

1 PANDAS & PANS

An Integrative Approach

- Dr. Jill Crista

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3 Course details

- 7 Modules on-demand
- Downloadable slides and resources mentioned are found in each Module under the Materials tab

- Quizzes are at the end of the lessons where they pertain
- Certificates of completion are sent for all student types
- CME/CE certificates - please allow 1 week
- Access for 1 year
- Survey
- 30-day money back guarantee, as long as not more than 25% of course materials have been downloaded or videos viewed.
- Copyrighted course assets and equal exchange ~
Please support my work and the voluminous hours I've spent collating my years of experience and research to put together this scientific presentation.
Please resist your healer's heart urge to share widely - even and especially if you're a parent!
I understand - I've been there.
And I paid my kids' doctors with gratitude.
- I ask for the same consideration.

4 Overview

- Course Outline
- 1. Symptoms
- 2. Mechanisms
- 3. Diagnostics
- 4. Conventional treatment approach
- 5. Integrative treatment approach

- 6. Recovery essentials
- 7. Cases

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- Paradigm Shift

6 Overview

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7 Autoimmune encephalopathies

- PANDAS = pediatric autoimmune neuropsychiatric disorder associated with streptococcal infection
- PANS = pediatric acute-onset neuropsychiatric syndrome
- A third category? "PLANS" or "NADAL"
- Autoimmune encephalitis (AE) found to be as common as infectious encephalitis (Mayo Clinic 2018)

- Antecedent state: immune depletion
- Autoimmune trigger: INFECTIONS &/or TOXICANTS
- Target tissues depend on specific type of AE
- PANDAS/PANS/BGE ~
brain stem/basal ganglia, GI, kidneys (theorized)

8 Overview

- Incidence: Lacking large population data, however roughly estimated as 1 in 200-250 children
- Prevalence: males>females 2.6:1
- FHx: autoimmune disease
- Autoimmune relapsing-remitting pattern
- Average 3 month pattern
- Challenge of mgmt:
Wax: flare/natural progression or new exposure?
Wane: treatment effect or natural remission?
- Some variation PANDAS vs PANS
- Different diagnostic criteria

9 Symptoms in order of prevalence

- Separation anxiety
- Inability to concentrate
- Urinary frequency, urgency, or urinary accidents

- Handwriting deterioration
- Alterations in sleep - insomnia, night terrors, inability to sleep alone
- Behavioral regression
- Hyper-alert appearance; enlarged pupils
- Hyperactivity
- Inattentiveness
- Tics
- Learning difficulties
- Short-term memory loss
- Aggression
- Sensory alterations - hypersensitive or insensitive
- Disordered eating
- Hallucinations, rarely

10 Clinically Observed Symptoms: PANS/PANDAS

- Separation anxiety (98%)
- Inability to concentrate (90%)
- Urinary frequency, urgency, or urinary accidents (90%)
- Handwriting deterioration (90%)
- Alterations in sleep - insomnia, night terrors, inability to sleep alone (80%)

- Behavioral regression
- Hyper-alert appearance; enlarged pupils (80%)
- Hyperactivity, inattentiveness (70%)
- Tics (70%)
- Learning difficulties (60%)
- Short-term memory loss (60%)
- Aggression (60%)
- Sensory alterations - hypersensitive or insensitive (40%)
- History of repeat UTIs or sinusitis
- Disordered eating (20%)
- Hallucinations (10%)
- Clinical observations O'Hara/Wells presentation WNDA Annual Conference 2021

11 PANS Phenotype (n=43)

- Anxiety 43 (100)
- Panic/Somatica 15 (35)
- Generalized anxiety disorder (GAD) 20 (47)
- Separation anxiety disorder (SAD) 33 (77)
- Social phobia 12 (28)
- School avoidance 20 (47)

- Mood and behavioral symptoms 43 (100)
- Emotional lability and/or increased irritability 43 (100)
- Anxious/Depressed 19 (46)
- Withdrawal/Depression 10 (24)
- Somatic complaints 9 (22)
- Social problems 2 (5)
- Thought problems 21 (51)
- Attention problems 8 (20)
- Rule-breaking behavior 3 (7)
- Aggressive behavior 12 (29)
- Suicidality (n=33) 10 (30)
- Behavioral regression 36 (84)
- Deterioration in school performance 36 (88)
- Sleep disturbance 36 (84)
- Tics 30 (70)
- Simple 30 (70)
- Complex 12 (28)
- Sensory abnormalities 26 (61)
- Urinary problems 24 (56)

- Frequent urination (pollakiuria) 19 (44)
- Enuresis 11 (26)
- Handwriting deterioration; 7–14 years (n=30) 17 (57)
- Food restriction 20 (47)
- ADHD diagnosis 20 (47)
- Inattention 11 (26)
- Impulsivity/hyperactivity 14 (33)
- Oppositionality 11 (26)
- Irrational thinking and/or psychotic symptoms 12 (28)
- Visual hallucinations 5 (12)
- Olfactory hallucinations 4 (9)
- Auditory hallucinations 3 (7)
- Mydriasis 10 (23)
- Choreiform movements 9 (21)
- Anorexia (not caused by PANS-OCD) 5 (12)
- Visuospatial/Motor impairment (n=42) 28 (67)
- Obsessive compulsive symptoms
- Harm to self and/or others 39 (91)
- Ordering and/or arranging, symmetry 30 (70)

- Contamination 29 (67)
- Sexual and/or religious 16 (37)
- Collecting and/or hoarding 14 (32)

12 Stanford PANS Clinic Cohort (n=220)

- Anxiety (97%)
- Sensory amplification (97%)
- Sleep issues (93%)
 - Insomnia, nightmares, restless sleep, reverse cycling, REM motor disinhibition = REM Behavior Disorder (RBD)
- Obsessions & compulsions (92%) [major criteria]
- Mood disorder (92%)
- Irritability/aggression (90%)
- Behavioral regression (73%)
- Deterioration in school (72%)
- Urinary symptoms (66%)
- Eating restriction (53%) [major criteria]
-
- Frankovich, Stanford PANS clinic, presentation Neuroimmune conference May23

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14 PANDAS Dx Criteria

- Category 1 ~Presence of OCD (compulsions) and/or tics, particularly multiple, complex or unusual tics
[must be severe enough to meet criteria for OCD or a tic disorder and interfere with the patient's ability to function at pre-illness levels]

- Category 2 ~Age Requirement
[first evidence between 3yo and puberty]
- Category 3 ~Acute onset and/or episodic (relapsing-remitting) course
[with abrupt, dramatic, debilitating exacerbations of existing symptoms, at which time the symptoms seem to “explode” in severity]
- Category 4 ~ Association with Group A Streptococcal (GAS) infection
[evidence of GAS infection found without apparent pharyngitis]
- Category 5 ~ Association with Neurological Abnormalities
[abnormal results on neurological examination. Motoric hyperactivity and adventitious movements such as choreiform movements or tics are particularly common]
- Comorbidities ~ anorexia, urinary frequency, mydriasis, insomnia, abd pain boys>girls
- PMID: 28989283

15 PANS Dx Criteria

- Category 1 ~ An abrupt, acute, dramatic onset of obsessive-compulsive disorder or eating restriction
[many treating docs see a nuanced acute onset, owing to congenitally acquired infxns]
- Category 2 ~ 2 co-morbid symptoms (also sudden onset):
 1. Anxiety (commonly severe separation anxiety)
 2. Sensory dysregulation (light, sound, and/or pain) or motor abnormalities (handwriting deterioration, piano fingers, tics, or motoric hyperactivity)
 3. Behavioral (developmental) regression
 4. Deterioration in cognitive functioning (school performance)
 5. Mood disorder (emotional lability, depression, irritability, rage)
 6. Urinary symptoms (polyuria, urge, enuresis)
 7. Severe sleep disturbances
 [most have 5-6 co-morbid symptoms]

- Category 3 ~ Symptoms not better explained by a known neurologic or medical disorder
- Category 4 ~ Age requirement – any, as long as pediatric
- Comorbidities ~ mydriasis, generalized abdominal pain
- PMID: 28989283

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17 Differential Diagnoses

- Obsessive-compulsive disorder (non-PANDAS/PANS)
- Tourette syndrome
- Sydenham's chorea (acute rheumatic fever)
- Abuse and/or trauma
- Other encephalidities (AE, NMDA-R)
- Medications, recreational drugs
- Post-concussive autoimmune hypophysitis
- Tumor
- Cerebral vasculitis, autoimmune vasculitis, Behcet's syndrome (Herpes?)
- And of course, myriad unrecognized contributing environmental and infectious factors (ie: novel viruses)

18 PANDAS or SC?

- Is PANDAS actually Sydenham's chorea 2.0?
- Both are the result of a Strep infection.
- Both conditions have OCD sx and involuntary or unpredictable movements as part of their dx criteria.
- May have ID'd what distinguishes them - different Strep proteins may lead more to one than the other, but it remains a diagnostic challenge.
- About 1/3 with PANDAS or OCD have the choreiform movements seen in SC.
- SC may cause more severe OCD symptoms, while also resolving sooner than PANDAS.
- Be mindful of this close look-alike. SC is a common sx of rheumatic fever
- and therefore may require treatment strategies for RF.
- PMID: 25301689

19 Distinguishing from other AEs

- Distinguish by symptomatology that's missing.
- IE: NMDA-R AE
 - seizures
 - myoclonus
 - coma
 - focal neurological signs

20 Genetic Predisposition?

- PANS: HLA alleles:
HLA-B 38, 52, 55

- My own observations:
 - Snps related to IgG: Fcγ Receptors
 - Snps related to NTs: COMT, MAOA
 - Snps related to detox:
 - Phase I: CYP1A2, CYP1B1, CYP3A4 (mold)
 - Phase II: GSTM1, MTHFR, SUOX
 - Snps related to histamine: DAO

21 OCD in children

- Obsessive-compulsive uncoupling
- Obsessions = thoughts ~
 - Often involves a silent experience of intrusive thoughts
 - Intrusive thoughts interrupt normal cognition = looping/lack of focus
 - Cause = neuroinflammation impeding normal brain chemistry/fxn
- Compulsions = behaviors ~
 - Involves a sense of lack of control
 - Take control of what they can
- *By listening to these with an investigative mind, they often point to the causal issue.
 - controlling adherence to routines/everyone else must as well - adrenals
 - avoidance of certain people - strep carriers
 - food avoidance - digesting increases LPS, neurological dysphagia
 - must look left or bad things - a need for craniosacral re-alignment
 - hand-washing - fear of further infection/need for immunomodulation

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- Symptoms
- Next up:
- Mechanisms

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- Mechanisms

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5 PANDAS/PANS mechanisms

- Overview of what the research tells us to date ... (expect changes as our knowledge evolves)
- Pre-existing immune depleted state
- Microbiome alteration
- T-cell mediated damage to the brain triggered by infection AND toxicants
- Microglial activation → chronically “primed” neuroinflammation
- Damage to dopamine receptors & cholinergic interneurons
Altered central dopamine, glutamate, ACh utilization → excitatory
- Impaired innate safety systems
Cell danger response → limbic/vagal dysfunction
- CNS structural alterations

6 PANDAS/PANS Mechanism

- Bad parenting!???

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8 PANDAS/PANS Mechanism

- "It's impossible to know the feeling of losing a child

- "It's impossible to know the feeling of losing a child, and have that child sitting right in front of you."

9 PANDAS/PANS Mechanism

- "Maybe you're just a little tired. Try taking a nap."
- "Have you considered parenting classes?"
- "You just need to be more strict."
- "Kids have tantrums."
- "Maybe she's just a picky eater, have you tried ice cream?"

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11 Pre-existing immune depleted state

- Top 2 negative sequela for those with immune depletion ~

1. Increased risk of infections
2. Increased risk of developing an autoimmune disorder

- ↑ rate of IgA deficiency in pediatric OCD compared to children with ASD and anxiety.
- ↑ rate of IgA deficiency in pediatric OCD compared to adults with OCD.
- Dendritic cell role. May have specificity to Strep &/or nasal infection. Strep inhibits dendritic cell maturation.
- PMID: 30892924, 30516814, 26417101, 19712038

12 Infection and risk for mental disorders

- Do infections increase the risk of subsequent mental disorders during childhood and adolescence?
- Population-based cohort study using Danish nationwide registers.
- >1 million individuals born in Denmark between 1995 and 2012
- All treated infections were identified in a time-varying manner, including severe infections requiring hospitalizations and less severe infection treated with anti-infective agents in the primary care sector.
- Findings ~
Severe infections requiring hospitalizations increased the risk of hospital contacts due to mental disorders by 84% and the risk of psychotropic medication use by 42%.

Less severe infection treated with anti-infective agents increased the risks by 40% and 22%, respectively; the risks differed among specific mental disorders.

- PMID: 30516814, 26417101, 19712038

13 Immune system of the brain

- 2/3 of the brain is glial (immune), 1/3 is neurons

- 3 glial types - microglia, astrocytes, oligodendrocytes
- Microglia ~
Brain "macrophages", scavengers
Modulate neurogenesis, influence synaptic remodeling, and regulate neuroinflammation by surveying the brain microenvironment
- Astrocyte ~
Involved with glutamate and GABA activity, clean up synaptic cleft, BBB integrity
- Oligodendrocyte ~
Myelinating, axonal metabolic support
-
- Journal of Leukocyte Biology 2008, Dilger and Johnson

14 Innate activation

- Innate I/S of brain can be activated in 4 ways ~
 - 1. Pathogens
 - 2. Vagal afferens pathway from enteric n.s./hepatic projections (Kupffer cells)
 - 3. Non-canulized pathway (inflam cytokines)-some xBBB through passive diffusion (IL-1 β)
 - 4. Pathways involving blood vessels and astrocytes (ie: heat-shock proteins)
- Journal of Leukocyte Biology 2008, Dilger and Johnson

15 Inflammasome

- Systemic inflammation shifts the brain microenvironment towards a proinflammatory state

Systemic inflammation shifts the brain microenvironment towards a proinflammatory state.

- OCD patients had higher levels of IL-18, IL-1Ra, and TNF, compared to the healthy controls.
- Blood cells of OCD patients have increased expression of NLRP3 inflammasome - an important component of the innate immune system.
- Expression of genes encoding for NLRP3, caspase-1, ASC, IL-1 β , IL-1RN, and TNF are significantly increased in peripheral whole blood of psychiatric patients compared to matched healthy controls.
- "The findings support the inflammation hypothesis for markedly ill psychiatric patients across diagnostic groups."
- The paradigm change in mental health.
- PMID: 27149601, 31786499, 36911567

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17 What defines "self" vs "other"

- Autoimmune = loss of tolerance to "self"
- "Self" largely determined by our gut microbiome
- We're more microbe than man - outnumbered by gut microbiome in both cell count and total DNA
- Autoimmune dzs are linked to unique microbiome composition (ie: lower Firmicutes/Bacteroidetes ratio), reduction of gut commensals, altered gut integrity
- Fecal microbiota transplantation (FMT) or inoculation with specific microbes in animal models of ADs support the hypothesis that alterations of gut microbiota influence autoimmune responses and disease outcome.
- Ie: changes to the gut commensals and periodontal disease have been proposed as important factors in the pathogenesis of RA
- PMID: 35534624, 32731813, 32038645, 29920643

18 Microbiome- Gut-Brain Axis

- Bidirectional crosstalk between the gut and the brain
- Various afferent and efferent pathways influence Dz pathogenesis - vagus n., I/S, bacterial metabolites
- Bottom up ~
Antibiotics, environmental/infectious agents, intestinal NTs/neuromodulators, sensory vagal fibers, cytokines, metabolites all convey information to CNS about the intestinal state
- Top down ~
Conversely, the HPA axis, CNS regulatory areas of satiety, and neuropeptides released from sensory nerve fibers affect the gut microbiota composition
- Such interactions influence the pathogenesis of disorders where inflammation is implicated, such as mood

disorder, ASD,
ADHD, MS, obesity

- Microbiome dysbiosis shown to affect cognitive function
- PMID: 30892924, 28948967, 32130879, 35087123, 34205336, 29903615

19 Microbiome-microglial connection

- Brain microglia not only respond to local brain signals but also input from the periphery, including the GI tract and microbiome
- Microbiome plays a pivotal role in regulating brain microglial maturation and function in the brain, as well as production/consumption of NTs.
- Microbial products (LPS) and microbially produced metabolites act as signalling molecules that have direct and indirect effects on the CNS and the ENS (motility)
- Altered microbial composition is reported in neurological disorders with known brain microglial involvement in humans
- Circadian rhythm: The composition of the gut microbiota is subject to diurnal variation and is entrained by host circadian rhythms. In turn, a diverse microbiota is essential for optimal regulation of host circadian pathways.
- PMID: 30385457, 26046241, 30614568, 31478105, 29903615

20 Biomes, BBB, and OCD

- During dysbiosis, gut-brain axis pathways are dysregulated and associated with altered permeability of the BBB and neuroinflammation
- Post-prandial endotoxemia (plasma LPS) is found in approximately 1/3 of those eating Westernized diet, more common with dysbiosis
- LPS caused the loss of dopaminergic neurons (in substantia nigra pars compacta) and microglia migration in a dose-dependent manner in a rat study

- Imbalance in the gut and oropharyngeal microbiomes observed in OCD cases ~
Increase of bacteria from the Rikenellaceae family, associated with gut inflammation
Decrease of bacteria from the Coprococcus genus, associated with DOPAC synthesis
- MS-twin study: FMT from MS-affected twin into mice promoted the dz in vivo
vs FMT of twin unaffected by MS
- PMID: 35087123, 33362788, 28893994, 31588712

21 Restricted eating

- Certain gut microbiota-related compounds and food antigens can trigger the production of autoantibodies cross-reacting with appetite-regulating hormones and neurotransmitters.
- Alterations in the gut microbiome and I/S may serve not only to maintain and exacerbate dysregulated eating behavior, but may serve as biomarkers of increased risk for developing an eating disorder.
- Mice receiving FMT from those with anorexia nervosa (AN) displayed increased anxiety- and compulsive-like behavior relative to controls.
- Conversely, case report of FMT from healthy control to pt with AN increased short chain fatty acids and serotonin, associated w normalized eating.
- Increases in multiple Clostridium species belonging to the order Clostridiales.
- Gastroparesis observed w neurotoxins:
mycotoxins, Borrelia spp, Bartonella, algal blooms/aquariums
- PMID: 33953692, 33652962, 33546416, 31504398, 31510101

22 Restricted eating or self medicating?

- Intermittent fasting increases microbiome diversity; significantly reduces the ratio of Firmicutes to Bacteroidetes and increases the relative abundance of Allobaculum.
- Intermittent fasting attenuates LPS-induced neuroinflammation and memory impairment including enhancement of neurotrophic support.
- Intermittent fasting contributes to aligned circadian rhythms through interactions with the gut microbiome.
- β -hydroxybutyrate (BHB), a physiological ketone body produced by the liver in condition of fasting, low blood sugar, or carbohydrate-free (like ketogenic) diet consumption had an inhibitory effect on NLRP3-inflammasome.
- Intermittent fasting attenuates LPS-induced acute lung injury in mice by modulating macrophage polarization.
- PMID: 33223514, 24886300, 25686106, 36028098, 33530881

23 Lung microbiome effect on the brain

- The lung tissue in particular has an important role in autoimmune diseases of the brain, such as MS.
- There's a tight interconnection between the lung microbiota and immune reactivity in the brain.
- A dysregulation in the lung microbiome significantly influenced the susceptibility of rats to developing autoimmune diseases of the CNS.
- Shifting the microbiota towards LPS-enriched phyla induces a type-I-interferon-primed state in brain-resident microglial cells.
- PMID: 35197636, 35417673, 35197592, 32140452, 19793773

24 Gut-lung-immune axis

- The gut-lung axis highlights both host-microbe interactions but also microbe-microbe interactions involving inter-kingdom microbial crosstalks (ie: bacterial and fungal.)
- Water-damaged buildings host biofilm including indoor airborne bacterial endotoxin as well as fungi modifying

- water-damaged buildings host bioterror, including indoor airborne bacterial endotoxin, as well as fungi, modifying the lung microbiome.
- LPS endotoxin enhances the negative health effects of many mycotoxins on respiratory and gastrointestinal tissue.
- Further justification for both environmental + infection management.
- PMID: 35197636, 35417673, 35197592, 32140452, 19793773

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26 T-cell mediation

- Intranasal infections of all types preferentially generate Th17, not just Strep
- Th17 → IL17 linked to increased risk for autoimmunity

- Mouse studies: glyphosate, mold mycotoxins, and mercury exposure drives increase in Th17
- Pts with depressive sx's had increased amyloid proteins + fecal IL-17
- Mouse studies: microbiome regulates Th17 cell-mediated depressive-like behaviors and other CNS disorders
- Naïve CD4 T-cell differentiates into either T-reg or Th17 depending on the Transforming Growth Factor (TGF) 'soup flavor'
- Microbiome plays a role in TGF types/quantity
- PMID: 32731813, 32038645, 29510522, 29920643, 28935500, 35963408, 20049214

27 Strep throat becomes "Strep nose"

- From throat to nose ~
 GAS-pharyngitis triggers Th17 response
 Formation of Abs in cervical lymphatic chain dendritic cells
 In turn sends these Abs back to throat but also the nose
- Mouse study: repeated intranasal challenge w GAS-inoculated mice promoted migration of GAS-specific Th17 cells from NALT into the brain, BBB breakdown, serum IgG deposition, microglial activation, and loss of excitatory synaptic proteins under conditions in which no viable bacteria were detected in CNS tissue.
- Proposed anti-GAS mimetic Abs affects DR1 & DR2 receptors, and/or cholinergic interneurons
- Th1 may also play a role → strep, Herpes/EBV, H. Pylori
- Discuss more about infectious triggers in next module
- PMID: 28951419, 26657857, 26417101

28 Throat to nose

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 GAS-pharyngitis triggers Th17 response

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- Not just a Strep problem ~
Intranasal infections of all types preferentially generate Th17
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29 Olfactory access

- "Smelling is a form of physical contact."
- Molecules interact with olfactory nerve terminals
- Olfactory bulb void of BBB
- Part of limbic system
- Terminates in nasal mucosa
- Th17 + mycotoxins uptake
- Trigger microglia activation

30 The "elevator to the brain"

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31 Basal ganglia

- From throat to nose ~
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In turn sends these Abs back to throat but also the nose
- Proposed anti-GAS mimetic Abs affects DR1 & DR2 receptors, and/or cholinergic interneurons
- Mouse study: repeated intranasal challenge w GAS-inoculated mice promoted migration of GAS-specific Th17 cells from NALT into the brain, BBB breakdown, serum IgG deposition, microglial activation, and loss of excitatory synaptic proteins under conditions in which no viable bacteria were detected in CNS tissue.
- Not just a Strep problem ~
Intranasal infections of all types preferentially generate Th17
- PMID: 28951419, 26657857

32 Strep antibody impacts on hypothalamus

- Elevated anti-streptococcal antibodies more prevalent in patients with recent narcolepsy onset.
- Narcolepsy; deficiency in hypocretin/orexin secretion from hypothalamus.
- Thought to be largely genetically determined, but environmental factors were investigated based on the high discordance rate (approximately 75%) of monozygotic twins.
- Retrospective, case-control study concluded that Streptococcal infections are probably a significant environmental trigger for narcolepsy.
- Compared to age-matched controls, increased ASO found in 51% within 3 years of onset, compared to 19% ($P < 0.0005$) and 20% of patients with long-standing disease ($P < 0.0005$).
- ASO and Anti-DNase B titers were highest close to narcolepsy onset, and decreased with disease duration.
- PMID: 19725248

33 PANDAS/PANS mechanisms

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- Impaired innate safety systems
Cell danger response → limbic/vagal dysfunction

Self danger response → micro, vagal dysfunction

- CNS structural alterations

34 Microglial activation

- Microglia are the brain's resident immune cells, similar to macrophages. (#monkeys)
- Activated microglia are classically associated with inflammation, neuronal damage, and neurodegeneration, and often secrete inflammatory cytokines in various neuro Dzs, including Alzheimers.
- Microglial activation is not always associated with inflammation. Novel roles have emerged in brain development, homeostasis, and plasticity.
- Microglial dysfunction has been implicated in the onset and progression of several neurodevelopmental and neurodegenerative diseases.
- Activated or "primed" microglia lose their motility projections, get stuck in place and in the more inflammatory stage (M1, aka #monkeypoo.)
- Once primed, the only way out is autophagy via maturation to M2 stage.
- Primed glial cells may recruit adjacent microglia and mast cells, and remain more sensitive to systemic inflammatory responses for the rest of that cell's lifecycle (#monkeyseemonkeydomonkeypoo.)
- Contrast to tumor-associated brain macrophages (partly derived from microglia,) express M2>M1 stage.
- PMID: 24487234 , 27859676, 24303218, 22632727, 28948967

35 Microglial dysfunction

- There's evidence for microglial dysregulation and neuroinflammatory etiology in PANDAS (also OCD, Tourette's.)
- Defective microglia lead to OCD behaviors [mice]~ pathological grooming, hyperanxiety, social impairment deficits
- Evidence from animal studies that synaptic pruning might be altered in PANDAS though the evidence is limited

Evidence from animal studies that synaptic pruning might be altered in FTD, though the evidence is limited.

- Additional potential contributions of microglial abnormalities beyond neuroinflammation are failures in neuroprotection, lack of support for neuronal survival.
- SSRIs may reduce this effect, but in a lab-induced condition, what about wild-type with different toxicant triggers?
- Reiteration: the influential role of the microbiome-microglia axis.
- The role of mast cells: histamine is both a neurotransmitter and an immune modulator. Can regulate microglia in vivo, via the H4 receptor.
- PMID: 28053994, 36911567, 30385457, 29354029, 27859676

36 Mast cells

- Reside in virtually all vascularized tissues. Differently differentiated based on recruitment trigger, location, milieu.
- Secrete a wide variety of biologically active products in 50-200 granules, including diverse cytokines and growth factors, including histamine, heparin, a variety of cytokines, chondroitin sulfate, and neutral proteases.
- MUCH more than, and not always, histamine, and not always degranulation.
- Within 30 min releases heparin, etc but in the next 24 hours, releases cytokines and other inflammatory mediators without ever releasing histamine.
- Non-redundant roles in many types of innate or adaptive immune responses, including immediate and chronic IgE-associated allergic disorders and enhancing host resistance to certain venoms, parasites, and fungi.
- Influence many other biological processes, including responses to bacteria and virus, angiogenesis, wound healing, fibrosis, autoimmune and metabolic disorders, and cancer.
- Functions reflect their ability to secrete, upon appropriate activation by a range of immune or non-immune stimuli, a broad spectrum of cytokines (including many chemokines) and growth factors, with potential autocrine, paracrine, local, and systemic effects.
- "Cluster bomb" effect.

- PMID: 27381299, 19527167, 19201896, 29431211

37 Neurotransmitter dysregulation

- PMID: 29431212

38 Neurotransmitter dysregulation

- Proposed mechanism for the protective effect of MCPT4 against Group B Streptococcus (GBS) dissemination and preterm birth.
- MCPT4, Mast cell protease 4; MC, mast cells; SfbA, streptococcal fibronectin binding protein; ECM, extracellular matrix
- PMID: 29431211

39 Mast cells & the gut

- Dr. Theoharides - "the gateway to inflammation in the body"
- "It is well established that mast cell activation can ~
 - Generate epithelial and neuromuscular dysfunction
 - Promote visceral hypersensitivity
 - Alter motility patterns in functional gastrointestinal disorders (FGIDs), postoperative ileus, food allergy, inflammatory bowel disease."
- Colonic mast cell infiltration and mediator release from IBS patients, but not controls markedly enhanced the firing of mesenteric nerves, and stimulated mobilization of Ca(2+) in dorsal root ganglia neurons known to mediate nociception.
- Effects were inhibited by histamine H(1) receptor blockade.
- Can use biopsy from upper GI or colonoscopy. CD117 to look for mast cells. >20 mast cells significant for MCAS.
- Symptoms related to eating ~

Post-prandial flushing
Post-prandial fatigue
Post-prandial brain fog
Post-prandial drop in bp
Gastroparesis
GI: heartburn, N/V, constipation, diarrhea
Food avoidances related to histamine concentration, esp left-overs

- PMID: 19527167, 19201896, 29431211

40 Mast cells

- Mast cells are key players of Candida commensalism and pathogenicity at mucosal surfaces.
- Empirically, increased recruitment at the stage of Evasion → Invasion of fungi.
- Mold mycotoxins enhance mast cell recruitment, survival, and degranulation.
- PMID: 27381299, 19527167, 19201896, 29431211

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42 PANDAS/PANS mechanisms

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Cell danger response → limbic/vagal dysfunction
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43 Dopamine receptor involvement

- Dopa receptor1 & 2: posited targets of autoantibody attack, but don't forget LPS effect:
LPS caused the loss of dopaminergic neurons (in substantia nigra pars compacta) and microglia migration in a dose-dependent manner in a rat study
- Dopamine excess (possibly during flare only?)
- Possible dopamine deficiency when in remission
- Synaptic pruning of excitatory connections may be increased in PANDAS
- Glutamate excess
- Cholinergic interneuron antibody binding
- PMID: 26454143, 29233751, 26866234

44 Cholinergic interneurons

- Cholinergic interneuron (CIN) deficiency has been independently associated with tics in humans and with repetitive behavioral pathology in mice, making it a plausible locus of pathology

repetitive behavioral pathology in mice, making it a plausible focus of pathology.

- Pilot work suggests that IgG antibodies from children with PANDAS bind to cholinergic interneurons (CINs) in the striatum.
- IgG from children with PANDAS bound to CINs, but not to several other neuron types, more so than IgG from control subjects, in three independent cohorts of patients.
- Post-IVIG serum had reduced IgG binding to CINs, and this reduction correlated with symptom improvement.
- Baseline PANDAS sera decreased activity of striatal CINs and altered their electrophysiological responses, however post-IVIG PANDAS sera and IgG-depleted baseline sera did not alter the activity of striatal CINs.
- PMID: 32539528

45 Neurotransmitter dysregulation

- PMID: 28053994

46 Neurotransmitter dysregulation

- End result - increased dopa, glutamate, dysregulated ACh
- Gut microbiota regulate the production, transportation, and functioning of neurotransmitters.
- Persistent message "unsafe" to limbic system.
- PMID: 34205336

47 PANDAS/PANS mechanisms

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48 Cell danger response (CDR)

- My thanks to Drs. Neil Nathan and Ben Lynch for “making me” learn this.
- CDR is a universal response to environmental threat or injury that protects cells and hosts from harm.
- Under direct control by ancient pathways in the brain that are ultimately coordinated by centers in the brainstem.
(What happens if the basal ganglia is chronically inflamed?)
- Expands the role of mitochondria beyond being the “powerhouse of the cell” to also being a protector and communicator of the cell status.
- Mitochondria regulate the CDR (which controls innate immunity and healing), by monitoring and responding to the physical, chemical, and microbial/biological conditions within and around the cell.
- Threats that exceed the cellular capacity for homeostasis trigger the CDR.
- Chemical pollutants in the environment lower the threshold for CDR activation. In this way, mitochondria connect cellular health to environmental health

cellular health to environmental health.

- Once triggered, healing cannot be completed until the the danger has been eliminated or neutralized, after which the CDR is reversed through a choreographed sequence of anti-inflammatory and regenerative pathways, and return to an updated state of readiness.
- Although it's a cellular response, CDR has the power to change human thought and behavior, child development, physical fitness and resilience.
- PMID: 31877376, 23981537, 26056033

49 CDR "sickness behavior"/"sickness response"

- When the CDR is triggered, the priorities of the organism are reset to optimize survival.
- The response to danger involves an adaptive means of redirecting energy and includes ~
Withdrawal from social contact
Activation of innate immunity
Decreased speech
Fragmented sleep
Head, muscle and abdominal aches
Changes in the gut microbiome
Increased sensitivity to touch, sound, and light
- Similar to what many people experience when they have the flu or recovering from a serious injury.
- It is the CDR that produces these familiar signs and symptoms.
- Even though the term "sickness behavior" is a defined scientific term, I prefer "sickness response", as "behavior" can be misconstrued as a choice.
- PMID: 31877376, 23981537, 26056033, 25639499

50 CDR in chronic illness

- Abnormal persistence of the CDR lies at the heart of many chronic diseases.
- CDR produces a cascade of changes in cellular electron flow, oxygen consumption, redox, membrane fluidity, lipid dynamics, bioenergetics, carbon and sulfur resource allocation, protein folding and aggregation, vitamin availability, metal homeostasis, indole, pterin, 1-carbon and polyamine metabolism, and polymer formation.
- Persistent activation of CDR inhibits healing, alters metabolism and gut microbiome, impairs the collective performance of multiple organ systems, changes behavior into "sickness response", and chronic disease results.
- CDR is different from the immune response which involves activation of the immune system. Instead this is a cellular response to the danger - "batten down the hatches" of the cell while the immune system takes on the danger. Possible to have one without the other?
- Metabolic memory: past encounters with stressors are stored in the form of altered mitochondrial and cellular macromolecule content, resulting in metabolic memory of the past stressors.
- PMID: 31877376, 37114062

51 Stages of CDR

- 3 sequential stages, separated by quality control checkpoints, CD1, CD2, CD3.
(More about these details in bonus video by Dr. Neil Nathan.)
- Abnormal persistence of any phase of the CDR inhibits the healing cycle.
- Different tissues may be at different stages of the CDR.
- The importance of water: changes in mitochondrial dynamics during cell stress in tissues link increasing cytoplasmic disorder with increasing disorder of water molecules, and an increase in CDR-associated functions.
(MOA structured water tx?)
- The rise and fall of extracellular ATP (eATP) signaling is a key driver of the mitochondrial and metabolic reprogramming required to progress through the healing cycle.
- Sphingolipid and cholesterol-enriched membrane lipid rafts act as rheostats for tuning cellular sensitivity to purinergic signaling.

- PMID: 37120082

52 Stages of CDR

- PMID: 37120082

53 Purinergic signalling and oxidative shielding

- Purinergic signalling and oxidative shielding ~
First wave of danger signals consists of the release of metabolic intermediates like ATP and ADP, Krebs cycle intermediates, oxygen, and reactive oxygen species (ROS), and is sustained by purinergic signaling (ie: ATP outside the cell as a signal of the state of the cell.)
- Purinergic signalling = ATP acting as an extracellular signalling molecule (eATP).
- Purinergic signalling maintains the CDR and appears to play an important role in neurodegeneration, neuroprotection and neuroregeneration.
- Compelling evidence that ATP is a cotransmitter in most if not all nerves in the PNS and CNS (ie: co-released with Ach, dopa, glutamate, catecholamines.)
- Additional alterations interfering with methylation, vitamin D and tryptophan metabolism, histamine and heme concentrations, lysine and P5P (pyridoxal 5-phosphate) utilization.
- Antipurinergic treatments may be an effective target. (Animal models - suramin)
- SARS-CoV-2 spike protein alters microglial purinergic signaling.
- PMID: 31877376, 23981537, 26056033, 27573827, 23516405, 29253638, 37114062

54 Limbic dysregulation

- Limbic system in the brain gets stuck in hypervigilance.
- Related to a sense of safety, or rather lack thereof.
- Correlated to anxiety disorders and myofascial pain syndromes. Chronic pain and olfaction share common limbic

cortical regions.

- Autoimmune encephalitis describes a group of disorders characterised by symptoms of limbic and extra-limbic dysfunction occurring in association with antibodies against synaptic antigens and proteins localised on the neuronal cell surface.
- Anorexia nervosa neural roots appear to be related to dysfunctional, primarily limbic, circuits driving pathological thoughts and behaviors. Key limbic modulatory structures, such as the subcallosal cingulate and insula.
- PMID: 28470168, 36307317, 25724849, 27330568, 24703713

55 Olfactory-limbic connection

- The sense able to communicate effectively to the whole limbic system is the sense of smell.
- The olfactory nerve is circuitous and interacts with many different limbic centers in the brain.

56 Neurotransmitter dysregulation

- PMID: 28053994

57 Polyvagal Theory: a science of safety

- "Offers a neurophysiologic framework to consider why you act in the way you do. Actions are automatic and out of your conscious control."
- 3 defining principles ~
- The ANS has a hierarchy among which we move depending on sense of safety.
 - Ventral vagal
 - Sympathetic
 - Dorsal vagal
- Neuroception: "safety scan". The process of your ANS unconsciously scanning for cues of safety, danger and threat. Your nervous system then uses that information to control your HR, RR, muscle tension, GI function, pain tolerance - almost every system in your body changes because your vagus nerve links them all together.

- Co-regulation: “safer in community”. Considered by PVT as a biological imperative in order to survive. Concept - your nervous system needs to be in connection with other nervous systems in order to feel both physical and psychological wellbeing.

The key is coregulating with other nervous systems that have found their way to ventral vagal regulation.

- PMID: 35645742, 30115210

58 The wandering vagus nerve

- Vagus (Latin meaning wander)
- Extends from brain stem, along arteries, through heart, lungs, diaphragm, digestive system, liver, gallbladder, spleen, pancreas and kidneys.
- The neuroception of danger in one organ is very quickly transmitted to the other organs.
-
-

59 Polyvagal Theory

- Polyvagal Theory Explained Simply
- Lewis Psychology YouTube channel
- <https://www.youtube.com/watch?v=SlhFrBoEnxU>

60 PANDAS/PANS mechanisms

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1 PANDAS & PANS

An Integrative Approach

- Dr. Jill Quigg

- Dr. Jill Crista

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3

- Diagnostics

4 Overview

4 Overview

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

5 Diagnostics

- Clinical diagnosis
- PE and symptoms as clues
- General diagnostics
- Infectious triggers
- Environmental triggers

6 Diagnostics

- Reminder ~
These are

- CLINICAL DIAGNOSES

- If a P/P-specific test was negative, a child can still have PANDAS or PANS.

- IME, we are relying too much on antibody tests to diagnose these conditions. Because many of these kids have subclinical immune deficiency, many don't have a strong enough antibody response to affect the test. This may lead to a falsely normal test.
- Be mindful of the steroid effect on antibody-based labs.

7 Neuro P/E relevant to BGE

- Burdened appearance
- Dilated pupils
- Hypotonia
- Motor apraxia
- Dyspraxia
- Normal strength
- Normal reflexes, not hyperactive as in Wilson's dz
- Abnormal movements
- Chorea
- Choreiform movements, not age appropriate
- Tics
- Steriotypies
- Ballismus
- Overall rational irrationality (they realize or have insight into the abnormality)

- Presented by Dr. Elizabeth Latimer
- Autoimmune Encephalitis Post-Streptococcal Evaluation & Treatment Conference Oct 2019

8 Honor the triggers

- Once the autoimmune process has started...
- Environmental exposures and infections can and will flare them.
- ***the child knows where/who is carrying something that will put them at risk***
- And will tell you with their behavior - honor that.
- It's not pathological. It's the innate intelligence of the system at work.
- Certain spaces/places may be the trigger.
- Parents/siblings/caregivers may be the trigger.
- Parent self care is critical in order to not be a carrier.

9 Additional triggers

- Lose a tooth/dental visit
- Puberty onset
- Injury
- Sunburn
- Allergies
- Many bug bites/spider bite

- Family strife/move/loss of structure
- Loss of friendships
- Abuse

10 Symptoms with hints toward cause

- Congenital Borrelia (Lyme) ~
Atonia (reported 97% prevalence congenital Lyme by Dr. Charles Ray Jones)
- Bartonella ~
Rage/aggression
- EBV ~
Fatigue/"laziness", chronic sore throat
- Glyphosate + Mold ~
Anxious
- Glyphosate + Bartonella ~
Persistent, non-specific abdominal pain
- Mold ~
Urinary frequency/urgency without infection, dysautnomia, PoTS
- Mold + Bartonella ~
Hypermobility
- Candida ~
Despair, suicidality

11 Diagnostics

- Clinical diagnosis

- Clinical diagnosis

- PE and symptoms as clues
- General diagnostics
- Infectious triggers
- Environmental triggers

12 General diagnostics

- PANDAS/PANS (Cunningham)
- Other neuro antibodies
- Immune competence (IgGAME, PID, CVIDS, lymphocytes)
- Imaging - Neuroquant
- Food sensitivity
- Sinunasal microbiologics
- Drug metabolism
- Genetic predispositions/expressions
- Testing for coverage
- On the horizon

13 Cunningham Panel TM

- Considered (+) if one or more of these markers is elevated.
- Suggests that neuropsych sx's may be due to an

autoimmune process.

- 5 markers:
 1. Anti-Dopamine D1 Receptor (psychosis, OCD and tics)
 2. Anti-Dopamine D2L Receptor (uncontrolled motor movements, hyperactivity and impulsivity)
 3. Anti-Lysoganglioside-GM1 (sleep disturbances, behavioral regression, obsessions/compulsions)
 4. Anti-Tubulin (OCD-like symptoms and cognitive impairment/brain fog)
 5. Calcium/calmodulin-dependent protein kinase II (CaMKII) (involuntary movements, cognitive interference, emotional lability)
- CaMKII is a cell stimulation assay; measures the ability of a patient's autoantibodies to stimulate the CaMKII enzyme in human brain cells.
The CaMKII is involved in upregulating the production of neurotransmitters – dopa, epi, and NE.
- Best suited to classic PANDAS?

14 Autoantibodies

- Antinuclear antibodies multiplex, reflex to dsDNA, RNP, Sm, SS-A, SS-B
- Demyelination Antigens ~
Anti-tubulin IgM/IgG+IgA
Anti-myelin basic protein IgM/IgG+IgA
- BBB Disruption ~
Anti s100b IgM/IgG+IgA (*increases with exercise)
- Optical and ANS Disorders ~
Anti-neuron specific enolase IgM/IgG+IgA
- Peripheral Neuropathy ~
Anti-GM1 IgM/IgG+IgA
Anti-GM2 IgM/IgG+IgA

- Brain Autoimmunity ~
Anti-HSV1 IgM/IgG+IgA
Anti-cerebellum IgM/IgG+IgA
Anti-purkinje cell IgM/IgG+IgA
Anti-pituitary antibodies (APA) (hypophysitis post TBI)

15 Immunocompetence

- Quantitative IgG with IgG subclasses ~
Red top tube or SST? Depends on goals for testing.
Serum separator will bind some antibodies and under-report, esp in those with low Ig's.
(🙏 Dr. Paul Anderson)
- NOTE that all antibody-based testing will be affected by IVIG, including other autoimmune and infection.
- Lymphocyte Subset/Differential Panel ~
Offers the advantage of detecting the cell type that causes the immune defect.
- 3 types of lymphocytes: B, T and NK cells.
All share the same progenitor cells: hematopoietic stem cells in the bone marrow, which then give rise to multipotent progenitors, to early lymphocyte progenitors (ELP) and eventually to the differentiated progenitors of NK, B or T cells.
B and T lymphocytes are both antigen-specific lymphocytes and the main regulators of the adaptive immunity.
NK cells, in contrast, are not antigen-specific lymphocytes, thus belonging to the innate immune system.
- PMID: 30248214

16 B cell differentiation

- PMID: 30248214, 31694331

17 T cell differentiation

- PMID: 30248214

18 Identifying Primary Immunodeficiency

- Low absolute lymphocyte count (<3,000/mm³) suggests a cellular immunity defect and constitutes a strong indication for lymphocyte subset count (LSC).
*However, normal ALC cannot exclude such a defect.
- LSC is one of the initial screening tests by general pediatrician for investigation of an immunological patient, with LSC being affected by age (Table 2 - next slide.)
- Imperative to order LSC when a child presents with recurrent or opportunistic infections and the ALC is <3,000/mm³.
- Combination of good clinical examination with good interpretation of LSC will facilitate the dx of most of the common PID.
- Approximately 50%–60% of all identified PID are caused by defects in antibody production. Such patients usually develop upper and lower respiratory infections, especially from encapsulated bacteria, as well as chronic GI infections from *Giardia lamblia* or enterobacteria.
- A characteristic feature of these humoral immunity defects is the deterioration of the clinical profile after the first 6 months of life, as the levels of maternal antibodies start to recede.
-
- PMID: 30248214

19 T cell differentiation

- PMID: 30248214

20 Common Variable Immunodeficiency (CVID) in peds

- Mean age at symptom onset was 18 (3-204) months.
- All CVID patients with pediatric onset had decreased levels of total and memory B cells, CD4+ T cells, CD4+CD45RA+ naive T cells, and recent thymic emigrant (RTE) cells.
- On the other hand, they had increases in CD8+CD45RO+ memory T cells.
- Specific cellular abnormalities associated with the reduction in B and NK cells and increase in CD8+ T cells were found in patients with bronchiectasis.
- In pediatric CVID patients, low serum IgA levels and decreased numbers of naive T and RTE cells were determined as risk factors for chronic diarrhea.
-
- PMID: 31901904

21 Neuroquant MRI

- Specialized MRI must be run at specific Neuroquant centers.
 - TBAR with asymmetry
 - may need to order Brain Development report b/c TBAR changes may reflect neuronal development. (Dr. Gazda)
- Does not require contrast. Age- and gender-matched controls.
- Normal = 40-60 percentile.
- May display enlargement of the caudate.
 - Blue = edema/inflammation
 - Red = atrophy
- Thalamus >90% mold and Lyme. (Dr. Ackerly)
- Not ideal for child with tics as they can't remain still for imaging

Not ideal for child with ties, as they can't remain still for imaging.

- Also not ideal for sound sensitive child or child who cannot tolerate ears being covered.
- Braces/retainers will alter findings.

22 Neuroquant Ped Multistructure Atrophy Report

- zonulin stool, food allergy, micro/mycobiome

23 Neuroquant Triage Brain Atrophy Report TBAR

- zonulin stool, food allergy, micro/mycobiome

24 Food sensitivities

- Proteins vs Peptides
- Proteins ~
Measure immune system reactivity to whole, undigested, multi-dimensional (ie: 4D) proteins.
Challenges: only detect one aspect of "the elephant in the gut"
Limited to testing the water-soluble portions of proteins, leaving out non-water-soluble peptides (ie: gluten).
- Peptides ~
Measure immune system reactivity to the small, typically not water-soluble, 2D peptides created when whole proteins are digested.
Reduces cross-reactivity; increased sensitivity because peptides are highly specific to the food from which they are derived.
- Antibodies to a whole protein will not recognize or bind peptides, even if those peptides are found in that whole protein.

- Clinically, testing for food sensitivities at the peptide level in addition to whole protein eliminates uncertainty around food reactions.

25 Sinusnasal microbiologics

- Colonization involves a mixed microbial presence.
- Marcons - yes, it's still "a thing", but other culprits are Pseudomonas and Klebsiella
- Chronic rhinosinusitis patients undergoing endoscopic sinus surgery. Those with biofilm had ~
More severe disease preoperatively
Persistence of postoperative sx's
Ongoing mucosal inflammation
Increase infections
- Fungal cultures inherently under-report due to inappropriate medium and duration (fast-growing species eat all the food, miss more pathogenic species.)
- Dx via NGS qPCR and appropriate culturing.

26 Drug metabolism genetics

- Ultrasensitive to psychiatric medication ~
Due to BBB integrity or genetics?
- Better to know child's drug clearance before prescribing, especially if the effect is slower metabolism and reduced drug clearance, concentrating the drug.
- Testing provides Gene-Drug interaction chart.
- Also be familiar with co-enzymes that up- or down-regulate that pathway.
ie: B2, B6, NAD

27 Genetic predispositions/expressions

- PANS: HLA alleles:

HLA-B 38, 52, 55

- My own observations:
Snps related to IgG: Fcγ Receptors
Snps related to NTs: COMT, MAOA
Snps related to detox:
Phase I: CYP1A2, CYP1B1, CYP3A4 (mold)
Phase II: GSTM1, MTHFR, SUOX
Snps related to histamine: DAO
- Metagenomics/metabolomics

28 The fine art of insurance coverage

- Set up for IVIG coverage in case it's needed in the future (analogous to starting an IV in the ER)
- ****don't put PANDAS or PANS Dx in chart, unless you're in a state which mandates coverage****
- Test IgG and IgA (plus subclasses) ~
 - Using SST tubes
 - Test after 3 weeks without any integrative supportive measures (test the child's true nature.)
 - Test at the tail end of a steroid burst, if needed.
- Also engage parent help. Bring child in every time they get sick to get it on the medical record.
- Parent needs to keep school absence records, sports absence records, performance absences, etc.
- Cautions ~
Zinc lozenges, silver nasal sprays, propolis throat sprays turn positive Strep tests to negative.
Diet, supplements, sleep routines, chiropractic adjustments, and all the other integrative treatments really work!
We see immune numbers improve, which is great for the child, but bad for proving the need for treatment.

A hiatus helps reveal the baseline.

- Pneumococcal vaccine titers are not necessary, plus may be falsely lower in kids with hypogam. Push back against insurance on this.

29 On the horizon?

- Metagenomics: NGS qPCR of brain/CSF
- Metagenomic NGS is a novel diagnostic test with the potential to revolutionize the diagnosis of pediatric meningitis and encephalitis through unbiased detection of bacteria, viruses, parasites, and fungi in cerebrospinal fluid.
- "We recommend NGS should be considered as a front-line diagnostic test in chronic and recurring presentations and, given current sample-to-result turn-around times, as second-line in acute cases of encephalitis."
- PMID: 29305150, 34951470

30 Diagnostics

- Clinical diagnosis
- PE and symptoms as clues
- General diagnostics
- Infectious triggers
- Environmental triggers

31 Infectious triggers

- Group A Beta-Hemolytic Streptococcus Pyogenes
- Mycoplasma pneumonia
- Chlamydia pneumonia
- Bartonella species
- Borrelia species (Lyme and Tickborne Relapsing Fever [TBRF])
- Encephalitis viruses
- Influenza
- SARS-CoV-2
- Periodontal

32 Streptococci

- Streptococci are part of the normal human respiratory flora
- Commensal and non-commensal - most are protective
- Passed by respiratory droplets and saliva ~
Not considered highly transmissible on surfaces but is possible
- Immunity to one strain does NOT confer immunity to any other
- 20 different subgroups of beta-hemolytic strep; not a homogenous population ~
Hundreds of different strains (220 M proteins x 25 T proteins)
Capsule is different for each of the Lancefield groups
Exotoxins also different

- High antigenicity of Streptococcal exotoxins ~
Can turn on 20-40% of T-cells
This is how Strep doesn't need to be in the brain to affect the brain.
- B. J. B. Wood et al. (eds.), The Genera of Lactic Acid Bacteria © Chapman & Hall 1995

33 Group A Strep (GAS)

- GAS is the dominant respiratory pathogen ~
Accounts for 20%-40% of cases of pharyngitis in children; the remaining are caused by viruses
- GAS infections ~
Strep pharyngitis, otitis media, sinusitis, skin infections (perianitis)
Colonization posited in sinuses and GI
- GAS sequelae ~
Scarlet fever, cellulitis, necrotizing fasciitis, rheumatic fever, Streptococcal toxic shock syndrome, and post-Streptococcal glomerulonephritis
-

34 Strep shoots the messenger

- Rewires the immune system for its survival
- Unique in its abilities to ~
Direct I/S remodeling in nose/throat (possibly perianally)
Promote its own replication
Alter I/S responses
- "Shoots the messenger": GAS virulence factors modulate maturation and survival of dendritic cells (DC) aka the "delivery" cells, effects that are likely to have a critical impact on activation of innate and adaptive immune responses.
- Only 6 of 24 GAS strains tested induced surface expression of MHC class II and co-stimulatory molecules

- Only 6 of 24 GAS strains tested induced surface expression of MHC class II and co-stimulatory molecules consistent with DC maturation.
- The majority of the strains did not promote DC maturation, and many triggered DC apoptosis.
- PMID: 19712038

35 Strep Pharyngitis (GAS)

- Symptoms ~
 - Sore throat
 - Pain with swallowing
 - Red or swollen tonsils
 - Swollen cervical lymph nodes
 - Fever
 - Headache
 - Red petechiae or pinpoint dots on the roof of the mouth
 - Angular cheilitis
- Ddx ~
 - Viral cause. Children with Strep pharyngitis typically do not have cough, runny nose, hoarseness, mouth ulcers, or pink eye. These symptoms suggest a viral cause.
- Seasonality ~

- Seasonality ~
Winter & spring

36 Perianal Strep Dermatitis (GAS)

- Symptoms ~
Red rash around the anus with a well-defined margin
Sore rectum or anus
Anal pruritus
Pain with bowel movements or when wiping
Constipation
- Ddx ~
Candidiasis, pinworms, eczema, and contact dermatitis from soaps, detergents, and fragrances
- Seasonality ~
Winter & spring
- Culture all perianal rashes AND culture to confirm successful treatment.
Not uncommon to have pharyngeal culture neg, but perianal positive.

37 Skin infections: Suppurative

- Impetigo - honey-colored crust, superficial - heals without scarring.
- Ecthyma - deeper lesion, below dermis, indolent. Starts as a pustule and erodes to an ulcer. Often multiple lesions.
- Erysipelas - raised red rash with very sharp borders. In the lymphatics of the skin. Fever and pain from skin

swelling. IV Abx.

- Cellulitis - border vague and irregular. Skip areas/bare areas. Painful, may not have fever. Associated with a break in skin.
- Lymphangitis - rapidly progressive infection with initial cutaneous focus but spread of infection through lymphatics.
- Necrotizing fasciitis/streptococcal myositis - Streptococcal gangrene. Superficial and possibly deep layers of muscles are killed. Pain and swelling are disproportionate to everything else. Needs surgery.
- Streptococcal pupa fulminans - Skin and all structures underneath necrose. Blood vessels thrombose. + blood culture usually.

38 Skin: Nonsuppurative

- Sandpaper skin
- Desquamation fingers/toes (also mold)
- Fingernail/1st thumb - splinter hemorrhages
- Scarlet fever: strain dependent. Diffuse erythematous rash due to the production of pyrogenic exotoxin, most commonly assoc w pharyngitis.
- Scarlet fever - forms pastia's lines (bright red coloration of the creases under the arm and in the groin), strawberry tongue.
- Cuttata (drop like) necrotic

- Guttate (drop-like) psoriasis.
- Erythema marginatum - assoc w ARF. Rash location may change over time. Pink to red with central clearing and serpiginous (wavy) spreading edges and often are unnoticed by the patient or parent because they are painless and non-pruritic.
(distinction from Lyme erythema migrans.)
- PMID: 27051572; Steere, A., Strle, F., Wormser, G. et al. Lyme borreliosis. Nat Rev Dis Primers 2, 16090 (2016).
<https://doi.org/10.1038/nrdp.2016.90>

39 Other exposures

- Strep "carriers" ~
Check parent/siblings tonsils
Often child's are small and parents/siblings are enlarged or boggy (may also be EBV)
Check skin infections of other family members
- Pets ~
Animals cannot get infected by Strep as it's strictly a human pathogen
Transfer via saliva from licking carrier's face or skin infection
- Probiotics ~
Until we know which peptide or protein induces an immune reaction, I recommend avoiding Strep-based probiotics

40 Neonatal (Group B)

- Group B Streptococcus
- Debated the degree to which Group B Strep in mom before birth contributed to the development of PANDAS, but doctors specializing in PANDAS have reported a correlation.
-

- Vaginal swab culture

41 Why worry about Strep in PANS?

- Strep is kryptonite in kids with PANDAS -and- PANS
- Even though it may not have been the triggering infection, Strep can trigger flares in PANS.
-

42 Strep detection

- Culture culture culture ~
Antibody response is more complex than previously understood. A negative rapid strep test can still be culture positive. F/U negative rapid with culture.
- Rapid strep tests ~
Very high specificity (98-99%) = very few false positives.
However, sensitivity lower (90-95%) = greater chance of false negatives.
Package insert recommends F/U negative tests with a culture.
Lawsuits against docs who didn't F/U with culture, missed Strep, and serious sequelae.
- Cochrane Database Systematic Review 2016 ~
Out of 100 children with strep throat:
86 would be correctly detected with the rapid test
14 would be missed and not receive antibiotic treatment
- Is clinical over-reliance in rapid strep tests a contributing factor for the rise in PANDAS/PANS?
- PMID: 27374000

43 Additional Strep labs

- Anti-DNase B - repeat in 2–6 weeks for antibody rise or fall
Note: not anti-human DNA. DNase B or Deoxyribonuclease B is an antigen produced by group A streptococci which contributes to Strep's pathogenicity.
- ASO - repeat in 2–6 weeks for antibody rise or fall ~
Significant prevalence of seronegative ASO (Dr. Cleary)
- Streptozyme - similar to Anti-DNase B.
-
- How to test others if not your patient? (harder since EMR)

44 Mycoplasma pneumonia

- Look for it, and look again, and again. It's ubiquitous and often asymptomatic or only mild illness.
- Shares many of the same skills as Strep in evading the I/S and affecting the brain. Second most favorite places to play in the body are brain and CNS.
- Can cause encephalitis. CNS complications are seen more so in kids. Just like Strep, certain proteins on Mycoplasma mimic brain tissue.
- Been shown to be able to persist in an intracellular environment. Antibiotic resistance issues.
- Do not develop lifelong immunity to Mycoplasma.
- More common in the winter and is estimated to be much more common than previously understood.
- A super-spreader: takes up to 3 weeks before symptoms develop and is shed from the respiratory tract for many weeks after symptom abatement.
Equates to up to 6 weeks of potential transmissibility with one infection.

- Sometimes, Mycoplasma's main hideout is the tonsils. For children whose tonsils have become Mycoplasma reservoirs, removing the tonsils may be helpful.

45 Mycoplasma pneumonia symptoms

- Symptoms of respiratory Mycoplasma in children under 5:
 - Watery eyes
 - Runny nose or sneezing
 - Sore throat
 - Digestive changes such as diarrhea or vomiting
- Symptoms of respiratory Mycoplasma in children 5 years or older:
 - Feel tired
 - Low-grade fever
 - Sore throat
 - May have a headache
 - Slowly worsening dry cough that may last for weeks
- The cough is normally dry. Even though it commonly takes weeks for the cough to go away, it should stay dry. If the cough becomes productive, and is accompanied by worsening fever or chills, or feeling SOB, r/o "walking pneumonia".
- Mycoplasma may cause other non-lung symptoms, such as achy muscles and joints, skin rashes, heart symptoms, liver inflammation, and eye symptoms such as pink eye and anterior uveitis.
- Also mimics RBCs and can lead to hemolytic anemia. May be mistaken for Babesia, which infects RBCs and causes many of the same circulatory symptoms.

46 Mycoplasma detection

- IgG may or may not be positive with a positive IgM.
- IgM remains positive much longer than other microbes, so can be a false positive.
- Confirm IgM+ via immunofluorescence (Mayo) - titers vary wildly by the moment.
- T-cell option

47 Chlamydia pneumonia

- Respiratory infection, not the STI Chlamydia trachomatis.
- Obligate intracellular bacteria that infects the respiratory epithelial tissue and may play a role in chronic inflammatory dzs.
- Majority of individuals are exposed throughout their lifetimes with an antibody prevalence of 50% by age 20 and 80% by 60–70 years old.
- Predominantly asymptomatic or mild, but can result in the development of acute upper and lower respiratory illness including bronchitis, pharyngitis, sinusitis, and pneumonia/community-acquired pneumonia.
- CNS can also be a target.
- Co-infection of *C. pneumoniae* and *M. pneumoniae* with SARS-CoV-2 is associated with more severe features.
- PMID: 30687565, 23218799, 11371760, 33482238

48 C. pneumonia

- May contribute to a range of inflammatory diseases.
- Dissemination from the lung throughout the body can possibly lead to atherosclerosis, arthritis, as well as

neurological diseases, such as Alzheimer's, MS, and schizophrenia.

- May also be associated with biliary cirrhosis, diabetes, and Behcet's disease.

49 C. pneumonia detection

- T-cell
- Chronic infection is somewhat more difficult to determine and requires the detection of persistent IgG levels, which is complicated by the fact that IgG has a half-life of weeks to months and may therefore be present for some time following acute infection.
- It has been proposed that IgA levels may provide a better indication of chronic infection, but according to Dowell et al., the use of IgG and A serological markers alone should not be used.
- Identification of *C. pneumoniae* messenger RNA (mRNA) by PCR can also be used to determine whether *C. pneumoniae* is in a metabolically activated state.
- PCR detects presence within tissues (ie: tonsils.)
- PMID: 8665464, 11462186

50 Bartonella spp

- Include a number of different species, which are growing in number as detection improves.
- Transmitted through flea bites, tick bites, and scratches or bites from an infected animal. Vertical transmission during pregnancy.
- Best known as cat scratch fever, but that's misleading.
 - A scratch isn't required (vector bite).
 - Not just cats - also dogs, rabbits, and many other pets such as hamsters and gerbils.
- Can disperse far and wide in the body, and can migrate in and out of the blood. This causes a relapsing-remitting pattern, making it quite difficult to discern between a chronic Bartonella infection and a PANDAS or PANS flare.

- Each species causes a slightly different symptom picture, which makes diagnosis difficult. There are commonalities based on favorite tissues to infect, those being the brain, nervous system, and connective tissue, especially collagen.

51 Bartonella

- Formerly, considered an issue only for those with severe immune compromise.
- New research is supporting what many of us working with P/P kids have found—it's far more common and often chronic. May even be "asymptomatic", but with the rising prevalence of anxiety and hypermobility in kids, one wonders about that.
- Anxiety is the most common brain-related symptom with Bartonella, as well as neuropathies. We also see mood swings that can be quite drastic and seemingly unprovoked. These may present as out-of-control anger and rage events.
- Regarding connective tissue, research suggests that Bartonella impairs collagen synthesis and repair. (So does mold.) This mechanism accounts for the "Bartonella stretch marks."
- This collagen-interrupting effect is why many cases of hypermobility are due to undetected, chronic Bartonella in kids and teens living in moldy environments.
- We worry about Bartonella's effect on the connective tissue of our hardest-working tissues, such as the eyes and the heart, where it can weaken and infect the heart valves.
- Acute cases typically fit the classic s/sxs, but chronic Bartonellosis is missed frequently due to the variance in how it presents in different children.

52 Acute Bartonella spp

- Fever
- Ice-pick pains, especially of the ear
- Skin rashes or nodules
- Stretch marks that don't blanch

- Stretch marks that don't blanch
- Extremely enlarged lymph nodes
- Anger or rage events
- Hemolytic anemia
- Joint pain
- Uveitis
- Neuroretinitis
- Encephalitis
- Endocarditis

53 Pics

- Bartonella: Cutaneous lesion presentation depends on strain. "Bart striae" or non-blanching stretch marks.
- PMID: 33291688

54 Chronic Bartonella spp

- Anxiety
- Mood swings
- Memory problems
- Fatigue
- Low-grade fever
- Headache, migraine

- Eyes sensitive to light
- Red crescents at the back of the throat that come and go
- Generalized ear or throat pain
- Occasional problems with swallowing
- Crawling sensation on skin
- Nerve zinging, vibration, or pain
- Hypercoagulability
- Generalized lymphatic stagnation
- Gastritis, reflux
- Heart palpitations with or without chest pain
- Hypermobility
- Migrating joint and muscle pain
- Injuries slow to heal
- Plantar fasciitis, worse on first steps in the morning

55 Pics

- Bartonella throat crescents

56 Bartonella diagnostics

- Acceptable to treat based on a presumptive diagnosis.
- Famously difficult to detect due to their migratory pattern from the blood into tissues, evading the I/S.
- IFA, PCR, T-cell
- “ILADS folklore” - draw between 2-4pm
- May provoke with homeopathics for 1 week prior.

57 Borrelia

- Ticks that transmit Lyme Disease reported in 48.6% of US counties (*Ixodes scapularis* and *pacificus*)
- Technically refers to *Borrelia burgdorferi sensu lato*
Encompasses 18 known species
(ex: *B. burgdorferi sensu stricto*, *afzelii*, *garinii*, *mayonii*, *californiensis*, *japonica*, *andersonii*, *lusitaniae*, *bissettii*, *spielmanii*)
The most human pathogenic species to date (N of equator) ~
 - *B. burgdorferi sensu stricto* (US & Europe)
 - *B. afzelii*, *garinii* (Europe & Asia)
- Tick-borne relapsing fever *Borrelia* (TBRF) ~
B. hermsii, *turicatae*, *parkeri*, *miyamotoi*
- Louse-borne relapsing fever *Borrelia* (LBRF) ~
B. recurrentis
- Coinfection is the norm, not the exception ~
Bartonella, *Babesia*, *Anaplasma*, *Ehrlichia*, *Powassan*, *Franciscella* (Tularemia), *Rickettsia* (RMSF), Q Fever, etc

58 Covid

59 Prevention is Key

- Attractors ~
CO₂ is the tick attractor.
Also pheromones from Lyme carriers.
Certain mosquito-attracting (flavi)virus-induced skin volatiles:
Acetophenone, a volatile compound that is predominantly produced by the skin microbiota, is enriched in the volatiles from the infected hosts to potentially stimulate mosquito olfaction for attractiveness.
An effect partially combatted by Vitamin A.
- Defense ~
Treated clothing
Essential oil - lemon eucalyptus, yarrow (acaricidal); reapply often (min hourly)
Coming inside: clothes stripped and in hot dryer x 10 min
Tape roll pets
Tick tubes around outdoor spaces
- PMID: 35777355, 36905473

60 "Never had a tick bite" "Not outdoorsy"

- Tick saliva contains an anesthetic
- Also anticoagulant and immunosuppressive substances
- Provides a localized environment at the site of the bite to evade detection — enhancing infection
- Soft-sided ticks (TBRF) are "snackers" — may self-detach and find new host, won't necessarily engorge
- Migratory birds carry ticks anywhere the bird can go
(even Home depot)

61 Covid

- Tweezer removal method.

- YouTube & <https://dr crist a.com/2018-5-26-lyme-the-best-way-to-remove-a-tick/>

62 Covid

- Tweezer removal method.
- YouTube & <https://dr crist a.com/2018-5-26-lyme-the-best-way-to-remove-a-tick/>

63 Covid

- Tweezer removal method.
- YouTube & <https://dr crist a.com/2018-5-26-lyme-the-best-way-to-remove-a-tick/>

64 Tick bite management

- Save the tick - moistened paper towel inside ziploc x 2. Freezer.
- Treat bite area (tick feces) - andrographis tincture (Dr. Chesney), povidone iodine.
- Snap a pic of the bite area immediately and then every day after for 10days.
- Histamine reaction vs EM rash ~
EM has increased erythema at farthest edge from bite
Either may expand irregularly
Called "Erythema migrans" not "erythema in scopum" (target)
so "migration" is the unique feature
- Submit tick for testing - algorithm.

65 Covid

- Tweezer removal method.
- YouTube & <https://dr crist a.com/2018-5-26-lyme-the-best-way-to-remove-a-tick/>

66 Acute Borrelia spp "Lyme"

- Onset from 1 day to 1 month after bite.
- Tick saliva induces migration of Borrelia into the blood stream, and out of stationary phase.
- * if symptomatic at day 1, consider a possible reactivated persistent Borreliosis, treat as acute Lyme+
- Influenza-like illness ~
Low-grade fever (co-infxn higher), headache, stiff neck, malaise/lethargy, joint pn, muscle pn, localized L/A
- Sick within a day, also consider:
Powassan virus - transmitted in 15 minutes
Anaplasma/ehrlichia

67 Early disseminated

- Onset weeks to months after bite.
- Early disseminated Lyme can occur even if no acute sxs.
- Areas ~
HT - carditis, A-V block
Neurological - cranial/peripheral neuropathy
M/S - migratory arthralgias
Eye - all the "itis"s - uveitis keynote, retinal tears
Skin/lymphatics
Liver/kidney - LFTs, proteinuria

68 Late or "chronic" Lyme

- Onset months to years after tick bite.

- Can also occur w/o any prior sx.
- Dr. Horowitz's Lyme/MSIDS Questionnaire is the premiere sx list.
- May have never felt well since, or triggered by stressor (mold, MVA, surgery, dental, mental/emotional, pregnancy, puberty, menopause, etc)
- Correlated with extreme morbidity.
- Chronic progressive multisystem illness in:
 - M/S
 - Neuro
 - Skin - acrodermatitis chronica atrophicans (European)
 - Hormone

69 Non-Lyme Borrelia - TBRF

- Tick-borne relapsing fever
- Transmission - soft-sided ticks (don't engorge, they "snack" and may move hosts,) lice, fleas, possible spider bites
- Tests negative on Lyme disease tests.
-
-

70 In Children - Early Lyme

- Early Lyme disease:
 - Fever
 - Fatigue
 - Flu-like illness, including achiness and malaise
 - Headache
 - Stiff neck
 - Swollen lymph nodes

Swollen lymph nodes

Weakness or numbness in one side of face, or develops paralysis

Spreading red rash or target rash (less than half of cases)

Muscle and/or joint pain that migrates around the body

Swollen joints

Carditis or inflammation of the heart

•

71 In Children: Early TBRF

- Early Tickborne Relapsing Fever:
 - High fever, chills
 - Headache
 - Muscle and joint aches
 - Fever relapses and lasts for about 3 days
 - Rarely a rash

72 In Children - Persistent/Chronic Borrelia

- Persistent or chronic Lyme disease or Tickborne Relapsing Fever:
 - Fatigue
 - Brain fog
 - Problems remembering new learning
 - Child avoids play or friends
 - Mood changes, depression, anxiety
 - Insomnia
 - Headaches
 - Frequently changing vision
 - Rashes that come and go
 - Nerve pain, numbness, tingling, or random hot or cold feeling
 - Heart palpitations
 - Digestive problems
 - Muscle and/or joint pain that migrates around the body

Frequent musculoskeletal injuries
Generalized heightened body pain

73 Covid

- Tweezer removal method.
- YouTube & <https://drchrista.com/2018-5-26-lyme-the-best-way-to-remove-a-tick/>

74 Understanding Symptoms

- Borrelia OSPs bind to the glycosaminoglycan (GAG) chains of host proteoglycans, binding promotes tissue colonization
- Gravitates to ECM and other areas rich in GAG nutrients ~
Endothelial glycocalyx
Tubules of the teeth (peg teeth = congenital)
Eyes
Joints
Cardiac nerve bundles
CNS
Neuromuscular junctions (fibromyalgia TPs, congenital atonia)
GB
- Migrates (as seen in rash)
- Unilateral (ie: Bell's palsy)
- PMID: 29116038

75 Take-Aways

- "Lyme" has become an umbrella term used to describe many iterations of tick-borne infections
 - different infections/combinations of infections
 - different stages/states
- 2-tier reflex to WB missing an inordinate number of cases

- ER/Urgent care labs too early to detect
- Clinical diagnosis is sufficient to initiate Tx
- Known tick bite is not required to Dx
- Rash is not required to Dx
- Tx for 7-10 days is not sufficient
- Delayed onset of Tx is correlated to worse outcomes
- "Post treatment Lyme syndrome" is an erroneous Dx. IME culprit is surviving bacteria, but is blamed on the immune system gone awry
- "Antibiotic refractory" - a research term - IME from undertreated and/or missed acute Dz → widely disseminated, genetically savvy bacteria (more later)
- Reportable Dz - if they'll accept it (my story of Advanced Labs culture +)
- Vertical transmission has been reported, positive cord blood and culture positive neonate

76 Borrelia Testing

- Culture-enhanced PCR
- Draw between 2-4pm - better chance of catching migrating spirochete
- Alternate for suppressed pt: provocation with deep tissue massage from immediately prior to up to ~4-6 hrs before draw
- Off ALL antimicrobials (including herbal) of all kinds for the culture to be reliable (one dose GSE turned negative)
- Itraconazole will affect this test. It acts on an ergosterol biosynthesis pathway that Borrelia uses to defend itself.
- Food-based antifungals in small amounts are likely okay, but be cautious of the stronger ones that also work

against bacteria such as garlic, onions, thyme, oregano.

-

77 Borrelia Testing

- Immunoblot > WB
Band 31 highly correlated with autoimmune sequelae
- T-cell - best choice for hypogammaglobulinemia pts but limited by the strains tested, and potentially weaker reaction to Borrelia than co-infections.
- Phage -
Good for immunocompromised patients (hypogam+mold reduced T-cell)
Reactive for bacteria (Borrelia), not nec for parasites (Babesia)
- Provoke with Lyme Nosode ~
10 drops under tongue daily, 2wks prior
Administer away from anything by mouth for 15 minutes before and after the dose
- *Reminder - positive test NOT required for Dx or Tx

78 Encephalitis Viruses

- Predilection for the brain
- Can induce neuroinflammation even with mild infections
- Flare may occur weeks after infection

79 Covid

- Early antigen (EA) - add-on
- Chronic/reactivated pattern ~
VCA-IgG - pos
VCA-IgM - neg

vCA-IgM - neg

EA-IgG - pos

EBV-NA - highly pos

(if 3-4x positive, consider chronic/reactivated)

- vs Past infection pattern ~
EA - neg
NA - lower pos

80 Influenza

- Very commonly reported cause of PANS and flares by parents.
- Influenza symptoms:
 - Fatigue
 - Fever
 - Chills
 - Cough
 - Sore throat
 - Runny or stuffy nose
 - muscle or body aches
 - Headaches
 - Less commonly, vomiting and diarrhea
- Monitor for secondary bacterial infections - sinus, ear, lung, pneumonia
- If child is reporting fever sxs with no rise in temp ~
Concern for CDR1, innate immunodeficiency (mold/NK cell fxn)
Increased risk factor for autoimmune activity

81 Mold mycotoxin exposure makes flu worse

- Increase viral replication SIV
-

82 Mycotoxin exposure makes flu worse

82 Mycotoxin exposure makes HIV worse

- Low level exposure ~
- Promotes infection
- Increases inflammatory responses
- Immune organ damage
- Induce a switch in alveolar macrophage polarization from M1 to M2
- Confer poorer outcomes in SIV-infected in mice

83 SARS-CoV-2

- Multiple entry routes into the brain - olfactory bulb, thalamus, and brain stem may be infected through a trans-synaptic transfer of the virus. Additional vagal nerve delivery via dendritic cells.
- Induces release of chemokines, cytokines, and inflammatory signals to the BBB and infects the astrocytes, which causes neuroinflammation and neuron death; neurodegenerative implications.
- Pathogenic effect on the CNS with specific impact on the midbrain dopamine neurons which abundantly express ACE-2 receptors.
- Spike protein can reach different brain regions, irrespective of viral brain replication. Can itself cause BBB dysfunction and damage neurons either directly, or via activation of brain mast cells and microglia and the release of various neuroinflammatory molecules.
- Spike protein alters microglial purinergic signaling in vitro, may potentiate the Cell Danger Response.
- Published case report examined adolescents who acutely developed new OCD, neuropsychiatric, and motor dysfunction symptoms consistent with PANS, having a temporal correlation, 2 weeks after a diagnosis of Covid-19.

- "Highly likely that neural autoantibody production is facilitated by SARS-CoV-2 infection..."
- PMID: 35601258, 36899824, 33158605, 33936086, 37114062, 37606433, 35883527, 33748620, 35390636

84 Cytokine cascade

- Entry in the brain via ACE2 (abundantly expressed in midbrain.)
- TLR or NF- κ B signaling activate the pro-inflammatory self-defense inflammasome after viral attachment.
- Pro-inflammatory feedback loop activates CNS immune cells, astrocytes and microglia, which induce IL-1, IL-6, TNF- α , and IL-8.
- Several CNS-related illnesses are linked with elevated levels of these inflammatory cytokines.

85 Neurotoxic components

- "Superantigenic" neurotoxin-like motif exhibits a high tendency to bind T-cell receptors.
- PMID: 32989130 (Oct 2020)

86 Periodontal infections

- A major under-recognized contributor to PANDAS/PANS and neuroinflammation.
- ID via qPCR Next-Generation Sequencing. Also tests for resistance in strains.
- Dentist or periodontist collects a small amount of fluid from an infected pocket in the gums, as well as a saliva

sample.

- Avoid ozone for 1 week prior to sample collection as it's a potent antimicrobial.
- Treatments using ozone are well-tolerated by P/P ~
Multiple published case studies using ozone gas to treat "untreatable" periodontal conditions (3-4 month nightly rinse.)
Some evidence (15-day trial) ozone rinse is not as effective against gingivitis as commonly used chemicals (chlorhexidine) but is a viable alternative for chemically-sensitive. Need a longer duration study - empirically quite effective.
- PMID: 36570588, 32594645

87 Infectious triggers

- Group A Beta-Hemolytic Streptococcus Pyogenes
- Mycoplasma pneumonia
- Chlamydia pneumonia
- Bartonella species
- Borrelia species (Lyme and Tickborne Relapsing Fever [TBRF])
- Encephalitis viruses
- Influenza
- SARS-CoV-2
- Periodontal

88 Diagnostics

- Clinical diagnosis

Clinical diagnosis

- PE and symptoms as clues
- General diagnostics
- Infectious triggers
- Environmental triggers

89 Environmental triggers

- Top 7 from my clinical practice ~
 - 1. Herbicides
 - 2. Mold
 - 3. EMFs
 - 4. Mercury
 - 5. Pesticides
 - 6. Vaccine adjuvants
 - (Food dyes get a dis-honorable mention)
- Commonality? All are neurotoxins and immunotoxins.

90 Glyphosate (Roundup)

- Genetically modify crops to be "roundup ready".
- Allows the GM plant to survive the mechanism of the chemical.
- But not just for killing weeds anymore!
- Additionally used as a desiccant for non-GMO grains, spraying enough to kill the greenery via desiccation for easier harvest of grains, equating to higher than approved levels just before harvest.
- Increases incidence of Fusarium mold infestation in storage.
- "Coherent and compelling evidence that glyphosate and glyphosate-based formulations are a cause of non-Hodgkin lymphoma (NHL) in humans exposed to these agents."
- Successful legal case linking exposure to NHL resulted in it being quietly taken off the market for residential use.
- Commercial use allowed to continue!
- PMID: 34052177, 31342895

91 No human effects?

- Affects shikimate pathway - not found in human cells but is utilized by our gut microbiome
- Reduces gut immunity and confuses the definition of "self", increasing the incidence of autoimmunity via Th17 and mast cell infiltration
- Salmonella and Clostridia are resistant to it
- Glyphosate-induced intestinal dysbiosis impacts CNS, in emotional, neurological and neurodegenerative disorders
- In mice, low-level "subchronic" exposure increased anxiety and depressive-like behaviors
- Low-level exposure linked to autism spectrum disorder

- Animal studies, low-level maternal glyphosate exposure linked to increased incidence of ASD
- PMID: 31442459, 29635013, 20012598, 28848410, 32398374

92 Glycine backbone

- Core of the molecule is glycine
∴ may displace glycine metabolically
- Impacts ~
Neurotransmitter (calming NT)
Glutathione (one of the AAs)
Glycine membrane channels (leading to channelopathies)
- Possible fertility impacts ~
alters testicular morphology and testosterone levels

93 Glyphosate urine test

- Urine

94 Atrazine - "pre-emergent" herbicide

- Endocrine disrupting chemical with neuroendocrine/epigenetic toxicity.
- Targets hypothalamus-pituitary-gonadal (HPG) axis.
- Frogs: low exposure males become females, high exposure males can procreate.
- Evidence of crosstalk between systems affected by Atrazine exposure, causing widespread dysfunction and leading to changes in behavior, even with no direct link to the hypothalamus.
- EU banned Atrazine use in 2003 recognizing the health risks of Atrazine exposure as a public health concern with no way to contain contamination of drinking water

no way to contain contamination of drinking water.

- Yet, the US recently reapproved Atrazine's use in the fall of 2020.
- PMID: 27413107, 35410624
-

95 Atrazine

- Histological and morphological alterations in the ovaries and testes are observed; dependent on duration of exposure and dose.
- Green = increases
- Pink = reductions
- Grey indicates that both increases and reductions are reported
- Effects in males are in purple
- Alterations in females are in red (VO: vaginal opening)
- PMID: 28713818

96 Atrazine

- Abundance of DRs → dysfunction of dopaminergic systems → ↑anxiety/anxiety-like behavior
- Might destruction of DRs be a compensatory reaction to Atrazine exposure?
- PMID: 34564358

97 Atrazine urine test

- Urine

98 Glyphosate urine test

- Urine

99 MOLD

- Natural function of fungi is to compost and recycle
- Excrete 1° and 2° metabolites ~ inhaled, ingested, and dermally absorbed
- 1° metabolites ~ necessary for survival aldehydes, alcohols, odors, digestive enzymes, and structural elements (ie: beta-glucans)
- 2° metabolites ~ competitive antimicrobials, mycotoxins (energetically expensive for the mold to make)

100 Mold is tenacious

- Moisture ~ 1° element for growth, 2° is organic substrate
- Obvious or visible water not necessary
- Relative humidity above 50% promotes growth
- Grows on WD surface within 24-48 hours
- Difficult to kill ~ any intact spore is dormant, not dead (a dead spore is a fragment)

- Spore formation and release increases more when drying than when wet (survival of species)

101 More than "spore illness"

- Spores
 - IgE | Allergic rhinitis, asthma, hypersensitivity pneumonitis (CDC)
 - Non-IgE | Non-IgE mediated Asthma exacerbation (CDC)
 - Infection | Aspergillosis (CDC)
 - Mast cell | Recruitment, degranulation, enhanced survival
- Fragments
 - "Mold-othelioma"
- Other Mould Dangers
 - Chemicals | VOCs, aldehydes, alcohols, MPA
 - Mycotoxins | Colonization
- Biofilm
 - Water-damage=increased microbial diversity (ie: actinomycetes, endotoxin)
 - Quorum behavior
- PMID: 24368325, 20537281, 24368325, 23710148

102 Respiratory system vs Mold

- Mould
- Spores-
- Cladosporium 3-5 μ m
- Aspergillus 2-5 μ m
- Penicillium 1-5 μ m

- Penicillium 1-5m
- Fragments-
- 1-2m
- Mycotoxins-
- 0.1m

103 Mycotoxins

- Aflatoxin
 - Aspergillus flavus, A. parasiticus
- Chaetoglobosin A,C
 - Chaetomium globosum
- Citrinin
- Aspergillus, Penicillium, Monascus
- Enniatin B1
 - Fusarium spp
- Gliotoxin
 - Aspergillus fumigatus, Candida spp
- Ochratoxin A
 - A. ochraceus, A. niger, Penicillium verrucosum, P. nordicum, P. chrysogenum

- Patulin
- Aspergillus spp, Penicillium spp, Mucor, Fusarium spp
- Sterigmatocystin
 - Precursor of Aflatoxin, A. versicolor
- Trichothecenes (Roridin, Verrucaridin, Nivalenol, Deoxynivalenol, Diacetoxyscirpenol, Satratoxin)
 - Stachybotrys chartarum, Trichoderma viride, Fusarium spp, Myrothecium
- Zearalenone
 - Fusarium spp

104 Respiratory system vs Mold

- Mould
- Spores-
 - Cladosporium 3-5 m
 - Aspergillus 2-5 m
 - Penicillium 1-5 m
- Fragments-
 - 1-2 m
- Mycotoxins-
 - 0.1 m

105 Mycotoxin health impacts summarized

- *Lipophilic*
- Immunotoxic
- Neurotoxic
- Alimentary toxic
- Dermatotoxic
- Nephrotoxic
- Hepatotoxic
- Hepatocarcinogenic
- Genotoxic
- Teratogenic
- Carcinogenic
- PMID: 26474839, 27178040, 25449202,12221236, 26600019

106 Mold

- Mycotoxins have a long history of use as a biological warfare weapon.
- "Yellow rain" T-2 toxin use against the Hmong people in Southeast Asia.
- So, yes, they affect everyone.

107 Multisystem Multisymptom

- More common than not that each person in an exposure environment has a completely different presentation.

- Every living being is affected.
- Depends on type of mould, presence of mycotoxins, duration and dose of exposure, and individual susceptibility.

108 Mold

- Use book

109 Mold

- Use book

110 Mold

- Use book

111 Mold

- Use book

112 Research Study

- Use book

113 Mold

- Use book

114 What Explains Symptom Persistence?

- Occupational studies ~
Coin flip: ~50/50 persister/recovered
Do they stay symptomatic out of the building?
*likely different stats for home exposure
- CES study ~

- CFS Study -

Normal controls: +fungus, -mycotoxins

CFS pts from WDB: +fungus, +mycotoxins

- Damp or WDB exposure is the key
- Mould is the trigger
- Colonization is the result
- PMID: 23580077 Brewer et al, Detection of mycotoxins in patients with chronic fatigue syndrome

115 Mold Assessments

- Lab -
- VCS
- mold spore allergy (can be normal and still have mold-related illness)
- Mycotoxin antibody
- Mycotoxin urine

116 Electrosmog

- Book

117 eEMFs

- Electromagnetic frequency radiation (external) - the invisible toxin of our time.
- Emitted from mobile phones, Wi-Fi, Bluetooth devices, smart meters, microwave ovens, many electrical devices, power and transmission lines, and wiring problems involving bad grounding.
- Thermal effects: increase BBB permeability to macromolecules.
- Main action is non-thermal via voltage-gated ion channels leading to channelopathies: oxidative stress, sperm/

testicular damage, neuropsych effects including EEG changes, apoptosis, cellular DNA damage, endocrine changes, and calcium overload.

- Behavioral studies have particularly concentrated on the effects of eEMFs on learning, memory, anxiety, and locomotion.
- Study in adolescents: change in memory performance over 1 year was strongly negatively associated with eEMF dose.
- PMID: 26474271, 31463749, 20550949, 29573716, 26300312

118 Voltage-gated channelopathies

- Synaptic vesicles in the presynaptic terminal contain a high density of voltage-gated Ca²⁺ channels.
- When an action potential arrives at the distal end of the axon – the presynaptic terminals – the inrush of positive charge activates voltage-sensitive Ca²⁺ channels.
- Ca²⁺ entry then initiates the release of NTs into the synaptic cleft.
- When NTs, such as ACh or glutamate, activate cation (for example Na⁺ or Ca²⁺) channels, and are thus depolarizing, they can be described as excitatory.
- PMID: 15753022

119 eEMFs

- Signs ~
EEG changes consistent with voltage-gated calcium channel activation
- Symptoms ~
Sleep disturbance/insomnia
Headache
Depression/depressive symptoms

~~Depression, depressive symptoms~~
Fatigue/tiredness
Dysesthesia
Concentration/attention dysfunction
Memory changes
Dizziness
Irritability
Loss of appetite/body weight
Restlessness/anxiety
Nausea
Skin burning/tingling/dermographism

120 Screen reliance

- Only safe space for many P/P kids is virtual spaces
- Virtual school often required
- Screen addiction common (dopamine)
- eEMF Blocking ~
Lap pads, sleep canopies
- eEMF Grounding ~
Nature!, grounding mats
- eEMF Discharging ~
Movement (produces non-polarized internal or iEMFs)

121 eEMF Diagnostics

- Test spaces, no known "body" test at this time.
- Guard sleep space the most.

- Resources:
- Building Biology Institute (buildingbiologyinstitute.org)
- EMF Analysis (emfanalysis.com)
- Environmental Health Trust (ehtrust.org)
- Physicians for Safe Technology (mdsafetech.org)
- Tech Wellness (techwellness.com)
- *Beware of over-reliance on EMF protection gadgets.
Reduction of exposure is the best mitigation measure.
-

122 Mercury

- WHO March 2017 ~
 - Considered by WHO as 1 of the top 10 chemicals or groups of chemicals of major public health concern.
 - Even small exposure amounts may cause serious health problems, and is a threat to the development of the child in utero and early in life.
 - May have toxic effects on the nervous, digestive and immune systems, and on lungs, kidneys, skin and eyes.
- Comparison of typical exposures versus regulatory safety standards suggests that many people receive unsafe exposures.
- 1 in 6 women have mercury levels high enough to create a neurologic risk for their children.
- Norway was the first country that banned the use of mercury in all products in 2008 including dental amalgam, followed by Sweden and Denmark.

- 2018: the EU banned the use of dental amalgam for children under 15 and for pregnant/nursing women.
- PMID: 34941760, 24420334

123 Mercury sources

- Organic ~
Methylmercury - fish/water contamination from coal-fired power plants
Ethylmercury (Thimerosal) - vaccine adjuvant, preservative (ie: contact lens solutions)
- Inorganic/elemental ~
-“Silver” dental amalgams (about 50% mercury).
-Dentists like its malleability and hardness as compared to other materials.
-Continuously release elemental mercury vapor.
-Amalgam surface area that exceeds the safe level of airborne mercury in the intraoral cavity:
 Adult: >0.8 surface of a tooth
 Child: >0.6 surface of a tooth
- ∴ more than one small filling is harmful to a child's health
- PMID: 21782213, 34941760

124 Mercury sources

- Average amalgam filling - 1000mg
- Thermometers - 500mg
- Barometers
- Electronics
 LCD screens/monitors
 Laptop screen shutoffs

- Antiques; jewelry, clocks, glass/mirrors
- Old appliances & vehicle switches
- Medical
 - Preservative - eye, nasal, skin, injections
 - Skin ointments (hemorrhoid cream)
 - Antiseptics (Mercurochrome)
 - Pharmaceuticals (diuretics)
 - BP cuffs
- Some batteries
- Fluorescent lightbulbs - 4mg
- Food ~
 - Seafood: 1 can tuna - 15-60 mcg
 - High-fructose corn syrup
- Flu shot - 25 mcg per 0.5-mL dose

125 Dental mercury amalgams in children

- Evidence of safety of dental mercury amalgams in children has been based on 2 key studies from 2006 known as the Children's Amalgam Trials; followed >500 children each over 5/7 years.
- Both studies found no difference in neurobehavioral outcomes between the amalgam group and the composite (non-amalgam) group—although in both trials the amalgam group showed a statistically significant increase in urinary mercury levels

primary mercury levels.

- These two studies, in addition to being widely cited in the literature, are cited by the FDA and the ADA as providing evidence for the safety of amalgam.
- However, a 2011 reanalysis suggests harm, and >boys with common genetic variants.
 - Reanalysis used an exposure metric based on amalgam size and years of exposure
 - Found a significant association between amalgam and the porphyrin biomarkers for mercury-related enzyme blockage
- "Dental amalgams are a significant chronic contributor to mercury body burden."
- PMID: 24420334, 21053054

126 Dental amalgams disperse

- Mercury doesn't stay in the tooth!
- A study quantifying the excretion and distribution of mercury in biological samples after dental amalgams found ~
 - Concentrations of Hg in the biological samples of those with amalgams were found 6-8 times higher than the non-amalgam users (control).
 - Spike in Hg in RBCs, plasma, and urine on 1st day of filling, but not in hair or nails.
 - Accumulation in hair and nails by day 12, but reduced in RBCs, plasma, and urine.
- Mercury levels in the blood, urine or other biomarkers do not reflect the mercury load in critical organs.
- Gestational mercury exposure ~
 - Gestational exposure in infants of mothers who did not consume fish, had an elevated risk of URIs requiring a doctor visit.
 - Alterations in both T cells and gene expression in placenta at birth.
- Amalgams continuously release elemental mercury vapor (up to 20 micrograms per day.)
Odorless and tasteless.
Primarily absorbed in lungs where it can disperse widely, even xBBB.

- PMID: 27464660, 30743244, 34129869

127 Exposure estimates

- Organic mercury is more genotoxic than inorganic/elemental, yet "Amalgam-related Hg exposure [which is inorganic/elemental form] exceeds that from fish or other sources for the majority of the population."
- The highest allowable average mercury concentration in fish per serving when eating 1 serving per week = 0.46 µg/g
- Whereas, estimates of Hg exposure from amalgam fillings "based on the least conservative of the scenarios evaluated, it was estimated that some 67.2 million Americans would exceed the Hg dose associated with the reference exposure level (REL) of 0.3 µg/cubic meter of air established by the EPA."
- Exposure estimates are consistent with previous estimates presented by Health Canada, and amount to 0.2-0.4 µg/day per amalgam-filled tooth surface, or 0.5-1 µg/day per amalgam-filled tooth, depending on age/other factors.
- PMID: 21782213, 34941760

128 Dentists and dental hygienists

- Study of dentists in Iran found that the mean of the mercury level in the urine, nail, and blood was higher than the standard of the WHO.
- "So, in accordance with Article 10 of the European Union Regulations (EUR), in the context of the Minamata Convention (MC) on Dental Amalgam (DA), in order to avoid the dangers of mercury exposure in dentists, it is necessary for Iran and other countries to approve laws and to implement a national plan to reduce mercury levels and replace the appropriate materials."

- “Numerous studies have reported neurobehavioural effects in dental personnel occupationally exposed to chronic low levels of mercury (Hg).”
 - elevation of amyloid protein expression, deterioration of microtubules and increase or inhibition of transmitter release at motor nerve terminal endings.
 - neurodegenerative diseases such as Alzheimer’s, MS and mood disorders.
 - idiopathic disturbances in motor functions, cognitive skills and affective reactions.
- PMID: 33312669, 30589214

129 Amalgams vs fish

- Reference Dose of safety - level of exposure that is reasonably certain to be without appreciable risk for a population exposed over a long period of time.
- EPA set RfD for methylmercury consumption in women of childbearing age (and their fetuses). No other population of defined, not even children.
Reference Dose = 0.1 mcg/kg/day methylmercury. [45 lb child = 2 mcg/day]
- Amount of elemental mercury vapor from one amalgam filling =
1 surface = up to 20 mcg/day.
The lower the body weight, the more increased the concentration.
- “Throughout the world, efforts are underway to phase down or eliminate the use of mercury dental amalgam.” (PMID 24420334) Yet there are no RfDs set for amalgams in the US, not even for those with lower body weight.
- *I acknowledge this is comparing different forms of mercury

- I acknowledge this is comparing different forms of mercury and so may have different health/absorption/accumulation effects

130 Mercury health impacts

- Neuro ~
As vapor: can xBBB and lipid cell membranes, and can be accumulated into the cells in its inorganic forms.
Methylmercury can xBBB and placental barriers, causing serious damage in the CNS.
Animal studies: motor and cognitive impairment and neural loss.
- Nephrotoxic.
- Oral microbiome ~
Marked differences in the composition of the oral microbiome, associated with dental decay, found with even low concentrations of salivary mercury.
- Gut ~
Gut connection to neurotoxicity: Healthy intestinal microbiota demethylates MeHg and promotes excretion through feces.
But in so doing, it impacts the gut microbiota and metabolites related to gut-brain interactions.
Induces changes of intestinal microbial community structure which induces changes to regulating neuron activity.
Elemental Hg induces archaea (methanogens) conversion to methylmercury in vitro.
- PMID: 29777524, 32887894, 31918252, 33242089

131 Mercury, mast cells, and histamine

- Mercury induces histamine release from basophils.
- Mercury induces inflammatory mediator release from mast cells, specifically VEGF and IL-6.
- Animal models:
Induces a Th-2-dominated autoimmune syndrome with tissue injury in the form of a vasculitis and arthritis.
Sensitizes mast cells for mediator release and interleukin-4 expression.

Impacts mast cell survival.

- Links to autoimmunity, disruption to BBB and subsequent neuroinflammation.
- PMID: 20222982, 11222498, 19604304, 22103852, 9492216

132 Oral galvanism

- Electromotive forces and electrical currents discharged from a tooth when two or more dissimilar metals coexist in the mouth (i.e. as used to make the "amalgam".)
- Interact with salivary electrolytes, worse acidic saliva.
- Also occurs with contact between occluding metallic restorations.
- Can be measured (biological dentist): the threshold for pathological values of 5 microA for galvanic currents and 100 mV for galvanic voltage.
- A long-lasting influence (>15 hours) of galvanism can, in sensitive and genetically susceptible individuals, influence lymphocyte proliferation and surface molecule expression.
- "After removal of the electro-active restorations, both the contents of metals in saliva and galvanic currents decreased in comparison with the levels before the treatment."
- German study concluded that the removal of dental amalgam leads to "the permanent improvement of various chronic complaints in a relevant number of patients in various trials."
- PMID: 14917837, 15789284, 19178813, 15451237, 16804514

133 Mercury s/sxs

- Symptoms are variable and nonspecific. Neuropsych sxs have high cross-over with P/P.
- Poor resistance to infection, especially to yeast and yeast overgrowths.
- Anxiety, depression, "mercurial mood", irritability, suspicious, impulsive
- Memory problems, incoordination, movement abnormalities, a sense of internal vibration, paresthesias particularly of the hands and feet

1 PANDAS & PANS

An Integrative Approach

- Dr. Jill Crista

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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

1 PANDAS & PANS An Integrative Approach

- Dr. Jill Crista

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- 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 Programmed bias

- Bring awareness to your medical programming
- May be triggered by the sheer accessibility of the things presented in this section
- Accessible has been labeled "simplistic" "ineffectual" "dangerous"
- By who? By those standing to gain from the separation
- "Doctor as guru" (dependence) over "doctor as teacher" (empowerment)
- It's okay to put some trust in nature!
- Your grandmother's grandmother did - and you are living proof of that trust

- You are not just “part of nature”, you are nature
... and so is your patient
- (and you will never be without a job)

6 Integrative approach

- Acute vs chronic presentation
- Core 4 ~
Anti-inflammatories
Antimicrobials
Immune modulation
Infection/toxicant prevention
- Treatment cautions
- Then, once out of acute, and in order to prevent/heal, use tools in the next module - Recovery Essentials
-

7 Medication Compatibility Chart

- A living document
- Updated as new information becomes available.

8 Adjust doses for children

- All doses will be given as adult doses for continuity.
- Adjust by weight using Clark’s Rule for ages 2-17.
- Clark’s Rule:
 - First, divide the child’s weight in pounds by 150 (or the child’s weight in kilograms by 68.)

- Find the fraction or decimal, whichever makes it easier to make sense of liquid vs capsule.
- Then multiply the fraction or decimal by the typical adult dose to find the child's dose.

-

9 Getting herbs into kids

- Ask parents: savory vs sweet, hot vs cold, texture issues, time of day
- Forms: teas, glycerites, powders, mixed/cooked into food, popsicles, chews
- Mixers: honey, black strap molasses, coconut, butter, nut butters, ranch dressing, ketchup, mustard, spaghetti sauce, curry, salsa, teriyaki, broth
- Chasers: pickle juice, chai
- First few doses (this is my sneakiest tip): Fry an onion 5 min prior. Aroma boosts stomach acid & primes the body for bitter. Once this positive association is set, subsequent dosing goes easier.
- Have multiple options to plan ahead for refusals - they will happen!
It's natural.

10 Integrative treatment overview

- 1. Guard the gates
halt T-cell migration to CNS
- 2. Immune modulation
prevent autoimmune tendencies/gut health
- 3. Address neurotransmitter imbalance
balance dopa & glutamate to reduce destruction
- 4. Reduce neuroinflammation/leaky BBB

- 4. Reduce neuroinflammation/leaky BBB
get good stuff in and bad stuff out
- 5. Manage trauma/stress
adrenal/nervous system burnout
- 6. Structural integrity
chronic brain stem/cervical congestion/jaw development

11 Acute vs Chronic

- Important to identify at what stage the patient is presenting.
- Different level of intervention for acute vs chronic.
- Acute - don't mess around! These kids take their own lives.
Conventional approach + Core 4 - Infection/toxicant prevention
(Guard the Gates)

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14 Putting It Together

- Select 1 Flame Tamer and 1 Mast Cell Manager.
- Choose the 1 or 2 Botanical Avatars that fit the child.
- Add 1 Botanical Antimicrobial to fit the child's current infection load.
- Optimize Vitamin D.
- Add Core immune modulation.

- Choose 2 methods for each of the Nasal, Throat, and Dental gates.
- Explore various ways to close the Exposure Gate, starting with hand-washing (family/caregivers), removing glyphosate and mold, reducing infection exposures.
- Assess after 4 weeks, add more support/tweak and/or Rx if needed to any Core area.
- (Acute - conventional approach + Guard Gates)

15 Integrative approach

- Acute vs chronic presentation
- Core 4 ~
 - Anti-inflammatories
 - Antimicrobials
 - Immune modulation
 - Infection/toxicant prevention
- Treatment cautions
- Then, once out of acute, and in order to prevent/heal, use tools in the next module - Recovery Essentials
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17 Flame Tamers

- The target is neuroinflammation, specifically the microglia.
 - Pro-resolving mediators
 - Feverfew
 - Resveratrol
 - Rosemary
 - Pine extract

18 Pro-resolving mediators

- Also referred to as specialized pro-resolving mediators (SPMs) ~
18-hydroxyeicosapentaenoic acid
17-hydroxydocosahexaenoic acid
14-hydroxydocosahexaenoic acid
- The most anti-inflammatory aspect of fish oils - not just "rebranded" fish oil.
- Resolve inflammation rather than suppress the inflammatory process.

- Helpful in inflammatory processes that become self-perpetuating and pathogenic; CIRS, MCAS, and autoimmune diseases such as PANDAS/PANS.
- Reduce neuroinflammation and microglial activation.
- PMID: 34822458, 28483532, 33486004

19 EFAs are not created equally

- Wild vs farmed salmon
- Poorly fed fish that can't exercise = bad fat
- Fish with bad fat = humans with bad fat

20 Pro-resolving mediators

- Quells inflammation from dental plaque buildup (many PANDAS/PANS kids are behind on dental care.)
- A method to increase EFAs for histamine-sensitive children.
- Especially helpful for a child who's had a concussion or has concomitant ASD with head banging.
- Works well in combination with almost every supplement, herb, and medication
- Daily:
Capsule: 500 mg daily
- Flare:
Capsule: 1000 mg twice daily
- Caution:
May interact with anticoagulant medication.

21 Feverfew

21 Feverfew

- Tanacetum parthenium ~ leaves and flowers
- Sesquiterpene lactone ~ parthenolide (not triterpenoid saponin/avatar)
- Anti-inflammatory and neuromodulatory effects
- "Hormone headaches"
- Ameliorates colon inflammation through regulating Treg/Th17 balance in a gut microbiota-dependent manner.
- Parthenolide inhibits the LPS-induced secretion of IL-6 and TNF- α and NF- κ B nuclear translocation in microglia.
- PMID: 32373209, 33374525, 22359368

22 Feverfew

- For appetite-improving effect, use 30 minutes before meals. Combines well with Gotu kola.
- Effect is dose dependent. Before abandoning this herb, try a higher dose.
- Daily:
 - Tea: 1 cup twice daily
 - Glycerite: ½ tsp twice daily
 - Capsules: 350 mg twice daily
- Flare:
 - Tea: 2 cups up to four times daily
 - Glycerite: 1 tsp up to four times daily
 - Capsules: 700 mg up to four times daily
- To prep the tea:
 - Yield: 2 cups

Prepare tea by steeping 1 Tbsp dried Fevertew leaves and flowers in 2 cups of boiling water for 5 minutes, covered. Strain and add honey to taste. Cool to a comfortable drinking temperature.

- Caution:
May cause allergic reaction in those with ragweed allergies.
May interact with anticoagulant medication.

23 Resveratrol

- NLRP3 inflammasome is implicated in OCD, psych disorders ~
Resveratrol regulates microglia M1/M2 polarization in conditions of neuroinflammatory injury.
Suppresses the NLRP3 inflammasome pathways in microglia.
- Resveratrol inhibits NLRP3 inflammasome activation by preserving mitochondrial integrity and augmenting autophagy.
- Specific mycotoxin protective effects ~
Attenuation of intestinal inflammation and oxidative damage linked to the alteration of gut microbiota and butyrate from mycotoxins.
- Attenuates allergic asthma and reduces DNA damage in bronchial epithelia, as well as enhancing NK cell cytotoxicity.
- Combats known mycotoxin mechanisms, for example, by activating the Nrf-2 pathway and alleviating Nf-kappa-B neuroinflammation.
- Reduces achiness and neuropathic pain.
- PMID: 25535911, 34739715, 34130737, 28268115, 28283884, 30619345, 32186748, 31035454, 27316789, 31090224, 33770763

24 Resveratrol

- Usually easy to get kids to take the liquid, tastes sweet.
- Studies suggest a minimum therapeutic dose for mycotoxin exposure of 1 gram daily to meet the desired plasma concentration

concentration.

- Daily:
Liquid or capsule: 500 mg daily
- Flare:
Liquid or capsule: 500 mg three times daily
- Caution:
May cause low blood pressure at high doses.
-

25 Rosemary

- *Rosmarinus officinalis* ~ use the needle-like leaves
- Long history of use and benefits in mental health and cognition. Worn as a crown for sharp thinking.
- Rosmarinic acid inhibition of the NLRP3 inflammasome exerts antioxidant, anti-inflammatory, and neuroprotective effects
- Rosmarinic acid regulates microglial M1/M2 polarization under conditions of neuroinflammation
- Rosmarinic acid mitigates LPS-induced neuroinflammatory responses
- Inhibition of the NLRP3 inflammasome. Exerts antioxidant, anti-inflammatory, and neuroprotective effects via phase 2 enzyme induction initiated by activation of the KEAP1/NRF2 transcriptional pathway, which in turn attenuates NLRP3 activation.
- Antifungal and antimycotoxigenic activity against multiple mold species.
- PMID: 31644378, 25053064, 29318480, 35052628

26 Rosemary

- Crosses the BBB. Aroma induces brain calming and mood lightening effect.
- For appetite-improving effect, use 30 minutes before meals
- Daily:
Tea: ½ cup twice daily
Glycerite: ¼ tsp twice daily
Capsules: 350 mg daily
- Flare:
Tea: 1 cup three times daily
Glycerite: ½ tsp three times daily
Capsules: 700 mg three times daily
- To prep the tea:
Yield: 2 cups
Prepare tea by steeping 1 Tbsp dried Rosemary leaves in 2 cups of boiling water for 5 minutes, covered. Strain, and add honey to taste. Cool to a comfortable drinking temperature.
- Also consider essential oil topical applications
- Caution:
May cause dry eyes and mouth.
Children sensitive to phenols may tolerate the tea best.
May lower blood sugar and iron absorption at high doses.
May interact with anticoagulant medications.

27 Pine Extract

- Multiple boreal conifer species ~ needle and bark
- Potent antioxidant and anti-inflammatory activity
- Protective against activated microglial neuroinflammation

and also T cells.

- Attenuates the release of proinflammatory cytokines in LPS-stimulated microglia in part via Inhibition of NF- κ B and AP-1 activation.
- Mild antihistamine effect.
- Improves attention, learning, and memory.
- Prevents hippocampal excitotoxicity-derived memory impairment in acute stress in mouse models.
- PMID: 28642096, 26367267

28 Pine Extract

- Pycnogenol® is an extract from pine bark.
- Taiga is from pine needles.
- Daily:
Pine bark extract capsule: 100 mg daily
Pine needle extract capsule: 320 mg daily
- Flare:
Pine bark extract capsule: 200 mg twice daily
Pine needle extract capsule: 320 mg twice daily
- Caution:
Overpowering taste. May cause a bad taste in the mouth at high doses.
May cause nausea at high doses.

29 Integrative approach

- Acute vs chronic presentation

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Antimicrobials
Immune modulation
Infection/toxicant prevention
- Treatment cautions
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30 Integrative treatment overview

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31 Putting It Together

31 Putting it together

- Select 1 Flame Tamer and 1 Mast Cell Manager.
- Choose the 1 or 2 Botanical Avatars that fit the child.
- Add 1 Botanical Antimicrobial to fit the child's current infection load.
- Optimize Vitamin D.
- Add Core immune modulation.
- Choose 2 methods for each of the Nasal, Throat, and Dental gates.
- Explore various ways to close the Exposure Gate, starting with hand-washing (family/caregivers), removing glyphosate and mold, reducing infection exposures.
- Assess after 4 weeks, add more support/tweak and/or Rx if needed to any Core area.
- (Acute - conventional approach + Guard Gates)

32 Mast cell managers

- Mast cells are a major player in the "flare potential" of a child with PANDAS or PANS.
- The more mast cells that are recruited, the easier it is to trigger them.
- Preventing mast cells from being recruited and triggered is the focus.
 - Vitamin C
 - PEA
 - Quercetin and Luteolin
 - Nettles

- Perilla
- DAO
- Antihistamine Medications

33 Vitamin C

- Mast cell stabilizer; attenuates degranulation by inhibiting peroxidation of membrane phospholipids.
- Acts as a scavenger of free radicals, involved in collagen synthesis, detoxification, and is also required for the synthesis of several hormones and neurotransmitters.
- In humans, vitamin C reduces the duration of common cold symptoms, even if its effect is not clear.
- Supplementation improves the function of the human immune system, such as antimicrobial and NK cell activities, lymphocyte proliferation, chemotaxis and delayed-type hypersensitivity.
- Vitamin C depletion has been correlated with histaminemia which has been shown to damage endothelial-dependent vasodilation.
- PMID: 35781358, 23830380

34 Vitamin C

- Many kids are low in this basic vitamin! Before adding pharmaceutical antihistamines, first optimize Vitamin C status.
- I prefer liposomal Vitamin C for kids with PANDAS and PANS.
- Daily:
Liposomal liquid: 1,000 mg daily
- Flare:
Liposomal liquid: 1,000 mg up to five times daily

- Caution:
May cause diarrhea at high doses.
May falsely elevate glucose labs.
- *synergism with vitamin E, B6.

35 PEA - palmitoylethanolamide

- Made naturally endogenously in our brains as a neuroprotector, especially during transient hypoxia and episodes of low blood sugar.
- The main protective mechanism is to prevent mast cell degranulation.
- Some activity in resolution of inflammation.
- Unfortunately, PEA gets depleted from microglial activation. The result being that kids with PANDAS/PANS don't have this tried-and-true way to shut down mast cells.
- The inflammation begets more inflammation. Supplementing this nutrient stops the cycle, and can reduce pain.
- Cell study research suggests neuroprotective activity against Covid.
- PMID: 33917573, 33636368, 27423516, 26055231

36 PEA

- PEA is made from phenylalanine, which is found in diet beverages. One tip that a child needs this supplement is if he's craving artificially sweetened drinks.
- There's some evidence that this nutrient works best when combined with luteolin (next section).
- Daily:
Powder or capsule: 300 mg twice daily
- Flare:
Powder or capsule: 600 mg twice daily

• Effect of capsule: 600 mg three daily

- Caution:
Best absorbed with a fatty meal or with liposomes.

37 Quercetin & Luteolin

- "Vitamin yellow" ~ neon yellow antioxidant bioflavonoids
- Mast cell stabilizers;
Anti-inflammatory and antipruritic effects
More effective than cromolyn in blocking human mast cell cytokine release
- Hinders microglial activation to alleviate neurotoxicity via the interplay between NLRP3 inflammasome and mitophagy.
- Regulatory effects on M1/M2 macrophage polarization and oxidative/antioxidative balance.
- GI protective ~ anti-inflammatory, preserves the length of intestinal villi and mucosal thickness, increases the production of butyrate, improves gut dysbiosis in antibiotic-treated mice.
- Preserves oral cavity health by mitigating inflammation and microbial dysbiosis.
- Cytoprotective against mold mycotoxins.
- PMID: 35010945, 34082381, 30799996, 27423516, 22470478, 24382176, 32845255, 34899728, 26802676, 26134454, 25532488

38 Quercetin & Luteolin

- I've found that liposomal forms are the fastest acting.
- Daily:
Liposomal liquid or capsule: 300 mg twice daily
- Flare:
Liposomal liquid or capsule: 600 mg up to four times daily

- Caution:
May be an issue for kids who don't tolerate phenols.
In those cases, I use low-phenol forms.

-
-

39 Nettles

- *Urtica dioica* ~ leaves (mast cell), root, seed
- Rich in quercetin, rutin, and ellagic acid.
- Shown to possess antioxidant, hypotensive, anti-inflammatory, anti-diabetic, analgesic, antioxidant and antiproliferative properties.
- Ameliorates allergy symptoms and lowers skin irritability ~
Antihistaminic; antagonist and negative agonist activity against the H1 receptor
Mast cell stabilizing; inhibition of mast cell tryptase preventing degranulation and release of a host of pro-inflammatory mediators
inhibits prostaglandin formation through inhibition of central enzymes in pro-inflammatory pathways COX-1, COX-2, and Hematopoietic Prostaglandin D2 synthase (HPGDS)
- Neuroprotective ~
Improves memory function and cognition
Reduces chronic stress-related dysfunctions of the CNS in animal models
Positive effects on microvasculature
- PMID: 37171512, 35399803, 29844782, 19140159

40 Nettles

- Fig. 2 Potential neuroprotective mechanism of action of *U. dioica* and of its components
- PMID: 37171512

41 Nettles

- Used as a staple green in many indigenous diets. Very safe to use as food and in higher doses than many herbs.
- Randomized, double-blind, placebo-controlled, clinical trial using 150mg qid x 1mo reduced IFN- γ levels but no significant difference in allergic rhinitis over control.
(Not high enough dose, short duration, and/or the control "green matter" was also beneficial.)
- Daily:
Glycerite: 2 tsp twice daily
Capsule: 600 mg twice daily
- Flare:
Glycerite: 2 tsp up to four times daily
Capsule: 600 mg up to four times daily
- Caution:
Fresh plant will sting; cook or dry, or handle with gloves
Source of oxalates
- PMID: 29844782

42 Nettle Lemonade

- Mast cell...
- a
- PMID:

43 Perilla

- *Perilla frutescens* ~ leaves and seeds

- Rich in luteolin.
- Inhibitory effect of mast cell-mediated immediate-type allergic reactions in vivo.
- Potently suppresses IgE-mediated immediate hypersensitivity reactions.
- Attenuates airway inflammation.
- Inhibits NLRP3 inflammasome assembly, reduced the excessive accumulation of ROS, leading to reduced inflammation.
- Protective effect of Nrf2-ARE activator on dopaminergic neuronal loss in a Parkinson's disease model.
- Additional antimicrobial properties; inhibits several virulence attributes of *C. albicans* including biofilm formation and yeast-to-hyphal transition.
- PMID: 35058774, 28167258, 27986566, 24871572, 10946827, 36978975, 36302165, 32822688

44 Perilla

- Anti-histaminic effects are dose dependent. If you've tried this herb at a lower dose and didn't get the desired effects, try increasing the dose.
- Daily:
Glycerite: ½ tsp twice daily
Capsule: 150 mg twice daily
- Flare:
Glycerite: 1 tsp up to three times daily
Capsule: 300 mg up to three times daily

- Caution:
May cause rare allergic reactions if applied on the skin.

-

45 DAO

- Diamine oxidase (DAO) is an enzyme that breaks down histamine in the gut.
- Excessive mast cell histamine release and/or high histamine diets may deplete this enzyme.
- Genetic snps affect production.
- Gut-brain axis ~ gut-brain histamine activates microglia.
- While a low-histamine diet can make a huge difference in a child's overall histamine load, sometimes his enzyme system could use a little help.
- Daily:
Capsule: 10,000 HDU up to 15 minutes before largest meal
- Flare:
Capsule: 10,000 HDU up to 15 minutes before every meal
- Caution:
Pork sourced - allergy, religious abstention

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50 Avatar (definition) - Ideal

- Abilities to “bend” (aka work with) all of the elements ~ air, earth, fire, water

51 In an ideal world

- An ideal remedy for PANDAS and PANS would do the following:
 - Serve as a broad-spectrum antimicrobial
 - Modulate the immune system
 - Neutralize neuroinflammation
 - Act as an antioxidant for the brain and nervous system
 - Reduce dopamine and glutamate
 - Normalize acetylcholine
 - Boost GABA (gamma-aminobutyric acid) and serotonin
 - Heal the gut
 - Foster a healthy microbiome
- Oh, if only there was one treatment that hit all those marks!

52 Botanical Avatars

- Ideal medicinal botanicals for PANDAS and PANS because they hit each of the previous points AND they’re antimicrobial.
- I use at least one of these herbs as the foundation of treatment, to which all other methods are added if needed.
 - Chinese Skullcap (*Scutellaria baicalensis*)
 - Oregon Grape (*Berberis aquifolium*)

- Thorough-wax (Bupleurum species)
- Brahmi (Bacopa monnieri)
- Magnolia (Magnolia species)
- Silk Tree (Albizia julibrissin)
- Gotu Kola (Centella asiatica)

53 For the herb nerds

- ∴ Look for triterpenoid saponins
- Tie that binds
- Lipophilic ~ nervous system, intracellular, mitochondria
- Immune modulation
- Steroidal in nature (anti neuroinflammatory)
- Restore neurotransmitter imbalance
- Antioxidant
- Restore programmed pruning

54 Avatar how-to

- I often combine 2 or 3 of these herbs, depending on the specific benefits I'm seeking for the child.
- To safely combine them, I adjust the dose by half if using 2 of these herbs at once, or by a third if using 3 at once.
- In the acute flare phase, I commonly add Botanical Antimicrobials (see the next section). While Botanical Antimicrobials may be better antimicrobials, they don't have the full spectrum of mechanisms needed in PANDAS/PANS. We need a Botanical Avatar base.

PANS. WE NEED A BOTANICAL AVATAR BASE.

- For the prophylactic phase, the Botanical Avatars are often enough to prevent infection and gain ground on healing the gut and the brain.

55 Working with botanicals successfully

- Herbs aren't drugs. We dose them differently.
- The keys to success with herbal medicine treatments are to use a strong enough dose, dose frequently, and work around the taste factor.
- Weak doses and repeating too infrequently are common reasons for herbal failures.
- For tips on using herbal medicines with kids, see the "Getting Herbs into Kids" slide.
- Adult doses are given as a standard. See the "Dose Adjustment for Children" slide.

56 Botanical cautions

- Worsens neurotransmitter imbalance and/or depersonalization risk
- If it's good for Parkinson's research first to understand why/how.
- Who makes my "bad-atar" list?
dopaminergic
- Turmeric, boswellia, schisandra, lemon balm, passionflower, kava, plus many 'calming' herbs due to effect on dopa
- May be useful after a flare if child hits bottom/despair
-
- And now for some PANS/PANDAS Avatars...

- PMID: 20513244

57 Chinese Skullcap

- *Scutellaria baicalensis* ~ root
- Triterpenoid saponin ~ wogonoside
- Flavonoid rich ~ antioxidant
- Personality ~ as if perfectly prepped to handle the rocky inner world of a child with PANDAS or PANS, this herb grows best in rocky terrain.
- This is different from North American skullcap, or *Scutellaria lateriflora*, which has been used for millennia by Native Americans for nervous disorders and inflammatory ailments. The Chinese variant is slightly more specific to PANDAS and PANS.
- Not only is it a good bug killer, Chinese skullcap is soothing to the nervous system, usually without causing drowsiness. It can be given before school or other times that provoke anxiety, yet require focus.
- Because of its ability to regulate the T cell balance, I choose this Avatar for kids who also have allergies.
-
- PMID: 33224253, 31236960, 29143798, 27730005, 27845861, 22196758, 28859441

58 Chinese Skullcap benefits

- Antibacterial:
Demonstrates inhibitory activity against *Babesia duncani*, and stationary phase forms of *Borrelia*
Action against *Mycoplasma pneumoniae*

Action against mycoplasma pneumonia

- Antiviral
- Reduces anxiety
- Purinergic G protein-coupled receptor (GPCR) antagonist: helpful in turning off purinergic signaling to address CDR
- Protects the brain and nervous system:
Protects against dopamine neurotoxicity
Inhibits LPS-stimulated microglia
Significantly reduces secretion of inflammatory cytokines from stimulated microglia
- Reduces inflammation
- Regulates immune Th1/Th2 balance
- Improves intestinal barrier function
- Modulates gut microbiota for more beneficial species
- Nephroprotective
- PMID: 33224253, 31236960, 29143798, 27730005, 27845861, 22196758, 28859441

59 Chinese Skullcap dosing

- Chinese skullcap can be used for acute and prophylactic antibiotic therapy. It's safe to use long term. If needed, it can be combined with Botanical Antimicrobials and certain Pharmaceutical Antimicrobials. (See the Medication Compatibility Chart in the appendix.)
- The glycerite has a mildly bitter aftertaste. Nothing that a little xylitol gum can't overcome.
- Acute Treatment:
Glycerite: 1 tsp, 3 times daily with food
Capsule: 870 mg, 3 times daily with food

- Prophylactic:
Glycerite: ½ tsp, 2 times daily with food
Capsule: 435 mg, 2 times daily with food
- Caution:
Rarely, kids may get too relaxed to focus on school with Chinese skullcap.
May drop blood sugar or cause stomach upset. Take with food.

•

60 Oregon Grape

- *Berberis aquifolium* ~ root
- Triterpenoid saponins ~ stigmasterol glucoside
- Broad-spectrum antimicrobial
- Personality ~ happiest on misty days with partial sun in soil rich in humus. (A positive response to humic acid may be a hint that this herb is indicated.)
- Oregon grape has more specific activity against Strep than Chinese skullcap. As with Chinese skullcap, it also protects and heals the brain changes seen with P/P.
- Oregon grape helps with kids whose moods change drastically with blood sugar dips. It's also a nice match for kids with digestive issues, such as leaky gut, food allergies, and belly pain.
- Also consider Barberry (*Berberis vulgaris*), Goldenseal (*Hydrastis canadensis*) which have very similar activity.
- PMID: 31981716, 29232416, 28656094, 23840629, 26616870, 28403947, 27898425

61 Oregon Grape benefits

–

- Broad-spectrum antibacterial, moderate activity against *Streptococcus pyogenes*
- Antiparasitic
- Protects the brain and nervous system:
 Inhibits the release of glutamate in nerve terminals
 Protects against glutamate-induced neural cell injury
 ↓ ROS gen, lipid peroxidation, DNA fragmentation,
 while improving glutathione content + SOD activity in glutamate-injured cells
 Reduces neuroinflammation
 Improves repair in glutamate-injured cells
 Antagonist at both dopamine D1/D2 receptors
- Reduces inflammation
- Reduces histamine
- Balances unstable blood sugar
- Promotes the gut microbiota to produce butyrate, leading to increased energy metabolism
- PMID: 31981716, 29232416, 28656094, 23840629, 26616870, 28403947, 27898425

62 Oregon Grape dosing

- Oregon grape can be used for both acute and prophylactic antibiotic therapy. In many cases, its antimicrobial activity is strong enough to be used solo, without having to combine with a Botanical Antimicrobial. It's safe to use long term. If needed, it can be combined with certain Pharmaceutical Antimicrobials. (See the Medication Compatibility Chart in the appendix.)
- When combined with oral antibiotics, the butyrate stimulating effect is negated, so I add supplemental butyrate.
- The glycerite is bitter, which may take more than xylitol gum to overcome.
- Acute Treatment:
 Glycerite: 1 tsp, 3 times daily

Capsule: 500 mg, 3 times daily

- Prophylactic:

Glycerite: ½ tsp, 2 times daily

Capsule: 250 mg, 2 times daily

- Caution:

Bitter flavor.

May cause digestive upset.

May alter the gut microbiome if used in high doses for long periods.

63 Chinese Thoroughwax

- Bupleurum spp ~ root

- Triterpenoid saponins ~ saikosaponins, buddlejasaponin, sandrosaponins

- Multiple species researched - B. falcatum, marginatum

- Personality ~ This plant has a unique characteristic where the stem seems to pierce the leaf and grow right through it. In other words, rather than flow around the leaf, it barrels straight through, taking the harder route. Also could be seen that the leaf "flows around" the stem.

- Thorough-wax has been used for thousands of years in Asia. The American species can be found in and around Glacier National Park. It's the primary ingredient in a Chinese formula called "free and easy wanderer."

- Significant anti-inflammatory activity, antioxidant, anti-histaminic, analgesic

- Alleviates symptoms of ADHD

- PMID: 28314599, 21749378, 29956627, 28593176, 32742347, 16939901, 28293263, 24438177

64 Chinese Thoroughwax benefits

- Antimicrobial, moderate activity against *Streptococcus pyogenes*
- Antiviral, activity against Influenza A (H1N1), more potent inhibitory activity and selectivity than the positive control, Ribavirin
- Modulates the immune system
- Significantly reduces inflammation
- Anti-histamine
- Improves attention
- Neuroprotective:
 - Significant reduction in memory impairment
 - Decelerates the activation of microglia and astrocytes in the hippocampus
 - Preserves the morphology of neurons, reduce apoptosis and significantly inhibit amyloid- β deposition in the hippocampus
 - Inhibits increased glutamate (after limbic region stimulation in rats - this stim may have increased dopamine)
- Hepatoprotective and supports detoxification
- Antispasmodic, antitussive
- Diaphoretic, antipyretic
- Analgesic
- Anti-ulcer
- PMID: 28314599, 21749378, 29956627, 28593176, 32742347, 16939901, 28293263

65 Chinese Thoroughwax dosing

- Due to its long history of use in traditional Chinese formulas, it's rather difficult to find Thorough-wax on its own in

capsule form. I use the glycerite to make sure I'm not getting other herbs by default in a formula. It has a mild flavor most kids don't mind. It pairs well with maple syrup if masking is needed.

-
- Acute Treatment:
Glycerite: 1 tsp, 3 times daily
- Prophylactic:
Glycerite: ½ tsp, 2 times daily
- Caution:
May increase dopamine in some kids, so proceed cautiously. Start with half the dose and slowly increase, watching for signs of agitation.
Leaves a prickly feeling in the mouth and throat. This is normal and goes away on its own.

66 Brahmi

- Bacopa monnieri ~ whole plant
- Triterpene saponins ~ bacosides, brahminosides
- Personality ~ This water-loving herb grows in ponds, wetlands, and generally mucky areas. It's a match for anything "boggy," such as boggy tonsils and boggy brains. I use this with the child whose brain feels waterlogged, yet inflamed—a unique combination of dampness and heat.
- Brahmi's use goes back centuries in traditional Ayurvedic medicine, where it's touted as a brain tonic and cognitive aid. That claim is bearing out as scientists find multiple nootropic compounds.
- I think of Brahmi as a "chill" agent. Kids often feel the change in inflammation, saying their brains don't feel as swollen. It helps sharpen the mind and reduces pain. It's a nice choice before school.

- Useful for kids restricting food, as it protects the brain during hypoglycemic episodes.
- PMID: 27473605, 28583132, 23772955, 23975094, 23975094, 29676230, 25884228

67 Brahmi benefits

- Antibacterial, mild, activity against pathogenic *Staphylococcus aureus*
- Antifungal, mild
- Antioxidant
- Increases cerebral blood flow
- Inhibits inflammatory pathways in the brain
Inhibits the release of inflammatory cytokines from microglial cells
Inhibits enzymes associated with inflammation in the brain
- Neurotransmitter modulation (acetylcholine, serotonin, dopamine)
- Preservation of dopamine D1/D2 receptors
- Protects the brain in low blood sugar states
- Reduces neuropathic pain ~ allodynia and hyperalgesia
- Hepatoprotective
- PMID: 27473605, 28583132, 23772955, 23975094, 23975094, 29676230, 25884228

68 Brahmi dosing

- Brahmi needs to be combined with Botanical Antimicrobials for acute and prophylactic antibiotic therapy. It's safe to use long term. If needed, it can be combined with certain Pharmaceutical Antimicrobials.
- Acute Treatment:
Glycerite: 1 tsp, 3 times daily
Capsule powder: 650 mg, 3 times daily

Capsule, powder: 650 mg, 3 times daily
Capsule, extract: 350 mg, 3 times daily

- Prophylactic:
Glycerite: ½ tsp, 2 times daily
Capsule, powder: 650 mg, 1 time daily
Capsule, extract: 350 mg, 1 time daily
- Caution:
May cause dry mouth, tummy cramps, and diarrhea at too high of doses.

•

69 Magnolia

- Magnolia spp ~ flowers and bark
 - Triterpenoid saponin ~ germacranolides, parthenolide
 - Personality ~ As one of the oldest species of trees on the planet, this Avatar is a nice match for the child who's an "old soul." Folklore tells that the bark may be chewed to kick a tobacco habit. This may have to do with how easily it crosses the blood-brain barrier. I find it helpful for teens who can't kick screen time habits.
 - Magnolia is protective and regenerative to the brain and nervous system. It has a relaxing effect and helps to normalize our response to stress. It's especially useful for the child who gets completely maxed out by the stress of daily life, resulting in anxiety and depression.
-
- PMID: 24062717, 25953946, 17879752, 29627576, 34400262, 34362632, 32664494

70 Magnolia benefits

- Antimicrobial, mild

- Antidepressant, anxiolytic
- Neuroprotective:
 - Crosses BBB easily, wide range of activity
 - Reduces neuroinflammation
 - Protects the NMDA (N-methyl-D-aspartate) receptor
 - Neurotrophic
 - Inhibits dopamine biosynthesis
- Antispasmodic, improves asthma symptoms
- Antithrombotic (caution low platelets)
- Hepatoprotective
 - Regulates GI hormones and metabolism
 - Protects the intestinal lining
 - Fosters beneficial microbiome species
- PMID: 24062717, 25953946, 17879752, 29627576, 34400262, 34362632, 32664494

71 Magnolia dosing

- Magnolia can be used for prophylactic antibiotic therapy. It's often combined with Botanical Antimicrobials in the acute phase. This Avatar may not be suited for long-term use in certain situations. If needed, it can be combined with Botanical Antibiotics and select Pharmaceutical Antimicrobials.
- Acute Treatment:
 - Glycerite: 1 tsp, 3 times daily
 - Capsule: 500 mg, 3 times daily
- Prophylactic:
 - Glycerite: ½ tsp, 2 times daily
 - Capsule: 250 mg, 2 times daily
- Caution:

Caution:

May cause drowsiness.

May interact with anticoagulant medication.

•

72 Silk Tree

- Albizia julibrissin ~ flowers and bark
- Triterpenoid saponins ~ hehuanoside, julibroside, etc
- Personality ~ referred to as “the sleep tree” and also “happiness bark.”
Its leaves slightly close or wilt at night, which tells us how to match it.
It’s the perfect remedy for the child or teen who drags through the day, then lights up at night when they should be sleeping.
- Also called the Mimosa tree, which is a little misleading. Be careful to use the correct herb: Albizia. There’s another commonly used herb, called Mimosa pudica. Same word “mimosa” but a different herb.
- Silk tree provides uplifting calm. One little guy I worked with said it took the static out of his brain. It has a mood-stabilizing effect that neutralizes the brain chemistry imbalances we often see with PANDAS and PANS.
- Mild sedative effects - not necessarily one for the morning.
However, children with intense anxiety early in the day may benefit.
- PMID: 12127229, 24884469, 28764915, 34303280, 33550033, 31057652, 32278761

73 Silk Tree benefits

- Antimicrobial, mild
- Antifungal, antiparasitic, mild
- Immune modulation

- Reduces inflammation
- Nootropic, memory retention
- Engages the parasympathetic nervous system
- Stabilizes the mood
- Brain healing nootropic:
 - Boosts serotonin
 - Reduces dopamine
 - Suppresses LPS-induced microglia activation
 - Pro-apoptotic (microglial pruning)
- Anticonvulsant
- Antioxidant
- Mild sedative and relaxation effects
- Antipyretic
- PMID: 12127229, 24884469, 28764915, 34303280, 33550033, 31057652, 32278761

74 Silk Tree dosing

- Mild antimicrobial activity and cleans up cellular debris. I usually combine this with Botanical Antimicrobials.
- Silk tree can be used for prophylactic antibiotic therapy. It's often combined with Botanical Antimicrobials in the acute phase. It's safe to use long term. If needed, it can be combined with certain Pharmaceutical Antimicrobials.
- Acute Treatment:
 - Glycerite: 1 tsp, 3 times daily, best later in the day
 - Capsule: 500 mg, 3 times daily, best later in the day
- Prophylactic:
 - Glycerite: ½ tsp, at bedtime

Capsule: 500 mg, at bedtime

- Caution:
May cause drowsiness.
- Boost effect with NAGs.

75 Gotu Kola

- Centella asiatica ~ leaves
- Triterpenoid saponins ~ centellosides (asiaticosides, centellosides, brahminosides, madecassosides, etc)
- Personality ~ known as the herb of enlightenment. Eaten as a leafy green in many parts of Asia and is said to restore vigor.
- As a powerful antioxidant, it leads to generalized reduced inflammation—from the brain to the gut to the joints. As a tonic to the brain and nervous system, it minimizes the impacts of excessive worry and chronic stress.
- I use it mostly as a tea before meals to reduce food refusal. Crosses BBB within 5-15 minutes. Drinking the tea before the meal protects the brain from post-prandial spikes in endotoxin.
- Especially helpful for kids with digestive issues, food sensitivities, and leaky gut, where eating exposes their brains to increased endotoxins.
-
- PMID: 30516814, 29354820, 26848139, 22001429, 33022343, 33039960, 29436598

76 Gotu Kola benefits

- Neuroprotective - xBBB in 5-15 min

- Antibacterial, mild
- Antiviral, mild
- Antifungal, mild
- Neuroprotective:
 - Preserves glutathione
 - Protects against dopamine/glutamate neurotoxicity
 - Reduces LPS-induced microglia activation
- Restores mucosal barrier and gut microbiota homeostasis
- Antioxidant - ↓ oxidative stress comparable to vit C/GSH
- Reduces joint pain
- Improves locomotor dysfunction
- PMID: 30516814, 29354820, 26848139, 22001429, 33022343, 33039960, 29436598

77 Gotu Kola dosing

- Gotu kola is best combined with additional Botanical Antimicrobials for acute and prophylactic antibiotic therapy. It's very safe to use long term. If needed, it can be combined with certain Pharmaceutical Antimicrobials.
- Acute Treatment:
 - Glycerite: 1 tsp, 3 times daily
 - Capsule: 400 mg, 3 times daily
- Prophylactic:
 - Glycerite: ½ tsp. 2 times daily

Capsule: 200 mg, 2 times daily

- To prep for meals:
Tea: 1–2 cups 10–15 minutes before eating
The tea has a slight musky spice flavor.
- Prepare tea by steeping 1 Tbsp dried Gotu kola leaves in 2 cups of boiling water for 5 minutes. Strain, and add honey to taste. Cool to a comfortable drinking temperature.
- Caution:
May increase skin sensitivity to sunlight.

78 Astragalus

- Triterpenoid saponin ~ astragaloside
- Immune modulation
- Antimicrobial
- Attenuates progression of autoimmune encephalomyelitis:
Remarkably modulate T cell differentiation in CNS
↓ BBB leakage
Reduce ROS production by up-regulation of T-SOD → GSH
Reduce neuroinflammation by inhibition inflammatory cytokines
- Neurotrophic:
Differentiates neural stem cells
Restoration of dopaminergic neurons
- Dose: 500mg-1gram qd-bid
- PMID: 29481521. 27725851. 25150364

79 Panax Ginseng

- Triterpenoid saponins - ginsenosides
- Immune modulation
- Neuroprotective ~ attenuates dopamine-induced apoptosis
- Suppress intracellular oxidative stress
- Stabilize excitable cells
- Regulate voltage-gated ion channels (Ca, Na, K, Cl)
& ligand-gated ion channels (GABA_A, 5HT, nicotinic ACh, NMDA)
- *Mixed data on dopamine effects, caution during flares
- Used mostly as nasal spray in P/P (ginsenosides)
- PMID: 12877931, 24678300, 28412215

80 Integrative approach

- Acute vs chronic presentation
- Core 4 ~
 - Anti-inflammatories
 - Antimicrobials
 - Immune modulation
 - Infection treatment prevention

infection/toxicant prevention

- Treatment cautions
- Then, once out of acute, and in order to prevent/heal, use tools in the next module - Recovery Essentials
-

81 Integrative treatment overview

- 1. Guard the gates
halt T-cell migration to CNS
- 2. Immune modulation
prevent autoimmune tendencies/gut health
- 3. Address neurotransmitter imbalance
balance dopa & glutamate to reduce destruction
- 4. Reduce neuroinflammation/leaky BBB
get good stuff in and bad stuff out
- 5. Manage trauma/stress
adrenal/nervous system burnout
- 6. Structural integrity
chronic brain stem/cervical congestion/jaw development

82 Putting It Together

- Select 1 Flame Tamer and 1 Mast Cell Manager.
- Choose the 1 or 2 Botanical Avatars that fit the child.
- Add 1 Botanical Antimicrobial to fit the child's current infection load.
- Optimize Vitamin D.

- Add Core immune modulation.
- Choose 2 methods for each of the Nasal, Throat, and Dental gates.
- Explore various ways to close the Exposure Gate, starting with hand-washing (family/caregivers), removing glyphosate and mold, reducing infection exposures.
- Assess after 4 weeks, add more support/tweak and/or Rx if needed to any Core area.
- (Acute - conventional approach + Guard Gates)

83 Botanical Antimicrobials

- Botanical antimicrobials typically have multiple mechanisms and action against multiple microbes. I've classified them by their strongest action, but their activity likely is broader spectrum, depending on the herb. These are safe to use with children old enough to eat solid food.
 - Antibacterial:
 - Strep: Echinacea, Thyme, Oregano
 - Staph: Thyme, Echinacea, Oregano
 - E. Coli: Thyme, Oregano
 - Mycoplasma pneumonia: Chinese skullcap
 - Pseudomonas: Thyme, Oregano
 - Bartonella: Cryptolepis, Japanese knotweed
 - Borrelia: Cryptolepis, Japanese knotweed, Black walnut
 - Babesia duncani: Cryptolepis, Japanese knotweed

84 Botanical Antimicrobials (continued)

-
- Antiviral:
 - Coronaviruses*: Black elderberry, Licorice, Olive leaf
 - Adenovirus: Black elderberry
 - Rhinovirus: Black elderberry
 - Influenza: Black elderberry, Licorice, Thyme, Echinacea, Japanese knotweed
 - Herpes family (EBV, Chickenpox/Shingles): Licorice, Black elderberry, Thyme, Oregano
- Antiparasitic: Black walnut, Neem
- Antifungal: Thyme, Oregano, Rosemary, Sage

85 Thyme

- *Thymus vulgaris* - leaves
- Broad-spectrum antibacterial ~
Streptococcus pyogenes, *Staphylococcus aureus*,
Escherichia coli, *Salmonella Typhimurium*, *Pseudomonas aeruginosa*
- Antiviral ~
 Influenza, Herpes viruses
- Antifungal ~
Candida (multidrug resistant), *Aspergillus*, *Trichophyton*
- Can be combined with all Botanical Avatars to boost acute and prophylactic antibiotic therapy.
- Safe to use long term.

- Can be combined with certain Pharmaceutical Antimicrobials.
- May spare a child from having to take additional antifungals during antibiotic therapy.
- PMID: 34579365, 33212200, 33176697, 32512899, 31359292

86 Thyme

- Acute Treatment:
Glycerite: $\frac{3}{4}$ tsp, 3 times daily
Capsule: 350 mg, 3 times daily
Tea: 1 cup, 4 times daily
- Prophylactic:
Glycerite: $\frac{1}{4}$ tsp, 2 times daily
Capsule: 175 mg, 2 times daily
- To prep the tea:
Yield: 2 cups
Prepare tea by steeping 1 Tbsp dried Thyme leaves in 2 cups of boiling water for 5 minutes, covered.
Strain, and add honey to taste. Cool to a comfortable drinking temperature.
- Caution:
Thyme tea and glycerite may cause temporary tingling in the mouth.

87 Echinacea

- Echinacea spp - root
- Antibacterial ~
Streptococcus pyogenes, Staphylococcus aureus
- Antiviral ~ Influenza
- Echinacea reduces overall recurrence and severity of respiratory infections and is very safe to use with children

infections and is very safe to use with children.

- Meta-analysis of randomized-controlled Echinacea trials reported that Echinacea “potently lowers the risk of recurrent respiratory infections and complications thereof.”
- Seems to help the most susceptible individuals the most.
- In children with recurrent tonsillitis, Echinacea can be combined with Azithromycin to boost its efficacy.
- PMID: 32487336, 20036523, 25784510

88 Echinacea

- Echinacea can be combined with all Botanical Avatars to boost acute and prophylactic antibiotic therapy.
- Very safe to use long term.
- Can be combined with certain Pharmaceutical Antimicrobials.
- Acute Treatment:
Glycerite: 1 tsp, 3 times daily
Capsule: 1000 mg, 2 times daily
- Prophylactic:
Glycerite: ½ tsp, 2 times daily
Capsule: 500 mg, 2 times daily
- Caution:
May cause temporary tingling in the mouth.

89 Oregano

- *Origanum vulgare* - leaves
- Antibacterial ~

Streptococcus pyogenes, Staphylococcus aureus,
Escherichia coli, Pseudomonas aeruginosa

- Antiviral ~ Herpes viruses
- Antifungal ~Candida species, Trichophyton species, Microsporium species
- Potent, broad-spectrum antimicrobial herb, effective against many drug-resistant species, including fungi.
- Prevents Strep biofilm. For chronic tonsillitis due to Strep, tea form is best.
- Option for patients with concomitant SIBO.
- Like Thyme, Oregano may spare a child from having to take additional antifungals during antibiotic therapy.
- PMID: 31450579, 30792999, 29452197, 25631514

90 Oregano

- Can be combined with all Botanical Avatars to boost acute and prophylactic antibiotic therapy.
- Safe to use long term.
- Can be combined with certain Pharmaceutical Antimicrobials.
- Acute Treatment
 - Glycerite: $\frac{3}{4}$ tsp, 3 times daily
 - Capsule: 150 mg of 10:1 extract, 3 times daily
 - Tea: 1 cup, 4 times daily (needs a minimum of 24 hours for anti-Strep effect)
- Prophylactic:
 - Glycerite: $\frac{1}{4}$ tsp, once daily
 - Capsule: 150 mg of 10:1 extract, once daily

- To prep the tea:
Yield: 2 cups
Steep 1 Tbsp dried Oregano leaves in 2 cups of boiling water for 5 minutes, covered.
Strain, and add honey to taste. Cool to a comfortable drinking temperature.
- For the prophylactic phase, pulse, 2–3 consecutive days on, 4-5 days off
- Caution:
Abdominal cramping, nausea, and diarrhea at higher doses or if using the oil extract.

91 Black Elderberry

- Sambucus nigra - flowers and berries
- Antibacterial ~
Streptococcus pyogenes, mild
- Antiviral ~
Influenza, Common cold Coronavirus, Adenovirus, Rhinovirus
- Reduces the duration and symptoms of the common cold and influenza, such as fever, pain, congestion, and cough.
- Reduced duration and severity equate to reduced inflammation. High in antioxidant bioflavonoids, which further reduces inflammation.
- Meta-analysis of RCTs poses it as a “a potentially safer alternative to prescription drugs for routine cases of the common cold and influenza.” I have found this to be true in practice.
- PMID: 30670267, 27023596, 21352539, PMC7347422

92 Black Elderberry

- Can be combined with all Botanical Avatars to boost acute and prophylactic antibiotic therapy.

- very safe to use long term.
- Can be combined with certain Pharmaceutical Antimicrobials.
- Acute Treatment:
Glycerite or Syrup: 1 tsp, 3 times daily
Capsule: 500 mg, 3 times daily
- Prophylactic:
Glycerite or Syrup: ½ tsp, 2 times daily
Capsule: 250 mg, 2 times daily
- Caution:
Black elderberry syrup may contain added sweetener.
May stain teeth if taken immediately after using a whitening agent.
-

93 Licorice

- Glycyrrhiza glabra - root
- Antibacterial ~
Mild—Escherichia coli, Staphylococcus aureus, Enterococcus faecalis, Pseudomonas species, Salmonella paratyphi
- Antiviral ~
Herpes viruses (EBV, HSV I/II, CMV, Zoster), Influenza, Hepatitis viruses
- Antiparasitic ~ Mild—Babesia, Plasmodium species

- Soothing expectorant and anti-inflammatory. Sipping the tea eases a sore, scratchy throat.
- Preliminary research on using Licorice for SARS-CoV-2 due to positive previous research on SARS viruses.
- Traditional Chinese medicine - used for viral infections of the liver. Good for children exposed to mycotoxins which are hepatotoxic, such as Aflatoxin.
- PMID: 34579633, 32106571, PMC7808814

94 Licorice

- Can be combined with all Botanical Avatars to boost acute and prophylactic antibiotic therapy.
- Safe to use long term.
- Can be combined with certain Pharmaceutical Antimicrobials.
- Acute Treatment:
Glycerite: $\frac{3}{4}$ tsp, 3 times daily
Capsule: 300 mg, 3 times daily
Tea: 4 cups, sipped throughout the day
- Prophylactic:
Glycerite: $\frac{1}{4}$ tsp, 2 times daily
Capsule: 150 mg, 2 times daily
- To prep the tea:
Yield: 2 cups
Prepare tea by boiling 1 teaspoon licorice root powder in 2 cups of water for 5 minutes, covered. Strain. Cool to a comfortable drinking temperature.
- Caution:
May increase blood pressure.

95 Olive leaf

- *Olea europaea*

- Rich in phenolic compounds with antimicrobial, anti-inflammatory, anti-oxidant, analgesic, antipyretic, immunomodulatory, and antithrombotic activities.
- SARS-CoV-2 ~
Randomized, triple-blinded clinical trial in hospitalized Covid-19 pts - improved the clinical status of the patients and decrease the length of hospitalization.
Data suggest by modulating the expression of SOD2, NF-kB and also ACE2 and TMPRSS2, whose expression is required for SARS-CoV-2 virus entry.
Anti-inflammatory effect on senescent and small airway epithelial cells.
"...great benefit in the control of associated inflammatory cytokine storm and disseminated intravascular coagulation (DIC) in COVID-19 patients."
- Activity against several infectious agents, namely herpes simplex type 1 (HSV-1), Epstein Barr virus (EBV), gram positive bacteria (*Bacillus cereus*, *B. subtilis* and *Staphylococcus aureus*), gram negative bacteria (*Pseudomonas aeruginosa*, *Escherichia coli* and *Klebsiella pneumoniae*) and fungi (*Candida albicans* and *Cryptococcus neoformans*);
activity against Acyclovir-resistant HSV.
- PMID: 37627504, 35496299, 36319585, 36899824, 34200316, 32050880, 34834807, 17873849

96 Olive leaf

- Can be combined with all Botanical Avatars to boost acute and prophylactic antibiotic therapy.
- Safe to use long term.
- Can be combined with certain Pharmaceutical Antimicrobials.
- Acute Treatment:
Glycerite: 1 tsp, 3 times daily
Capsule: 500 mg, 3 times daily
- Prophylactic:
Glycerite: ½ tsp, 2 times daily
Capsule: 250 mg, 2 times daily

Capsule: 200 mg, 2 times daily

- Caution:
Hypotensive, hypoglycemic

97 Cryptolepis

- *Cryptolepis sanguinolenta* - root
- Ghanaian quinine;
bitter root tea traditionally used for malaria
"chambered charm" "strong blood"
- Antibacterial ~
Borrelia species
Bartonella species
- Antiparasitic ~*Babesia duncani*
- Activity against both the growing and non-growing forms of *Borrelia*, *Bartonella*, and at least one species of *Babesia*.
- PMID: 33763384, 32154254, 29750083

98 Cryptolepis

- Can be combined with all Botanical Avatars to boost acute and prophylactic antibiotic therapy.
- Safe to use long term in lower prophylactic doses.
- Can be combined with certain Pharmaceutical Antimicrobials.
- Acute Treatment:
Glycerite: 1 tsp, 3 times daily
- Prophylactic:
Glycerite: 1/2 tsp, 3 times daily

Glycerite: ½ tsp, 2 times daily

- Caution:
Bitter flavor.
Best suited in lower quantities for long-term dosing.

99 Japanese Knotweed

- Polygonum cuspidatum - root
- Antibacterial ~
Borrelia species, Bartonella species
- Antiviral ~ Influenza
- Antiparasitic ~ Babesia duncani
- Invasive weed with the tenacity and vigor of bamboo.
- Rich in resveratrol; anodyne, anti-inflammatory properties.
- Similar to Cryptolepis, Japanese knotweed has activity against both growing and non-growing forms.
- PMID: 34719206, 33763384, 32154254, 25658356

100 Japanese Knotweed

- Can be combined with all Botanical Avatars to boost acute and prophylactic antibiotic therapy.
- Safe to use long term.
- Can be combined with certain Pharmaceutical Antimicrobials.
- Acute Treatment:
Glycerite: 1 tsp, 3 times daily
Capsule: 600 mg, 3 times daily

- Prophylactic:
Glycerite: ½ tsp, 2 times daily
Capsule: 300 mg, 2 times daily
- Caution:
May interact with anticoagulant medication.

101 Black Walnut

- *Juglans nigra* - green outer flesh of the nut, leaves, bark
- Antibacterial ~
Borrelia species, oral *Staphylococcus aureus* (mild)
- Antiparasitic ~ *Acanthamoeba*
- Best known for its purgative properties. Long history of use in expelling parasites.
- While we might believe that expelling parasites would harm the gut microbiome, Black walnut helps to increase microbiome diversity and reduces Th17.
- Black walnut also has activity against growing and dormant *Borrelia*.
- It can be safely combined with the other two herbs that specialize in this, *Cryptolepis* and Japanese knotweed.
- PMID: 33915494, 32154254, 27816681, 26358271

102 Black Walnut

- Can be combined with all Botanical Avatars to boost acute and prophylactic antibiotic therapy.
- Best used in short-term or pulsed long-term doses.
- Can be combined with certain Pharmaceutical Antimicrobials.
- Acute Treatment:
Glycerite: ¼ tsp, 3 times daily
Capsule: 300 mg, 3 times daily

Capsule: 250 mg, 3 times daily

- Prophylactic:

Glycerite: 1/8 tsp, 2 times daily

Capsule: 125 mg, 2 times daily

- Caution:

May cause digestive upset, cramping, and diarrhea.

Best used in short-term or pulsed long-term dosing, 1 week on, 2 weeks off.

-

103 Antimicrobial implications

- Pharmaceutical antibiotics have a negative effect on the gut microbiome, affecting its diversity and function - an effect we don't see with botanical antimicrobials.
- Antibiotics impact microglia function, modulate microglia-synapse interaction.
- Correlation with antibiotic use and depression, amongst other neuroinflammatory disorders such as Parkinson's and Alzheimer's.
- Fungal overgrowth, worsened in colonized mold-sick pt
- When needed, support microbiome+microglia via probiotics & SCFAs
- PMID: 34685628, 33513791, 31791704

104 Using Pharmaceuticals Functionally

- 5 critical discernment points relating to Pharmaceutical Antimicrobials:
 - Determining when they're needed
 - Dose, delivery, and duration
 - Persister infections and resistance factors

- Gut microbiome impact
- Fungal overgrowth
-

105 Utility of long-term antibiotic prophylaxis?

- "Our study has confirmed the usefulness of the preliminary diagnostic criteria for PANDAS and PANS, revealing also the importance of early diagnosis to reduce the risk of evolution toward disabling chronic neurologic sequelae.
- Long-term antibiotic prophylaxis has resulted in a substantial benefit to reduce neurological symptoms for the majority of PANDAS and PANS patients over a 7-year period."
- Retrospective analysis.
- No control group.
- PMID: 31140830

106 Antimicrobial combinations

- Combining certain herbs with Rx reduces impact and resistance
- Oregon grape root preserves SCFA production
- Oregano combine safely w fluconazole & cipro ~
 ↓drug resistance
 ↓free-rad formation+S/E
- Meta-analysis of 17 trials, over 1400 children and adolescents ~
 Combinations w Chinese herbal formulas improved tx efficacy for Mycoplasma pneumonia (built around Chinese skullcap)
 Reduced overall symptoms and duration

Improved lung X-ray findings
Yet didn't increase adverse events

- PMID: 25364204, 32028237, 34177587

107 Integrative treatment overview

- 1. Guard the gates
halt T-cell migration to CNS
- 2. Immune modulation
prevent autoimmune tendencies/gut health
- 3. Address neurotransmitter imbalance
balance dopa & glutamate to reduce destruction
- 4. Reduce neuroinflammation/leaky BBB
get good stuff in and bad stuff out
- 5. Manage trauma/stress
adrenal/nervous system burnout
- 6. Structural integrity
chronic brain stem/cervical congestion/jaw development

108 Putting It Together

- Select 1 Flame Tamer and 1 Mast Cell Manager.
- Choose the 1 or 2 Botanical Avatars that fit the child.
- Add 1 Botanical Antimicrobial to fit the child's current infection load.

- Optimize Vitamin D.
- Add Core immune modulation.
- Choose 2 methods for each of the Nasal, Throat, and Dental gates.
- Explore various ways to close the Exposure Gate, starting with hand-washing (family/caregivers), removing glyphosate and mold, reducing infection exposures.
- Assess after 4 weeks, add more support/tweak and/or Rx if needed to any Core area.
- (Acute - conventional approach + Guard Gates)

109 Integrative approach

- Acute vs chronic presentation
- Core 4 ~
Anti-inflammatories
Antimicrobials
Immune modulation
Infection/toxicant prevention
- Treatment cautions
- Then, once out of acute, and in order to prevent/heal, use tools in the next module - Recovery Essentials
-

110 Integrative treatment overview

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chronic brain stem/cervical congestion/jaw development

111 PANDAS/PANS Mechanism

- The way out of this brain problem
is largely through the gut

112 Regulate Immunity

- Immune modulation is the goal of this Core section.
- Improves autoimmunity vs worsening it (outmoded concept)
 - Immunity Nutrients
 - Butyrate
 - Probiotics
 - Fecal Microbiota Transplant (FMT)
 - Helminth Therapy
 - Oral Immunoglobulins

- Peptides
- Ultra-Low-Dose Naltrexone (ULDN)
- Exosomes
- Intravenous Immunoglobulins (IVIG)

113 Immunity Nutrients

- “Seasoned chicken” is my goofy acronym for the immunity nutrients that get depleted in autoimmune disease: SEAZnDCK.
- Nutritional support for 2-3 days at the first signs of infection:
 - Selenium: 200 mcg twice daily
 - Vitamin E: 800 IU
 - Vitamin A: 50,000 IU
 - Zinc: 30 mg twice daily (*take with food to prevent nausea)
 - Vitamin D: 50,000 IU
 - Vitamin C: 2,000 mg every 2 hours up to 10,000 mg (*may cause loose stool at high doses)
 - Vitamin K: 400 mcg
- Some can be used longer term with your oversight.
- IV is an option for kids struggling with food refusal or swallowing issues.

114 Vitamin D

- Role in both innate & adaptive immunity ~

T-cell regulator

Upregulates monocyte genes

- Study looking at gut microbiota and Strep, kids with PANDAS had a significant deficiency in Vitamin D as compared to normal controls.
- Adequate Vitamin D reduces acute respiratory tract infections and severity in children, including Influenza, and possibly Covid.
- In a randomized clinical trial for Covid, a single high-dose of vitamin D was compared against a single low-dose in adults at a high risk. The high dose offered statistically significant protection, even with just a single dose.
- Vit D receptor in intestine & kidney significantly down-modulated after mycotoxin exposure.
- Promote lung tissue repair in *particle-induced pulmonary injury*.
- PMID: 32038645, 33371905, 32847594, 20219962, 30698894, 25483621, 25912039, 26404359,18569389

115 Vitamin "sunshine"

- Fat-soluble ~
Can bioaccumulate
Monitor labs
- I typically dose to meet specific lab values for at least 3 months in order upregulate receptors ~
60–90 ng/mL
150–225 nmol/L
- Use liposomal or emulsified forms for optimal absorption.

116 Vitamin A

- Critical for many biological processes including the maintenance and modulation of immunity, and the homeostasis of epithelium and mucosa.

- Affects cell integrity, cytokine production, innate immune cell activation, antigen presentation, and lymphocyte trafficking to mucosal surfaces.
- Has been reported to influence the gut microbiota composition and diversity.
- Vitamin A deficiency results in the imbalanced production of inflammatory and immunomodulatory cytokines, intestinal inflammation, weakened mucosal barrier functions, and disruption of the gut microbiome.
- Infections decrease the intestinal absorption of Vitamin A, thereby contributing to secondary deficiency.
- Vitamin A deficiency is associated with more severe and persistent Mycoplasma pneumonia infections.
- 2022 Cochrane Database Systematic Review confirmed that Vitamin A supplementation is associated with a clinically meaningful reduction in morbidity and mortality in children.
- PMID: 36501067, 32175413, 35294044

117 Vitamin A

- Fat-soluble ~
Can bioaccumulate
Is hepatotoxic at high levels.
Monitor labs and dose accordingly.
- Can be super-dosed in a single dose at the first onset of viral symptoms. May cause a mild fever.
- Dose ~
A single adult super-dose is 100,000 IU.
Maintenance: dose via labs.
3.33 IU per mcg.

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- Use liposomal or emulsified forms for optimal absorption.
- PMID: <https://ods.od.nih.gov/factsheets/VitaminA-Consumer/>

118 Butyrate

- Short-chain fatty acid (SCFA) produced by beneficial microbiome that nourishes enterocytes.
- Butyrate benefits ~
 - Calms the microglia (#monkeys)
 - Stimulates brain repair
 - Balances brain chemistry
 - Gives the brain mitochondria a boost
 - Impacts the gut-brain-immune axis
- "...we hypothesise that butyrate and other volatile SCFAs produced by microbes may be involved in regulating the impact of the microbiome on behaviour including social communication."
- Some antibiotics halt the manufacture of Butyrate in the microbiome.
- Botanical antimicrobials don't seem to have this same effect. In fact, most of them stimulate Butyrate, as in the case of Oregon grape.
- PMID: 27346602,

119 SCFAs and the brain

- Oral application of a mixture of the three major SCFAs acetate, propionate, and butyrate in germ-free mice, was

sufficient to restore the normal maturation process of the microglia.

- SCFAs can modulate neurotransmitters, like glutamate, glutamine, GABA, and neurotrophic factors.
- Propionate and butyrate can influence the cell signaling system via modification of the intracellular potassium levels, and regulate the expression levels of tryptophan 5-hydroxylase 1, involved in the synthesis of serotonin, and tyrosine hydroxylase, which is involved in the biosynthesis of dopamine, adrenaline, and noradrenaline.
- In mouse models of Parkinson's, oral and IV sodium phenylbutyrate was found to protect the loss of dopaminergic neurons and improve motor function.
- PMID: 33362788, 21902286, 21372141, 22723850

120 Butyrate

- The challenge is taste. Parents often mask with ranch dressing (dairy or nondairy) and/or vanilla to mask the flavor.
- Butyrate is quite effective when administered as an enema as well. Sometimes that little nugget of information is motivation for a kid to opt for plugging their nose and getting it down.
- Daily:
Powder, liquid or capsule: 375 mg twice daily with food
- Flare:
Powder, liquid or capsule: 500 mg three times daily with food
- Caution:
Tastes like rotten eggs.
May cause reflux. Best taken with food.
- IV:
Sodium phenylbutyrate. (Requires training.)

121 Postbiotics

- The “peristaltic wave” of the future.
- Different concept than probiotics which have the goal of increasing the biota, post-biotics are the metabolites of a healthy biota, affecting the milieu.
- Expanding: “you are the sum of the company you keep”
- To: “you are the sum of the products of the company you keep”
- Freeze-dried, sterilized, non-viable processed stool from healthy donor.
- Careful screening of donors ~
Breastfed, vaginal birth, minimal if any antibiotics (<5), no Hx anxiety/depression
30+ plant-based foods per week (diversity of diet = diversity of microbiome)
- Much more than SCFAs (lipids, AAs, bile acids, peptides, nucleotides, etc) yet has SCFAs in optimal ratios
60:20:20 acetate:butyrate:propionate.
- Empirical data showing ox stress benefit. No human studies as of yet.
- Dose: “dusting” up to 1/4 cap to start.
Maintenance -1/d. Flare tx - up to 2 bid.

122 Probiotics

- Multiple studies have shown improvement in depression, anxiety, OCD, and the perception of stress.
- Anxiety or eating disorders ~
Review article: pts with generalized anxiety or eating disorders (anorexia nervosa, bulimia nervosa, and binge-eating disorders) show a specific profile of gut microbiota. This imbalance can be partially restored after a single or multi-strain probiotic supplementation.
- Fears ~
Mouse model: probiotic tx after fear conditioning inhibited microglial activation and had similar therapeutic effects as the microglial cell repopulation.
Conclusions: Probiotic tx after fear conditioning might prevent long-term fear extinction which could be

CONCLUSIONS: Probiotic tx after fear conditioning might promote long-term fear extinction which could be associated with the mitigation of synaptic pruning of activated microglial cells; Probiotics may be applicable as therapeutic strategy to inhibit microglial activation and treat fear-related disorders.

- PMID: 31144383, 34022177, 28868181

123 Probiotic strains

- Psychobiotics ~
Bifidobacterium adolescentis produces GABA
Lactobacillus plantarum JYLP-326 relieves anxiety, depression, and insomnia
Lactobacillus gasseri CP2305 (postbiotic) significantly reduced of State Trait Anxiety Inventory (STAI)-trait scores (6 month trial)
- Sleep ~
Lactobacillus casei Shirota YIT9029, LcS suppresses sleep latency and increased sleep intensity (in healthy adults)
- Histamine friendly ~
Bifidobacterium infantis, B. bifidum, B. longum, B. lactis, B. breve
Lactobacillus salivarius, L. plantarum
Avoid L. reuteri 6475
- Mold mycotoxins ~
Lactobacillus plantarum C88/MON03, L. rhamnosus GAF01
L. casei strain Shirota
- PMID: 32839473, 37033942, 28443383, 33652962, 18544899, 22384111, 28129335, 24738739, 23030351, 21816119

124 Spore-based probiotics

- Spore-based probiotic study ~
Healthy men and women (n = 75) screened for post-prandial dietary endotoxemia. Subjects whose serum

endotoxin concentration increased by at least 5-fold from pre-meal levels at 5-h post-prandial were considered "responders" and randomized to receive either placebo or tx.

- Given spore-based probiotic supplement for 30d [Bacillus indicus (HU36), Bacillus subtilis (HU58), Bacillus coagulans, and Bacillus licheniformis, and Bacillus clausii]
- Oral spore-based probiotic supplementation was associated with 42% reduction of post-prandial dietary endotoxin & significant post-prandial reductions in inflammatory markers IL-1 β , IL-12p70, and ghrelin.
- PMID: 31144383, 34022177, 28868181

125 Probiotics

- Variables were divided into those that demonstrated a significant (upper panel) and those that did not (lower panel) have a significant probiotic effect. Responses were coded a lower (green to yellow) or higher (yellow to red) compared to baseline. An unchanged (yellow) response was also identified. PMID: 28868181

126 Probiotic dosing tips for P/P kids

- For multi-strain, introduce one strain at a time and watch for 2 weeks.
- Postbiotics and spore-based probiotic ~
Dose: start VERY low, die-off common. 1 capsule over 1-2 weeks, then 1 capsule over 4-7 days, then 1 capsule over 2 days, until maintenance dose of 1/day.
- Use supplemental pro/postbiotics with prescription antibiotics for prevention of Clostridia.
- Avoid/Cautions ~
Avoid Strains: _____

AVOID Streptococcus strains

Caution with prebiotics (fungal overgrowth)

127 Fecal microbiota transplant (FMT)

- Empirical reports of success
- Both the donor and recipient gut milieu seems to matter
- Safety: Safety trial: Human RCT using FMT from lean donor in obese, metabolically uncompromised patients
Led to sustained changes in the intestinal microbiome and bile acid profiles that were similar to those of the lean donor.
No changes in BMI at week 8.
Imho - duration too short, dose mb too low, but was found to be safe.
- Precedent: Huntington's dz: neurodegenerative disorder which also involves psychiatric, cognitive and motor sx's
(possible genetic role in P/P)
Mouse study: wild-type donor FMT positively modulated cognitive outcomes, particularly in females.
- Efficacy: Emerging evidence supports the possibility that controlling inflammation in the recipient intestine might facilitate engraftment by reducing host immune system pressure on the newly transferred microbiota.
- PMID: 31301451, 33907321, 36035436, 35854629

128 HDCs / Helminth therapy

- HDCs ~
Hymenolepis diminuta cysticercoids (rat tapeworm cysticerci)
Part of normal flora in many non-industrialized areas.
From grain beetles; eaten unknowingly in food supply.
Remain in lumen; low risk of colonization in human;
intermediary host required.

- Helminth secretome ~
Excretory/secretory products
Helminth derived miRNAs are delivered in exosomes.
Exosomes are internalized by immune host cells; exert the expansion of Treg cells, resulting in the control of inflammation.
- PMID: 28484453, 25712154, 27297184

129 Effect on host immune cells

- Polarization toward Th2 response (preventing Th1 or Th17 immune response) characterized by Th2 cytokines.
- Differentiation of macrophages toward the M2 phenotype, resulting in a Th2 immune response.
- Prevent dendritic cell synthesis of pro-inflammatory cytokines and promote the production of immunoregulatory molecules such as IL-10 and TGF β .
Induces regulatory T cell (Treg) phenotype, promoting the protection/suppression of inflammation produced by a Th1 autoimmune disease.
- Myeloid-derived suppressor cells (MDSC) function as immunoregulators, producing reactive oxygen/nitrogen species that inhibit the function of T cells.
- PMID: 28484453, 25712154

130 Oral Immunoglobulins

131 HDCs / Helminth therapy

- HDC Oral Dose ~
Start low and titrate slowly. May temporarily increase neuro sx's. May induce mast cells/increase IgE and histamine.
Target dose: ~1ml po every 3 weeks x 3 mo min, then reassess.
May be mixed in room-temp or cool liquid but must contain fat and drink the whole amount.

- Helminth-derived peptides ~ on the horizon.
- Safety ~
Slight risk with helminths of infection. Avoid if child is constipated (less than 1 BM/day) or taking immunosuppressive medications.
Helminth-derived peptides vs actual helminths alleviates concerns associated with live infection in kids with immune depletion.
- PMID: 28484453, 25712154

132 Oral Immunoglobulins

- Resilience factors. Sourced from colostrum.
- May or may not improve lab immunoglobulin numbers, but have an immune-modulating effect clinically - reduced susceptibility to GI and respiratory infections, and shorten recovery times.
- Oral immunoglobulins don't seem to aggravate or flare the autoimmunity like subcutaneous immunoglobulins can.
- Ideally supplement as Colostrum in order to be closer to its natural whole food form ~
Colostrum supplementation has been shown to protect against side effects of antibiotics, anti-inflammatory drugs and steroids, and psychophysical stress.
- Immunoglobulins are also available as a supplement.
- Colostrum is easy to get into kids - tastes like a milkshake.
- Bovine-free alternatives available.
- PMID: 34444709, 27100711, 37189633

133 Oral Immunoglobulins

- Unlike the Immunity Nutrients, withhold Oral Immunoglobulins during an active infection as it can cause more mucous—it's doing its job, but that can cause more discomfort to an already snotty kid.

- Rx:
EnteraGam (serum-derived bovine Ig): 1 packet bid
- Daily:
Colostrum powder, chew, or capsule: 1,500 mg twice daily
IgG capsule: 500 mg twice daily
- Caution:
May increase mucous during acute respiratory illnesses.
Low risk of worsening constipation.

-

134 Peptides

- Protein messengers ~
Depending on the peptide, can turn the immune system either up or down.
Send different types of messages to different types of tissue.
- In PANDAS and PANS, we focus on the gut-brain-immune messages.
- Body Protection Compound (BPC), Thymosin Beta, Cerebrolysin

135 Body Protection Compound (BPC) peptide

- Gastric peptide intended to maintain gut barrier protection from infections that aren't cleared by stomach acid, with additional wide beneficial effect, both peripherally and centrally.
- Gut-brain axis ~ anxiolytic, anticonvulsive, antidepressant effects
- Animals: brain neuronal damages were resolved as well as disturbed memory, locomotion, and coordination.
- Counteracts encephalopathies; counteracts dopamine disturbances (dopamine receptors blockade, receptors super sensitivity development, or receptor activation, over-release, nigrostriatal damage, vesicles depletion); inflammation reduction; nerve recovery.

- Empirically reduces tics.
- Anti-inflammatory; heals wounds, tendon injuries, muscle healing and function recovery.
- Add this peptide with children taking NSAIDs. (Reduced stomach lesions and encephalopathy.)
- Being studied as potential COVID-19 treatment.
- PMID: 34380875, 34798584, 29134359, 37242459

136 Body Protection Compound (BPC)

- Dissolves easily in water, so can be used in children who don't swallow pills.
- Acts fairly quickly.
- Daily:
Powder or capsule: 500 mcg once daily
- Flare:
Powder or capsule: 500 mcg twice daily
- Caution:
May increase mucous production.
May induce a low-grade fever after the first few doses.
-

137 Thymosin Beta 4

- Activity is similar to the nasal peptide Thymosin Alpha-1 to be discussed in the next section.
- Neuroprotective and fortifies the BBB.

- Animal studies suggest a reparative role in a range of encephalopathies.
- Appears to use a cholinergic pathway to force defective microglia into autophagy.
- Reduces food sensitivities by fortifying the gut wall barrier integrity.
- Particularly useful for children exposed to molds that affect the myocardium. Assists with myocardial tissue regeneration.
- Use the 4-fragment to concentrate the active fragment.
- May use freeze-dried thymus gland for a more "whole food" version of this supplement.
- Being studied as potential COVID-19 treatment.
- PMID: 34335970, 33967626, 31877278, 30552633

138 Thymosin Beta 4

- Dissolves easily in water, so can be used in children who don't swallow pills.
- Daily:
TB4-FRAG+ powder or capsule: 150 mcg once daily
- Flare:
TB4-FRAG+ powder or capsule: 150 mcg twice daily
- Caution:
May increase mucous production.
May induce a low-grade fever after the first few doses.
-

139 Cerebrolysin

- Modified version of the IV peptide for oral administration; little longer duration to see the effects seen IV.
- Reduces neuroinflammation and improves vascular changes in the brain.
- Human and animal studies suggest benefit in headaches, migraines, post-concussion, stroke, and other vascular and neurodegenerative changes in the brain. I have found it to also be helpful in PANDAS/PANS.
- Typically, it takes about 2 weeks to see any changes, and longer term dosing has been beneficial to reduce the frequency of flares, despite exposures and triggering events.
- Specially-formulated capsules can be opened and stirred into cool or room temp fluids.
- Pork sourced; stronger taste than the milk-shake taste of BPC.
- PMID: 33515100, 29752991

140 Cerebrolysin

- Dissolves easily in water, so can be used in children who don't swallow pills. ("pork" taste.)
- Daily:
Powder or capsule: 100 mg once daily
- Caution:
May induce transient headache
May increase mucous production.
May induce a low-grade fever after the first few doses.

141 Ultra-Low-Dose Naltrexone (ULDN)

- ULDN manages autoimmunity aspect.
- Structure almost identical to endogenous endorphins. High affinity binding to mu opiate receptor. Receptor antagonist. Short acting.
- Low dose has long-term effect of up-regulating endorphin receptors, results in pain relief esp of neuropathic pain, anti-inflammatory effects, improved immunity.
- Reduces neuroinflammation via an immunometabolic modulatory role on the microglia and mast cells.
- Attenuates learning and memory disturbances with associated neuroinflammation.
- Over time, improved sleep, reduced pain, reduced flares, and improved autoimmune markers.
- Not the doses used for treatment of substance use disorder in this application.
- PMID: 34445130, 32905811, 29885638

142 ULDN: Off-label use

- Compounding pharmacy.
- It works best over a long period of time. 6-9 months for full effect. Duration of tx often more than a year.
- Low-dose (2.0-4.5mg) and ultra-low-dose (0.1-1.5mg). Due to BBB permeability in kids with P/P, I've found that the ultra-low-dose formulation is much better tolerated.
- Usually given hs.
*Give first doses in the morning on a day when the child can sleep, if needed.
Initially, may induce nightmares. Give it in am and then shift it to nighttime after 3-7 days.
- Caution ~
May reduce sensitivity to novocaine and other pain medications. Compensate with a slightly increased dose of the

may reduce sensitivity to rofecoxib and other pain medications. Compensate with a slightly increased dose of the pain medication.

Have parents alert dentist and oral surgeon if child needs dental work or oral surgery.

Also alert any doctors involved in managing pain.

143 Exosomes

- Mesenchymal stem cell-derived (MSC) Exosomes are on the cutting edge of cell-free stem-cell-based therapies for PANDAS and PANS.
Source is important (umbilical cord mesenchymal stem cells).
- Immunomodulatory and regenerative properties.
- Act like a messenger guardian over the microglia. Result is decreased neuroinflammation and autoimmune activity.
- Empirically, observe clinical improvement and normalization of autoantibody markers.
- Cell studies: mechanisms ~
Reduce pro-inflammatory Th1, Th17 cytokines, and IL-6, IL-12p70, IL-17AF, IL-22.
Upregulate T-regs.
Dampen LPS-induced expression of inflammation-related genes by microglia.
- Activity on enterocytes ~
Animal studies: involved in intestinal epithelial integrity.
- PMID: 31117376, 30898154, 36751776, 37440921,

144 Exosome administration

- IV administration - specialized training beyond course scope.
- The origin of the Exosomes is of extreme importance. Some can be inflammatory.
Use mesenchymal stem cell-derived exosomes with PANDAS/PANS.

- Still considered an experimental therapy.
- Cautions ~
Risk of inducing inflammation, even if the perfect sourcing was used.
Risk of seizure.
- Possible future nasal applications ~
Rat model: Intranasally administered exosomes reached the brain and reduced microglia-mediated neuroinflammation in rats with perinatal brain injury.

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- Select 1 Flame Tamer and 1 Mast Cell Manager.
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- Add 1 Botanical Antimicrobial to fit the child's current infection load.
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- Explore various ways to close the Exposure Gate, starting with hand-washing (family/caregivers), removing glyphosate and mold, reducing infection exposures.
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- (Acute - conventional approach + Guard Gates)

147 Integrative approach

- Acute vs chronic presentation
- Core 4 ~
 - Anti-inflammatories
 - Antimicrobials
 - Immune modulation
 - Infection treatment

infection/toxicant prevention

- Treatment cautions
- Then, once out of acute, and in order to prevent/heal, use tools in the next module - Recovery Essentials
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149 Nasal Gate

- A strong Nasal Gate minimizes infection and brain inflammation.
- Reminder: infections of the throat also affect the nose. When the nose is triggered, neuroinflammatory chemicals get an "elevator ride" via the olfactory bulb to the limbic system. Inhaled mold mycotoxins can as well.
- Nasal mucosa traps germs and dissolves toxins, and the cilia sweep the border clean. But microbes and inhaled toxins paralyze the cilia.

- Topical Nitric Oxide
- Nasal Probiotics
- Steam Inhalation
- Nasal Photobiomodulation
- Intranasal Colloidal Silver
- Intranasal Propolis
- Aromatherapy/Essential Oils
- Thymosin Alpha-1 Intranasal

150 Nasal Nitric Oxide

- Mucosal Nitric oxide (NO) ~
Protective surface chemical made by our respiratory passages.
Noxious to germs. When released, NO temporarily sanitizes the region against microbes, including Strep species, Influenza, and SARS-CoV-2.
Also has the potential to disperse biofilm and make microbes more susceptible to antibiotic therapy.
- Inducible via humming ~
Empirically, the level of nasal microbial contamination is correlated to the frequency of vocal tics.
- Administer via NO nasal spray, as needed.
- PMID: 33992687, 27378676, 26856845, 23562771, 23547821

151 Nasal Probiotics

- Supports the sinubiome by enhancing diversity.

- Certain strains play a protective role against pathogens and restore weak barriers in the nasal and sinus tissue.
- Lactobacillus sakei ~
Folkloric use: snort the juice from fermented kimchi to ward off infection.
Modulates allergic Th2 responses enhancing Treg generation.
- Lactobacillus casei ~
Restores airway epithelial integrity in CRS pts with nasal polyps.
- PMID: 34212544, 30154801, 22972842

152 Nasal Probiotics

- Easy on kids and can be used in very young children.
- Mix the probiotic powder in water and swab the nostrils, then sniff.
Safe to swallow if a sniff was too vigorous.
- Use qd to bid. Easy to add to the end of the tooth brushing routine.
- A helpful tip: L. sakei is used to cure meats. A child who craves cured meats may be needing nasal barrier help.

153 Steam Inhalation

- Certain herbs' antimicrobial oils become more potent once they're in steam form.
- Steam can access hard-to-reach sinus tissue to clear congestion, ease allergies, soothe irritated passages.
- Many common kitchen herbs, such as oregano, thyme, basil, rosemary, and sage, become superpowers once they're steamed. These herbs can also be made into tea to be gargled for sore throats.
- Some parents worry that tenting a towel over an anxious child's head would only increase anxiety, but I hear over and over again from kids that they feel calmer under the towel.
- Handout in resources for Thyme, substitute any herb above.
How-to video on my website.

- PMID: 34770961, 29452197

154 Thyme steam inhalation instructions

- Thyme Steam Inhalation

-

- SUPPLIES

- Large bowl or pot

- Large lightweight towel

-

- INGREDIENTS

- 2–3 cups boiling water

- 5–10 drops of Thyme essential oil, or

- 2–3 tablespoons dried Thyme, or

- 1/2–3/4 ounce fresh Thyme

-

- DIRECTIONS

- Fill large pot/bowl with boiling water.

- Depending on Thyme source:

- Drop 5–10 drops of Thyme essential oil into the bowl.

- Stir in dried Thyme, and steep for 5 minutes.

- Drop in the fresh Thyme, and steep for a few minutes until leaves wilt and turn dark green.

- Lean your head over the bowl close enough to feel the steam, cover your head with the towel, and create a tent to

1 PANDAS & PANS An Integrative Approach

- Dr. Jill Crista

2 Disclaimer

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3

- Recovery
Essentials

4 Overview

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

5 Recovery Essentials

- Structure
- Brain food
- Peace of Mind
- Dream Team

6 Structure

- Routine Calm
- Structural Alignment
- Structured Breath
- Structure of Movement
- Structured Water
- Necessity of Nature

7 Routine calm

- Chronobiology: circadian rhythm rebalance - moving with the tide of biology rather than against it.
- Routine is a gift to the adrenals, which govern immunity, inflammation, and blood sugar fuel to the brain.
- Wake, eat, move, and sleep around the same times each day.
- Morning -
Get outside immediately after waking, before 8am ideal
Use full-spectrum daylight lightbulbs before 3pm, not after
- Timing of meals
- Evening -
Turn lights down
Turn temp down
- Sleep rule "2 before 12".
- PMID: 32130879 When Rhythms Meet the Blues: Circadian Interactions with the Microbiota-Gut-Brain Axis

8 Structural alignment

- Physical structure is something that needs to be constantly realigned in a kid with P/P.
- The constant pressure of BGE changes the alignment of the cranial bones, and restricts blood flow in and waste products out.
- When the cranial bones are out of alignment, the brain's lymphatics can't drain. The brain's function is also impaired, especially the cranial nerves which govern our senses.
- Cervical congestion is also observed.
- Also address oral palate narrowing/jaw development/tongue placement - holistic dentist
- CST after every dentist visit. Sustained jaw opening amplifies the improper alignment.
- Glymphatics drain the brain ~
Dr. Bredesen's latest findings - sleep on side for maximal glymphatic drainage.

9 Breath

- In its protective wisdom, the body adjusted its systems to under-breathe. The brain tells the respiratory system to breathe only enough to survive, not thrive. Why?
- Germs and toxins carried in the air may have a free "elevator ride to the brain" via the olfactory nerve.
- Many kids need to be taught breathing techniques to resuscitate natural breathing instincts.
- Additionally, terror of their thoughts commonly over-rules natural autonomic respiratory rates (sympathetic state.)
- Adequate belly breathing engages the vagus nerve. Most kids with P/P hold their bellies too tight to engage their vagus nerve.
- Better if exhale is longer than the inhale. Children can hum to help lengthen the exhale.
- Breathing techniques can be learned in calm times to prep for crisis moments, and as a quick part of the pre-meal routine to prep the body for eating.

- Make breath part of the scheduled structure.

10 We're made to move

- Improved cognitive effects from short bouts of movement (ie: walk to school, recess).
- Physical activity has a positive effect on attention.
- Additional improvement in academic performance and executive functions (inhibition, working memory, cognitive flexibility and planning.)
- Physical exercise inhibits inflammation and microglial activation via neuroprotective myokines.
- Exercise facilitates the M1-to-M2 polarization of microglia by enhancing autophagy via the BDNF/AKT/mTOR pathway (in neuropathic pain model.)
- Association of calf muscle pump stimulation with sleep quality.
- PMID: 19356688, 29054748, 36288601, 31324021, 27686225

11 Structured water

- Water is water is water, right!? Wrong.
- A special phase of water (aka the fourth phase or exclusion zone/EZ water) is ordered and acquires features that are different from bulk or liquid water.
- The transition of ordered EZ water to bulk water serves as an important trigger of many cellular physiological functions, and in turn cellular health.
- Maintains a unique electrical charge (our battery) and helps conduct the electrical impulses of the brain and nervous system, as well as drive a "current" within our blood vessels, taking the workload off the heart as a pump.
- Referred to as exclusion zone water because the structure of the water creates a hydrogel of pure water in the form of H_2O_2 which not only creates a selectively polarized internal and surface charge, it also excludes colloidal

form of H₂O₂, which not only creates a selectively polarized internal and surface charge, it also excludes colloidal and molecular solutes from extensive regions next to the hydrophilic surface.

- Hydrogel water-to-solid ratios sometimes reach tens of thousands to one. Yet can hold a frequency.
- In nature water becomes structured as it bounces, falls, and squeezes through limestone. We make it intrinsically the same way, by simply moving (ie: rebounder.)
- PMID: 30920538, 32708867, 30202249

12 Nature is a necessity

- Bulk or liquid water

13 Nature is a necessity

- Shinrin-yoku or forest bathing/forest medicine = appreciation with all 5 senses.
- Increases NK activity, the number of NK cells, and the intracellular levels of anti-cancer proteins.
- Reduces BP and HR.
- Reduces stress hormones, such as urinary adrenaline and noradrenaline and salivary/serum cortisol.
- Increases the activity of parasympathetic nerves and reduces the activity of sympathetic nerves to stabilize the balance of autonomic nervous system.
- Improves sleep.
- Increases the levels of serum adiponectin and dehydroepiandrosterone sulfate.
- Reduces the scores for anxiety, depression, anger, fatigue, and confusion, and increases the score for vigor, showing preventive effects on depression.
- May have preventive effect on COVID-19 by boosting immune function and by reducing mental stress.

14 Commune with nature every every every every every every day

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15 Recovery Essentials

- Structure
- Brain food
- Peace of Mind
- Dream Team

16 Brain Food

- Organic matters most
- Additional dietary considerations

- Disordered eating
- Joy seeking

17 Organic!

- Organic!!!
- Are there additional considerations? Certainly! Caution creating issues around food/eating.
- Kharrazian AIHM 2017 slide/info about the possibility of food cross-reactivity to cerebellar, myelin basic protein, streptococcus - and also his take on dairy, eggs
- Histamine
- Timing may be more important than content (intermittent fasting data from earlier - benefits to microbiome-gut-brain axis)

18 Additional dietary considerations

- Are there additional dietary considerations? Certainly!
- ***BUT be cautious of creating issues around food/eating!***
- Diet high in antioxidants are not only beneficial for mental health, they're also protective against pesticides, insecticides, mycotoxins.
- Good fats reduce inflammation and nourish nervous system.
- Sufficient B-vitamins as psychobiotics.
- Sufficient protein prevents blood sugar sweeps. Aim for 1g/kg body weight.
- Be mindful of histamine.
- Dr. Kharrazian: possibility of food cross-reactivity to cerebellar, myelin basic protein, streptococcus - dairy, eggs.

- Timing may be more important than content (intermittent fasting data from earlier - benefits to microbiome-gut-brain axis)
- PMID: 32358751, 32340112, 30904906

19 Extra-virgin olive oil (EVOO)

- RCT: 30 pts with impaired fasting glucose (common in food-restrictive kids), receive a lunch with or without 10 g (2 1/4 tsp) EVOO.
- Markers measured before, 60 and 120 min after lunch: Serum LPS, Apo-B48, markers of oxidative stress [oxidized LDL (oxLDL) and soluble Nox2-derived peptide (sNox2-dp), a marker of nicotinamide-adenine-dinucleotide-phosphate oxidase isoform Nox2 activation], and plasma polyphenols.
- Gut-derived LPSs increase post-prandial oxidative stress via Nox2 activation in patients with impaired fasting glucose tolerance.
- At 120 min, LPS (β - 15.73, $p < 0.001$), Apo-B48 (β - 0.14, $p = 0.004$), sNox2-dp (β - 5.47, $p = 0.030$), and oxLDL (β - 42.80, $p < 0.001$) significantly differed between the two treatment groups.
- EVOO administration significantly mitigated post-prandial oxidative stress-related inflammation, potentially triggered by LPS.
- PMID: 29766292

20 B-vitamins and the biome

- B-vitamins function as psychobiotics.
- Are obligate cofactors and co-enzymes for many aspects of the nervous system.
- Primary source-diet (we can't synthesize), secondary-microbiome.
- Important cofactors mediating multiple metabolic pathways in humans, esp liver detox, neurological health, and I/S surveillance and homeostasis.

- Involvement as psychobiotics in brain energetic metabolism (kynurenines/tryptophan pathway) for neurological functions.
- Studies exhibit malfunctioning related to deficiency.
- Microbiome made up of B-producers and B-consumers.
- **B-consumer biome is in competition with our cells for these nutrients.
- Can be administered orally or as IM/IV if the child has leaky gut or is restricting food. (Parenting tip: mentioning this option has helped parents get their child to take their B's.)
- PMID: 36583209, 36271691, 31058161

21 B fulfilled

- I start with Vitamin B2, Riboflavin ~
Nourishes the brain and nerves, and it has the lowest possibility of causing any kind of reaction.
Typical therapeutic dose is 50 mg daily.
- Next, I add Vitamin B6, Pyridoxine ~
High dopamine can deplete Vitamin B6. When this vitamin is low, the brain chemistry shifts to the more excitatory brain chemical glutamate.
Typical therapeutic dose is 100 mg daily.
- If a child is struggling with fatigue or nerve tingling, I optimize Vitamin B12, Cobalamin ~
Especially needed if a child has had heavy exposure to silly gas or weed killer. Silly gas forces this vitamin into its inactive form. Glyphosate, the chemical in weed killer, can impair the area of the intestines where we absorb Vitamin B12.
Typical therapeutic dose is 1,000 mcg daily.
- In kids who've been exposed to mold, I optimize Vitamin B1, Thiamine ~
Molds emit alcohols that can chew through this vitamin very quickly. Since mold mycotoxins are stored in the fat

and cause the most problems there, I use the fat-soluble form called Benfotiamine.
Typical therapeutic dose is 150 mg daily.

- Bs may cause nausea, impedes sleep if taken too late in the day.

22 Histamine

- One area where a child might benefit from temporary dietary restrictions, especially if mold exposed.
- Histamine intolerance is a very common reason for disordered eating, small appetites, and reactions after eating.
- Histamine reactions can happen soon after eating and include ~
 - Irritability
 - Redness or flushing
 - Pruritus
 - Allergic reactions
 - Headache
 - Reflux, nausea or indigestion
 - Joint pain
 - Worsening asthma soon after eating

23 High histamine foods to avoid

- Leftovers
- Packaged and processed foods
- Fermented foods
- Aged cheeses

- Cured meats
- Fruit and citrus juices (except lemon)
- Strawberries
- Spinach
- Raw tomatoes
- Vinegar
- Soured foods
- Fish (flash frozen salmon is okay)
- Bone broth
- Collagen (also feeds Bartonella)

24 Disordered eating

- By asking why a child isn't eating, we may be able to point to an area of intervention.
Ask why, don't assume.
- Fear of Choking ~
Swallowing involves an intricate interplay of nerves and muscles, run right through the area of inflammation in the brain of a P/P kid.
If a child fears choking, it's quite likely a valid fear.
To help kids swallow with more ease, take measures that are used with post-stroke patients, such as puréeing food and adding thickeners to liquids.
This fear gets better as inflammation reduces.
- Fear of Contamination ~
Tells you his gates are being breached.

Add measures to Guard the Gates, ie: spices high in Strep-killing essential oils to support the sense of safety in the limbic system to allow a kid to eat.

Add cinnamon to sweet foods, or thyme and oregano to savory foods. Even smelling the essential oils may be enough to give green light to eat.

25 Disordered eating mechanisms

- Histamine Intolerance ~

Feeling sick or fluey soon after eating is classic histamine intolerance.

In these cases, kids will simply avoid feeling bad by not eating. The reactions can be so bad that hunger feels like the least bad option.

Add Mast Cell Stabilizers, such as Perilla and Quercetin/Luteolin, or antihistamine medication 15–20 minutes before eating, while following a low-histamine diet may help.

- Mental Health Flare ~

Having mental health flares after eating is a sign that the gut microbiome is disrupted.

Gut-derived exotoxin agitation of the microglia can flare any of the neuropsychiatric symptoms.

The Botanical Avatars Gotu kola and Chinese skullcap reduce gut-derived inflammatory endotoxins such as LPS (lipopolysaccharide), as do Flame Tamers Feverfew and Rosemary. Any or all of these glycerites may be taken 15 minutes before meals to prevent microglial activation.

26 Disordered eating mechanisms

- Belly Pain ~

While you're working on fostering a beneficial microbiome, you may need to soothe an achy belly.

Hot or cold teas of mint and ginger not only reduce pain but also inflammation. These are easy additions to mealtimes.

Aloe juice is also soothing, gives the gut immunity a boost, acts as a binder, and comes conveniently as single-serving bottled juices for when you're on-the-go.

- Eating-Related Trauma ~

Sometimes the eating issue has been so severe in the past, there's now a lot of "energy" around it. Parents become hyper-aware of intake, and kids can feel it. Kids feel this as pressure and trauma.

Trauma can shut down the vagus nerve

trauma can shut down the vagus nerve.

Humming can turn it back on. Humming stimulates the vagus nerve to induce a feeling of calm and relaxation, and turns on digestion. A happy vagus nerve tells the body it's safe to eat.

Hum for 5-10 minutes before the mealtime. It doesn't have to be constant. Maybe he hums along to a favorite song or as part of a breathing technique. Either way, hum.

- Fry an Onion!

27 Joy seeking for brain nourishment

- "The web of laughter" ~
Laughter interacts with several frontal and limbic regions, including cingulate, orbitofrontal, medial prefrontal and anterior insular regions involved in interoception, emotion, social reward and motor behaviour.
- Humor therapy has been shown to be effective in improving depression and anxiety in those with health problems.
- PMID: 36126672, 37340873

28 Joy seek

- Play, stories, music, art, dance, sports, animals, games, curiosity, friends, food, photography, creating, unplanned time, jumping on the bed, etc.

29 Recovery Essentials

- Structure
- Brain food
- Peace of Mind
- Dream Team

30 Peace of Mind

- Avoid talking it into being

- AVOID TALKING IT INTO BEING
- Mindfulness
- Limbic & Vagal
- Treat yeast
- Neural nutritional support
- Homeopathy
- Nasal ginsenosides
- Addiction

31 Prisoners in their own minds

- Even after the worst of it passes, these children find themselves continuously looking over their shoulder, expecting and waiting for the mind torture to happen again.
- The physical change to their brains traumatizes their mental-emotional state.
- The images and obsessions playing in a child's mind are frightening, grotesque, and unnerving.
- It isn't uncommon for a child to believe her parent has been replaced by an imposter or to have a "daymare" of killing her pet, sibling, teacher, or you—or even harming herself.
- It's important to understand the level of trauma a P/P child is living with every day, 24-7.

32 Mindfulness

- For long-term recovery into adulthood, kids with P/P need mental health skills and support. Many of my patients who are now young adults are thriving with this skillset.
- Virtual mindfulness resources available for kids, teens, and young adults recovering from P/P, especially those

virtual mindfulness resources available for kids, teens, and young adults recovering from PTSD, especially those unable to leave their bedrooms.

- Interactive practices, meditations, and even online retreats.
- Compared to higher-force interventions such as IVIG, you might be thinking, "why bother?" While it might seem too "fluffy", I can report from working with families that Mindfulness saved the day in more instances than I can count.
- Teens often report that the Mindfulness recordings helped their parents also chill out, and that was the medicine needed at the moment.
- With practice, Mindfulness can become a stabilizing presence in a child's and parent's life.

33 Avoid talking it into being

- *Trigger warning to psychologists, psychiatrists, counselors, social workers.
- Talking about an intrusive thought will take it from thinking to being. From thought to reality.
- Neuroscience is showing that our brains can't tell the difference between concentrated thought and reality. In studies on exercise, people who did concentrated visioning of themselves exercising every day for a half hour, grew muscle on par with those who had actually exercised for a half hour.
- Be cautious of growing these unwanted thoughts by talking about them. Their compulsions manage their obsessions. Temporarily, consider letting the compulsions fly. They are a healing salve on the scary thoughts.
- Let your child determine the timing. I have seen children who were forced into counseling or prodded to talk about their visions become very unstable and a danger to themselves.

- Tame your own curiosity.
- Later, after the storm of brain inflammation passes, kids probably will need to talk . . . a lot, and to professionals.

34 P/P brains are different than externally traumatized brains

- I'm not recommending to avoid counseling or psychiatry. They're a key part of the Dream Team (next).
- I'm suggesting that you ask that member of your Dream Team to avoid talking the visions into reality with your child. They must contain their academic curiosity and do what's best for the child.
- Trauma from PANDAS/PANS is different than historical trauma, because the trauma is happening right now.
- The child is IN the war.
- We wouldn't sit a child down who's in the middle of a war zone and ask her to rehash the horrific events of that day. We'd spend the time praising her for her strength, reassuring her that it will get better, and consoling her suffering.
- There are plenty of other things to talk about. And talking about other things keeps her mental highways open to more flexible thought.
- Acknowledge that I'm not trained in psychology or psychiatry. I'm speaking from many heart-wrenching experiences. And if you'd like to understand more, check out Dr. Joe Dispenza's work.
- So what CAN you do?

35 What would you rather think about?

- Prompt by parents (and you if handling this part of the Dream Team.)
- Will have to do so over and over and over and over again. This very powerful question was taught to me by my mentor and seasoned clinical psychologist, Jan Engels-Smith.
- "What would you rather think about?"

- Of course if they could, they would be thinking about puppies and unicorns. But their inflamed brains pressure the negative thoughts, compulsions, and visions.
- Ask, ask, and ask again. Go ahead. Be annoying. Be a broken record on repeat.
- Repeating “what would you rather think about?” keeps the wiring fluid.
- They will get mad at everyone for continuously asking. Do it anyway.
- Eventually, they’ll start to ask it to themselves.
-

36 Limbic retraining with Aromatherapy

- Utilizes the olfactory route to effect change in the limbic system.
- Mechanisms ~
- First-order neurons transmit the odor-evoked response to the olfactory bulb.
- In the olfactory bulb, the axons of mitral cells (a) and some tufted cells (secondary neurons) form the olfactory tract.
- The axons of some mitral cells or lateral branches enter the anterior olfactory nucleus and pass to the contralateral olfactory bulb.
- Additional secondary neurons enter the olfactory striatum (medial, lateral, and medial) and then project to central olfactory areas, including the olfactory tubercle, piriform cortex, amygdala, and the entorhinal cortex.
- The entorhinal cortex partially transmits to the hippocampus. Eventually, the central olfactory-area signals are transmitted through the thalamus to the orbitofrontal cortex.
- An additional olfactory signaling pathway passes directly from the central olfactory area to the prefrontal cortex.
- These impulses induce the release of neurotransmitters such as serotonin or endorphin. which act as a “bridge”

between nerves and other bodily systems.

- PMID: 35496310, 23531112, 30525233, 33411049, 31604545

37 Limbic retraining

- PMID: 35496310

38 Limbic retraining

- Aromatherapies that have a calming effect and assist in limbic retraining are:

Lavender
Blue tansy
Lemon balm
Bergamot
German chamomile
Black spruce

Use high-quality oils free of pesticides and solvents and store them in glass containers.
Much fewer side-effects than psychotropic drugs.

- Additional aids: limbic retraining programs, frequency-specific microcurrent, homeopathy, prayer, and many other modalities available.
- PMID: 35496310

39 Cell danger response

- Dr. Naviaux's ground-breaking work using anti-purinergics (suramin - a P2-purinoceptor antagonist) to re-establish cellular safety signals. Suramin Autism Treatment-1 (SAT-1) trial.
- Double-blind, placebo-controlled, translational pilot study to examine the safety and activity of low-dose suramin in children with ASD.
- Ten male subjects with ASD, ages 5-14 years, were matched by age, IQ, and autism severity into five pairs, then

ten male subjects with ASD, ages 6–14 years, were matched by age, IQ, and autism severity into five pairs, then randomized to receive a single, IV infusion of suramin (20 mg/kg) or saline.

- 75% of the pathways that were altered by suramin in children with ASD were also altered in the mouse models.
- Autism Diagnostic Observation Schedule-2 (ADOS-2) comparison scores improved in the suramin group and did not change in the placebo group.
- Expressive One-Word Picture Vocabulary Test (EOWPVT) scores did not change.
- Secondary outcomes also showed improvements in language, social interaction, and decreased restricted or repetitive behaviors.
- Not an approved use in US. It's been used to treat African sleeping sickness (trypanosomiasis) for over 100 years, and remains on the WHO list of essential medications.
- No data on PANDAS/PANS.
- PMID: 23516405, 28695149

40 Botanical anti-purinergics for CDR

- Targeting P2 receptors in purinergic signaling: a new strategy of active ingredients in traditional Chinese herbals for diseases treatment

41 Botanical anti-purinergics for CDR

- Botanicals that target P2 receptors in purinergic signaling "exhibit superior pharmacological activities on diversified P2R channels."
- Botanical Avatars ~
Chinese skullcap (*Scutellaria baicalensis*)
Astragalus
Ginsengs
- Botanical Antimicrobials ~

Botanical / Pharmacological Japanese knotweed

- Red sage - *Salvia miltiorrhiza* (Dan shen)
- Sweet Annie - *Artemisia annua* (Qinghao)
- Rhubarb - *Rheum palmatum* (Dahuang)
- *Ligusticum walliichi* (Chuan xiong) (may be called Sichuan lovage root)
- *Gardenia jasminoides* Ellis (Zhizi)
- Ginger - cholinergic activity as well
- PMID: 29795391, 33751327, 27002391, 25752193, 32441354

42 Vagus nerve stimulation

- "When the CDR is chronically activated, the coordination between the two limbs of the vagus nerve is disrupted."
- Humming, laughing, gargling, vocalizing, belly breathing.
- Safe and Sound Protocol - suitable for children. Listening with headphones. Non-invasive acoustic vagus nerve stimulator and builds sense of safety. Can be delivered in-clinic or remotely.
- Transcutaneous vagal nerve stimulation (tVNS) - may alter the functions of the limbic-cortical and peripheral networks underlying the hyperarousal component of PTSD and thus improve patient health and well-being. Suitable for children with refractory epilepsy. P/P kids?
- PMID: 28824913

43 Yeast is a mental beast

- Animal models: *C. albicans* infection aggravates neuroinflammation via CNS dissemination and local induction of encephalitogenic cytokines.
- Clinical pearl ~

Candida pearls

- If things are going sideways, make sure the child doesn't have yeast overgrowth. Yeast overgrowth is often missed, and it predictably messes with a child's mental game.
- If found, treat it aggressively and for longer than you think is needed. Die-off symptoms after initiating antifungal therapies are diagnostic.
- Many Candida strains are resistant to current medications. Combining herbs, such as garlic, with the medications can reduce resistance.
- PMID: 34901093, 28584446, 25969836

44 Neural support

- DHA ~ (Docosahexaenoic acid)
Helpful with mold exposure. Protects the brain, nervous system, and eyes from mycotoxin effects.
Therapeutic dose is up to 3 grams daily until symptoms reduce, then maintenance dose of 500 mg daily.
Vegetarian sources from algae.
- PQQ ~ (Pyrroloquinoline quinone)
CoQ's cousin. Improved function of the mitochondria, heart, and brain.
Helps with learning, memory, and reduction of brain fatigue.
Protects the brain from the damage of excess excitatory NTs during flares.
Nourishing the brain with PQQ during a flare can prevent the post-flare exhaustion.
Therapeutic dose is 20 mg daily.
- Phosphatidylserine ~
Important for proper brain function. Gets used up in kids with P/P. Phosphatidylserine blocks excessive amounts of excitatory brain chemistry.
Repairs and prunes neuronal circuits, thereby keeping a focus on desired nerve tracts to reduce brain chaos.
Results in improved focus and better sleep.
Therapeutic dose is 100 mg in the morning and 200 mg before bed. In rare cases, it can initially cause insomnia while the low tank is filling.
- PMID: 22686216 21755181 21585770 22657162

• PMID: 23000340, 24700404, 34000770, 32007400

45 Inositol

- Though not technically a B-vitamin, it's often referred to as Vitamin B8.
- Particularly helpful for severe OCD and tics, especially where sleep is a struggle.
- Typically use the myo-inositol form.
- Therapeutic dose is much higher than other B-vitamins at 3,500 mg taken bid. Powdered form very well tolerated.
- PMID: 21352883, 32215361

46 Low-dose lithium

- Lithium is a natural element. Stigmatized due to high dose Rx use for bipolar disorder and mania.
- Can be toxic in high doses. Must be monitored with regular blood testing. But the low-dose version can be used safely OTC for mood stabilization in kids with P/P.
- Low dose has subtle mood-elevating effect, anti-neuroinflammatory effects, and lesser known mitochondrial activation effects (CDR).
- Pool story: Changing nothing else with their child's regimen, a family changed their pool chemicals to a mineral blend based around lithium. Within days, their child became stable and a pleasure to be around. Nearly a month after the pool had to be winterized, she relapsed. We tried low-dose lithium, and the stable child returned.
- A systematic review reported that across studies, LDL was reported to be safe.
- Adult therapeutic low-dose is 10 mg taken twice daily, best taken earlier in the day.
- One caution with Lithium is that it has a litany of drug interactions, even in low doses. Check the Medication Compatibility Chart.
- PMID: 35236261 36136722

47 Lithium increases mitochondrial function, reduces inflammation, and protects the BBB

- make into handout
- Not exhaustive list

48 Lithium reduces neuroinflammation and induces BDNF

- make into handout
- Not exhaustive list

49 Homeopathy

- Homeopathy uses the principles of "like cures like" and the "law of minimum dose."
- The principle of "like cures like" states that a substance, which in large doses would cause similar symptoms to the patient, is then administered in minute amounts to treat the same symptoms. Hence like cures like.
- The "law of minimum dose" says that the more minute the amount of a substance, the greater will be its therapeutic effect.
- "It's as if we give the body a red herring reason that it's upset, so it has something to organize a response around. In other words, we tell the body it isn't mad at brain cells, it's actually mad at the remedy. And since it's in such a small dose, the body gets to be successful, and fully resolve the issue. This is very calming to a body, and a brain."
- List in handouts - not an exhaustive list but a place to start.
- Extremely easy and safe to use with kids of all age. Can be administered on sugar pellets or in a little sip of water held in the mouth for 30 seconds. I usually use the 30c OTC potency with P/P kids.
- To prevent "discharging" the remedy, here are some guidelines:
Storage: Do not expose to cell phone or microwave radiation, or full-strength essential oils
Pellets: Do not touch them before popping them under your child's tongue

Liquid: Use a glass cup only

50 Nasal ginsenosides

- The "hope hit." May be used if there's a mood or energy crash after a flare. Nasal spray is fast acting.
- Compounded blend of ginseng extracts and nicotinamide riboside. Ginsenosides from ginseng are the very parts that make a Botanical Avatar work so well, the triterpenoid saponins.
- Ginsenosides protect the brain from excess excitatory brain chemicals, reduce microglial activation, and restore normal brain neuron function.
- Has an effect on the same ion channels affected by glyphosate. Is a perfect follow-up nasal spray for kids who play outdoor sports on chemically-sprayed fields.
- Healing to tissues. The more it's used, the less it's needed.
- Cautions ~
In some children, this has a very stimulating effect. Start by using it in the morning only, with the lowest dose, and in only one nostril to test it out.
Some compounding pharmacies combine this with methylcobalamin. If a child has methylation issues, skip or substitute with hydroxocobalamin.
- PMID: 28412215, 24678300

51 Addiction

- Extremely high risk of addiction based on chemistry and structural changes in the brain.
- Chicken or egg?
- PET imaging studies have shown that addiction to a number of substances of abuse is associated

to a number of substances of abuse is associated with a decrease in dopamine D(2/3) receptor binding and decreased presynaptic dopamine release in the striatum.

- Not just substances - screens/gaming, gambling, high-risk behaviors, etc.
- If opiate, encourage appropriate MAT tx, ie: bupropion treatment. If trained properly, can be done in your office (if not addiction or psychiatric clinic, bypasses some FDA reporting/charting requirement.)
- PMID: 22015315

52 Recovery Essentials

- Structure
- Brain food
- Peace of Mind
- Dream Team

53 Dream Team

- Beliefs
- Parent, caregiver, and sibling support
- Medical support village

54 Yes, their world gets smaller

- False belief ~
smaller = less support
- Parents need to be given permission to rewrite that belief.

Their child can have disruptive behaviors AND they can be supported.

1 PANDAS & PANS

An Integrative Approach

- Dr. Jill Crista

2 Disclaimer

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3

- Cases

4 Overview

- Course Outline
- 1. Symptoms
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5 Success Plan

- Set your parents up for success from the beginning. Like it or not, they're in this for the long haul.
- Expect the child/teen to refuse treatment. It's normal, and actually a good sign - starting to take their power back, click in to the world of reality. And unfortunately, the first place children tend to practice this rediscovered skill is with their parent.
- Refusal moments are the child reclaiming a sense of control.
- Give the child control over remedy choice—not whether he will take it, but which one he will take.
- Start from the beginning—have 2 options for each item. The child gets to take control via choice. "Do you want this one or this one today?" Set the pattern. It isn't an option to refuse all remedies, only "which" remedy.
- When you hear, "I'm not taking that." Be ready with, "Okay, it looks like you're choosing this one instead." And if you still hear, "I'm not taking that either," you're equipped with the knowledge that the hidden goal is control. State that he has a choice.: "It's your choice, this one or this one. Which one do you want? It's in your hands."
-

- And if all else fails, I never judge if they bribe. I did.

6 Core 4 Variety

- Four different PANDAS/PANS kids from my practice, named for the biggest pain point for the child: Anxious, Starved, Insomniac, and Strep-Magnet.
- Each are different in how I chose the specific Cores of treatment.
- I often add extra nutrients such as the things in Recovery Essentials, but these display how to apply the Core 4.
- Anytime you see individual glycerites listed, they usually were mixed together whenever they could be dosed at the same time. That allows parents to focus on getting one remedy down rather than five.

7 Anxious

- Anxious had compulsions that made learning and socializing difficult.
- Very concerned about infection exposure. (Sign of low immunity and breeched barriers.)
- Focused on remedies that reduced anxiety and brightened the mind.
- The herb combination is a daytime combination and not suited for bedtime, unless noted.
- Mixed the herbal glycerites and divided in half, flavoring each with his chosen flavors—one mint and one ginger. (Build in the control over choice.)
- Dosed by weight at Flare dose until fears calmed + 2-3 weeks.
- Tame the Flame:
Flame Tamer: Resolvins in the morning, Rosemary (added as glycerite to the Avatar formula taken in the morning, at lunch and after school/before dinner.)
Mast Cell Managers: Vitamin C (anytime of day), PEA in the morning.

-

8 Anxious, cont

- Beat the Bugs:
Botanical Avatars: Brahmi, Thorough-wax, Gotu kola
Botanical Antimicrobial: Japanese knotweed
(Mix above as a glycerite to take in the morning, at lunch, and after school/before dinner.)
Black elderberry syrup after dinner.
- Regulate Immunity:
Vitamins A + D weekly
Butyrate after dinner (Self-conscious of "fart breath", so took it at night.)
- Guard the Gates:
Nasal essential oil inhalation stick every morning on the way to school, repeat whenever he feared exposure.
Nasal probiotic swab every evening after brushing teeth.
Sage tea gargle after brushing teeth in the morning. (Parents made a batch every week and kept refrigerated. A ½ cup was taken out the night before and set by the bathroom sink.)
Switch to xylitol toothpaste.

9 Starved

- Starved had a fear of choking, feeling like she couldn't swallow correctly.
- She was hungry but couldn't eat.
- She'd also have histamine flares after eating, so many of her remedies were taken 15 minutes before eating.
- Also added blended soups, ground up meats, and used thickeners for fluids to help her swallow.
- Had a persistent Strep presence which turned out to be due to perianal Strep and mold exposure. Once addressed, her eating difficulties went away.
- Tame the Flame:
Flame Tamers: Feverfew and Rosemary added to glycerite and taken 15 minutes before eating.
Mast Cell Managers: Liposomal Quercetin/Luteolin, DAO taken 15 minutes before eating.

10 Starved, cont

- Beat the Bugs:
Botanical Avatars: Gotu kola, Chinese skullcap, Oregon grape, Brahmi taken 15 minutes before eating.
Botanical Antimicrobials: Oregano, Licorice, Black walnut pulsed on the weekends.
Perianal Strep: Topical silver cream qd.
- Regulate Immunity:
Butyrate, Colostrum and Peptides mixed together and taken in the morning and night.
- Guard the Gates:
Nasal propolis spray twice daily.
Propolis throat spray twice daily. (Gargles are hard for kids with swallowing difficulties. Their choking fear amplifies. It's kinder to use sprays.)
Switch to Dentalcidin toothpaste.

11 Insomniac

- This poor guy could NOT sleep. Anytime someone in the house got a little snuffle, he'd be up all night.
- Focused his formulas on afternoon and nighttime dosing, with a little extra antiviral kick.
- Tame the Flame:
Flame Tamers: Resolvins, Feverfew (added to above glycerite formula)
Mast Cell Manager: Vitamin C
- Beat the Bugs:
Botanical Avatars: Silk tree, Chinese skullcap, Oregon grape, Magnolia taken at 4pm and 6pm, and added 9pm if still awake.
Botanical Antimicrobials: Licorice tea in the morning.

12 Insomniac, cont

- Regulate Immunity:
Vitamins A + D weekly.
SEAZnDCK whenever someone else at home was sick.
- Guard the Gates:
Nasal colloidal silver in the morning.
Thyme steam inhalation as part of the bedtime routine. (He found this very relaxing. Parents made 1 gallon once per week, pour out enough for the steam, and microwave it in the bowl to be used for the steam treatment.)
Switch to Myrrh toothpaste.

13 Strep Magnet

- The name explains it all. This was a very sick boy. He wasn't able to attend school or soccer after PANDAS/PANS hit. An example of how to combine naturopathic medicine with antibiotics and IVIG.
- Severe compulsions, mood issues, and tics, as well as trouble eating and sleeping. Due to pretty hefty environmental exposures from weed killer on his soccer field and mold in his home, we needed to begin with a heavier medical intervention.
- Tame the Flame:
Flame Tamers: Vitamin C, Resolvins, Feverfew (higher as steroids wore off).
Mast Cell Managers: Quercetin/Luteolin
NSAIDs: Ibuprofen on a 2-week suppressive course, then prn.
- Beat the Bugs:
Botanical Avatars: Oregon grape in the morning with Augmentin, Silk tree in the evening with Augmentin.
Botanical Antimicrobials: Thyme twice daily added to each glycerite below for Strep and fungal overgrowth.
Pharmaceutical Antimicrobials: Augmentin 875 mg twice daily. Itraconazole pulsed.

14 Strep Magnet, cont

- Regulate Immunity:
Vitamin D: Daily dosing for more stable protection.
Butyrate (to compensate for lowering effect from Augmentin): Twice daily with Augmentin.
Probiotics: Once daily away from Augmentin by 1 hour.
Peptide - BPC 157: Twice daily.
Ultra-Low-Dose Naltrexone: Taken in the evening.
IVIg: 1.5–2.0 g/kg over 2 consecutive days, every 6 weeks. Co-administered IV steroids, diphenhydramine, and ibuprofen.
- Guard the Gates:
Colloidal silver nasal spray in the morning.
Nasal probiotic swab in the evening after brushing teeth.
Switch to Dentalcidin toothpaste.

15 Strep Magnet, cont

- He also benefitted from an ultra-low dose of sertraline. Later, we found he had Bartonella, so we added Cryptolepis twice daily at the same time as the Augmentin. Once Bartonella was addressed, he no longer required the sertraline.
-
- I'm happy to report that this boy is now a man. He has graduated from technical college and is enjoying independent living with a little extra support from his parents when needed.

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17 PANDAS/PANS Mechanism

- Integrating Therapeutics → Family Bliss!

18 Resources

- Survey
- CE/CME certificate

19 Books

- Greek

20 Education

- Greek

21 Mentorship with Dr. Neil Nathan

- Prerequisite training for our mentorship is the basic training via the mentorship or my mold certification course (accessible on my website.)
- Email askdrnathan@gmail.com for details.
-
- Other books & trainings ~

- Neuroimmune.org
- MAPS conference
- PANDAS Physician Network conferences
- Mentorship with Dr. Nancy O'Hara
- Book by Dr. Nancy O'Hara
Demystifying PANS/PANDAS
- Book by Dr. Kenneth Bock
Brain Inflamed
- Book by Dr. Angelica Lemke
Healing Complex Children with
Homeopathy

22

- Diagnostics

23 PANDAS/PANS Mechanism

- Vierge Lighthouse in Brittany