



# PANDAS & PANS Treatment Guidelines (v1.6)

Developed by the UK PANDAS & PANS Physicians Network

November 2018

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# Foreword

The UK guidelines for the treatment of paediatric autoimmune neuropsychiatric syndrome (PANS) and paediatric autoimmune neuropsychiatric disorder associated with streptococcus (PANDAS) were first published in May 2018 following a meeting of the UK PANS & PANDAS physicians network meeting & the UK PANS/PANDAS support group. The guidelines are based on the US treatment guidelines published by the US physicians' network but have been modified to adapt to UK medical practice. GP's are encouraged to start treatment and investigations early. The list of initial treatments and "first line" investigations are outlined on page 4 of this document. Early treatment is likely to improve the outcome of these patients.

The UK PANDAS & PANS Physicians Network Group

October 2018

# Quick reference guide

If you suspect your patient may have PANS or PANDAS, you may use the following guidelines:

- Explain that an initial treatment may begin before the diagnosis is clear and note the importance of both medical and psychological assessments, which may guide further treatment.
- Start treatment with antibiotics upon presentation of definitive symptoms. Do not wait until test results are received before treating.
- If improvement in symptoms, consider that evidence of PANS/PANDAS.
- Treat any infection present upon results of tests and refer to secondary or tertiary care for appropriate medical and psychological assessment and intervention.

	Tests	Treatment
<b>Primary care</b>	<p><b>Recommended First Line Tests:</b>            U+E, LFT, FBC            ASOT            Anti-Dnase B Titres            IgG, IgA, IgM            Anti-Nuclear Antibody (ANA)            Vitamin D<sub>3</sub>            Free T<sub>3</sub>, Free T<sub>4</sub>, TSH</p> <p><b>Recommended Second Line Tests</b>            Mycoplasma Pneumoniae IgG &amp; IgM            Ferritin            ANCA</p>	<p>Initial antimicrobial therapy            Choose one of the following and administer orally for 14 days:</p> <p>Penicillin V            Amoxicillin            Co-amoxiclav            Cephalexin            Clindamycin            Azithromycin            Clarithromycin</p>
<b>Secondary care</b>  CAMHS	<p>Full physical assessment and history.            Repeat ASOT Anti-Dnase B, ANA, TFT, IgG's, metabolic panel,            Cardiac Echo            ECG with QTc if on long term azithromycin            Evaluation for other infections on the basis of history, (may include: EBV, Varicella, HHV6, HSV, enterovirus, GI infections, Kawasaki, Lyme, ENT infections).            Rule out seizure disorders.</p>	<p>As above, also, consider the use of prophylactic therapy.</p> <p>Subsequent treatment as recommended by tertiary provider.</p>
<b>Tertiary &amp; Quaternary care</b>	Multidisciplinary approach established	Recommendations for IVIG to secondary care

Toxicity monitoring & interactions should be considered before starting treatment and with long term therapy. Consider immune suppression and VZV status before starting long term steroids. Monitor QTc interval with long term azithromycin or if giving in combination with drugs known to prolong QTc interval.

# 1.0 Introduction

## 1.0 Background

PANS (and similarly its subset PANDAS) are emerging clinical conditions affecting children. PANDAS is a term used to describe post-streptococcal neuropsychiatric disorder. The diagnosis of PANS has been developed to capture a pattern of acute psychiatric presentation that is considered to be pathognomonic of an as yet undetermined underlying autoimmune process. This term should not be used to describe psychiatric presentations where other diagnoses (such as Sydenham's chorea or the rare paraneoplastic conditions) apply. The ICD classification of this presentation includes both a mental health code for the organically determined syndrome observed (ICD11 6E60-6g) and the code for the underlying disorder, which may be best described with ICD11 code 8E4A0.

PANS is a clinically heterogeneous disorder with a number of aetiologies and disease mechanisms, presenting with: unusually abrupt onset obsessive compulsive disorder or severe eating restrictions, with at least two concomitant cognitive, behavioural, or neurological symptoms. PANDAS presentations are defined by: an acute onset of Obsessive-Compulsive Disorder (OCD) and/or tic symptoms, association with group A streptococcal infection and associated neurological abnormalities. (PPN Definitions) (2) As these syndromes display highly similar presentations, this guideline will address them as a single entity.

## 2.0 Purpose

2.1 This guideline is designed to provide initial practical clinical guidance for the management of infections in PANS and its subset PANDAS. It is intended to provide clarity regarding the early detection and treatment for those children presenting with PANS symptoms in light of the recent suite of guidance produced by the PANDAS/PANS research consortium (PRC).

(3)

## 3.0 Scope

3.1 This procedure is designed to assist primary care GP's in the early detection of PANS, assist paediatrician's and CAMHS evaluation and consideration as a differential diagnosis, and for neurology and immunology; recommendations for a

comprehensive treatment pathway. A multi-disciplinary approach drawing on multiple disciplines will be key in resolving symptoms, improving overall health and overcoming barriers in both health and social care.

## 4.0 Course of action

**4.1** The onset of PANS or PANDAS symptoms are closely associated with infections. Both the initial onset and subsequent exacerbations are usually incited by a variety of recognisable infections. The most common infection sites are found in the upper respiratory tract. The specific microbe most commonly recognised has been GAS. *Mycoplasma pneumoniae*, as well as influenza and other common viruses have also been noted, although they are not as well described. The variety and relative frequency of non-streptococcal triggers of onset and exacerbation strongly suggests that nonspecific immune activation mechanisms may also contribute importantly to symptom development (7)

**4.2** The diagnosis of PANS relies on the recognition of a highly unusual pattern of 'abrupt, dramatic' behavioural or psychiatric presentation. It should be borne in mind that psychiatric symptoms may present abruptly and dramatically as a result of a child experiencing an acute event that may not be immediately apparent from the history (e.g., a choking episode whilst unsupervised may cause food refusal). Atypical presentations are more likely to occur in children with developmental vulnerabilities, disorders or delays and an acute stress reaction in an unusual form may be the first indicator of previously unrecognised developmental pathology. Children with OCD may mask obsessive-compulsive symptoms until the condition is quite advanced at which point an "abrupt presentation" may represent an uncovering of symptoms rather than an acute onset of OCD.

A diagnosis of PANS should be made only when "symptoms are not better explained by a known neurological or medical disorder," such as Sydenham's chorea, autoimmune encephalitis, neuropsychiatric lupus, central nervous system vasculitis, and others. By definition, PANS is always a diagnosis of exclusion. Clinicians are encouraged to begin with a broad differential diagnosis and narrow it to PANS only after eliminating all other possibilities. (4)

PANS is divided in to three specific presentations:

- new onset
- relapsing remitting

chronic static, and chronic progressive.

**4.3** PANS criteria define a broad spectrum of neuropsychiatric conditions, the syndrome is presumed to result from a variety of disease mechanisms and to have multiple aetiologies, ranging from psychological trauma or underlying neurological, endocrine, and metabolic disorders to post infectious autoimmune and neuroinflammatory disorders, such as paediatric autoimmune neuropsychiatric disorder associated with streptococcal infections (PANDAS), cerebral vasculitis, neuropsychiatric lupus, and others. In cohorts of well-characterized PANS patients from specialist clinics, evidence of post infectious autoimmunity and/or neuroinflammation is found in more than 80% of cases. However, there is inadequate information available on the incidence and course of PANS type presentations in community-based studies. Thus, treatment of PANS depends on a decision that intervention in the presenting case will be more helpful than non-intervention. Where treatment is to be taken forward there are four complementary modes of intervention:

1. Treating the symptoms with supportive interventions, psychotherapies (particularly cognitive behavioural therapy), and psychoactive medications.
2. Reducing/removing the source of the inflammation with antimicrobial interventions.
3. Treating disturbances of the immune system with immunomodulatory and/or anti-inflammatory therapies.
4. Support for school and families - education and psychosocial support

## 4.4 Diagnostic criteria

### 4.41 Pans

1. Abrupt, dramatic onset of obsessive-compulsive disorder or severely restricted food intake
  2. Concurrent presence of additional neuropsychiatric symptoms, (with similarly severe and acute onset), from at least two of the following seven categories:
    - I. Anxiety
    - II. Emotional lability and/or depression
    - III. Irritability, aggression, and/or severely oppositional behaviours
    - IV. Behavioural (developmental) regression
    - V. Deterioration in school performance (related to attention deficit/hyperactivity disorder [ADHD]-like symptoms, memory deficits, cognitive changes)
    - VI. Sensory or motor abnormalities
    - VII. Somatic signs and symptoms, including sleep disturbances, enuresis, or urinary frequency
- Symptoms are not better explained by a known neurologic, psychiatric or medical disorder, such as Sydenham chorea (SC).

### 4.42 PANDAS

1. Presence of OCD and/or tics, particularly multiple, complex or unusual tics
2. Age Requirement (Symptoms of the disorder first become evident between 3 years of age and puberty)
3. Acute onset and episodic (relapsing-remitting) course
4. Association with Group A Streptococcal (GAS) infection
5. Association with Neurological Abnormalities

### 4.43 Differential diagnosis

1. Obsessive compulsive disorder
2. Anorexia nervosa
3. Avoidant/restrictive food intake disorder (ARFID)
4. Tourette syndrome
5. Transient tic disorder
6. Bipolar disorder
7. Sydenham chorea
8. Autoimmune encephalitis
9. Systemic autoimmune disease
10. Wilson's disease
11. Early onset psychosis
12. Autism

## 4.5 Diagnostic requirements

For a patient to be diagnosed with PANS, they must have the following:

1) An abrupt, acute, dramatic onset (within 24 – 48 hours) of obsessive-compulsive disorder (OCD), severely restricted food intake or tics/involuntary movements.

a) OCD may include:

Contamination obsessions and compulsions

Obsessions that harm will come to others and/or related compulsions

Sexual or religious obsessions

Repeating compulsions

Symmetry and exactness obsessions

Ordering/arranging compulsions

Counting compulsions

Checking obsessions or compulsions

Excessive reassurance seeking

Need to touch, tap or rub

Intrusive images, words, music or nonsense sounds

Ritualised eating behaviours

b) Severely restricted food intake may be related to contamination fears, obsessional fears of choking, or other obsessional fears including a new obsession with body image or weight

2) Concurrent presence of additional neuropsychiatric symptoms with similarly severe and acute onset from at least 2 of the following categories:

a) Anxiety (heightened anxiety, separation anxiety, irrational fears, panic episodes)

b) Emotional lability and/or depression

c) Irritability, Aggression, and/or Severe Oppositional Behaviours

d) Behavioural (Developmental) Regression (increase in temper tantrums, loss of age-appropriate language, clingy behaviour not related to anxiety). NOTE: If the separation anxiety is a manifestation of behavioural regression, it should not also be counted under anxiety.

e) Sudden Deterioration in School Performance (due to difficulties with memory, concentration, hyperactivity, impulsivity, new deficits of visuospatial skills).

- f) Motor or Sensory Abnormalities (dysgraphia, clumsiness, tics, new sensory sensitivities to light, noises, smells, tastes or textures)
  - g) Somatic Signs and Symptoms, including Sleep Disturbances, Enuresis or Urinary Frequency.
- 3) Symptoms are not better explained by a known neurologic or medical disorder (such as Sydenham chorea, systemic lupus erythematosus, Tourette disorder, or others)

## 4.6 Non-Group A Streptococcus (GAS) Infections

### 4.6.1 Upper respiratory tract infections

The onset and exacerbations of PANS are very frequently associated with common upper respiratory tract infections, the specific causative organism is rarely identified. Acute rhinosinusitis, otitis media, and acute or chronic sinusitis are often anecdotally observed with initial onset or exacerbations of PANS. Sinusitis is one of the more common infections inciting PANS. Guidelines for the appropriate management of acute and chronic rhinosinusitis should be followed. Although over-diagnosis should be avoided, close attention to those meeting diagnostic criteria for acute or chronic sinusitis is encouraged. When antimicrobial therapy is indicated, **amoxicillin-clavulanate** is generally preferred for acute sinusitis in children with moderate or severe PANS or PANDAS, and for those who have recently been treated with other antibiotics. For frequently recurrent or chronic sinusitis, specialist referral should be considered. Therapies that avoid antimicrobials should be used initially whenever possible.

### 4.6.2 Influenza

Influenza has often been documented anecdotally at both initial onset and exacerbations of PANS. The clinical diagnosis and treatment of influenza is considered appropriate without laboratory testing for anyone with compatible symptoms during active community influenza epidemics; current guidelines for diagnosis and treatment should be followed. In adults, antiviral treatment with **either oral oseltamivir or inhaled zanamivir** is most effective within the first 48 hours of illness. However, the initiation of antiviral treatment should not be withheld beyond that 48-hour window for children, who may excrete the virus for longer periods than adults

### 4.6.3 *Mycoplasma pneumoniae*

*M. pneumoniae* is a suspected, but not yet proven, trigger of PANS. Most *M. pneumoniae* infections are indistinguishable from common viral upper respiratory tract infection. Although cough is a common symptom in the acute infection, the characteristic persistent cough syndrome, often presenting sequentially in multiple family members, is less common.

A definitive diagnosis is best made using a combination of mycoplasma serology and PCR. Mycoplasma serology (IgG & IgM) should be performed acutely and in convalescence (2 weeks after the acute illness). PCR testing may be performed on nasopharyngeal or pharyngeal secretions during the acute illness.

A rising IgG titre, which requires acute and convalescent sera, may also be diagnostic. A single elevated IgG titre with neither an IgM response nor a positive PCR is not indicative of current infection, combined molecular diagnosis and serologic testing together provide the most accurate diagnosis.

*M. pneumoniae*, diagnosed serologically with IgM antibody and IgG serologic titre rises or polymerase chain reaction, has been linked to several neurologic syndromes, including encephalitis, acute disseminated encephalomyelitis, transverse myelitis, peripheral nerve palsy, cerebellar disease, and myasthenia gravis. Among the neurologic syndromes associated with PCR-documented *M. pneumoniae* infection, cases could be separated clinically into active infection and post infectious syndromes. These occurred, respectively, within 7 days or 7 days or longer after the onset of prodromal respiratory. Separately, Tourette's syndrome exacerbations have also been linked to *M. pneumoniae* and *M. pneumoniae* antibodies were demonstrated far more commonly in Tourette syndrome patients than in controls. These findings make it likely that Mycoplasma might also induce PANS, although well-documented cases have yet to be described. *M. pneumoniae* pneumonia **can be treated** with **macrolides**.

#### 4.6.4 Lyme Borreliosis

OCD sometimes occurs in patients with Lyme disease. Other PANS-like neuropsychiatric and cognitive symptoms of the post-Lyme disease syndrome include distractibility, poor schoolwork, irritability, depression, insomnia, and sensitivity to light and/or sound. Oppositional behaviour, anxiety disorders, and ADHD are also reported. In addition, a case report described a child with Lyme disease who presented with acute onset Tourette syndrome that resolved with antibiotic treatment. The diagnosis of Lyme disease requires positive screening serology that must be confirmed by Western blot testing. Expert input (Lyme national reference laboratory, Porton Down) is required to interpret Lyme serology & western blots.

#### 4.6.5 Other inciting infections

A number of additional infections, including **gastrointestinal infections, dental infection, herpes simplex, varicella, Epstein-Barr virus, enterovirus**, and others, including **Kawasaki disease**, have been mentioned in association with the onset or exacerbation of PANS symptoms in a small number of cases. Given their number and variety, it seems likely that many apparent infectious triggers may activate symptoms through nonspecific immune activation mechanisms. All intercurrent infections should be considered and managed on an individual basis, according to existing guidelines. In some instances, onset and exacerbations may occur in the absence of any recognizable infection, suggesting that additional disease mechanisms may be involved.

#### 4.6.6 Treatment of GAS in children with PANS or PANDAS

With a new diagnosis of PANS or PANDAS it is recommended to **provide an initial course of antimicrobial treatment for acute streptococcal infection, regardless of whether or not GAS is identified at the time of diagnosis** (similar to recommendations for the initial management of rheumatic fever). Although data from controlled clinical trials are lacking, aggressive diagnosis and treatment of GAS infection seems prudent as a means of mitigating risk for neuronal injury. In practice, the majority of children with recent-onset PANDAS experience a reduction in neuropsychiatric symptoms within days or weeks after antimicrobial treatment active against acute GAS infection.

#### 4.6.7 Antimicrobial Management of Non-streptococcal PANS

Among PANS patients with no evidence for a GAS initiation, it has been our practice to **provide an initial course of antimicrobial treatment as for acute streptococcal infection as described earlier, even though GAS is not identified at the time of diagnosis, because negative studies do not absolutely rule out a hidden source of infection, as described earlier**. This is similar to the recommendations for the initial management of rheumatic fever however, in cases without a clear link to GAS infection, long-term antimicrobial prophylaxis is not currently recommended. The risk of symptom exacerbations may be independent of GAS infections and antibiotic prophylaxis would offer no protection against future recurrences. For these patients, close monitoring and early treatment for GAS infection in the patient and family members is advised (Table 4). GAS cultures should be obtained during symptom flares. Positive cultures should be managed as described earlier, under “Primary Antimicrobial Treatment for Streptococcal Infections.” Repeated GAS-incited flares would change the diagnosis from non-streptococcal PANS to PANDAS.

#### 4.6.8 Duration of antimicrobial prophylaxis.

A recommendation for the duration of prophylaxis will depend on an emerging experience with late relapses during prolonged follow-up of children and young adults with PANDAS. Anecdotal experiences with late relapses suggest that the preventive regimen should continue for at least a year or two after symptoms have abated. For children in remission, some clinicians optionally suspend antibiotic prophylaxis during the summer months when GAS exposures are expected to be less common. Prophylaxis is resumed in the fall when the child returns to school. If the child remains symptom free during the academic year, antibiotics may be discontinued completely the following summer. Continuing prophylaxis to age 18 in the most severe cases seems reasonable, but should be individualised, based on the frequency and severity of neuropsychiatric exacerbations, time since previous exacerbation, and risk of GAS exposure (e.g., crowded living conditions, younger siblings at home, or GAS outbreaks at school)

#### 4.6.9 Vitamin D

Currently there is indirect evidence to support optimization of Vitamin D levels among children with infection triggered neuropsychiatric symptoms. The optimum level of serum 25-hydroxy vitamin D level has not been established. On the basis of this limited evidence, **we currently treat PANS patients with vitamin D<sub>3</sub> as needed to maintain serum 25-hydroxy vitamin D level above 30 ng/mL (75 nmol/L)**. This can usually be accomplished with a combination of a standard childhood multivitamin plus a vitamin D<sub>3</sub> supplement of 1000 units daily for children 5 years of age or less or

2000 units daily for those 6 years or older, doses well within the recommended dose in the British National Formulary. Serum 25-OH vitamin D level may be monitored every 3–12 months, depending on adequacy of levels. It is notable that wintertime, excess body fat, and black or Asian race are significant risk factors for vitamin D insufficiency. Omega-3, fish oils, and cod liver oil may contain substantial amounts of vitamin D but their use can lead to hypervitaminosis.

## Management of specific PANS PANDAS Symptoms

### 4.7 Psychiatric and Behavioural Interventions

As the diagnosis is explained to them, children and families affected by PANS/PANDAS will require a clear account of the need for both physical and psychological treatments. For example, Cognitive Behavioural Therapy (CBT) is used routinely with many patients with PANS/PANDAS. It is an important part of the treatment tool kit for patients with many conditions and should be offered to patients where appropriate.

It is very helpful for children, families and teachers to have written information in an age appropriate format to help them to understand the neuropsychiatric origins of psychological difficulties and psychiatric disorders in PANS. Decisions on treatment should be made in the context of a full assessment that will include consideration of the supports that a child may require at home and in the classroom. A multi-disciplinary approach, informed by a holistic assessment and a shared understanding of the implications of the diagnosis, will reduce the risk of misunderstanding as a child with symptoms that fluctuate with immune stimuli can be particularly challenging to systems. Educational remediation and other supportive interventions (e.g. to address attentional, visuo-spatial and sensori-motor difficulties) may reduce stress levels and diminish the need for more specific treatments.

Although symptoms may improve as a result of medical interventions influencing the auto-immune process of the underlying disease the established therapeutic approaches of mainstream child and adolescent mental health services (CAMHS) can make an important contribution in PANS. Psychological and psychiatric interventions will be best managed in a setting that allows good communication between all clinicians involved in PANS treatment. The development of specialist Neuropsychiatry and CAMHS Liaison services can facilitate good care provision.

Thienemann and colleagues (JCAP 2017) provide a summary of psychiatric and behavioural interventions with an evidence base of effectiveness for psychiatric symptoms seen in PANS and PANDAS presentations.

#### **4.7.1 OCD symptoms**

Cognitive behavioural therapy (CBT) (specifically exposure/response prevention [ERP]) and minimizing family accommodation to OCD behaviours have been repeatedly shown to be among the most effective interventions for paediatric OCD (Barton & Heyman 2016, OCD 2004, Lebowitz et al. 2011). While large-scale studies of these interventions in PANS/PANDAS have not been conducted, pilot studies suggest behavioural therapies are still highly effective in treating the OCD symptoms of children with PANS/PANDAS (Storch et al. 2006)

Selective serotonin reuptake inhibitors (SSRI) are the preferred medication for treatment of OCD in PANS, based on multiple placebo-controlled clinical trials (Geller 2003; Grados and Riddle 2001; Pediatric OCD Treatment Study Team 2004, 2011) (Gabbay and Coffey 2003; Coffey and Wieland 2007). Fluoxetine, sertraline, fluvoxamine, and clomipramine are approved for treating paediatric OCD and have the most evidence to support their use (ibid). Clinical experience suggests both that SSRI's may be helpful and that using a low dose and slow titration minimizes the risk of side effects. Upward titrations should be adjusted no faster than 2-week intervals.

#### **4.7.2 Restriction of food or fluid intake**

The sudden onset of reduced and restricted food intake fulfils the first criterion for PANS, even in the absence of more typical OCD symptoms (Swedo et al. 2012; Toufexis et al. 2015). Paediatric management should be mindful of the high levels of anxiety that can be associated with restricted food/fluid intake in childhood. Medical evaluation should be done to rule out other medical disorders (e.g., eosinophilic esophagitis, structural or neurological causes of dysphagia, and nausea) and assess for medical instability related to restricted intake of food and/or fluids. For those with severely limited oral intake, assessment should include checking orthostatic vital signs, ECG, and electrolytes, including phosphate and magnesium and monitoring for refeeding syndrome. Hospitalisation may be required for children who are medically unstable because of restricted intake of food and/or fluids (Chang et al. 2015; Golden et al. 2015).

For patients with high anxiety and compulsive behaviours, an exposure and response prevention approach may prove helpful. This involves gradual exposure to foods or situations that cause anxiety or fear, within a support framework that encourages incremental progress toward expanding diet and increasing intake. Occupational therapy interventions that include targeting posture, breathing, and relaxation may be helpful adjuncts, especially for patients who fear of choking or vomiting. When the problems with eating involve obsessions or compulsions, a psychopharmacological approach similar to that used for OCD may help.

Many PANS patients experience ongoing eating abnormalities and require interventions used in other eating disorder treatments to directly target other factors contributing to the eating restrictions (Lock 2015). The evidence base specifies Family-Based Treatment (FBT) as a treatment for adolescent anorexia nervosa (AN) and CBT as a treatment for bulimia nervosa (BN). These treatments can be useful in PANS presentations that are similar to either. The psychopharmacological evidence base for AN and BN should be considered in cases where non-pharmacological modalities are not sufficient in aiding recovery.

#### **4.7.3 Tics**

Based on preliminary studies, as many as 70% of PANS/PANDAS patients either present with or develop tics (Murphy et al. 2015; Swedo et al. 2015). PANS patients with tics have been reported to be more severely affected at home and at school, with poorer school performance, handwriting, visual-spatial memory, and self-esteem (Murphy et al. 2015). Some PANS/PANDAS patients' tics first present with complex motor and vocal tics, rather than presenting with a progression from simple tics to complex motor and phonic tics that is typical of Tourette syndrome (Tucker et al. 1996).

In most cases, psycho-education for the patient and the children and adults around them affected by tics will be a sufficient intervention. Families should be advised to make use of relevant information available on-line for patients with Tourette Syndrome (eg. [https://www.tourettes-action.org.uk/storage/downloads/1374586646\\_Tic-tips---managing-your-TS.pdf](https://www.tourettes-action.org.uk/storage/downloads/1374586646_Tic-tips---managing-your-TS.pdf)).

Tics are not considered a treatment target unless they cause pain, significant interference in function, or create unresolvable embarrassment or teasing. Comprehensive behavioural intervention for tics (CBIT), habit reversal training (HRT), and cautious monitored pharmacotherapy are the treatments of choice (Piacentini et al. 2010; Murphy et al. 2013).

In HRT, children learn to be aware of their tics and their antecedent premonitory urge. They help design a "competing response," which is a motor behaviour that makes doing the tic impossible. When children practice this, resisting or suppressing the tic, as in response prevention for OCD, they stop reinforcing the urge and the urge frequency diminishes. Examples of competing responses include staring or looking up to extinguish a blinking tic and slow, rhythmic diaphragmatic breathing for vocal tics. Relaxation training, analysing, and addressing situations that worsen tics and family reinforcement of applying HRT strategies comprise other elements of CBIT. Exposure with Response Prevention may also be effective intervention for severe tics (Wile and Pringsheim 2013). Many clinicians consider the alpha-2 adrenergic agonists clonidine and guanfacine to be the first-line pharmacologic intervention for tics. However, a recent meta-analysis has suggested that alpha-2 agonists may have minimal benefit in tic patients without ADHD (Weisman et al. 2013). Antipsychotics may be indicated for severe tics, although their use should be restricted for as short a duration as necessary. Weight gain is a

common complication of antipsychotic treatment of tics and this risk should be considered in the context of other symptoms. Aripiprazole and risperidone are antipsychotics that are commonly and successfully used for the treatment of Tourette Syndrome (Budman 2014; Weisman et al. 2013). An ECG should be obtained before and during treatment with antipsychotic medications to rule out a prolonged QTc.

#### **4.7.4 Irritability**

Irritability, aggression, and unprovoked violent behaviours are among the most troubling symptoms of PANS. Parents frequently report mood lability and impulsive aggression in children with PANS/PANDAS. Sensory sensitivities, irritability, fatigue, anxiety, and cognitive changes may cause the child to adapt poorly to environmental changes, making them vulnerable to aggressive behaviours.

Environmental interventions may decrease the frequency of aggressive behaviour. Modulating stimulation, minimising demands and promoting adequate nutrition & sleep may each help. In the moment, distraction may be one of the most effective tools, for example, the use of favourite toys (that are unlikely to be used as weapons), singing, dancing, television, food, crying, and acting silly may re-engage the child's "cortex" and truncate the episode. Designing a home plan for calling for help and remaining non-punitive with the child is important.

As a general rule, medication for irritable behaviour should only be considered after there has been an evaluation of the impact of environmental and psychotherapeutic options. For irritability related to anxiety, sedative antihistamines or benzodiazepines are currently the most commonly used medication to help de-escalate acute situations but treatment of the underlying anxiety should be the priority. Antipsychotic medications or mood stabilisers can reduce the frequency and intensity of aggressive behaviours. After a careful evaluation of the balance of risks and benefits, short term treatment with antipsychotics may be indicated for children whose aggressive behaviour risks harming themselves or others. (Correll & Blader, 2015)

#### **4.7.5 Anxiety/Separation Anxiety**

Separation anxiety frequently interferes with PANS children's comfort and family function, restricting both the child's and parent's activity. Fortunately, with treatment of the underlying causes of PANS, the suffering and burden may be short-lived. If symptoms are resolving, accommodating the anxiety for a short time may be tolerable. As soon as possible, the child should go back to his bedroom and classroom. When separation anxiety persists, the parent may become exhausted and require respite, so efforts should be made to integrate other attachment figures into care. Parents may also benefit from behavioural interventions for caregivers, if family accommodation of anxiety is part of the clinical picture (Jones et al. 2015; Norman et al. 2015).

CBT is helpful for both generalized and separation anxiety and may involve the cognitive skills of reappraisal and problem solving. Children learn to assess the probability and the likely severity of feared events and generate backup plans should the problem arise. For example, a child might work through the probability that no one would pick him up from school, articulate realistic outcomes of being left at school, and list possible actions the child might take if left. The child might role-play those actions and, with parents, and design a gradual exposure plan with rewards for following through. Notifying the school of the issue and identifying “safe” individuals and ways to access them may aid in this endeavour.

Should pharmacotherapy be necessary, an SSRI like sertraline (in accordance with NICE guidelines) could be used.

#### **4.7.6 ADHD**

Some ADHD symptoms first recognised within a diagnosis of PANS/PANDAS may have pre-existed and met independently criteria for a diagnosis of ADHD. Hyperactivity within PANS/PANDAS may reflect anxiety, complex tic sequences, restlessness exacerbated by cognitive and physical fatigue, sensory overload, pain or urge to urinate, or agitated catatonia (Elia et al 2005). Inattention may reflect sleep deprivation, mood lability, intrusive thoughts of OCD or the cognitive “fog” some PANS/PANDAS patients describe. Academic frustrations may contribute to impulsivity and disruptive behaviours.

If the treatment team considers symptoms consistent with ADHD, management of ADHD symptoms in the context of PANS/PANDAS is based on our understanding of ADHD management in general. Typical classroom accommodations, possibly with pharmacotherapy, may help the child tolerate the classroom and help the classroom tolerate the child. Useful changes have included preferential seating (front and side), permission to take breaks without interrupting the class, extended time for tests, and resource assistance for math and executive function support and training.

Stimulants (methylphenidate and amphetamine compounds), the first-line medication for idiopathic ADHD, may be tolerated and helpful. Methylphenidate may be preferable to amphetamine preparations as they may have a smaller risk of exacerbating tics or compulsive behaviours in children with non-PANS/PANDAS ADHD (Borcherding 1990; Castellanos 1997; Pringsheim 2011). Atomoxetine, a second line treatment for ADHD symptoms, appears to possess anti-inflammatory properties through modulation of noradrenaline signaling, and in so doing reduces the expression of proinflammatory cytokines, downregulates cell adhesion molecules important in leukocyte infiltration, and strengthens the blood–brain barrier (O’Sullivan et al 2010). Alpha-2 adrenergic agonists, guanfacine, and clonidine can sometimes be less helpful for ADHD symptoms alone but may be the “treatment of choice” for PANS/PANDAS hyperactivity and impulsivity because they may also produce improvements in tics, anxiety, and sleep disruptions.

#### **4.7.7 Depression**

Dysphoria and depressive symptoms are common in PANS/ PANDAS, particularly during later stages of the illness (Frankovich et al. 2015; Murphy et al. 2015; Swedo et al. 2015). For mild mood symptoms, supportive interventions, with the child and/or their parents or with the child and family together, may be sufficient. However, children with more severe depression, suicidal ideation, or self-injurious behaviour, require more intensive treatment. Psychotherapy or psychotherapy combined with an SSRI is the standard of care for children and young people with major depressive episodes (Hopkins et al. 2015). Evidence-based psychotherapies for depression including interpersonal therapy (IPT) and CBT may be particularly useful for children with PANS too.

In Interpersonal Therapy for Adolescents, the therapist, family, and school recognize that the child is “sick” and unable to function at usual capacity (Mufson et al. 2004). In CBT for depression, planning pleasant (and for PANS patients, probably low-key) experiences comprises part of the behavioural element. When depressive symptoms are sustained and/or impairing, clinical experience suggests treatment with an SSRI may be helpful. The medications are started at a low dose, and parents are advised to watch for emergent adverse effects, particularly worsening mood, irritability, agitation, hyperactivity, suicidal thoughts, or sleeplessness.

When a child’s symptoms are consistent with bipolar affective disorder, medications for this indication, given with the same caution, are likely to be necessary. In families with a history of bipolar disorder, antidepressant medications must be used with extreme caution because of the increased risk of precipitating mania.

#### **4.7.8 Psychosis**

At least 25% of children with PANS/PANDAS report auditory, olfactory or visual hallucinations distinct from OCD intrusive images (Frankovich et al. 2015). Information about the nature of these experiences may be sufficient to support children with transient symptoms. If symptoms are disturbing or impairing, then antipsychotic medications may be warranted, despite their associated adverse effects. Medication choice should consider minimizing adverse effects and being aware of interactions with other medications. For chronic psychotic symptoms, diagnosis and ongoing treatment need to be reassessed.

## 4.8 General Strategies for Management of Paediatric Acute-Onset Neuropsychiatric Syndrome Based on Disease Trajectory

If following assessment by a multidisciplinary team, treatment for an underlying physical cause or immunomodulatory therapy in a child with suspected PANS/PANDAS is decided alongside psychiatric interventions detailed above, the following tables would apply. The recommendations should be approached in a logical systematic manner according to the clinical presentation:

**Table 1**

Disease Trajectory	Recommendation
<b>New-onset or acute flare</b>	<ol style="list-style-type: none"> <li>1. Work-up infections and other causes of acute neuropsychiatric deteriorations per guidelines <sup>1</sup>*a</li> <li>2. Refer for CBT/psychiatric assessment and provide other supportive therapies <sup>2</sup></li> <li>3. Consider early use of corticosteroids (oral bursts or IV pulses) to abort or shorten flares (Tables 2 and 3).</li> <li>4. Consider high-dose IVIG (Tables 2 and 4).</li> </ol>
<b>Relapsing-remitting</b>	<p>Include all recommendations for “new-onset or acute flare” plus;</p> <ol style="list-style-type: none"> <li>1. Evaluate for possibility of recurrent infections/exposures triggering flares.</li> <li>2. If GAS infection is a frequent trigger for relapses, evaluate/treat close contacts and consider prophylaxis according to guidelines <sup>3</sup></li> <li>3. Keep in mind that most flares are viral triggers. See (2) – (4) above for treatment of each flare.</li> <li>4. Evaluate immune system competency: pursue immunodeficiency work-up if patient has recurrent sinopulmonary disease or fevers per guidelines <sup>4</sup></li> </ol>
<b>Chronic-static or chronic progressive</b>	<p>Include all recommendations for “new-onset or acute flare” plus;</p> <ol style="list-style-type: none"> <li>1. Pursue immunomodulatory therapies according to symptom categories below: <ul style="list-style-type: none"> <li><b>Mild-to-moderate neuropsychiatric symptoms:</b> <ol style="list-style-type: none"> <li>I.NSAIDs (Table 3).</li> <li>II.Oral corticosteroid burst (Table 3) to see whether baseline improves. Caution: use of combination NSAIDs + corticosteroids may result in gastritis; but these medications can be used safely in tandem.</li> </ol> </li> <li><b>Mild-to-moderate neuropsychiatric symptoms with no response to NSAIDs and/or short burst of corticosteroids:</b> (Repeat) oral prednisone – prolonged taper (Table 3). Pulse corticosteroids (oral dexamethasone or IV methylprednisolone) (Table 3).</li> <li><b>Moderate-to-severe neuropsychiatric symptoms:</b> Oral prednisone–taper or pulse corticosteroids (Table 3). High-dose IVIG or other induction steroid-sparing agent (Table 4).</li> <li><b>Severe-to-extreme neuropsychiatric symptoms:</b> Refer to subspecialists for further evaluation for AE, NPSLE, CNS vasculitis, and consideration of using established (published and institutionally based) treatment protocols. Consider high-dose IV corticosteroids and/or other immunotherapies (Tables 3 and 4).</li> </ul> </li> </ol>

a\* If the patient meets criteria for another brain inflammatory disease, follow the corresponding treatment guidelines (when published guidelines are not available, use institutionally based guidelines). immunotherapy, or other aggressive immunomodulation regimens should be managed by clinicians with experience using these therapies, either as the

primary prescriber or in close consultation with those managing the patient. There are no reported clinical trials and only limited clinical experience to support these approaches. This is not a definitive treatment algorithm; rather, it is a framework to aid in clinical decision making. Before initiating any of the therapies, clinicians must consider the risk/benefit ratio for their individual patients and provide careful/informed counselling about risk of side effects.

AE, autoimmune encephalitis; CBT, cognitive behavioural therapy; CNS, central nervous system; GAS, group A Streptococcus; IV, intravenous; IVIG, intravenous immunoglobulins; NPSLE, neuropsychiatric systemic lupus erythematosus; NSAIDs, nonsteroidal anti-inflammatory drugs; PANS, paediatric acute-onset neuropsychiatric syndrome; TPE, therapeutic plasma exchange

## 4.9 Considerations Before Pursuing Immunomodulatory Therapy

Table 2

Further work-up	Rationales
Lumbar puncture, EEG, MRI. (if feasible)	It is imperative to rule out more specific disorders before starting immunomodulatory therapy (AE, CNS vasculitis, NPSLE, ADEM, infectious encephalitis, etc.) (Graus et al. 2016). Corticosteroids may mask/treat another brain inflammatory disease and impede accurate diagnosis of another disorder. Rule out seizure disorders (i.e., ESES) and metabolic/genetic disorders. Follow established guidelines (institutionally based or published) for evaluation of these other brain diseases. If mild-to-moderate disease, no memory impairment or encephalopathy, the clinician may choose to defer the LP.
Screen for: (1) Tuberculosis: Purified Protein Derivative (PPD) skin test or interferon-gamma release assay such as Quantiferon (R) or T spot assay (R); see age-appropriate guidelines. Corticosteroids may reactivate latent infection.	Consider other tropical diseases according to the patients travel history.
Hepatitis B serology	If patient has already had IVIG and has positive hepatitis B serology, check hepatitis B PCR
Ensure that the patient's environment (family and/or medical setting) is equipped to handle escalation in psychiatric symptoms.	Many patients have transient worsening of psychiatric symptoms after corticosteroid burst/pulse and occasionally after initiation of other immunomodulators. If patient has rage/violence, life threatening impulsivity, mood instability, suicidality, etc., ensure that the environment can maintain safety in case the patient has escalated behaviour.

ADEM, acute disseminated encephalomyelitis; AE, autoimmune encephalitis; CNS, central nervous system; EEG, electroencephalography; ESES, electrical status epilepticus in sleep; IgA, immunoglobulin A; IVIG, intravenous immunoglobulins; LP, lumbar puncture, MRI, magnetic resonance imaging; NPSLE, neuropsychiatric systemic lupus erythematosus; PCR, polymerase chain reaction; PPD, purified protein derivative.

## 4.10 General Approach to Using Induction Corticosteroids and/or Nonsteroidal Anti-Inflammatory Drug Therapies in PANS/PANDAS

Table 3

	Mild	Moderate	Severe
<p><b>Early in flare or early in initial presentation (&lt;14 days).</b></p> <p><i>Early application of corticosteroids (once infection is ruled out) and NSAIDs may abort or limit duration of disease flares</i></p>	<p>(A) Refer to CBT and supportive therapy. or (B) NSAIDs+(A) (5-day course). or <i>if no improvement or deteriorating baseline then (C)</i></p>	<p>(A) Refer to CBT and supportive therapy. (B) prednisone 1–2 mg/kg/day · 5 days+(A). or (C) oral dexamethasone pulse (20 mg/m<sup>2</sup> divided twice daily for 3 days) +(A).  or (D) IV MP pulse · 1 (30 mg/kg/dose) +(A)</p>	<p>(A) Refer to CBT and supportive therapy. or (B) oral dexamethasone pulse (20 mg/m<sup>2</sup> divided twice daily for 3 days) alone or in combination with adjunct therapy (Table 4) +(A). (C) IV MP one to three consecutive daily pulses (30 mg/kg/dose/day · 3 days) alone or in combination with adjunct therapy (Table 4) +(A).</p>
<p><b>Late in flare (2–4 weeks).</b></p> <p><b>Very delayed care (&gt;4 weeks).</b></p> <p><i>Application of corticosteroids late into the disease often requires higher dosing and/or more prolonged tapers. Steroid bursts may be followed by NSAIDs, with caution.</i></p>	<p>A) Refer to CBT and supportive therapy. or  (B) NSAIDs+A (5-day course).  Or  (C) prednisone 1–2 mg/Kgs/day · 5 days+(A). If no response, re-evaluate for underlying infection per guidelines. If no infection and baseline worsening, go to next column.</p>	<p>Same as above box, except: (B) consider adding a 1-month prednisolone taper or oral prednisolone burst. The mentioned pulse therapy approaches do not need tapers.  (A) Refer to CBT and supportive therapy. or (B) prednisone 1–2 mg/kg/day x 5 days+(A). Consider adding a 1–2-month prednisone taper. or (C) oral dexamethasone pulse (20 mg/m<sup>2</sup> divided twice daily for 3 days) +(A). or (D) IV MP one to three consecutive daily pulses (30 mg/kg/dose/day 3 days) +(A). patient may need weekly or monthly pulses to maintain effect. Add steroid-sparing agent (Table 4) if patient is responsive to steroids but does not hold.</p>	<p>A) Refer to CBT and supportive therapy. or (B) oral dexamethasone pulse (20 mg/m<sup>2</sup> divided twice daily for 3 days) alone or in combination with steroid sparing agent (Table 4)+(A). Long-standing disease will likely need more persistent corticosteroids.  (C). IV MP one to five consecutive daily pulses (30 mg/kg/dose/day for up to 5 days) alone or in combination with adjunct therapy (Table 4). Consider weekly IV MP pulses for up to 6 weeks (if tolerated) +(A).</p>

Optimal dosing approaches and utilization of adjunct immunomodulation have not been determined for PANS, but the approaches outlined in this table serve as a starting point for clinicians and academicians who treat patients with PANS and who are planning trials. Important steroid warning: Most patients have transient worsening of psychiatric symptoms while on corticosteroids. If patient has rage/violence, life threatening impulsivity, mood instability, suicidality, etc. and caregivers (including medical personnel) are unable to manage potentiation of these behaviours, give corticosteroids in psychiatric unit or medical-psychiatric unit or bypass corticosteroids and go straight to IVIG or another steroid-sparing agent (Table 4). If no response to initial corticosteroid burst/pulse or relapse after steroid burst/pulse, consider reassessing for underlying infection per guidelines (Chang et al. 2015; Cooperstock et al. 2017) with attention to the possibility of sinusitis or close contact with GAS or asymptomatic acquisition of GAS. If no infection, repeat steroid bursts/pulses and/or give corticosteroid sparing agent (Table 4).

#### 4.11 Corticosteroid-Sparing Agents That Have Been Used in PANS/PANDAS

Table 4

	<b>Intravenous Immunoglobulins (IVIG)</b>	<b>Therapeutic Plasma Exchange (TPE)*</b>
<b>New onset.</b>	One to six monthly courses of IVIG in moderate-to-severe disease or in severe-to-extreme if TPE not available.	Use in severe cases if patient has life-threatening disease.
<b>Relapsing-remitting course.</b>		Not indicated unless patient is in a severe flare.
<b>Very delayed care, chronic-static, or chronic progressive course</b>	Trial of IVIG. If patient responds, then symptoms recrudescence, patient is deemed immune therapy responsive, thus consider referral for decision for maintenance immune treatment.	Response to TPE may be transient.

\*IVIG supplies are currently in limited supply across the UK and is a “grey indication” within current NHS guidelines. IVIG is only used in a minority of patients as other treatments are usually successful. Use of TPE is limited in the UK and is only considered if an active inflammatory component is present.

## 5.0 Authors

The Children's e-Hospital adapted UK PANDAS/PANS Physician Network guidelines have been edited by Dr Tim Ubhi. The original guideline was developed by the UK PANDAS Physicians Network in collaboration with PANS PANDAS UK. It has been designed for the purposes of supporting Doctors and allied health professionals to detect, diagnose and treat children presenting with symptoms of PANS or its subtype PANDAS. All parties involved in (but not limited to) the development of that guidance are as follows:

**Dr Andrew Curran**

Consultant Paediatric Neurologist  
Alder Hey Children's Hospital

**Professor Rajat Gupta**

Consultant Paediatric Neurologist  
Birmingham Children's Hospital

**Dr Amy Herlihy**

General Practitioner, Special Kids Medical Centre, Cork, Ireland

**Dr Marinos Kyriakopoulos**

Consultant Child and Adolescent Psychiatrist  
National and Specialist Inpatient Children's Unit (Acorn Lodge), South London and Maudsley NHS Foundation Trust

**Dr Ming Lim**

Reader in Paediatric Neurology | King's College London  
Consultant Paediatric Neurologist | Children's Neurosciences Centre  
Evelina London Children's Hospital | King's Health Partners Academic Health Science Centre, Kings College, London.

**Dr Goodwin McDonnell**

General Practitioner, Dublin, Ireland

**Dr Sanjay Patel**

Paediatric Infectious Disease & Immunology Consultant  
University Hospital Southampton NHS Foundation Trust

**Georgia Tuckey**

Parent, PANS PANDAS UK

**Dr Tim Ubhi**

Consultant Paediatrician  
Clinical Director of The Children's e-Hospital

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