

# Key Recent PANS, PANDAS & BGE Research

Supported by novel animal disease models and clinical research, key advances in our understanding of PANS, PANDAS, and post-infectious basal ganglia encephalitis (BGE) have emerged over recent years. Large epidemiological studies continue to support the relationship between infectious triggers and neuropsychiatric disorders. Advances in our understanding of neuroimmune dysregulation are shaping future findings in diagnostic and treatment outcomes. The studies included in this document are only a small sample of the scientific advancements being made in PANS/PANDAS. For more on research: <https://aspire.care/resources/research>



COLUMBIA UNIVERSITY  
DEPARTMENT OF PATHOLOGY  
AND CELL BIOLOGY

## Th17 lymphocytes drive vascular and neuronal deficits in a mouse model of postinfectious autoimmune encephalitis

MP. Platt, KA. Bolding, CR. Wayne, S Chaudhry, T Cutforth, KM. Franks, D Agalliu. Proceedings of the National Academy of Sciences Mar 2020, 117 (12) 6708-6716; DOI: [10.1073/pnas.1911097117](https://doi.org/10.1073/pnas.1911097117)

- Findings show the role of Th17 lymphocytes in the impairing CNS function in AE syndromes; they play a pivotal role in allowing autoantibodies to enter the CNS due to persistent microglial activation as a result of multiple GAS infections.

## Yale SCHOOL OF MEDICINE

### Antibodies Bind to Striatal Cholinergic Interneurons and Alter Their Activity

J Xu, Rong-Jian Liu, S Fahey, L Frick, J Leckman, F Vaccarino, RS. Duman, K Williams, S Swedo, and C Pittenger. Am Jnl of Psychiatry 16 Jun 2020 DOI: [10.1176/appi.ajp.2020.19070698](https://doi.org/10.1176/appi.ajp.2020.19070698)

- In PANDAS patients, a high level of IgG antibodies concentrated in the striatum bind specifically to striatal cholinergic interneurons (CINs). This alters activity of the neurons by modifying the signals of other nearby cells.
- The striatum is associated with voluntary motor control, among other functions, and is known to be involved in OCD. When the antibody binds to these neurons, it reduces their activity.
- After treatment with IVIG, the IgG binding to CINs was reduced, and this reduction correlated with symptom improvement.



PANS: Pediatric Acute-onset Neuropsychiatric Syndrome  
Department of Pediatrics - Division of Allergy, Immunology & Rheumatology

### Association of PANS With Microstructural Differences in Brain Regions Detected via Diffusion-Weighted MRI

Zheng J, Frankovich J, McKenna ES, et al. JAMA Netw Open. 2020;3(5):e204063.

DOI: [10.1001/jamanetworkopen.2020.4063](https://doi.org/10.1001/jamanetworkopen.2020.4063)

- All assessed brain regions had statistically significantly increased median diffusivity.
- The deep gray matter demonstrated the most profound increases in diffusivity consistent with the cardinal clinical symptoms of obsessions, compulsions, emotional dysregulation, and sleep disturbances.



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### Pro-inflammatory dopamine-2 receptor-specific T cells in paediatric movement and psychiatric disorders

Pilli, D., Zou, A., Dawes, R., Lopez, J.A., Tea, F., Liyanage, G., Lee, F.X., Merheb, V., Houston, S.D., Pillay, A., Jones, H.F., Ramanathan, S., Mohammad, S., Kelleher, A.D., Alexander, S.I., Dale, R.C. and Brilot, F. (2020). Clin Transl Immunol, 9: e1229. DOI: [10.1002/cti2.1229](https://doi.org/10.1002/cti2.1229)

- Autoreactive D2R-specific T cells and a pro-inflammatory Th1 and Th17 cytokine profile characterize a subset of pediatric patients with movement and psychiatric disorders, further underpinning the theory of immune dysregulation in these disorders.

## Autoantibody Biomarkers for Basal Ganglia Encephalitis in Sydenham Chorea and PANDAS

Chain JL, Alvarez K, Mascaro-Blanco A, Reim S, Bentley R, Hommer R, Grant P, Leckman JF, Kawikova I, Williams K, Stoner JA., Swedo SE., Cunningham MW. Jnl Frontiers in Psychiatry. Vol.11, 2020.  
DOI: [10.3389/fpsy.2020.00564](https://doi.org/10.3389/fpsy.2020.00564)

- In children with PANDAS and Sydenham chorea (SC), antibodies were present that reacted against human antigens: tubulin, lysoganglioside Gm1, and dopamine receptors D1 and D2. These auto-antibodies were not found in comparable levels in the psychiatric contrast groups or healthy controls.
- Titers of the auto-antibodies were lower following treatment/recovery from SC or PANDAS than during the acute phase. Changes were seen in the activity of the calcium/calmodulin-dependent protein kinase II (CaMKII) pathway during the course of illness.
- Findings provide support for a pathologic role of the antibodies and confirm important aspects of the disease mechanism of PANDAS and Sydenham chorea.

## Cognitive, Graphomotor, and Psychosocial Challenges in PANDAS

MK. Colvin, S Erwin, PR. Alluri, A Laffer, K Pasquariello, KA. Williams. The Jnl of Neuropsychiatry and Clinical Neuroscience. 2 Dec 2020 DOI: [10.1176/appi.neuropsych.2003006](https://doi.org/10.1176/appi.neuropsych.2003006)

- Findings indicated relative difficulties with aspects of executive and motor functions.
- Although evaluations were performed following the resolution of acute symptoms, ongoing and significant academic difficulties and emotional, behavioral, and social concerns were targets for clinical intervention and support.

## Evaluation of Intravenous Immunoglobulin in PANS

Melamed, RH. Kobayashi, M O'Connor, AL Kobayashi, A Schechterman, M Heffron, Sharon Canterberry, H Miranda, N Rashid. 2021 Mar;31(2):118-128. DOI: [10.1089/cap.2020.0100](https://doi.org/10.1089/cap.2020.0100)

- IVIG [Octagam 5%] successfully ameliorated psychological symptoms and dysfunction, with sustained benefits in PANS patients.
- All psychometric endpoints exhibited statistically significant decreases following 6 infusions as well as durability of response for at least 8 weeks, and up to 46 weeks, following the final infusion.
- Patients with PANS can benefit from a 6-cycle course of IVIG.

## A Double-Blind Randomized Placebo-Controlled Pilot Study of Azithromycin in Youth with Acute-Onset Obsessive-Compulsive Disorder

TK. Murphy, EM. Brennan, C Johnco, EC Parker-Athill, B Miladinovic, Eric A. Storch, A B. Lewin. JCAP. S2017 Sep;27(7):6 40-651. DOI: [10.1089/cap.2016.0190](https://doi.org/10.1089/cap.2016.0190)

- Double-blind pilot study suggests azithromycin may be helpful in treating PANS diagnosis patients, especially those with elevated levels of both OCD and tic symptoms.
- 41.2% met the criteria for treatment response on the CGI-S OCD by week four in comparison to 7.1% of the placebo group.
- Tic severity moderated treatment response, with greater tic severity being associated with enhanced treatment response on the CGI-S OCD.

## ICD-11 Includes Code for PANDAS

In May 2019, the World Health Organization (WHO) adopted the 11th edition of the International Classification of Diseases (ICD-11). This updated version will go into effect on January 1, 2022 in member countries. WHO has already released a preview that will allow countries to plan how to use the new version, prepare translations, and train health professionals. The ICD-11 includes PANDAS for the first time in coding related to post-infectious tics and autoimmune disorders related to the central nervous system.

<https://icd.who.int/browse11/l-m/en#/http://id.who.int/icd/entity/49601112>

# Diagnostic Guidelines & Treatment Recommendations

The PANS/PANDAS Research Consortium (PRC) convened by Susan Swedo, MD, former Chief of the Section on Behavioral Pediatrics at the National Institute of Mental Health (NIMH), published two special issues of the *Journal of Child and Adolescent Psychopharmacology*. The February 2015 issue focuses on clinical evaluation. The July 2017 issue provides detailed guidelines on a combination of psychotherapeutic, antimicrobial, and immunomodulatory treatments. The PRC consists of a diverse group of clinicians and researchers from complementary fields of pediatrics: general and developmental pediatrics, infectious diseases, immunology, rheumatology, neurology, and child psychiatry.

## **Clinical Evaluation of Youth with Pediatric Acute-Onset Neuropsychiatric Syndrome (PANS): Recommendations from the 2013 PANS Consensus Conference. Special Issue: Pediatric Acute-Onset Neuropsychiatric Syndrome**

Chang K, Frankovich J, Cooperstock M, Cunningham M, Latimer E, Murphy T, Pasternack M, Thienemann M, Williams K, Walter J, Swedo S. *Journal of Child and Adolescent Psychopharmacology*. Vol. 25, No. 1, Feb 2015: 3-13. DOI: [10.1089/cap.2014.0084](https://doi.org/10.1089/cap.2014.0084). PMID: 25325534

- "The goals were to clarify the diagnostic boundaries of PANS, to develop systematic strategies for evaluation of suspected PANS cases, and to set forth the most urgently needed studies in this field."

## **Overview of Treatment of Pediatric Acute-onset Neuropsychiatric Syndrome**

Swedo S, Frankovich J, and Murphy T. *JCAP*, Vol. 27, No. 7, Sep 2017. DOI: [10.1089/cap.2017.0042](https://doi.org/10.1089/cap.2017.0042)

- Postinfectious autoimmunity and/or neuroinflammation is found in more than 80% of PANS cases
- PANS treatment utilizes three complementary modes of intervention: 1: Treat symptoms with psychotherapeutic interventions. 2: Remove the source of inflammation with antimicrobials. 3: Treat immune system with anti-inflammatory and/or immuno-modulatory therapies.

## **Clinical Management of Pediatric Acute-onset Neuropsychiatric Syndrome:**

### **Part I - Psychiatric and Behavioral Interventions**

Thienemann M, Murphy T, Leckman J, Shaw R, Williams K, Kappahn C, Frankovich J, Geller D, Bernstein G, Chang K, Elia J, and Swedo S. *JCAP*, Vol. 27, No. 7, Sep 2017. DOI: [10.1089/cap.2016.0145](https://doi.org/10.1089/cap.2016.0145)

- While treating inflammatory process and infectious trigger, treat symptoms to improve treatment compliance and lower suffering from symptoms.
- Must tailor all psychotherapeutic interventions (psychological, behavioral, and psychopharmacologic) to the patient's individual symptom presentation.
- Expect differing responses to psychotropic medication in each patient. Patients may require a marked reduction of the initial treatment dose.

## **Clinical Management of Pediatric Acute-onset Neuropsychiatric Syndrome:**

### **Part II - Use of Immunomodulatory Therapies**

Frankovich J, Swedo S, Murphy T, Dale R, Agalliu D, Williams K, Daines M, Hornig M, Chugani H, Sanger T, Muscal E, Pasternack M, Cooperstock M, Gans H, Zhang Y, Cunningham M, Bernstein G, Bromberg R, Willett T, Brown K, Farhadian B, Chang K, Geller D, Hernandez J, Sherr J, Shaw R, Latimer E, Leckman J, Thienemann M, and PANS/PANDAS Consortium. *JCAP*, Vol. 27, No. 7, Sep 2017. DOI: [10.1089/cap.2016.0148](https://doi.org/10.1089/cap.2016.0148)

- Base recommendations for immunomodulatory therapies (IVIg, PEX immunosuppressive drugs) on symptom severity and disease course. Principles to treat other brain inflammatory diseases (AE, NPSLE, etc.) apply to PANS, especially in the more severe cases.
- (1)Patients prescribed immunotherapy do better and relapse less frequently than those 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.
- Consider immunomodulatory therapy early, as NSAIDs or a short course of oral corticosteroids in recent-onset cases may be enough for remission. More intensive and longer immunotherapeutic interventions may be needed for long-standing symptoms.

## **Clinical Management of Pediatric Acute-onset Neuropsychiatric Syndrome:**

### **Part III - Treatment and Prevention of Infections**

Cooperstock M, Swedo S, Pasternack M, Murphy T, and for the PANS/PANDAS Consortium. *JCAP*, Vol. 27, No. 7, Sep 2017. DOI: [10.1089/cap.2016.0151](https://doi.org/10.1089/cap.2016.0151)

- Provides an approach to retrospectively diagnosing GAS infection to meet an operational definition of PANDAS
- Proposes an initial course of anti-streptococcal treatment for all newly diagnosed PANS cases
- Proposes the use of chronic secondary antimicrobial prophylaxis for children with PANDAS who have severe neuropsychiatric symptoms or recurrent GAS exacerbations
- Provides guidelines for patients with non-GAS triggered PANS, including attention for GAS pharyngitis or dermatitis in the patient and close contacts.
- Closely monitor all patients with PANS PANDAS for intercurrent infections, including sinusitis and influenza; diagnose and treat promptly according to current standard guidelines.

# ABOUT ASPIRE

## Our Mission

To improve the lives of children and adults affected by PANS, PANDAS, and immune-related encephalopathies.

## Our Vision

We aspire to create a world where children and adults affected by PANS, PANDAS and related encephalopathies obtain a timely diagnosis from informed providers and receive effective, proven and affordable treatments and support in all areas of daily living, without discrimination.

## Who We Are

We are experienced leaders in the PANS advocacy community. We are parents, providers and experts in our field who believe collaboration and empowered action are the keys to the world we seek: one where no one suffers through PANS and immune-related encephalopathies without access to a knowledgeable provider, insurance coverage for standard-of-care treatments or the support that comes with public awareness.

We work collaboratively to improve the quality of life for those affected by PANS, PANDAS and immune-related encephalopathies. We focus our efforts on empowering and connecting our community with tools and resources for advocacy, education, support, and awareness.



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Alliance to Solve PANS & Immune-Related Encephalopathies

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