PANDAS are not Black & White

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PANDAS are not Black & White

They are Gray

Pediatric
Autoimmune
Neuropsychiatric
Disorders
Associated with
Streptococcal infections

PANDAS

- Pediatric
  - 3-12 year olds
  - M>F
- Autoimmune
  - Type II hypersensitivity reaction (antibody cross-reactivity)
  - Mechanism similar to rheumatic fever
- Neuropsychiatric Disorders
  - Obsessive compulsive disorder (OCD)
  - Tic disorder (TD)
  - Tourette syndrome
- Streptococcal infections
  - Group A Beta Hemolytic Streptococci (GABHS)

Why are PANDAS Gray?

- Do they exist?
- Diagnosis
- Treatment
- Prophylaxis

Do PANDAS Exist?

- 1994 case: 9 YO F w/ rheumatic chorea & OCD → Sx resolved with plasma exchange
- Neuropsychiatric features of rheumatic fever → ~70% had OCD Sx
- 1995 PITANDS
  - Pediatric Infection Triggered Autoimmune Neuropsychiatric Disorders
- 1998 PANDAS coined
- Subsequent investigations→ controversial results

Clinical Practice & Epi in Mental Health 2008, 4:13

Do PANDAS Exist?

Supportive studies	Nonsupportive studies
Murphy et al. [11••]	Kurlan et al. [12••]
Motor/behavior changes were noted to occur in relationship to positive GAS culture with support that repeated GAS increased risk.	GAS infections were not the only or even the most common antecedent event associated with exacerbations of tic disorders and/or OCD.
Snider et al. [44]	Singer et al. [14]
Penicillin and azithromycin prophylaxis were found to be effective in decreasing streptococcal infections and neuropsychiatric symptom exacerbations among children in the PANDAS subgroup.	Results do not support the hypothesis that PANDAS and TS are secondary to antineuronal antibodies.
Rizzo et al. [15]	Morris et al. [18•]
Positive anti-basal ganglia antibodies were present in higher rates in patients with TS than controls. Results supported the association between streptococcal infection and anti-basal ganglia antibodies in patients with TS.	Results confirmed an inability to distinguish PANDAS, TS, and controls by antibody measurements and raised concerns about the presence of an autoimmune mechanism in PANDAS.
Morer et al. [20]	Singer et al. [19]
No anti-basal ganglia antibodies were detected by immunohistochemistry in any samples, although two proteins were found in sera from patients only. The study supported the hypothesis of an autoimmune process underlying OCD or TS in some patients.	ELISA measurements did not differentiate between PANDAS and controls, suggesting a lack of major antibody changes in this disorder.
Mell et al. [31]	Schrag et al. [32•]
Patients with OCD, TS, or tic disorder were more likely than controls to have had prior streptococcal infection in the 3 months before onset date.	Results showed no increased risk of antecedent diagnosis of streptococcal infections among children diagnosed with tic disorder or OCD.

ELISA enzyme-linked immunosorbent assay, *GAS* group A streptococci, *OCD* obsessive-compulsive disorder, *PANDAS* pediatric autoimmune neuropsychiatric disorders associated with streptococcal infection, *TS* Tourette syndrome

Curr Infect Dis Rep (2010) 12: 103-109

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Diagnosing PANDAS

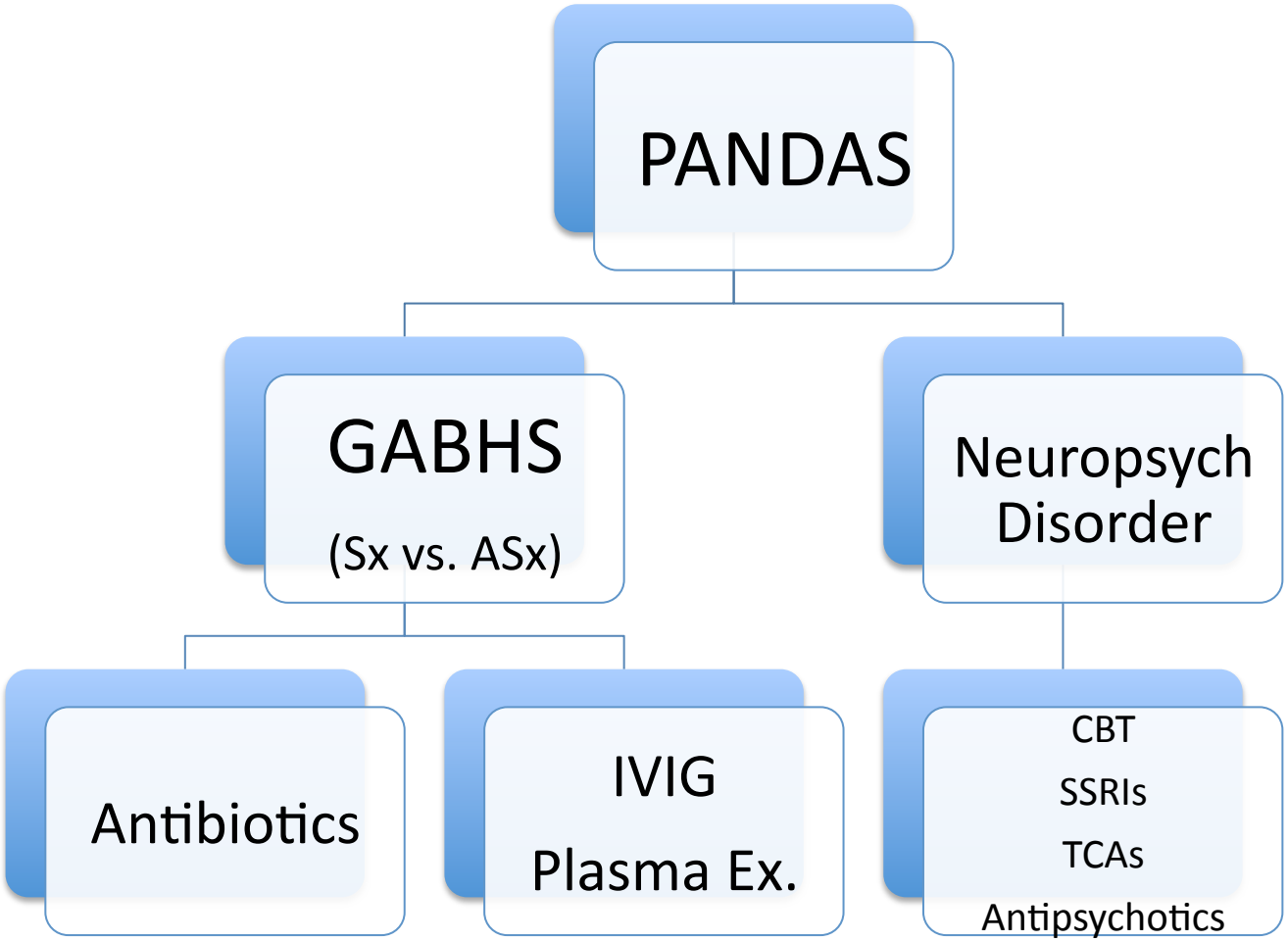
1. Pre-pubertal onset
2. OCD &/or TD per DSM-IV criteria
3. Abrupt onset & episodic course of Sx
4. Presence of neurological abnormalities during periods of Sx exacerbations
5. Temporal relationship of exacerbations w/ GABHS infection

Journal of Pediatrics Vol. 106, No.5

Diagnosing PANDAS

- Limitations
  - May not be able to distinguish PANDAS from other subsets of OCD or TD
  - Children in PANDAS studies had multiple neuropsychiatric comorbidities
    - ADHD, depression, anxiety, etcetera

Treatment


PANDAS
GABHS
(Sx vs. ASx)
Neuropsych Disorder
Antibiotics
IVIG
Plasma Ex.
CBT
SSRIs
TCAs
Antipsychotics

PANDAS Prophylaxis

- Penicillin prophylaxis is effective in preventing recurrences of rheumatic fever
  - Hypothesis that this would reduce neuropsychiatric exacerbations

Clinical Question

P	Patients meeting PANDAS criteria
I	Antibiotic Prophylaxis
C	Placebo
O	Infection rate Neuropsychiatric exacerbation rate Neuropsychiatric exacerbation severity

Search Strategy

Databases	-Cochrane, Embase, Medline, Pubmed, Google Scholar, Trip Database
Search Terms	-PANDAS, pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections, antibiotics, penicillin, azithromycin, erythromycin, prophylaxis, OCD, TD, Tourette Disorder
Limits	-Humans, English, Age 0-18 years, 1993-present
Results	-362 citations
Excluded	-Case reports -Patients not meeting PANDAS criteria -Treatment reports/studies
Analysis	-2 clinical trials

ORIGINAL ARTICLES

A Pilot Study of Penicillin Prophylaxis for Neuropsychiatric Exacerbations Triggered by Streptococcal Infections

Marjorie A. Garvey, Susan J. Perlmutter, Albert J. Allen, Susan Hamburger, Lorraine Lougee, Henrietta L. Leonard, M. Elizabeth Witowski, Billinda Dubbert, and Susan E. Swedo

Biol Psychiatry 1999;45:1564-1571

Garvey et al

D	-Randomized double blind cross over study -8 month duration -Children recruited over 3 years
P	-N=37 -PANDAS criteria -4-15 YO -TD or OCD per DSM-III-R or DSM IV -Hx of ≥ 2 strep-associated exacerbations
I	-Penicillin V 250mg PO BID x4 months, placebo x4 months
C	-Placebo x4 months, penicillin V 250mg PO BID x4 months
O	-Number of strep infections -Number of exacerbations -Overall severity of Sx

Garvey et al: Results

Table 1. Streptococcal Infections and Neuropsychiatric Symptom Exacerbations Throughout the Study Period

A Distribution of Streptococcal Infections According to Randomization Order

	Months after baseline							
Randomization order	1	2	3	4	5	6	7	8
PCN/PLA	1	0	3	1	6	2	1	1
PLA/PCN	3	2	2	4	3	3	2	1

Total penicillin = 14
Total placebo = 21

NSS

B Distribution of Exacerbations According to Randomization Order

	Months after baseline							
Randomization order	1	2	3	4	5	6	7	8
PCN/PLA	3	7	7	5	10	6	5	3
PLA/PCN	2	6	0	6	5	3	3	2

Total penicillin = 35
Total placebo = 38

NSS

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Total penicillin = 35
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Garvey et al: Results

Scores @ month 4	**Penicillin**	**Placebo**
GAS	76.36	78.86
CGI	3.64	3.93
YGTSS	13.39	12.97
CY-BOCS	3.27/2.52	3.96/2.96

GAS: Global Assessment Scale
CGI: Clinical Global Impression
YGTSS: Yale Global Tic Severity Scale
CY-BOCS: Child Yale-Brown Obsessions & Compulsions; Scale

Garvey et al: Conclusion

- Did not achieve an acceptable level of streptococcal prophylaxis
  - No conclusions can be drawn

Garvey et al: Strengths

- Blinding
  - Formulation
  - ADRs
- Tried to account for rise in strep infections during winter months
- Used validated Sx questionnaires

Garvey et al: Limitations

- Randomization method not stated
- Small sample size, no power calculation
- Definition of strep-associated exacerbation → 3 months
- Sx scores
  - YBTSS score 0-10 subclinical
  - CY-BOCS score 0-7 subclinical
- Co-interventions allowed, but not published
- Treated all +ve throat cultures→ contamination
  - Revised protocol during last year
- No comment on strep resistance rates
- Compliance assessment
- Sx monitored monthly, method not stated
- Global rating obtained from parents at month 8
- No ITT
- No comment on ADRs

Antibiotic Prophylaxis with Azithromycin or Penicillin for Childhood-Onset Neuropsychiatric Disorders

Lisa A. Snider, Lorraine Lougee, Marcia Slattery, Paul Grant, and Susan E. Swedo

Biol Psychiatry 2005;57:788-792

Snider et al

D	-Double blind RCT -12 month duration -Children recruited over 3 years
P	-N=23 -PANDAS Criteria -5-9 YO -TD or OCD per DSM-IV
I	-Azithromycin 500mg PO q week or penicillin V 250mg PO BID
C	-Retrospectively to no prophylaxis
O	-Primary: number of strep infections -Secondary: number of exacerbations

Snider et al: Results

Table 3. Summary of Streptococcal Infections and Neuropsychiatric Exacerbations

Streptococcal Infections[a]	Baseline Year	Study Year
Penicillin ($n = 11$)	1.9 (1.2 SD)	.1 (.3 SD)
Azithromycin ($n = 12$)	2.4 (1.1 SD)	.1 (.3 SD)
Neuropsychiatric Exacerbations[a]	**Baseline Year**	**Study Year**
Penicillin ($n = 11$)	2.1 (1.0 SD)	.5 (.5 SD)
Azithromycin ($n = 12$)	1.8 (.6 SD)	.9 (.5 SD)

[a] $p < .01$.

Snider et al: Conclusion

- Antibiotic prophylaxis was effective in decreasing strep infections & neuropsychiatric Sx exacerbations
  - If compliance is assured
  - Interpret results with caution

Snider et al: Strengths

- Blinding of formulation
- Compliance assessment
- Used validated Sx questionnaires

Snider et al: Limitations

- Randomization method not stated
- Small sample size
- Definition of strep-associated exacerbation
- Sx questionnaire scores not provided → ?disease severity
- Co-interventions allowed, but not published
- Treatment of +ve cultures →clinical status of patient?
- Penicillin as active comparator
- No comment on strep resistance rates
- Retrospective comparison
  - Chronic disorder that waxes/wanes
  - Close prospective follow-up
- Parent & child reports to assess Sx severity not based on a validated scale
- No ITT
- No comment on ADRs

Summary

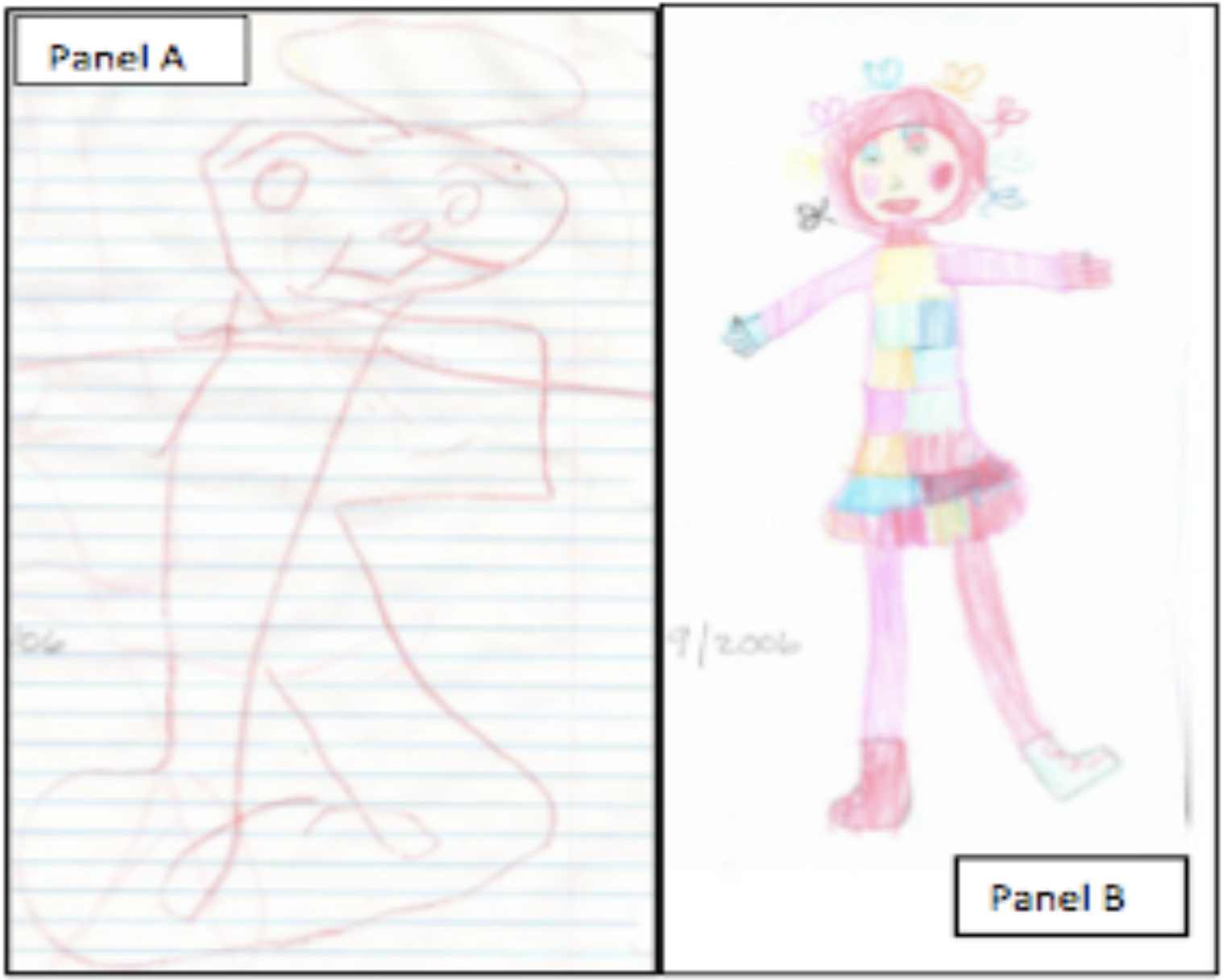
- Goals of Therapy

Cure disease/disorder	**?**
Reduce morbidity, symptoms	Mixed data, clinical significance?
Prevent ADRs	?
Maintain/improve quality of life	?

So why are some clinicians still interested in prophylaxis?

Ongoing Interest

- No methodologically sound study has been conducted
- Severe cases of TD/OCD
- May help diagnose PANDAS
- Could prophylaxis be SSRI, TCA, Antipsychotic sparing??


Panel A
Panel B

Questions

Rheumatic Fever

- 5 major criteria
  - Migratory arthritis (mostly in large joints)
  - Carditis & valvulitis
  - CNS involvement (sydenham chorea)
  - Erythema marginatum
  - Subcutaneous nodules
- 4 minor criteria
  - Arthralgia
  - Fever
  - Elevated ESR or CRP
  - Prolonged PR interval

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Secondary prophylaxis for rheumatic fever - Selection of therapy

	Continuous regimen	
	Adults >27 kg	**Children ≤27 kg**
Penicillin G benzathine intramuscular (Bicillin LA)	1.2 million units every 4 weeks*	600,000 units every 4 weeks*•
Penicillin V oral	250 mg orally twice daily	250 mg orally twice daily
Sulfadiazine	1000 mg orally once daily	500 mg orally once daily
Allergy to penicillin and sulfadiazine:		
Azithromycin$^{\Delta}$	250 mg orally once daily	5 mg/kg orally once daily (up to 250 mg)

* In high-risk situations, administration every three weeks is justified and recommended.
• For small children and infants: 25,000 units per kg intramuscularly every 4 weeks or 3 weeks (high-risk).
Δ Macrolide susceptibility testing should be pursued prior to use of this drug class. Erythromycin is an acceptable alternative to azithromycin, although the latter has fewer adverse effects and permits once daily dosing. Erythromycin dosing for adults: 250 mg orally twice daily. Dosing for children: 20 mg/kg/day divided twice daily (maximum 500 mg per day).

Modified with permission from: Gerber MA, Baltimore RS, Eaton CB, et al. Prevention of Rheumatic Fever and Diagnosis and Treatment of Acute Streptococcal Pharyngitis: A Scientific Statement From the American Heart Association Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee of the Council on Cardiovascular Disease in the Young, the Interdisciplinary Council on Functional Genomics and Translational Biology, and the Interdisciplinary Council on Quality of Care and Outcomes Research. Circulation 2009; 119(11):1541-51.

Sydenham Chorea

- Most frequent neurological manifestation of RF
- Rapid, uncoordinated jerking movements affecting primarily face, feet, & hands

Definitions

- Tics
  - Sudden, repetitive, non-rhythmic movements (motor tics) and utterances (phonic/vocal tics) involving discrete muscle groups
- TS
  - One of several tic disorders
  - DSM-IV
    - Multiple motor tics + at least 1 vocal tic for >1 year

PANDAS Pathophysiology

- Ab targeted to the dominant epitope of GABHS N-acetyl-beta-D-glucosamine may alter neuronal signal transduction thus causing alterations in behavior & movement control
- Ab can induce calcium-calmodulin dependent protein (CaM) kinase II activity

Clinical Practice & Epi in Mental Health 2008, 4:13

ASO Titers

- Virulence factor produced by strep
- Blood test to measure ABs against streptolysin O
- Vary w/ age, season, & geography
  - Healthy school age children: 200-300 units/mL
  - Carriers have very low titers, just above detectable
- Post pharyngitis: Peak 4-5 weeks, rapid decline, 6 months, slower decline

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Anti-DNAse B Titer

- Blood test to measure Abs against DNAse B
- Detectable for 6-9 months post inection

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OCD

- Emerging data from morphological & functional neuroimaging studies
  - Alteration in the orbitofrontal-caudate-thalamic circuits
- Adult onset OCD
  - 2ndry to ischemic stroke or traumatic brain injury involving the basal ganglia
- Serotonin component

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