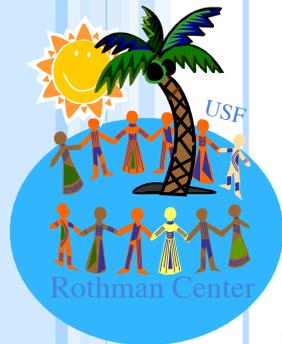


Psychiatry & Immunology: The Evolving PANS/PANDAS Profile

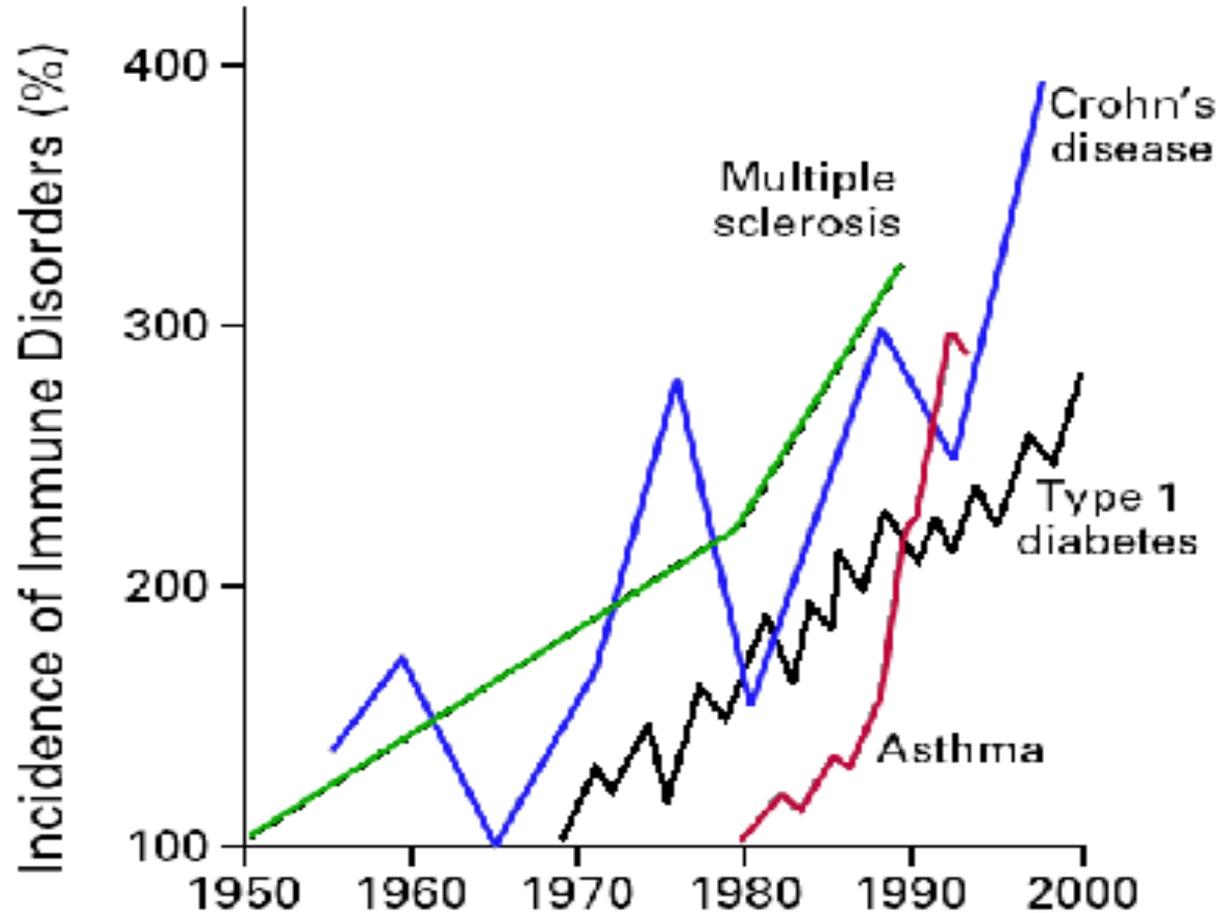


Tanya Murphy, MD, MS
Professor, Pediatrics & Psychiatry
Director, Rothman Center
University of South Florida

DISCLOSURES

- Research support from **National Institute of Mental Health, Shire Pharmaceuticals, Pfizer, Inc, F. Hoffmann-La Roche Ltd., Neurocrine Biosciences, Psyadon Pharmaceuticals, Teva Pharmaceuticals and PANDAS Network.**

THE INCREASING INCIDENCE OF IMMUNE DISORDERS



PANS/PANDAS ONSET

Infection Symptoms

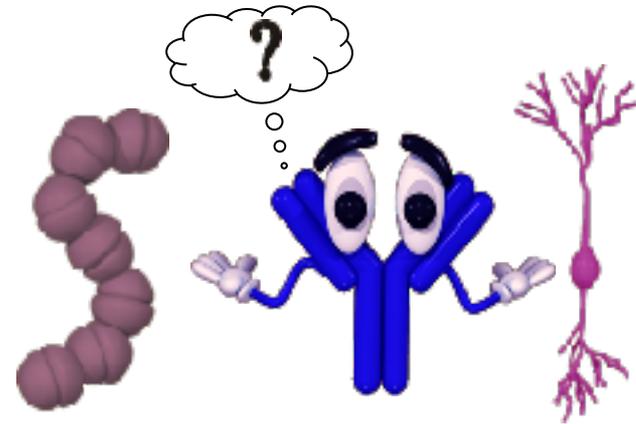
- Pharyngitis
- Sinusitis
- Cough/pneumonia
- Dermatitis (impetigo, perianal, vulvovaginitis)

Possible Infectious Triggers

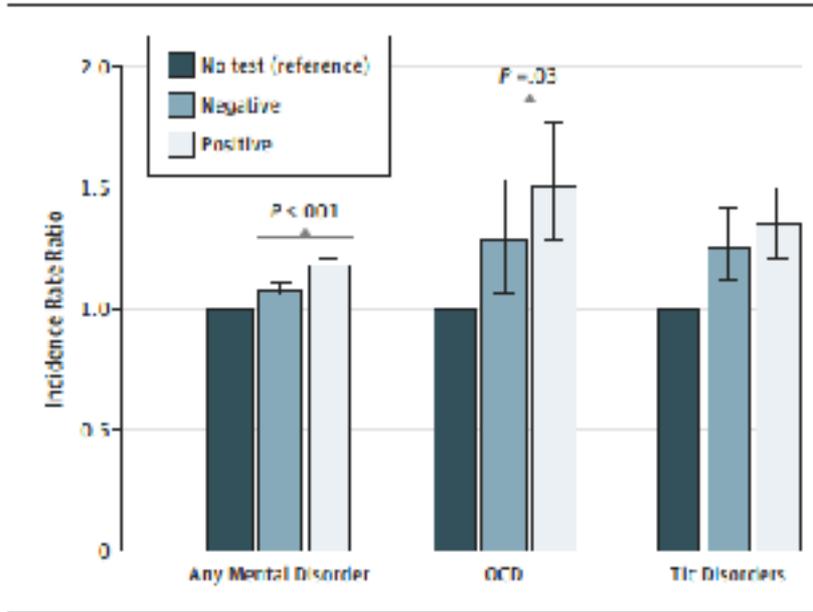
- Group A streptococcus (PANDAS)
- Mycoplasma pneumonia (PANS)
- Viruses: less reports but influenza A esp. H1N1, maybe EBV (PANS)
- Lyme disease (PANS)

EVIDENCE FOR AN ASSOCIATION BETWEEN GAS AND PANDAS

- Clinical association
- Epidemiologic studies
- Prospective study
- Molecular mimicry between GAS and neural antigens
- Animal models



ASSOCIATION OF STREPTOCOCCAL THROAT INFECTION WITH MENTAL DISORDERS: TESTING KEY ASPECTS OF THE PANDAS HYPOTHESIS IN A NATIONWIDE STUDY ORLOVSKA ET AL. 2017



- Data from over 1 million youth
- GAS associated with especially OCD and tics but other mental disorders as well
- Some increase with non-strep pharyngitis – supports PANS or possibly missed GAS on testing

PANS SURVEY PAPERS

CALAPRICE ET AL. 2017

- 698 patients represented 2/3rd M, 1/3rd F
- 12% ASD pre-existing
- 73% reported frequent infections
 - 51% reported frequent sore throats
 - 44% reported frequent ear infections
 - 39% reported chronic sinusitis

5-YEAR-OLD BOY AWOKE

"A CHANGED CHILD"

- Day 1
 - frequent urination was noted the preceding day
 - fears that he was "dirty" & washing excessively
 - separation anxiety, frequent meltdowns
- 2 weeks later
 - he developed tics
 - handwriting deterioration
 - difficulties with concentration
- 4 weeks later
 - motor clumsiness that remitted within a week
- 5 weeks later
 - episode of spasmodic torticollis that remitted within 1 day (treated in the ER)
- 6 weeks later
 - ASO was 680 and anti-DNase B >1360

TREATMENT PLAN

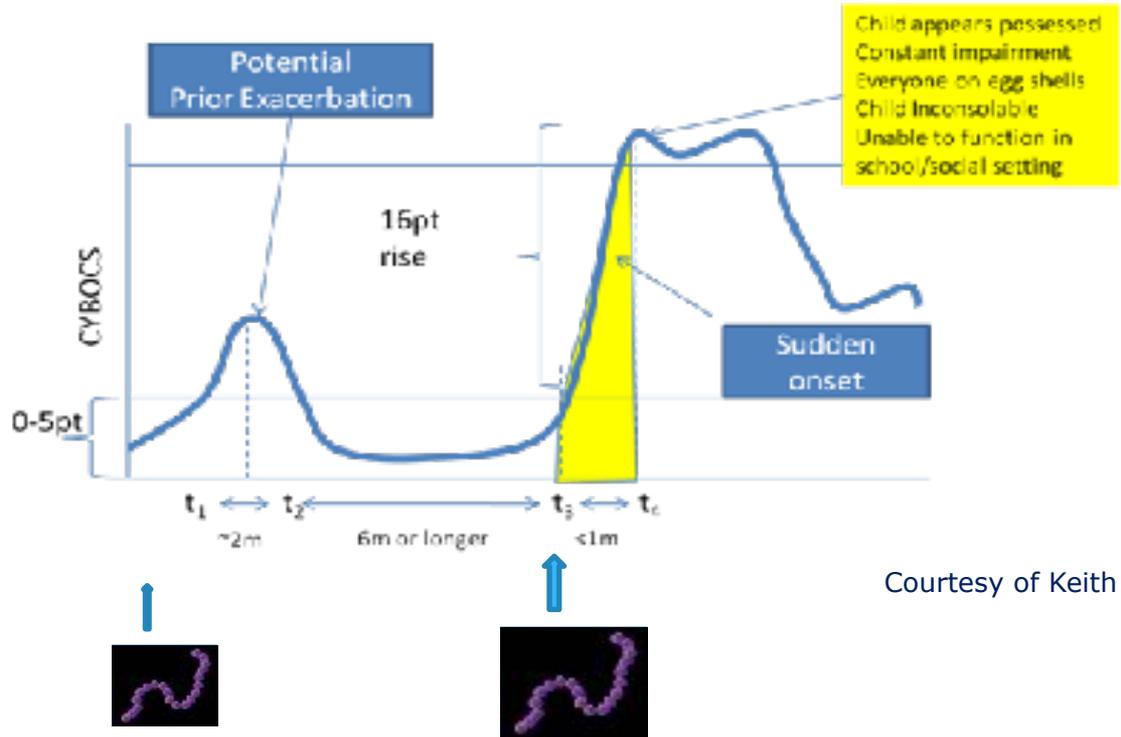
- ▶ Based on clinical presentation – not “one size fits all”
 - ▶ **Psychotherapeutic**
 - Psychotherapy—CBT is often effective
 - Psychoactive medication– useful for partial remission or agitation
 - ▶ **Antibiotics**
 - Active infection
 - Secondary antimicrobial prophylaxis (severe cases)
 - ▶ **Immunomodulatory/Anti-inflammatory**
 - NSAIDs
 - Corticosteroids
 - IVIG
 - Less commonly: TPE, Rituximab/MMF (severe cases)

NEW-ONSET OR ACUTE FLARE, RELAPSING-REMITTING, CHRONIC-STATIC OR CHRONIC-PROGRESSIVE

○ Recommendations

- Work-up infections and other causes of acute neuropsychiatric deteriorations (Murphy and later by Hirsch)
- Refer for CBT and provide other supportive therapies (later by Bubrick)
- Consider early use of corticosteroids (oral bursts or IV pulses) to abort or shorten flares (later by Williams)
- Consider high-dose IVIG or other immunomodulatory therapies in moderate-to-severe cases (later by Williams)

ONSET OF OCD & GAS OCCUR IN CLOSE PROXIMITY



STREP DIAGNOSIS



3/4/2018

ACUTE GAS INFECTIONS

- GAS Pharyngitis
- Scarlet fever
- Perianal dermatitis
- Vulvovaginitis
- Impetigo



Brinker A. 2017

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.

STREP SPECIFIC ANTIBODIES

- Measure ASO and anti-DNaseB
- 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
- Preschool children may not show titers to meet lab's threshold for positive titers
- Titers can remain elevated for months or years even in those with no symptoms
- Some support that higher risk for exacerbations when titers have prolonged elevation
- 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 after onset of neuropsychiatric symptoms.
- Culture-documented streptococcal dermatitis.

PANDAS Pre-Treatment

Fact or Opinion

Read the story.

Brad and Amy

Brad and Amy are brother and sister. They both like playing sports. Brad is on the soccer team. "Soccer is better than any other sport," Brad says. Amy likes basketball. She plays at the park down the street. Brad and Amy have a little brother named Steve. Steve would rather read a good book than play sports. He does like to watch his brother and sister play, though. He sits on the sidelines and cheers for them. They are both good at their sports!

Decide whether each sentence is a fact (F) or an opinion (O).

F Dad is on the soccer team.

F Soccer is better than any other sport.

F Amy plays basketball at the park.

F Steve is Brad and Amy's little brother.

F Brad and Amy are both good at their sports.

F Steve sits and cheers for his brother and sister.



Write a fact from the story.

Amy plays at the park
down the street.

Write an opinion from the story.

Soccer is better than any
other sport.

13

PANDAS Post Treatment

Alphabetical Order

1. anybody	16. headlight
2. agree	17. headphones
3. anyone	18. headquarters
4. anytime	19. judge
5. anywhere	20. lawyer
6. citizen	21. something
7. court	22. somehow
8. defendant	23. someone
9. eyeball	24. something
10. eyebrow	25. sometime
11. eye glasses	
12. expert	
13. eyeliner	
14. headband	
15. handband	

“STREP THROAT”

- Very contagious
- GAS is naturally transient pathogen in most situations even without treatment
- Primary reason for antibiotics is to prevent autoimmune illnesses
- Subclinical infections or chronic carrier states are not uncommon
- Reinfections are difficult to sort out from carrier states

OBSERVATIONS ON STREP AND PANDAS

- 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 without much treatment
- Having high strep titers does not equal PANDAS
- Strep titers do not change very much over course of 1-5 months

ANTIMICROBIALS

- ▶ 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

3/4/2018

β – Lactams

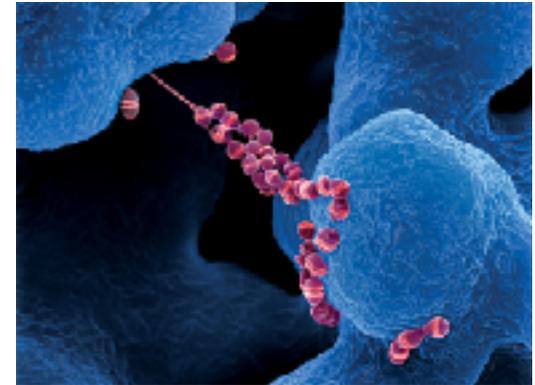
- Penicillin V
- Amoxicillin±Clavulanate
- Benzathine penicillin G
- Cephalexin
- Cefadroxil
- Cefdinir

○ Macrolides/Lincosamides

- Azithromycin
- Clarithromycin
- Clindamycin
- Erythromycin

Tetracycline (not typically for PANDAS; resistance in GAS)

- Doxycycline
- Minocycline



ANTIMICROBIAL TREATMENT OF ACUTE STREPTOCOCCAL 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 et al. 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 reserved for the more severely affected patient or with a history of frequent relapses
 - Consult with pediatric infectious diseases specialist or a member of the consortium
 - If used, follow guidelines for prevention of RF
- Continue for at least 1-2 years after symptoms have abated
 - May continue to age 18 in the most severe cases
- May suspend treatment over the summer when exposures are less common.
 - Resume in the fall when the patient returns to school
- Gut microbiome/GI issues have not been systematically explored in this population

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 et al. 2017

RELAPSING-REMITTING, IN ADDITION

- Evaluate for possibility of recurrent infections and/or exposures triggering flares
 - If GAS infection is a frequent trigger for relapses, evaluate/treat family members and other close contacts and consider prophylaxis
 - Keep in mind that many flares are viral triggers
 - Evaluate immune system competency: pursue immunodeficiency work-up if patient has recurrent sinopulmonary disease or fevers. If immunodeficiency is present, IVIG may reduce the number and severity of recurrent infections

PERHAPS MULTIPLE MECHANISMS FOR ONE OUTCOME...

Similar Mechanisms in Antibiotics and Psychotropics

- Antibiotics have neurological effects (i.e. isoniazid class of antibiotics possesses monoamine oxidase activity)
- Psychotropics have immunomodulatory effects (i.e. SSRI's can significantly impact leukocyte populations)

Immunomodulatory Effects of Antimicrobials

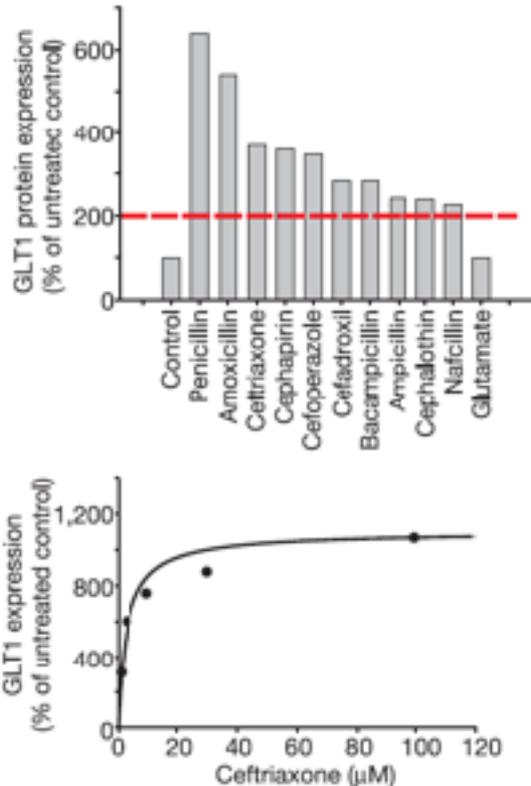
- Macrolides, and cyclines have caused widespread interest due to their anti-inflammatory properties
 - Tetracyclines have therapeutic implications in several chronic inflammatory airway diseases
 - Prevent IgE production by targeting T-cell pathways

Similar targets of antibiotics and psychotropics have important implications in the development of treatments for PANDAS and other immune-related disorders

“MY CHILD IS ADDICTED TO AUGMENTIN”

- Due to decreased infections?
- Immune modulating role of antibiotics
- Clavulanate (Augmentin ingredient)
 - Crosses BBB and has neuropsychiatric effects
- Impact on neurotransmission?
 - Decrease glutamatergic neurotoxicity

NEUROPROTECTION BY BETA LACTAM ANTIBIOTICS?



- Glutamate neuronal excitotoxicity is modulated by the glutamate transporter GLT1
- Ceftriaxone (CTX) increased GLT1 expression in vivo as well as in vitro
- CTX had a neuroprotective effect in an in vivo model of ischemic brain injury and in mice with ALS

Rothstein JD et al. 2005

CLAVULANIC ACID

- Mechanism of action: irreversibly binds to and inactivates bacterial β -lactamase
 - Used in conjunction with amoxicillin to overcome antibiotic resistance
- Neuroprotective role: crosses the blood-brain barrier and demonstrates anxiolytic and antidepressive properties
 - May cause increased release of dopamine
 - May decrease glutamate and enhance NAAG stability, leading to greater mGlu3R activation
 - mGlu3R activation leads to release of trophic factors

THE LARGEST COHORT OF CHILDREN AND ADOLESCENTS WITH PANDAS: PRELIMINARY DESCRIPTIVE ANALYSIS

FALCINI ET AL. 2015

- Cohort of N=242 (76% M)
- 89% with motor tics, 41% with OCD
- GAS infection was confirmed in all patients
 - Not clear how confirmed
 - 15% positive culture at time of assessment
 - **Most had elevated ASO (~80%)**
 - 53.31% had ASO > 550
 - DNaseB > 650 in 31.5%
- Mean age of onset was 6.5 years
- Clinical treatment where all patients received benzathine benzylpenicillin
- Effective in 75% of cases with complete or partial remission of symptoms.

PROSPECTIVE IDENTIFICATION AND TREATMENT OF CHILDREN WITH PANDAS

M. MURPHY & PICHICHERO. 2002

- Followed 12 children with PANDAS over 3-years
- Acute OCD with acute GAS pharyngitis
- Once antibiotics effectively treated GAS infection, OCD remitted
- Recurrence of OCD occurred with acute GAS infection and responded to antibiotic therapy.

DESCRIPTIVE ANALYSIS OF A COHORT OF 103 ITALIAN CHILDREN AND ADOLESCENTS

FALCINI ET AL. 2014

- N=103 (78 male, 25 female)
- 58/103 (46.6%) had family history of OCD, tics, or other neurologic diseases
- Mean age of onset was 77.2 +27.6 months
- Mean age of diagnosis was 102.8 +32.7 months
- 60.2% of subjects reported history of pharyngitis, otitis and/or upper airway infections
- 93% has increased TAOSL with anti-Dnase between 650 and 1200.
- 7 subjects did not present with *S. pyogenes* infection
 - 3 had recent *M. pneumoniae* infection
 - 1 had recent *B. burgdorferi* infection
- Of the 77 patients evaluated by MRI, EEG, and ECG, all were normal
- 66.9% of subjects showed a complete or partial remission of initial symptoms with amoxicillin and benzathine benzylpenicillin treatment

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
- **Azithromycin v. Placebo** – Murphy et al. 2017
 - 4 weeks RCT, 31 children with PANS
 - Significant reduction in OCD severity (CGI-S OCD)
 - Tic severity moderated treatment response
 - Increase in QTc observed
- **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

A PILOT STUDY OF PENICILLIN PROPHYLAXIS FOR NEUROPSYCHIATRIC EXACERBATIONS TRIGGERED BY STREPTOCOCCAL INFECTIONS

GARVEY ET AL. 1999

- 37 children with PANDAS
- 4 months PCN prophylaxis vs. placebo
- No significant difference in improvement between groups.
- Limitations
 - Carryover/order effects
 - Too many received treatment while in placebo arm

ANTIBIOTIC PROPHYLAXIS WITH AZITHROMYCIN OR PENICILLIN FOR CHILDHOOD-ONSET NEUROPSYCHIATRIC DISORDERS

SNIDER
ET AL. 2005

- 12 month parallel design
- Prophylactic doses of penicillin and azithromycin (n=23)
- Decreased number of exacerbation and strep infections compared with pre-treatment year

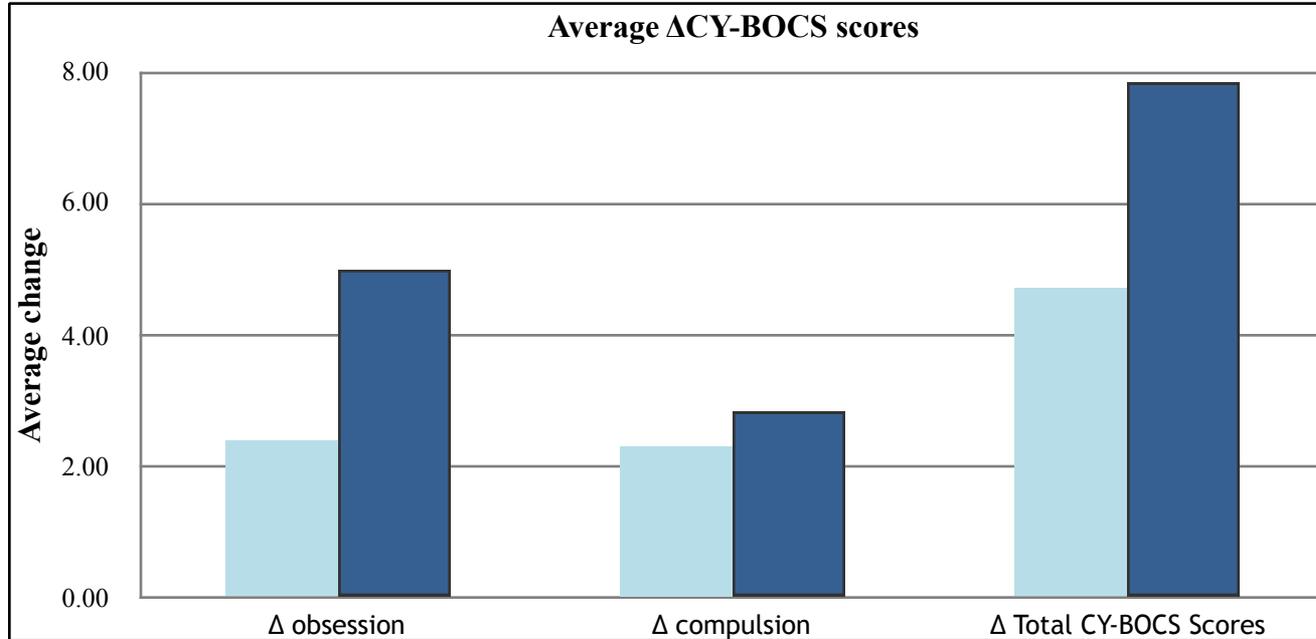
DOUBLE BLIND RANDOMIZED CLINICAL TRIAL CEFDINIR FOR NEW ONSET OCD/TICS MURPHY ET AL. 2014

- Ages 4-13
- New onset of OCD/tics
- Did not require infectious trigger
- Dosed at 14mg/kg (max 600mg)/day with target length of RCT of 30 days
- Chosen for palatability, safety and efficacy for Group A Streptococcus
- Placebo matched for taste, color, consistency

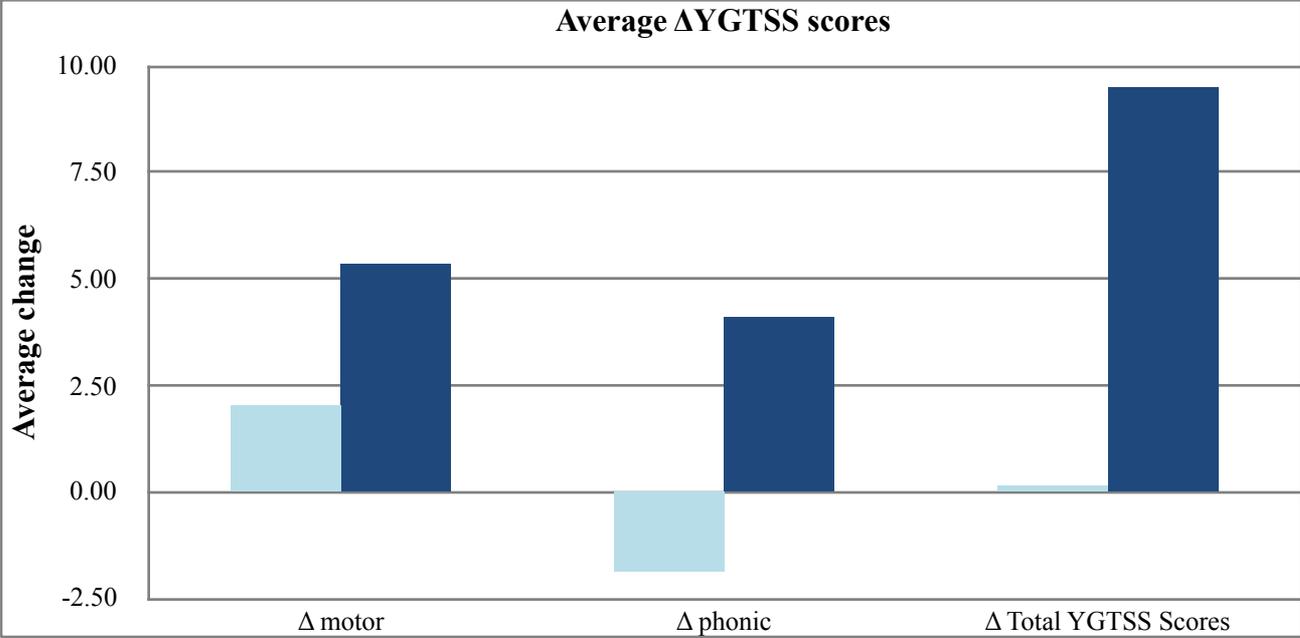
CEFDINIR RCT FOR PANDAS

Demographics	ALL (N=19)	PLACEBO (N=10)	ANTIBIOTIC (N=9)
Age	7.4±1.9	7.5±1.9	7.2±2.0
Gender	F 4 (21.1%) M 15 (78.9%)	F 3 (30%) M 7 (70%)	F 1 (11.1%) M 8 (88.9%)
Diagnosis %			
OCD	26.3%(n=5)	40% (n=4)	11.1% (n=1)
OCD/Tics	31.6% (n= 6)	20% (n=2)	44.4% (n=4)
Tics	42.1% (n=8)	40% (n=4)	44.4% (n=4)

OCD SEVERITY CHANGE



TIC SEVERITY CHANGE



3/4/2018

CEFDINIR SUMMARY

- No significant differences were observed between the placebo or active group after week 4.
- Adverse effects were minor.
 - Most common adverse effect were gastrointestinal related
- Overall, cefdinir was well tolerated and may be an effective treatment for youth with a recent-onset of neuropsychiatric disorders whose symptoms include OCD and/or tics.

MACROLIDE ANTIBIOTIC TREATMENT OF PANS/PANDAS – CASE REPORTS

- Clarithromycin – Ercan. 2008
 - 5 year old
 - OCD after *Mycoplasma pneumoniae*
 - All OCD symptoms disappeared within a week
- Erythromycin – Dehning. 2009
 - 7 year old male presents with motor and vocal tics after *M. pneumoniae*.
 - Full remission of tics within 2 weeks of erythromycin
 - Tics recurred multiple times, but he and his family were tested for *pneumoniae* and treated with erythromycin
 - After 2 months, patient was tic free and remained so for at least 2 years

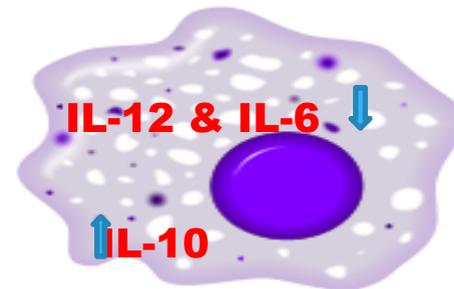
AZITHROMYCIN-EFFECTIVE AGAINST PANS TRIGGERS (GAS, LYME DISEASE, MYCOPLASMA PNEUMONIA)

Background

- TLR4 and IL-12 signaling pathways are involved in streptococcal infections.
- A recent clinical study investigating the occurrence of polymorphisms in TLR4 and TLR2 in susceptibility to GAS infections suggested mutations in TLR4 were associated with vulnerability to recurrent GAS infection.
- IL-12, IL-6 and TNF- α are released during GAS infection and some evidence that these proinflammatory cytokines are increased in OCD, TS and PANDAS

Immunomodulatory effects

- Reduces secretion of inflammatory cytokines
- Enhances development of Th2 response (vs. Th1 chronic inflammation)
- Down regulates expression of TLR 4
- Enhances neutrophil function & oxidative burst early in infection; dampens neutrophil function in late stages of infection



Macrophage

A DOUBLE BLIND RCT OF AZITHROMYCIN

MURPHY ET AL. 2017

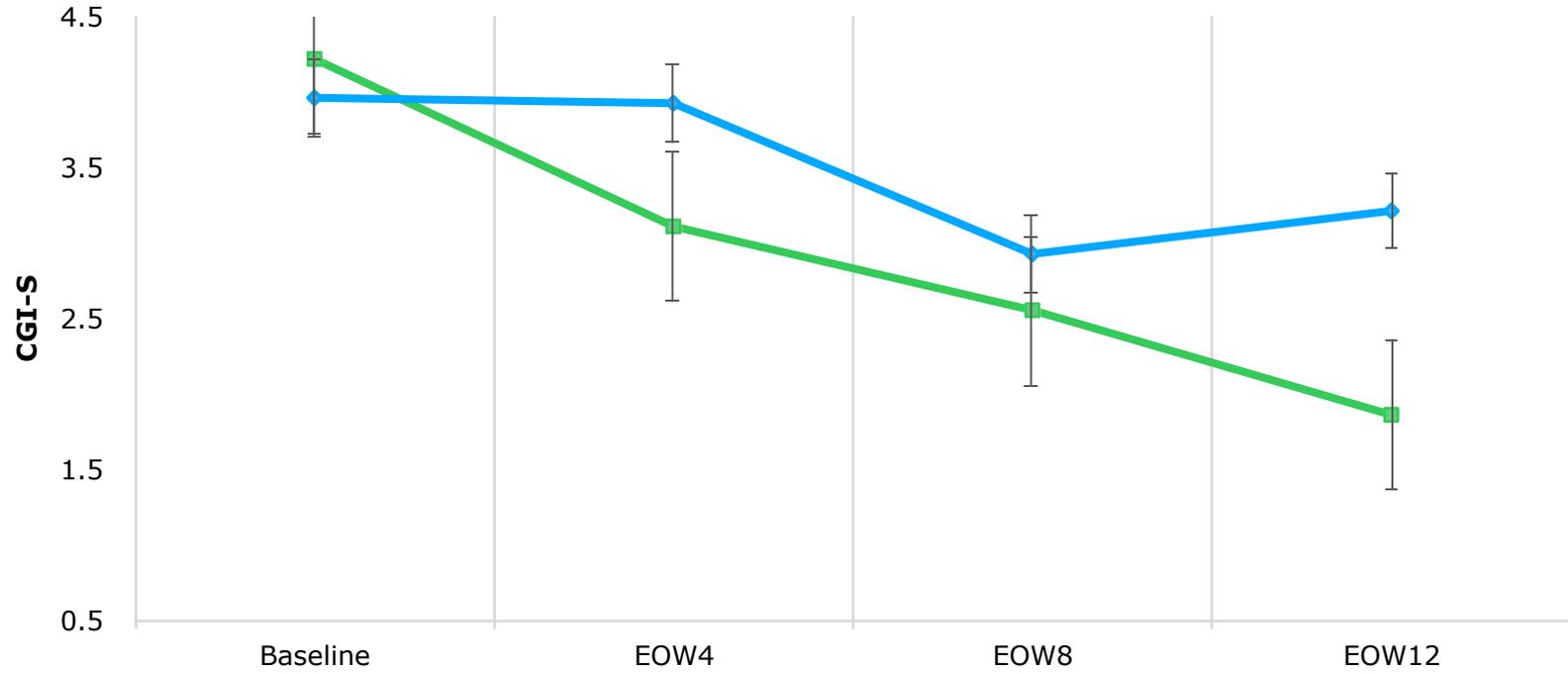
- 31 youth 4-14 yrs randomized for 4 weeks
 - Placebo (N= 14)
 - Azithromycin (N= 17)
- Current episode OCD of recent onset (<6 months); average ~10wks
- Schedule
 - 12 weeks total: 4 weeks RCT, 8 weeks open label
 - Dosing 10mg/kg/day (500mg max)
 - All received open label probiotic BID throughout study
 - Visits every 2 weeks, EKGs, ratings
 - Labs and samples collected for research immune markers at BL, Weeks 4, 8, 12
- Obsessive-compulsive symptom severity was assessed using the CGI-S OCD and CY-BOCS.

FINDINGS - OCD

- The azithromycin group showed a superior reduction in OCD severity on the CGI-S OCD in comparison to the placebo group ($p = .001$) by the end of week 4
 - Mean decrease in of 26% in the azithromycin vs 0% change in placebo group.
- 39% in the azithromycin arm met treatment responder criteria on the CGI-I OCD at the end of week 4 in comparison to 7% of the placebo group ($p = .053$)
 - At the end of 4 weeks, 2 participants in the azithromycin group were completely remitted compared to 0 in the placebo group

AVERAGE OCD SEVERITY

◆ Placebo ■ Azithromycin

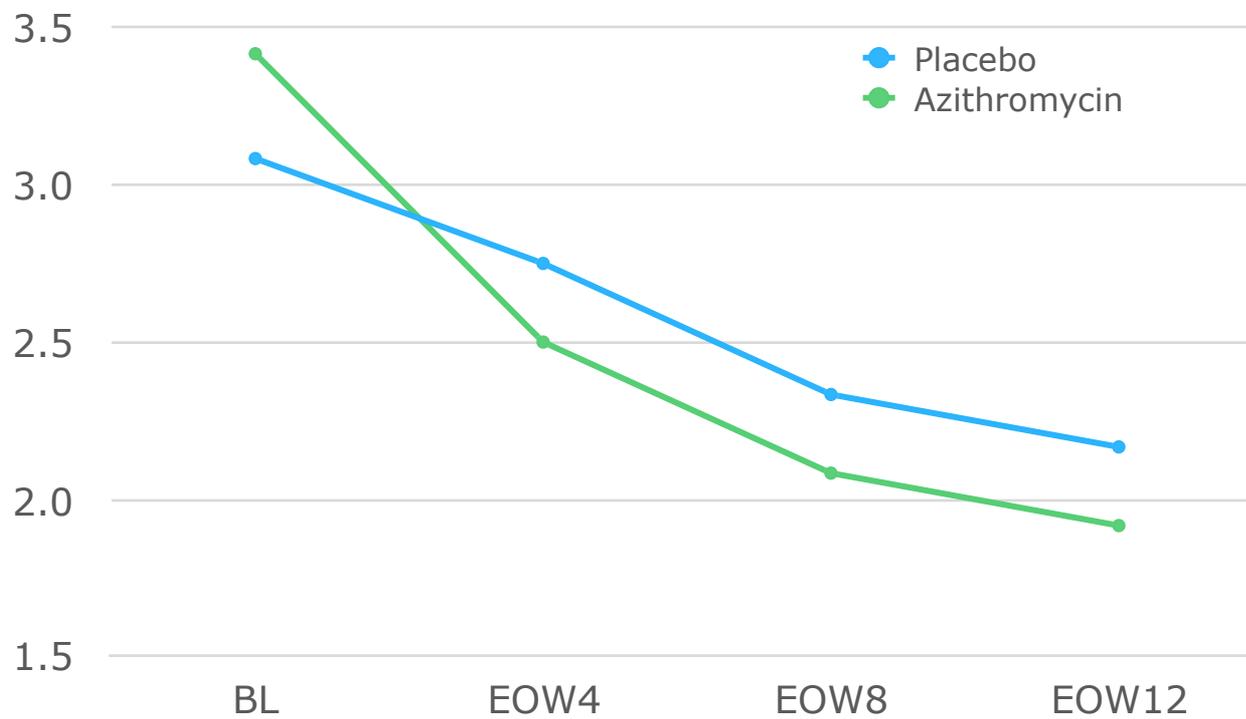


Randomized Trial 

Open Label 8 weeks 



Tic CGI-S



Randomized Trial



Open Label 8 weeks



AZITHROMYCIN RCT - MODERATORS

- Three-way interaction between group, time, and YGTSS score was significant in predicting change in OCD symptoms on the CGI-S OCD ($p = .024$), suggesting the **YGTSS (tic) severity had greater impact on treatment outcome in the azithromycin group in comparison to the placebo group** ($p = .016$)
- Most youth with response to azithromycin had evidence of GAS trigger

AZITHROMYCIN RCT – OPEN LABEL

- At the end of 4 weeks on open label azithromycin, 50% (n=7) of those who started the study in the placebo arm were considered to be responders
- Participants who received 4 weeks of azithromycin in the blinded phase of the study, continued to see improvement in the open-label phase.
 - From azithromycin group- 4 additional responders
- Overall, 59.38% (n=19) of all participants met treatment responder criteria after 4 weeks on open label azithromycin treatment

ADVERSE EFFECTS

- Overall, adverse effects were minor and primarily GI with no study drop outs due to side effects
- A 12 point increase in QTc was noted in the active group with no change in placebo group but no clinically significant QTc prolongation was observed

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).



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 vit D3 treatment observed
 - Deficiency has been observed in a number of autoimmune diseases
 - Vit 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 expression, a rate-limiting enzyme in the production of dopamine, epinephrine, and norepinephrine
 - Mayo clinic study (N=12,595) found strong correlation between low vit 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 $>30\text{ng/mL}$ (75 nmol/L) for youth
- If deficient and unable to maintain with proper diet, consider daily MVI and
 - Vit D3 1000 U (< 5 years old)
 - Vit D3 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 prior to evaluation** in the clinic: 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
- ▶ **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.



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 choice is more obvious in PANDAS, where youth present with a sudden, acute onset of symptoms temporally associated with GAS infection
- Although many improve on antibiotics, many youth have residual symptoms, other immune therapies and standard behavioral treatment are often needed
- Considerations for proper diet, Vitamin D deficiency, and probiotics



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The Team