

## **1 PANDAS & PANS**

### **An Integrative Approach**

- Dr. Jill Crista

## **2 Disclaimer**

- By proceeding, the viewer agrees that the contents of this site, such as text, graphics, images, video, and other material contained on the Dr. Crista site are for informational purposes only.
- Dr. Jill Crista does not provide medical advice, diagnosis or treatment. The content is not intended to be a substitute for professional medical advice, diagnosis, or treatment.
- Always seek the advice of your physician or other qualified health provider with any questions you may have regarding your medical condition. Never disregard professional medical advice or delay in seeking it because of something you have read on the Dr. Crista site.
- If you think you may have a medical emergency, call your doctor or 911 immediately.
- Dr. Crista does not recommend or endorse any specific tests, physicians, products, procedures, opinions, or other information that may be mentioned on the site.
- Reliance on any information provided by Dr. Crista, Dr. Crista's employees, others appearing on the site at the invitation of Dr. Crista, or other visitors to the site is solely at your own risk.
- If you are taking this course as a parent or member of the public, you understand that the information herein is intended for medical practitioners with the medical training and discernment to know how to apply the therapies and treatments included, and that the treatments discussed, including doses, may not be appropriate for your child.
- All material in this course is copyright protected unless stated otherwise. Contact Dr. Crista for permissions of use.

## **3**

- Diagnostics

## **4 Overview**

- Course Outline
- 1. Symptoms
- 2. Mechanisms
- 3. Diagnostics
- 4. Conventional treatment approach
- 5. Integrative treatment approach
- 6. Recovery essentials
- 7. Cases

## **5 Conventional management**

- 1. Control inflammation  
NSAIDs, steroids
- 2. Prevent/treat infection  
Prophylactic Abx + perianal Strep tx
- 3. Remove reservoirs of infection  
Tonsillectomy
- 4. Correct neurotransmitters  
SSRIs/SNRIs
- 5. Manage behaviors  
CBT
- 6. Immune modulation  
IVIg, Rituximab, CellCept, Plasmapheresis

- Flowchart from PANDAS Physician Network website

## 6 Control inflammation

- Ibuprofen ~  
NSAID. MOA: non-selective inhibitor of cyclooxygenase (COX) which is required for the synthesis of prostaglandins via the arachidonic acid pathway.
- Trial period/flare management  
10mg/kg bid-tid x 2 weeks.
- Maintenance dose varies (Naproxyn may be used for maintenance.)
- Tell parents this is intended as prescription strength, may not match OTC dosing, so watch closely for s/e's
- S/E - nausea, reflux, bloating, tinnitus, edema, and stomach, intestinal or unusual bleeding
- If significant improvement from trial dose, then you know that  
"taming the flame" is an important target of tx.  
Variety of options other than, or used with, NSAIDs

## 7 Control inflammation

- Corticosteroids ~  
Dexamethasone. MOA: glucocorticoids modulate the inflammatory response by repressing the expression of pro-inflammatory cytokines by immune cells.  
C/I - hypersensitivity to dexamethasone, uncontrolled infection, systemic fungal infection  
S/E - thrush, acne, increased risk of infection, dyspepsia, insomnia, wt gain, h/a, htn, hyperglycemia, confusion/ amnesia, vertigo, growth stunting, bone loss, bruising, muscle atrophy

- Oral Burst/Taper ~ PANDAS Physician Network  
Oral prednisone 2 mg/kg for 1 week  
-then taper to 1 mg/kg the second week  
-0.5 mg/kg the third week  
-0.5 mg/kg QOD for the final week  
The maximal initial starting dose is 60 mg per day.  
Am dosing and/or before 3pm to mitigate problems with sleeping
- Per Stanford PANS clinic "for autoantibody-mediated encephalitis, NSAIDS and oral steroids often won't come close."  
IV: 3mg/kg/d by continuous IV infusion x 3d/mo x 6mo  
Follow with Rituximab or Cellcept (mycophenolic acid/mold derivative)

## 8 Prevent infection

- Prophylactic Antibiotics ~  
Triggering event is long gone  
GABHStrep is target = "cell wall" beta-lactam antibiotics  
ex: Penicillins, Cephalosporins, Cephamycins  
Per some specialists, dose really matters, don't go too low  
le: Augmentin (875mg amoxicillin + 125mg clavulanate) bid  
Clavulanate - also beta-lactamase inhibitor  
S/E - diarrhea, candida, liver/kidney toxicity

- Per Stanford PANS Clinic, to keep in remission ~  
IM Penicillin (long-acting) q2-3 weeks  
Even if were compliant on oral AB  
Sydenham's chorea similarity  
More fitting for PANDAS than PANS?
- PMID: 33728634 2021 Cochrane Review. Different antibiotic treatments for Group A Streptococcal pharyngitis.

## 9 Perianal Strep

- Commonly persistent. Tonsils/gut serve as co-infected reservoirs.
- Studies show that treating all the potential reservoir locations, rather than just a topical cream, is most effective.
- Topical silver sulfadiazine or pharmaceutical antibiotics \*Along\* with oral antimicrobials, until there's no sign of infection on culture.
- ALWAYS re-culture to make certain is eradicated.
- 
- PMID: 30627524

## 10 Antimicrobial sources

- Many are derived from mold, some are actual mycotoxins  
Compare to enviro testing (if available) before prescribing  
Will affect susceptibility and side-effects if use same source Rx as environment.
- Penicillium  
Penicillin, amoxicillin
- Acremonium  
\*Cephalosporins
- Actinomycetes/actinobacteria  
Tetracyclines, macrolides, aminoglycosides, rifamycins
- Actinobacteria  
Ivermectin

## 11 Side-effects as mold clues

- Penicillin
- Allergy - IgE-mediated pruritus, rash, GI  
Correlated with exposure to environmental Penicillium
- "IgE-mediated allergy wanes over time, with 80% of patients becoming tolerant after a decade."...why? tolerance or move?
- "Cross-reactivity between penicillin and cephalosporin drugs occurs in only about 2% of cases."
- +penicillin skin testing, high-risk anaphylactic cases, +spores
- ∴ Low- to moderate-risk missed w skin testing, +mycotoxins
- PMID: 30644987, 405332

## 12 Side-effects as mold clues

- Tetracyclines
- S/E - photophobia  
Correlated with mold exposure  
Vitamins A & D deficiency also correlated,  
common in mold-exposed patients,  
esp if being treated with LT Rx binders
- PMID: 14650691, 26269110

### 13 Side-effects as mold clues

- Macrolides
- S/E - Tinnitus  
Correlated with mold exposure  
Neurotoxic. "First pass" effect at the sinuses  
Cavernous sinus - many nerve pass-throughs  
Internal carotid artery, abducens nerve (cranial nerve VI)  
Cranial nerves III, IV, V1, V2, (oculomotor, trochlear, ophthalmic, and maxillary)
- S/E - Cholestatic hepatitis  
Inflam/congestion of bile ducts also correl with mold exposure

### 14 Remove reservoirs of infection

- Tonsils and sinuses can become reservoirs of infection.
- Much scientific debate about tonsillectomy. In a survey conducted by the PANDAS Physician Network, parents reported anecdotal evidence that tonsillectomy may have benefit.
- IME some benefit, and some don't. Leaves parents conflicted over whether surgery is the right decision.

- Where I've seen clear benefit of tonsillectomy are in the children with a specific combination of factors:  
Free of perianal Strep, verified by culture.  
Been dairy free for more than 6 weeks. (Common cause of enlarged, chronically infected tonsils.)  
Free of cavities or dental infections.  
Gut microbiome has been addressed.  
Tonsils have been aggressively tx'd, yet remain large, boggy, cryptic, and may form tonsilloliths.  
Tonsils are large enough to cause snoring or obstructive sleep apnea.
- Tonsillectomy in these cases reduces infection and recurrence of autoimmune flares, and improves sleep.
- Culture or NGS-PCR test the removed tissue.  
If + for biofilm species, must be treated or may persist in other tissues/sinuses.  
Prevotella - Gram neg anaerobe - most commonly found by Dr. Trifiletti.  
Also commonly find Pseudomonas and Klebsiella.

## 15 PANDAS Physician Network Website: Tonsillectomy

- "While there have been no published research on the effect of tonsillectomy on PANS or PANDAS patients, there has been unpublished findings and anecdotal evidence that show tonsillectomy may have benefit. Many PANS/ PANDAS patients have damaged or cryptic tonsils, but the potential benefit of tonsillectomy is not limited to patients with those tonsil characteristics.
- In an unpublished research study done at Georgetown Medical Center, PANDAS patients had their tonsils removed, analyzed, and the children subsequently tracked for over six months. The tonsils relative to non-PANDAS patients had many pathogens, most prominent being staphylococcus (staph). Streptococcus pyogenes was not found in PANDAS patients but was present in non-PANDAS controls. Other notable pathogens included MRSA, E. coli, Pseudomonas and Serratia marcescens. The absence of Streptococcus in the PANDAS cohort suggests that once the patient has been "sensitized" other pathogens can induce neurologic symptoms in susceptible patients.
- In addition, the tonsils belonging to PANDAS patients contained elevated levels of TH17, indicating a consistent immune response to the pathogens lodged within the tonsils. TH17 has been found in animal PANDAS research to be a potential agent for opening the blood brain barrier, allowing inflammation in targeted regions of the brain.



- The Georgetown study and physician experience indicates that removal of the tonsils can provide remission of PANS and PANDAS symptoms for some patients. There is no marker to determine which patient a tonsillectomy will result in remission of PANS/PANDAS symptoms.
- A clear benefit of tonsillectomy that was found in the Georgetown study and further observed by practitioners who see many PANS/PANDAS patients, is that those PANS/PANDAS cases that have undergone tonsillectomy, have a significantly lower chance of recurrence post-immunotherapy such as IVIG. Since immunotherapy suppresses the potential cause of basal ganglia encephalitis and in some cases like IVIG "reboots" the immune response, then removing a consistent infectious trigger housed within the tonsil or removing a repository for new pathogen agitators would most likely be beneficial."

## 16 What factors lead to the benefit?

- 2016 Review by Windfuhr. Tonsillectomy remains a questionable option for pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS).
- "The positive outcome after TE as reported in case studies may be influenced by the postoperative medication and is not supported by the results of large-scale studies. In the light of the considerable postoperative morbidity rate, it appears wise to indicate TE for PANDAS only in supervised clinical studies."
- Options to address sinus and tonsil health is covered in the next module.
- PMID: 28025607

## 17 Correct neurotransmitters

- SSRIs/SNRIs
  - Ultra low dose required (consistent with toxin-based syndromes)
  - Postulate that flare increases permeability of BBB
  - Equates to "sprinkles" of typical initial dose, ie: 1/8-1/4 normal dose
    - ex: 6.25mg sertraline, 2mg fluoxetine
  - Tendency to increase dose bc not responding = miss therapeutic window
  - Often will cut dose rather than increase
  - Also must account for normal wax/wane of dz
- Must weigh the costs to the brain living in torture vs S/Es of Rx
  - "Never belittle the history" & "assess for safety" (behaviors/nourishment)
  - Views rage attacks as "defensive aggression" ie: cornered animal
  - Often won't remember bc "no one's home" during the event
  - Safety for all is imperative. Monitor triggers (hunger, fatigue, infection risk)
  - Dr. Margot Thienemann, Stanford PANS Clinic
  - \*Recommend Stanford CME she offers: 1st steps when you meet w PANDAS/PANS pt
- EMDR - helpful also for parents who are perpetually in dread, waiting for next flare

## 18 Manage behaviors

- CBT ~
  - Cognitive-Behavioral Therapy
  - My bias - worsens limbic imbalance
  - False 'belief' or wiring? Or are they reacting to triggers we haven't yet identified.
  - Highlights the need for paradigm shift - recognize trauma-induced vs physiologically-induced behaviors
  - I encourage a middle ground - honor the sensory input and temper the reaction.
  - Utilize CBT or other like measures with modification to help the child gain skills.
- MCBT more fitting
- CBT is best for the parents!
- Cautionary Tale

## 19 Intravenous Immunoglobulin Therapy (IVIG)

- Not every child with PANDAS or PANS needs this to recover.
- Hesselmark et al, cohort of Swedish patients: Antibiotics and IVIG were rated as the most successful treatments by participants and were associated with higher patient satisfaction.
- The purpose is suppression of Ig production, resulting in loss of autoantibodies/memory cells.
- Dose and route of administration are paramount.  
Dose: 1.5-2 g/kg given over 2 days given IV [note: dose typo in my book]
- Needs to be high dose to accomplish suppression. SQ cannot hit the peak plasma level required for suppression.
- Requires repetition to maintain the suppression - IME q 4-8 weeks. The "one and done" has not been durable.
- Insurance often pressures you to use the typical supportive dose or SQ. This is NOT recommended. Can flare autoimmunity.
- Must check IgA w subclasses (as well as IgG w subclasses) to choose IVIG brand. Some include IgA (risk of thrombosis if not also IgA deficient.)
- I suggest referring to collaborative Allergist/Immunologist for administration. Home health services are available, but I don't recommend this if you don't have the specialty, and especially not for the first few rounds.
- PMID: 31009235

## 20 IVIG supportive care

- IVIG side effects ~  
Occur on days of infusion + a few days following.  
Low-grade fever, headache, flushing, itching, back pain, increased blood pressure, and fatigue.  
May also see a temporary autoimmune thyroiditis, which tends to go away once the child is done with treatments after 6-9 mo's.

- S/E management ~  
Diphenhydramine, ibuprofen on infusion days + few days following.  
May use IV glutathione push or steroids to prevent severe headaches.  
Write on the order \*SLOW INFUSION RATE\* ~ 6-8 hours per day: many AEs can be prevented. Home health nurses will go faster if not stipulated every time.
- Many side effects can be prevented with 3 simple things ~  
IV hydration - 500 mL hydration IV bag just before the IVIG  
Slow drip rate  
Glutathione

## 21 IVIG genetic prognostics?

- Is it possible to screen for who will respond best to IVIG and who might respond better using it as step therapy to Rituximab or Plasmapheresis?
- Empirically, best responders have genetic snp of Fcγ Receptors. Could Ig senescence be a contributing factor for persistence?
- 2010 Review: "Possible mechanisms of action of IVIg in autoimmune and inflammatory diseases are: intact Fc-dependent blockage of IgG (as in ITP), inhibition of membrane attack complexes (C5b-C9) and activated components C3b and C4b (as in Kawasaki's disease), and anti-idiotypes against autoantibodies (as in acquired hemophilia due to autoantibodies against factor VIII). IVIg also contains various cytokines and natural antibodies that may act against pathogens, altered molecules, cells, autoreactive B cell clones, and tumors."
- PMID: 19590986

## 22 Immune modulation

- Rituximab ~  
Humanized chimeric anti-CD20 monoclonal antibody, which is expressed on the surface of pre-B and mature B-lymphocytes. After binding to CD20, rituximab mediates B-cell lysis.  
"we still do not fully understand the mechanisms of action ... Direct signaling, complement dependent cellular cytotoxicity and antibody dependent cellular cytotoxicity all appear to play a role."
- Plasmapheresis ~ **Ochratoxin**  
"Blood cleaning" procedure - child's blood is removed through IV catheter and processed by a plasmapheresis machine, which spins it to separate the formed elements (RBCs, WBCs, platelets) from the plasma. The plasma is removed and replaced with equal volumes of albumin. The albumin is mixed with the child's blood components and returned to his body through a second IV catheter. Multiple procedures are needed, often requires insertion of a central line.  
Carries significant, but manageable risks, it should be done only in pediatric apheresis centers.
- PMID: 20350658. Other Sources: PANDAS Physician Network, Journal of Child and Adolescent Psychopharmacology Vol. 25, No. 1

23

- Diagnostics