Table and Text Excerpt from: "Treatment of Pediatric Acute-onset Neuropsychiatric Syndrome (PANS)"
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Table 1. General principles for treating PANS[1]:

1) Establish that PANS is the correct "diagnosis of exclusion" by completing a comprehensive diagnostic evaluation[2]

2) Provide symptomatic relief with psychiatric medications and behavioral interventions, prioritizing treatment of symptoms causing the greatest distress and interference[3]

3) Treat underlying infections and consider use of therapeutic or prophylactic antibiotics[4]

4) Treat symptoms resulting from neuroinflammation or post-infectious autoimmunity with anti-inflammatory or immunomodulatory therapies, dependent on symptom severity and disease trajectory[5]

5) Evaluate effectiveness of the treatment regimen at frequent intervals, making modifications as warranted by improvement or worsening of symptoms.

6) Treatment can be tapered downward or stopped when symptoms resolve. However, treatment may be necessary again at some point in the future, given the relapsing-remitting nature of PANS symptoms.

"Immune therapies are the second cornerstone in the treatment of PANS, as detailed in Part II of the Guidelines: Use of Immunomodulatory Therapies.[5] Although immune treatments should be considered for all PANS patients, they are used only in cases where there is clear evidence of neuroinflammation or post-infectious autoimmunity as the underlying cause for the PANS symptoms (approximately 80% of patients). Such evidence might come from the physical examination, laboratory assays, or paraclinical assessments, as described in the PANS diagnostic guidelines.[2] The guidelines for use of anti-inflammatory medications and/or immune modulation in immune-related PANS are based on decades of experience with their use in the treatment of other post-infectious autoimmune conditions (such as asthma, reactive arthritis, and post-infectious encephalitis) and neuroinflammatory disorders (including neuropsychiatric lupus, cerebral vasculitis, and the neurologic manifestations of Sjogren's syndrome, among others). Anti-inflammatory and immunomodulatory therapies have proven useful for these conditions, even when the inciting infection has long since been cleared and biomarkers of inflammation are no longer found in blood or CSF. In such instances, the only evidence that there is ongoing neuroinflammation may be the therapeutic effects of anti-inflammatory and immunomodulatory interventions. However, their use is not without risks, and continued immunotherapy is warranted only when treatment produces clear and convincing symptomatic improvements. Clinicians should continually evaluate the impact of the interventions and stop therapy when the PANS symptoms no longer respond to the chosen immune intervention. If PANS symptoms fail to improve after intensive interventions, such as high-dose corticosteroids, consideration should be given to the possibility that the current symptoms represent damaged neural circuits, rather than ongoing neuroinflammation. In those cases, immunotherapy should be stopped, and therapeutic efforts redirected towards rehabilitation and supportive therapies." (Pp 1, 6-7 of Swedo SE, Frankovich J, Murphy TK; in press, JCAP)

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Table 4: Corticosteroid-sparing agents (therapies used with/or to replace steroids) in PANS/PANDAS. Goal is to achieve remission with minimal steroid use. (From Frankovich et al[5])

	IVIG	**TPE**	**Rituximab or MMF[a]**
New onset	1 – 6 monthly courses of IVIG in Moderate to Severe disease or in Severe-Extreme if TPE not available.	Use in Severe-Extreme cases	Patient has Moderate-Extreme impairment. AND Patient has proven responsiveness to corticosteroids, IVIG, or TPE. OR Patient has evidence of inflammation/ autoimmunity and objective signs of organic brain disease.
Relapsing remitting course	Consider repeated dosing of IVIG if: 1. Underlying immunodeficiency. 2. Frequent flares preceded by infections. 3. Deteriorating baseline.	Not indicated unless patient is in a Severe-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. OR 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 concurrent rituximab or MMF if there is evidence of autoimmunity.	Patient has Moderate-Extreme impairment. AND Patient has proven responsiveness to corticosteroids, IVIG, or TPE. OR Patient has evidence of inflammation/ autoimmunity and objective signs of organic brain disease.

[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.*

Abbreviations: PANS, Pediatric Acute-onset Neuropsychiatric Syndrome; PANDAS, Pediatric Autoimmune Neuropsychiatric Disorders associated with Streptococcal infections.; IVIG, intravenous immunoglobulins; TPE, therapeutic plasma exchange; MMF, mycophenylate mofetile.

APPENDIX C: Use of corticosteroid-sparing agents in PANS (From Frankovich et al[5])

	DESCRIPTION/BENEFIT	ADVERSE EFFECTS	DOSING
Intravenous Immunoglobulin (IVIG)	IVIG is derived from pooled plasma from human donors and processed using rigorous purification steps. Several potential immunomodulatory roles including effects on Fc receptor activity (saturating FcR) and F(ab)2 activity (anti-idiotypic antibodies) and other mechanisms. 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 following IVIG when IVIG is given around the time of a new viral illness.	Common infusion related side effects include nausea, myalgia, fever, chills, rigors, chest discomfort, and hypotension (often dose related or due to rapid administration). Post-infusion 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. A transient fever can be seen in the first 24 hours. Rarely, symptomatic hemolysis can occur and manifest up to 1-week post-infusion. 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), dermatologic reactions, hemolytic reactions, neutropenia, renal failure, transfusion-related lung injury, and seizures.	Induction: 1.5 - 2 g/kg, max dose 70 g/dose. If patient has clear improvement and then recrudesces, subsequent doses should be dosed at 1 g/kg. 2nd & 3rd doses have been given at 4-6 week intervals by PANS consortium members. Some patients are treated with rheumatology protocols which utilize 2 g/kg monthly (max dose 70 g/dose). If patient becomes dependent on IVIG to maintain good baseline, consider adding in or replacing with Rituximab or MMF.
Therapeutic Plasma Exchange (TPE)	Removes autoantibodies triggering immune responses leading to brain inflammation. 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.	TPE often requires an intensive care admission and this may be psychiatrically traumatizing to some children. 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 following TPE. TPE can cause hypogammaglobulinemia.	1 volume therapeutic exchanges every other day for 10- 12 days (5-6 runs) (Perlmutter et al. 1999). 1.5 volume therapeutic exchanges over 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 present), thus adjunct therapy is recommended. In infection triggered PANS, TPE alone can be effective if infectious driver is eliminated.
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 over 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 following rituximab include: CMV related retinitis/colitis, progressive myelitis leukoencephalipathy (JC virus), pneumonia, empyema, etc.	Most autoimmune diseases are treated with the protocol used in rheumatoid arthritis of 750 mg/m2 (max dose 1000 mg) x 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 re-dosing at 6 month intervals.

IVIG related headaches generally respond well to steroids (1-2 mg/kg prednisone equivalent, max 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). Pre-medication 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.

Abbreviations: PANS, Pediatric Acute-onset Neuropsychiatric Syndrome; OTC, over-the-counter; MMF, mycophenolate mofetil; IgA, immunoglobulin A; IV, intravenous; CMV, cytomegalovirus; JC, John Cunningham.

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