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.