Antibiotics can be used as a therapeutic tool to alleviate symptoms and/or as a prophylactic dose to prevent or reduce future flare-ups post immunotherapy.

I. Therapeutic Antibiotics

Antimicrobial based treatment should be based on each child’s specific presentation. Clearly, children with symptoms of streptococcal infection should be tested and treated appropriately. Additionally, research has shown that current commercially available serology for Group A strep has an approximate 37% false negative rate (even when both ASO and anti-DNase B are done). Throat cultures may also miss 5% – 15% of GAS infections (more if the swab is inadequate to reach nasopharyngeal bacteria). Thus, therapeutic antibiotic therapy is recommended for all PANDAS/PANS patients who have history of GAS exposure (family member or close peer contacts).

With a new diagnosis of PANS, a physician should consider an initial course of antimicrobial treatment for acute streptococcal infection, regardless of whether or not GAS is identified at the time of diagnosis.

So-called “beta-lactams” are the most effective antibiotics for GAS infections; these include penicillin, amoxicillin (including Augmentin) and cephalosporins. Erythromycin, azithromycin and clindamycin are also reported to be effective in the treatment of GAS infections; however, regional resistance has been reported. Some members of the PANS/PANDAS Consortium provide initial treatment for 3 weeks, awaiting resolution of neuropsychiatric symptoms. The response to antibiotics can occur quickly – full or partial remission of OCD, anxiety, and many of the comorbid symptoms of PANS and PANDAS within 24-48 hours. Typically, however, the response occurs after a week or two of therapy. If no improvement is seen after 10-14 days, a physician may consider an alternate class of antibiotic treatment for an additional 10-14 days. If the antibiotics produce significant symptomatic improvements, they might be continued at treatment-level doses for an additional 2 – 4 weeks.

A follow-up swab a week after finishing antibiotic treatment should be done for those with a documented strep throat infection. Re-treatment is recommended if still positive. Following the initial treatment course, prophylactic antibiotics may be useful for PANDAS (but are less clearly indicated for PANS, since they are effective only in preventing GAS infections). If the decision is made to use prophylactic antibiotics, the dosage and choice of antibiotics can be guided by AHA recommendations for prophylaxis in acute rheumatic fever (see AAP Redbook). If the child’s symptoms return at a lower prophylactic dose, the dose may need to be adjusted.

If a child has a poor response, or continues to have frequent exacerbations, his family members should be examined for illness and tested for GAS. Recurrent exposure to GAS can trigger symptoms in PANDAS children, even if the patient does not develop a full-blown infection.

II. Antibiotic Prophylaxis

Long term prophylactic antibiotics to prevent future strep infections may be appropriate for severely affected children, for those who have received immunotherapy, and for those with multiple strep associated neuropsychiatric exacerbations.
Continuing prophylaxis until age 18 for severe cases is appropriate, but should be individualized. Physicians considering prophylaxis should consult guidelines for prophylaxis for rheumatic fever.

While there have been short-term (1 year) studies that proved prophylaxis effective post IVIG and plasmapheresis, there have been no long-term studies.

Typical antibiotics used for prophylaxis include Augmentin (approximately 400mg/day), azithromycin (approximately 250mg/day) or penicillin (250mg po bid). (Note that dosing depends on weight and patient tolerance.)

**A brief summary of AHA guidelines for rheumatic fever:**

- Greater of 5 years or until age 21 if the patient does not have carditis
- Greater of 10 years or age 21 if the patient has carditis but no residual heart disease
- Greater of 10 years or age 40 if the patient has carditis and persistent heart disease (i.e, valve disease)

(Please consult the actual guidelines when determining the length of prophylactic therapy.)

### III. Support for antibiotics in PANDAS

Azithromycin and penicillin have been utilized in the treatment of PANDAS with observations of improvement in neuropsychiatric symptoms. In a study designed to decrease Group A strep (GAS) infections, researchers at NIMH conducted a twelve-month parallel design comparing prophylactic doses of penicillin and azithromycin. Eleven subjects were maintained on penicillin and 12 were maintained on azithromycin during the 12-month study. During the study year, the mean number of neuropsychiatric exacerbations was reduced as well as the mean number of streptococcal infections. No side effects or reports of any adverse effects from the medications were reported. The authors suggest that both antibiotics may be safe and effective in preventing Group A strep infections and in decreasing the number of neuropsychiatric exacerbations in these children without any significant differences between groups. In a small pilot study of cefdinir at treatment doses (14mg/kg), children with recent onset neuropsychiatric symptoms had improvements in OCD and tics, with the OCD improvement reaching clinical significance. In addition to these controlled trials, there is a large pool of anecdotal reports from practitioners and parents that antibiotics can significantly reduce the severity of symptoms.

### IV. Dental Considerations

It has been well established that during certain types of dental work, patients may be at increased risk of bacteremia during the dental work.¹ This is the rational for the American Heart Association’s 2007 endocarditis guidelines to recommend that patients who are high risk for endocarditis, receive antibiotic prophylaxis, during certain types of dental procedures.² For certain high risk patients, prophylaxis is reasonable for all dental procedures that involve manipulation of gingival tissue or the periapical region of teeth or perforation of the oral mucosa.

PPN’s expert committee members have experienced that PANS/PANDAS patients may have exacerbations of their symptoms after dental work, which involves manipulation of the gingival tissue, pericardial regions of the teeth or perforation of oral tissue as well (procedures such as extraction, cleaning, fillings, and oral surgery). Although the
exact mechanisms are not known, this bacteremia may stimulate an immune response which is responsible for worsening clinical status.

Therefore, patients may benefit from antibiotic prophylaxis starting the day before, until 4-7 days after the procedure. The dosing to prevent PANS/PANDAS exacerbation is higher than that used for endocarditis prophylaxis for dental procedures and should be at least equivalent to the dosing for therapeutic strep pharyngitis.

V. Side effects

There are risks of long-term use of antibiotics, including the potential for allergic reactions (at any point during therapy) and development of antibiotic-resistant microbes. In the most serious cases, this could result in intestinal overgrowth with pathologic organisms, such as C. difficile, and serious gastrointestinal complications. Use of narrow-spectrum antibiotics (particularly penicillin) minimizes this risk. Some clinicians advocate use of probiotics, such as Culturelle (but not at the same time of the day; allow 2-3 hour window in between).

VI. Further antibiotics research

Antibiotics have been demonstrated to have benefits to the patient beyond the eradication of pathogens. Given the complex and enmeshed relationship between the brain and the immune system, it is not surprising that a number of classical psychotropic compounds have been found to have immunomodulatory properties and that antimicrobial agents display psychotropic effects. Research studies are being planned to explore direct effects of antibiotics on CNS function.

BETA-LACTAM ANTIBIOTICS (PENICILLINS & CEPHALOSPORINS)

Beta-lactam antibiotics (penicillins and cephalosporins) were found to promote the expression of glutamate transporter GLT1 and have a neuroprotective role in vivo and in vitro models. Given the potential role of glutamatergic therapies in OCD, beta-lactams could be expected to exhibit efficacy in these neuropsychiatric disorders, but further study is needed. In a recent study investigating the effects of cephalosporin in a mouse model of major depressive disorder (MDD), ceftriaxone, of the cephalosporin family, was shown to exhibit antidepressant properties increasing glutamate uptake, thought to be impaired in MDD2.

COMBINATION OF AMOXICILLIN AND CLAVULANATE (AUGMENTIN)

The combination of amoxicillin and clavulanate (Augmentin) is a particularly useful β-lactamase inhibitor, but it appears to have therapeutic effects that extend beyond its antimicrobial properties. These are thought to be related to the clavulanate (clavulanic acid), as it readily crosses the BBB and has demonstrated anxiolytic properties in rodents and non-human primates. It also displays significant potential as an antidepressant and anxiolytic agent, and Phase IIb clinical trials for major depressive disorder are pending. Additionally, an informal study by ENTs who looked at tonsillectomy patients post procedure with and without Augmentin, found that those on Augmentin had a materially lower level of complaints.

MACROLIDES (SUCH AS ERYTHROMYCIN & AZITHROMYCIN)

Macrolides (such as erythromycin and azithromycin) antibiotic effects are mediated by inhibition of bacterial protein synthesis. They are often used to treat upper respiratory tract infections (URIs), including GAS pharyngitis with adequate efficacy (>90%). Despite high intracellular penetration and extensive tissue distribution, CNS
penetration of azithromycin is poor. The main drawback of AZM for GAS eradication has been reports of macrolide-resistant GAS as well as an increased risk of selection for resistant endemic pathogens over a longer course treatment. Effects on immunomodulation appear to extend beyond their antimicrobial actions as the macrolides have been shown to alter cytokines balance in animal studies and human trials. For example, after stimulation with a combination of lipopolysaccharide (LPS) and IFN, AZM has been shown to act primarily on the lymphokine CD4 T helper 1 cell line reducing the production of the pro-inflammatory cytokines IL-12 and IL-6, and increase the production of the anti-inflammatory cytokine IL-10 in macrophage cell lines. Azithromycin has also been reported to suppress iNOS mediated nitric oxide production and to decrease mRNA expression, thereby promoting apoptosis of inflammatory cells and a decrease in nuclear transcription factors. Consistent with this hypothesis, a few in vitro studies point to azithromycin’s actions to downregulate NF-kB signaling, costimulatory molecules and alter the function of antigen presenting cells. Innate immunity is thus impacted as well. TLR4 and IL-12 are reduced after azithromycin treatment; both of these signaling pathways are involved in inflammatory processes as well as in immune responses to streptococcal infections. A recent clinical study investigating the occurrence of polymorphisms in TLR4 and TLR2 susceptibility to GAS infections suggested mutations in TLR4 (D299G, T399I) were associated with vulnerability to recurrent GAS infection. Further, soluble immune activating factors such as IL-12, IL-6 and TNF-a released during GAS infection may contribute to autoantibody production.

TETRACYCLINES
Tetracyclines are not typically used for PANDAS (but shown here for illustrative purposes of non-microbial benefits). Tetracyclines are broad spectrum antibiotics which exert their antibiotic effects through inhibition of protein translation. They are not typically used to treat PANDAS, as they have limited effects on GAS and other upper respiratory pathogens. However, minocycline and doxycycline have been shown to exhibit immunomodulatory properties that may be useful in PANS/PANDAS, including inhibition of oxidative stress9. In Fragile X Syndrome (FXS), where matrix metalloproteinases (MMP) have been thought to play a major role in the pathological mechanism, minocycline has been shown to lower MMP9 levels which are high in FXS, and it also strengthens brain connections in the animal models of FXS9, 10. MMPs have been implicated in axonal guidance, synaptogenesis, neurotransmission, synaptic plasticity and behavioral learning11, 12 and highlight the need for more research in humans in order to guide clinical management.

VII. Future Perspective
The interplay between the immune system and the Central Nervous System (“CNS”) makes antimicrobial agents potential therapeutic alternatives for some neuropsychiatric disorders. The overlap between immune and CNS pathways and signaling molecules suggests that disruption of the immune system may have secondary effects that extend beyond its localized actions. With this knowledge, the potential exists to characterize the mechanism driving the clinical pathologies in disorders that seem to have a clear immunological component, as many neuropsychiatric disorders have now been observed to have. Similarly, in autoimmune disorders with observed psychiatric presentations, and neuropsychiatric symptoms following infection, this area may be an opportunity to both understand the pathological mechanism and develop more targeted therapeutic alternatives. Characteristic markers of immune activation including increased expression of pro-inflammatory cytokines have been observed in psychiatric disorders and have been implicated in their pathological mechanism. Although promising, it must be noted that, as with any therapeutic intervention, the application of antibiotics for these disorders may rest heavily on clinician judgment and medical history and future research. In disorders such as PANDAS where onset is usually sudden and a clear connection has been delineated, the choice may be clear.
VIII. Current Antibiotic Trials

Current clinical trials underway to measure the effectiveness of antibiotics on PANDAS patients:

- SSRI plus Antibiotic Treatment vs SSRI Trial for PANDAS; Stefano Pallanti, Florence Italy
- EMTICS: Efficacy of Amoxicillin/Clavulanic Acid in Patients Affected by Tic Disorder Colonized by Group A Streptococcus (AntibioTICS) Francesco Cardona, University of Roma
- Augmentin Treatment for PANS, Dan Geller, MGH

IX. Resources


