Treatment of Infections in PANS/PANDAS
Research support from the National Institute of Mental Health, Shire Pharmaceuticals, Pfizer, Inc, F. Hoffmann-La Roche Ltd., Neurocrine Biosciences, Psyadon Pharmaceuticals, Teva Pharmaceuticals and PANDAS Network.
Treatment Plan

- Based on clinical presentation – not “one size fits all”
  - Psychotherapeutic
    - Psychotherapy
    - Psychoactive medication
  - Antibiotics
    - Active infection
    - Secondary antimicrobial prophylaxis (severe cases)
  - Immunomodulatory/Anti-inflammatory
    - NSAIDs
    - Corticosteroids
    - IVIG; Less commonly: TPE, Rituximab/MMF (severe cases)

Swedo, Frankovich, Murphy. 2017
Infectious Triggers

➢ Increasing evidence suggests molecular mimicry as the central mechanism behind PANDAS/PANS (Cunningham et al; Pittenger et al)

➢ Evidence of inciting GAS infection has been observed in 40-70% of PANS cases → PANDAS (Cooperstock et al. 2017)

Signs of Infection

○ Pharyngitis
○ Sinusitis
○ Cough/pneumonia
○ Dermatitis (impetigo, perianal, vulvovaginitis)

Possible Infectious Triggers

○ Group A streptococcus (PANDAS)
○ Mycoplasma pneumonia (PANS)
○ Viruses: less reports but influenza A esp. H1N1, maybe EBV (PANS)
○ Lyme disease (PANS)
GAS Infection

"Strep Throat"
- Very contagious
- GAS is a transient pathogen in most situations even without treatment
- Subclinical infections or chronic carrier states are not uncommon
- Reinfections are difficult to sort out from carrier states
OCD Onset & GAS Proximity

Potential Prior Exacerbation

Child appears possessed
Constant impairment
Everyone on egg shells
Child Inconsolable
Unable to function in
school/social setting

Sudden onset

0-5pt

16pt rise

CYBOCS

t₁ ↔ t₂
~2m

6m or longer

<1m

Courtesy of Keith Moore
Observations on Flares

- Close exposure to strep can drive neuropsychiatric symptoms even when the child has no signs of infection
- Not all flare ups will be strep
- A few with PANDAS will get better that first ‘micro-episode’
Lab Workup

- **All patients meeting PANS criteria**
  - Complete blood cell count with manual differential
  - Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP)
  - Comprehensive metabolic panel
  - Urinalysis
  - **Throat culture, anti-streptolysin O (ASO) and anti-DNAse B**
  - **If history of URI/cough, Mycoplasma IgG/IgM**

- **Also to be considered:**
  - Antinuclear antibody (ANA) or fluorescent antinuclear antibody (FANA) if elevated inflammatory markers, fatigue, rashes, or joint pain exist.
  - Antiphospholipid antibody work up if patient has chorea, petechiae, migranes, stroke, thrombosis, thrombocytopenia, or levido rash.
  - Ceruloplasmin and 24 urine copper tests to evaluate Wilson’s disease if abnormal liver function or Kayser-Fleisher rings present.

Chang et al. 2017
Streptococcal Titers

- **Strep Specific Antibodies**
  - ASO more specific after pharyngeal infection and anti-DNase B after skin infection
  - ASO rises first, then DNAs eB
  - Age effects on titers (highest levels expected at ages 6-12 years old)

- **Reliance on Titers**
  - No information on specific timing of strep infection unless 2 sets of titers 4-6 weeks apart show significant increase
  - Titers can remain elevated for months or years even in those with no symptoms--having high strep titers *does not* equal PANDAS
  - Preschool children may not show titers to meet lab’s threshold for positive titers
  - Many clinicians do not consider other etiologies when low—as many as 40% may not show elevated titers
Adequate for a diagnosis of PANDAS

- A rise in serial antibody level, regardless of rapid test or culture result.
- Acute pharyngitis with a positive GAS throat culture, with or without a rising antibody level.
- Pharyngitis with characteristic palatal petechiae or scarlatinaform rash.
- Pharyngitis without a throat swab or serology, but intimate exposure to proven GAS case.
- Asymptomatic pharyngeal colonization documented after an intimate exposure.
- Asymptomatic pharyngeal colonization after a negative throat swab documented within the prior 3-4 months.
- Single ASO or ADB antibody level within 6 months after onset of neuropsychiatric symptoms if >95th percentile for age.
- Both ASO and ADB are elevated at >80th percentile for age in the same serum sample within 6 months onset of neuropsychiatric symptoms.
- Culture-documented streptococcal dermatitis.

Cooperstock et al. 2017
Treatment

- Treatment of active infection and prophylaxis from recurring infections
- The choice is more obvious in PANDAS presentations with a sudden, acute onset of symptoms temporally associated with Group A streptococcal (GAS) infection
- Many antimicrobials possess immunomodulatory properties
- Potentially optimize Vitamin D levels to enhance immune system

**β-Lactams**
- Penicillin V
- Amoxicillin±Clavulanate
- Benzathine penicillin G
- Cephalexin
- Cefadroxil
- Cefdinir

**Macrolides/Lincosamides**
- Azithromycin
- Clarithromycin
- Clindamycin
- Erythromycin

Tetracycline (not typically for PANDAS; resistance in GAS)
- Doxycycline
- Minocycline
Management of Infection in PANDAS

- Rule out co-existing infectious causes
- Patients with “adequate” evidence for an association with streptococcal infection may be given a provisional diagnosis of PANDAS.
- For those with PANDAS, an initial course of treatment for GAS is suggested, including re-culture and follow-up management according to primary antimicrobial treatment for acute streptococcal infections.
- For those with documented GAS pharyngitis, a follow-up throat swab 2-7 days after treatment is prudent. Retreat if still positive.
- Ongoing vigilance for streptococcal infections in the patient and all family members is also warranted.

Cooperstock et al. 2017
### Treatment of Acute GAS Pharyngitis

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Duration</th>
<th>Dosage Details</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Penicillin V</strong> po – 10 days</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Children: 250mg bid or tid</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adolescents or adults: 500mg bid</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Amoxicillin</strong> po – 10 days</td>
<td></td>
<td></td>
</tr>
<tr>
<td>50mg/kg qd, max 1g</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Benzathine penicillin G</strong> IM once</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;27kg: 600,000 U</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;27kg: 1.2 M U</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>If allergic to penicillin:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Cephalexin</strong> po – 10 days</td>
<td></td>
<td></td>
</tr>
<tr>
<td>20mg/kg bid, max 500mg/dose</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Cefadroxil</strong> po – 10 days</td>
<td></td>
<td></td>
</tr>
<tr>
<td>30mg/kg qd, max 1 g</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Clindamycin</strong> po – 10 days</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7mg/kg tid, max 300mg/dose</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Azithromycin</strong> po – 5 days</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12mg/kg once, max 500mg, then 6mg/kg qd, max 250 mg, for 4 days.</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Clarithromycin</strong> po – 10 days</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7.5mg/kg bid, max 250mg/dose</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Cephalexin

- Preferred, second to penicillin
- BID or TID

Azithromycin

- Regional GAS resistance (5-10%)
- Easy administration
- Acts against most *Mycoplasma pneumonia*
- Potential immunomodulatory activities
- Caution if prolonged QT or prolonging medications (e.g. SSRIs, anti-psychotics)

Cefadroxil

- Q daily
- A ten day course of Cefadroxil showed the lowest failure rate (8.0%) within the treatment groups, followed by penicillin (15.6%) and then erythromycin (19.7%)
- Caution if amoxicillin allergic

Clindamycin

- Unfavorable taste
- Resistance may be emerging
- May disturb the protective throat and fecal microbiome more than other antimicrobials
## Antibiotic Treatment – Parent PANS Survey

<table>
<thead>
<tr>
<th>Antibiotic (Hi/Regular)</th>
<th>Used  % (N), (n=698)</th>
<th>Perceived Effective % (N)</th>
<th>Discontinuation: Tolerability % (N), (n=varies)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amoxicillin</td>
<td>34% (235)</td>
<td>46% (109)</td>
<td>5% (10)</td>
</tr>
<tr>
<td>Azithromycin</td>
<td>31% (216)</td>
<td>61% (132)</td>
<td>3% (7)</td>
</tr>
<tr>
<td>Amoxicillin Clavulanate</td>
<td>26% (184)</td>
<td>62% (115)</td>
<td>9% (16)</td>
</tr>
<tr>
<td>Cefdinir</td>
<td>15% (105)</td>
<td>63% (66)</td>
<td>12% (12)</td>
</tr>
<tr>
<td>Clindamycin</td>
<td>11% (80)</td>
<td>61% (49)</td>
<td>3% (3)</td>
</tr>
<tr>
<td>Penicillin</td>
<td>10% (67)</td>
<td>54% (36)</td>
<td>8% (5)</td>
</tr>
<tr>
<td>Cephalosporin, other</td>
<td>5% (36)</td>
<td>55% (20)</td>
<td>15% (5)</td>
</tr>
<tr>
<td>Doxycycline</td>
<td>3% (21)</td>
<td>62% (13)</td>
<td>22% (5)</td>
</tr>
</tbody>
</table>

Calaprice, Tona, Murphy. 2017
Secondary Antimicrobial Prophylaxis

- Insufficient evidence to support long-term strep prophylaxis for children with PANDAS (mixed findings).
- Could prevent neural injury from future GAS-associated exacerbations.
- May prolong symptom remissions and decrease the number of exacerbations.
- Long-term prophylaxis is generally referred to the most severely affected patient.
  - Consult with pediatric infectious diseases specialist or a member of the consortium.
  - If used, follow guidelines for prevention of RF.
- Gut microbiome/GI issues have not been systematically explored in this population.
- Duration of antibiotic therapy for PANS/PANDAS is relatively prolonged but not measured in decades (continue at least 1-2 years after symptoms have abated).
- May suspend treatment over the summer when exposures are less common, and resume in the fall when the patient returns to school.
- May continue to age 18 in the most severe cases.
## Antibiotic Prophylaxis – Parent PANS Survey

<table>
<thead>
<tr>
<th>Prophylactic Antibiotic (≥30 Days)</th>
<th>Used % (N), (n=698)</th>
<th>Perceived Effective % (N)</th>
<th>Discontinuation: Tolerability % (N), (n=varies)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Azithromycin</td>
<td>30% (209)</td>
<td>76% (158)</td>
<td>4% (9)</td>
</tr>
<tr>
<td>Amoxicillin clavulanate</td>
<td>28% (196)</td>
<td>78% (152)</td>
<td>6% (12)</td>
</tr>
<tr>
<td>Amoxicillin</td>
<td>18% (129)</td>
<td>57% (74)</td>
<td>8% (10)</td>
</tr>
<tr>
<td>Penicillin</td>
<td>11% (76)</td>
<td>71% (54)</td>
<td>4% (3)</td>
</tr>
<tr>
<td>Cefdinir</td>
<td>9% (65)</td>
<td>63% (41)</td>
<td>7% (4)</td>
</tr>
<tr>
<td>Clindamycin</td>
<td>6% (44)</td>
<td>61% (27)</td>
<td>4% (2)</td>
</tr>
<tr>
<td>Cephalosporin, other</td>
<td>3% (25)</td>
<td>72% (18)</td>
<td>12% (3)</td>
</tr>
</tbody>
</table>
Multiple Effects of Antimicrobials

- Treatment of active infection and prophylaxis from recurring infections is most important.
- Many possess immunomodulatory properties
  - Antibacterials have therapeutic relevance in the treatment of inflammatory diseases, but can also generate immune adverse events (i.e. hypersensitivity syndrome)
  - Macrolides and cyclines have caused widespread interest due to their anti-inflammatory properties
  - Tetracyclines have therapeutic implications in several chronic inflammatory airway diseases.
- Multiple effects make antimicrobials a more appealing option for treating infection-triggered neuropsychiatric symptoms
Antibiotic RCTs for PANS/PANDAS

- **Penicillin v. Placebo** – Garvey et al. 1999
  - 4 months RCT, 37 children with PANDAS
  - No significant difference in improvement between groups.
  - Limitations
    - Carryover/order effects
    - Too many received treatment while in placebo arm

- **Penicillin v. Azithromycin v. Placebo** – Snider et al. 2005
  - 12 month parallel design, n=23
  - Decreased number of exacerbation and strep infections compared with pre-treatment year

- **Cefdinir v. Placebo** – Murphy et al. 2014
  - 30 days, n=19
  - OCD and tics improved following 30 day treatment
    - Moderate treatment effects observed with tic symptoms
    - No significant group differences

- **Azithromycin v. Placebo** – Murphy et al. 2017
  - 4 weeks RCT, 31 children with PANS, ~10mg/kg (max 500mg)
  - Significant reduction in OCD severity (CGI-S OCD)
    - Tic severity moderated treatment response
    - Increase in QTc observed
Average OCD Severity

<table>
<thead>
<tr>
<th>Time</th>
<th>Placebo</th>
<th>Azithromycin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>4.5</td>
<td>4.0</td>
</tr>
<tr>
<td>EOW4</td>
<td>3.5</td>
<td>3.0</td>
</tr>
<tr>
<td>EOW8</td>
<td>2.5</td>
<td>2.0</td>
</tr>
<tr>
<td>EOW12</td>
<td>1.5</td>
<td>1.0</td>
</tr>
</tbody>
</table>

Randomized Trial

Open Label 8 weeks
Diet and Microbiome

Proper diet
- Important in maintaining overall health (including brain health).
- Essential for proper growth and development of youth.
- May be difficult to maintain for PANS/PANDAs with food intake restrictions.
- Deficiencies have been reported to impact the immune system and increase infection frequency (i.e. Vitamin D).
- Highly influential in regulating composition of GI microbiota.

Microbiome
- Growing evidence shows influence in neurotransmission and behavior associated with neuropsychiatric conditions (including studies in: ASD, ADHD, depression, anxiety).
- Gut microbiota has been associated with the synthesis of metabolites and neurotransmitters including serotonin, melatonin, GABA, acetylcholine, and histamine (no current evidence if levels are clinically significant).
- Bidirectional communication between microbiota-gut-brain axis through various pathways (e.g. vagus nerve, immune system, neuroendocrine pathways, bacteria-derived metabolites).

Sandhu et al. 2017
Probiotics

- Limited present study into the clinical significance of probiotics toward neuropsychiatric disorders.
- May be useful for helping prevent pediatric antibiotic associated diarrhea (commonly C. difficile).
  - Systematic review provides moderate support for a protective effect of probiotics against pediatric antibiotic associated diarrhea, noting that *Lactobacillus rhamnosus* or *Saccharomyces boulardii* at 5-40 billion colony forming units/day may be appropriate (Goldenberg et al. 2015)
- May help regulate the immune system and reduce infection frequency.
  - Potential immunomodulatory properties through affecting the microbiome.
  - Systematic review showed probiotics better than placebo in reducing frequency of acute URTI. However, authors rated the quality of studies listed as low (Hao, Dong, Wu 2015)
  - Non-viable microbial cells and components have been observed to influence the immune system (Taverniti, Guglielmetti. 2011)
Reduced serum 25(OH)D levels have been reported in PANDAS (Stagi et al. 2017).

Steroid hormone: Immune enhancing and immunomodulatory effects.

- Reduction in inflammatory markers with vitamin D3 treatment observed.
- Deficiency has been observed in a number of autoimmune diseases.
- Vitamin D3 receptors present in many classes of immune cells.
- Pediatric trials have demonstrated a reduction in respiratory infections.
- Deficient serum levels may lead to imbalance of neurotransmitters affecting neuropsychiatric disorders.
  - Can regulate tyrosine hydroxylase (TH) expression, a rate-limiting enzyme in the production of dopamine, epinephrine, and norepinephrine.
  - Mayo clinic study (N=12,595) found strong correlation between low vitamin D levels and current depression (Hoang et al. 2011).
Supplementation

- Monitor for insufficiency (risk factors include wintertime, excess body fat, and race).

- Optimum serum 25-hydroxy vitamin D level has not been established for PANS/PANDAS. However, general Endocrine Society guidelines are >30ng/mL (75 nmol/L) for youth.

- If deficient and unable to maintain with proper diet, consider daily MVI/vitamin D3 1000 U (< 5 years old); 2000 U (> 6 years old). Precaution: hypervitaminosis (e.g. cod liver oil may contain substantial vitamin D).
Case Presentation

- Jack is an 8 year old boy presenting to the clinic and reporting the rapid onset or increased severity in the following symptoms beginning 7 weeks ago: motor and phonic tics, OCD symptoms that included contamination worries that lead him to refuse food, a need to confess guilty thoughts, high levels of separation anxiety, daytime enuresis, deterioration of handwriting and academic performance, sensory sensitivities, hyperactivity, defiance, severe mood lability and dilated pupils.

- Jack has a history of mild separation anxiety, frequent urination and dysuria. Otherwise, he is of above-average intelligence.
  - Positive for strep (11 months ago) - no associated neuropsychiatric symptoms
  - **First episode:** (7 months ago) - positive for strep, severe separation anxiety, frequent urination, and defiance. Given a 5 day course of azithromycin by PCP, symptoms cleared
Jack: Labs

- CBC, CMP, EKG & urinalysis WNL
- Immunoglobulins: wnl, except
  - IgG 854 (range 572-1474)
  - IgA 213 (range 62-236)
  - IgM 59 (range 30-208)
  - IgE 124 (range 0-90)
- Raji Cell 25.8 (range 0-15.1)

- Mycoplasma pneumoniae
  - IgG abs <100 (range 0-99)
  - IgM <770 (range 0-769)

- GAS Antibodies
  - Antistreptolysin O 73.4 (range 0-200)
  - Anti-DNase B 298 (range 0-170)

Unremarkable labs with minor elevations indicating some inflammation and one elevated strep titer.
First line treatment: 12 week course of Azithromycin 10 mg/kg, and probiotics
  ○ Response: Tics were diminished at about 4 weeks (100% reduction on YGTSS). By week 6, his OCD symptoms were improved (35% reduction on CYBOCS).

After 8 weeks: Added CBT to target residual OC symptoms.

After 12 weeks: he was much improved in all symptom domains (CGI-I=very much improved).

After 11 months, began tapering Azithromycin
  ○ Response: Both Jack and his mother are pleased with the taper – no symptoms.

Overall: some mild and occasional flares in mood and behavior, but typically symptom free.
## Jack: Severity Measures

<table>
<thead>
<tr>
<th>Measure</th>
<th>Pre Treatment</th>
<th>Post Treatment*</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYBOCS (OCD)</td>
<td>31</td>
<td>14</td>
</tr>
<tr>
<td>YGTSS (tics)</td>
<td>16</td>
<td>0</td>
</tr>
<tr>
<td>CGI-S OCD</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>CGI-S Tic</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td>CGI-S Cog</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>CGI-S Mood</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Inattention</td>
<td>2.33</td>
<td>1.11</td>
</tr>
<tr>
<td>Hyperactivity</td>
<td>2.22</td>
<td>0.56</td>
</tr>
<tr>
<td>ODD</td>
<td>0.88</td>
<td>0.75</td>
</tr>
<tr>
<td>Mood</td>
<td>77</td>
<td>23</td>
</tr>
<tr>
<td>CGAS</td>
<td>44</td>
<td>70</td>
</tr>
</tbody>
</table>

*12 weeks of azithromycin
Conclusions

- Support that those on antibiotics have more improvement than those on placebo
  - Fairly high placebo response but similar to SSRI trials
- Evidence exists for multiple effects of antimicrobials
  - Response to immune treatment will provide support for a neuroimmunological basis but not necessarily an infectious one
- The use of antibiotics for psychiatric disorders relies heavily on clinician judgment, medical history, and future research
- The antimicrobial choice is more obvious in PANDAS, where youth present with a sudden, acute symptom onset temporally associated with GAS
- Although many improve on antibiotics, many youth have residual symptoms, other immune therapies and standard behavioral therapies are often needed
- Considerations for proper diet, Vitamin D deficiency, and probiotics.
References


Rothman Center for Pediatric Neuropsychiatry