HB2721: Peer Reviewed Studies
Confirming Appropriate Use of Antibiotics and Immunotherapy
For Treatment of PANDAS/PANS

ABX https://www.ncbi.nlm.nih.gov/pubmed/26866234 *Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infections (PANDAS)*. Orefici G, Cardona F, Cox CJ, Cunningham MW. Ferretti JJ, Stevens DL, Fischetti VA, editors. *Streptococcus pyogenes: Basic Biology to Clinical Manifestations* [Internet]. Oklahoma City (OK): University of Oklahoma Health Sciences Center; 2016 Feb 10. "PANDAS is clearly a subtype of PANS (Murphy, et al., 2015b; Murphy, Parker-Athill, Lewin, Storch, & Mutch, 2015a; Chang, et al., 2015) and not all PANS cases have an underlying streptococcal infection—but all PANDAS cases are associated with streptococcal infections, at least temporally. When these diseases appear, treatment with antibiotics can be successful, and a treatment trial of cefdinir by Murphy and colleagues indicated that therapy with cefdinir, a β lactam antibiotic, provided notable improvements in tic symptoms rated by the Yale Global Tic Severity Scale (YGTSS) and OCD symptoms rated by the Children's Yale-Brown Obsessive Compulsive Scale (CY-BOCS). However, the differences within the groups as a whole were not significant. β-lactam antibiotics have been proposed to be neuroprotective above and beyond their antibiotic efficacy (Murphy, Parker-Athill, Lewin, Storch, & Mutch, 2015a)."

ABX http://jamanetwork.com/journals/jamaotolaryngology/fullarticle/2089440*The role of tonsillectomy in the treatment of pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS)*. Demesh D, Virbalas JM, Bent JP. JAMA Otolaryngol Head Neck Surg. 2015 Mar;141(3):272-5. doi: 10.1001/jamaoto.2014.3407. "Ten patients met strict diagnostic criteria for PANDAS. Comparisons were made between parental reports of symptom severity at diagnosis, after antibiotic treatment (in 10 patients), and after tonsillectomy (in 9). From a baseline severity score of 10, antibiotics alone improved symptoms to a median (interquartile range [IQR]) score of 8 (6.5-10.0) (P = .03). Nine children who subsequently underwent tonsillectomy reported symptom improvement in comparison with treatment with antibiotics alone, including those with no response to antibiotics."

ABX https://www.ncbi.nlm.nih.gov/pubmed/24187894 *Suspect PANDAS in children with acute neuropsychiatric symptoms. Infection behind the disease - long-term antibiotic therapy should be considered*. Bejerot S, Bruno K, Gerland G, Lindquist L, Nordin V, Pelling H, Humble MB, Lakartidningen. 2013 Oct 9-15;110(41):1803-6. Review. Swedish. "long-term antibiotic therapy should be considered."

ABX https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3440267/ *Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections*. Tan J, Smith CH, Goldman RD. Can Fam Physician. 2012 Sep;58(9):957-9. "Positive results have been found using antibiotic prophylaxis and immunomodulatory therapy in children with PANDAS."

ABX https://www.ncbi.nlm.nih.gov/pubmed/22234571 *Successful treatment with benzathine penicillin of two patients suspected of suffering from PANDAS.* Redondo-Granado MJ, García-Saseta P, Vizcaíno-López I, Palencia-Luaces R. Rev Neurol. 2012 Jan 16;54(2):125-7. Spanish.

ABX https://www.ncbi.nlm.nih.gov/pubmed/19226494 *Tic disappearance after penicillin treatment in a patient with PANDAS.* Aguilera-Albesa S, Sánchez-Carpintero R, Villoslada-Díaz P. Rev Neurol. 2009 Feb 16-28;48(4):221-3. Spanish

ABX https://www.ncbi.nlm.nih.gov/pubmed/18079308 *Mycoplasma pneumoniae infection and obsessive-compulsive disease: a case report*. Ercan TE, Ercan G, Severge B, Arpaozu M, Karasu G. J Child Neurol. 2008 Mar;23(3):338-40. "After treatment with oral clarithromycin, all his obsessive-compulsive disease symptoms disappeared."

ABX https://www.ncbi.nlm.nih.gov/pubmed/15820236 *Antibiotic prophylaxis with azithromycin or penicillin for childhood-onset neuropsychiatric disorders*. Snider LA, Lougee L, Slattery M, Grant P, Swedo SE. Biol Psychiatry. 2005 Apr 1;57(7):788-92. "Penicillin and azithromycin prophylaxis were found to be effective in decreasing streptococcal infections and neuropsychiatric symptom exacerbations among children in the PANDAS subgroup."

ABX www.ncbi.nlm.nih.gov/pubmed/10933123 *Infection-triggered anorexia nervosa in children: clinical description of four cases*. Sokol MS. J Child Adolesc Psychopharmacol. 2000 Summer; 10(2):133-45. "The patients responded to conventional treatment plus antibiotics with weight restoration and decreased eating disorder and obsessive-compulsive symptoms."

IVIG and PEX http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(98)12297-3/fulltext?version=printerFriendly *Therapeutic Plasma Exchange and Intravenous Immunoglobulin for Obsessive-Compulsive Disorder and Tic Disorders in Childhood,* Perlmutter, Susan J et al. The Lancet, 1999, Volume 354 , Issue 9185 , 1153 – 1158 "Plasma exchange and IVIG were both effective in lessening of symptom severity for children with infection-triggered OCD and tic disorders."

IVIG and PEX https://www.ncbi.nlm.nih.gov/pubmed/15871831 Fernández Ibieta MAn Pediatr (Barc). 2005 May;62(5):475-8.*Neuropsychiatric Disorders Associated with Streptococci: A Case Report* "Current recommendations include penicillin treatment of each exacerbation with positive throat culture, and more aggressive therapies (intravenous immunoglobulin or plasmapheresis) when symptoms are severe."

PEX http://www.ncbi.nlm.nih.gov/pubmed/16239863 *PANDAS with Catatonia: A Case Report. Therapeutic response to lorazepam and plasmapheresis.* J Am Acad Child Adolesc Psychiatry. 2005 Nov;44(11):1145-50."Plasmapheresis resulted in significant and rapid clinical improvement of obsessive-compulsive disorder symptoms and a simultaneous decrease in basal ganglia swelling, consistent with an immune-mediated pathophysiological process involving group A beta-hemolytic streptococci."

IVIG http://www.bloodmed.com/contentimage/guidelines/2854.pdf *Evidence-Based Guidelines on the Use of Intravenous Immune Globulin for Hematologic and Neurologic Conditions* Paula Robinson, David Anderson, Melissa Brouwers, Thomas E. Feasby, and Heather Hume, on behalf of the IVIG Hematology and Neurology Expert Panels. Transfus Med Rev. 2007 Apr;21(2 Suppl 1):S3-8. "Use in Canada Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS). In the opinion of the expert panel, it is reasonable to consider IVIG among the options for treatment. IVIG is recommended as an option for treatment of patients with PANDAS. (Review of Lancet, 1999, listed above.) Based on consensus by the expert panel, diagnosis of PANDAS requires expert consultation."

IVIG https://www.ncbi.nlm.nih.gov/pubmed/17397768 *Guidelines on the use of intravenous immune globulin for neurologic conditions.* Feasby T, Banwell B, Benstead T, Bril V, Brouwers M, Freedman M, Hahn A, Hume H, Freedman J, Pi D, Wadsworth L. Transfus Med Rev. 2007 Apr;21(2 Suppl 1):S57-107. "A panel of 6 clinical experts, one expert in practice guideline development and 4 representatives from the…Canadian National Advisory Committee on Blood and Blood Products…met to review the evidence and reach consensus on the recommendations for the use of IVIG for…22 neurological conditions. Recommendations for use of IVIG were made for 14 conditions, including acute disseminated encephalomyelitis, chronic inflammatory demyelinating polyneuropathy, dermatomyositis, diabetic neuropathy, Guillain-Barré syndrome, Lambert-Eaton myasthenic syndrome, multifocal motor neuropathy, multiple sclerosis, myasthenia gravis, opsoclonus-myoclonus, pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections, polymyositis, Rasmussen's encephalitis, and stiff person syndrome. Intravenous immune globulin is recommended as an option for treatment of patients with PANDAS. Based on consensus by the expert panel, diagnosis of PANDAS requires expert consultation. Based on consensus by the expert panel, a total dose of 2 g/kg given over 2 days is recommended as a reasonable option."

IVIG https://www.blood.gov.au/system/files/documents/NBA_IVIgCriteria_Second Edition_Internals-WEB_updated_ref.pdf *Criteria for the Clinical Use of Intravenous Immunoglobulin in Australia Second Edition July 2012* "Paediatric autoimmune neuropsychiatric disorder associated with streptococcal infection (PANDAS) Level of Evidence 2a PANDAS was first described in the early 1990s. PANDAS is characterised by rapid-onset tics associated with obsessive compulsive disorder (OCD) in the context of recovery from streptococcal infection. Molecular mimicry between streptococcal antigens and the central nervous system is thought to underlie the cause. Symptomatic therapy is used with variable response. A single randomised placebo-controlled trial using IVIg for PANDAS showed very prolonged and significant improvement in obsessive-compulsive symptoms, anxiety, depression, emotional lability and overall function compared with placebo. Improvements in symptoms were still evident at one-year follow-up. Refer to the current product information sheet for further information. The aim should be to use the lowest dose possible that achieves the appropriate clinical outcome for each patient.

IVIG http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4213893/ *Intravenous Immunoglobulin in Pediatrics: A Review* Med J Armed Forces India. 2014 Jul; 70(3): 277–280. "There are many disorders for which IVIG is used as a treatment in children. Some of the common indications can be grouped as: a) Neurology – Guillain Barre syndrome, Chronic inflammatory demyelinating polyradiculopathy (CIDP), Dermatomyositis and inflammatory myopathies, Myasthenia gravis, rare childhood epilepsy (Lennox gastaut seizure, Landau Kleffner seizure), Opsoclonus myoclonus ataxia, PANDAS (Paediatric autoimmune neuropsychiatric disorders associated with streptococcal infection) – OCD, anxiety, depression, emotional lability."

IVIG and PEX http://www.tandfonline.com/doi/pdf/10.1080/21645515.2015.1061161 Giovanna Vitaliti, Omidreza Tabatabaie, Nassim Matin, Caterina Ledda, Piero Pavone, Riccardo Lubrano, Agostino Serra, Paola Di Mauro, Salvatore Cocuzza & Raffaele Falsaperla (2015) *The usefulness of immunotherapy in pediatric neurodegenerative disorders: A systematic review of literature data*, Human Vaccines & Immunotherapeutics, 11:12, 2749-2763 "In the studies we analyzed, IVIG was (sic) found to be efficient in the treatment of post-streptococcal neurodegenerative disorders, even if in PANDAS, plasma-exchange (PE) showed a higher efficiency."

IVIG http://online.liebertpub.com/doi/full/10.1089/cap.2014.0067 *The Use of Intravenous Immunoglobulin in the Treatment of Twelve Youths with Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infections* Kovacevic Miro, Grant Paul, and Swedo Susan E. Journal of Child and Adolescent Psychopharmacology. February 2015, 25(1): 65-69. Please note that under the section entitled, Clinical Significance, "For optimum symptom relief, it is necessary to utilize a combination of immunomodulatory therapy, antibiotic prophylaxis, and targeted symptom treatments, as described at the PANDAS Physicians Network (PPN) (www.pandasppn.org). The website presents a systematic graduated approach to treatment of PANDAS/PANS based on the best practice standards of expert clinicians from across the United States. In addition to providing suggestions for recognition and diagnosis of PANDAS/PANS, it also offers guidance in the management of patients with varying levels of severity." For reference, the PANDAS Physicians Network website: https://www.pandasppn.org/therapeutic-options-for-pandas-and-pans/

PEX http://online.liebertpub.com/doi/abs/10.1089/cap.2014.0080 *Therapeutic Plasma Apheresis as a Treatment for 35 Severely Ill Children and Adolescents with Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infections* Latimer M. Elizabeth, L'Etoile Nathan, Seidlitz Jakob, and Swedo Susan E. Journal of Child and Adolescent Psychopharmacology. February 2015, 25(1): 70-75. "Therapeutic plasma apheresis is an invasive medical intervention that should be reserved for treatment of children and adolescents who are severely affected by PANDAS. In such patients, it appears to be a safe, well-tolerated, and beneficial treatment option."

IVIG http://www.ghrnet.org/index.php/ijnr/article/view/1633/1896 *Infection-Induced Autoimmune Encephalopathy: Treatment with Intravenous Immune Globulin Therapy. A Report of Six Patients*. Bouboulis Dennis. Mast Phyllis. International Journal of Neurology Research, Vol 2, No 1 (2016) "IVIg is a safe and beneficial therapy in IIAE, PANDAS and ASD impacting favorably on underlying humoral immune deficiency and infectious-induced CNS autoimmunity in this small and highly selected cohort."

IVIG http://www.jaacap.com/article/S0890-8567(16)31158-3/pdf *Randomized, Controlled Trial of Intravenous Immunoglobulin for Pediatric Autoimmune Neuropsychiatric Disorders Associated With Streptococcal Infection.* October 2016. Volume 55, Issue 10, Pages 860–867.e2. As reported by the PANDAS Physicians Network, "a new paper submitted to the Journal of the American Academy of Child & Adolescent Psychiatry describes the outcome of the NIMH double-blind placebo controlled study of IVIG for treatment of symptoms in children who meet the criteria of PANDAS. While the study has many interesting findings, the most significant is that children who had prophylactic antibiotics followed by an open-label IVIG had a >60% mean reduction in CYBOCS score. These symptom improvements were sustained through follow up at 6 months."

IVIG https://www.ncbi.nlm.nih.gov/pubmed/27900773 *Systemic Review of Immunoglobulin Use in Paediatric Neurological and Neurodevelopmental Disorders* Dev Med Child Neurol. 2017 Feb;59(2):136-144. "We conclude that it is likely that IVIG improves recovery in selected patients with paediatric autoimmune neuropsychiatric disorder associated with streptococcal infection (level 2). We recommend that IVIG should be considered in selected patients with a diagnosis of paediatric autoimmune neuropsychiatric disorder associated with streptococcal infection (grade B)." Oxford Centre for Evidence-based Medicine – Levels of Evidence (March 2009)

IVIG http://dx.doi.org/10.1016/j.jaci.2016.09.023 *Update on the use of immunoglobulin in human disease: A review of evidence* The Journal of Allergy and Clinical Immunology**.** March 2017 Volume 139, Issue 3, Supplement, Pages S1-S46 "The immune-based therapies should be used only in cases in which it is clear that the neuropsychiatric symptoms are related to an autoimmune response, as supported by laboratory evidence and in conjunction with neuropsychiatric professionals."

ABX, IVIG, and PEX https://www.ncbi.nlm.nih.gov/labs/articles/28234797/ *Autoimmune Encephalitis in Children: Clinical Phenomenology, Therapeutics, and Emerging Challenges.* RC Dale et al. Curr Opin Neurol. 2017 Feb 22. PANDAS and PANS are considered Infection Mediated Relapsing Remitting Central Nervous System Syndromes (see Table 1, p. 3). "In a systematic review of the treatment of adults and children with autoimmune encephalitis, there were three main themes that were present, regardless of auto-antibody association. (1) Patients given immune therapy do better than patients given no therapy. (2) Patients given treatment early do better than those given treatment late. (3) If a patient does not respond to first line therapy, second line therapy improves outcomes."

IVIG and PEX https://doi.org/10.1089/cap.2016.0148 *Clinical Management of Pediatric Acute-Onset Neuropsychiatric Syndrome: Part II—Use of Immunomodulatory Therapies.* Frankovich Jennifer, Journal of Child and Adolescent Psychopharmacology. July 2017. "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."