The sudden onset of new neuropsychiatric symptoms in children is often a challenge for both parents and physicians. For the physician, there is a broad differential diagnosis to consider, and decisions must be made about the selection of diagnostic studies as well as the choice of therapy. In addition, there is often a belief that, even without a documented etiology, an immediate pharmacologic treatment targeted toward an undiagnosed biological etiology will prevent worsening symptoms or permanent sequelae. Pediatric Autoimmune Neuropsychiatric Disorder Associated with Streptococcal infection (PANDAS) and Pediatric Acute-onset Neuropsychiatric Syndrome (PANS) are 2 entities that were 2 decades ago as a poststreptococcal autoimmune condition similar to Sydenham chorea, whereas PANS is a broader diagnosis without a single defined etiology or mechanism. In this commentary, we review updated information on PANDAS and PANS clinical symptoms, presumed etiologic associations, proposed autoimmune mechanisms, diagnostic testing, and recommended treatments. Our goal is to provide current information that will permit a clear and balanced approach when dealing with these controversial diagnoses.

Definitions

PANDAS
The concept of PANDAS was derived from observations that some individuals with Sydenham chorea (SC, acute rheumatic fever) have associated anxiety, emotional lability obsessive-compulsive symptoms, tics, or a combination. In 1998, investigators at the National Institute of Mental Health reported a series of 50 patients with similar features and proposed a distinct, clinical entity, PANDAS, with 5 specific diagnostic criteria: (1) presence of obsessive-compulsive disorder (OCD) and/or a tic disorder; (2) prepubertal symptom onset (age 3 years to the beginning of puberty); (3) episodic course characterized by acute, severe onset and dramatic symptom exacerbations; (4) temporal relationship between group A beta-hemolytic streptococcal (GABHS) infections and symptom onset and exacerbations; (5) association with neurologic abnormalities (eg, choreiform movements, motoric hyperactivity, tics).

Other investigators subsequently raised concerns about problematic aspects of the PANDAS criteria, including (1) the strength of GABHS association with the onset and recurrence of tics, OCD, or both; (2) the lack of data supporting the suppression of symptoms or prevention of recurrences with antibiotic therapy; (3) whether there is a meaningful distinction between PANDAS and tic disorders; and (4) the absence of neurologic/behavioral abnormalities during exacerbations. Despite these and other concerns discussed below, physicians continue to diagnose PANDAS and also create additional ambiguity by introducing terms such as “PANDAS variant” or “atypical PANDAS” based on the presence of other neuropsychiatric symptoms, or types of infections. Motivated in part by a desire to clarify psychiatric diagnostic criteria and expand potential etiologies, a workshop was convened in 2010 and proposed a new diagnostic entity: PANS.

PANS
The criteria for PANS include abrupt, dramatic overnight onset of OCD or severely restricted food intake; concurrent abrupt onset of additional severe neuropsychiatric symptoms from at

ADHD Attention-deficit hyperactivity disorder
CNS Central nervous system
CSF Cerebrospinal fluid
GABHS Group A beta-hemolytic streptococcal
IVIG Intravenous immunoglobulin
OCD Obsessive-compulsive disorder
PANDAS Pediatric Autoimmune Neuropsychiatric Disorder Associated with Streptococcal infection
PANS Pediatric Acute-onset Neuropsychiatric Syndrome
SC Sydenham chorea

From the 1Department of Pediatrics, Cincinnati Children’s Hospital Medical Center, Cincinnati, OH; 2Department of Neurology, University of Rochester Medical Center, Rochester, NY; and 3Johns Hopkins Hospital, Baltimore, MD
D.G. received honoraria and/or travel support from the Tourette Association of America/ Centers for Disease Control and Prevention, the American Academy of Pediatrics, and the Child Neurology Society, compensation for expert testimony for the US National Vaccine Injury Compensation Program, through the Department of Health and Human Services, research support from the National Institutes of Health (NIH) (National Institute of Mental Health, National Institute of Neurological Disorders and Stroke), funding for work as a clinical trial site investigator from Psysadon Pharmaceuticals (clinical trial, Tourette Syndrome) and EryDel (clinical trial, Ataxia Telangiectasia), book royalties from Elsevier and Wolters Kluwer. J.M. received honoraria from the American Academy of Neurology as Associate Editor of Neurology, grant support from NIH, Centers for Disease Control and Prevention, Beyond Batten Disease Foundation, Batten Research Alliance, Noah’s Hope, Batten Disease Support and Research Association, and Aboena Inc, compensation for expert testimony for the US National Vaccine Injury Compensation Program, through the Department of Health and Human Services, served as a consultant to Abide Inc, Censa Inc, and Teva Inc, and has received book royalties from Elsevier and from John Wiley & Sons. H.S. received research support from the NIH and the Tourette Association of America, funding for work as a clinical trial site investigator from Ecopepam Pharmaceuticals, served as a consultant for Teva Brand Pharmaceutical Products Research and Development, and received book royalties from Elsevier. The authors declare no conflicts of interest.
least 2 of the following 7 categories: (1) anxiety; (2) emotional lability and/or depression; (3) irritability, aggression, and/or severe oppositional behaviors; (4) behavioral (developmental) regression; (5) deterioration in school performance; (6) sensory or motor abnormalities, including heightened sensitivity to sensory stimuli, hallucinations, dysgraphia, complex motor, and/or vocal tics; (7) somatic signs and symptoms, including sleep disturbances, enuresis, or urinary frequency; and (8) symptoms are not better explained by a known neurologic or medical disorder. Three key differences within this new diagnosis worth emphasizing include (1) the PANDAS diagnostic criteria requires neurologic abnormalities (tics, motor hyperactivity, choreiform movements), whereas PANS can be diagnosed with only psychiatric symptoms; (2) PANDAS requires both an acute symptom onset and episodic (relapsing remitting) course whereas PANS can be diagnosed based solely on the initial presentation; (3) PANDAS has a proposed specific etiologic bacterial trigger (GABHS), whereas PANS has no specified precipitant. Nevertheless, similar to PANDAS, PANS presumes an infectious and autoimmune mechanism in most cases.12

Epidemiologic Studies—PANDAS

In the 20 years following publication of the seminal PANDAS case series, a large number of observational epidemiologic studies have sought to confirm PANDAS as a clinical entity distinct from idiopathic or familial tic disorders or OCD. These studies can be grouped based on study design and evaluated using standard recommended guidelines for establishing (1) strength of associations; (2) consistency of results under different circumstances; (3) biological gradient or “dose” (amount of exposure) and “effect” (symptom severity); and (4) timing of the temporal association.13 Using these guidelines, in the following sections we will review relative strengths and weaknesses of representative publications.

Studies of Consistency and Diagnostic Accuracy in Clinical Practice

In a study reported from an OCD/Tourette specialty clinic, 31 of 176 children referred for tics or OCD were previously diagnosed with PANDAS.8 Of these, however, only 12 (39%) met established PANDAS diagnostic criteria. Antibiotic treatments were common, even in the absence of any laboratory evidence of infection.8 This study illustrates the frequent diagnostic misclassification in PANDAS; this finding carries significant implications for confirming validity in the areas of consistency and timing, particularly for retrospective studies.

Systematic, Longitudinal Prospective Studies of Cohorts Designed to Identify Co-Occurrence of Streptococcal Infections and PANDAS Behavioral Symptoms

Two studies sought evidence for PANDAS in patients evaluated directly in the community. In the first, researchers enrolled 814 children ages 4-11 years from pediatric clinics. Streptococcal infections were present in 411 children, viral (presumed) pharyngitis in 207, and no infections (well care) in 196 children. At enrollment, 2 and 12 weeks after the visit, parents completed a 20-question survey about symptoms consistent with PANDAS. At 12 weeks, there were no differences across the 3 groups for obsessive-compulsive behaviors, tics, or other neuropsychiatric symptoms.14 In the second study, researchers’ enrolled 693 healthy children, aged 3-12 years, and collected streptococcal infection data (via throat cultures), observational motor examinations, and behavioral ratings for an 8-month period during the school year. Using a timing criterion of 3 months from the streptococcal infection to symptoms, the authors reported no increased risk of tics or chorea. They did identify increased “swaying” and “non-tic grimacing” in 37 (19%) children with vs 28 (6%) without infections, and nonspecific problem behaviors in 68 (35%) children with infections, vs 91 (18%) without. Further, they reported a dose-effect linking more streptococcal infections with more problem behaviors.15 Nevertheless, this study’s causality criteria, which included a strength, timing, and dose-effect, failed to confirm an association between a preceding streptococcal infection and a PANDAS diagnosis.

Retrospective Studies Using Claims Data

Several studies16-19 have used claims data to probe relationships between coded events as well as to assist in determining whether the diagnosis of a streptococcal infection precedes the new diagnosis of OCD or tic disorders at a rate greater than expected by chance. Unfortunately, threats to validity are abundant in these approaches—the clinical practice for diagnosing streptococcal infections and behavioral conditions varying widely. For example, with respect to timing, the onset of a behavioral diagnostic code does not necessarily indicate the onset of the symptoms. In a recent cohort study from Denmark, which included all 1 067 743 individuals born over an 18-year period, investigators identified individuals who had streptococcal testing ordered. From this cohort, they ascertained those provided with antibiotic prescriptions within 1 week (15 408) and considered this a proxy for a “streptococcal infection” positive group. In contrast, the lack of an antibiotic prescription (11 315) in the streptococcal test cohort was used as a proxy for “other infection.” No testing (13 712) was used to create matched controls, as a proxy for “no infection.” Compared with controls, odds of OCD were 51% higher in the treated-infection and 28% higher in the untreated-infection groups. Odds of tics were 35% and 25% higher in those groups.16 This study is broadly supportive in terms of strength. However, with respect to PANDAS, the certainty around the specific cause of infection is low, and the details about whether the effect is PANDAS (ie, dramatic onset and exacerbations), are nonexistent. Other unmeasured factors, such as possibly higher rates of healthcare utilization for individuals with OCD, might also confound these findings. Perhaps not surprisingly, results from these types of studies have been inconsistent.17-19
Prospective Longitudinal Studies Using Intensive Clinical Monitoring in Specialty Clinics

Two prospective multicenter studies employed expert clinicians and rigorous standardized criteria. These studies enrolled 71 children who met consensus PANDAS criteria at the time of enrollment. The objective was to identify, prospectively, whether a streptococcal infection preceded the exacerbation of OCD or tic symptoms, using predefined numerical criteria for severity. Participants received serial monthly and illness-based throat cultures and quarterly and illness-based antibody titers for 2 years. To help discern whether symptom exacerbations in PANDAS are unique, 93 children with idiopathic or familial chronic OCD or a tic disorder were enrolled as matched controls and tested on the same schedule. Clinical raters were blinded to culture results and antibody titers. These studies found that children meeting PANDAS criteria and non-PANDAS tic/OCD controls experienced similar rates of OCD or tic exacerbations in PANDAS are unique, 93 children with idiopathic or familial chronic OCD or a tic disorder were enrolled as matched controls and tested on the same schedule. Clinical raters were blinded to culture results and antibody titers. These studies found that children meeting PANDAS criteria and non-PANDAS tic/OCD controls experienced similar rates of infections and tic or OCD exacerbations, with 59 of 64 (92%) and 53 of 59 (90%) exacerbations occurring in the absence of any newly acquired streptococcal infections.

In aggregate, the aforementioned and prior epidemiologic studies provide little support for an association between GABHS and tics or OCD or for PANDAS as a distinct diagnosis, although such evidence cannot disprove that it may occur rarely.

Epidemiologic Studies—PANS

The PANS hypothesis is based on observations by clinicians that some children experience an abrupt and dramatic onset of OCD or restricted food intake with or without an apparent precipitant. The primary diagnostic criteria of PANS are the presence of clinical symptoms in the absence of any etiology; hence, there is no unifying, testable epidemiologic hypothesis. At present, attempts to demonstrate causality are primarily exploratory, retrospective studies. In the largest study to date, 698 participants were recruited through advocacy websites for PANDAS and PANS. Symptom history was ascertained through a newly created survey questionnaire. There was no attempt made to verify independently the cause (patient-reported antecedent events) or the effect (meeting the criteria for PANS), the temporal interval, the “dose,” or the presence and chronicity of other behavioral diagnoses. Clinical data such as immunologic test results were not independently verified. Of note, despite the definition of PANS provided in the survey, some participants reported a gradual, not acute, symptom onset and some reported pre-existing diagnoses such as attention deficit hyperactivity disorder (ADHD) and autism spectrum disorder. Because of highly biased participant sampling, nonvalidated causes, nonvalidated effects, and nonvalidated survey methods, data from this study should be considered neither valid nor generalizable. The required causality criteria of strength, dose-effect, and temporality were not fulfilled.

In another pilot study, claims data from employer-based health insurers were used to explore whether vaccinations, particularly the influenza vaccination, could be linked to conditions emphasized in PANS, such as anorexia (n = 551), OCD (n = 3222), vs 5 other neuropsychiatric (anxiety, tics, ADHD, major depression, bipolar disorder) and 2 highly prevalent acute medical (broken bone, open wound) conditions. Data over a 6-year period in children aged 6-15 years was abstracted from available records. Vaccinations assessed included influenza, hepatitis A and B, tetanus and diphtheria, meningitis, and varicella. Incident diagnoses were captured at 3, 6, and 12 months after vaccinations. The authors calculated 189 bivariate hazard ratios and identified at least 1 increased vaccine-linked hazard risk for OCD, anorexia, anxiety, ADHD, and tics (plus for broken bones), and at least 1 decreased vaccine-linked hazard risk for depression and bipolar disorder (plus for open wounds). The authors concluded that the low absolute risk and high public health benefit favored continued adherence to recommended vaccination schedules. As in the PANDAS claims-data studies, there is no distinction between, or knowledge of, a severe dramatic onset vs a gradual onset. The magnitudes of the hazard ratios—the strength of the association, were usually close to 1. Regarding temporality, the study shares the limitations of the claims-data studies of PANDAS.

Pathophysiological Studies—Is PANDAS an Autoimmune Disorder?

The pathophysiological hypothesis in PANDAS, but not PANS, states that GABHS infections trigger the production of antibodies that, in turn, cross-react against the central nervous system (CNS) and cause tics and OCD symptoms. In contrast to Tourette syndrome, where a preceding infection may exacerbate symptoms, in PANDAS the streptococcal infection and its induced cross-reacting antibodies are proposed as the cause of the symptoms. In this discussion, the term “autoimmune” indicates an acquired process targeting the nervous system involving either autoantibodies or autoreactive lymphocytes (T or B cells).

Autoantibodies and Requirements for Confirmation of Pathogenicity

B cells, or the antibodies they produce, cross the blood brain barrier into the CNS. Once there, antibodies identify and bind to their targeted antigens. In the case of proposed streptococcal-induced antibodies, the CNS antibody-binding sites (epitopes) are believed to resemble the antigenic infectious agent—a process called “molecular mimicry.” Several experimental factors are required to confirm antibody pathogenicity including (1) documentation of the presence of the antibody in the clinical condition—while appearing straightforward, it is essential to recognize that the mere presence of an antibody is insufficient proof of pathogenicity; (2) recognition that antibodies typically do not enter the targeted cell—rather, they bind to cell surface epitopes. Hence, antibodies binding to cell surface components (eg, receptors, ion channels, or synaptic proteins) are more likely to be associated with clinical symptoms. In contrast, autoantibodies binding to intracellular
proteins (eg, enzymes, mitochondria, tubulin) are not usually pathogenic; (3) confirmation of the presence of immunoglobulins at the pathological site; (4) validation that the antibody binds to the target (human) antigen in its native conformation and shape; (5) affirmation of clinical response to immunomodulatory therapy; and (6) substantiation of the passive transfer of the disorder to animal models. Indirect evidence might also include a higher familial incidence of autoimmune disease.

**Proposed Autoantibodies in PANDAS.** Studies attempting to identify definitive autoantibodies in PANDAS have yielded inconsistent results. In addition, studies involving serial sampling have shown no association between symptom exacerbations and serial changes in antineuronal antibodies. Several reports have suggested that individuals with “PANDAS possessing choreiform (‘piano-playing’) movements” have antineuronal antibodies similar to those identified in SC. In contrast, results from the 2 longitudinal studies containing children meeting the criteria for PANDAS, but excluding those with choreiform movements, failed to identify a temporal association between symptom exacerbation and elevations in these antibodies.

**Immunoglobulins Located at the Pathologic Site.** The precise site of abnormality in PANDAS is unknown. A single volumetric magnetic resonance imaging study suggested a larger caudate, putamen, and globus pallidum, but there was no correlation between basal ganglia size and symptom severity. A positron emission tomography study, utilizing a marker for activated microglia (neuroinflammation), evaluated 17 children with PANDAS and compared results with 12 children with Tourette syndrome and 15 healthy adults (controls). Compared with adults, both children with Tourette syndrome and PANDAS had increased signal in bilateral caudate nuclei, and the PANDAS group showed increased signal in the lentiform nuclei; these findings are difficult to interpret, in part because of the not age-matched control.

Studies attempting to confirm antibody binding in the striatum, using immunofluorescent histochemical methods, have been inconsistent. For example, 1 study detected binding at a 1:10 dilution in 14 of 22 (64%) children diagnosed with PANDAS compared with 2 of 22 (9%) in a GABHS control group. In contrast, another study found no association between diagnosis and immunofluorescent positivity or localization in PANDAS, Tourette syndrome, and controls (n = 30 in each group).

**Proposed Antibodies Bind in their Natural State.** Confirming pathogenicity requires demonstrating that the antibody binds to the target antigen in its native conformation and shape. Achieving this goal requires the use of flow-cytometry-based detection assays in which the suspected antigen is located at the cell surface of live eukaryotic cells. Once again, results are variable, with some studies showing positive results for SC but not PANDAS and others differing, depending on the cell lines utilized.

**Response to Immunomodulatory Therapy.** A positive therapeutic response to immunotherapy would further support an autoimmune etiology. As will be further discussed in the therapy section, results of several placebo-controlled studies, involving fewer than 40 individuals diagnosed with PANDAS are conflicting. In an initial study comparing 1-month outcomes for intravenous immunoglobulin (IVIG), plasmapheresis, and placebo, results supported additional investigation. However, a more recent study found that response rates at 6 weeks were no different for 17 children receiving IVIG compared with 18 children-receiving placebo.

**Passive Transfer of the Disorder to Animal Models.** Animal models have been used to assess the autoimmune hypothesis in SC/PANDAS. Lewis rats immunized with GABHS manifested several features relevant to SC and/or PANDAS including developing antibodies against dopamine receptors and developing obsessive grooming plus impairments in motor control. Transferring serum IgG obtained from these animals into the striatum of naïve rodents did cause similar behavioral and motor problems. In addition, the passive transfer of serum obtained from GABHS immunized mice, after bloodbrain barrier disruption, caused behavioral disturbances. The relevance of these findings for human disease, however, remains unclear, because micro-infusion of sera from children diagnosed with PANDAS into several striatal regions in rodents did not induce behavioral changes.

**Evidence for Autoimmune Susceptibility.** In many autoimmune disorders, a potential genetic vulnerability can predispose an individual to immune dysregulation. A study using structured diagnostic interviews of mothers with children diagnosed with OCD and/or tics (n = 107) found a prevalence of reported autoimmune disorders in 17.8%, a value greater than prevalence among women, based on historical control data. Limitations of this study, however, include ascertainment and recall bias and reliance on self-report without medical records.

**PANDAS: A Nonspecific and Heterogeneous Immune Dysregulation Syndrome?** Recognizing the lack of an accurate autoantibody biomarker, some investigators have suggested the possibility that PANDAS could represent a more heterogeneous immune dysregulation syndrome involving a large variety of possible alterations in T regulatory cells, cytokines, immunoglobulins, cerebrospinal fluid (CSF) oligoclonal bands, and immune-associated genes. Threats to
the validity of studies cited in support of this hypothesis are abundant. Further, a longitudinal study in PANDAS showed no correlation between cytokine levels and clinical exacerbation.\textsuperscript{31}

**Diagnosis: Medical Diagnostic Evaluations for PANDAS and PANS**

The preceding sections have emphasized concerns that PANDAS and PANS, even when diagnosed by experts using consensus criteria, do not clinically exclude other DSM5 diagnoses manifesting similar psychiatric symptoms. Biologically, psychiatric symptoms emerge from complex combinations of genetic and environmental factors for which medical diagnostic testing, including brain imaging and blood testing, do not have a practical role. In general, disorders in which diagnostic testing can identify a specific biological etiology typically involve multiple neural circuits and are not limited to a single symptom category. Thus, if a child presents with OCD or anxiety in the presence of seizures, delirium, or a movement disorder, it is appropriate for physicians to obtain an extensive diagnostic evaluation. The rationale for obtaining studies in a child with only psychiatric symptoms is much less clear.

In the 25-year history of PANDAS research, accumulated data have provided clinically relevant information regarding the low diagnostic value of streptococcal testing. Parents often present to clinics with a desire to “rule out PANDAS,” even when their child fails to fulfill clinical criteria. As everyone should be aware, there is no accurate medical diagnostic test to rule in/out PANDAS.

Streptococcal testing should not be considered equivalent to testing for PANDAS because both throat cultures and blood streptococcal antibody tests indicate exposure to streptococci but do not distinguish between otherwise healthy children with no OCD or tics and those suspected to have PANDAS. Prior reports have emphasized that diagnosing a streptococcal infection is not straightforward.\textsuperscript{1,33} Positive throat cultures can indicate active infection or a benign carrier state and do not prove that streptococci are causing OCD/tic symptoms. As shown in prospective longitudinal studies, throat cultures can remain positive in nearly 20% of children 12 months after an acquired infection.\textsuperscript{33} Similarly, elevated blood titers for streptococcal antibodies (ASO and Anti-DNAse B) only indicate a prior streptococcal infection, but provide no information about the time of onset or duration of that infection. Prospective studies have shown that these antibodies remained elevated for greater than 12 months in over 50% of children.\textsuperscript{53} Therefore, a single antibody titer elevation does not link a streptococcal infection to tic or OCD onset.

Substantial research efforts have been devoted to identifying the presence of specific antibrain antibodies which, in turn, could be used to diagnose PANDAS accurately. Unfortunately, published studies are inconsistent, raising concerns about methodology, appropriate control samples, and a failure to demonstrate an association between antibody titers and symptom recurrence.\textsuperscript{29,30} A panel of antibodies for diagnostic testing made commercially available has poor predictive value and test characteristics (specificity of just 10% for PANDAS and 6% for PANS).\textsuperscript{38}

In summary, published PANDAS data show that streptococcal cultures, antistreptococcal antibodies, and antibrain antibodies have a high potential to mislead both clinicians and parents. Moreover, recognizing that both antibody levels and behavioral symptoms fluctuate, and these fluctuations are not correlated, repeated longitudinal testing is also problematic.\textsuperscript{54} Thus, although protocol-based streptococcal testing remains critical for acute rheumatic fever,\textsuperscript{54} there is little evidence to support these tests in children with OCD or tics.

Diagnostic testing for suspected PANS in children presenting with OCD and/or severe food restriction remains more ambiguous, recognizing that unlike PANDAS, the definition of PANS does not include a specified trigger. To date, there is no significant evidence supporting any particular etiologies for PANS. As a corollary, there is no specific medical diagnostic testing for PANS. In a recently published consensus diagnostic statement,\textsuperscript{7} it was recommended that patients with PANS should have a complete blood cell count with manual differential, erythrocyte sedimentation rate (ESR), C-reactive protein, comprehensive metabolic panel, urinalysis, throat culture, antistreptococcal antibodies, and sometimes other tests. However, none of these recommendations has been shown to have an empirical justification. In support of their recommendation, the authors of this consensus statement published a case series including 19 PANS patients from among 47 evaluated, with test results reported in as few as 5 patients.\textsuperscript{55} ESR was elevated in 0 of 17 patients. Streptococcal antibody titers were not presented. Results showed no specific findings supporting any autoimmune process or etiology.

**Recommendations for Diagnostic Testing**

Faced with a child with new onset psychiatric symptoms, the desire to obtain medical diagnostic testing is understandable, despite the inconclusive nature of studies to date. In deciding on diagnostic testing strategies, we recommend that clinicians do not perform the PANDAS/PANS medical diagnostic testing\textsuperscript{7,55} in otherwise healthy children with mild to moderate, nondisabling OCD or tics. In our experience, this is the majority of children referred for PANDAS or PANS. The pre-test probability in such cases is extremely low. A positive test does not prove a child has PANDAS or PANS, and a negative test adds almost no new information. Moreover, inaccurate diagnoses pose risk to children and families, as noted in one extreme instance in which PANS was claimed to be an explanation for the northern New York state teenage girls’ “tics” and “seizures,” despite the existence of a better and more accurate diagnosis of conversion disorder (functional neurological symptom disorder).\textsuperscript{56} It is not uncommon in our practice that the diagnosis of PANDAS or PANS distracts families from pursuing clinically important psychiatric and behavioral interventions and sometimes leads to inappropriate, expensive, and risky treatments.

For children with fulminant onset, severe, and disabling symptoms, we propose stratification into 2 groups, based on
presence or absence of concurrent neurologic symptoms or signs.

**Children with Psychiatric plus Neurological Signs/ Symptoms**

In children with sudden-onset psychiatric symptoms plus neurologic symptoms or signs including, but not limited to, fluctuations of attention, arousal and orientation, seizures, a new non-tic movement disorder, new and profound sleep disturbances or autonomic symptoms, and/or abnormalities identified on a formal physical or neurological examination, we recommend extensive medical diagnostic testing to include neuroimaging and CSF studies.1 The specifics should be tailored to the individual case, guided both by the nature of the neurologic presentation plus past medical history, family history, travel history, and symptoms or signs in other organ systems. Further, ongoing serial clinical assessment is critical. Although the diagnosis of anti-N-methyl-D-aspartate receptor encephalitis is often cited in lists of potential neurological diagnoses with initial psychiatric symptoms,1,2 it should be noted that this disorder has a more neurologic and less psychiatric presentation in children.2

**Psychiatric-Only Presentations**

In the presence of psychiatric-only symptoms, the standard of care for diagnosis typically involves few or no medical tests. The consensus recommendations for a series of blood tests for PANS27 diverge from this accepted practice, despite a lack of published supportive data. However, we agree that in the small subset of such children with the acute onset of psychiatric symptoms that are also both severe and substantially disabling, the incentive to search for an etiology is compelling. If a psychiatrist or pediatrician believes it is appropriate in an individual case to pursue medical diagnostic testing, we propose following the individualized approach above for children with severe psychiatric plus neurologic symptoms, to include CSF and neuroimaging studies and not solely blood testing. If such testing provides strong evidence of inflammation or other possible medical causes, involvement of neurology, rheumatology, infectious disease, or other subspecialties is appropriate.

**Treatment Studies in PANDAS and PANS**

Difficulties identified in the prior sections regarding epidemiology, pathophysiology, and diagnostic testing for PANDAS and PANS also extend to treatment. It is important for the treating physician to recognize that there is scant scientific evidence that the treatment of tics, OCD, presumed PANS or PANS with antibiotics or immunomodulation is effective.

A variety of treatment approaches have been advocated for PANDAS and PANS. Although treatment with psychiatric medications and behavioral interventions are supported by rigorous randomized controlled trials,26 treatment with antibiotics and immunomodulatory interventions is based on less substantiated evidence.

Clinical trials of antibiotics have had small sample sizes and weak effects. Trials involving penicillin and azithromycin20,61 had serious design flaws.26 A pilot study of cefdinir failed to find significant reductions in tic or OCD scale scores.53 The repeated use of acute and long-term antibiotics, as recommended in the consensus PANS guideline,64 represents questionable antibiotic stewardship and, given the high prevalence of chronic psychiatric disorders in childhood, may increase risks for development of antibiotic resistance.

Most of the medical treatment approaches targeting immune modulation are supported by weak or conflicting evidence. A recent comprehensive review by Sigra et al identified 12 treatment studies with published outcome data.60 Eleven of the 12 studies were judged to have a moderate or high risk of bias, including selection bias, performance bias, detection bias, attrition, reporting bias, other bias, or a combination of these issues. The 1 exception was a randomized, controlled clinical trial comparing IVIG with placebo for treatment of PANDAS OCD in 35 children which showed no difference between the IVIG and placebo groups in OCD severity scores or proportion of responders.61 In contrast, follow-up open-label treatment trials reported improvement in all participants regardless of their initial treatment group assignment.

Sixty-five case reports or case series were also included in the review by Sigra et al.60 These described treatment with antibiotics, tonsillectomy/adenoidecotomy, IVIG, plasma exchange, corticosteroids, nonsteroidal anti-inflammatory drugs, anti-CD20 monoclonal antibodies, psychotropic medications, cognitive behavioral therapy, or a combination. Many of these reports are confounded by the use of combination therapy, ascertainment bias, and the fluctuating course of symptoms within PANS/PANDAS diagnoses. Although a detailed review of those studies is beyond the scope of this commentary, using traditional methods of evaluating the strength of evidence, there is currently insufficient data to clearly propose any antibiotic or immune modulating treatment for PANDAS and related disorders.60,65

Our conclusions conflict with those included in 2 of the 3 treatment guidelines published by the PANS Research Consortium in 2017. These proposed guidelines are intended to guide the primary care physician in treating children diagnosed with PANS or PANDAS.66 Unfortunately, these recommendations are based on the unsubstantiated view that PANS has an inflammatory or autoimmune etiology in most cases.66 The 3 published treatment guidelines address: (1) psychiatric and behavioral interventions67; (2) acute or prophylactic treatment with antibiotics62; and (3) treatment with immune-modulating drugs.65 Rather than use standard methodologies for their “evidence based reviews,” the authors produced the guidelines based on “clinical experiences to find agreement on treatment of PANS and PANDAS symptoms.”67 The antibiotic treatment guidelines present strength of evidence, but this is based on antibiotic efficacy for treating streptococcal pharyngitis, not psychiatric symptoms.64 The immunotherapy guidelines are based on “the expert opinions and clinical experiences of the members of the PANS Research Consortium.”68 Thus, none of these guidelines followed standard practices for unbiased systematic review of the evidence.69
We strongly emphasize that it is essential that the treating physician be cognizant of the lack of evidence supporting treatment recommendations when considering whether or not to follow the PANS Research Consortium’s recommendations, especially regarding immunomodulation. For example, the specific treatments recommended include the use of individual or a combination of medications with a high potential for toxicity (e.g., steroids, escalating to IVIG, plasmapheresis, rituximab, or mycophenolate). If accepted and implemented as standard practice, these approaches will likely lead to ineffective, potentially toxic, and expensive acute and long-term treatments. Further, we believe that adoption of these unproven therapies will inhibit well designed and placebo-controlled research that could truly improve patient care for these severely affected children. In our view, a more cautious treatment approach is warranted.

**Treatment Recommendations**

1. First line therapy for children who present with the acute onset of psychiatric symptoms should include those shown to be effective in high quality, randomized-controlled trials, such as cognitive behavioral therapy and selective serotonin uptake inhibitors.

2. In children presenting with psychiatric plus neurologic signs/symptoms who have undergone the suggested diagnostic workup, specific diagnosis-based treatment plus treatment for the neurologic symptoms should be initiated prior to the treatment of psychiatric symptoms, recognizing that these treatments may have some mood stabilizing effects.

3. In children presenting with fulminant, severe, disabling psychiatric-only symptoms who have undergone the suggested diagnostic workup and show clear evidence of an inflammatory or autoimmune etiology, treatment should be based on objective evidence of a specific etiology or an infectious, inflammatory process. In this situation, it is suggested that psychiatrists collaborate with appropriate specialists, such as rheumatologists or neuro-immunologists.

4. In children presenting with fulminant, severe, disabling psychiatric-only symptoms who have undergone the diagnostic workup described above and show no clear evidence of infectious, inflammatory, or autoimmune conditions, the use of antibiotics or immune modulating agents is not recommended. However, clinical research protocols with clear inclusion and exclusion criteria, a treatment sequence, dosages, assessment methods using validated rating scales, criteria for classification as a responder or nonresponder (based on degree and duration of symptom improvement), and plans for relapse therapy are mandatory.

**Concluding Remarks**

We have been personally involved in the evaluation and care of many children with suspected PANDAS or PANS and, thus, can attest to the high level of concern in parents and suffering and impairment for both the affected child and their families. Nevertheless, based on the facts discussed in this article, there remains a pressing need to define better the clinical manifestations, laboratory and neuroimaging findings, therapeutic responses, and clinical course in these disorders. Wherever possible, such investigations should reduce or eliminate reliance on reports of parents and use blinded researchers. We are especially concerned about unsubstantiated reports from clinical researchers who have concluded, despite the lack of rigorous human studies, that there is a prominent role for inflammation in cases with fulminant, severe, disabling psychiatric-only presentations. This assumption often leads to overuse of antibiotics and unwarranted exposure of children to powerful immunomodulatory agents. In conclusion, diagnostic testing should be systematic and nonvalidated immune modulating treatments should be considered only in cases with coexisting neurologic signs/symptoms or in extremely severe cases with psychiatric-only symptoms, and after expert consultation.

References


Submitted for publication Feb 20, 2018; last revision received Mar 25, 2018; accepted Apr 17, 2018.

Reprint requests: Donald L. Gilbert, MD MS, Pediatrics and Neurology, Cincinnati Children’s Hospital Medical Center, 3333 Burnet Ave, ML 2015, Cincinnati, OH 45229-3039. E-mail: donald.gilbert@cchmc.org


学霸图书馆
www.xuebalib.com

本文献由“学霸图书馆-文献云下载”收集自网络，仅供学习交流使用。

学霸图书馆（www.xuebalib.com）是一个“整合众多图书馆数据库资源，
提供一站式文献检索和下载服务”的24小时在线不限IP图书馆。

图书馆致力于便利、促进学习与科研，提供最强文献下载服务。

图书馆导航：

图书馆首页 文献云下载 图书馆入口 外文数据库大全 疑难文献辅助工具