Treatment of Infections in PANS/PANDAS

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Disclosures

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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)

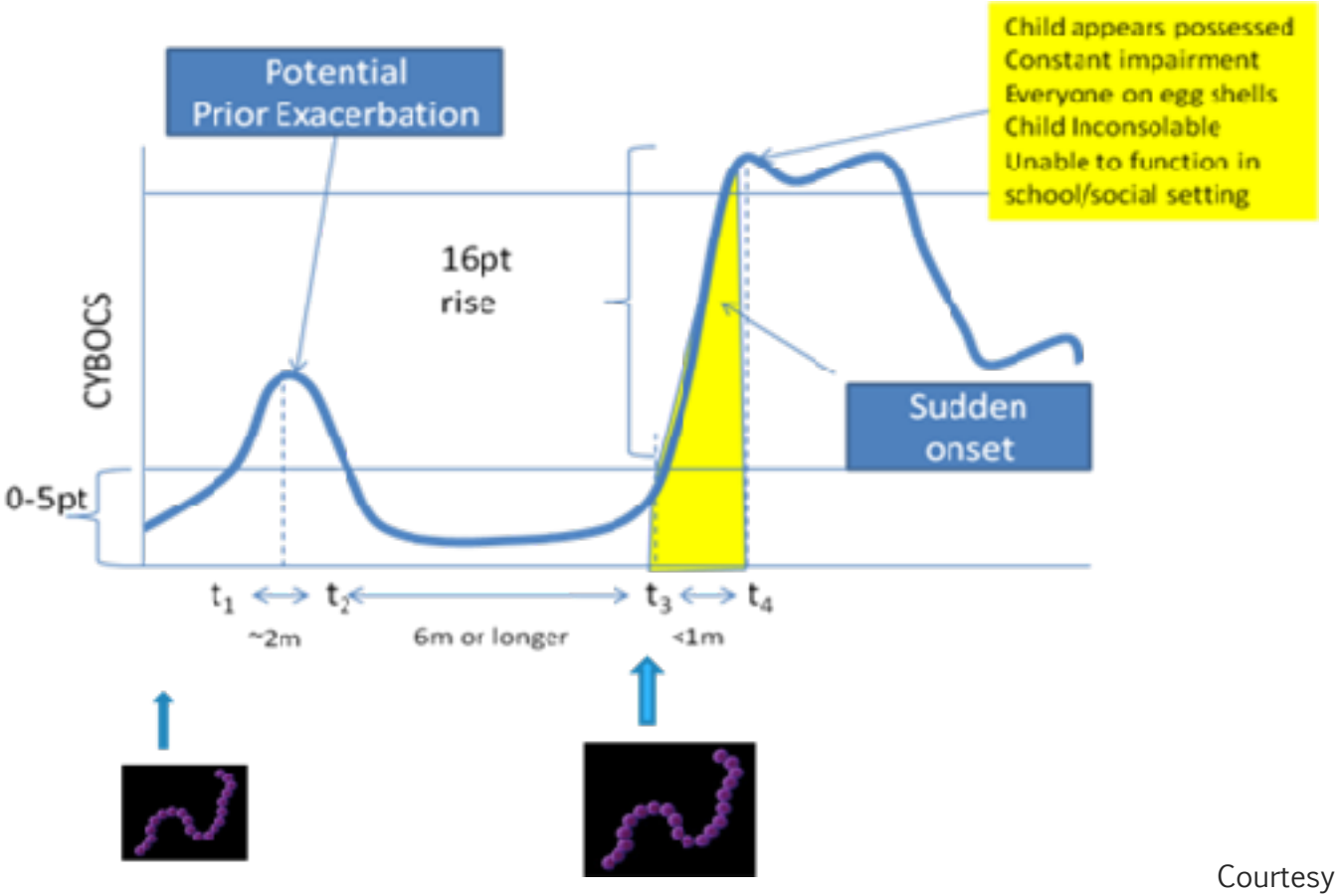
Possible Infectious Triggers

- 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



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 DNASeB
  - 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

PANDAS Diagnosis

- **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

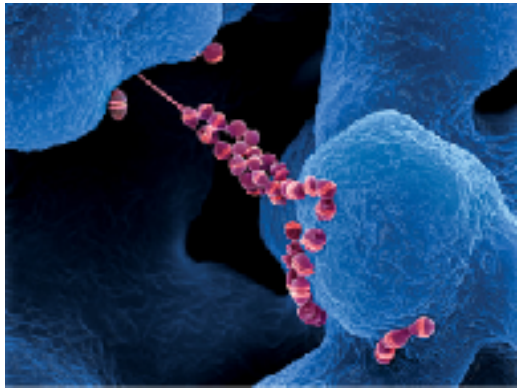
- Penicillin V
- Amoxicillin±Clavulanate
- Benzathine penicillin G
- Cephalexin
- Cefadroxil
- Cefdinir

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

Penicillin V po – 10 days
- Children: 250mg bid or tid
- Adolescents or adults: 500mg bid

Amoxicillin po – 10 days
- 50mg/kg qd, max 1g

Benzathine penicillin G IM once
- <27kg: 600,000 U
- >27kg: 1.2 M U

❑ *If allergic to penicillin*:

Cephalexin po – 10 days
- 20mg/kg bid, max 500mg/dose

Cefadroxil po – 10 days
- 30mg/kg qd, max 1 g

Clindamycin po – 10 days
- 7mg/kg tid, max 300mg/dose

Azithromycin po – 5 days
- 12mg/kg once, max 500mg, then 6mg/kg qd, max 250 mg, for 4 days.

Clarithromycin po – 10 days
- 7.5mg/kg bid, max 250mg/dose

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

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

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

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

Calaprice, Tona, Murphy. 2017

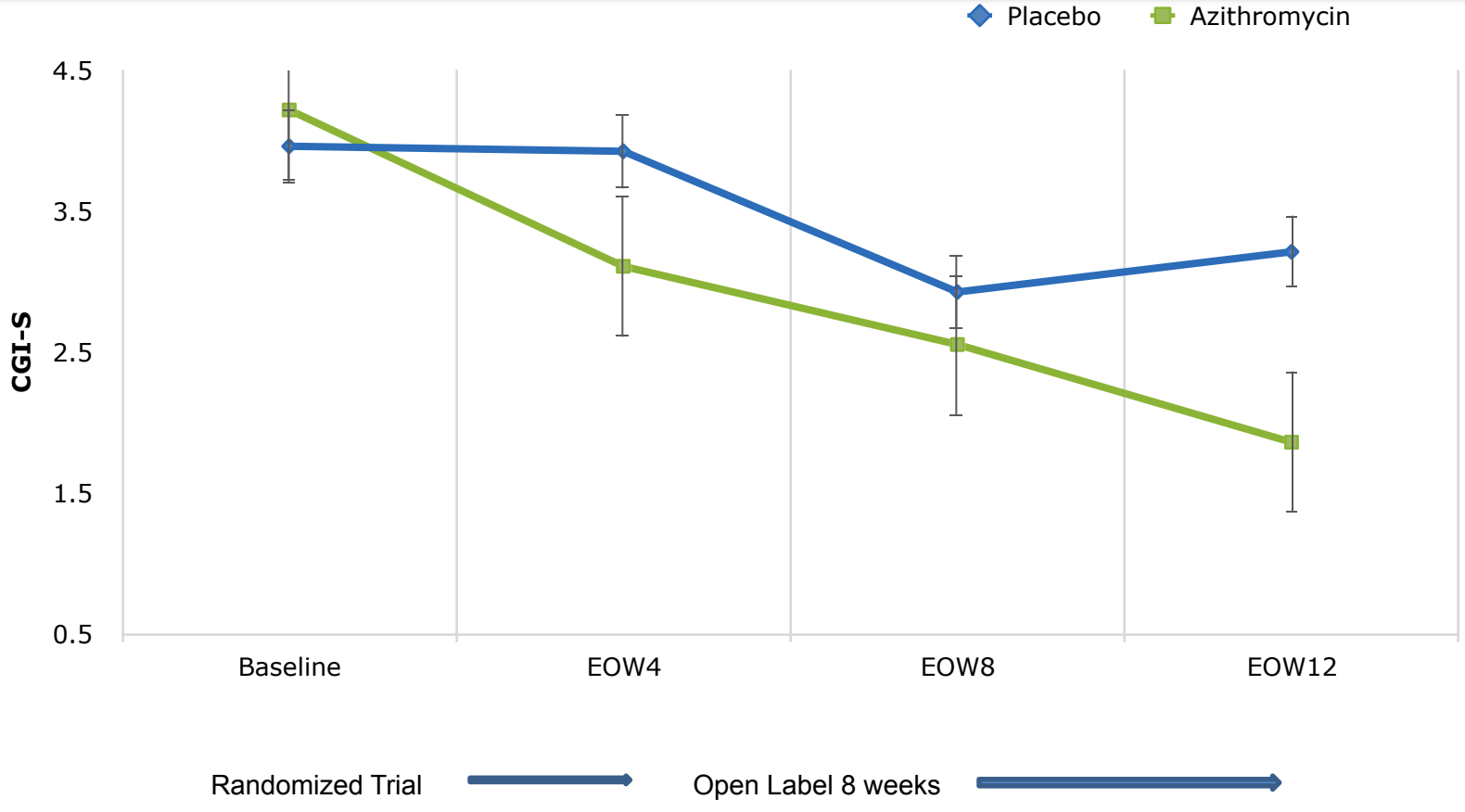
Multiple Effects of Antimicrobials

- 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



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)

Vitamin D

- 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).

Vitamin D, Continued

- 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.

Jack: Treatment

- **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

	Pre Treatment	Post Treatment*
CYBOCS (OCD)	31	14
YGTSS (tics)	16	0
CGI-S OCD	4	2
CGI-S Tic	6	1
CGI-S Cog	4	1
CGI-S Mood	3	1
Inattention	2.33	1.11
Hyperactivity	2.22	0.56
ODD	0.88	0.75
Mood	77	23
CGAS	44	70

*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.

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