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Review Article

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.
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.	(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).

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 immuneresponsive. 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.	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.
	Caution: The authors report rare cases of worsening PANS symptoms after IVIG when IVIG is given around the time of a new viral illness.		
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.	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.	1.5 volume therapeutic exchanges for 3–5 days (3–4 runs) (Latimer et al. 2015).
		Syncope, pseudoseizures, and pain amplification have been reported immediately after TPE.	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.
		TPE can cause hypogammaglobulinemia.	
	Benefit: Rapidly removes antibodies from plasma and quickly eliminates autoreactive immune responses caused by antibodies.		

(*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.