, follow the corresponding treatment guidelines (when published guidelines are not available, use institutionally based guidelines).

[b]Rituximab, combination immunotherapy, or other aggressive immunomodulation regimens should be managed by clinicians with experience using these therapies, either as the primary prescriber or in close consultation with those managing the patient. There are no reported clinical trials and only limited clinical experience to support these approaches. This is not a definitive treatment algorithm; rather, it is a framework to aid in clinical decision-making. Before initiating any of the therapies, clinicians must consider the risk/benefit ratio for their individual patients and provide careful/informed counseling about risk of side effects (see Appendix Tables A1–A3 for detailed discussion of side effects).

AE, autoimmune encephalitis; CBT, cognitive behavioral therapy; CNS, central nervous system; GAS, group A *Streptococcus*; IV, intravenous; IVIG, intravenous immunoglobulins; NPSLE, neuropsychiatric systemic lupus erythematosus; NSAIDs, nonsteroidal anti-inflammatory drugs; PANS, pediatric acute-onset neuropsychiatric syndrome; TPE, therapeutic plasma exchange.

Graus et al. 2016; Dale et al. 2017). Clinicians are also urged to ensure completion of infectious disease evaluation and metabolic evaluations. And lastly, clinicians are urged to consider safety precautions outlined in Table 2. These guidelines address initial or induction immunomodulatory therapy (outlined in Tables 3 and 4). Patients with dramatic sustained improvement to immunomodulatory therapy may relapse (especially if long-standing disease is present) when immunomodulation is stopped and/or the effect of the immunomodulation wears off. Chronic suppressive (i.e., maintenance) therapy may be indicated in some cases, but is outside the scope of these guidelines.

Tracking Response to Immune Therapies

As with any therapeutic intervention, it is important to determine the impact of the treatment. In addition to careful monitoring and charting of the physical and mental status examination, psychometric instruments can help track the disease course. Helpful, reliable, and valid measures include an assessment of overall functioning, such as the Children's Global Assessment Scale, a measure of the most common cardinal symptom, the Children's Yale-Brown Obsessive-Compulsive Scale, and other symptom-specific measures (Clinical Global Impairment Scale, adapted to target symptoms) (Guy 1976; Shaffer et al. 1983; Goodman et al. 1989). Close collaboration between the mental health professional and the clinician managing immune therapies is essential.

Treatment of PANS: Mild Impairment in Functioning Due to PANS Symptoms

Children with ''mild'' PANS/PANDAS have clinically significant symptoms and obvious impairments, but these are limited to

Table 2. Considerations Before Pursuing Immunomodulatory Therapy

Further work-up	*Rationales*
Lumbar puncture, EEG, MRI, and sleep study (if feasible).	It is imperative to rule out more specific disorders before starting immunomodulatory therapy (AE, CNS vasculitis, NPSLE, ADEM, infectious encephalitis, etc.) (Graus et al. 2016). Corticosteroids may mask/treat another brain inflammatory disease and impede accurate diagnosis of another disorder. Rule out seizure disorders (i.e., ESES) and metabolic/genetic disorders. Follow established guidelines (institutionally based or published) for evaluation of these other brain diseases. If mild-to-moderate disease, no memory impairment or encephalopathy, the clinician may choose to defer the LP.
Evaluate for immunodeficiency.	Inflammatory diseases/autoimmunity are more common in patients with immunodeficiency. Immunodeficiency predisposes to infection and infection may worsen on corticosteroids.
Obtain serum IgA before giving IVIG.	If deficient (<10 mg/dL), use IgA-depleted IVIG. If possible store a serum sample (one red top) in case further infectious or autoimmune work-up is needed.
Screen for: (1) Tuberculosis: PPD or interferon-gamma release assay such as Quantiferon (R) or T spot assay (R); see age-appropriate guidelines. (2) Endemic fungi if indicated: For United States, *Coccidioidomycosis* in Northern California and the Southwest; *Blastomyces* in the Midwest, South-central, and Southeast; *Histoplasma* in Central and Eastern states. (3) Parasitic diseases if indicated: *Toxoplasma gondii* (worldwide with high prevalence in people with cat interactions and rare meat consumption); *Trypanosoma cruzi* (Chagas disease endemic in Mexico, Central, and South America).	Corticosteroids may activate infection.
Hepatitis B serology.	Rituximab can reactivate hepatitis B virus. If patient has already had IVIG and has positive hepatitis B serology, check hepatitis B PCR.
Ensure that the patient's environment (family and/or medical setting) is equipped to handle escalation in psychiatric symptoms.	Many patients have transient worsening of psychiatric symptoms after corticosteroid burst/pulse and occasionally after initiation of other immunomodulators. If patient has rage/violence, life-threatening impulsivity, mood instability, suicidality, etc., ensure that the environment can maintain safety in case the patient has escalated behavior.

ADEM, acute disseminated encephalomyelitis; AE, autoimmune encephalitis; CNS, central nervous system; EEG, electroencephalography; ESES, electrical status epilepticus in sleep; IgA, immunoglobulin A; IVIG, intravenous immunoglobulins; LP, lumbar puncture, MRI, magnetic resonance imaging; NPSLE, neuropsychiatric systemic lupus erythematosus; PCR, polymerase chain reaction; PPD, purified protein derivative.

certain situations and/or settings. OC symptoms might occupy 1–2 hours, occur at intervals throughout the day, and cause minor disruptions at home and in school; however, they do not cause great distress or interfere with overall functioning. In general, the symptom severity falls within the ''troubled, but tolerable'' range.

The most appropriate therapy (once infection is ruled out) for children in the mild severity range may be ''tincture of time'' combined with cognitive behavioral therapy and other supportive therapies as described in the psychological/psychiatric guidelines (Thienemann et al. 2017). PANS/PANDAS is an episodic illness that can have spontaneous symptom remission; therefore, the child is not experiencing significant distress or disruption of daily activities, watchful waiting may be sufficient.

If symptoms continue beyond 2 weeks (especially if the symptoms are worsening and/or impairing function), oral nonsteroidal anti-inflammatory drugs (NSAIDs) may be helpful, as tolerated (Table 3 and Appendix Table A1) (Brown et al. 2017b; Spartz et al. 2017). Although the therapeutic mechanisms in PANS are presumed to be

Table 3. General Approach to Using Induction Corticosteroids and/or Nonsteroidal Anti-Inflammatory Drug Therapies in Pediatric Acute-Onset Neuropsychiatric Syndrome/Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infection

	Mild-to-moderate flare	*Moderate-to-severe flare*	*Severe-to-extreme flare*[a]
Early in flare or early in initial presentation (<14 days). *Early application of corticosteroids (once infection is ruled out) and NSAIDs may abort or limit duration of disease flares.*	(A) Refer to CBT and supportive therapy. or (B) NSAIDs+(A). or if no improvement or deteriorating baseline then (C) ↓.	(A) Refer to CBT and supportive therapy. or (B) prednisone 1–2 mg/kg/day × 5 days+(A). or (C) oral dexamethasone pulse (20 mg/m^2 divided twice daily for 3 days)+(A). or (D) IV MP pulse × 1 (30 mg/kg/dose)+(A).	(A) Refer to CBT and supportive therapy. or (B) oral dexamethasone pulse (20 mg/m^2 divided twice daily for 3 days) alone or in combination with adjunct therapy (Table 4)+(A). (C) IV MP one to three consecutive daily pulses (30 mg/kg·dose·day × 3 days) alone or in combination with adjunct therapy (Table 4)+(A).
Late in flare (2–4 weeks).	(A) Refer to CBT and supportive therapy. or (B) NSAIDs+A. or (C) prednisone 1–2 mg/kg·day × 5 days+(A). If no response, re-evaluate for underlying infection per guidelines. If no infection and baseline worsening, go to next column.	Same as above box, except: (B) consider adding a 1-month prednisone taper (see Appendix B2 for taper) to oral prednisone burst. The mentioned pulse therapy approaches do not need tapers.	(A) Refer to CBT and supportive therapy. or (B) oral dexamethasone pulse (20 mg/m^2 divided twice daily for 3 days) alone or in combination with steroid-sparing agent (Table 4)+(A). Long-standing disease will likely need more persistent corticosteroids. (C) IV MP one to five consecutive daily pulses (30 mg/kg·dose·day for up to 5 days) alone or in combination with adjunct therapy (Table 4). Consider weekly IV MP pulses for up to 6 weeks (if tolerated)+(A).
Very delayed care (>4 weeks). *Application of corticosteroids late into the disease often requires higher dosing and/or more prolonged tapers.* *Steroid bursts may be followed by NSAIDS, with caution (see Appendix Tables A1 and A2).*		(A) Refer to CBT and supportive therapy. or (B) prednisone 1–2 mg/kg·day × 5 days+(A). Consider adding a 1–2-month prednisone taper. or (C) oral dexamethasone pulse (20 mg/m^2 divided twice daily for 3 days)+(A). or (D) IV MP one to three consecutive daily pulses (30 mg/kg·dose·day × 3 days)+(A). patient may need weekly or monthly pulses to maintain effect. Add steroid-sparing agent (Table 4) if patient is responsive to steroids but does not hold.	

Optimal dosing approaches and utilization of adjunct immunomodulation have not been determined for PANS, but the approaches outlined in this table serve as a starting point for clinicians and academicians who treat patients with PANS and who are planning trials.

Important steroid warning: Most patients have transient worsening of psychiatric symptoms while on corticosteroids. If patient has rage/violence, life-threatening impulsivity, mood instability, suicidality, etc. and caregivers (including medical personnel) are unable to manage potentiation of these behaviors, give corticosteroids in psychiatric unit or medical-psychiatric unit or bypass corticosteroids and go straight to IVIG or other steroid-sparing agent (Table 4).

If no response to initial corticosteroid burst/pulse or relapse after steroid burst/pulse, consider reassessing for underlying infection per guidelines (Chang et al. 2015; Cooperstock et al. 2017) with attention to the possibility of sinusitis or close contact with GAS or asymptomatic acquisition of GAS. If no infection, repeat steroid bursts/pulses and/or give corticosteroid sparing agent (Table 4).

For details regarding side effects and dosing of NSAIDs and corticosteroids (including maximum dosing) go to Appendix Tables A1 and A2.

[a]If patient meets criteria for another brain inflammatory disease, use said treatment protocol.

AE, autoimmune encephalitis; CBT, cognitive behavioral therapy; GAS, group A *Streptococcus*; IV, intravenous; IVIG, intravenous immunoglobulins; MP, methylprednisolone; NSAIDs, nonsteroidal anti-inflammatory drugs; PANS, pediatric acute-onset neuropsychiatric syndrome.

the anti-inflammatory properties of the NSAIDs, it is interesting that these medications have reported benefits in other psychiatric conditions. For example, the use of celecoxib was helpful in reducing OCD symptoms in adult participants of two clinical studies (Sayyah et al. 2011; Shalbafan et al. 2015). Clinical trials have also shown benefit of NSAIDs in schizophrenia, bipolar disorder, and depression (Müller et al. 2004; Abbasi et al. 2012; Arabzadeh et al. 2015). In a recent retrospective study of consecutive patients trialed on NSAIDs, approximately one-third of the patients were reported to have improvement in some or all PANS symptoms and an additional one-third of the patients had deterioration after the NSAID was discontinued, suggesting possible efficacy (Spartz et al. 2017). In another retrospective study, NSAID use was associated with shorter duration of PANS flares compared with untreated flares (Brown et al. 2017b). Based on our clinical experience, NSAID trials in PANS patients should be 6 weeks long. The effect of NSAIDs can wane over time, so it is important to conduct periodic discontinuation trials, closely monitoring symptoms during the withdrawal period. If discontinuation of the NSAIDs results in recrudescence of symptoms, the medications can be restarted and continued for another 6 weeks or longer. Some patients have remained on NSAIDs chronically when continued benefit is demonstrated with on/off trials (Spartz et al. 2017).

It is the authors' experience that NSAIDs can be used safely in the long term if standard precautions are taken (Appendix Table A1). NSAIDs should be used with caution in the setting of restricted fluid intake (because of concern for renal toxicity in the setting of dehydration) and swallowing difficulties (because of concern for esophageal erosions) (Appendix Table A1). In some cases, NSAIDs can contribute to gastritis, gastroesophageal reflux disease, esophageal erosion, decreased appetite, constipation, diarrhea, and nausea (Ruperto et al. 2005; Sobel et al. 2014). Other possible side effects include hypertension, skin fragility (pseudoporphyria), sun sensitivity,

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. and patient has proven (documented by mental health professional) responsiveness to corticosteroids, IVIG, or TPE. and 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. and patient has proven responsiveness to corticosteroids, IVIG, or TPE. and 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). (A) Monthly IVIG until patient is no longer having period of improvement after IVIG and recrudescence as IVIG effect wanes. (B) Rituximab, MMF, etc. (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. and patient has proven responsiveness to corticosteroids, IVIG, or TPE. and patient has evidence of inflammation/autoimmunity and objective signs of organic brain disease.

Goal is to achieve remission with minimal corticosteroids.

[a]Rituximab and MMF are generally used when the patient has demonstrated steroid/IVIG responsiveness, but the patient is steroid/IVIG dependent and there is a chronic course. Duration of therapy needed is unknown. For other inflammatory brain diseases, MMF is used for up to 5 years and rituximab is used for 1–3 years ± additional years of MMF.

IVIG, intravenous immunoglobulins; MMF, mycophenylate mofetil; PANS, pediatric acute-onset neuropsychiatric syndrome; TPE, therapeutic plasma exchange.

rectal hemorrhage, epistaxis, hematoma, and hematuria. NSAIDs should not be used in the setting of ethanol use, especially if there is binge drinking. In two recent PANS studies, all side effects were self-limited and there were no significant (injurious) toxicities, including esophageal erosions, liver toxicity, and renal toxicity (Brown et al. 2017b; Spartz et al. 2017).

Brief courses of oral corticosteroids are another option for mild-to-moderate PANS, as the risks are minimal and the benefits can be dramatic, particularly if given within 1–3 days of symptom onset. However, if the child has mood instability, including rage or aggression, corticosteroids should be used with caution as they may exacerbate these symptoms. As with asthma, oral corticosteroid bursts (prednisone 1–2 mg/kg/day; given as single dose in morning or divided twice daily, maximum 60–120 mg daily, for 5 days) may hasten recovery and minimize residual symptoms. In a recent retrospective study of patients meeting PANS or PANDAS criteria, flares treated with corticosteroids lasted on average 6.4 weeks and flares not treated with corticosteroids lasted on average 11.4 weeks (multilevel model, $p < 0.01$) (Brown et al. 2017a). In this study, use of steroids in the setting of an infectious illness had less impact on neuropsychiatric symptoms (Brown et al. 2017a) and thus, these patients may need a repeat steroid burst or delay in the initial steroid burst.

Patients who improve with the corticosteroids but then relapse as the steroid effect wanes may benefit from an additional corticosteroid burst with or without a taper (see Appendix Table A2 for an example of burst and taper). Patients in a prolonged flare may also have improvement in their function after a course of corticosteroids. A slow taper will incur more side effects (Appendix Table A2) and should be considered only if symptoms are impairing enough to justify the side effects. Refer to Table 2 for the medical evaluation, which must be completed before initiating treatment with corticosteroids. See Table 3 for strategies regarding use of corticosteroids in PANS based on clinical severity and disease trajectory. See Appendix Table A2 for an outline of risks associated with corticosteroids.

There is not enough data to reconcile the strategies of ''tincture of time'' for self-recovery versus ''early aggressive therapy,'' which is the approach used in other brain inflammatory diseases (Van Mater 2014; Nosadini et al. 2015; Dale et al. 2017). If a patient has a history of flares that do not self-resolve, then strongly consider early use of corticosteroids followed by NSAIDs (Brown et al. 2017a, 2017b; Spartz et al. 2017).

Behavioral side effects of corticosteroids are always of concern. Not all patients are candidates for corticosteroid therapy as it may temporarily worsen OC symptoms, anxiety, rage, irritability/agitation, depression, emotional lability, and insomnia. Although these symptoms can be managed with appropriate psychotherapeutic and behavioral interventions, the clinician must use caution in patients whose PANS symptoms include aggression, rage, or impulsivity. For most patients with clinically significant symptoms, the risk/benefit ratio favors use of corticosteroids, as the temporary worsening of neuropsychiatric symptoms is offset by the potential benefits of returning the child to baseline functioning more quickly. Importantly, short courses of corticosteroids, especially at low doses, are rarely associated with long-term side effects (Da Silva et al. 2006).

Treatment of PANS: Moderate-to-Severe Impairment in Functioning Due to PANS Symptoms

Children with moderate-to-severe symptoms of PANS/PANDAS have symptoms that are distressing and impairing, but not overwhelming or incapacitating. Their OC symptoms may occupy 50%–70% of their waking hours. The OC symptoms along with other PANS symptoms cause significant interference with daily activities, but the children have at least short periods of relief. Their intake of food or fluid may be reduced, but they are not medically compromised. Rituals or separation anxiety may prevent the children from attending school, but they are able to leave the house with a loved one or have friends visit for brief periods. Ancillary symptoms are similarly impairing and might include embarrassing, painful, or disruptive adventitious movements, pollakiuria (urinary frequency), sleep disruptions, and cognitive impairment, leading to school difficulties including writing difficulties, loss of math and reading skills, reduced processing speed, and memory impairment. Emotional lability, irritability, and aggression are often the most problematic symptoms for children with moderate-to-severe symptoms of PANS. These patients may present to emergency departments because of rapid changes in their behavior and function. If a child's behavior has escalated to the point wherein he is a danger to himself or others, he would be considered to have ''extreme or life-threatening'' symptoms, as discussed hereunder.

Immunomodulatory therapy is typically warranted for PANS cases with moderate-to-severe impairment. Oral corticosteroids may be sufficient, particularly if given within a few days of symptom onset. In the aforementioned retrospective study, earlier steroid use was associated with earlier time to recovery from flare (Brown et al. 2017a). For more severe or chronic symptoms, a prolonged corticosteroids course (with taper) or corticosteroid pulses may be indicated. High-dose IV methylprednisolone (MP) pulses (IV MP 15–30 mg/kg, maximum dose 1 g, daily for 3–5 days) are more likely to result in a robust and rapid change in symptom severity, leading to its selection as initial therapy for most children and adults with autoimmune encephalitides such as anti-N-methyl-D-aspartate receptor encephalitis (NMDAR) (Dalmau et al. 2011). Some PRC-ITF members have adopted the protocol of high-dose pulsatile oral dexamethasone (dexamethasone 20 mg/m^2 divided twice daily for 3 days), which is used in treating another pediatric autoimmune CNS disorder, opsoclonus-myoclonus syndrome (Rostasy et al. 2006). In SC, higher doses of corticosteroids administered for a longer duration resulted in greater symptom reduction and shortened disease duration (Barash et al. 2005; Paz et al. 2006; Walker et al. 2007). Similarly, in PANS and PANDAS, longer steroid courses resulted in a longer duration of neuropsychiatric symptom improvement (Brown et al. 2017a).

However, it is important to keep in mind that high doses and prolonged use of corticosteroids are associated with more risks, including permanent injury to eyes (cataracts and glaucoma) and bones (avascular necrosis) and escalated psychiatric symptoms. Furthermore, corticosteroids should not be used when there is the possibility that symptoms are due to infection, metabolic disturbance, or neurodegenerative disorder (Vernino et al. 2007). See Appendix Table A2 for corticosteroid dosing regimens and discussion of associated risks. Careful assessment of the risks and potential benefits of steroid use must be done for each PANS case, especially because psychiatric symptoms may escalate initially and the patient could develop life-threatening behaviors. Table 3 provides a summary of the use of corticosteroids in moderate-to-severely ill patients.

In general, empiric use of corticosteroids in patients with unexplained new-onset neuropsychiatric deterioration is becoming the standard of care, once infections, metabolic disturbances, and neurodegenerative disorders are excluded (Vernino et al. 2007; Dalmau et al. 2011; Nosadini et al. 2015). To diagnose steroid-

responsive inflammatory brain disease, the clinical response to steroid administration should be unequivocal and persist for a week or more beyond the time of treatment (Vernino et al. 2007). However, patients with long-standing chronic-static or chronic-progressive disease often have diminished responses to corticosteroids and may require many months of combination immunomodulatory therapy before significant treatment gains are seen.

Because improvement with corticosteroids often wants after cessation of corticosteroids therapy, and long-term corticosteroid use may be associated with permanent toxicities (cataracts, bone infarcts, diabetes, hypertension, weight gain, etc.), steroid sparing immunomodulatory agents are often needed. For this reason, IVIG alone or in combination with corticosteroids is often preferred for treatment of moderate-to-severe PANS. The recommended induction dose of IVIG is 1.5–2 g/kg (maximum dose is typically 70 g, but on rare occasions up to 120 g has been used by PRC members) and 1–2 g/kg for second and subsequent dosing. This induction dose is equivalent to that used for other pediatric inflammatory disorders, including, but not limited to AE, Kawasaki disease, juvenile dermatomyositis, idiopathic thrombocytopenic purpura, and Guillain–Barre syndrome (Hughes et al. 2014; Nosadini et al. 2016). One clinical case series of 12 youth with PANDAS reported benefits of a 1.5 g/kg total dose (Kovacevic et al. 2015). The dose and timing of IVIG administration should be determined in collaboration with clinicians and pharmacists experienced in its use. Controlled trials only have evaluated single courses of IVIG, but the authors' unpublished experiences suggest that one to three repeated doses of IVIG may be appropriate for children who have a good initial response to IVIG, but then relapse as the IVIG is cleared from circulation. Of note, the response to IVIG is often delayed by 2–3 weeks, and some symptom domains may show more improvements than others. In such patients, additional improvements may be gained with each cycle of IVIG. Monthly IVIG has been used in a number of other brain inflammatory diseases, including relapsing-remitting MS, NPSLE, AE, and others (Fazekas et al. 1997; Leach et al. 1999; Zandman-Goddard et al. 2012). However, repeated doses of IVIG have not been systematically assessed for PANS. It is the authors' opinion that the burden of monthly IVIG (beyond 3–6 monthly doses) may outweigh the benefit in many cases. The burden-to-benefit ratio has to be considered critically for each individual patient until more data are available to give direction on this approach.

Although high-dose IVIG can be given in one day (as is the case with Kawasaki disease), it is the authors' experience that patients with PANS do not tolerate this high rate of infusion, primarily because of severe postinfusion headaches, many of which are accompanied by meningeal signs and likely attributable to aseptic meningitis. Severe headaches (including migraines) and aseptic meningitis are among the most commonly described side effects of IVIG, with rates of 2%–75% and 1%–11% reported, respectively (Pierce and Jain 2003; Orange et al. 2006; Bharath et al. 2015; Thornby et al. 2015; Cherin et al. 2016). Among patients receiving immunomodulatory doses of IVIG (2 g/kg), those with a history of headaches are at higher risk for IVIG-induced headaches and/or aseptic meningitis. Typically headaches will develop within six hours of infusion but may start as late as 72 hours after the infusion (Rappold et al. 2015; Cherin et al. 2016). Headaches typically last 3–7 days in patients with PANS (authors' experience).

Some centers have divided the total IVIG dose into as many as five daily doses given on five consecutive days with a low rate of infusion for patients who could not otherwise tolerate the treatment because of severe nausea, vomiting, and/or headaches. Although this approach may be necessary in some individuals, the efficacy is unknown. A clinical trial in children with Kawasaki disease found that IVIG had added anti-inflammatory effects if the dose (2 g/kg) is given for 10 hours on a single day compared with four smaller daily doses (400 mg/kg) (Newburger et al. 1991).

The authors recommend the following strategies to help mitigate and/or manage post-IVIG headaches: (1) Divide the total IVIG dose into *at least* two daily doses given on two consecutive days; (2) Employ aggressive hydration (before, during, and after IVIG); (3) Use anti-inflammatory medications (either regular dosing of NSAIDs or a corticosteroid burst); (4) Consider regular dosing of antinausea medications (may be contraindicated for patients with dystonic reactions or chronic constipation); (5) Be prepared that some patients may require opiate pain medications to manage severe headaches (again, use with caution in patients with constipation or on sedating medications).

Most other side effects of IVIG are self-limited or may be prevented with premedication; however, rare side effects, including anaphylaxis, thromboembolic events, hemolytic reactions, and renal failure, among others, may cause significant mortality and/or morbidity (Pierce and Jain 2003; Orange et al. 2006; Cherin et al. 2016). Patients with restricted eating and/or restricted fluid intake are especially vulnerable to headaches and hyperviscosity issues; these patients require close monitoring after IVIG and may require additional boluses of IV fluids. Transmission of occult infections is an additional risk of IVIG, as it is a pooled human donor product. The severity of PANS symptoms must outweigh all potential risks (See Appendix Table A3 for a more detailed discussion on side effects of IVIG and managing IVIG in patients with PANS).

According to the authors' experience, patients receiving early treatment of PANS usually require only one, two, or three courses of high-dose IVIG. However, long-standing disease takes more time and effort to improve. This is true for other inflammatory disorders such as arthritis, systemic lupus erythematosus (SLE), asthma, and AE, in which long-standing untreated or undertreated disease has a worse prognosis and requires considerably more aggressive treatment than disease treated early (Wallace et al. 2014; Nosadini et al. 2015; Dale et al. 2017).

Some PRC-ITF members have successfully employed monthly high-dose IVIG to treat long-standing PANS symptoms. However, the authors recommend that repeated doses of IVIG be used only for patients who clearly benefit from each IVIG infusion and then experience a recrudescence of symptoms when the IVIG effect starts to wane (often around 3–6 weeks). Spacing out and eventually discontinuing IVIG infusions should occur when there is no longer improvement following IVIG. At that point, time intervals between IVIG infusions should be increased, and if there is no further recrudescence of symptoms, IVIG should be discontinued. In lieu of repeated IVIG infusions, some of the PRC-ITF members add secondary immunomodulatory agents. In children who have an incomplete response to IVIG or have significant flares while on IVIG, corticosteroids and other immunosuppressive agents have been used in addition to the IVIG (when benefits outweigh the risks).

In some clinical settings, arranging for IVIG infusion may take a significant amount of time. In select cases, PRC members pursue oral or IV corticosteroids (after active infection is ruled out or treated) while waiting for IVIG to be approved. Based on authors' experience, a positive response to corticosteroids is a good indication that further immunomodulatory therapy will be helpful, but a tepid response to low-dose oral prednisone burst (1–2 mg/kg for five days) is not a predictor of IVIG or second-line failure.

Treatment of PANS: Extreme or Life-Threatening Impairment of Functioning Due to PANS Symptoms

Children with extremely severe symptoms of PANS suffer from OC symptoms that occupy 90%–100% of their waking hours and experience profound distress from separation anxiety, generalized anxiety, depression, and emotional lability. Children with restricted food and fluid intake (usually because of fears of contamination, choking, vomiting, etc.) can develop dehydration, significant weight loss (>10% of body weight), and vital sign instability (Toufexis et al. 2015). In these extreme cases, comorbid symptoms are also incapacitating and may include severe behavioral regressions, cognitive dysfunctions, memory impairment, social withdrawal, extreme irritability, aggression, emotional lability, violent imagery, hallucinations and/or delusions, sensory amplification, movement disorders (choreatic, dystonic, and stereotypic), and tics. Some children present with severe difficulty in walking and/or sitting without support. Not only are the symptoms extremely distressing to the child and his or her caregivers, but they may prevent him or her from leaving the house, attending school, and accomplishing activities of daily living (e.g., eating, showering, or toileting). Of note, the combination of escalated impulsivity, behavioral regression, mood lability, and irrational fears can lead to life-threatening impulsive actions. In such cases, the first goal of therapy must be to ensure everyone's safety, either with 24-hour monitoring at home or in the hospital (Thienemann et al. 2017). Inpatient psychiatric hospitalization is often the safest option, but severe separation anxiety may require accommodations for a parent to stay with the child.

If available, TPE is first-line therapy for extreme and life-threatening PANS, as it has been shown to produce the greatest degree of symptom improvement for the shortest period in PANDAS, NPSLE, and anti-NMDAR encephalitis (Perlmutter et al. 1999; Neuwelt 2003; Dalmau et al. 2011). Five single-volume exchanges for 7–10 days are considered optimal (Perlmutter et al. 1999; Szczepiorkowski et al. 2007), although a recent case series reported benefits of a shorter course of only three to four treatments (1.5 volume exchange during each TPE treatment) (Latimer et al. 2015). Details of the five-exchange treatment regimen are available upon request (Swedo, NIMH). TPE will cause hypogammaglobulinemia, so clinicians might consider adding IVIG as adjunctive therapy (at anti-inflammatory doses already discussed). Complications of TPE include line infection, thrombosis, anemia, syncope, pseudoseizures, and pain amplification. The last three symptoms typically occur in the hours to days after cessation of TPE.

In chronic autoimmune disorders (SLE, granulomatosis with polyangiitis, microscopic polyangiitis, etc.), TPE alone is not sufficient to provide lasting symptomatic improvements (Jones et al. 1981). Thus, in these disorders, TPE is generally used in conjunction with a maintenance immunosuppression regimen such as rituximab. Experience in PANS is limited, but suggests that TPE alone may produce only temporary improvements in patients with chronic-static or chronic-progressive illness. Adjunctive immunomodulation may be warranted in such cases.

If TPE is not available, then the combination of IV MP pulses and IVIG is a reasonable alternative. Rituximab, mycophenolate mofetil (MMF), and other immunomodulatory agents should be considered, in cases with evidence of neuroinflammation or autoimmunity (Chang et al. 2015) or in cases who have previously demonstrated sustained improvement after IV MP or IVIG but then relapse. Only clinicians experienced in the use of these therapies should use them. Also, the child must have an established relationship with a psychiatrist who is prepared to manage emerging psychiatric symptoms, particularly during induction therapy. PRC members have reported initial worsening of psychiatric symptoms during the induction with corticosteroids, MMF, and rituximab. Rarely, new-onset psychosis has been observed with all three of these agents, which resolved after discontinuation of the inciting medication.

Chronic-Static or Deteriorating Course of PANS Illness

At this time, it is not possible to predict the course of illness in patients with PANS. Many children will remit after a single course of immunotherapy and subsequent exacerbations can be forestalled by antibiotic prophylaxis and/or brief courses of corticosteroids applied early in the flares. Others have a persistent or deteriorating course and require ongoing or more intensive treatments. In addition to therapies that remove pathogenic autoantibodies, attention should be paid to eradicating their production. Antibiotics, or even surgery, can be effective if the presumptive antigenic source can be targeted (e.g., chronic sinusitis, enhancing sinus cyst, tonsillar abscess, or microabscesses). A small number of reports suggest that tonsillectomy and adenoidectomy may be helpful in PANS, perhaps by removing occult infections that are triggering symptom exacerbations (Heubi and Shott 2003; Fusco et al. 2010; Alexander et al. 2011; Demesh et al. 2015). However, systematic comparisons of PANS/PANDAS children who had a tonsillectomy/adenoidectomy with those who had not failed to detect any benefits of the surgery (Murphy et al. 2013; Pavone et al. 2014). Thus, the PRC is not recommending tonsillectomy or adenoidectomy as a routine intervention for PANDAS or PANS and supports use of the procedures only when indicated per current surgical guidelines (Baugh et al. 2011).

For some children with PANS, the clinical course suggests that a temporary postinfectious pathological immune response has evolved to become a chronic autoimmune condition, most likely because of loss of tolerance and ongoing T cell and/or B cell activity against self-antigens. Such cases may require more aggressive and persistent immunomodulatory therapies with demonstrated effectiveness against other brain inflammatory disorders. These might include: (1) repeated pulsing of high-dose IV MP and/or a more prolonged course of oral corticosteroids, (2) rituximab, (3) MMF, (4) cyclophosphamide, and (5) other treatments used to treat inflammatory brain disease (Hahn et al. 2001, 2012; Dalmau et al. 2011; Dale et al. 2017). Recommendations for use of these interventions are beyond the scope of these guidelines and patients should be referred to centers specializing in the treatment of neuroimmune disorders.

Refractory Disease Course

One must consider the possibility of injured neurocircuitry and the need to shift to primary rehabilitation mode in patients whose psychiatric symptoms are not (or are no longer) responsive to the mentioned immunomodulatory approaches (especially those who have no response to high-dose MP pulses).

Other Considerations

A recent clinical trial in PANS demonstrated efficacy of azithromycin over placebo (Murphy et al. 2017). PRC members suspect that the mechanism of action of azithromycin in PANS may, in part, be related to its anti-inflammatory properties (Sharma et al.

2007; Murphy et al. 2008; Altenburg et al. 2010a, 2010b; Obregon et al. 2012).

Conclusions

Choosing the optimal immunomodulatory treatment pathway for the patient with PANS/PANDAS requires consideration of the disease severity and trajectory, as well as an understanding of the PANS symptoms in the broader context of infection and inflammatory disease. The general ''principles'' used to treat other brain inflammatory diseases (AE, NPSLE, etc.) likely apply to PANS (especially those presenting with severe symptoms): (1) Patients given immunotherapy do better and relapse less frequently than patients given no treatment; (2) Patients given early treatment do better; (3) When patients fail first-line therapy, second-line therapy improves outcomes and reduces relapses (Titulaer et al. 2013; Nosadini et al. 2015). Immunomodulatory therapy should be considered early, because NSAIDs or a short course of oral corticosteroids may be sufficient for symptom remission in recent-onset cases, whereas those with long-standing symptoms often require more intensive and prolonged immunotherapeutic interventions.

Clinical Significance

Until further research informs clinicians about the effectiveness of immunomodulatory therapy for PANS and PANDAS, current literature and clinical experience must guide clinicians treating these children. This article fills the gap between evidence-based treatments and current knowledge by conveying guidelines from a panel of experts for use of immunomodulatory therapy in children with PANS and PANDAS

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(*Appendix follows* →)

Appendix

Table A1. Use of Nonsteroidal Anti-Inflammatory Drugs in Pediatric Acute-Onset Neuropsychiatric Syndrome

Indication: Use in patients with mild impairment.

Administration: Take with food, milk, or antacid to decrease GI adverse effects.

Precautions: Use sunscreen concurrently with NSAIDs. Maintain a well hydrated state. Discontinue if patient restricts fluids or has risk of dehydration for other reasons (intense sports in hot weather). Do not take concurrently with ethanol or other liver toxic medications. *Use with caution if patient is on corticosteroids. Do not use while patient is on high-dose corticosteroids.* Consider temporary discontinuation if patient develops viral gastroenteritis. Do not use if patient has moderate-to-severe swallow dysfunction because of risk of esophageal erosion if NSAID is not properly swallowed.

Adverse effects: CNS (drowsiness, dizziness, and blurred vision); GI (nausea, gastritis, esophageal erosion, gastrointestinal reflux disease, constipation, diarrhea, decreased appetite, and rectal bleeding; elevated liver enzymes); skin (photophobic reactions including pseudoporphyria skin rash and sun sensitivity); psychiatric symptoms (anxiety, depression, fatigue, and nervousness); hematology (epistaxis, hematuria, hematoma, and rectal hemorrhage); and cardiovascular (hypertension).

Monitoring: Periodic trials off of NSAIDs every 6 weeks. If a patient repeatedly deteriorates when NSAID is discontinued, it can be restarted and continued in the long term with continued trials off (every 1.5–6 months) or do a trial of corticosteroids to abort PANS flare. Laboratory work every 3–6 months if patient is on NSAIDs continuously: liver enzymes, BUN, creatinine, CBC with differential, and UA.

Mechanism: Inhibits prostaglandin synthesis by decreasing the activity of cyclooxygenase, which results in decreased formation of prostaglandin precursors. NSAIDs have antipyretic, analgesic, and anti-inflammatory properties. NSAIDs may also have immunomodulatory effects by decreasing the following immune responses: T cell proliferation and the production of proinflammatory cytokines (Iniguez et al. 1999), the Th17 response (Napolitani et al. 2009), and microglial activation (Mackenzie and Munoz 1998). It may also decrease blood–brain barrier permeability (Candelario-Jalil et al. 2007).

	Dosage	*Preparation*	*Consideration*
(1) Ibuprofen	10 mg/kg every 6–8 hours (maximum 600 mg/dose)	Tablet, chewable, capsules, or liquid.	Requires frequent dosing to maintain continuous anti-inflammatory action. Available OTC. Liquid and chewable preparations taste better than naproxen.
(2) Naproxen	10 mg/kg every 12 hours (maximum 500 mg/dose)	Tablets, capsules, or liquid.	Naproxen is a potent long-acting NSAID that only requires twice daily dosing. Generally tolerated by children. Liquid formulation available as prescription (250 mg/5 mL) but the taste is often intolerable.
(3) Sulindac	2–4 mg/kg·day every 12 hours; maximum 6 mg/kg·day; do not exceed 400 mg/day	Tablets; can be compounded into a suspension.	Sulindac is equal in potency to naproxen and is also long acting. It may have fewer GI side effects.
(4) Celecoxib	10–25 kg: 50 mg twice a day >25 kg: 100 mg twice a day	Capsules; can be compounded into a suspension.	Fewer GI side effects. Less potent than naproxen and sulindac but helpful if patient develops gastritis symptoms on other NSAIDs.

BUN, blood urea nitrogen; CBC, complete blood count; CNS, central nervous system; GI, gastrointestinal; NSAIDs, nonsteroidal anti-inflammatory drugs; OTC, over-the-counter; PANS, pediatric acute-onset neuropsychiatric syndrome; UA, urine analysis.

Table A2. Use of Corticosteroids in Pediatric Acute-Onset Neuropsychiatric Syndrome

Indications: Used to abort PANS flare. If used early in disease course, it can abort or shorten flare duration and theoretically minimize vascular and tissue inflammation/damage (Brown et al. 2017a). Introduction of corticosteroids late in the flare is less likely to result in dramatic responses and will require higher doses or more prolonged courses. If patient has longstanding untreated disease, a chronic-static, or a chronic-progressive course, a longer course of corticosteroids (oral burst+taper or weekly/monthly pulsing±adjunct immunotherapy) will be needed. More sophisticated brain imaging techniques are needed to help clinicians definitively determine presence of neuroinflammation; but in the absence of this technology, corticosteroid trials can guide the clinician in determining whether inflammation is playing a role in a brain disorder. If the child's symptoms improve in the weeks after an adequate corticosteroid trial (dosing based on disease trajectory and severity, Table 3), this suggests that inflammation may be driving the psychiatric symptoms.

Administration: Take with food, milk, or antacid to decrease GI adverse effects. Ensure adequate vitamin D levels and adequate consumption of calcium. Consider calcium and vitamin D supplementation.

Precautions: Corticosteroids should be used with caution and only in the setting wherein caregivers can manage likely escalation in psychiatric symptoms. Rapid withdrawal of steroids can cause pseudotumor cerebri and other headache syndromes. Corticosteroid-induced hypertension can cause headaches. *Combination of NSAIDs and corticosteroids may lead to gastritis.*

(*continued*)

Table A2. (Continued)

Psychiatric/behavior side effects: Temporary increase in obsessive-compulsive symptoms, tics, irritability, rage, psychosis, emotional lability, depressed or fluctuating mood, behavior regression, insomnia, life-threatening impulsivity, and behavioral outbursts can occur while the corticosteroids are in the body. Symptoms resolve rapidly in the days after a short course (i.e., 5-day oral prednisone burst) but take longer to resolve when a prolonged course is given (i.e., prednisone burst+taper) or when high-dose corticosteroids are used (i.e., oral dexamethasone pulse or IV methylprednisolone pulses described hereunder).

Physical side effects that occur with prolonged courses, frequent oral prednisone bursts, or high-dose corticosteroids: Temporary effects may include blurry vision, weight gain, Cushingoid appearance, altered glucose metabolism, dyslipidemia, and hypertension. Temporary effects resolve in the weeks to months after cessation of corticosteroids. Time to resolution of these temporary side effects is proportional to duration of time on corticosteroids and intensity of dosing (i.e., the more saturated the body, the longer it will take to normalize). Permanent effects may include cataracts, glaucoma, bone infarcts, osteopenia, type-2 diabetes, hypertension, and striae. IV methylprednisolone infusions can cause hypertension or hypotension, tachycardia or bradycardia, blurry vision, flushing, sweating, and metallic taste in mouth. *Weekly or monthly corticosteroid pulses (see hereunder) are thought to have fewer physical side effects as compared with prolonged oral prednisone courses.*

Monitoring: If prolonged courses, frequent bursts, or high-dose corticosteroids are used, the following should be considered: periodic ophthalmological examinations to evaluate for cataracts and glaucoma, imaging of painful limbs to evaluate for avascular necrosis of bones and/or referral to orthopedics, assessment/precautions for osteopenia, HbA1C, routine blood pressure monitoring, and periodic assessment of dyslipidemia.

Mechanisms: Potent anti-inflammatory and immunosuppressive effects through multiple mechanisms, including down regulation of cytokine gene expression in leukocytes and down regulation of leukocyte adhesion molecule gene expression in endothelial cells (thus inhibiting adhesion-dependent leukocyte migration from the vascular space into extravascular tissues).

	Purpose	*Dosing*
Low dose burst Oral prednisone burst	Fast acting and effective if used early in a flare and if patient has good baseline functioning. Strategy is the same as in asthma.	1–2 mg/kg·day of prednisone or prednisolone[a] (given once daily, or divided twice a day, maximum 60–120 mg daily) for 5 days.
Prolonged course Oral prednisone burst+taper	Can improve baseline functioning in patients with chronic-static symptoms.	1–2 mg/kg·day prednisone or prednisolone (given once daily, or divided twice daily, maximum 60–120 mg daily) for 5–10 days; then taper for 4–8 weeks. Long-standing disease requires longer tapers.
	Taper helps minimize risk of symptom recrudescence after burst completion and/or allows time for other steroid-sparing agents to take effect.	Taper strategy: decrease current dose by 10%–25% every 3–7 days such that the large step-down doses occur early in the taper, and the tail of the taper is prolonged. See the following for specific example of a taper.[b]
Intermediate dose pulse Oral dexamethasone pulse	This strategy is considered more aggressive than the oral prednisone burst but less aggressive than IV methylprednisolone pulse.	20 mg/m^2·day divided twice daily for 3 days. If patient has response but then recrudesces (especially if patient has had long-standing disease), it will need to be repeated monthly±adjunct therapy (Table 4).[c]
	Intermittent pulsing may have fewer physical side effects than prolonged oral prednisone courses.	Maximum dose ranges from 9 to 16 mg/day for treatment of asthma to 30 mg/day for treatment of MS. For treatment of an acute exacerbation of MS, 30 mg/day for 1 week followed by 4–12 mg/day for 1 month.
High dose pulse Intravenous methylprednisolone pulse	Fast acting in moderate-to-severe cases to achieve an immediate, profound anti-inflammatory effect and to minimize toxicity related to long-term continuous therapy in moderate to high daily doses.	15–30 mg/kg·dose (maximum 1000 mg/dose ·24 hours). 30 mg/kg·dose is the preferred dosage for treatment of most inflammatory brain diseases.
	Intermittent pulsing to treat moderate to severe flares can quickly abort psychiatric symptoms.	For severe long-standing PANS, 3–5 daily pulses are used during induction treatment or once weekly dosing for 6 weeks to test whether disease is immunoresponsive. If there is no response to this aggressive approach or the response is not sustained, then immunomodulatory therapy is aborted.
	Repeated weekly pulsing can improve baseline of chronic-static cases with presumably fewer side effects than prolonged oral tapers.	For other inflammatory brain diseases, 3 daily pulses are used during induction treatment and then one pulse is given once monthly with adjunct therapy (typically cyclophosphamide or MMF).

[a]If liquid formulation is desired, use prednisolone because it tastes better and is more readily available as compared with prednisone.

[b]For example: 30 mg BID for 5–10 days; then step dose down every 3–7 days according to the following: 30 mg in AM/20 mg in PM; 30 mg in AM/10 mg in PM; 30 mg in AM only; 25 mg in AM only; 20 mg in AM; 17.5 mg in AM; 15 mg in AM; 12.5 mg in AM; 10 mg in AM; 7.5 mg in AM; then 5 mg in AM. Many patients start having recrudescence after tapering <15 mg, so further taper may have to be suspended until after another agent (e.g., IVIG) is initiated.

[c]This approach was derived from a protocol used to treat opsiclonus-myoclonus syndrome, which is a presumed CNS autoimmune disease in children (Rostasy et al. 2006).

CNS, central nervous system; GI, gastrointestinal; HbA1C, hemoglobin A1C; IV, intravenous; IVIG, intravenous immunoglobulin; MMF, mycophenolate mofetil; MS, multiple sclerosis; NSAIDs, nonsteroidal anti-inflammatory drugs; PANS, pediatric acute-onset neuropsychiatric syndrome.

Table A3. Use of Corticosteroid-Sparing Agents in Pediatric Acute-Onset Neuropsychiatric Syndrome

	Description/benefit	*Adverse effects*	*Dosing*
IVIG	IVIG is derived from pooled plasma from human donors and processed using rigorous purification steps.	Common infusion-related side effects include nausea, myalgia, fever, chills, rigors, chest discomfort, and hypotension (often dose related or because of rapid administration).	Induction: 1.5–2 g/kg, maximum dose 70 g/dose. If patient has clear improvement and then recrudesces, subsequent doses should be dosed at 1 g/kg. Second and third doses have been given at 4–6-week intervals by PANS Consortium members.
	Several potential immunomodulatory roles including effects on Fc receptor activity (saturating FcR) and F(ab)2 activity (anti-idiotypic antibodies) and other mechanisms.	Postinfusion headaches (HA)[a] are common including aseptic-like meningitis. Aggressive hydration pre/post and half way through IVIG infusion can help minimize HA. Use of OTC NSAIDs or corticosteroids during and after IVIG can also help prevent/manage HA.	Some patients are treated with rheumatology protocols that utilize 2 g/kg monthly (maximum dose 70 g/dose).
	Benefit: Broadly impacts immune function and autoimmune responses and may help moderate the autoantibody responses. Caution: The authors report rare cases of worsening PANS symptoms after IVIG when IVIG is given around the time of a new viral illness.	A transient fever can be seen in the first 24 hours. Rarely, symptomatic hemolysis can occur and manifest up to 1-week postinfusion. Anaphylaxis can occur, especially in patients with IgA deficiency (if IgA deficient, use formulation that does not contain IgA). Other rare side effects include renal failure, thrombosis (including sinus venous thrombosis), dermatological reactions, hemolytic reactions, neutropenia, transfusion-related lung injury, and seizures.	If patient becomes dependent on IVIG to maintain good baseline, consider adding in or replacing with rituximab or MMF.
TPE	Removes autoantibodies triggering immune responses leading to brain inflammation.	TPE often requires an intensive care admission and this may be psychiatrically traumatizing to some children.	1 volume therapeutic exchanges every other day for 10–12 days (5–6 runs) (Perlmutter et al. 1999).
	TPE is a process of separating blood components using centrifugation and a semipermeable membrane. This allows for disease-promoting blood components to be removed while the remaining components are returned to the patient. Plasma proteins, including antibodies-promoting disease, can be removed from the patient's blood. Benefit: Rapidly removes antibodies from plasma and quickly eliminates autoreactive immune responses caused by antibodies.	Related to IV access: pain, bleeding, infection, and, thrombosis. Risks of sedation. Risks of fluid shifts. Complications related to citrate anticoagulation/calcium chelating, and replaced with albumin. Risks of exposure to blood products. Syncope, pseudoseizures, and pain amplification have been reported immediately after TPE. TPE can cause hypogammaglobulinemia.	1.5 volume therapeutic exchanges for 3–5 days (3–4 runs) (Latimer et al. 2015). As soon as TPE is stopped, autoantibodies will continue to be produced (if autoimmune disease is present), thus adjunct therapy is recommended. In infection-triggered PANS, TPE alone can be effective if infectious driver is eliminated.

(*continued*)

TABLE A3. (CONTINUED)

	Description/benefit	*Adverse effects*	*Dosing*
Rituximab	FDA approved for use in microscopic polyangiitis, granulomatosis with polyangiitis (formerly Wegener's), and rheumatoid arthritis. It is frequently used in idiopathic thrombocytopenic purpura, lupus nephritis, and autoimmune encephalitis. A chimeric antibody directed against CD20, a surface protein found on B cells that leads to rapid B cell depletion. Benefit: B cell depletion frequently occurs within 24–48 hours after infusion and can be sustained for 3 months to >1 year. In chronic-static or refractory cases, benefits may not be seen for 6 months.	PANS patients can have escalation of psychiatric symptoms and pain symptoms after the first round (lasting 1–5 months), but the second round at 6 months is generally better tolerated. Infusion reactions are frequent, especially with the first dose, but can be mitigated by slowing the infusion rate and premedication with corticosteroids, acetaminophen, and diphenhydramine. Serious infections have been reported but are rare. Reported infections after rituximab include CMV-related retinitis/colitis, progressive myelitis leukoencephalipathy (JC virus), pneumonia, and empyema.	Most autoimmune diseases are treated with the protocol used in rheumatoid arthritis of 750 mg/m^2 (maximum dose 1000 mg) × 2 doses separated by 2 weeks. Although the effect can last up to a year, many patients relapse at the 6-month mark so most protocols aimed to treat chronic autoimmune disease require redosing at 6-month intervals.
MMF	An inhibitor of inosine monophosphate dehydrogenase, a rate-limiting enzyme for de novo synthesis of guanosine nucleotides. Several potential immunomodulatory roles including inhibition of lymphocyte proliferation, suppression of glycosylation and expression of some adhesion molecules, and suppression of nitric oxide. Benefit: Decreased B and T lymphocyte proliferation. Decreased antibody response. Induction of apoptosis of activated T lymphocytes. Decreased lymphocyte and monocyte recruitment to sites of inflammation. Suppression of tissue damage.	Pans patients can have sensory disturbances after introduction, generally better tolerated when patient is remitting on induction corticosteroids. Common side effects include cytopenia, dizziness, nausea, diarrhea, and abdominal pain. Rare side effects include dermatologic reactions, hemolytic reactions, and abnormal renal or hepatic function tests. Increased risk of infections and sepsis. Reported infections following MMF include: CMV, herpes zoster, BK virus, hepatitis B, and hepatitis C. Malignant neoplasms have been reported but are rare.	MMF: 600 mg/m^2/dose twice daily (max dose 1500 mg/dose) For patients who do not tolerate MMF, mycophenolic acid (MPA) can be used but has a different dosing regimen.

[a]IVIG-related headaches generally respond well to steroids (1–2 mg/kg prednisone equivalent, maximum dose 60–120 mg/day) when given along with and/or 2–5 days after the infusions. For patients who do not tolerate corticosteroids, NSAIDs can be used (IV ketorolac or ibuprofen around the clock). Premedication with diphenhydramine (or other antihistamines) and acetaminophen can also improve tolerability. Nausea can be treated with ondansetron and it may be needed around the clock during and after the infusion. Some patients may need opiates to manage severe headaches.

CMV, cytomegalovirus; IgA, immunoglobulin A; IV, intravenous; IVIG, intravenous immunoglobulin; JC, John Cunningham; MMF, mycophenolate mofetil; OTC, over the counter; PANS, pediatric acute-onset neuropsychiatric syndrome; TPE, therapeutic plasma exchange.

Cigna Drug and Biologic Coverage Policy

Subject **Immune Globulin**

Effective Date……11/15/2018
Next Review Date……10/15/2019
Coverage Policy Number……..5026

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INSTRUCTIONS FOR USE

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Coverage Policy

Cigna covers intravenous immune globulin (IVIG) or subcutaneous immune globulin (SCIG) as medically necessary for primary immunodeficiency (PID) or other covered conditions listed when meeting the specified criteria.

Cigna covers intravenous immune globulin (IVIG) as medically necessary for all other conditions listed when meeting the specified criteria.

Initial authorizations are restricted to 6 months unless otherwise specified within the individual criteria listed below by indication.

A reauthorization for 6 months (up to 12 months for primary immunodeficiency disorders) is covered as medically necessary when ALL of the following criteria are met:

- The medical condition or disease under treatment has not fully resolved and the treatment has not exceeded any applicable duration listed below.
- There continues to be a sustained beneficial response to IVIG as evidenced by treatment notes or a clinical narrative detailing progress to date and the expected frequency and duration of any proposed IVIG use going forward.
- The requested frequency and dosage of IVIG is supported by evidence-based literature.

- Where clinically appropriate, titration has occurred to the minimum dose and frequency to achieve sustained clinical effect.

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 immune globulin therapy

Specific Criteria by Medical Condition

- **Primary Immunodeficiency**

Condition	Criteria for Use
Hypogammaglobulinemia (including Common Variable Immunodeficiency [CVID])	**ALL of the following are met:** • **Immunologic evaluation including** documented serum IgG below the lower limits of normal of the laboratory's reported value on at least two occasions • **Impaired Antibody Response (EITHER of the following):** o Lack of protective antibody titers (tetanus and diphtheria or HiB) measured 3–4 weeks after immunization o Inadequate responsiveness to pneumococcal polysaccharide vaccine (Pneumovax® 23) 4–8 weeks after vaccination as defined by **EITHER** of the following: ▪ Age < 6 years, < 50% of serotypes are protective (i.e. ≥ 1.3 mcg/mL per serotype) ▪ Age ≥ 6 years, < 70% of serotypes are protective (i.e. ≥ 1.3 mcg/mL per serotype) • **Recurrent Infection (ALL of the following):** o History of recurrent bacterial sinopulmonary infections requiring multiple courses or prolonged antibiotic therapy o Evidence of management of underlying conditions such as asthma or allergic rhinitis that may predispose to recurrent infections where applicable o Supporting diagnostic imaging and/or laboratory results where applicable
IgG subclass deficiency	**ALL of the following are met:** • **Immunologic evaluation** including documented normal total serum IgG with one or more subclasses, excluding isolated subclass IgG4, below the lower limits of normal of the laboratory's reported value on at least two occasions • **Impaired Antibody Response** – Inadequate responsiveness to pneumococcal polysaccharide vaccine (Pneumovax® 23) 4–8 weeks after vaccination as defined by **EITHER** of the following: o Age < 6 years, < 50% of serotypes are protective (i.e. ≥ 1.3 mcg/mL per serotype) o Age ≥ 6 years, < 70% of serotypes are protective (i.e. ≥ 1.3 mcg/mL per serotype) • **Recurrent Infection (ALL of the following)** o History of recurrent bacterial sinopulmonary infections requiring multiple courses or prolonged antibiotic therapy o Evidence of management of underlying conditions such as asthma or allergic rhinitis that may predispose to recurrent infections where applicable o Supporting diagnostic imaging and/or laboratory results where applicable
Selected Specific Primary Immunodeficiency Disorders	**ONE of the following criteria is met:** • Agammaglobulinemia defined as serum IgG < 200 mg/dl

Condition	Criteria for Use
	• Extremely low (< 2%) or absent B cell count ($CD19^+$) • Documentation of a recognized genetic defect supporting diagnosis (see Appendix 1, Appendix 2, and Appendix 3) • Transient hypogammaglobulinemia of infancy with serum immunoglobulins below the age-specific normal range and **BOTH** of the following: o Evidence of recurrent bacterial sinopulmonary infections requiring antibiotic therapy (IVIG is only used for up to six months before re-evaluating the need for continued treatment) o Inadequate responsiveness to pneumococcal polysaccharide vaccine (Pneumovax® 23) 4–8 weeks after vaccination defined as < 50% of serotypes are protective (i.e. ≥ 1.3 mcg/mL per serotype) • Hyperimmunoglobulinemia E syndrome as evidenced by: o Elevated serum IgE level, the presence of staphylococcus-binding IgE, eosinophilia, and recurrent lung and/or skin infections (abscess, chronic eczematous dermatitis) **AND** o Impaired Antibody Response (**EITHER** of the following): ▪ Lack of protective antibody titers (tetanus and diphtheria or HiB) measured 3–4 weeks after immunization ▪ Inadequate responsiveness to pneumococcal polysaccharide vaccine (Pneumovax® 23) 4–8 weeks after vaccination as defined by **EITHER** of the following: • Age < 6 years, < 50% of serotypes are protective (i.e. ≥ 1.3 mcg/mL per serotype) • Age ≥ 6 years, < 70% of serotypes are protective (i.e. ≥ 1.3 mcg/mL per serotype)
Specific antibody deficiency (SAD)	**ALL of the following criteria are met:** • **Immunological evaluation** including documented normal serum IgG, IgG subclass, IgA, and IgM • Normal responses to protein antigens (tetanus and diphtheria toxoid) measured 3-4 weeks after immunization • **Inadequate responsiveness** to pneumococcal polysaccharide vaccine (Pneumovax® 23) 4–8 weeks after vaccination as defined by **EITHER** of the following: o Age < 6 years, < 50% of serotypes are protective (i.e. ≥ 1.3 mcg/mL per serotype) o Age ≥ 6 years, < 70% of serotypes are protective (i.e. ≥ 1.3 mcg/mL per serotype) • **Recurrent Infection (ALL of the following):** o History of severe and recurrent bacterial sinopulmonary infections despite documentation of both: ▪ Prevnar 7 or Prevnar 13 vaccination ▪ Documented failure/inadequate response, contraindication, or intolerance to the use of prophylactic antibiotic therapy o Evidence of management of underlying conditions such as asthma or allergic rhinitis that may predispose to recurrent infections where applicable o Supporting diagnostic imaging and/or laboratory results where applicable

- **Secondary Immunodeficiency**

Condition	Criteria for Use
Acquired immunosuppression	Prevention of infection in individuals meeting **ALL** of the following: • Presence of hypogammaglobulinemia (serum IgG < 400 mg/dL) • Immunosuppression is attributed to **ONE** of the following: o Major surgery (for example, cardiac transplant) o Hematologic malignancy o Extensive burns o Collagen-vascular disease • Recurrent sinopulmonary infection or history of serious bacterial infection(s)
B-cell Chronic Lymphocytic Leukemia (CLL)	Treatment when **BOTH** of the following are met: • Serum IgG less than 500 mg/dL • Recurrent sinopulmonary infection or history of serious bacterial infection(s)
HIV-infected children	**ONE of the following criteria is met:** • Primary prophylaxis of bacterial infections when hypogammaglobulinemia (serum IgG < 400 mg/dL) is present • Secondary prophylaxis of frequent recurrent serious bacterial infections (e.g., > 2 serious bacterial infections in a 1-year period despite combination ART) when antibiotic prophylaxis is not effective
Multiple Myeloma	Treatment when there is history of serious bacterial infection(s) or there is a recurrent life-threatening infection.

- **Transplantation**

Condition	Criteria for Use
Hematopoietic cell transplant (HCT)	Prevention of infection in HCT recipients (for example, stem cell or bone marrow transplantation) with hypogammaglobulinemia (serum IgG < 400 mg/dL) and **EITHER** of the following: • Within the first 100 days after transplant • After 100 days and evidence of recurrent infections OR evidence of graft-versus-host-disease (GVHD)
Solid organ transplants	Treatment for **EITHER** of the following: • Desensitization for highly-allosensitized transplant candidates (i.e. PRA > 50%) o Authorization for a maximum dose of 2 grams/kg monthly for 4 consecutive months. Additional infusions at 12 months and 24 months may be authorized if the individual has not undergone transplantation. • Antibody-mediated rejection (AMR) o Initial authorization for a maximum dose of 2 grams/kg monthly for 3 months. Reauthorization for up to 3 months is dependent on documented beneficial clinical response.

- **Hematology**

Condition	Criteria for Use
Anemia related to chronic parvovirus B19 infection	Treatment when there is a severe refractory anemia and evidence of viremia
Evan's syndrome	Treatment when there is failure, contraindication, or intolerance to available alternative therapies (i.e. azathioprine, cyclophosphamide, cyclosporine or prednisone)

Condition	Criteria for Use
Fetal Alloimmune Thrombocytopenia (FAIT)	Treatment when **ALL** of the following: • Documentation of maternal antibodies to paternal platelet antigen • **ONE** of the following: o Previous pregnancy complicated by FAIT o Fetal blood sampling documents thrombocytopenia
Hepatitis C-associated Thrombocytopenia	Treatment for **ANY** of the following: • Clinically significant bleeding associated with thrombocytopenia • Preoperative treatment prior to a major surgical procedure (for example, splenectomy) • Receiving antiviral treatment for hepatitis C infection or treatment is contraindicated
HIV-associated Thrombocytopenia	Treatment for **ANY** of the following: • Clinically significant bleeding associated with thrombocytopenia • Preoperative treatment prior to a major surgical procedure (for example, splenectomy) • Receiving treatment for HIV infection with antiretroviral therapy **AND** failure, contraindication, or intolerance to corticosteroids
Immune (Idiopathic) Thrombocytopenia – Adult	Platelet count < 30,000/mm^3 and **ONE** of the following are met: • Clinical need to rapidly increase the platelet count (examples include, but are not limited to: active bleeding, prior to major surgical procedure, risk of cerebral hemorrhage) • Not a candidate for splenectomy or experienced relapse post-splenectomy **AND** failure, contraindication, or intolerance to **ALL** of the following: o Corticosteroids o Thrombopoietin receptor agonists (eltrombopag [Promacta®] or romiplostim [Nplate®]) o Rituximab (Rituxan®)
Immune (Idiopathic) Thrombocytopenia – Pediatric	**ONE of the following are met:** • Clinical need to rapidly increase the platelet count (examples include, but are not limited to: active bleeding, prior to major surgical procedure, risk of cerebral hemorrhage) • Prevention of bleeding during the first 12 months of persistent disease if responsive to previous treatment with IVIG
Immune Thrombocytopenia (ITP) in pregnancy	Treatment when **ALL** of the following are met: • Diagnosis of thrombocytopenia • Failure, contraindication, or intolerance to corticosteroids or clinical need to rapidly increase the platelet count
Neonatal isoimmune hemolytic disease in conjunction with phototherapy	Acute treatment only
Post-transfusion purpura	Acute treatment only
Warm type autoimmune hemolytic anemia (characterized by predominance of IgG antibodies as opposed to cold type that is predominated by IgM antibodies)	Treatment when there is failure, contraindication, or intolerance to available alternative therapies (i.e. azathioprine, cyclophosphamide, cyclosporine, prednisone, plasmapheresis, or splenectomy)

- **Neurology**

Condition	Criteria for Use
Chronic Inflammatory Demyelinating Polyneuropathy (CIDP), including Multifocal Acquired Demyelinating Sensory and Motor Neuropathy (MADSAM) (Lewis-Sumner Syndrome)	**For initial authorization**: Treatment when **ALL** of the following **required** elements are met: • Progressive or relapsing motor and/or sensory symptoms of more than one limb **AND** hyporeflexia or areflexia in affected limbs present for at least 2 months as documented by objective measurement • Electrophysiologic findings indicate demyelinating neuropathy (3 of the following 4 criteria are met per the American Academy of Neurology): o Partial conduction block* of ≥ 1 motor nerve o Reduced conduction velocity* of ≥ 2 motor nerves o Prolonged distal latency* of ≥ 2 motor nerves o Prolonged F-wave latencies* of ≥ 2 motor nerves or the absence of F waves • Other causes of demyelinating neuropathy have been excluded (from the European Federation of Neurological Societies and the Peripheral Nerve Society): o Borrelia burgdorferi infection (Lyme disease), diphtheria, drug or toxin exposure probably to have caused the neuropathy o Hereditary demyelinating neuropathy o Prominent sphincter disturbance o Diagnosis of multifocal motor neuropathy o IgM monoclonal gammopathy with high titre antibodies to myelin-associated glycoprotein o Other causes for a demyelinating neuropathy including POEMS syndrome, osteosclerotic myeloma, diabetic and non-diabetic lumbosacral radiculoplexus neuropathy, PNS lymphoma and amyloidosis. * Definitions from the American Academy of Neurology • **Partial conduction block** is a drop of at least 20% in negative peak area or peak-to-peak amplitude and a change of < 15% in duration between proximal and distal site stimulation. • **Possible conduction block or temporal dispersion** is a drop of at least 20% in negative peak area or peak-to-peak amplitude and a change of at least 15% in duration between proximal and distal site stimulation. • **Reduced conduction velocity** is a velocity of < 80% of the lower limit of the normal range if the amplitude of the compound muscle action potential (CMAP) is > 80% of the lower limit of the normal range or < 70% of the lower limit if the CMAP amplitude is less than 80% of the lower limit. • **Prolonged distal latency** is more than 125% of the upper limit of the normal range if the CMAP amplitude is more than 80% of the lower limit of the normal range or more than 150% of the upper limit if the CMAP amplitude is less than 80% of the lower limit. • **Absent F wave or F-wave latency** is more than 125% of the upper limit if the CMAP amplitude is more than 80% of the lower limit or latency is more than 150% of the upper limit if the CMAP amplitude is less than 80% of the lower limit. **When available**, results of other pertinent testing to support diagnosis should be provided. This includes, but is not limited to, the following: o Cerebrospinal fluid (CSF) examination demonstrating elevated CSF protein with leukocyte count <10/mm3

Condition	Criteria for Use
	o MRI showing gadolinium enhancement and/or hypertrophy of the cauda equina, lumbosacral or cervical nerve roots, or the brachial or lumbosacral plexuses o Nerve biopsy showing unequivocal evidence of demyelination and/or remyelination by electron microscopy or teased fibre analysis **For reauthorizations**, significant improvement in clinical condition has been documented by an objective measurement such as the inflammatory neuropathy cause and treatment group (INCAT) sensory sum score; assessment of grip strength via a hand-held dynamometer (e.g., Jamar, Vigorimeter); or Medical Research Council (MRC) scales or other similar, validated neurological scales **AND**, when applicable, a reduction in the level of sensory loss should be noted (see Appendix 4). **For long-term treatment**, evidence that the dose has been periodically reduced or the treatment withdrawn, and the effects measured.
Guillain-Barré Syndrome (GBS) – including Acute Inflammatory Demyelinating Polyneuropathy (AIDP)	Acute treatment when **ALL** of the following criteria have been met: • Initial treatment within 4 weeks of the onset of symptoms • No concomitant use of plasmapheresis • Treatment may be repeated once but should not extend beyond 8 weeks from the onset of symptoms
Lambert-Eaton Myasthenic Syndrome (LEMS)	Treatment when there is failure, contraindication, or intolerance to other symptomatic therapies (for example, acetylcholinesterase inhibitors such as Mestinon and immunosuppressants such as prednisone, azathioprine)
Multifocal Motor Neuropathy (MMN)	Treatment when **BOTH** of the following are present: • Progressive symptoms present for at least 1 month • Diagnosis of *definite* or *probable* MMN as defined by the American Association of Neuromuscular and Electrodiagnostic Medicine (see Appendix 5)
Myasthenia Gravis	Treatment when **ANY** of the following is present: • Before planned thymectomy or during the post-operative period following thymectomy • During an acute crisis (for example, significant dysphagia, respiratory failure, inability to perform physical activity) – duration of treatment should not exceed 5 days • During initiation of immunosuppressive treatment **Note:** IVIG for the treatment of myasthenia gravis is not covered as maintenance therapy.
Opsoclonus-Myoclonus-Ataxia Syndrome	Treatment when there is a documented diagnosis
Rasmussen Encephalitis	Treatment when there is failure to conventional therapy (corticosteroids, antiepileptic agents)
Relapsing-Remitting Multiple Sclerosis	Treatment as a single agent when there is failure to any **TWO** of the following products indicated for the treatment of relapsing-remitting multiple sclerosis: • Dimethyl fumarate (Tecfidera®)* • Fingolimod (Gilenya™)* • Glatiramer acetate (Copaxone®)* • Interferon beta-1a (Avonex® or Rebif®)* • Interferon beta-1b (Betaseron®, Extavia®)* • Natalizumab (Tysabri®)* • Teriflunomide (Aubagio®)*

Condition	Criteria for Use
	Note: Individual plans may require prior authorization or pre-certification
Stiff Person Syndrome (Moersch-Woltmann Syndrome)	Treatment when **BOTH** of the following are met: • Anti-GAD antibody testing performed • Failure to available standard medical therapy (for example, diazepam, baclofen, phenytoin, clonidine, or tizanidine)

- **Rheumatology**

Condition	Criteria for Use
Dermatomyositis or Polymyositis	Treatment when **BOTH** of the following are present: • Documented dermatomyositis or polymyositis established by biopsy • **ONE** of the following o Failure of standard medical therapy (corticosteroids AND immunosuppressives) o Profound, rapidly progressive and/or potentially life threatening muscular weakness
Kawasaki disease	Acute treatment when given in conjunction with aspirin within ten days of onset of symptoms

- **Infectious Disease**

Condition	Criteria for Use
Measles post-exposure prophylaxis	Prophylaxis when **ANY** of the following are met: • Pregnant women without evidence of measles immunity • Severe primary immunodeficiency • Individuals who have received a bone marrow transplant until at least 12 months after finishing all immunosuppressive treatment, or longer in individuals who have developed graft-versus-host disease • Individual on treatment for acute lymphoblastic leukemia (ALL) within and until at least 6 months after completion of immunosuppressive chemotherapy • Individuals with a diagnosis of AIDS or HIV-infected persons with severe immunosuppression defined as CD4 percent <15% (all ages) or CD4 count <200 lymphocytes/mm^3 (aged >5 years) and those who have not received MMR vaccine since receiving effective antiretroviral therapy (ART)
Toxic Shock Syndrome (Staphylococcal or streptococcal)	Acute treatment for **ANY** of the following: • The infection is refractory to aggressive treatment • Presence of an undrainable focus • Persistent oliguria with pulmonary edema
Tetanus	Post-exposure prophylaxis or treatment when Tetanus Immune Globulin is unavailable
Varicella	Post-exposure prophylaxis when Varicella Immune Globulin is unavailable

- **Dermatology**

Condition	Criteria for Use
Autoimmune mucocutaneous blistering diseases; such as: • **Bullous Pemphigoid** • **Epidermolysis Bullosa Acquisita** • **Pemphigoid (a.k.a., Cicatricial Pemphigoid)** • **Pemphigus Foliaceus** • **Pemphigus Vulgaris**	Treatment when **EITHER** of the following criteria is met: • Failure, contraindication or intolerance of conventional therapy (corticosteroids, azathioprine, cyclophosphamide, mycophenolate mofetil) • Rapidly progressive disease in which a clinical response cannot be affected quickly enough using conventional agents. In these situations, IVIG therapy should be given along with conventional treatment(s) and the IVIG used only until conventional therapy takes effect

Condition	Criteria for Use
	Note: IVIG for the treatment of autoimmune mucocutaneous blistering disease is covered only for short-term therapy **(no longer than 6 consecutive months**) and not as a maintenance therapy
Stevens–Johnson Syndrome (SJS)/ Toxic Epidermal Necrolysis (TEN)	Acute treatment only

***See appendices for the following information:**

- Appendix 1 – Standard Reference Ranges for Serum Immunoglobulin Levels
- Appendix 2 – Standard Reference Ranges for Serum Immunoglobulin G Subclasses (G1, G2, G3, G4)
- Appendix 3 – Selected Genetic Based Primary Immunodeficiency (PID) Disorders
- Appendix 4 – Examples of Objective Measurements to Assess Clinical Response (CIDP Reauthorization Criteria)
- Appendix 5 – American Association of Neuromuscular and Electrodiagnostic Medicine Consensus Criteria for the Diagnosis of Multifocal Motor Neuropathy

Cigna does not cover the use of immune globulin for any other indication including the following because it is considered experimental, investigational or unproven (this list may not be all-inclusive):

- Hashimoto encephalopathy
- Inclusion body myositis (IBM)
- Lyme neuropathy
- Maintenance therapy for myasthenia gravis (MG)
- 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

FDA Approved Indications

Product	FDA Approved Indications
Bivigam®	Bivigam is an Immune Globulin Intravenous (Human), 10% Liquid, indicated for the treatment of patients with primary humoral immunodeficiency (PI). This includes, but is not limited to, the humoral immune defect in common variable immunodeficiency (CVID), X-linked agammaglobulinemia, congenital agammaglobulinemia, Wiskott-Aldrich syndrome, and severe combined immunodeficiencies.
Carimune® NF	**Immunodeficiency** Carimune NF is indicated for the maintenance treatment of patients with primary immunodeficiencies (PID), e.g. common variable immunodeficiency, X-linked agammaglobulinemia, severe combined immunodeficiency. Carimune NF is preferable to intramuscular Immune Globulin (Human) preparations in treating patients who require an immediate and large increase in the intravascular immunoglobulin level, in patients with limited muscle mass, and in patients with bleeding tendencies for whom intramuscular injections are contraindicated. The infusions must be repeated at regular intervals. **Immune Thrombocytopenic Purpura (ITP)** Acute A controlled study was performed in children in which Carimune was compared with steroids for the treatment of acute (defined as less than 6 months duration) ITP. In this study sequential platelet levels of 30,000, 100,000, and 150,000/µL were all achieved faster with Carimune than with steroids and without any of the side effects associated with steroids. However, it should be noted that many cases of acute ITP in childhood

Product	FDA Approved Indications
	resolve spontaneously within weeks to months. Carimune has been used with good results in the treatment of acute ITP in adult patients. In a study involving 10 adults with ITP of less than 16 weeks duration, Carimune therapy raised the platelet count to the normal range after a 5 day course. This effect lasted a mean of over 173 days, ranging from 30 to 372 days. <u>Chronic</u> Children and adults with chronic (defined as greater than 6 months duration) ITP have also shown an increase (sometimes temporary) in platelet counts upon administration of Carimune. Therefore, in situations that require a rapid rise in platelet count, e.g. prior to surgery or to control excessive bleeding, use of Carimune should be considered. In children with chronic ITP, Carimune therapy resulted in a mean rise in platelet count of 312,000/µL with a duration of increase ranging from 2 to 6 months. Carimune therapy may be considered as a means to defer or avoid splenectomy. In adults, Carimune therapy has been shown to be effective in maintaining the platelet count in an acceptable range with or without periodic booster therapy. The mean rise in platelet count was 93,000/µL and the average duration of the increase was 20–24 days. However, it should be noted that not all patients will respond. Even in those patients who do respond, this treatment should not be considered to be curative.
Cuvitru®	Cuvitru is an Immune Globulin Subcutaneous (Human) (IGSC), 20% Solution indicated as replacement therapy for primary humoral immunodeficiency (PI) in adult and pediatric patients two years of age and older. This includes, but is not limited to, common variable immunodeficiency (CVID), X-linked agammaglobulinemia, congenital agammaglobulinemia, Wiskott-Aldrich syndrome, and severe combined immunodeficiencies.
Flebogamma® 5% DIF	Flebogamma 5% DIF is an immune globulin intravenous (human) solution indicated in adults and pediatric patients 2 years of age and older for the treatment of primary immunodeficiency (PI), including the humoral immune defects in common variable immunodeficiency, x-linked agammaglobulinemia, severe combined immunodeficiency, and Wiskott-Aldrich syndrome.
Flebogamma® 10% DIF	Flebogamma 10% DIF is an immune globulin intravenous (human) solution indicated for the treatment of: **Primary Immunodeficiency (PI)** Flebogamma 10% DIF is indicated as replacement therapy in primary immunodeficiency (PI) including the humoral immune defects in common variable immunodeficiency, x-linked agammaglobulinemia, severe combined immunodeficiency, and Wiskott-Aldrich syndrome. **Chronic Primary Immune Thrombocytopenia (ITP)** Flebogamma 10% DIF is indicated for the treatment of patients 2 years of age and older with chronic primary immune thrombocytopenia to raise platelet count.
Gammagard® Liquid	**Primary Immunodeficiency (PI)** Gammagard Liquid is indicated as replacement therapy for primary humoral immunodeficiency (PI) in adult and pediatric patients two years of age or older. This includes, but is not limited to, common variable immunodeficiency (CVID), X-linked agammaglobulinemia, congenital agammaglobulinemia, Wiskott-Aldrich syndrome, and severe combined immunodeficiencies. **Multifocal Motor Neuropathy (MMN)** Gammagard Liquid is indicated as a maintenance therapy to improve muscle strength and disability in adult patients with Multifocal Motor Neuropathy (MMN).
Gammagard® S/D	**Primary Immunodeficiency (PI)** Gammagard S/D is indicated for the treatment of primary immunodeficiency (PI) associated with defects in humoral immunity, in adults and children two years and older. This includes, but is not limited to, congenital agammaglobulinemia, common variable immunodeficiency, Wiskott-Aldrich syndrome, and severe combined immunodeficiencies.

Product	FDA Approved Indications
	B-cell Chronic Lymphocytic Leukemia (CLL) Gammagard S/D is indicated for prevention of bacterial infections in patients with hypogammaglobulinemia and/or recurrent bacterial infections associated with B-cell Chronic Lymphocytic Leukemia (CLL). **Idiopathic Thrombocytopenic Purpura (ITP)** Gammagard S/D is indicated for the treatment of adult Chronic Idiopathic Thrombocytopenic Purpura to increase platelet count and to prevent and/or to control bleeding. **Kawasaki Syndrome** Gammagard S/D is indicated for the prevention of coronary artery aneurysms associated with Kawasaki syndrome in pediatric patients.
Gammaked™	**Primary Humoral Immunodeficiency (PI)** Gammaked is indicated for treatment of primary humoral immunodeficiency in patients 2 years of age and older. This includes, but is not limited to, congenital agammaglobulinemia, common variable immunodeficiency, X-linked agammaglobulinemia, Wiskott-Aldrich syndrome, and severe combined immunodeficiencies. **Idiopathic Thrombocytopenic Purpura (ITP)** Gammaked is indicated for the treatment of adults and children with Idiopathic Thrombocytopenic Purpura to raise platelet counts to prevent bleeding or to allow a patient with ITP to undergo surgery. **Chronic Inflammatory Demyelinating Polyneuropathy (CIDP)** Gammaked is indicated for the treatment of CIDP in adults to improve neuromuscular disability and impairment and for maintenance therapy to prevent relapse.
Gammaplex®	**Primary Humoral Immunodeficiency (PI)** Gammaplex is an Immune Globulin Intravenous (Human), 5% Liquid indicated for replacement therapy in primary humoral immunodeficiency (PI) in adults and pediatric patients 2 years of age and older. This includes, but is not limited to, the humoral immune defect in common variable immunodeficiency, X-linked agammaglobulinemia (XLA), congenital agammaglobulinemia, Wiskott-Aldrich syndrome, and severe combined immunodeficiencies. Gammaplex is an Immune Globulin Intravenous (Human), 10% Liquid indicated for replacement therapy in primary humoral immunodeficiency (PI) in adults. This includes, but is not limited to, the humoral immune defect in common variable immunodeficiency, X-linked agammaglobulinemia, congenital agammaglobulinemia, Wiskott-Aldrich syndrome, and severe combined immunodeficiencies. **Chronic Immune Thrombocytopenic Purpura (ITP)** Gammaplex is indicated for the treatment of adults with chronic immune thrombocytopenic purpura (ITP) to raise platelet counts.
Gamunex®-C	**Primary Humoral Immunodeficiency (PI)** Gamunex-C is indicated for treatment of primary humoral immunodeficiency in patients 2 years of age and older. This includes, but is not limited to, congenital agammaglobulinemia, common variable immunodeficiency, X-linked agammaglobulinemia, Wiskott-Aldrich syndrome, and severe combined immunodeficiencies. **Idiopathic Thrombocytopenic Purpura (ITP)**

Product	FDA Approved Indications
	Gamunex-C is indicated for the treatment of patients with Idiopathic Thrombocytopenic Purpura to raise platelet counts to prevent bleeding or to allow a patient with ITP to undergo surgery. **Chronic Inflammatory Demyelinating Polyneuropathy (CIDP)** Gamunex-C is indicated for the treatment of CIDP to improve neuromuscular disability and impairment and for maintenance therapy to prevent relapse.
Hizentra®	**Primary Humoral Immunodeficiency (PI)** Hizentra is indicated as replacement therapy for primary humoral immunodeficiency (PI) in adults and pediatric patients 2 years of age and older. This includes, but is not limited to, the humoral immune defect in congenital agammaglobulinemia, common variable immunodeficiency, X-linked agammaglobulinemia, Wiskott-Aldrich syndrome, and severe combined immunodeficiencies. **Chronic Inflammatory Demyelinating Polyneuropathy (CIDP)** Hizentra is indicated for the treatment of adult patients with chronic inflammatory demyelinating polyneuropathy (CIDP) as maintenance therapy to prevent relapse of neuromuscular disability and impairment. Limitations of Use: Hizentra maintenance therapy in CIDP has been systematically studied for 6 months and for a further 12 months in a follow-up study. Maintenance therapy beyond these periods should be individualized based upon the patient's response and need for continued therapy.
HyQvia®	HyQvia is an immune globulin with a recombinant human hyaluronidase indicated for the treatment of Primary Immunodeficiency (PI) in adults. This includes, but is not limited to, common variable immunodeficiency (CVID), X-linked agammaglobulinemia, congenital agammaglobulinemia, Wiskott-Aldrich syndrome, and severe combined immunodeficiencies Limitation of Use: Safety and efficacy of chronic use of recombinant human hyaluronidase in HyQvia have not been established in conditions other than PI.
Octagam® 5%	Octagam is an immune globulin intravenous (human) 5% liquid indicated for treatment of primary humoral immunodeficiency (PI), such as congenital agammaglobulinemia, common variable immunodeficiency, X-linked agammaglobulinemia, Wiskott-Aldrich syndrome and severe combined immunodeficiencies.
Octagam® 10%	Octagam 10% is indicated in Chronic Immune Thrombocytopenic Purpura to rapidly raise platelet counts to control or prevent bleeding in adults.
Panzyga® 10%	**Primary Humoral Immunodeficiency Diseases (PI)** Panzyga is indicated for treatment of primary humoral immunodeficiency (PI) in patients 2 years of age and older. This includes, but is not limited to, congenital agammaglobulinemia, common variable immunodeficiency, X-linked agammaglobulinemia, Wiskott-Aldrich syndrome, and severe combined immunodeficiencies. **Chronic Immune Thrombocytopenia (ITP)** Panzyga is indicated for the treatment of adult patients with ITP to raise platelet counts to control or prevent bleeding.
Privigen®	**Primary Humoral Immunodeficiency** Privigen is indicated as replacement therapy for primary humoral immunodeficiency (PI). This includes, but is not limited to, the humoral immune defect in congenital agammaglobulinemia, common variable immunodeficiency (CVID), X-linked agammaglobulinemia, Wiskott-Aldrich syndrome, and severe combined immunodeficiencies.

Product	FDA Approved Indications
	Chronic Immune Thrombocytopenic Purpura Privigen is indicated for the treatment of patients with chronic immune thrombocytopenic purpura (ITP) to raise platelet counts. **Chronic Inflammatory Demyelinating Polyneuropathy (CIDP)** Privigen is indicated for the treatment of adults with chronic inflammatory demyelinating polyneuropathy (CIDP) to improve neuromuscular disability and impairment. Limitation of Use: Privigen maintenance therapy in CIDP has not been studied for periods longer than 6 months. After responding during an initial treatment period, not all patients require indefinite maintenance therapy with Privigen in order to remain free of CIDP symptoms. Individualize the duration of any treatment beyond 6 months based upon the patient's response and demonstrated need for continued therapy.

FDA Recommended Dosing

The frequency and amount of immunoglobulin therapy may vary from patient to patient. The proper dosing amount can be determined by monitoring clinical response.

Product	FDA Recommended Dosing
Bivigam	The recommended dose of Bivigam for replacement therapy in primary humoral immunodeficiency (PI) is 300 to 800 mg/kg body weight administered every 3 to 4 weeks. The dosage may be adjusted over time to achieve the desired trough levels and clinical response. Bivigam dose adjustments may be required in patients who fail to maintain trough total IgG concentrations of at least 500 mg/dL with a target of 600 mg/dL. Starting with the second infusion, the dose will be adjusted proportionally, targeting a trough of more than equal to 600 mg/dL, based on the previous trough and the associated dose.
Carimune NF	**Adult and Child Substitution Therapy** The recommended dose of Carimune NF in primary immunodeficiency is 0.4 to 0.8 g/kg of body weight administered once every three to four weeks by intravenous infusion. The first infusion of Carimune NF in previously untreated agammaglobulinemic or hypogammaglobulinemic patients must be given as a 3% immunoglobulin solution. Subsequent infusions may be administered at a higher concentration if the patient shows good tolerance. **Therapy of Idiopathic Thrombocytopenic Purpura (ITP)** <u>Induction</u> The recommended dose of Carimune NF for the treatment of ITP is 0.4 g/kg of body weight on 2–5 consecutive days. An immunoglobulin solution of 6% is recommended for use in ITP. <u>Acute ITP – Childhood</u> In acute ITP of childhood, if an initial platelet count response to the first two doses is adequate (30–50,000/µL), therapy may be discontinued after the second day of the 5 day course. <u>Maintenance – Chronic ITP</u> In adults and children, if after induction therapy the platelet count falls to less than 30,000/µL and/or the patient manifests clinically significant bleeding, 0.4 g/kg of body weight may be given as a single infusion. If an adequate response does not result, the dose can be increased to 0.8–1 g/kg of body weight given as a single infusion.
Cuvitru	***Refer to the prescribing information (product label) for complete dosing information. The following is from the "Highlights of Prescribing Information" section of the product label.* For subcutaneous infusion only. • Administer at regular intervals from daily up to every two weeks (biweekly). • Individualize dose based on the patient's pharmacokinetic and clinical response.

Product	FDA Recommended Dosing
	• Monitor serum IgG trough levels regularly to guide subsequent dose adjustments and dosing intervals as needed. • Switching from Immune Globulin Intravenous (Human) treatment (IGIV) or adult patients switching from HyQvia ([Immune Globulin Infusion 10% (Human) with Recombinant Human Hyaluronidase]: • Begin treatment one week after the patient's last IGIV or HyQvia infusion. • Begin treatment one week after the patient's last IGIV or HyQvia infusion. • Establish initial weekly dose by converting the monthly IGIV or HyQvia dose into equivalent weekly dose and increasing it using a dose adjustment factor. Initial Weekly dose = Previous IGIV or HyQvia dose (in grams)/No. of weeks between IGIV or HYQVIA doses x 1.30. • Frequent dosing (2-7 times per week): Divide the calculated weekly dose by the desired number of times per week. • Biweekly dosing: Multiply the calculated weekly dose by 2.
Flebogamma 5% DIF	Treatment of Primary Immunodeficiency (PI): 300 to 600 mg/kg body weight (6.0 to 12.0 mL per kg) administered every 3 to 4 weeks. As there are significant differences in the half-life of IgG among patients with PI, the frequency and amount of immunoglobulin therapy may vary from patient to patient. Adjust the dose according to the clinical response. Adjust the dosage over time to achieve the desired trough IgG levels and clinical responses. No randomized controlled trial data are available to determine an optimum target trough serum IgG level.
Flebogamma 10% DIF	Treatment of Primary Immunodeficiency (PI): 300 to 600 mg/kg body weight (3.0 to 6.0 mL/kg) administered every 3-4 weeks. Treatment of Chronic Primary Immune Thrombocytopenia (ITP): 1 g/kg body weight (10ml per kg) daily for 2 consecutive days As there are significant differences in the half-life of IgG among patients with PI, the frequency and amount of immunoglobulin therapy may vary from patient to patient. Dosing should be adjusted according to the clinical response. The dosage may be adjusted over time to achieve the desired serum trough IgG levels and clinical responses. No randomized controlled trial data are available to determine an optimum target trough serum IgG level.
Gammagard Liquid	**Primary Immunodeficiency** – 300 to 600 milligram/kg every 3 to 4 weeks based on clinical response **Multifocal Motor Neuropathy** – Dose range 0.5 to 2.4 grams/kg/month based on clinical response **Primary Immunodeficiency** – Initial dose is 1.37 x previous intravenous dose divided by # of weeks between intravenous doses. Maintenance dose is based on clinical response and target IgG trough level.
Gammagard S/D	**Primary Immunodeficiency (PI)** The recommended dose of Gammagard S/D for patients with PI is 300-600 mg/kg infused at 3 to 4 week intervals. Adjust dose according to the clinical response; the frequency and dose of immunoglobulin may vary from patient to patient. No randomized controlled clinical trials are available to determine an optimum target trough serum IgG level. **B-cell Chronic Lymphocytic Leukemia (CLL)**

<table>
<tr><th>Product</th><th>FDA Recommended Dosing</th></tr>
<tr><td></td><td>The recommended dose of Gammagard S/D for patients with hypogammaglobulinemia and/or recurrent bacterial infections due to B-cell CLL is 400 mg/kg body weight infused at every 3 to 4 week intervals.

Idiopathic Thrombocytopenic Purpura (ITP)
The recommended dose of Gammagard S/D for patients with chronic ITP is 1 g/kg. The need for additional doses can be determined by clinical response and platelet count. Up to three separate doses may be given on alternate days if required.

Kawasaki Syndrome
The recommended dose of Gammagard S/D for patients with Kawasaki syndrome is either a single 1 g/kg dose or a dose of 400 mg/kg for four consecutive days beginning within seven days of the onset of fever, administered concomitantly with appropriate aspirin therapy (80-100 mg/kg/day in four divided doses).</td></tr>
<tr><td>Gammaked</td><td>**Refer to the prescribing information (product label) for complete dosing information. The following is from the “Highlights of Prescribing Information” section of the product label.
• Intravenous Administration Only: ITP and CIDP
<table>
<tr><th>Indication</th><th>Dose</th><th>Initial Infusion Rate</th><th>Maintenance Infusion Rate (if tolerated)</th></tr>
<tr><td>ITP</td><td>2 g/kg</td><td>1 mg/kg/min</td><td>8 mg/kg/min</td></tr>
<tr><td>CIDP</td><td>Loading dose
2 g/kg
Maintenance dose
1 g/kg</td><td>2 mg/kg/min</td><td>8 mg/kg/min
Every 3 weeks</td></tr>
</table>
o Ensure that patients with pre-existing renal insufficiency are not volume depleted; discontinue Gammaked if renal function deteriorates.
o For patients at risk of renal dysfunction or thrombosis, administer Gammaked at the minimum infusion rate practicable.

• Intravenous or Subcutaneous Administration: PI
DO NOT ADMINISTER SUBCUTANEOUSLY FOR ITP PATIENTS.
<table>
<tr><th>Route of Administration</th><th>Dose</th><th>Infusion Rate</th><th>Maintenance Infusion Rate (if tolerated)</th></tr>
<tr><td>Intravenous (IV)</td><td>300-600 mg/kg</td><td>1 mg/kg/min</td><td>8 mg/kg/min
Every 3-4 weeks</td></tr>
<tr><td>Subcutaneous (SC)</td><td>1.37 x current IV dose in mg/kg/IV dose interval in weeks</td><td><u>Adult:</u>
20 mL/hr/site

<u>Pediatric:</u>
10 mL/hr/site (< 25 kg)
15 mL/hr/site (≥ 25 kg)</td><td><u>Adult:</u>
20 mL/hr/site

<u>Pediatric:</u>
10 mL/hr/site (< 25 kg)
20 mL/hr/site (≥ 25 kg)
Weekly</td></tr>
</table>
</td></tr>
<tr><td>Gammaplex</td><td>Treatment of Primary Humoral Immunodeficiency
The recommended dose of Gammaplex for patients with PI is 300 to 800 mg/kg (6 to 16 mL/kg), administered every 3 to 4 weeks. Adjust the dosage over time to achieve the desired serum trough levels and clinical response. If a patient misses a dose, administer the missed dose as soon as possible, and then resume scheduled treatments every 3 or 4 weeks, as applicable.

Treatment of Chronic Idiopathic Thrombocytopenic Purpura</td></tr>
</table>

<table>
<tr><th>Product</th><th>FDA Recommended Dosing</th></tr>
<tr><td></td><td>The recommended dose of Gammaplex for patients with ITP is 1 g/kg (20 mL/kg) on 2 consecutive days, providing a total dose of 2 g/kg. Carefully consider the relative risks and benefits before prescribing the high dose regimen (i.e. 1 g/kg/day for 2 days) in patients at increased risk of thrombosis, hemolysis, acute kidney injury, or volume overload. Adequate data on the platelet response to the low dose regimen (e.g. 400 mg/kg per day for 5 consecutive days) are not available for Gammaplex.</td></tr>
<tr><td>Gamunex-C</td><td>*Refer to the prescribing information (product label) for complete dosing information. The following is from the “Highlights of Prescribing Information” section of the product label.*
• Intravenous Administration Only: Idiopathic Thrombocytopenic Purpura (ITP) and Chronic Inflammatory Demyelinating Polyneuropathy (CIDP)
<table>
<tr><th>Indication</th><th>Dose</th><th>Initial Infusion Rate</th><th>Maintenance Infusion Rate (if tolerated)</th></tr>
<tr><td>ITP</td><td>2 g/kg</td><td>1 mg/kg/min</td><td>8 mg/kg/min</td></tr>
<tr><td>CIDP</td><td>Loading dose
2 g/kg
Maintenance dose
1 g/kg</td><td>2 mg/kg/min</td><td>8 mg/kg/min
Every 3 weeks</td></tr>
</table>
• Ensure that patients with pre-existing renal insufficiency are not volume depleted; discontinue Gamunex-C if renal function deteriorates.
• For patients at risk of renal dysfunction or thrombosis, administer Gamunex-C at the minimum infusion rate practicable.

• Intravenous or Subcutaneous Administration: Primary Humoral Immunodeficiency (PI)
• DO NOT ADMINISTER SUBCUTANEOUSLY FOR ITP PATIENTS.
<table>
<tr><th>Route of Administration</th><th>Dose</th><th>Infusion Rate</th><th>Maintenance Infusion Rate (if tolerated)</th></tr>
<tr><td>Intravenous (IV)</td><td>300-600 mg/kg</td><td>1 mg/kg/min</td><td>8 mg/kg/min
Every 3-4 weeks</td></tr>
<tr><td>Subcutaneous (SC)</td><td>1.37 x current IV dose in mg/kg/IV dose interval in weeks</td><td><u>Adult:</u>
20 mL/hr/site

<u>Pediatric:</u>
10 mL/hr/site (< 25 kg)
15 mL/hr/site (≥ 25 kg)</td><td><u>Adult:</u>
20 mL/hr/site

<u>Pediatric:</u>
10 mL/hr/site (< 25 kg)
20 mL/hr/site (≥ 25 kg)
Weekly</td></tr>
</table>
</td></tr>
<tr><td>Hizentra</td><td>*Refer to the prescribing information (product label) for complete dosing information. The following is from the “Highlights of Prescribing Information” section of the product label.*
For subcutaneous infusion only.
<u>PI</u>
Before switching to Hizentra, obtain the patient's serum IgG trough level to guide subsequent dose adjustments.
• Weekly: Start Hizentra 1 week after last Immune Globulin Intravenous (Human) (IGIV) infusion.
Initial weekly dose = <u>Previous IGIV dose (in grams)</u> × 1.37
No. of weeks between IGIV doses
• Biweekly (every 2 weeks): Start Hizentra 1 or 2 weeks after the last IGIV infusion or 1 week after the last weekly IGSC infusion. Administer twice the calculated weekly dose.</td></tr>
</table>

<table>
<tr><th>Product</th><th>FDA Recommended Dosing</th></tr>
<tr><td></td><td>

Frequent dosing (2 to 7 times per week): Start Hizentra 1 week after the last IGIV or IGSC infusion. Divide the calculated weekly dose by the desired number of times per week.
Adjust the dose based on clinical response and serum IgG trough levels.

<u>CIDP</u>

Initiate therapy with Hizentra 1 week after the last IGIV infusion.
Recommended subcutaneous dose is 0.2 g/kg (1 mL/kg) body weight (bw) per week.

In the clinical study after transitioning from IGIV to Hizentra, a dose of 0.4 g/kg (2 mL/kg) bw per week was also safe and effective to prevent CIDP relapse.

If CIDP symptoms worsen, consider re-initiating treatment with an IGIV approved for the treatment of CIDP, while discontinuing Hizentra.

If improvement and stabilization are observed during IGIV treatment, consider re-initiating Hizentra at 0.4 g/kg bw per week, while discontinuing IGIV.
If CIDP symptoms worsen on 0.4 g/kg bw per week, consider re-initiating therapy with IGIV, while discontinuing Hizentra.

Monitor patient's clinical response and adjust duration of therapy based on patient need.

</td></tr>
<tr><td>HyQvia</td><td>**Refer to the prescribing information (product label) for complete dosing information.
For subcutaneous use only.

Initiation of Treatment with HyQvia
• For patients previously on another IgG treatment, administer the first dose approximately one week after the last infusion of their previous treatment.
• Increase the dose and frequency from a 1-week dose to a 3- or 4-week dose
• Initiating treatment at a full monthly dose was not evaluated in the clinical trial.

For patients switching from Immune Globulin Intravenous (Human) [IGIV] treatment:
Administer HyQvia at the same dose and frequency as the previous intravenous treatment, after the initial dose ramp-up.

For patients naïve to IgG treatment or switching from Immune Globulin Subcutaneous (Human) [IGSC]:
Administer HyQvia at 300 to 600 mg/kg at 3 to 4 week intervals, after initial ramp-up.

Individualization of Dose:
If HyQvia is administered at the same dose and frequency, the serum IgG levels from HyQvia should be comparable to serum IgG levels from intravenous treatment.</td></tr>
<tr><td>Octagam 5%</td><td>The dose of Octagam 5% liquid for replacement therapy in primary humoral immunodeficiency diseases is 300 to 600 mg/kg body weight (6-12 ml/kg) administered every 3 to 4 weeks. The dosage may be adjusted over time to achieve the desired trough levels and clinical responses.

If a patient is at risk of measles exposure (i.e., outbreak in US or travel to endemic areas outside of the US) and receives a dose of less than 400 mg/kg every 3 to 4 weeks, the dose should be increased to at least 400 mg/kg. If a patient has been exposed to measles, this dose should be administered as soon as possible after exposure.</td></tr>
<tr><td>Octagam 10%</td><td>Administer Octagam 10% at a total dose of 2 g/kg, divided into two doses of 1 g/kg (10mL/kg) given on two consecutive days.</td></tr>
<tr><td>Panzyga 10%</td><td>For intravenous use only.

Dose
<table>
<tr><th>Indication</th><th>Dose</th><th>Initial Infusion Rate (first 30 min)</th><th>Maximum Infusion Rate in New</th><th>Maximum Infusion Rate in</th></tr>
</table>
</td></tr>
</table>

<table>
<tr><th>Product</th><th>FDA Recommended Dosing</th></tr>
<tr><td></td><td>
<table>
<tr><td></td><td></td><td></td><td>Patients** (as tolerated)</td><td>Experienced Patients*** (as tolerated)</td></tr>
<tr><td>Treatment of Primary Humoral Immunodeficiency (PI)*</td><td>300 to 600 mg/kg body weight (3-6 mL/kg) administered every 3 to 4 weeks</td><td>1 mg/kg/min (0.01 mL/kg/min)</td><td>8 mg/kg/min (0.08 mL/kg/min)</td><td>12 or 14 mg/kg/min (0.12 or 0.14 mL/kg/min)</td></tr>
<tr><td>Treatment of Chronic Immune Thrombocytopenia (ITP)</td><td>2 g/kg, divided into two daily doses of 1 g/kg (10 mL/kg) given on two consecutive days</td><td>1 mg/kg/min (0.01 mL/kg/min)</td><td>8 mg/kg/min (0.08 mL/kg/min)</td><td></td></tr>
</table>
*Significant differences in the half-life of IgG among patients with PI may necessitate the dose and frequency of immunoglobulin therapy to vary from patient to patient. Determine the proper dose and frequency by monitoring the clinical response. Adjust dose over time to achieve the desired trough levels of IgG and clinical responses.
**Patients receiving Panzyga (or another IGIV) for the first time or more than 8 weeks since a prior treatment.
*** Experienced patients received greater than 3 (12 mg/kg/min) to 6 (14 mg/kg/min) infusions every 3-4 weeks.

Following the initial infusion, the infusion rate may be gradually increased every 15-30 minutes to a maximum of 14 mg/kg/min (0.14 mL/kg/min) in PI and to 8 mg/kg/min (0.08 mL/kg/min) in chronic ITP in adults, as tolerated. The recommended ramp-up for an infusion is 1, 2, 4, and 8 mg/kg/min (0.01, 0.02, 0.04, and 0.08 mL/kg/min) in new PI and ITP patients (i.e., patients who have not previously received any IGIV product), and 1, 4, 8, and 12 or 14 mg/kg/min (0.01, 0.04, 0.08, and 0.12 or 0.14 mL/kg/min) in experienced PI patients (i.e., patients who have previously received any IGIV product).
</td></tr>
<tr><td>Privigen</td><td>
Dosage for Primary Humoral Immunodeficiency (PI)
The recommended dose of Privigen for patients with PI is 200 to 800 mg/kg (2 to 8 mL/kg), administered every 3 to 4 weeks. If a patient misses a dose, administer the missed dose as soon as possible, and then resume scheduled treatments every 3 or 4 weeks, as applicable. Adjust the dosage over time to achieve the desired serum IgG trough levels and clinical responses. No randomized, controlled trial data are available to determine an optimal trough level in patients receiving immune globulin therapy.

Dosage for Chronic Immune Thrombocytopenic Purpura (ITP)
The recommended dose of Privigen for patients with chronic ITP is 1 g/kg (10 mL/kg) administered daily for 2 consecutive days, resulting in a total dosage of 2 g/kg. Carefully consider the relative risks and benefits before prescribing the high dose regimen (e.g., 1 g/kg/day for 2 days) in patients at increased risk of thrombosis, hemolysis, acute kidney injury, or volume overload.

Chronic Inflammatory Demyelinating Polyneuropathy (CIDP)
Privigen may be initially administered as a total loading dose of 2 g/kg (20 mL/kg) given in divided doses over two to five consecutive days. Privigen may be administered as a maintenance infusion of 1 g/kg (10 mL/kg) administered in a single infusion given in one day or divided into two doses given on two consecutive days, every 3 weeks. Maintenance therapy beyond 6 months has not been studied.
</td></tr>
</table>

Drug Availability

Product	Drug Availability
Bivigam	Supplied in single-use vials: 5GM, 10GM
Carimune NF	Supplied in single-use vials: 6GM, 12GM
Cuvitru	Supplied in single-use vials: 1GM, 2GM, 4GM, 8GM
Flebogamma 5% DIF	Supplied in single-use vials: 0.5GM, 2.5GM, 5GM, 10GM, 20GM
Flebogamma 10% DIF	Supplied in single-use vials: 5GM, 10GM, 20GM
Gammagard Liquid	Supplied in single-use vials: 1GM, 2.5GM, 5GM, 10GM, 20GM, 30GM
Gammagard S/D	Supplied in single-use vials: 5GM, 10GM
Gammaked	Supplied in single-use vials: 1GM, 2.5GM, 5GM, 10GM, 20GM
Gammaplex	Supplied in single-use vials: 5GM, 10GM, 20GM
Gamunex-C	Supplied in single-use vials: 1GM, 2.5GM, 5GM, 10GM, 20GM, 40GM
Hizentra	Supplied in single-use vials: 1GM, 2GM, 4GM, 10GM
HyQvia	Supplied in dual vial unit of (2) single-use vials: 2.5 GM, 5GM, 10GM, 20GM, 30GM of Immune Globulin with 200U, 400U, 800U, 1600U, 2400U respectively of Recombinant Human Hyaluronidase
Octagam 5%	Supplied in single-use vials: 1GM, 2.5GM, 5GM, 10GM, 25GM
Octagam 10%	Supplied in single-use vials: 2GM, 5GM, 10GM, 20GM
Panzyga 10%	Supplied in 1 g, 2.5 g, 5 g, 10 g, 20 g, and 30 g single-use bottles.
Privigen	Supplied in single-use vials: 5GM, 10GM, 20GM, 40GM

General Background

Pharmacology

Immune globulin is a sterile, purified preparation of human immunoglobulin derived from pooled human plasma of healthy donors. Immune globulin has diverse mechanisms of action including anti-infective, immunoregulatory, and anti-inflammatory properties. These preparations provide replacement therapy for patients with immunodeficiency conditions, as well as, treatment for a variety of immunologically mediated or idiopathic diseases and syndromes.

Guidelines

- **Primary Immunodeficiency Disorders (PID)**

American Academy of Allergy, Asthma and Immunology (AAAAI)

IVIG is indicated as replacement therapy for patients with primary and selected secondary immunodeficiency diseases characterized by absent or deficient antibody production and, in most cases, recurrent or unusually severe infections. IVIG has also been used in a number of diseases that result in a secondary humoral immunodeficiency.

In 2015, American Academy of Allergy, Asthma & Immunology (AAAI) and the American College of Allergy, Asthma & Immunology (ACAAI); and Joint Council of Allergy, Asthma & Immunology (JCAAI) published the Practice Parameter for the Diagnosis and Management of Primary Immunodeficiency. The practice parameter states that immune globulins are a part of standard therapy for various Primary Immunodeficiency, including combined immunodeficiencies, Wiskott-Aldrich Syndrome, agammaglobulinemia, common variable immunodeficiency and specific innate immune defects.

Summary statement 105 states “The diagnosis of SAD should be given to patients older than 2 years with recurrent respiratory tract infections, normal immunoglobulin and IgG subclass levels, and impaired response to pneumococcal capsular polysaccharide” and summary statement 106 states “Patients with SAD might benefit from additional immunization with conjugate pneumococcal vaccines, intensified use of antibiotics, and in some cases a period of IgG replacement therapy.” (Bonilla 2015)

The AAAAI Basic and Clinical Immunology Interest Section working group published a 2012 document on the use and interpretation of diagnostic vaccination in PID. The intent of the document was to provide guidance on the use of vaccination for diagnostic purposes in consideration of PIDD and to identify areas for future research. There are two types of pneumococcal vaccines which are available; these include PCVs (Prevnar 7 and Prevnar 13) and PPV23s (Pneumovax). The working group document states that PPV23 is currently the most useful agent for evaluating clinically relevant T-independent antibody responses in those patients who are infection-prone.

Summary statement 16 states "PPV is used diagnostically in both adults and children having completed their primary pneumococcal conjugate vaccine (PCV) series who are suspected of immunodeficiency to ascertain response to polysaccharide antigens" and summary statement 30 states "a diagnosis of specific antibody deficiency (SAD) can be made if the response to PPV23 is deficient but the responses to protein antigens (e.g. tetanus toxoid or diphtheria toxoid), conjugate vaccines (Haemophilus influenza type b, PCV7, or PCV13), or both are intact and total immunoglobulin levels are normal" (Orange 2012).

In a 2012 Choosing Wisely statement, AAAAI noted that low levels of immunoglobulins without impaired antigen-specific IgG antibody responses are not an indication for immunoglobulin replacement therapy. However, IgG levels < 150 mg/dL and genetically defined/suspected disorders may be an indication for therapy. Typically, measurement of IgG subclasses is not useful in determining the need for immunoglobulin therapy. AAAAI also stated that selective IgA deficiency is not an indication for administration of immunoglobulin (AAAAI, 2012).

In earlier publications AAAAI stated that selective IgA deficiency (SIGAD) is not an indication for IVIG replacement therapy. In some cases IVIG may be considered when there is poor specific IgG antibody production with or without IgG2 subclass deficiency or if there is inadequate response to antimicrobial therapy in a patient with a concomitant specific antibody defect. The use of gamma globulin therapy for the treatment of SIGAD without a demonstrable impairment of specific antibody formation is controversial (Orange, 2006; Bonilla, 2005). Regarding specific antibody deficiency (SAD), Bonilla et al noted that mild antibody deficiencies are initially treated with antibiotic prophylaxis and generally do not require IVIG replacement for the control of recurrent bacterial infections.

- **Secondary Immunodeficiency**

B-cell Chronic Lymphocytic Leukemia (CLL) and Multiple Myeloma

National Comprehensive Cancer Network (NCCN)

NCCN Guidelines recommend the use of IVIG as an adjunctive treatment in multiple myeloma (MM) when there is a recurrent life-threatening infection (NCCN, 3.2018). Some malignancies are associated with immune deficits. Patients with MM are frequently hypogammaglobulinemic, but the total level of immunoglobulin production is high while the reserve of antibody production is limited. For chronic lymphocytic leukemia (CLL) and recurrent sinopulmonary infections that require intravenous antibiotics or hospitalization, NCCN Guidelines recommend antimicrobials as appropriate, and if the serum IgG is less than 500 mg/dL, starting monthly IVIG 0.3-0.5 g/kg and adjusting the dose and interval to maintain an IgG nadir level of approximately 500 mg/dL (NCCN, 1.2018). Center for Disease Control and Prevention (CDC) guidelines recommend that allogeneic HCT recipients with severe hypogammaglobulinemia (IgG <400 mg/dL) and with recurrent infections receive IVIG prophylaxis; IVIG is not routinely recommended in other patient groups or in autologous HCT recipients (NCCN, 2.2017).

HIV-Infected Children

National Institutes of Health (NIH); Centers for Disease Control and Prevention (CDC); HIV Medicine Association of the Infectious Diseases Society of America (IDSA); Pediatric Infectious Diseases Society; American Academy of Pediatrics (AAP)

Recommendations for the use of IVIG for the prevention and treatment of opportunistic infections in HIV-exposed and HIV-infected children include the following 3 scenarios:

- Primary prophylaxis of bacterial infections when there is hypogammaglobulinemia (i.e. IgG < 400mg/dL). The recommended IVIG dose is 400 mg/kg body weight every 2-4 weeks.
- Primary post-exposure prophylaxis of varicella-zoster virus (VZV) as an alternative (if VariZIG cannot be administered within 96 hours [up to 10 days]). The recommended IVIG dose is 400 mg/kg body weight administered once should be considered.

- Secondary prophylaxis of frequent recurrent serious bacterial infections (e.g. > 2 serious bacterial infections in a 1-year period despite combination ART) when antibiotic prophylaxis is not effective. The recommended IVIG dose is 400 mg/kg body weight every 2-4 weeks (DHHS, 2017).

• Transplantation

Hematopoietic Cell Transplant

American Society for Blood and Marrow Transplantation (ASBMT)

The ASBMT provides recommendations for preventing infections in individuals who have undergone hematopoietic cell transplantation (HCT). The guidelines group all transplantation of blood- or marrow-derived hematopoietic stem cells together regardless of transplant type (i.e., allogeneic or autologous) or cell source (Tomblyn, 2009). The ASBMT guidelines do not recommend IVIG for routine prophylaxis of bacterial infections in HCT recipients within the first 100 days after transplantation. IVIG prophylaxis against bacterial infection may be considered for HCT recipients with severe hypogammaglobulinemia (i.e. serum IgG level of < 400 mg/dL). The IVIG dose and frequency for a hypogammaglobulinemic HCT recipient should be individualized to maintain trough serum IgG concentrations above 400 mg/dL, as the half-life of IVIG among HCT recipients (generally, 1-10 days) is much shorter than the half-life among healthy adults (generally, 18-23 days). In the absence of severe hypogammaglobulinemia, IVIG administration to HCT recipients over 90 days after HCT is not recommended as a means of preventing infections (Tomblyn, 2009).

Solid Organ Transplants

International Society of Heart and Lung Transplantation (ISHLT) - Desensitization and Antibody-Mediated Rejection (AMR)

The ISHLT published guidelines for the care of heart transplant recipient states that most of the recommendations are based on expert consensus and not on randomized controlled clinical trials. These guidelines include recommendations for the risk-assessment and prophylaxis strategies for allosensitized candidates. Desensitization therapy should be considered when the calculated panel reactive antibody (PRA) is considered by the individual transplant center to be high enough to significantly decrease the likelihood for a compatible donor match or to decrease the likelihood of donor heart rejection where unavoidable mismatches occur. Choices to consider as desensitization therapies include IVIG infusion, plasmapheresis, either alone or combined, rituximab, and in very selected cases, splenectomy. The guidelines state that a large randomized controlled clinical trial is needed to assess the effectiveness of desensitization strategies and their impact on outcomes after heart transplant (Costanzo, 2010). The ISHLT also includes recommendations for the treatment of antibody-mediated rejection (AMR) with initial therapy including immunoadsorption and corticosteroid or plasmapheresis/low dose of IVIG and corticosteroid (Costanzo, 2010).

Kidney Disease Improving Global Outcomes (KDIGO) - **Antibody-Mediated Rejection (AMR)**

KDIGO published clinical practice guideline recommendations include implications stating that most patients should receive the recommended course of action while suggestions imply that different choices will be appropriate for different patients. KDIGO recommends corticosteroids for the initial treatment of acute cellular rejection. The guideline suggests treating acute AMR with one or more of the following alternatives, with or without corticosteroids, plasma exchange; intravenous immunoglobulin; anti-CD20 antibody (rituximab); lymphocyte-depleting antibody. It is stated that therapeutic strategies that include combinations of plasma exchange to remove donor-specific antibody, and/or IVIG and rituximab to suppress donor-specific antibody production have been used to successfully treat acute humoral rejection. However, the optimal protocol remains to be determined. There are no randomized controlled trials with adequate statistical power to compare the efficacy of these different strategies (KDIGO, 2009).

• Hematology

Hepatitis C-Associated Thrombocytopenia and HIV-Associated Thrombocytopenia

American Society of Hematology (ASH)

For ITP associated with human immunodeficiency virus (HIV) or hepatitis C, ASH recommends treating the underlying virus. If treatment is needed, IVIG is the recommended initial option for hepatitis C-associated ITP and one of the options for HIV-associated ITP (Neunert, 2011).

Immune (Idiopathic) Thrombocytopenia – Adult and Pediatric

American Society of Hematology (ASH)
The American Society of Hematology uses terminology from an International Working Group (IWG), which is a panel of experts in adult and pediatric immune thrombocytopenia (ITP). While they note these definitions have not been validated, the authors of the ASH guidelines state they incorporated the IWG terminology whenever possible. The IWG defines newly diagnosed ITP as from the time of diagnosis to 3 months, persistent ITP as 3-12 months from diagnosis, and chronic ITP as greater than 12 months from diagnosis. The IWG also provides definitions of treatment response for ITP. No response or loss of response is defined as a platelet count < 30 x 10^9/L, a less than 2-fold increase in platelet count from baseline, or bleeding (Neunert, 2011).

For newly diagnosed adult ITP, ASH recommends treatment if the platelet count is less than 30 X 10^9/L. The preferred treatment is longer courses of corticosteroids over shorter courses of corticosteroids or IVIG. IVIG is recommended in combination with corticosteroids if there is a need for a rapid increase in platelet count and is recommended first-line if corticosteroids are contraindicated. The initial recommended dose of IVIG is 1 gram/kg as a one-time dose, with a repeated dose if needed. For patients who fail initial corticosteroid therapy, splenectomy is recommended. Thrombopoietin receptor agonists (e.g. eltrombopag, romiplostim) are recommended if splenectomy fails or for those who are not candidates for splenectomy and failed at least one other treatment option and can be considered prior to splenectomy if failed another therapy such as corticosteroids or IVIG. Another treatment option for those at risk for bleeding who fail corticosteroids, IVIG, or splenectomy is rituximab (Neunert, 2011).

For newly diagnosed pediatric ITP, ASH recommends observation only regardless of the platelet count if there is no bleeding or mild bleeding, such as skin manifestations only. If treatment is needed, IVIG is considered a first line agent or a short course of corticosteroids. ASH recommends a single dose of IVIG at 0.8-1 gram/kg if using for initial management. Rituximab or high-dose dexamethasone can be considered in pediatric patients with continued ITP symptoms (i.e. significant ongoing bleeding) despite treatment with IVIG, conventional-dose corticosteroids, or anti-D. Rituximab or high-dose dexamethasone are also options to avoid splenectomy or if splenectomy fails (Neunert, 2011).

Immune (Idiopathic) Thrombocytopenia – Pregnancy
American Society of Hematology (ASH)
For ITP in pregnancy, IVIG or corticosteroids should be given (Neunert, 2011).

• Neurology
Neuromuscular Disorders - Chronic Inflammatory Demyelinating Polyneuropathy CIDP, Guillain-Barré syndrome (GBS), Lambert–Eaton Syndrome, Multifocal Motor Neuropathy (MMN), Myasthenia Gravis (MG)
American Academy of Neurology (AAN)
The AAN guidelines for the treatment of neuromuscular disorders state that IVIG is efficacious and should be offered as treatment for GBS in adults and for CIDP. The AAN states that IVIG is probably effective for myasthenia gravis and multifocal motor neuropathy and possibly effective for Lambert-Eaton myasthenic syndrome (LEMS) and dermatomyositis in adults not responding to prior treatment (Patwa, 2012).

The AAN guidelines conclude that evidence is insufficient to support or refute use of IVIG in the treatment of immunoglobulin M paraprotein–associated neuropathy, inclusion body myositis, polymyositis, diabetic radiculoplexoneuropathy, Miller Fisher syndrome, and post-polio syndrome (Patwa, 2012).

In 1991, the AAN published research criteria for the diagnosis of CIDP. The criteria were intended to serve as guidance for clinicians and to establish diagnosis criteria for research purposes. The criteria include 4 categories (clinical, physiologic studies, pathologic features, and cerebrospinal fluid [CSF] studies) that are further divided into mandatory, supportive, and exclusion. The diagnostic categories include definite, probable, and possible CIDP (AAN AIDS Task Force, 1991).

American Association of Neuromuscular and Electrodiagnostic Medicine (AANEM)
The AANEM provides a consensus statement for the use of IVIG in neuromuscular conditions. Based on an evidence review, recommendations include IVIG use in Guillain-Barré syndrome (GBS), CIDP, MMN, exacerbations of myasthenia gravis, Lambert–Eaton syndrome, dermatomyositis, and stiff person syndrome.

If untreated, CIDP can result in permanent disability which has been attributed to irreversible axon loss. For this reason, the AANEM advises timely treatment of CIDP to prevent progression or relapses that can lead to disability. IVIG, prednisone, and plasma exchange have been shown to be equally efficacious as first-line therapy for CIDP. Although their efficacy and toxicity are similar in the short term, use of steroids long term can result in many adverse effects. Long-term toxicity has not been shown to occur after periodic use of IVIG or plasma exchange. The consensus statement also concludes that evidence is lacking and IVIG cannot be recommended for use in Fisher syndrome, chronic neuropathies associated with IgM and IgG monoclonal proteins, and neuropathies associated with cryoglobulins. In addition the statement notes that there are no objective data to support IVIG for use in inclusion body myositis, idiopathic neuropathies, idiopathic brachial neuritis, or diabetic lumbosacral radiculoplexopathy. The consensus statement further concluded that even in recommended conditions, there is little evidence to guide the clinician in the proper dosing of IVIG and the duration of therapy (Donofrio, 2009).

The AANEM provides criteria for the diagnosis of definite or probable multifocal motor neuropathy. The detailed criteria are provided in Appendix 5 (Olney, 2003).

European Federation of Neurological Sciences (EFNS)/Peripheral Nerve Society (PNS) – Chronic Inflammatory Demyelinating Polyradiculoneuropathy (CIDP)
The EFNS/PNS guidelines on the management of CIDP were developed in 2006 and updated in 2010. These guidelines provide diagnostic criteria in addition to treatment recommendations. These diagnostic criteria differ from the American Academy of Neurology CIDP diagnostic criteria of 1991. The AAN criteria were developed to diagnose and categorize for research purposes and the EFNS/PNS criteria are developed to be more applicable for clinical practice. The EFNS/PNS diagnostic criteria include inclusion and exclusion clinical criteria, electrodiagnostic criteria, and supportive criteria (e.g. CSF studies, nerve biopsy). EFNS/PNS provide diagnostic categories for CIDP of definite, probable, or possible (EFNS/PNS, 2010).

The EFNS/PNS guidelines provide a level A recommendation (i.e. established as useful/predictive) for the use of IVIG as principal treatment for sensory and motor CIDP. IVIG is also recommended for pure motor CIDP. For individuals who have an inadequate response or require high maintenance doses, the EFNS/PNS guidelines suggest considering addition of an immunosuppressant or immunomodulatory drug (EFNS/PNS, 2010).

European Federation of Neurological Sciences (EFNS)/Peripheral Nerve Society (PNS) - Multifocal Motor Neuropathy
EFNS/PNS provide diagnostic criteria for definite or probable multifocal motor neuropathy (MMN) which includes meeting specified clinical criteria (including the presence of progressive symptoms for more than 1 month), electrophysiological criteria for conduction block, and supportive criteria. EFNS/PNS recommend IVIG as first-line treatment (dose of 2 grams/kg [total cumulative dose] given over 2-5 days) and as maintenance therapy when initial treatment is effective. The guidelines note that the frequency of maintenance therapy is determined by the response and is typically 1 gram/kg every 2-4 weeks or 2 gram/kg every 1-2 months (Van Schaik, 2011).

Relapsing-Remitting Multiple Sclerosis (RRMS)

American Academy of Neurology (AAN)
The AAN published MS guidelines in 2002 and those remain current today. Recommendations are based on studies of IVIG that involved small numbers of patients, lacked complete data on clinical and MRI outcomes, or had used methods that have been questioned. These current AAN MS guidelines recommend IVIG to reduce the attack rate in RRMS and finds evidence to suggest that IVIG is of little benefit with regard to slowing disease progression (Goodin, 2002).

European Federation of Neurological Sciences (EFNS)
IVIG is recommended as second or third-line therapy when other conventional treatments are not tolerated or unable to be utilized due to concomitant diseases. IVIG is not recommended for treatment of secondary progressive MS, as add-on therapy for acute exacerbations, or for chronic symptoms in MS. The authors found insufficient evidence to make recommendations regarding use in clinically isolated syndrome or primary progressive MS (Elovaara, 2008).

Stiff Person Syndrome (Moersch-Woltmann Syndrome)

European Federation of Neurological Sciences (EFNS)

IVIG is recommended as second or third-line therapy in patients with significant disability requiring assistive devices (e.g. a walker) that had an inadequate response to diazepam and/or baclofen (Elovaara, 2008).

- **Rheumatology**

Dermatomyositis or Polymyositis

American Academy of Neurology (AAN)

AAN guidelines state IVIG may be considered for the treatment of nonresponsive dermatomyositis in adults (Patwa, 2012).

European Federation of Neurological Sciences (EFNS) – Neurological Diseases

IVIG may be considered as treatment for patients with polymyositis not responding to first-line immunosuppressive treatment (Elovaara, 2008).

- **Infectious Disease**

Measles Post-Exposure Prophylaxis

Use of IVIG is recommended for measles post-exposure prophylaxis for pregnant women without evidence of measles immunity and immunocompromised patients. Severely immunocompromised patients include the following groups of individuals: severe primary immunodeficiency; bone marrow transplant until at least 12 months after finishing all immunosuppressive treatment, or longer in those who have developed graft-versus-host disease; currently receiving treatment or within 6 months of completing immunosuppressive chemotherapy for acute lymphoblastic leukemia (ALL); diagnosis of AIDS or HIV-infected individuals with severe immunosuppression (CD4 percent < 15% [all ages] or CD4 count < 200 lymphocytes/mm^3 [aged > 5 years] and those who have not received MMR vaccine since receiving effective antiretroviral therapy (CDC, 2013).

Clinical Efficacy

- **Secondary Immunodeficiency**

Acquired Immunosuppression

AHFS Drug Information® supports the use of IVIG for individuals with iatrogenically induced or disease-associated immunosuppression. Individuals include those undergoing major surgery (e.g. cardiac transplant) or those with hematologic malignancy, extensive burns, or collagen-vascular disease (AHFS, 2017).

- **Transplantation**

Solid Organ Transplants

Antibody-Mediated Rejection (AMR)

Antibody-mediated rejection (AMR) is characterized by the presence of donor-specific antibodies, graft dysfunction, and biopsy often demonstrating C4d-positive staining (Takemoto, 2004). Lefaucheur et al compared two strategies of specific antibody removal in the treatment of AMR – high dose IVIG based regimen (2 grams/kg, administered over 2 days every 3 weeks for 4 doses) and combining plasmapheresis (PP), IVIG and anti-CD20. All cases used in this comparison trial had histologically documented AMR, donor-specific anti-HLA antibodies (DSAs) at the time of the rejection episode and sera available 3 months post-rejection (n = 24). Results showed that the combination of high-dose IVIG with PP and anti-CD 20 is superior to a protocol utilizing only high-dose IVIG in treatment of AMR. The combination PP/IVIg/anti-CD20 is associated with better removal of anti-HLA donor-specific antibodies and potentially better graft outcomes (Lefaucheur, 2009).

Billing et al reported results from a pilot study on antihumoral therapy (AHT) consisting of high-dose IVIG and rituximab in 20 pediatric renal transplant recipients. Donor-specific HLA antibodies (HLA DSA) were quantified by Luminex-based bead array technology. Loss of eGFR decreased significantly from 7.6 ml/min/1.73 m^2 during 6 months prior to AHT to 2.1 ml/min/1.73 m^2 (P = 0.0013) during 6 months after AHT. Fourteen patients (70%) responded: nine of nine patients (100%) without and five of 11 (45%) with transplant glomerulopathy (P = 0.014). C4d positivity in PTC decreased from 40 ± 18.5% in the index biopsy to 11.6 ± 12.2% (P = 0.002) in the follow-up biopsy. In four of nine biopsies (44%) C4d staining turned negative.

During 2 follow-up, the median loss of eGFR in each of the four 6-month periods remained significantly lower compared with prior to AHT. Class I DSA declined in response to AHT by 61% (p = 0.044), class II DSA by 63% (p = 0.033) 12 months after intervention. AHT with IVIG and rituximab significantly reduces or stabilizes the progressive loss of transplant function in pediatric patients with chronic AMR over an observation period of 2 years, apparently by lowering circulating DSA and reducing intrarenal complement activation (Billing, 2012).

The treatment of AMR in cardiac recipients is largely empirical and includes high-dose corticosteroids, plasmapheresis, IVIG, and rituximab. Data consists primarily of case series and case reports which have documented successful treatment of AMR with rituximab based therapy (Velez, 2009).

Desensitization
Current desensitization therapies described in medical textbooks and published literature include IVIG, IVIG combined with rituximab, and plasma exchange/plasmapheresis with or without IVIG. A trial of 101 adult patients who were highly sensitized to HLA antigens (PRA >/= 50% monthly for 3 months) and awaiting kidney transplant were randomized to IVIG 2 grams/kg (maximum dose of 180 grams) for 4 months with additional infusions at 12 months and 24 months or placebo. IVIG significantly decreased PRA levels compared to placebo. IVIG demonstrated an advantage in transplantation rate and time to transplantation over placebo (Jordan, 2004).

Vo et al examined the efficacy, outcomes and cost-effectiveness of desensitization using high-dose IVIG (2 grams/kg for 2 doses) and rituximab in 207 highly sensitized patients. Efficacy results/data were compared with end stage renal disease (ESRD) patients listed on the UNOS wait list/dialysis treatment. Parameters examined included efficacy of sensitization; patient and graft survival; survival rates on dialysis versus highly sensitized transplantation; acute rejection rate; and cost of desensitization versus dialysis at 36 months. Of the 207, 146 (71%) were transplanted. At 48 months, patient and graft survival were 95% and 87.5% respectively. Estimated patient survival at the end of 3 years was 96.6% for patients in the desensitized group compared with 79% for an age, end-stage renal disease etiology, and PRA matched group of patients remaining on dialysis during the study period. The authors concluded that desensitization with IVIG + rituximab is clinically and cost-effective with an estimated 17.6% greater probability of 3-year survival associated with desensitization versus dialysis alone (Vo, 2013).

- **Hematology**

Chronic Parvovirus B19 Infection

There are no published clinical trials evaluating the efficacy of IVIG for this indication. Six case series describe the use of IVIG for chronic parvovirus B19 infection in a total of 27 patients. Therapy with IVIG 1-2 g/kg (divided and given over 1–10 days) consistently induced symptom resolution and improved anemia. Remissions lasted from one month to four years, although many patients relapsed without additional IVIG. Many of the included patients had experienced parvovirus symptoms for a prolonged duration (12–24 months) but these resolved within 2–4 weeks of IVIG therapy. Four of these case series included AIDS patients, as symptomatic parvovirus B19 infection is rare in patients with healthy immune systems. The results of these case series are consistent with multiple single case reports (Bhattacharyya, 2005; Kerr, 2003; Mareschal-Desandes, 2003).

Evan’s Syndrome

Evans's syndrome is a rare disease in which autoimmune hemolytic anemia and immune thrombocytopenic purpura, without a known underlying etiology, coexist. Steroids and immunoglobulins are the mainstay of treatment for this condition. Other treatments described in the literature for patients not responding to steroids include azathioprine, cyclophosphamide, danazol, vincristine, gammaglobulin, and splenectomy (Molla, 2001).

Fetal Alloimmune Thrombocytopenia (FAIT)

A Cochrane review evaluated 4 trials enrolling 206 individuals treated with IVIG and/or corticosteroids for fetal alloimmune thrombocytopenia (FAIT). One trial compared IVIG and a corticosteroid and the other trials compared IVIG combined with corticosteroids to IVIG alone. There were no statistically significant differences in outcomes between the treatment arms in any of the 4 trials. The authors concluded that optimal therapy for FAIT is not established (Rayment, 2011).

Neonatal Isoimmune Hemolytic Disease in Conjunction with Phototherapy

Five controlled clinical trials have evaluated IVIG in neonatal isoimmune hemolytic disease. All found a significant benefit when IVIG was added to phototherapy, compared to phototherapy alone. The IVIG doses given ranged from 500–1,000 mg/kg given as a single dose, to 500–800 mg/kg/day for three days. In a Cochrane systemic review of the three single-dose trials (189 patients), 15% of patients given IVIG needed blood exchange transfusions, compared to 52% of patients given phototherapy alone (relative risk 0.28, 95% CI 0.17–0.47, number needed to treat 2.7). The fourth trial (37 patients) did not report number of blood exchange transfusions but did report a lower rate of total blood transfusions with IVIG (42%) compared to phototherapy alone (67%, $p<0.05$). In the final trial (61 patients), fewer infants required exchange transfusion with a three-day IVIG course (0%, $p<0.05$ vs. both other groups) compared to either a one-day IVIG course (15%, $p<0.05$ vs. phototherapy alone) or phototherapy alone (33%). In two of the included trials, the addition of IVIG significantly reduced mean duration of hospitalization ($p<0.05$ vs. phototherapy alone) (Alcock, 2002).

Post-Transfusion Purpura

Post-transfusion purpura is due to alloimmunization against platelet antigens which leads to acute thrombocytopenia after the transfusion of any platelet-containing product. It is a rare transfusion-related complication. Standard treatment for the condition consists of corticosteroids, IVIG, or plasmapheresis (Rafei, 2017).

Warm Type Autoimmune Hemolytic Anemia

Autoimmune Hemolytic Anemia is an uncommon disorder caused by the immune system destroying its' own red blood cells. The disorder can be classified as cold or warm. Most patients with cold type autoimmune hemolytic anemia can manage the disorder by wearing appropriate clothing and avoiding exposure to cold. Treatment for warm type autoimmune hemolytic anemia includes corticosteroids, immunosuppressive drugs, and splenectomy. Intravenous immunoglobulins (IVIG) are used in warm type autoimmune hemolytic anemia alone or in combination with prednisone (Zanella, 2014).

- **Neurology**

Myasthenia Gravis

A small, 3 year study examined thymectomy plus prednisone compared to prednisone monotherapy in individuals diagnosed for less than 5 years with generalized non-thymomatous myasthenia gravis and with elevated circulating concentrations of the acetylcholine-receptor antibody. Results demonstrated improvements in time weighted average Quantitative Myasthenia Gravis scores, and lower average need for alternate day prednisone in the surgical group as compared to the prednisone monotherapy group. In addition, less individuals in the surgical arm needed azathioprine therapy or experienced exacerbations requiring hospitalization, compared to the prednisone monotherapy group. All results reached statistical significance. The authors stated individuals with non-thymomatous myasthenia gravis experienced improved clinical outcomes over the 3 year study when thymectomy was performed (Wolfe, 2016).

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).

Rasmussen Encephalitis

AHFS Drug Information® supports the use of IVIG for Rasmussen encephalitis. Specifically AHFS states that IVIG may be considered in "children with intractable epilepsy if they have not responded to antiepileptic agents and corticosteroids, especially if they are otherwise candidates for surgical resection." (AHFS, 2017)

Relapsing-Remitting Multiple Sclerosis (RRMS)

A Cochrane review of immunomodulators and immunosuppressants for MS was published in 2013 and included 44 trials and 17,401 participants. Four of the trials involved immunoglobulins in 739 participants. Two trials were in RRMS (n = 190) and 2 trials were in progressive forms of MS (n = 549). The authors concluded that intravenous immunoglobulins have an unfavorable risk-benefit balance for people with RRMS and there was no benefit in preventing disability progression in progressive forms of MS (Filippini, 2013).

- **Rheumatology**

Kawasaki Disease

AHFS Drug Information® supports the use of IVIG in conjunction with aspirin therapy for initial treatment of the acute phase of Kawasaki disease (AHFS, 2017).

- **Infectious Disease**

Toxic Shock Syndrome (Staphylococcal or Streptococcal)

The AHFS states that use of IVIG may be considered as an adjunct in the treatment of staphylococcal or streptococcal toxic shock syndrome and supports the American Academy of Pediatrics (AAP) suggestions that IVIG may be considered in the management of staphylococcal or streptococcal toxic shock syndrome when the infection is refractory to several hours of aggressive therapy, an undrainable focus is present, or the patient has persistent oliguria with pulmonary edema (AHFS, 2017).

Tetanus

Although tetanus immune globulin (TIG) is the immune globulin of choice, IVIG can be used as an alternative for the treatment or for post-exposure prophylaxis of tetanus when TIG is unavailable (AHFS, 2017).

Varicella

IVIG is an alternative to varicella-zoster immune globulin (VZIG) for post-exposure prophylaxis of varicella infection in susceptible individuals when VZIG is unavailable (AHFS, 2017).

- **Dermatology**

Immune Mediated Blistering Disease

A systematic review evaluated data for the use of IVIG in autoimmune mucocutaneous blistering diseases (AMBD). Twenty-three studies that treated 260 patients with IVIG were identified of which 22 were case series and one was a randomized controlled trial. The majority (245 patients) showed improvement with IVIG therapy. A corticosteroid-sparing effect was noted with IVIG and there was not a significant incidence of serious adverse effects (Gurcan, 2010).

Stevens Johnson Syndrome/Toxic Epidermal Necrolysis (SJS/TEN)

A retrospective review evaluated the effectiveness of IVIG in reducing mortality in 16 patients with toxic epidermal necrolysis (TEN). The dose of IVIG was 1 gram/kg every day for 4 days for 15 patients and 1 patient received a dose of 0.4 gram/kg. The investigators evaluated each patient using the SCORTEN system, which is a validated predictor of TEN mortality. Based on the SCORTEN evaluation, 5.81 patients (36.3%) were expected to die while the actual mortality rate was 1 patient (6.25%). All of the 16 patients showed clinical improvement and disease resolution (Trent, 2003).

Experimental, Investigational, or Unproven Uses

There is insufficient evidence in the peer-reviewed, published scientific literature to support safety and efficacy of intravenous immune globulin (human) (IVIG) in Lyme neuropathy, Hashimoto encephalopathy (HE), inclusion body myositis (IBM), maintenance therapy for myasthenia gravis, neonatal sepsis, pediatric acute-onset neuropsychiatric syndrome (PANS) or pediatric autoimmune neuropsychiatric disorder associated with group A streptococci (PANDAS), primary progressive multiple sclerosis (MS), secondary progressive MS, acute MS exacerbations, clinically isolated syndrome (MS), and recurrent pregnancy loss.

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.

The clinical practice guidelines state the treatment of IBM with IVIG is unlikely to be effective and is not recommended as routine therapy (Orange, 2006).

IVIG is not recommended as maintenance treatment in myasthenia gravis (Feasby, 2007).

The American Academy of Pediatrics provides guidelines for the management of neonatal sepsis. There are no recommendations made or discussion of IVIG for the use in suspected or proven early-onset neonatal sepsis (Polin, 2012). In addition, a Cochrane review concluded that the use of IVIG in suspected or proven neonatal infection is not recommended (Ohlsson, 2015).

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 patients 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 patients with PANS. Randomized, controlled clinical trial studies are needed before immunological interventions become a standard of therapy.

IVIG is not recommended for treatment of secondary progressive MS, as add-on therapy for acute exacerbations, or for chronic symptoms in MS. Additionally, there is insufficient evidence to make recommendations regarding use in clinically isolated syndrome or primary progressive MS (Elovaara, 2008).

Data evaluating IVIG for prevention of recurrent pregnancy loss is limited, and significant differences between treatment and placebo groups have not been consistently demonstrated in the published scientific literature. A Cochrane review of 20 randomized trials indicated there was no improvement in live births with various immunotherapies, including intravenous immune globulin (Wong, 2014). A randomized, controlled trial evaluating use of IVIG compared to placebo for recurrent secondary miscarriage found no benefit of IVIG over placebo (Christiansen, 2015).

Note: The standard threshold for lower limit of normal is two standard deviations below the mean. This number may vary among different laboratories.

Appendix 1

Standard Reference Ranges for Serum Immunoglobulin Levels

The following standard reference ranges may be used for evaluation if the testing laboratory's reference ranges are not submitted.

Normal Serum Immunoglobulin Levels (mg/dL)			
Age	**IgA**	**IgG**	**IgM**
0 – 30 days	1 – 7	**611 – 1542**	0 – 24
1 mo	1 – 53	**241 – 870**	19 – 83
2 mo	3 – 47	**198 – 577**	16 – 100
3 mo	5 – 46	**169 – 558**	23 – 85
4 mo	4 – 72	**188 – 536**	26 – 96
5 mo	8 – 83	**165 – 781**	31 – 103
6 mo	8 – 67	**206 – 676**	33 – 97
7 – 8 mo	11 – 89	**208 – 868**	32 – 120
9 – 11 mo	16 – 83	**282 – 1026**	39 – 142
1 yr	14 – 105	**331 – 1164**	41 – 164
2 yr	14 – 122	**407 – 1009**	46 – 160

Normal Serum Immunoglobulin Levels (mg/dL)			
Age	**IgA**	**IgG**	**IgM**
3 yr	22 – 157	**423 – 1090**	45 – 190
4 yr	25 – 152	**444 – 1187**	41 – 186
5 – 7 yr	33 – 200	**608 – 1229**	46 – 197
8 – 9 yr	45 – 234	**584 – 1509**	49 – 230
10 yr & older	68 – 408	**768 – 1632**	60 – 263

Immunoglobulins, Serum Quantitative. Effective February 16, 2016. Accessed 3/14/2017. Available at: http://www.aruplab.com/guides/ug/tests/0050630.jsp

Appendix 2

Standard Reference Ranges for Serum Immunoglobulin G Subclasses (1, 2, 3, 4)

The following standard reference ranges may be used for evaluation if the testing laboratory's reference ranges are not submitted.

Normal Serum Immunoglobulin G Subclass Levels (mg/dL)				
Age	**IgG1**	**IgG2**	**IgG3**	**IgG4**
Cord Blood	435-1084	143-453	27-146	1-47
0-2 months	218-498	40-167	4-23	1-33
3-5 months	143-394	23-147	4-70	1-14
6-8 months	190-388	37-60	12-62	1-16
9-23 months	288-880	30-327	13-82	1-65
2 years	170-950	22-440	4-69	0-120
3-4 years	290-1065	28-315	4-71	0-90
5-6 years	330-1065	57-345	8-126	2-116
7-8 years	225-1100	42-375	9-107	0-138
9-10 years	390-1235	61-430	10-98	1-95
11-12 years	380-1420	73-455	16-194	1-153
13-14 years	165-1440	71-460	12-178	2-143
15 years & older	240-1118	124-549	21-134	7-89

Immunoglobulin G Subclass Levels (1, 2, 3, 4). Effective February 16, 2016. Accessed 3/14/2017 Available at: http://www.aruplab.com/guides/ug/tests/0050577.jsp

Appendix 3

Selected Genetic Based Primary Immunodeficiency Syndrome (PID)

Condition	Features
Autosomal recessive agammaglobulinemia (ARA)	• Recurrent sinopulmonary bacterial infections • Extremely low or absent IgG, IgM and IgA • IGHM, CD79a, CD199b, BLNK, or LRRC8 gene impaired
Autosomal recessive hyperimmuno-globulin M syndrome (HIM)	• Group of disease characterized by normal or elevated levels of serum IgM with low or absent IgG and IgA levels. • AICDA or UNG gene impaired

Condition	Features
Combined immunodeficiency disorders (not all-inclusive)	• Ataxia-telangiectasia (A-T) • Wiskott Aldrich syndrome (WAS), • DiGeorge syndrome (DGS) • Nijmegen breakage syndrome (NBS) • Warts, hypogammaglobulinemia, immunodeficiency, and myelokathexis (WHIM)
Congenital Hypogammaglobulinemia	• Late onset • Inducible Co-Stimulator (ICOS) impaired
Congenital/X-linked agammaglobulinemia (XLA)	• Bruton's Disease • BTK gene impaired
Hyperimmuno-globulinemia E syndrome (HIES)	• Includes recurrent lung and skin infections (e.g., chronic eczema) • Facies with coarse and/or asymmetric features • Type 1 is characterized by STAT3 mutation (also known as Job syndrome) • Type 2 is characterized by DOCK8 mutation
Hypogammaglobulinemia, unspecified	• Primary hypogammaglobulinemia • Normal cellular immunity • Does not meet diagnostic criteria for a specific disorder
ICF Syndrome	• Abnormal Facies • Respiratory Tract Infections • Hypogammaglobulinemia • Characteristic Chromosomal Abnormalities
Specific Antibody Deficiency (SAD)	• Generally does not require IVIG replacement for control of recurrent bacterial infections • Rare patients will have infection susceptibility with normal vaccine responses
Selective IgG subclass deficiencies (IGGSD)	• Persistent absence of IgG1, IgG2, and/or IgG3 • Generally does not require IVIG replacement for control of recurrent bacterial infections • Rare patients will have infection susceptibility with normal vaccine responses
Severe combined immunodeficiency disorder (SCID)	• Complete absence of specific immunity • Most susceptible to entire range of possible pathogens • May be life threatening
Transient hypogammaglobulinemia of infancy	• Recurrent bacterial sinopulmonary infections and frequent viral illnesses • Only requires short-term IVIG replacement for recurrent severe bacterial infections

Appendix 4

Examples of Objective Measurements to Assess Clinical Response (CIDP Reauthorization Criteria)

Measurement Tool	Description
Medical Research Council (MRC) Scale for Muscle Strength - MRC Sum Score	• Ranges from 0 ("total paralysis") to 60 ("normal strength") • Summation of the MRC grades (range, 0–5) given in full numbers of the following muscle pairs - upper arm abductors, elbow flexors, wrist extensors, hip flexors, knee extensors, foot dorsal flexors

Measurement Tool	Description
	• Patient effort is graded on a scale of 0-5 as follows: o Grade 5 - Muscle contracts normally against full resistance. o Grade 4 - Muscle strength is reduced but muscle contraction can still move joint against resistance. o Grade 3 - Muscle strength is further reduced such that the joint can be moved only against gravity with the examiner's resistance completely removed. As an example, the elbow can be moved from full extension to full flexion starting with the arm hanging down at the side. o Grade 2 - Muscle can move only if the resistance of gravity is removed. As an example, the elbow can be fully flexed only if the arm is maintained in a horizontal plane. o Grade 1 - Only a trace or flicker of movement is seen or felt in the muscle or fasciculations are observed in the muscle. o Grade 0 - No movement is observed
Hand-held dynamometer (e.g., Jamar, Vigorimeter)	Hand held device for measuring grip strength
Inflammatory Neuropathy Cause and Treatment group (INCAT) sensory sum score	• Ranges from 0 (“normal sensation”) to 20 (“most severe sensory deficit”) • Sensory scale comprises pin prick and vibration sense plus a two point discrimination value in the arms and legs

*Studies demonstrate that the MRC sum score, hand grip strength measured by the Vigorimeter, and the INCAT sensory summary score demonstrate good clinimetric properties in patients with immune mediated polyneuropathies (CIDP, GBS, etc.) The Rankin and modified Rankin are primarily used in stroke patients.

Appendix 5

American Association of Neuromuscular and Electrodiagnostic Medicine (AANEM) Consensus Criteria for the Diagnosis of Multifocal Motor Neuropathy

Criteria for **definite** multifocal motor neuropathy

1) Weakness without objective sensory loss in the distribution of two or more named nerves. During the early stages of symptomatic weakness, the historical or physical finding of diffuse, symmetric weakness excludes multifocal motor neuropathy.
2) Definite conduction block (see Table 1 of the complete reference) is present in two or more nerves outside of common entrapment sites.*
3) Normal sensory nerve conduction velocity across the same segments with demonstrated motor conduction block.
4) Normal results for sensory nerve conduction studies on all tested nerves, with a minimum of three nerves tested. The absence of each of the following upper motor neuron signs: spastic tone, clonus, extensor plantar response, and pseudobulbar palsy.

Criteria for **probable** multifocal motor neuropathy

1) Weakness without objective sensory loss in the distribution of two or more named nerves. During the initial weeks of symptomatic weakness, the presence of diffuse, symmetric weakness excludes multifocal motor neuropathy.
2) The presence of either:
   a. Probable conduction block in two or more motor nerve segments that are not common entrapment sites, or

b. Definite conduction block in one motor nerve segment and probable conduction block in a different motor nerve segment, neither of which segments are common entrapment sites.

3) Normal sensory nerve conduction velocity across the same segments with demonstrated motor conduction block, when this segment is technically feasible for study (that is, this is not required for segments proximal to axilla or popliteal fossa).
4) Normal results for sensory nerve conduction studies on all tested nerves, with a minimum of three nerves tested.
5) The absence of each of the following upper motor neuron signs: spastic tone, clonus, extensor plantar response, and pseudobulbar palsy.

* *Median nerve at wrist; ulnar nerve at elbow or wrist; peroneal nerve at fibular head* (Olney, 2003).

Coding/Billing Information

Note:

1) This list of codes may not be all-inclusive.
2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement.

Covered when medically necessary subject to the criteria indicated in the Coverage Policy:

CPT®* Codes	Description
90283	Immune globulin (IgIV), human, for intravenous use
90284	Immune globulin (SCIg), human, for use in subcutaneous infusions, 100 mg, each

HCPCS Codes	Description
E0779	Ambulatory infusion pump, mechanical, reusable, for infusion 8 hours or greater
E0781	Ambulatory infusion pump, single or multiple channels, electric or battery operated, with administrative equipment, worn by patient
J1459	Injection, immune globulin (Privigen), intravenous, non-lyophilized (e.g., liquid), 500 mg, 500 mg
J1555	Injection, immune globulin (Cuvitru), 100 mg
J1556	Injection, immune globulin (Bivigam), 500 mg
J1557	Injection, immune globulin, (Gammaplex), intravenous, non-lyophilized (e.g., liquid), 500 mg, 500 mg
J1559	Injection, immune globulin (Hizentra), 100 mg
J1561	Injection, immune globulin, (Gamunex-c/Gammaked), non-lyophilized (e.g., liquid), 500 mg
J1566	Injection, immune globulin, intravenous, lyophilized (e.g., powder), not otherwise specified, 500 mg
J1568	Injection, immune globulin, (Octagam), intravenous, non-lyophilized (e.g., liquid), 500 mg
J1569	Injection, immune globulin, (Gammagard liquid), intravenous, non-lyophilized, (e.g., liquid), 500 mg
J1572	Injection, immune globulin, (Flebogamma/ Flebogamma dif), intravenous, non-lyophilized (e.g., liquid), 500 mg
J1575	Injection, immune globulin/hyaluronidase, (HyQvia), 100 mg immune globulin
J1599	Injection, immune globulin, intravenous, non-lyophilized (e.g., liquid), not otherwise specified, 500 mg

ICD-10-CM Diagnosis Codes	Description
A35	Other tetanus
A48.3	Toxic shock syndrome

B20	Human immunodeficiency virus [HIV] disease
B34.3	Parvovirus infection, unspecified
C90.00-C90.02	Multiple myeloma
C91.10-C91.12	Chronic lymphocytic leukemia of B-cell type
D59.0	Drug-induced autoimmune hemolytic anemia
D59.1	Other autoimmune hemolytic anemias
D69.3	Immune thrombocytopenic purpura
D69.41	Evans syndrome
D69.51	Posttransfusion purpura
D69.59	Other secondary thrombocytopenia
D71	Functional disorders of polymorphonuclear neutrophils
D80.0	Hereditary hypogammaglobulinemia
D80.1	Nonfamilial hypogammaglobulinemia
D80.3	Selective deficiency of immunoglobulin G [IgG] subclasses
D80.7	Transient hypogammaglobulinemia of infancy
D81.0	Severe combined immunodeficiency [SCID] with reticular dysgenesis
D81.1	Severe combined immunodeficiency [SCID] with low T- and B-cell numbers
D81.2	Severe combined immunodeficiency [SCID] with low or normal B-cell numbers
D81.6	Major histocompatibility complex class I deficiency
D81.7	Major histocompatibility complex class II deficiency
D81.89	Other combined immunodeficiencies
D81.9	Combined immunodeficiency, unspecified
D82.0	Wiskott-Aldrich syndrome
D82.1	Di George's syndrome
D83.0	Common variable immunodeficiency with predominant abnormalities of B-cell numbers and function
D83.2-D83.9	Common variable immunodeficiency
D89.89†	Other specified disorders involving the immune mechanism, not elsewhere classified
G04.81	Other encephalitis and encephalomyelitis
G11.3	Cerebellar ataxia with defective DNA repair
G25.82	Stiff-man syndrome
G35††	Multiple sclerosis
G61.0	Guillain-Barre syndrome
G61.81	Chronic inflammatory demyelinating polyneuritis
G61.82	Multifocal motor neuropathy
G61.89	Other inflammatory polyneuropathies
G62.89	Other specified polyneuropathies
G70.01	Myasthenia gravis with (acute) exacerbation
G70.80	Lambert-Eaton syndrome, unspecified
G71.3	Mitochondrial myopathy, not elsewhere classified
G71.8	Other primary disorders of muscles
G72.89	Other specified myopathies
G73.3	Myasthenic syndromes in other diseases classified elsewhere
H55.89	Other irregular eye movements
L10.0	Pemphigus vulgaris

L10.1	Pemphigus vegetans
L10.2	Pemphigus foliaceous
L10.3	Brazilian pemphigus [fogo selvagem]
L10.4	Pemphigus erythematosus
L10.5	Drug-induced pemphigus
L10.89	Other pemphigus
L10.9	Pemphigus, unspecified
L12.0	Bullous pemphigoid
L12.1	Cicatricial pemphigoid
L12.30	Acquired epidermolysis bullosa, unspecified
L12.31	Epidermolysis bullosa due to drug
L12.35	Other acquired epidermolysis bullosa
L12.8	Other pemphigoid
L12.9	Pemphigoid, unspecified
L13.8	Other specified bullous disorders
L14	Bullous disorders in diseases classified elsewhere
L51.1	Stevens-Johnson syndrome
L51.2	Toxic epidermal necrolysis [Lyell]
L51.3	Stevens-Johnson syndrome-toxic epidermal necrolysis overlap syndrome
M30.3	Mucocutaneous lymph node syndrome [Kawasaki]
M33.00-M33.19	Dermatopolymyositis
M33.20-M33.29	Polymyositis
M33.90-M33.99	Dermatopolymyositis, unspecified
M35.9†	Systemic involvement of connective tissue, unspecified
M36.0	Dermato(poly)myositis in neoplastic disease
P55.0-P55.9	Hemolytic diseases of newborn
P61.0	Transient neonatal thrombocytopenia
T86.11	Kidney transplant rejection

†**Note: Experimental/Investigational/Unproven/Not Covered when used to report Pediatric autoimmune neuropsychiatric disorder associated with group A streptococci (PANDAS) and pediatric acute-onset neuropsychiatric syndrome (PANS)**

††**Note: Experimental/Investigational/Unproven Not Covered when used to report primary progressive multiple sclerosis (MS), secondary progressive MS, acute MS exacerbations, or clinically isolated syndrome**

Experimental/Investigational/Unproven/Not Covered:

ICD-10-CM Diagnosis Codes	**Description**
A69.22	Other neurologic disorders in Lyme disease
F28	Other psychotic disorder not due to a substance or known physiological condition
G63	Polyneuropathy in diseases classified elsewhere
G70.00	Myasthenia gravis without (acute) exacerbation
G72.41	Inclusion body myositis [IBM]

G93.49	Other encephalopathy
O26.20-O26.23	Pregnancy care for patient with recurrent pregnancy loss
P36.0-P36.9	Bacterial sepsis of newborn

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POLICY Document for Intravenous Immune Globulin (IVIG)

The overall objective of this policy is to support the appropriate and cost effective use of the medication, lower cost site of care and overall clinically appropriate use. This document provides specific information to each section of the overall policy.

Section 1: Site of Care

- Policy information specific to site of care (outpatient, hospital outpatient, home infusion)

Section 2: Clinical Criteria

- Policy information specific to the clinical appropriateness for the medication

Section 1: Site of Care

SITE OF CARE MANAGEMENT PROGRAM GUIDELINES FOR HOSPITAL OUTPATIENT SPECIALTY MEDICATION INFUSION

A. INTRODUCTION

There is a wide variation in the site-of-service utilization patterns for specific medications and therapy classes. This is driven by several factors. Some of these specialty medications are derived from pooled blood plasma, and therefore have the potential for an increased risk of infusion-related complications. This is particularly the case with the IVIG products. There are multiple products in this class that differ in the manufacturing, purification and viral inactivation processes. These differences can affect patient tolerance and a physician's decision to utilize a more acute site of care such as the outpatient hospital. However, many patients that have been established on this treatment with one to several infusions safely administered may be candidates for infusions in a less acute lower-cost site of care. Outpatient hospital infusion costs may be 2-3 times more compared to other sites of care suggesting an immediate opportunity exists for lowering spend on select specialty medications that require infusion.
Services for patients requiring infused specialty medications may be provided through a physician's in office infusion program or free standing ambulatory infusion center. These options provide access to quality care at a lower cost that may be more convenient for the patient. In addition, many patients who receive home or in office infusion therapy have been shown to experience better outcomes, fewer complications and, improved quality of life and preference, including more personalized attention which helps avoid stress.

This document describes the medical necessity criteria required for hospital outpatient infusion of the medications included in this policy.

B. GENERAL REQUIREMENTS: OUTPATIENT MEDICAL NECESSITY

Infusion in a hospital outpatient setting may be considered medically necessary for medications included in this policy when the criteria below OR individual medication policy criteria are met as outlined section C.

1. Clinical documentation that supports one or more of the following:
    a. History of repeated moderate adverse reactions not responding to conventional interventions OR,
    b. Laboratory confirmation of autoantibody development (autoantibodies to IgA, anti-infliximab, etc)
    c. The patient is medically unstable which may include respiratory, cardiovascular, or renal conditions that may predispose the member to a severe adverse event that cannot be managed in an alternate setting without appropriate medical personnel and equipment.
    d. The patient has previously experienced a severe adverse event during or immediately after an infusion including but not limited to: anaphylaxis, anaphylactoid reactions, myocardial infarction, thromboembolism, or seizures.
    e. Significant venous access issues requiring phlebotomy
2. Patient specific criteria that meets the following:
    a. All alternate non-hospital outpatient settings are not within a reasonable distance from the member's home (10-30miles) AND,
    b. The patient's home has been determined to be inappropriate for home infusion by a social worker, case manager or previous home nurse assessment or home infusion services are not available due to limited network access

C. MEDICATION SPECIFIC CRITERIA FOR HOSPITAL OUTPATIENT MEDICAL NECESSITY

In addition to the general criteria in Section B, the following guidelines will be applied:

1. IVIG - One or more of the following criteria must be met:

- **a.** To determine tolerance of the therapy, one infusion or cycle as applicable may be permitted in the hospital outpatient setting
- **b.** Product (brand) changes – one infusion may be permitted if an ambulatory infusion center is not available within a reasonable distance from the member's home.
- **c.** Urgent treatment for conditions requiring acute intervention including but not limited to: acute ITP with bleeding, Kawasaki disease, and Myasthenic crisis with respiratory impairment.
- **d.** Patients with laboratory confirmed IgG or IgE autoantibodies to IgA. Note: routine screening for IgA autoantibodies is not currently recommended.
- **e.** Patients who have experienced anaphylaxis or an anaphylactoid reaction with intravenous immunoglobulin products.

f. Pediatric patients who are less than 21 years of age. The use of non-hospital based alternate site infusion services are at the discretion of the prescribing physician.
g. An inability to tolerate large volume load and the dosing cannot be divided into several smaller infusions.
h. Patients with a history of renal impairment or thromboembolic complications.

For patients with a history of renal impairment, sucrose containing IVIG products are not recommended. Oliguric renal failure is the most common occurring 1-10 days after infusion.
The most important risk factor for thromboembolic complications is advanced age although the presence of several risk factors greatly elevates the risk including: diabetes, hypertension, CAD, smoking, hyperlipidemia, and history of prior cerebrovascular disease.

D. GENERAL CONSIDERATIONS: HOME INFUSION

Home Infusion therapy has the potential to deliver cost-effective, quality care.
Efforts to support patients who can receive infused medications care in a lower-cost setting versus an inpatient or clinic-based setting seems appealing, particular if that lower-cost setting is the patient's home.
The home infusion provider will complete an assessment to determine the appropriateness of a patient, caregiver if applicable, and their home prior to initiating care. This assessment may include an evaluation of the following:

1. Accessibility to 911 services and urgent care. Volunteer services may be acceptable if urgent care is readily available.
2. Adequate refrigeration is available if required.
3. Home is not located in a high crime area as determined by local authorities
4. Home environment does not meet general cleanliness standards determined by onsite home nursing assessment

E. BACKGROUND

IVIG

A comprehensive review of the adverse events associated with the administration of IVIG is outside of the scope of this document. Others have prepared excellent reviews of the adverse reactions associated with IVIG, which should be read by those involved with the prescribing and administration of immunoglobulin. Various properties of IVIG preparations can trigger potential adverse events; these properties include sodium content, osmolarity, sugar content, IgA content, and volume load. Recent trends in the manufacture of these products have eliminated some adverse effects observed in early products, but other effects have emerged. Head-to-head comparisons among the available products continues to be lacking in the literature. Given the uncertainty and lack of comparative literature regarding the various available formulations of IVIG, it is reasonable to use higher-acuity sites of service for

patients with a history of serious adverse events with multiple products. This is consistent with the site-of-care recommendations from the American Academy of Allergy, Asthma, and Immunology.

Evaluations of the safety and efficacy of IVIG in the home infusion setting are also lacking in the published literature. Many controlled trials studying the efficacy of IVIG for various conditions do include the home as a site of infusion, but a differentiation of adverse events between sites of infusion is not a primary reported outcome. The phase III trial of IVIG for the treatment of Alzheimer's disease allowed for home infusion of IVIG after 3 tolerated infusions in a controlled setting. This suggests that, when approving this protocol, the FDA had convincing evidence to support home administration.

A retrospective analysis of 1,085 home infusions for neuroimmunologic conditions in 70 patients demonstrated a notably low non-serious adverse event rate of 4.7%. However, this study was limited to 1 specific formulation of IVIG and used lower infusion rates than would be considered typical in the studied population; this may have contributed to the low observed reaction rate. Interestingly, 23 patients in this study were naïve to IVIG (32.8%) and only 2 of these patients experienced minor adverse events.

Others evaluating home infusion have demonstrated an adverse event rate of 21.4% in a similar cohort. Comparable to the previous study, a significant proportion of these patients were new to therapy (42.6%). A statistically significant difference between these patients and those treated previously was not observed. In addition, a comparison between neuroimmunologic and immune deficiency patients did not identify a statistically significant difference in adverse reactions.
These studies support the safety of IVIG infusions at home for patients previously treated, as well as those new to the therapy.

Section 2: Clinical Criteria

Intravenous Immune Globulin (IVIG):

Bivigam®, Carimune® NF, Flebogamma® DIF, Gammagard® Liquid, Gammagard® S/D, Gammaked™, Gammaplex®, Gamunex®-C, Octagam®, and Privigen®

POLICY

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.

II. REQUIRED DOCUMENTATION

The following information is necessary to initiate the prior authorization review:
A. Primary immunodeficiency
1. Diagnostic test results (when applicable)
a. Copy of laboratory report with serum immunoglobulin levels: IgG, IgA, IgM, and IgG subclasses

b. Vaccine response to pneumococcal polysaccharide vaccine (post-vaccination *Streptococcus pneumoniae* antibody titers)
c. Pertinent genetic or molecular testing in members with a known genetic disorder
d. Copy of laboratory report with lymphocyte subset enumeration by flow cytometry

2. IgG trough level for those continuing with IVIG therapy

B. Secondary hypogammaglobulinemia (CLL, HIV, BMT/HSCT recipients)
1. Copy of laboratory report with pre-treatment serum IgG level (when applicable)

C. Chronic inflammatory demyelinating polyneuropathy (CIDP) and multifocal motor neuropathy (MMN)
1. Pre-treatment electrodiagnostic studies (electromyography [EMG] or nerve conduction studies [NCS])
2. For CIDP, pre-treatment cerebrospinal fluid (CSF) analysis (when available)

D. Dermatomyositis and polymyositis
1. Pre-treatment electrodiagnostic studies (EMG/NCS)
2. Pre-treatment muscle biopsy report (when available)

E. Idiopathic thrombocytopenic purpura (immune thrombocytopenia)
1. Laboratory report with pre-treatment platelet count

III. CRITERIA FOR INITIAL APPROVAL

1. Primary Immunodeficiency

Initial authorization of 12 months may be granted for members with any of the following diagnoses:

a. Severe combined immunodeficiency (SCID) or congenital agammaglobulinemia (eg, X-linked or autosomal recessive agammaglobulinemia):
i. Diagnosis confirmed by genetic or molecular testing, or
ii. Pretreatment IgG level < 200 mg/dL, or
iii. Absence or very low number of T cells (CD3 T cells < 300/microliter) or the presence of maternal T cells in the circulation (SCID only)

b. Wiskott-Aldrich syndrome, DiGeorge syndrome, or ataxia-telangiectasia (or other non-SCID combined immunodeficiency):
i. Diagnosis confirmed by genetic or molecular testing (if applicable), and
ii. History of recurrent bacterial infections (eg, pneumonia, otitis media, sinusitis, sepsis, gastrointestinal), and
iii. Impaired antibody response to pneumococcal polysaccharide vaccine (see Appendix A)

c. Common variable immunodeficiency (CVID):
i. Age 4 years or older
ii. Other causes of immune deficiency have been excluded (eg, drug induced, genetic disorders, infectious diseases such as HIV, malignancy)
iii. Pretreatment IgG level < 500 mg/dL or ≥ 2 SD below the mean for age
iv. History of recurrent bacterial infections
v. Impaired antibody response to pneumococcal polysaccharide vaccine (see Appendix A)

d. Hypogammaglobulinemia (unspecified), IgG subclass deficiency, selective IgA deficiency, selective IgM deficiency, or specific antibody deficiency:
    i. History of recurrent bacterial infections
    ii. Impaired antibody response to pneumococcal polysaccharide vaccine (see Appendix A)
    iii. Any of the following pre-treatment laboratory findings:
        i. Hypogammaglobulinemia: IgG < 500 mg/dL or ≥ 2 SD below the mean for age
        ii. Selective IgA deficiency: IgA level < 7 mg/dL with normal IgG and IgM levels
        iii. Selective IgM deficiency: IgM level < 30 mg/dL with normal IgG and IgA levels
        iv. IgG subclass deficiency: IgG1, IgG2, or IgG3 ≥ 2 SD below mean for age assessed on at least 2 occasions; normal IgG (total) and IgM levels, normal/low IgA levels
        v. Specific antibody deficiency: normal IgG, IgA and IgM levels

e. Other predominant antibody deficiency disorders must meet a., b., and c.i. in section 4. above.

f. Other combined immunodeficiency must meet criteria in section 2. above.

Re-authorization of 12 months may be granted when the following criteria are met:
1. A reduction in the frequency of bacterial infections has been demonstrated since initiation of IVIG therapy, AND
2. IgG trough levels are monitored at least yearly and maintained at or above the lower range of normal for age (when applicable for indication), OR
3. The prescriber will re-evaluate the dose of IVIG and consider a dose adjustment (when appropriate).

Gammagard Liquid, Gamunex-C, and Gammaked may be administered intravenously or subcutaneously for primary immunodeficiency.

B. B-cell Chronic Lymphocytic Leukemia (CLL)
1. Initial authorization of 6 months may be granted when the following criteria are met:
    a. IVIG is prescribed for prophylaxis of bacterial infections.
    b. Member has a history of recurrent sinopulmonary infections requiring intravenous antibiotics or hospitalization.
    c. Member has a pretreatment serum IgG level <500 mg/dL.
2. Re-authorization of 6 months may be granted when the following criterion is met:
    a. A reduction in the frequency of bacterial infections has been demonstrated since initiation of IVIG therapy.

C. Prophylaxis of Bacterial Infections in HIV-Infected Pediatric Patients
1. Initial authorization of 6 months may be granted to pediatric members with HIV infection when the following criteria are met:

a. Member is ≤ 12 years of age.
b. IVIG is prescribed for primary prophylaxis of bacterial infections and pretreatment serum IgG < 400 mg/dL, or
c. IVIG is prescribed for secondary prophylaxis of bacterial infections
    i. History of recurrent bacterial infections (> 2 serious bacterial infections in a 1-year period)
    ii. Member is not able to take combination antiretroviral therapy.
    iii. Antibiotic prophylaxis was tried but was not effective (eg, trimethoprim-sulfamethoxazole).

2. Re-authorization of 6 months may be granted when the following criterion is met:
    a. A reduction in the frequency of bacterial infections has been demonstrated since initiation of IVIG therapy.

D. Prophylaxis of Bacterial Infections in BMT/HSCT Recipients

1. Initial authorization of 6 months may be granted to members who are BMT/HSCT recipients when the following criteria are met:
    a. IVIG is prescribed for prophylaxis of bacterial infections.
    b. Either of the following:
        i. IVIG is requested within the first 100 days post-transplant.
        ii. Member has a pretreatment serum IgG < 400 mg/dL.
2. Re-authorization of 6 months may be granted when the following criterion is met:
    a. A reduction in the frequency of bacterial infections has been demonstrated since initiation of IVIG therapy.

E. Chronic Inflammatory Demyelinating Polyneuropathy (CIDP)

1. Initial authorization of 3 months may be granted when the following criteria are met:
    a. Moderate to severe functional disability
    b. Electrodiagnostic studies are consistent with multifocal demyelinating abnormalities
    c. Elevated CSF protein (when available)
2. Re-authorization of 12 months may be granted when the following criteria are met:
    a. Significant improvement in disability and maintenance of improvement since initiation of IVIG therapy
    b. In those who are clinically stable and receiving long-term treatment (ie, more than 1 year), the dose has been tapered and/or treatment withdrawn to determine whether continued treatment is necessary
    c. IVIG is being used at the lowest effective dose and frequency

F. Multifocal Motor Neuropathy (MMN)

1. Initial authorization of 3 months may be granted when the following criteria are met:
    a. Weakness without objective sensory loss in 2 or more nerves
    b. Electrodiagnostic studies are consistent with motor conduction block
    c. Normal sensory nerve conduction studies

2. Re-authorization of 12 months may be granted when the following criterion is met:
    a. Significant improvement in disability and maintenance of improvement since initiation of IVIG therapy

G. Dermatomyositis or Polymyositis

1. Initial authorization of 3 months may be granted when the following criteria are met:
    a. Diagnosis established by clinical features (eg, proximal weakness, rash), elevated muscle enzyme levels, electrodiagnostic studies, and muscle biopsy (when available); supportive diagnostic tests include autoantibody testing and muscle imaging (eg, MRI), and
    b. Standard first-line treatments (corticosteroids or immunosuppressants) have been tried but were unsuccessful or not tolerated, or
    c. Member is unable to receive standard first-line therapy because of a contraindication or other clinical reason.
2. Re-authorization of 12 months may be granted when the following criterion is met:
    a. Significant improvement in disability and maintenance of improvement since initiation of IVIG therapy

H. Guillain-Barre Syndrome (GBS)

Authorization of 2 months total may be granted when the following criteria are met:

1. Physical mobility is severely affected such that member requires an aid to walk.
2. IVIG therapy will be initiated within 2 weeks of symptom onset.

I. Myasthenia Gravis

Authorization of 1 month may be granted to members who are prescribed IVIG for worsening weakness, acute exacerbation, or in preparation for surgery.

1. Worsening weakness includes an increase in any of the following symptoms: diplopia, ptosis, blurred vision, difficulty speaking (dysarthria), difficulty swallowing (dysphagia), difficulty chewing, impaired respiratory status, fatigue, and limb weakness. Acute exacerbations include more severe swallowing difficulties and/or respiratory failure.
2. Pre-operative management (eg, prior to thymectomy)

J. Lambert-Eaton Myasthenic Syndrome (LEMS)

Authorization of 12 months may be granted for LEMS.

K. Kawasaki Syndrome

Authorization of 1 month may be granted for pediatric members who are prescribed IVIG for Kawasaki syndrome.

L. Idiopathic Thrombocytopenic Purpura (Immune Thrombocytopenia)

1. Newly diagnosed ITP (diagnosed within the past 3 months) or initial therapy: authorization of 1 month may be granted when the following criteria are met:
    a. Children (< 18 years of age)
        i. Significant bleeding symptoms (mucosal bleeding or other moderate/severe bleeding) or

ii. High risk for bleeding* (see Appendix B), or
iii. Rapid increase in platelets is required* (eg, surgery or procedure)

b. Adults (≥ 18 years of age)
i. Platelet count < 30,000/mcL, or
ii. Platelet count < 50,000/mcL and significant bleeding symptoms, high risk for bleeding or rapid increase in platelets is required*, and
iii. Corticosteroid therapy is contraindicated and IVIG will be used alone or IVIG will be used in combination with corticosteroid therapy

2. Chronic/persistent ITP (≥ 3 months from diagnosis) or ITP unresponsive to first-line therapy: authorization of 6 months may be granted when the following criteria are met:
   a. Platelet count < 30,000/mcL, or
   b. Platelet count < 50,000/mcL and significant bleeding symptoms, high risk for bleeding* or rapid increase in platelets is required*, and
   c. Relapse after previous response to IVIG or inadequate response/intolerance/contraindication to corticosteroid or anti-D therapy
3. Adults with refractory ITP after splenectomy: authorization of 6 months may be granted when either of the following criteria is met:
   a. Platelet count < 30,000/mcL, or
   b. Significant bleeding symptoms
4. ITP in pregnant women: authorization through delivery may be granted to pregnant women with ITP.

* The member's risk factor(s) for bleeding (see Appendix B) or reason requiring a rapid increase in platelets must be provided.

M. Fetal/Neonatal Alloimmune Thrombocytopenia (F/NAIT)

Authorization of 6 months may be granted for pregnant women who are prescribed IVIG for F/NAIT.

N. Parvovirus B19-induced Pure Red Cell Aplasia (PRCA)

Authorization of 6 months may be granted for parvovirus B19-induced PRCA.

O. Stiff-person Syndrome

Authorization of 6 months may be granted for treatment of stiff-person syndrome in members who have experienced an inadequate response or intolerance, or have a contraindication to first-line therapy such as a benzodiazepine (eg, diazepam) and/or baclofen.

IV. CONTINUATION OF THERAPY

Reauthorization criteria apply to members who are currently receiving IVIG therapy through a paid pharmacy or medical benefit. All other members (including new members) must meet initial authorization criteria.

V. DOSAGE AND ADMINISTRATION

Approvals may be subject to dosing limits in accordance with FDA-approved labeling, accepted compendia, and/or evidence-based practice guidelines.

VI. OTHER

When Gammagard Liquid, Gamunex-C and Gammaked will be administered subcutaneously, they may be approved for primary immunodeficiency only.

VII. APPENDICES

Appendix A: Impaired Antibody Response to Pneumococcal Polysaccharide Vaccine

- Age 6 years and older: antibody levels are not ≥ 1.3 mcg/mL for at least 70% of serotypes in the vaccine
- Age 2 to 5 years: antibody levels are not ≥ 1.3 mcg/mL for at least 50% of serotypes in the vaccine
- Not established for children less than 2 years of age

Appendix B: Examples of Risk Factors for Bleeding (not all inclusive)

- Undergoing a medical or dental procedure where blood loss is anticipated
- Comorbidity (eg, peptic ulcer disease, hypertension)
- Mandated anticoagulation therapy
- Profession or lifestyle predisposes patient to trauma (eg, construction worker, fireman, professional athlete)

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