AARM

Association for the Advancement of Restorative Medicine

Restoring patient wellness.
Building physician practices.

2018 RESTORATIVE MEDICINE REGIONAL CONFERENCE

February 3 & 4, 2018
Toronto, Ontario

Proceedings

(Page numbers for each session are noted on the schedule)

Please complete the separate Evaluation Forms and return to the registration desk before you leave to receive CME/CE credits.

Conference Agenda

Saturday, February 3

Sunday, February 4

What Hidden Toxins Are Lurking In The Supplements You Prescribe?

There is a common misconception that physician supplement brands use only organic herbs and organic herbal extracts. In reality, the majority of cultivated herbs used in these products are conventionally grown, using pesticides, herbicides, and chemical solvents!

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Heather Zwickey, PhD

Immunology Fundamentals and Current Updates

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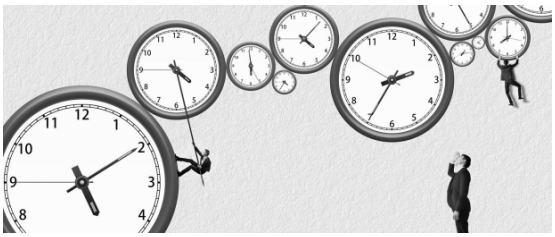
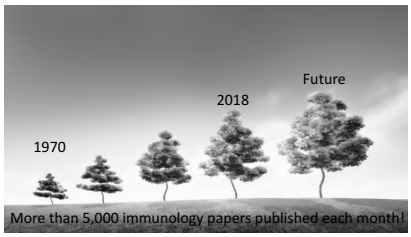
Outcomes

- Recall immunology terminology
- Describe the immune response to infectious disease
- Apply immunological principles to infectious disease – with respect to cytokine balance.

Depending on when you went to medical school…

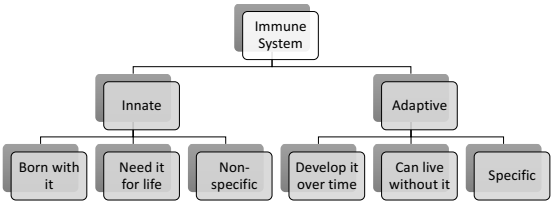


Immunology field is growing!



Immunology Review Goal

Innate vs Adaptive Immunity



Cells Involved

Innate	Adaptive
Macrophages	B Cells
Dendritic Cells	T Cells (CD4 and CD8)
Neutrophils	NKT Cells
Eosinophils	
Basophils	
Mast Cells	

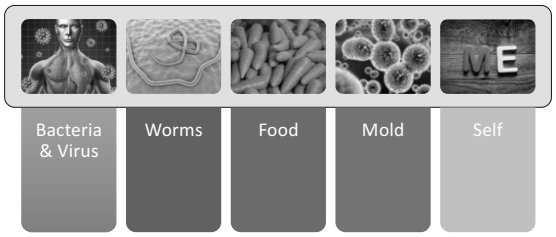
How we identify cells

CD –
Cluster of
Differentiation

Cells Involved

Innate	Markers	Adaptive	Markers
Macrophages	CD11b	B Cells	CD19
Dendritic Cells	CD11c, MHC	T Cells	CD3 + CD4 or CD8
Neutrophils	CD15	NKT Cells	CD56 + CD3
Eosinophils	CD11b, CD193		
Basophils	2D7, CD123		
Mast Cells			

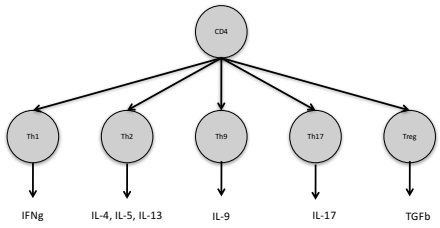
Types of Antigen



Types of Immune Responses

Reactions	T Cell Response
Bacteria and Virus	Th1
Worms (some parasites)	Th2
Asthma	Th9
Fungi (some parasites and extracellular bacteria)	Th17
Food	Treg/Th3 *Dominant

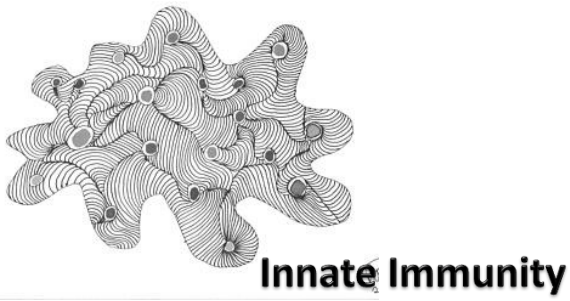
CD4 T cell Subtypes



Immune Reaction Table

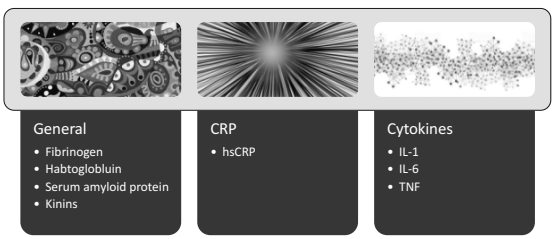
Reaction Type	T Cell Response	Cytokines	Antibodies
Bacteria/Virus	Th1	IFNgamma TNFalpha	IgG/IgA
Worms	Th2	IL-4, IL-5, IL-13	IgE
Fungus	Th17	IL-17, IL-23 *IL-6	IgG
Asthma	Th9	IL-9, IL-10	IgE
Food	Treg/Th3	TGFbeta, IL-10	IgA

Process Overview



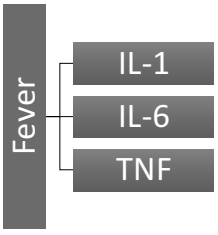
Tick Bite…

Proteins



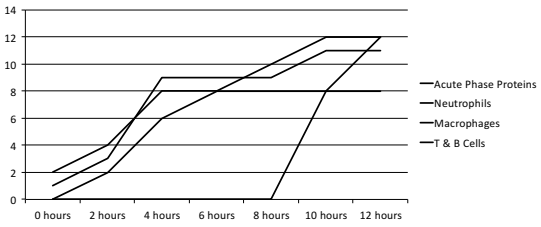
Recall Systemic Inflammation

- Acute phase
  - Defensins
  - Kinins
  - Complement
- Innate phase
  - Inflammatory cytokines
  - Cellular response
    - Macrophages
    - Dendritic Cells
    - Neutrophils



Sickness Behavior

Timing – Acute Phase through Innate Phase

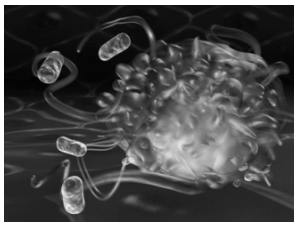


Innate Response

Macrophages and Dendritic Cells (DCs) phagocytose Borrelia

Macrophages and DCs carry the organism (antigen) to the draining lymph node

The neutrophils and acute phase proteins keep things in check until the specific immunity arrives.

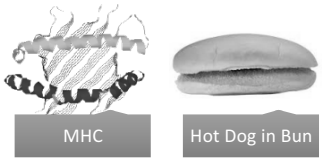


APCs

Antigen presenting cells

- Macrophage
- Dendritic cell (DC)
- B cell

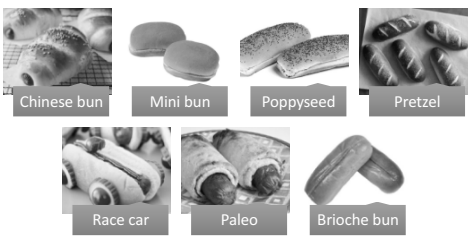
Chops up antigen and puts it in the MHC molecule



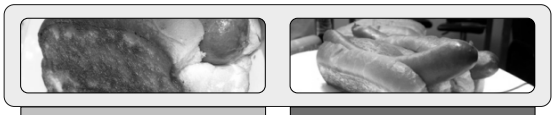
Antigen Presentation

MHC Class II	MHC Class I
Extracellular (exogenous) antigen	Intracellular (endogenous) antigen
Stimulates CD4 T cells (Thelpers-Th)	Stimulates CD8 T cells (Tkillers-CTL)
HLA – DP HLA – DQ HLA –DR	HLA – A HLA – B HLA – C

Thousands of MHC Haplotypes



Antigenic Variation

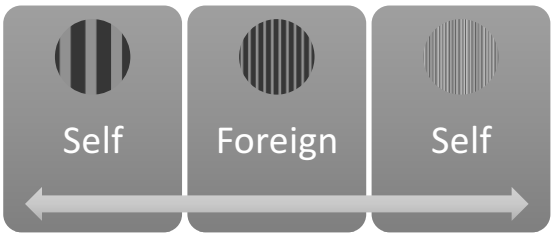


Change in the antigen…

…means it may no longer fit in the MHC

Therefore, T cells may no longer respond or antibodies may no longer bind to it.

Molecular Mimicry



Therefore, when attacking foreign antigen, self antigen may also be attacked, causing autoimmunity.

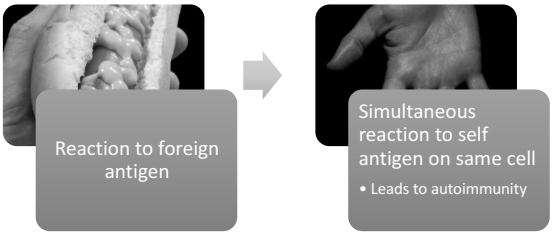
Epitope Spreading

Hot Dog
- Initial response

Baloney
- Similar antigen

As response continues, new hidden or cryptic antigens are targeted.

Bystander Activation



Reaction to foreign antigen

Simultaneous reaction to self antigen on same cell
- Leads to autoimmunity

Borrelia burgdorferi

- Microbe has 5 oligopeptide binding proteins
- Implications: Limited number of peptides to bind to HLA molecules
- Likely binds to specific HLAs
  - Some people will be more susceptible than others

Groshong AM, Dey A, Bezsonova I, Caimano MJ, Radolf JD. Peptide Uptake Is Essential for Borrelia burgdorferi Viability and Involves Structural and Regulatory Complexity of its Oligopeptide Transporter.*mBio*. 2017;8(6):e02047-17. doi:10.1128/mBio.02047-17.

Co-infection (2-15%)

B. burgdorfi → A. phagocytophilum

B. burgdorfi → Babesia microti

Pattern Recognition Receptors: PRRs & TLRs

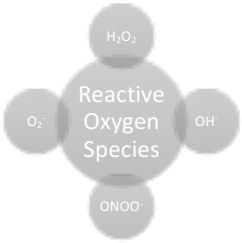
Pattern Recognition Receptors (PRR)

- On macrophages, DCs, Neutrophils
- Recognize bacterial and viral proteins as dangerous

Toll Like Receptors (TLR)

- Subset of PRRs
- Stimulation leads to "danger" response

Danger signal leads to…



Immunological Danger

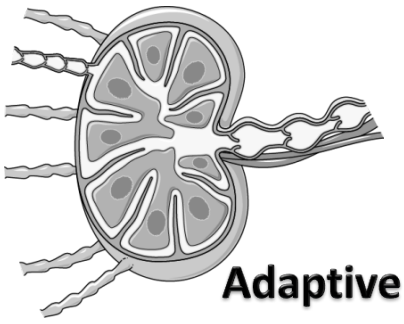
- Reactive Oxygen Species
- Leukotrienes and Prostaglandins
- Costimulatory Molecules (CD86)
- Cytokines

Mini-Quiz

1. Which cytokine makes people tired and malaised?

2. Which cell types will be the first to phagocytose Borrelia? (There are 3.)

3. Which proteins tell the cell that an infection has occurred?



Adaptive Immunity

Where we're at…

- It's 4-8 hours post infection
- Macrophages and DCs are at the lymph node
  - They have antigen in their MHC molecules
  - They're activated
  - They're making ROS
  - Some are dying and releasing microbes in the lymph node
  - Some are waiting for B and T cells to help activate them
- Where are the B and T cells?

B cells

B cells make antibodies

You already have antibodies specific for anything you may encounter one day.

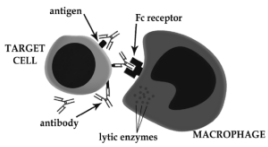
Exposure to antigen increases the number of antibodies, 100-1000 fold.

IgM, IgD, IgG, IgE, and IgA

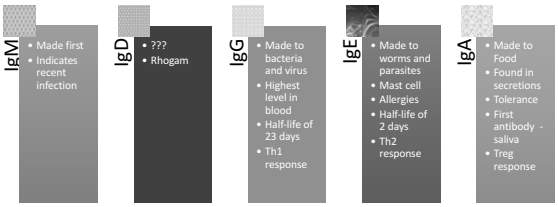
Antibody Function

- Opsinization
- Neutralization
- ADCC
- Fc Receptor

Antibodies are adapters



Antibody Isotypes



Antibody Details

Best for infections

Protection from Breast milk

Antibody	Characteristics	Location	Cytokine for Switch
IgM	Pentameric Made first High concentration means recent infection Can be made at 5 months of gestation ½ life = 2-7 days	Blood	IL-2
IgD	Monomeric Unknown function ½ life = 3 days	Blood	Unknown
IgG	Monomeric Highest level in serum Can cross the placenta (passive immunity) Associated with a **Th1 response** ½ life = 23 days	Blood	IFN$_\gamma$
IgE	Monomeric Response to parasites Involved in allergies Associated with a **Th2 response** ½ life = 2 days	Blood	IL-4
IgA	Monomeric or Dimeric, Found in secretions—Breast Milk Import role in infections—first Ab encountered Associated with **Th3 response** Can also be **Th1** – for mucosal pathogens ½ life = 3 days	Saliva, Breast milk, Secretions, Gut, Tears, Vaginal fluid	TGFβ

Antibody response

- Macrophages release Borrelia antigen in lymph node
- One B cell specific for antigen activated – Monoclonal activation
- Antibodies bind – isotype is T cell dependent
- Antigen cleared

Polyclonal antibody response

Macrophages release Borrelia antigen in lymph node

Many B cells specific for Borrelia antigens activated – Polyclonal activation

Antibodies bind – isotype is T cell dependent

Antigen cleared. More ideal response because many antigens attacked simultaneously.

T cells

CD4 T cells make cytokines in response to a specific antigen.

CD8 T cells kill the cell displaying the specific antigen.

It takes 2 signals to activate a T cell.

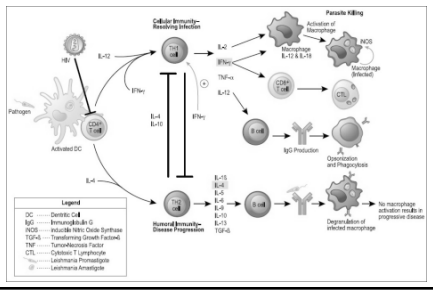
T cell activation

MHC	Binds to TCR	Signal 1
CD86	Binds to CD28	Signal 2
Cytokines	Bind to receptor	Th type

Overview of Immune Response

Overview of Immune Response				
APC	**Makes cytokine**	**Triggers**	**CD4 T cells make:**	**B cells make:**
DC	IL-12	Th1	IFNγ	IgG
DC	IL-4	Th2	IL-4, IL5, IL-13	IgE
DC	IL-4 + TGFβ	Th9	IL-9, IL-10	IgE
DC	IL-23	Th17	IL-17	IgG
DC	IL-10	Treg/ Th3	TGFβ	IgA

Cytokines tell the T cell what type of response to initiate

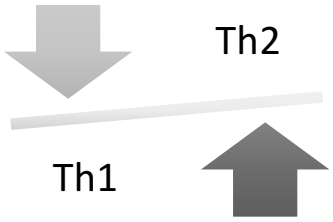


Th1/Th2

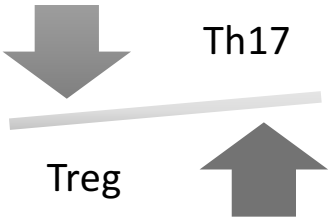
Th1/Th2 – Balance
If Th2 is high, it shuts down Th1 and vice versa.

The genes are regulated so that you don't make both responses at the same time.

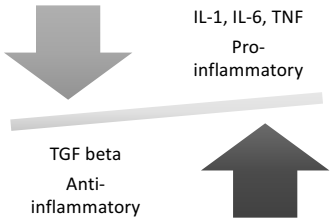
Balance



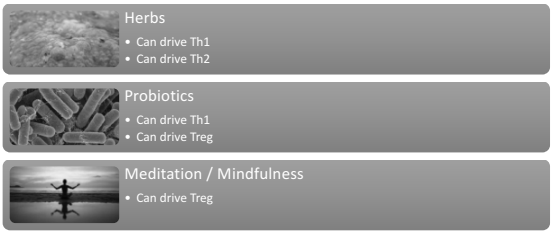
Balance



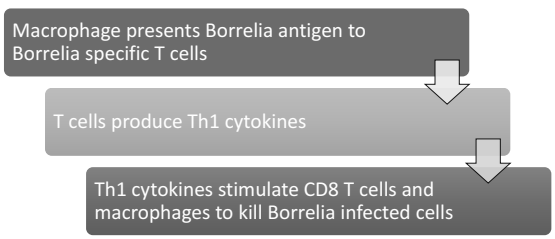
Balance



Manipulating cytokines can be therapeutic



T cell Response



Herb and Cytokines

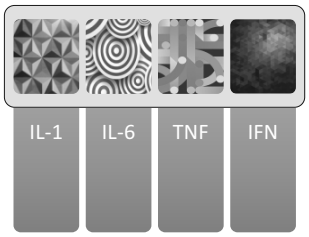
	Herbs	Cytokines elicited	Ref
Increase Th1	Astragalus Oregon Grape	Increases IFNg & IL-2 Increases IL-12 & IFNg	PMID: 12883732 PMID: PMC1782893
Increase Th2	Marijuana	Decreases IFNg	PMID: PMC4002943
Increase Treg			
Decrease pro-inflammatory	Ginger Curcumin Resveratrol	Decreases IL-6 Decreases IL-6 Decreases IL-1	PMID: PMC3712229 PMID: PMC4427355 PMID: PMC3488075

Immunological Relationship to Symptoms

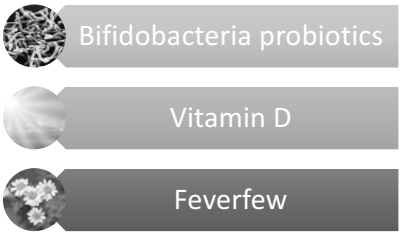
- Borrelia antigen 'swims' through extracellular matrix
  - As antigen presentation expands, CD8s attack cells progressively further and further from the original antigen from the tick bite.

Immunological Relationship to Symptoms

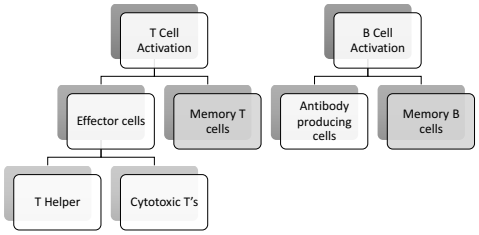
- Arthritis
- Fibromyalgia
- Fatigue
- Multiple Sclerosis
- Lupus



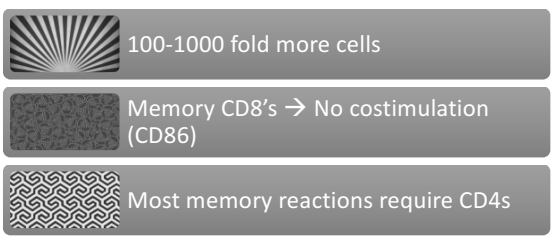
Decrease IL-1, IL-6, TNF, and IFNgamma



End of Response



Memory Cells

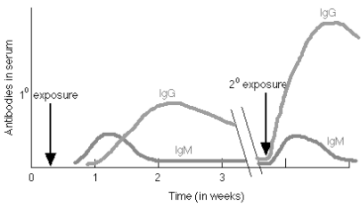


Characteristics of Memory

Memory responses are significantly shorter than the initial response

Initial response → 7 days
Memory response → 3-4 days

Memory can last as long as 23 years



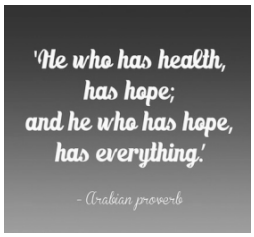
Mini-quiz 2

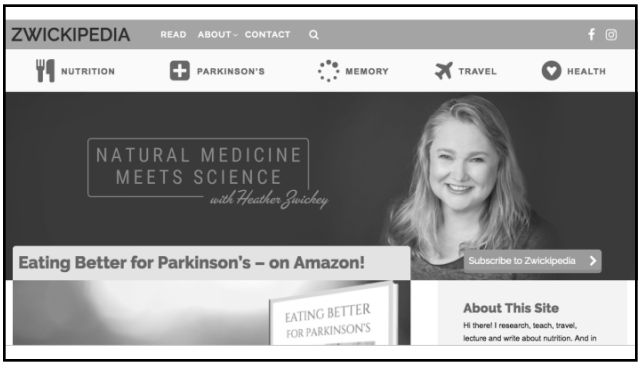
1. Which cytokines and antibodies are involved in a Th1 response?
2. What is the ideal cytokine to increase to combat Lyme disease?
3. Which cytokines would you want to decrease during chronic Lyme?

Summary

1. Cytokines are responsible for many symptoms that people feel.
2. The ideal response to an infection is Th1 – IFNgamma and IgG
3. Infections can lead to autoimmune disease.
4. Cytokine types are in balance with each other.
5. Manipulating the cytokine response can improve health.

Thank you!





Disclosures

Zamia
Nutrition by Heather Zwickey

NIH National Center for Complementary and Integrative Health

Heather Zwickey, PhD

Optimizing the Immune System in Chronic Infections

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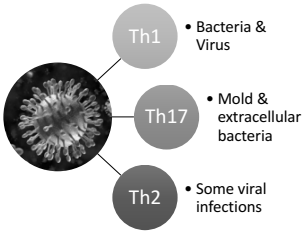
Ideal Responses to Infection

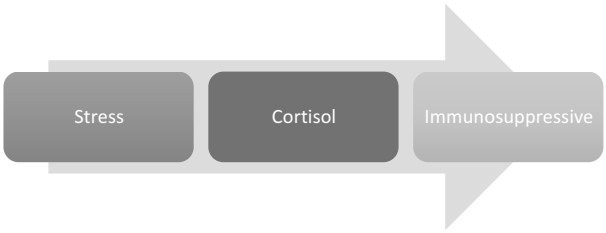


Environmental Effects

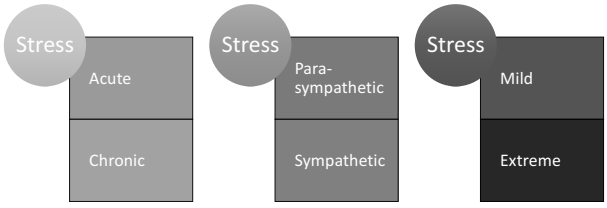
Response to Infection

# of microbes	Virulence
Stress	Immune balance	"Health"

Historically…



Now… More complex than that.



Immune Balance

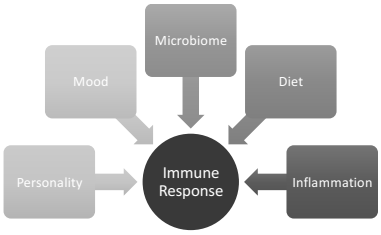
Th1

Able to quickly fight off infection

Th2

Seem to get many infections

"Health" impacts on infection

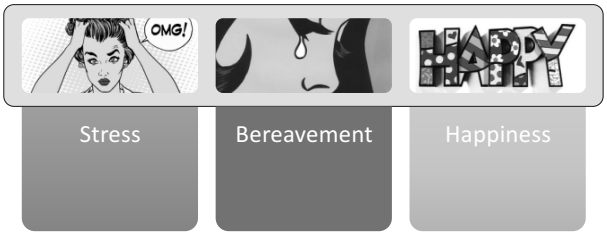


Objectives

After this lecture, you should be able to:

- Revisit the immune response to stress during infection
- Approach Th1/Th2 balance in chronic infection
- Discuss Gut/Brain Axis in chronic infection

Well-studied Moods

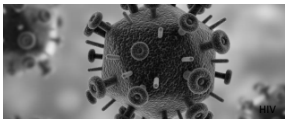


Stress

Why do we know so much about stress?

Bereavement

Why do we know so much about bereavement?



Happiness

Why do we know anything about happiness?

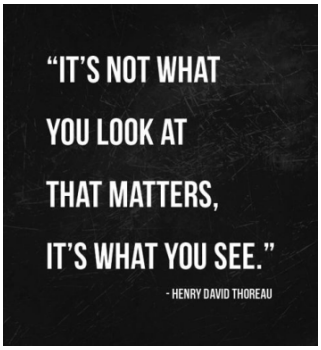
Stress – What is it?

Stress: the perception of threat to the physiological or psychological well being

and

the perception that the individual's responses are inadequate to cope with it.

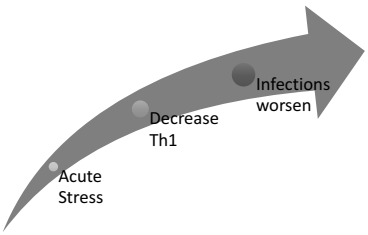
☆ **Abililty to Cope** ☆



Studies with medical students

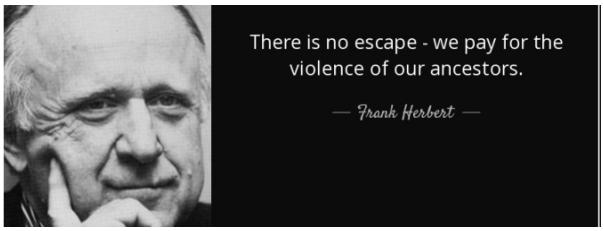
- Exams and social support effect the response to Hepatitis vaccine response
- Isolate peripheral blood leukocytes
  - Treat with catecholamines
  - Shuts down IL-12 production
  - Reduces Th1 which increases Th2
  - Th2 is "allergy"

Implications for chronic infection



Other ways we study stress

Why?

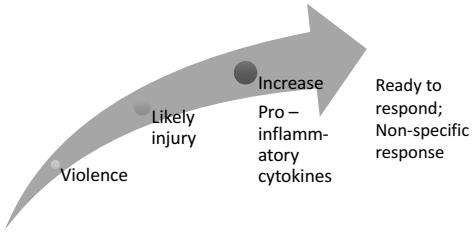


Ancestors

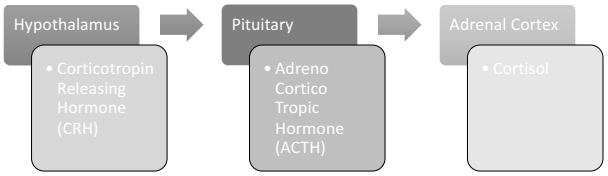
Anger → Violence → Injury

Persistent anger leads to longer wound healing time.

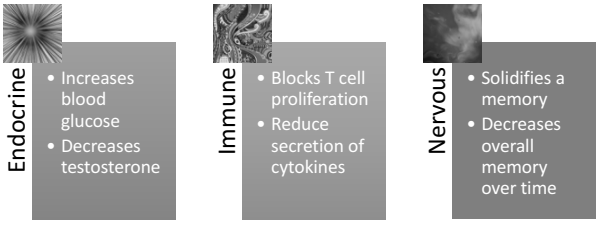
Implications



Stress Response Review



High Cortisol Effects (Acute Stress)



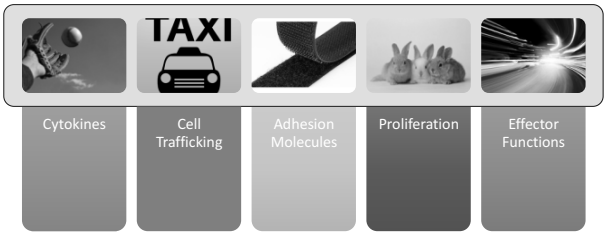
Chronic High Cortisol

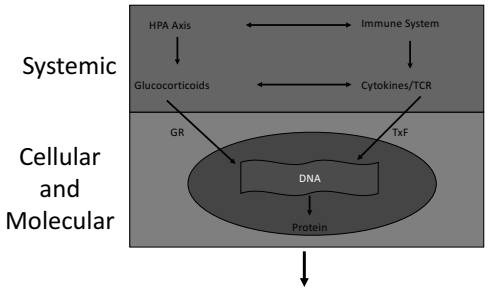
Inability to Respond to Infection

Chronic Stress

- Decrease in specific immunity
- BUT, increase in pro-inflammatory cytokines
  - IL-1, IL-6, TNF
- IL-6 – higher in women; More catastrophizing
  - IL-6 triggers CRP production
  - Chronic stress = chronic inflammation

Effects of Hormones on the Immune System





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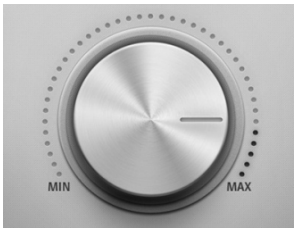
Glucocorticoid Mechanism of Action

- Glucocorticoid receptors are transcription factors
  - Cytokine genes have Glucocorticoid Response Elements
  - Glucocorticoids can regulate how much cytokine is made



Hormones and Cytokines

Hormone	Endocrine Activity	Immune Effect
Testosterone	Sex steroid hormone	Decreases Th1 (increases Th2) Decreases pro-inflammatory cytokines
Estrogen	Sex steroid hormone	Increases Th1 & Th17 Increases antibody High in RA and SLE
Progesterone	Helps maintain pregnancy; Luteal phase	Shifts from Th1→Th2 Inhibits IL-6, TNF, IFNg Pre-eclampia = high Th1
Prolactin	Lactation; Sexual health in men and women	Increase Th1, Increases antibodies, may increase Th17 (autoimmunity)
Oxytocin	Bonding	Anti-inflammatory, Antibiotic, Wound Healing
DHEAS	Precursor for Testosterone and Estrogen	Decreases IL-6 and IL-12; Increases IL-10

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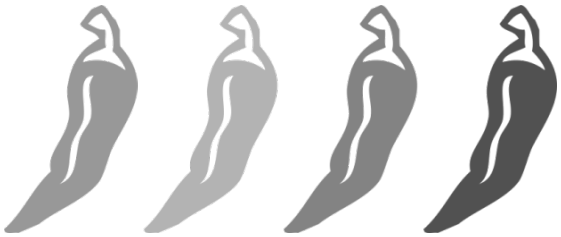
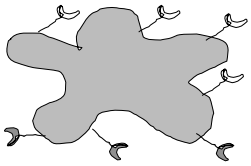
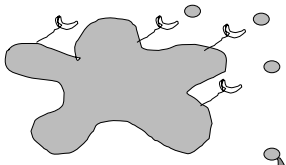
Level of Stress Matter (Mild vs Extreme)

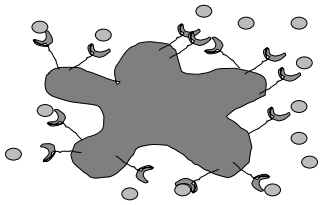




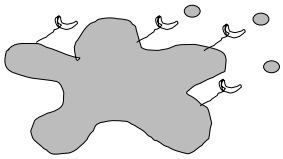
Macrophages
Express both
α and β adrenergic
receptors



α receptors are
high affinity-
Bind low concentrations of epi



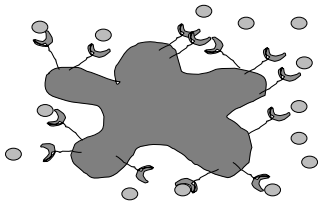
β receptors are
low affinity-
Bind high concentrations of epi



α receptors are
high affinity-
Bind low concentrations of epi

Low Stress– bind α-receptor
Results upon infection:
- **increases phagocytosis,**
- **increases TNFa,**
- **increases IL-6**

High Stress– bind β-receptor
Results upon infection:
- **decreases phagocytoisis,**
- **decreases antigen processing and presentation,**
- **decreases production of IL-12.**



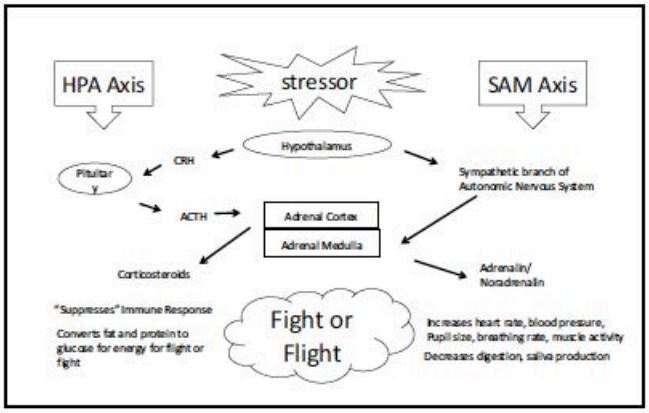
β receptors are
low affinity-
Bind high concentrations of epi

Catecholamine Effects (Adrenalin)

Endocrine
- Decreases prolactin
- Decreases testosterone
- Studied in the military

Immune
- Decrease Treg
- Increase Th1
- Decrease Th17
- Different than cortisol

Nervous
- Degrades memory in simulated interrogation
- Recovers faster than biomarker



Advocating for vacations and siestas

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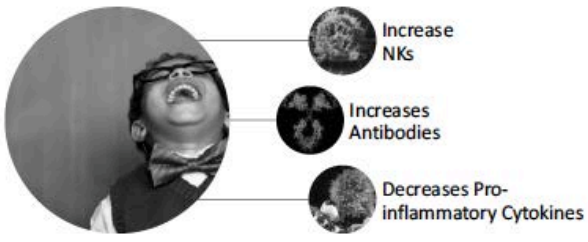
IT'S NOT STRESS THAT KILLS US, ITS OUR REACTION TO IT.

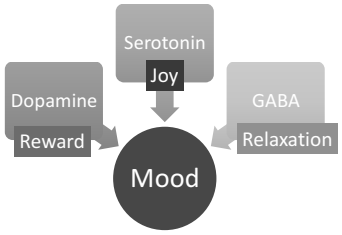
Does all of this reverse with relaxation?

- As adrenalin declines, people feel stable and comfortable, but maintain feelings of motivation
- Immune system recovers
  - Alpha adrenergic receptors engaged instead of beta

Laughter



Neurotransmitters and Microbiome



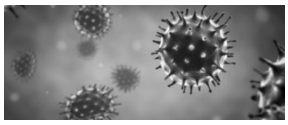
Neurotransmitter Summary

Neurotransmitter	Mood Effect	Gut Effect	Immune Effect
Dopamine	Pleasure/ Depression	Colon contraction	Drives Th17 or Treg depending on level
Serotonin	Happy/Anxiety	Bowel movements	Serotonin and IFNgamma compete for tryptophan
GABA	Relaxation/ Depression/Mania	Intestinal motility; Pain reduction	Decrease inflammatory cytokines

Cell	Express Receptors:
CD4 T cell	β adrenergic receptor Dopamine receptor Acetylcholine receptor 5HT receptor Opioid receptor (?)
CD8 T cell	Dopamine receptor 5HT receptor
B cell	Dopamine receptor
NK cell	Dopmine receptor Opioid receptor
Macrophage	Dopamine receptor α and β adrenergic receptor
Dendritic cell	Dopamine receptor Opioid receptor

Effects of Endorphins on Immunity

- Opioid abusers have higher incidence of infections
  - Impaired immunity
- Opioid treatment results in reactivation of latent viruses
  - *If you're placing a patient on opioids, consider this*
  - Slows clearance
  - Increases risk of secondary infections
- Influenza
  - Morphine impairs immunity in lungs
  - Opioids decrease NK cell activity
  - Opioids increase risk of pneumonia

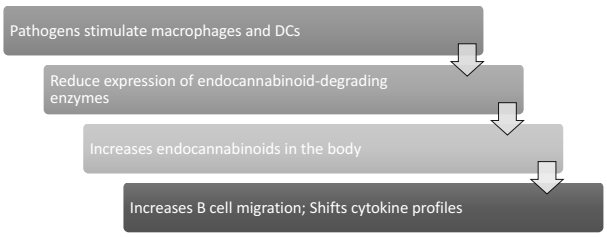


Alireza Tahamtan,1 Masoumeh Tavakoli-Yaraki,2 Talat Mokhtari-Azad,1 Majid Teymoori-Rad,1 Louis Bont,3 Fazel Shokri,4 and Vahid Salimi1, "Opioids and Viral Infections: A Double-Edged Sword" Front Microbiol. 2016; 7: 970.*

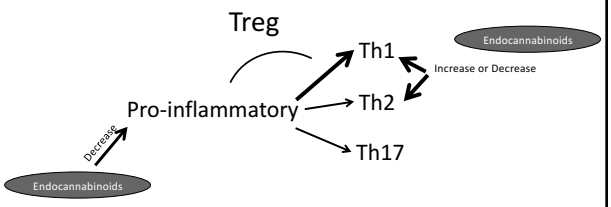
Endocannabinoids

- Endogenous set of neurochemicals
  - Discovered through effects of Cannabis sativa
  - CB1R is expressed in the brain and peripheral tissues
    - Associated with cognition and movement
  - CB2R is on lymphoid cells
    - B, T, Mac, DC, Neuts, and NKs
    - Involved in psychiatric disorders including schizophrenia, depression, and bipolar disorder

Effects of Endocannabinoids on Immunity

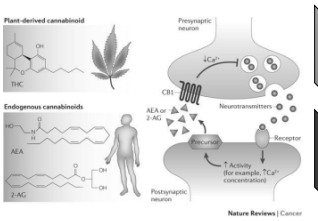


Endocannabinoids and Immunity



Rupal Pandey, Khalida Mousawy, Mitzi Nagarkatti, and Prakash Nagarkatti. Endocannabinoids and immune regulation. Pharmacol Res. 2009 Aug; 60(2): 85–92.

Endocannabinoids ≠ Cannabis



Endo
- Endocannabinoids modulate Th1 and Th2

Plant
- Plant derived cannabinoids increase Th2

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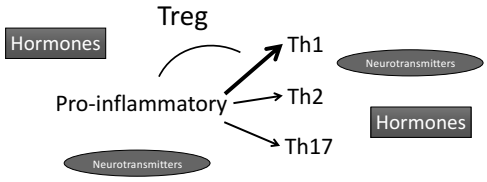
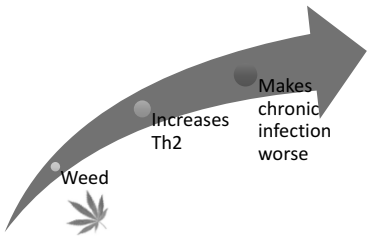
Stimulating Endocannabinoids without Cannabis

Balance

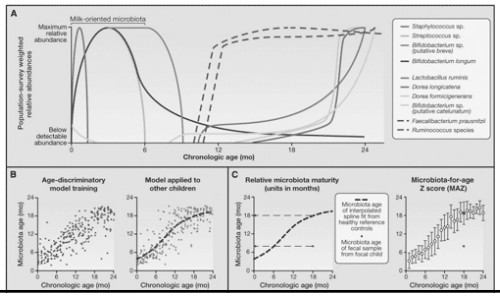


Implications



Diet & Microbiome

Microbiome Development



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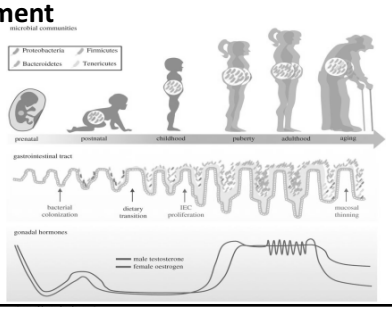
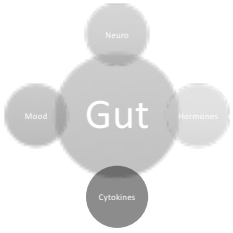
Immune development follows microbiome development



It's all connected…



- Gut is huge source of neurotransmitters and cytokines
- Microflora produce neurotransmitters (Dopamine, Serotonin, and GABA) and influence production of neurotransmitters
- Microflora can impact immune outcomes

Diversity Between People

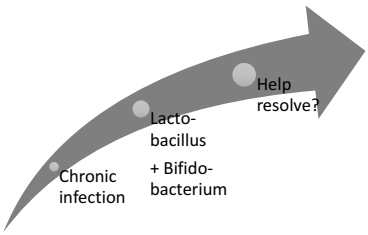
No 2 people have the same microbiome

However, several microbe species can induce the same gene functions

Several microbe species have the same metabolic function

Microbiome can impact inflammation

Implications



Adding level of complexity

Bacteroides + Vegetarian Diet = Treg

Bacteroides + Meat Diet = Th1

Summary

Chronic infection is negatively impacted by stress

Clinicians should choose therapies that drive Th1 or Th17 to resolve infection

Things that drive Th2 (allergies, weed) can make infection worse

Summary

Moods impact the immune system and vice versa

Hormones impact the immune system and vice versa

The microbiome impacts the immune system and vice versa

Thank you!!!

Thanks to

Association for the Advancement of Restorative Medicine

NIH National Center for Complementary and Integrative Health

Zamia

Nutrition by Heather Zwickey

HERBAL MEDICINE FOR CHRONIC INFECTIONS

Dr. Jillian Stansbury

AARM
Association for the Advancement of Restorative Medicine

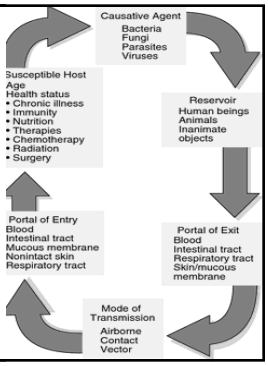
HERBS FOR INFECTIONS

This Presentation will Categorize Herbs for Infections Based On:

- **Adrenal Herbs and Adaptogens for Immune Support**
- **Thyroid Support Herbs for Immune Support**
- **General Herbal Support**
- **Immune Polysaccharides**
- **Herbs to Deter Biofilms**
- **Anti-Microbials**

CONTRIBUTORS TO CHRONIC INFECTIONS

- **Sugar**
- **Poor Diet**
- **Stress**
- **Poor Sleep**
- **Alcohol, Smoking, Drugs**
- **Nutritional Deficiencies**
- **Meds, steroids such as Prednisone**
- **Intestinal Dysbiosis and Poor Digestion**



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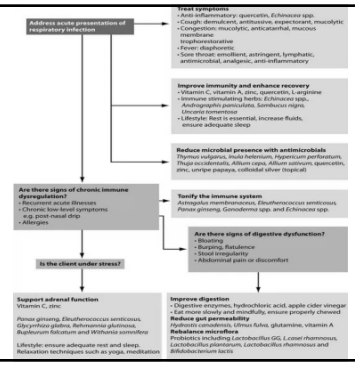
TREATMENT PROTOCOLS FOR RESPIRATORY INFECTION



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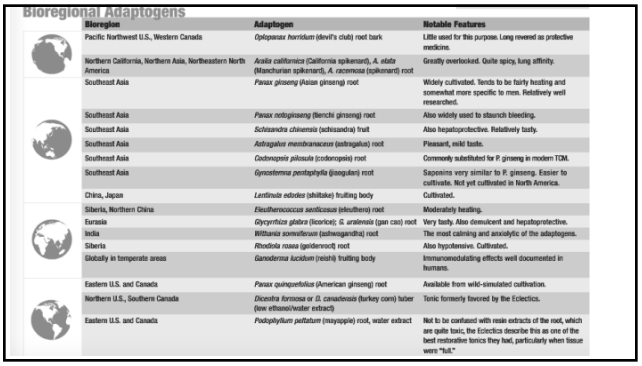
ADRENAL SUPPORT FOR CHRONIC INFECTIOUS ILLNESSES



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ADRENAL HERBS

All Cultures have used herbs, now known to affect Adrenal Glands for:

Exhaustion

Reproductive Issues

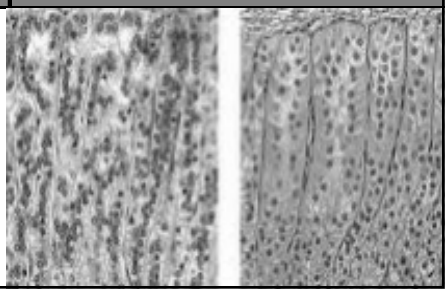
Altered Immunity

Sleep Disturbance

Stress Symptoms

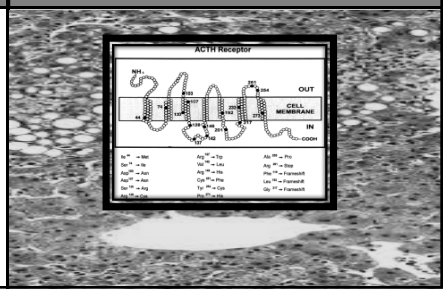
ADRENAL CORTEX FEEDBACK LOOP

Investigations into the HPA and Stress show altered cortisol responses acutely, and down regulation of the entire adrenal gland chronically.



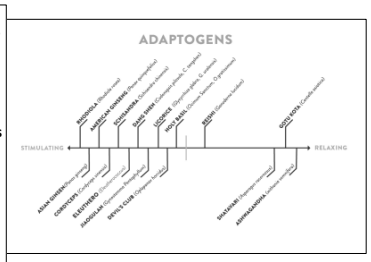
ADRENAL DOWN REGULATION

Down regulation involves a decrease in the number of cortisol receptors in tissues, or ACTH receptors on the adrenal glands themselves, and ADAPTOGENIC herbs may help restore tissue status.



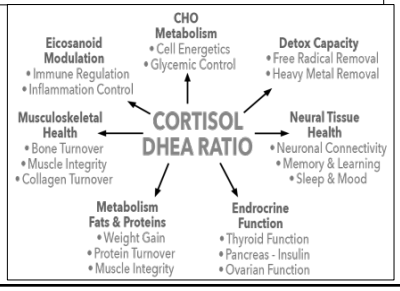
ADRENAL SUPPORT FOR CHRONIC INFECTIONS:

- **Stress and High Cortisol can suppress WBCs and other immune factors**
- **Low cortisol may also increase infection susceptibility**
- **Licorice is an example of an herb to support adrenal function, and is also shown to have anti-viral effects**
- ***Eleutherococcus* and all of the Adaptogenic herbs have substantial research regarding resisting and treating chronic infections.**



INDICATIONS FOR ADAPTOGENS AND LICORICE

Subtle signs of adrenal weakness, or blunting of the HPA axis include easy fatigue, poor stamina, poor memory, depression, irritability, and frequent infections – the same symptoms that indicate the use of adaptogenic herbs.



STRESS, HIGH CORTISOL, AND INFECTIONS

- **Stress and High Cortisol can suppress WBCs and other immune factors.**
- **Flu virus symptoms are exacerbated by stress.**
- **Herpes simplex cold sores may flare with stress.**
- **High cortisol can suppress wound healing, allow fungal growth.**

Immunosuppression Mechanisms

Neural and Endocrine Responses

- **Autonomic nervous system changes**
- **Release of Neuropeptides**
- **Alterations in Th1 and Th2 Ratios**

HIGH CORTISOL SYMPTOMS

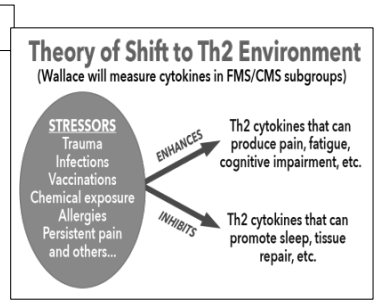
- Anxiety
- Mood Swings
- Poor Sleep
- Food Cravings
- Increase Abdominal Fat
- Brain Fog
- Irritability
- Insulin Resistance
- Blood Sugar Dysregulation
- Frequent Infections
- Auto-immune Phenomena
- Hypertension
- Depression
- Muscle Loss
- Bone Loss
- Premature Aging
- Hair Loss
- Skin Disorders
- Allergic Phenomena
- Eczema

ADRENAL FUNCTION

Allergies and infections can increase as a result of adrenal disorders, as cortisol suppresses WBCs and alters cytokine response.

Eksp Klin Farmakol. 1998 Sep-Oct;61(5):37-41. *A comparative study of the mechanisms of the immunosuppressive action of morphine and adrenaline in leukocytes in vitro.* Dolmatova LS, Romashina VV

Image from afsafund.org.

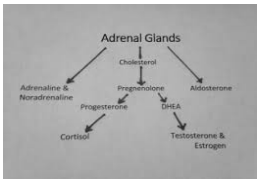


ADAPTOGENS IMPROVE ADRENAL RESPONSE

Glycyrrhiza glabra
LICORICE
Panax ginseng
GINSENG
Eleutherococcus
SIBERIAN GINSENG
Rhodiola rosea
ARCTIC ROSE
Withania somnifera
ASHWAGHANDA
Ocimum sanctum
HOLY BASIL

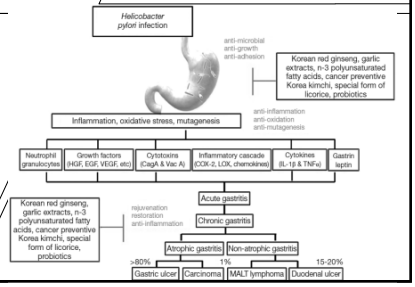
INDICATIONS FOR ADAPTOGENS AND LICORICE

Subtle signs of adrenal weakness, or blunting of the HPA axis include easy fatigue, poor stamina, poor memory, depression, irritability, and frequent infections – the same set up symptoms that indicate the need for adaptogenic herbs



LICORICE
Glycyrrhiza glabra

- Licorice supports adrenal function and hormone balance
- Licorice is especially indicated for H. pylori and enteric infections.



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LICORICE FOR INFECTIONS

Glycyrrhiza glabra

A multi-purpose herb with adaptogenic effects on the HPA Axis.

Anti-Viral
Immune Modulator
Anti-Ulcer
Anti-Inflammatory

LICORICE and CORTISOL RESEARCH

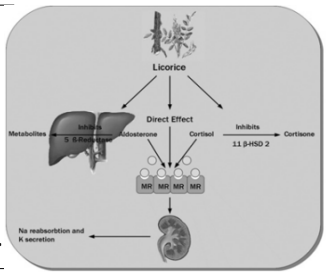
Licorice supports adrenal function, in part, by effecting cortisol metabolizing dehydrogenase enzymes.

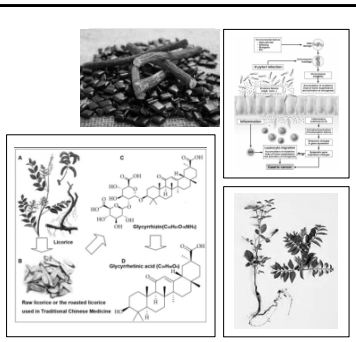
Licorice increases blood levels of cortisol and decreases urinary cortisol excretion in both animal and human studies.

J Hypertens. 2000 Mar;18(3):241-8. ***The role of the 11beta-hydroxysteroid dehydrogenase type 2 in human hypertension.*** Ferrari P1, Lovati E, Frey FJ.

LICORICE CORTISOL RESEARCH

- **Blunting of responsiveness to glucocorticoids and the circadian rhythm of cortisol and DHEA occurs in various diseases, as well as in general aging.**
- **Weakness in the HPA axis amplifies age-related changes in the neuroendocrine system.**





LICORICE CONTAINS STEROID-LIKE MOLECULES – SUCH AS GLYCYRRHIZIN

LICORICE GLYCYRRZINATES

Doses of 500 mg or less of glycyrrhetinic acid inhibit dehydrogenase enzymes only transiently, while 1000 and 1550 mg may cause long lasting cortisone-like effects.

Glycyrrhizinates may also reduce new releases of cortisol by inhibiting conjugation of metabolic precursors, deoxycorticosterone and dehydroepiandrosterone, in the adrenal gland.

J Clin Endocrinol Metab. 1994 Mar;78(3):581-5. *Kinetics and dynamics of orally administered 18 beta-glycyrrhetinic acid in humans.* Krähenbühl S1, Hasler F, Frey BM, Frey FJ, Brenneisen R, Krapf R.
Mol Cell Endocrinol. 2011 Apr 10;336(1-2):102-9. *Liquorice and glycyrrhetinic acid increase DHEA and deoxycorticosterone levels in vivo and in vitro by inhibiting adrenal SULT2A1 activity.* Al-Dujaili EA1, Kenyon CJ, Nicol MR, Mason JI.

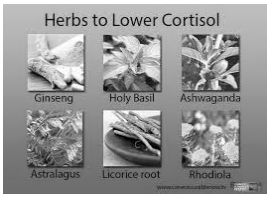
ADAPTOGENIC AND AMPHOTERIC EFFECTS OF LICORICE

These polar effects of raising serum cortisol in Addison's patients and lowering it in other populations is evidence of the ability of licorice's adaptogenic action.

Licorice may normalize HPA axis and optimize cortisol regardless of where the baseline cortisol lies – deficient or excess.

LICORICE CORTISOL RESEARCH

A small pilot study showed serum cortisol levels in Addison's disease patients on prescription cortisone acetate to increase when licorice is added, and cortisol delivery to all tissues improves.



Herbs with Anti-Microbial Effects Via Mitochondrial Membrane Disruption

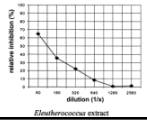
- **Glabridin is a polyphenolic flavonoid found *Glycyrrhiza glabra* roots.**
- **It has been shown to be active against the malaria-causing plasmodium organism via affects on its mitochondrial membrane.**

Eleutherococcus senticosis Siberian Ginseng

- **Eleutherococcus is one of the northern hemisphere's primary adaptogens that has been researched for many decades.**
- **Listed in the USP as early as the 1800s for fatigue, stress, and infections**

Eleutherococcus Traditional Uses

- ***Eleutherococcus senticosus*, Siberian Ginseng or Eleuthero.**
- **The plant is known as Shigoka in Japan and Ciwujia in China where is has been widely used to invigorate qi/chi, meaning general energy and vitality.**



ELEUTHEROCOCCUS

Traditional uses emphasis Eleuthero for fatigue, poor stamina and stress intolerance.

Eleuthero is also used for nervous and mood disorders such as depression, mental fatigue, and poor concentration.

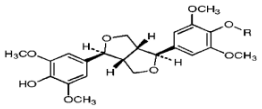
Eleuthero is helpful to treat chronic and acute infections, improve immune function, protect against toxins including hepatotoxins, neurotoxins, and cerebral vascular inflammation.

Eleuthero may improve cardiovascular inflammation, treat ischemic disorders, hypertension, and hepatitis.

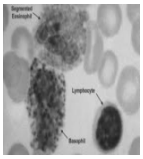
ELEUTHERO

Eleuthero has fairly extensive molecular, animal and human research demonstrating anti-stress, antiulcer, anticancer, anti-oxidant, and anti-inflammatory activity.

Int J Biol Macromol 2013 Aug;59:290-4. *Ultrasound extraction optimization of Acanthopanax senticosus polysaccharides and its antioxidant activity.* Zhao Z1, Xu X, Ye Q, Dong L.
Toxicol In Vitro. 2007 Dec;21(8):1530-7. *(+)-Syringaresinol-di-O-beta-D-glucoside, a phenolic compound from Acanthopanax senticosus Harms, suppresses proinflammatory mediators in SW982 human synovial sarcoma cells by inhibiting activating protein-1 and/or nuclear factor-kappaB activities.* Yamazaki T1,



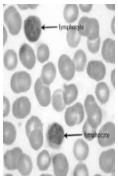
ELEUTHERO & IMMUNE MODULATION



***Eleuthero* improves basic immune status and has immune modulating effects.**

A human placebo controlled study evaluated the effects of 10 ml of *Eleuthero* tincture 3 times a day for 4 weeks on immune parameters in healthy subjects.

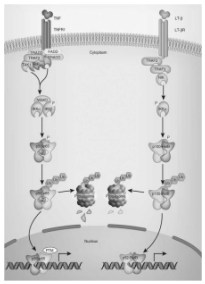
***Eleuthero* significantly increased the number of immune competent cells, particularly T Helper lymphocytes, as well as cytotoxic and natural killer cells.**



Arzneimittelforschung. 1987 Oct;37(10):1193-6. *Flow-cytometric studies with eleutherococcus senticosus extract as an immunomodulatory agent*. Bohn B1, Nebe CT, Birr C.

ELEUTHERO & IMMUNOPROTECTION

Animal studies show Eleuthero to restore macrophage and B and T lymphocyte levels when suppressed due to cadmium toxicity, enhance survival following parathion exposure, and protect animals from endotoxic shock, reducing production of inflammatory mediators, NF-kappaB activation, preventing the infiltration of inflammatory cells into the heart, liver and lung.



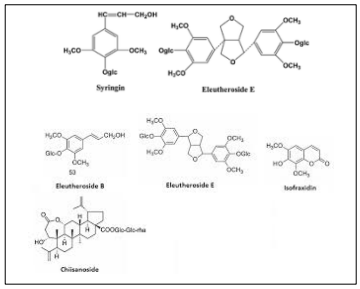
J Toxicol Environ Health A. 2014;77(21):1311-8. *Effect of Acanthopanax senticosus on the accumulation of cadmium and on the immune response of spleen cells.* Smalinskiene A1, Savickiene N, Zitkevicius V, Pangonyte D, Sadauskiene I, Kasauskas A, Ivanov L, Lesauskaite V, Savickas A, Rodovičius H

Zhongguo Yao Li Xue Bao. 1984 Dec;5(4):278-81. *Effect of aqueous extracts of Acanthopanax senticosus on parathion toxicity in mice.* Ferguson PW, Medon PJ, Watson CF.

J Ethnopharmacol. 2008 Aug 13;118(3):495-502. *Protective effect of Acanthopanax senticosus extract*

ELEUTHERO MECHANISMS

Eleuthero's medicinal actions are credited to the Eleutherosides, a group of phenylpropanoid and lignin glycosides in the roots and stems, including syringin (eleutheroside B) and syringaresinol (eleutheroside E), schisandrin and sesamin.

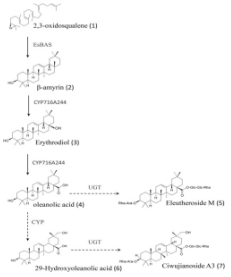


Appl Microbiol Biotechnol. 2014 Sep;98(17):7319-29. *Bio-technological production of eleutherosides: current state and perspectives.* Murthy HN1, et al.

Nat Prod Res. 2010 Oct;24 (16):1523-7. *A new 3,4-seco-lupane-type triterpenoid from the pulp of Acanthopanax senticosus (Rupr. et Maxim) Harms.* Yan ZW1, et al

ELEUTHERO CONSTITUENTS

Ciwujianosides are mast cell stabilizers, reducing histamine release provoked by immunoglobulins.
One study reported the anti-histamine effects to be approximately 6800 times stronger than that of disodium cromoglycate at a similar dosage.



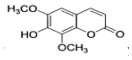
J Pharm Sci. 1992 Jul;81(7):661-2.*Ciwujianosides D1 and C1: powerful inhibitors of histamine release induced by anti-immunoglobulin E from rat peritoneal mast cells.*
Umeyama A1, Shoji N, Takei M, Endo K, Arihara S.

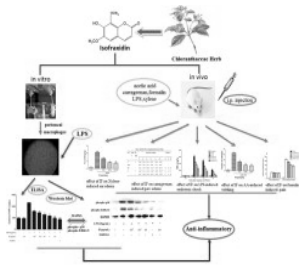
ELEUTHERO CONSTITUENTS

Eleuthero also contains coumarins including isofraxidin, and flavones.

The coumarin, isofraxidin is credited with anti-oxidant, anti-inflammatory activities, and immune modulating actions.

Isofraxidin inhibits cyclooxygenase expression in the lungs which regulates the production of prostaglandins, and inhibits NF Kappa B pathways offering tissue protective effects.





ELEUTHERO'S IMMUNE POLYSACCHARIDES

Eleuthero also contains immune polysaccharides with significant immuno-stimulatory activities as demonstrated by granulocyte and carbon clearance tests, and may help protect against other pathogens and toxins.

One mouse investigation showed the polysaccharide fraction to suppress tuberculosis from propagating the lungs.

Another animal study showed the polysaccharides to inhibit tumor growth.

Arzneimittelforschung. 1985;35(7):1069-75.*Immunostimulating action of polysaccharides (heteroglycans) from higher plants.*Wagner H, Proksch A, Riess-Maurer I, Vollmar A, Odenthal S, Stuppner H, Jurcic K, Le Turdu M, Fang JN.

Int J Immunopharmacol. 1991;13(5):549-54. *Immunomopharmacological effects of polysaccharides from Acanthopanax senticosus on experimental animals.* Shen ML1, Zhai SK, Chen HL, Luo YD, Tu GR, Ou DW.

Zhonghua Zhong Liu Za Zhi. 1989 Sep;11(5):338-40. *Immunoregulatory effect of polysaccharide of Acanthopanax senticosus (PAS). I. Immunological mechanism of PAS against cancer].* Xie SS1.

ELEUTHERO DOSAGE & DELIVERY

Traditional medicines include teas, syrups, and powders at a wide variety of dosages depending on whether Eleuthero is a lead or supportive herb in various formulas. Encapsulations and Solid Extracts also available in the modern era.

Treatment Dosage: Modern encapsulations will use 250 to 1000 mg in a single dose that is repeated several times a day.

1:1 to 1:4 Tinctures are dispensed at a dose of ½ to 1 tsp 2 to 4 times daily.

ELEUTHERO SIDE EFFECTS

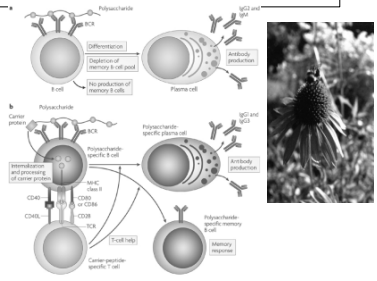
Side effects:
There are no commonly reported side effects.
Human trials have not shown adverse events or significant side effects with the use of 300 mg/day for several months' time.

Arch Gerontol Geriatr Suppl. 2004;(9):69-73. *Effects of Siberian ginseng (Eleutherococcus senticosus maxim.) on elderly quality of life: a randomized clinical trial.* Cicero AF et al.
Arzneimittelforschung. 1987 Oct;37(10):1193-6. *Flow-cytometric studies with eleutherococcus senticosus extract as an immunomodulatory agent*. Bohn B, et al

IMMUNE POLYSACCHARIDES

IMMUNE POLYSACCARHIDES

- **"Immune Polysaccarides" are large molecules known to enhance immune responses.**
- **One mechanism may be via local effects in the gut that triggers immune response via the carbohydrate aspect of the cytoskeleton.**



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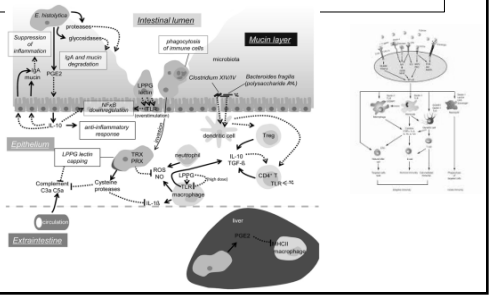
HERBS WITH IMMUNE POLYSACCARHIDES

- **Echinacea**
- **Astragalus**
- **Glycyrrhiza**
- **Ganoderma**
- **Lentinula**
- **Baptisia**
- **Seaweed**
- **Panax ginseng**
- **Aloe vera**



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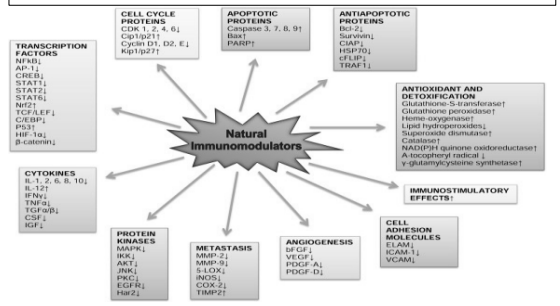
VARIED EFFECTS OF IMMUNE MODULATORS



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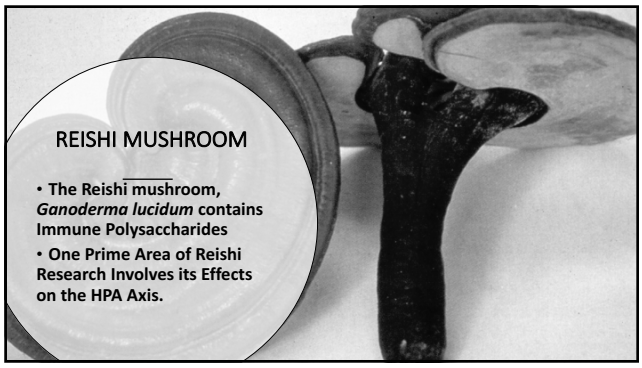
MEDICINAL MUSHROOMS FOR CHRONIC INFECTIONS

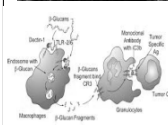
MUSHROOMS CONTAIN IMMUNE POLYSACCHARIDES



BETA GLUCAN

Many medicinal mushrooms may contain beta glucans.

Polyporus umbellatus contains beta glucans shown to be a potent activator of B cells, macrophages and dendritic cells.



The Five Key Immune Responses Targeted By Beta Glucan

1. Production of white blood cells
2. Cellular mobilization
3. Phagocytic capacity
4. Production of reactive oxygen intermediates
5. Help shift from an overstimulated TH2 to a TH1 cell mediated immune response.

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BETA GLUCANS

Shitake mushrooms, *Lentinus edodes* also contains the beta glucan lentinan thought to contribute the immune potentiating properties of this

Immunomodulatory β-Glucan from *Lentinus edodes* Activates Mitogen-activated Protein Kinases and Nuclear Factor-κB in Murine RAW 264.7 Macrophages

BETA GLUCANS

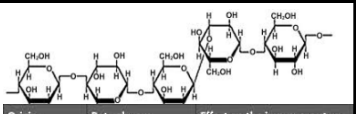
- Glucans are natural occurring plant carbohydrates that stimulate immunity.
- Glucans are taken into cells such as macrophages due to the pattern recognition receptor, Dectin-1.
- Once taken up glucans colocalize with endosomes within minutes, and in the golgi appartus in minutes to hours.
- Clathrins support the uptake of Glucans, and caveolin inhibit uptake.

BETA GLUCANS

Beta glucans contribute greatly to water holding properties in plants and have many anti-cancer and immunomodulating effects, and anti-inflammatory effects on the GI.

Beta glucans may help lower cholesterol.

Beta glucans also occur in brewer's yeast, *Saccharomyces cerevisiae*, contributing to immune-modulating effects.



Origin	Beta glucan	Effect on the immune system
Brewer's yeast (Baker's yeast)	Long 1,3/1,6 branches	★★★★★
Mushroom, fungus, seaweed	Short 1,3/1,6 branches	★★★★
Barley, oat	1,3/1,4 branches	★
Bacteria	1,3 (no branches)	—

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SULFATED POLYSACCARHIDES IN SEAWEEDS

- Seaweeds are some of the richest sources of sulfated polysaccharides.
- Sulfated glycans may interact with cellular polysaccharides in a manner that enhances immune response.

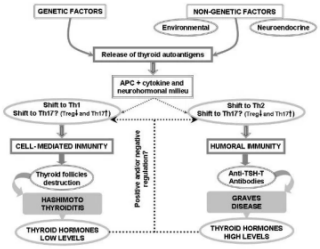
Fucose-Containing Sulfated Polysaccharides from Brown Seaweeds Inhibit Proliferation of Melanoma Cells and Induce Apoptosis by Activation of Caspase-3 in Vitro

THYROID SUPPORT FOR CHRONIC INFECTIOUS ILLNESSES

Thyroid Support for Chronic Infections:

- **Low thyroid increases susceptibility to infections, low body temperature allow opportunistic infections.**
- **High thyroid suppresses WBCs and increases allergic reactivity and infections.**

*** Supporting thyroid function may help those with Lyme dz, intestinal dysbiosis, chronic URIs, and other infections**



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OUR UNDERSTANDING OF THYROID HORMONES IS RAPIDLY EVOLVING

- Recent clinical research is advancing our understanding of thyroid hormone signaling defects and syndromes of hormone resistance.
- Mental retardation, obesity, metabolic disorders, and a number of cancers are affected by thyroid hormones.
- Our new understanding is beginning to be translated into therapeutic strategies for treating hyperlipidemia and obesity, cardiac disease, cancer, and cognitive function

Thyroid Hormone Resistance Syndromes

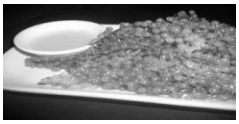
- Two forms of resistance to thyroid hormones are recognized:
  - Generalized resistance to thyroid hormones (GRTH)
    - 75% of reported cases are familial
    - mutations in the thyroid hormone receptor
  - Selective pituitary resistance to thyroid hormones (PRTH)
    - mutations in the thyroid hormone receptor

J Clin Invest. 2012 Sep 4;122(9):3035-43. 2012 Sep 4. *Mechanisms of thyroid hormone action.* Brent, GA

SEAWEED FOR HYPOTHRYOIDISM

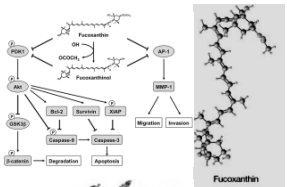
- **Seaweeds are high in numerous highly bioavailable minerals and halides including iodine.**
- **Seaweeds also contain sulfated polysaccharides and Beta Glucans with immune modulating and anti-inflammatory affects.**

Cell Mol Biol 2002 Jul;48(5):563-9. *Bioavailability of seaweed iodine in human beings.*



FUCUS VESICULOSUS - Bladderwrack

Fucus vesiculosus **contains the flavonoid fucoxanthin reported to have the greatest antioxidant activity of all the edible seaweeds tested. This may contribute to stabilizing effects in thyroiditis.**



Bioscience, Biotechnology and Biochemistry, 63(3): 605-607 (1999) *Fucoxanthin as the major antioxidant in Hijikia fusiformis, a common edible seaweed.* Yan, X.J., Y. Chuda, M. Suzuki and T. Nagata

Journal of the science of food and agriculture. 81 (5): 530-534. (2001) *Antioxidant activity of fresh and processed edible seaweeds.* Jimenez-Escrig A., I. Jimenez-Jimenez, R. Pulido and F. Saura-Calixto

KELP FORMS AND DELIVERY

Kelp may be consumed as a food, a tincture, and in encapsulations.

The fishy flavor and gummy texture make kelp less suitable to consume as a tea.

There is no officially approved or standardized dosage, however most herbalists recommend 4-6 grams of the crude dried seaweed to treat metabolic function, which would deliver roughly 400 to 500 micrograms of iodine.

HERBS WITH
ANTIMICROBIAL EFFECTS

HERBAL ANTIMICROBIAL MECHANISMS

Naturally Occurring Molecules can Affect:

- **Viral and bacterial adhesion to cell membranes**
- **Cellular Entry**
- **Mitochondrial Take Over**
- **Golgi Protein Manufacture**
- **And other cellular replication Affects**

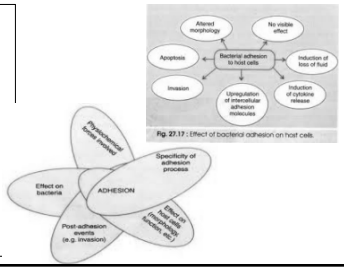


Fig. 27.17 : Effect of bacterial adhesion on host cells.

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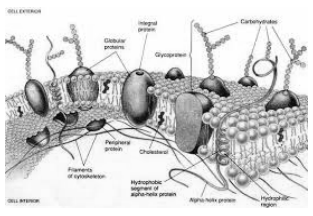
HERBS THAT AFFECT MICROBIAL ATTACHMENT AND CELLULAR DISRUPTION

CELL MEMBRANE, MITOCHONDRIAL, AND REPLICATIONS AFFECTS

Glycoprotein Receptors

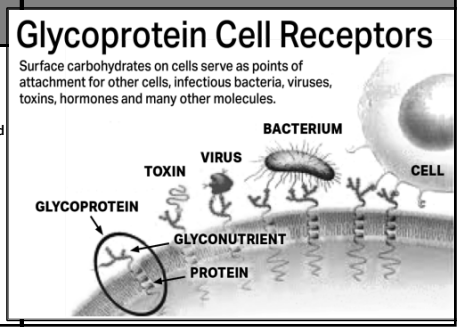
GLYCOPROTEIN RECEPTORS

- **Glycoprotein receptors extend outward from the cell surface like whiskers.**
- **Glycoprotein receptors help direct immune responses, cell adherence, apoptosis, and the ability to discern SELF FROM NON-SELF.**



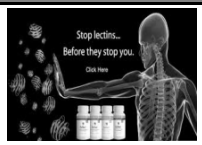
GLYCOPROTEIN RECEPTORS

- **Glycoprotein receptors are comprise of proteoglycans – simple carbohydrates combined with amino acids.**
- **Bacteria and viruses can attach to and enter cells via glycoprotein receptors.**
- **Our immune system can recognize proteoglycan combinations as being foreign.**



LECTINS ARE NOT ALL BAD!

- Many allergenic foods such as soy, nut, and shellfish trigger immune reactions due to the lectins they contain.
- However, many immune supportive and anti-cancer plants, such as *Phytolacca*, *Viscum*, and Castor oil, support immune and white blood cell activities due to the lectins they contain.



Lectin name: Symbol	Source	Specificity
N-acetylglucosamine binding lectins:		
Wheat Germ Agglutinin (WGA)	*Triticum vulgaris*	GlcNAcβ1-4GlcNAcβ1-4GlcNAc, Neu5Ac (sialic acid)
Elderberry lectin (SNA)	*Sambucus nigra*	Neu5Acα2-6Gal/GNAcβ-R
Morelica Anemonin Lectin (MAL)	*Maackia amurensis*	Neu5Ac/Gca2-3Galβ1-4GlcNAcβ1-R
Galactose and N-acetylgalactosamine binding lectins:		
Ricinus communis Agglutinin, ricane, RCA120 (RCA)	*Ricinus communis*	Galβ1-4GlcNAcβ1-R
Peanut Agglutinin (PNA)	*Arachis hypogaea*	Galβ1-3GalNAcα1-Ser/Thr (T-Antigen)
Jacalin (AIL)	*Artocarpus integrifolia*	(Sia)Galβ1-3GalNAcα1-Ser/Thr (T-Antigen)
Hairy vetch lectin (VVL)	*Vicia villosa*	GalNAcα-Ser/Thr (Tn-Antigen)
Mannose binding lectins		
Concanavalin A (ConA)	*Canavalia ensiformis*	Branched α-mannosidic structures; high α-mannose type, hybrid type and biantennary complex type N-Glycans
Lentil lectin (LCH)	*Lens culinaris*	Pentasaccharide core region of bi- and triantennary complex type N-glycans
Snowdrop lectin (GNA)	*Galanthus nivalis*	α-1-3 and α 1-6 linked high mannose structures
Fucose binding lectins:		
Ulex europaeus agglutinin (UEA)	*Ulex europaeus*	Fucα1-2Galβ-R
Aleuria Aurantia Lectin (AAL)	*Aleuria aurantia*	Fucα1-2Galβ1-4(Fucα1-3/4)Galβ1-4GlcNAc, R2-GlcNAcβ1-4

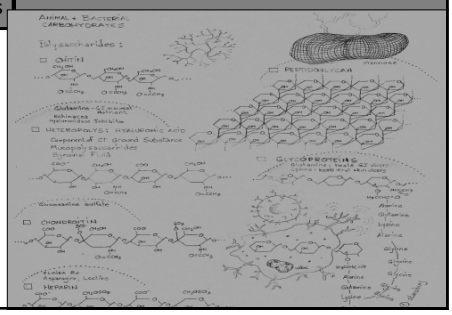
GLYCOPROTEINS AND CARBOHYDRATE CHAINS

BACTERIAL CARBOHYDRATE
- Peptidoglycan

INSECTOID CARBOHYDRATE
- Chitin

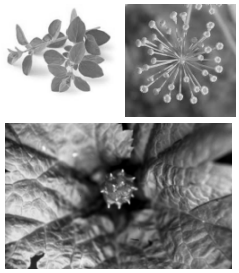
CRUSTACEAN GLYCOPROTEIN
- Glucosamine

MAMMALIAN GLYCOPROTEIN
- Chondroitin
- Mucopolysaccarhides
- Lectin
- Heparin



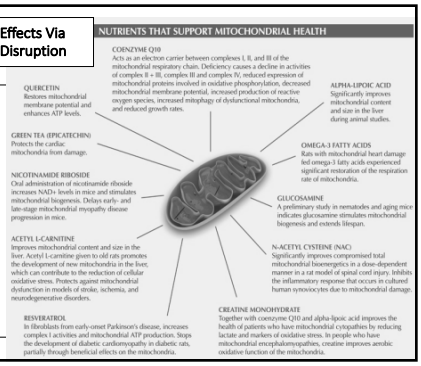
Herbs with Anti-Microbial Effects Via Mitochondrial Membrane Disruption

- Many essential oils disrupt fungal and bacterial mitochondrial membranes, including Oregano, Fennel, Tea Tree and others.
- Some antimicrobial plants lyse bacteria by inhibiting mitochondrial efflux-pumps.
- ***Hydrastis canadensis*** acts in this manner along with other antimicrobial mechanisms.



Herbs with Anti-Microbial Effects Via Mitochondrial Membrane Disruption

- ***Mahonia/Berberis***
- ***Azadirhata*** (Neem)
- ***Tricosanthes***
- ***Achillea*** (Yarrow)
- ***Coptis*** (Gold Thread)



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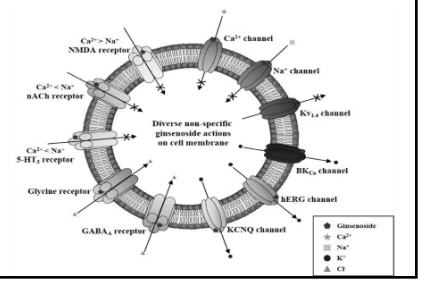
Mitochondrial Membrane Toxins

Sanguinarine from *Sanguinaria canadensis* affects external mitochondrial membranes and interferes with the negative charges usually held, and inhibits oxidative phosphorylation and ATP synthesis

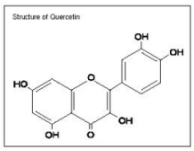
Herbs with Immune Modulating Effects Via Cell Membrane Activity

Ginsenosides may induce apoptosis of cancer cells via altering mitochondrial membrane potentials in cancer cells.



FATTY ACID SYNTHESIS DISRUPTORS

- **Fatty acid synthase is involved in cell membrane synthesis and fungal growth and agents that inhibit FAS may have antifungal effects by disrupting the fungal cell membranes.**
- **Quercetin, trans-chalcone, ellagic acid, luteolin, galangin, and genistein may all inhibit fatty acid synthase.**

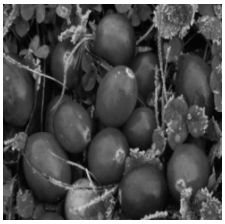


BACTERIAL ADHERENCE DISRUPTORS
An Apple a Day

Phloretin, an antioxidant flavonoid found abundantly in apples is reported to deter E coli from forming a biofilm in the gut.

E COLI ADHESION

- ***Vaccinium*** **species deter bacteria via inhibiting their adherence to cells and inhibiting bacterial enzymes.**

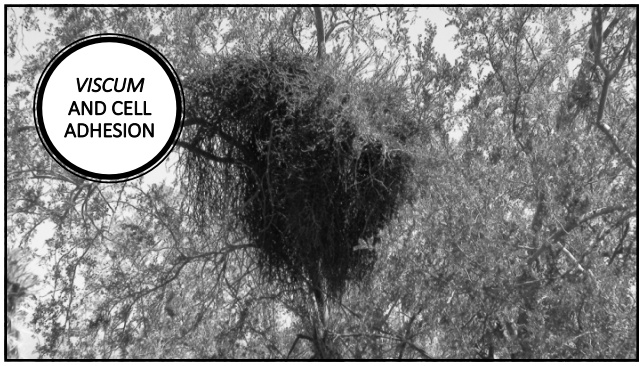


BETA GLUCANS AND FUNGAL CELL MEMBRANES

β-glucans are a particular group of cell wall carbohydrates occurring in some mushrooms, seaweeds cereals grains including barley and oats.

All β-glucans are glucose polymers but have slightly differing molecular structures depending on the source.

β-glucans have immunomodulatory and anticancer properties via binding to lectins on human cells.



VISCUM AND CANCER

Viscum **affects cell to cell adhesion and can induce apoptosis in cancer cells.**

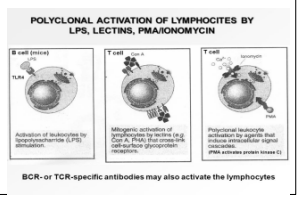
Lectins are credited with cell adhesion effects.

H1N1 AND FLU VIRUS ADHERENCE

- ***Sambucus*** **berries limit the ability of respiratory and influenza viruses to enter cells.**
- **Elderberry syrup is a classic cold and flu remedy.**

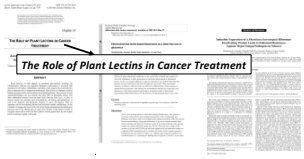
PHYTOLACCA SPECIES

- **Lectins in** ***Phytolacca*** **can affect cell to cell adhesion, communication and white blood cell activity.**

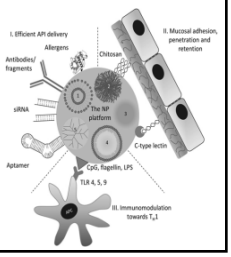


PHYTOLACCA

- ***Phytolacca*** **lectins have historically been used topically on the breast and cystic masses, suggesting an ability to penetrate the skin or otherwise affect underlying lymphatic, cancer and fluid flow.**



RICINIS CASTORIS TOPICALLY FOR IMMUNE-MODULATING EFFECTS



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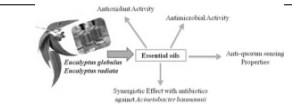
ESSENTIAL OILS FOR ACUTE & CHRONIC INFECTIONS

ESSENTIAL OILS AS ANTI-MICROBIAL AGENTS

All essential oils are anti-microbial with Tea Tree, Oregano and Lavender essential oils being popular in natural products.

Individual aromatic molecules such as carvacrol, thymol, and cinnamaldehydes have been shown to disintegrate the outer membranes of bacterial cell walls and reduce ATP resources intracellularly.



ESSENTIAL OILS AS ANTI-MICROBIAL AGENTS

Eugenol, an aromatic component of clove oil has antifungal activity via inhibition of fungal wall proteins necessary to transport amino acids through fungal membranes.

RESEARCH ON THE ANTIMICROBIAL EFFECTS OF ESSENTIAL OIL

Research Titles:

- *Antimicrobial Activity of Essential Oil extract of Ocimum basilicum L. Leaves on a Variety of Pathogenic Bacteria*
- *Antimicrobial Activity of Essential Oils Against Helicobacter pylori*
- *Antimicrobial Effect of Some Essential Oils*

RESEARCH ON THE ANTIMICROBIAL EFFECTS OF ESSENTIAL OIL

Research Titles:

- *Antimicrobial activity of essential oils extracted from medicinal plants against the pathogenic microorganisms*
- *Chemical composition and antimicrobial activity of Eucalyptus camaldulensis Dehnh essential oil from Malaysia*
- *Composition and antimicrobial activity of essential oils of Artemisia Judaica, A Herba-alba and A. Arboescens from Libya*

Table 3 - (Table 2 continued). Antimicrobial activity of the evaluated essential oils against food-related microorganisms, as detected in the agar disc-diffusion test (mm) [a].

	Mint	Pennyroyal	Orange [b]	Oregano	Rosemary	Ampicilin	Chlor. [c]
S.aureus	25.1 ± 1.4 ^{de}	16.0 ± 0.4 ^{i}	21.5 ± 1.1 ^{f}	22.9 ± 1.0 ^{ef}	28.2 ± 0.9 ^{c}	36.4 ± 1.8 ^{b}	26.1 ± 0.5 ^{cd}
E.faecalis	14.1 ± 0.5 ^{f}	13.7 ± 0.6 ^{f}	17.1 ± 0.5 ^{d}	16.0 ± 0.7 ^{de}	14.9 ± 0.7 ^{ef}	27.0 ± 0.4 ^{a}	23.6 ± 0.2 ^{b}
L.monocytogenes	15.4 ± 1.3 ^{f}	13.9 ± 0.6 ^{fg}	21.2 ± 2.7 ^{a}	25.4 ± 1.3 ^{d}	26.5 ± 1.4 ^{cd}	31.1 ± 0.9 ^{b}	28.4 ± 1.0 ^{bc}
L.plantarum	19.6 ± 0.9 ^{ef}	24.0 ± 2.3 ^{cd}	14.1 ± 0.6 ^{hi}	17.4 ± 1.1 ^{fg}	12.1 ± 0.5 ^{i}	32.0 ± 0.9 ^{a}	29.2 ± 1.0 ^{ab}
B.cereus	21.4 ± 1.7 ^{d}	17.1 ± 0.2 ^{g}	33.1 ± 1.2 b	26.2 ± 0.6 ^{c}	26.4 ± 0.5 ^{c}	12.1 ± 0.2 ^{g}	27.9 ± 0.7 ^{c}
B.subtilis	21.1 ± 0.8 ^{g}	17.7 ± 0.9 ^{fg}	85.0 ± 0.0 ^{a}	18.0 ± 1.7 ^{efg}	36.0 ± 0.6 ^{c}	31.1 ± 1.8 ^{d}	29.9 ± 0.5 ^{d}
Y.enterocolitica	24.7 ± 1.8 ^{d}	0.0 ± 0.0 ^{h}	26.7 ± 1.5 ^{cd}	18.9 ± 1.2 ^{f}	16.7 ± 0.5 ^{f}	21.7 ± 0.5 ^{e}	28.1 ± 0.5 ^{bc}
E.coli	0.0 ± 0.0 ^{h}	0.0 ± 0.0 ^{h}	0.0 ± 0.0 ^{h}	14.5 ± 0.4 ^{f}	12.2 ± 0.3 ^{g}	18.9 ± 0.5 ^{d}	26.1 ± 0.6 ^{a}
S.Typhimurium	0.0 ± 0.0 ^{f}	0.0 ± 0.0 ^{f}	0.0 ± 0.0 ^{f}	12.0 ± 0.8 ^{d}	10.5 ± 0.0 ^{e}	27.1 ± 0.5 ^{a}	24.4 ± 0.5 ^{b}
E.aerogenes	0.0 ± 0.0 ^{d}	0.0 ± 0.0 ^{d}	0.0 ± 0.0 ^{d}	11.4 ± 0.5 ^{c}	10.2 ± 0.3 ^{c}	0.0 ± 0.0 ^{d}	23.0 ± 0.7 ^{a}
P.vulgaris	41.5 ± 2.1 ^{a}	0.0 ± 0.0 ^{h}	27.7 ± 3.0 ^{c}	23.7 ± 0.6 ^{d}	14.9 ± 2.3 ^{g}	21.1 ± 1.0 ^{de}	22.4 ± 0.8 ^{de}
P.aeruginosa	0.0 ± 0.0 ^{c}	0.0 ± 0.0 ^{c}	0.0 ± 0.0 ^{c}	12.7 ± 0.5 ^{b}	0.0 ± 0.0 ^{c}	0.0 ± 0.0 ^{c}	0.0 ± 0.0 ^{c}

[a] Inhibition area including 9mm disc diameter, expressed as the mean of four replicates ± SD. Inhibition degrees: 10 -13,9mm: weak; 14-18mm: moderate; >18mm: strong. Means followed by the same letter in the same row are not significantly different (P<0.05).
[b] Orange oil were obtained from the plant leaves.
[c] Chloramphenicol.

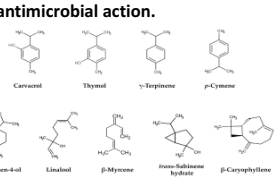
ANTIMICROBIAL EFFECTS OF OREGANO OIL

Table 2 - *In vitro* antimicrobial activities of oregano essential oil on some microorganisms

Microorganism	Minimum inhibitory concentration	Minimum lethal concentration
Escherichia coli	0.5 mg/mL	-[1]
Salmonella typhimurium	0.5 mg/mL	0.5 mg/mL
Shigella dysenteriae	0.5 mg/mL	1.0 mg/mL
Clostridium perfringens	0.5 mg/mL	0.5 mg/mL
Staphylococcus aureus	0.5 mg/mL	2.5 mg/mL
Bacilus cereus	0.5 mg/mL	-[1]

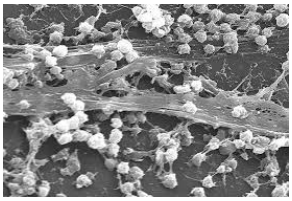
[1] Not determined.

- **Oregano Oil contains Borneol, Thymol, and Carvacrol, among other individual essential oils, each having potent antimicrobial action.**



Research Titles:

- *Effect of Oregano Essential Oil on Biofilms Formed by Staphylococci and E. coli*
- *Effects of Oregano, Carvacrol, and Thymol on S. aureus and S. epidermis Biofilms*



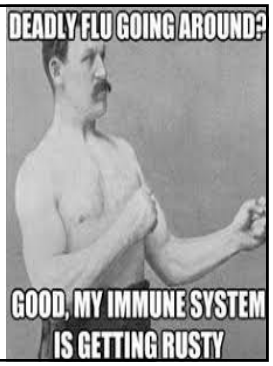
OREGANO OIL CAN PENETRATE AND CLEAR BIOFILMS

OREGANO OIL IS SAFE TO CONSUME ORALLY

- **Thymol, Eugenol, Carvacol are on the FDA's GRAS list**
- **Oral capsules are useful for intestinal infections.**
- **Steam inhalations are useful for respiratory infection.**
- **Topical salve and washes are useful for skin infections.**

SUMMARY OF AVOIDING ANTIBIOTICS AND BUILDING IMMUNE RESISTANCE

- **Address Lifestyle factors**
- **Optimize Nutrition**
- **Get Adequate Sleep**
- **Offer Adapogens Where Needed**
- **Offer Thyroid Suport Where Needed**
- **Offer Specific Antimicrobial Herbs to Treat Acute Situations**
- **Offer Deep Immune Support to Resolve Chronic Infections**



THANK YOU!!!

Identifying and Resolving The Lyme Paradox

Darin Ingels, ND, FAAEM

AARM
Association for the Advancement of Restorative Medicine

Lyme Disease: What Is It?

Lyme disease is a bacterial infection of *Borrelia burgdorferi* and other species, a bacteria transmitted through the bite of a tick (*Ixodes species*). However, new evidence suggests other biting insects may transmit LD as well.

In the early 1970's, mysterious cases of rheumatoid arthritis developed in several children in Lyme, CT. Many of the children recalled having a rash and/or being bit by a tick.

In 1981, Dr. Willy Burgdorfer who had been studying Rocky Mountain Spotted Fever discovered the spirochete that caused the illness in these children.

Lyme Disease: What Is It?

There at at least 5 subspecies of *Borrelia burgdorferi* and at least 100 other strains of *Borrelia* in the United States. There are more than 300 strains worldwide.

More than 95% of reported cases in the United States come from Connecticut, Delaware, Maine, Maryland, Massachusetts, Minnesota, New Hampshire, New Jersey, New York, Pennsylvania, Rhode Island, Vermont, Virginia and Wisconsin.

There are at least 300,000 new cases of Lyme disease reported each year in the United States with now millions of people living with Lyme disease annually.

Lyme Disease: Canadian Stats

In Canada, there have been less than 1000 cases of Lyme disease reported in 2016 (987).

However, there has been more than 6-fold increase in Lyme cases since 2009.

In 2015, 91% of all cases were reported from Ontario, Nova Scotia and Quebec, with Nova Scotia having the most cases (26 per 100,000).

As in the US, the incidence of Lyme is growing rapidly and likely grossly underreported. In Ontario, Public Health officials state Lyme is only caused by *Borrelia burgdorferi*, but research has proven this to be untrue.

Lyme Disease: What Is It?

Ixodes scapularis and pacficius (Blacklegged ticks)

Lyme Disease: What Is It?

Lyme disease is the #1 spreading vector-borne epidemic worldwide.

Borrelia species can infect any tissue or organ system. Therefore, multiple symptoms are observed with patients with LD.

Borrelia species may also change forms and have a relatively slow replication cycle. Most bacteria replicate every 20 minutes to 8 hours. *Borrelia* replicate every 1 to 16 days.

Borrelia species are the ultimate shape-shifters. They can exist as a spirochete (corkscrew form), cyst form, cell-wall deficient form and uncoiled filamentous form.

What Are The Symptoms Of Acute Lyme Disease?

- Headaches and neck stiffness
- Fever
- Arthritis with swollen joints and/or spine pain
- Muscle pain
- Erythema migrans ("bullseye" rash)
- Fatigue
- Chills
- Swollen lymph nodes
- Heart palpitation
- Shortness of breath
- Memory loss
- Facial palsy (Bell's palsy)

What Are The Symptoms Of Acute Lyme Disease?

Erythema migrans rash

What Are The Symptoms Of Acute Lyme Disease?

Acute symptoms can occur anywhere from 3-30 days following a tick bite.

CDC states up to 70% of people infected with Lyme disease get the erythema migrans (EM) rash, but others suggest less than 40% of infected people get the stereotypical EM rash. The EM rash is pathognomonic for LD, which means there is no other organism that causes this type of rash. ***Most people with LD have no recollection of ever being bitten by a tick!***

Lyme disease symptoms are often vague and resemble numerous other infectious disease and autoimmune conditions. Misdiagnosis is common.

What Are The Symptoms Of Chronic Lyme Disease?

- Fatigue
- Abdominal pain and bowel changes
- Memory loss or cognitive impairment
- Numbness or tingling of extremities
- Sensory distortion of skin (burning sensations), especially in hands or feet
- "wandering" symptoms
- Light or sound sensitivity
- Dizziness or vertigo
- Sleep disturbances
- Rheumatism
- Cardiac problems: MVP, heart block, heart palpitations, chest pain
- Balance or coordination problems. Become "clumsy"
- Newly acquired "dyslexia"
- Endocrine disruption: hypothyroidism, irregular menses, etc.

Lyme Disease: The Great Imitator

- Autism
- Multiple Sclerosis
- ALS (Lou Gehrig's disease)
- Chronic fatigue syndrome
- Fibromyalgia
- Infectious mononucleosis
- Polymyalgia rheumatica
- Reiter's syndrome
- Rheumatoid arthritis
- Lupus
- Parkinson's disease
- Alzheimer's disease
- many, many more…

Coinfections with Lyme Disease

Ticks and can spread numerous other infections, which cause similar symptoms of LD.

1. Babesia
2. Bartonella
3. Anaplasma
4. Ehrlichia
5. Mycoplasma
6. Rickettsia
7. Powassan virus
8. Colorado Tick Fever
9. Heartland virus
10. Tularemia
11. Many others…

Why The Rise in Lyme Disease?

Worldwide, we are seeing an increase the in the number of cases of LD as well as other vector-borne illnesses.

We have already seen epidemics of Dengue virus in South America, Ebola virus in Western Africa and Chikungunya virus in Central and South America (now spreading to North America).

Ticks, fleas, mosquitos, flies and even snails can transmit these illnesses.

The World Health Organization (WHO) anticipates that climate change will result in an increased incidence of vector-borne diseases.

Why The Rise in Lyme Disease? According to the WHO…

Climate change and vectorborne diseases

Many vulnerability assessments anticipate climate change will result in increased incidence of communicable diseases including vectorborne diseases (VBDs). VBDs are transmitted by the bites of infected mosquitoes and other insects (vectors). Their incidence is particularly dependent on climatic factors because:

- Insects have no internal control over their physiological temperatures and the ambient temperature determines their reproduction rate, biting behavior and survival: their distribution may expand as the earth warms.
- Humidity and availability of water for breeding are also determinants of vectors' distribution, longevity and behavior.
- The incubation period of pathogens inside vectors is temperature-dependent (and tends to decrease at warmer temperatures).
- Human behavior is likely to be affected by climate change which will alter our interaction with vectors and the diseases they carry.

http://www.wpro.who.int/mvp/climate_change/en/

Why The Rise in Lyme Disease?

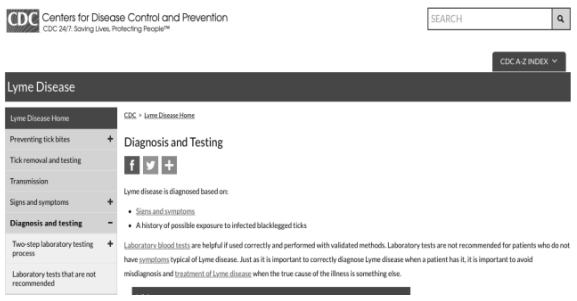
Diagnosis of Lyme Disease

The CDC criteria for LD was designed for surveillance purposes and do not necessarily reflect active infection with *Borrelia species.*

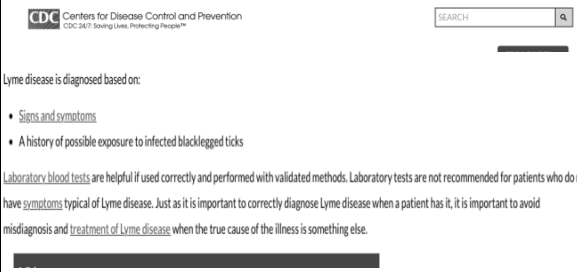
The diagnosis of LD is a **CLINICAL DIAGNOSIS**!

There are over 100 strains of *Borrelia* in North America and more than 300 strains worldwide. Current testing only tests for *Borrelia burgdorferi.* We now know that half of West Coast cases of Lyme disease are caused by *Borrelia miyomotoi.*

Diagnosis of Lyme Disease



Diagnosis of Lyme Disease



Diagnosis of Lyme Disease

CDC Criteria

1. Positive ELISA blood test. This is the screening test most doctors use through reference labs.
2. If the ELISA test is positive, they will then run a Lyme Western Blot, which is a more detailed antibody test looking at specific antibodies (called "bands") associated with the organism. They will look at IgG and IgM antibodies.
3. If 5 out of 10 IgG bands are positive or 2 out of 3 IgM bands are positive, the test is considered "positive".

These criteria have not changed in more than 40 years of research on LD.

Diagnosis of Lyme Disease

CDC Criteria:

IgM: 23 kd (OspC), 39 kd (BmpA), 41 kd (Fla)

* *must have 2 of 3 bands*

IgG: 18 kd, 21 kd (OspC), 28 kd, 30 kd, 39 kd (BmpA), 41kd (Fla), 45 kd, 58 kd, 66 kd, 93 kd

* *must have 5 of 10 bands*

Diagnosis of Lyme Disease

Alternative Criteria:

IgM: 23-25 (OspC), 31, 34, 39 (BmpA), 41 or 93 kd bands.

*Equivocal: *one band positive*

*Positive: *2 or more bands positive*

IgG: 23-25 (OspC), 31, 34, 39 (BmpA), 41or 93 kd bands.

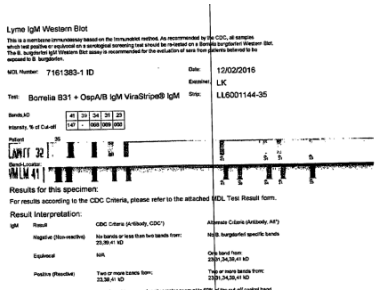
*Equivocal: *1 or 2 bands positive*

*Positive: *3 or more bands positive*

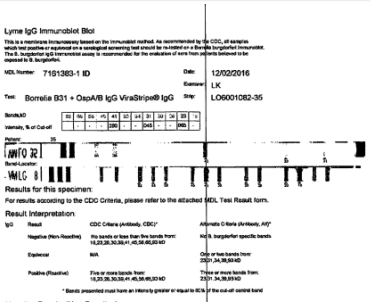
Diagnosis of Lyme Disease

Test	Specimen	Date Collected / Comment	Results: Normal	Results: Abnormal	Reference/Units/Comments
Lyme disease Western blot (IgM / IgG)		11/29/2016	IgGCDC Neg IgGAlt Equiv	IgMCDC Pos IgMAlt Pos	IgM: 41, 34, 31, 23 IgG: 41, 23 See attached report.
313 Verified 12/3/2016	Serum - 1				
Bartonella henselae IgG/IgM by ELISA		11/29/2016	IgM Neg (Index=0.32) IgG Neg (Index=0.49)		* IgM Index range: Neg: <= 0.89, Equivocal: 0.90 - 1.10, Pos: >= 1.11 * IgG Index range: Neg: <= 0.89, Equivocal: 0.90 - 1.10, Pos: >= 1.11
355 Verified 12/6/2016	Serum - 1				
Babesia microti IgG/IgM by ELISA		11/29/2016	IgM Neg (Index=0.02) IgG Neg (Index=0.31)		* IgM Index range: Neg: <= 0.89, Equivocal: 0.90 - 1.10, Pos: >= 1.11 * IgG Index range: Neg: <= 0.89, Equivocal: 0.90 - 1.10, Pos: >= 1.11
433 Verified 12/6/2016	Serum - 1				
Anaplasma phagocytophilum IgG/IgM by IFA		11/29/2016		Positive	Anaplasma IgG antibody detected (>=1:80).
439 Verified 12/5/2016	Serum - 1				

Diagnosis of Lyme Disease



Diagnosis of Lyme Disease



Diagnosis of Lyme Disease

Test	Specimen	Date Collected / Comment	Results: Normal	Results: Abnormal	Reference/Units/Comment
Lyme disease Western blot (IgM / IgG)		3/30/2016	IgM:CDC Neg IgM:Alt Neg IgG:CDC Neg IgG:Alt Equiv		IgM: No bands present. IgG: 93/83, 41, 34 See attached report.
313 Verified 4/2/2016	Serum - f				
Chlamydia pneumoniae IgG / IgM by ELISA		3/30/2016	IgM Neg (Index=0.03) IgG Neg (Index=0.37)		* IgM Index range: Neg: <= 0.89, Equivocal: 0.90 - 1.10, Pos: >=1.11 * IgG Index range: Neg: <= 0.89, Equivocal: 0.90 - 1.10, Pos: >=1.11
327 Verified 3/31/2016	Serum - f				
Mycoplasma pneumoniae IgG / IgM by ELISA		3/30/2016		IgM Pos (Index=1.53) IgG Pos (Index=4.69)	* IgM Index range: Neg: <= 0.89, Equivocal: 0.91 - 1.09, Pos: >= 1.10 * IgG Index range: Neg: <= 0.90, Equivocal: 0.91 - 1.09, Pos: >= 1.10
340 Verified 4/5/2016	Serum - f				
Bartonella henselae IgG/IgM by ELISA		3/30/2016	IgM Neg (Index=0.05)	IgG Pos (Index=1.47)	* IgM Index range: Neg: <= 0.89, Equivocal: 0.90 - 1.10, Pos: >=1.11 * IgG Index range: Neg: <= 0.89, Equivocal: 0.90 - 1.10, Pos: >=1.11
355 Verified 4/1/2016	Serum - f				
Lyme disease C6 Peptide by ELISA		3/30/2016	Neg (Index=0.33)		* Index range: Neg: <= 0.90, Equivocal: 0.91 - 1.09, Pos: >=1.10
417 Verified 4/1/2016	Serum - f				
Lyme disease IgG / IgM by ELISA		3/30/2016	Neg (Index=0.56)		* Index range: Neg: <= 0.90, Equivocal: 0.91 - 1.09, Pos: >=1.10
427 Verified 4/4/2016	Serum - f				
Babesia microti IgG/IgM by ELISA		3/30/2016	IgM Neg (Index=0.00)	IgG Pos (Index=1.11)	* IgM Index range: Neg: <= 0.89, Equivocal: 0.90 - 1.10, Pos: >=1.11 * IgG Index range: Neg: <= 0.89, Equivocal: 0.90 - 1.10, Pos: >=1.11
433 Verified 4/6/2016	Serum - f				

Diagnosis of Lyme Disease

Lyme IgM Western Blot

This is a membrane immunoassay based on the immunoblot method. As recommended by the CDC, all samples which test positive or equivocal on a serological screening test should be re-tested on a Borrelia burgdorferi Western Blot. The B. burgdorferi IgM Western Blot assay is recommended for the evaluation of sera from patients believed to be exposed to B. burgdorferi.

MDL Number: 6627981-1 ID — Date: 04/01/2016

Examiner: LK

Test: Borrelia B31 + OspA/B IgM ViraStripe® IgM — Strip: LL5003068-15

Bands,kD	41	39	34	24	23
Intensity, % of Cut-off	066	-	-	-	-

Patient: 15

Band-Locator:

Results for this specimen:

For results according to the CDC Criteria, please refer to the attached MDL Test Result form.

Result interpretation:

IgM Result	CDC Criteria (Antibody, CDC*)	Alternate Criteria (Antibody, Alt*)
Negative (Non-reactive)	No bands or less than two bands from: 23,39,41 kD	No B. burgdorferi specific bands
Equivocal	N/A	One band from: 23,31,34,39,41 kD
Positive (Reactive)	Two or more bands from: 23,39,41 kD	Two or more bands from: 23,31,34,39,41 kD

Diagnosis of Lyme Disease

Lyme IgG Immunoblot Blot

This is a membrane immunoassay based on the immunoblot method. As recommended by the CDC, all samples which test positive or equivocal on a serological screening test should be re-tested on a Borrelia burgdorferi Immunoblot The B. burgdorferi IgG immunoblot assay is recommended for the evaluation of sera from patients believed to be exposed to B. burgdorferi.

MDL Number: 6627981-1 ID — Date: 04/01/2016

Examiner: LK

Test: Borrelia B31 + OspA/B IgG ViraStripe® IgG — Strip: LO6004077-15

Bands,kD	93	66	58	45	41	39	34	31	30	28	23	19
Intensity, % of Cut-off	072	059	036	-	264	036	072	-	-	-	-	-

Patient: 15

Band-Locator:

Results for this specimen:

For results according to the CDC Criteria, please refer to the attached MDL Test Result form.

Result interpretation:

IgG Result	CDC Criteria (Antibody, CDC)*	Alternate Criteria (Antibody, Alt)*
Negative (Non-Reactive)	No bands or less than five bands from: 18,23,28,30,39,41,45,58,66,93 kD	No B. burgdorferi specific bands
Equivocal	N/A	One or two bands from: 23,31,34,39,93 kD
Positive (Reactive)	Five or more bands from: 18,23,28,30,39,41,45,58,66,93 kD	Three or more bands from: 23,31,34,39,93 kD

Diagnosis of Lyme Disease

CDC Criteria: The Pitfalls

1. Many patients with LD are seronegative, which means they do not produce antibodies to the *Borrelia* organism.
2. For a band to be considered positive, the patient antibody must be at least 60% of the control, which mean people who do make a lot of antibody will be considered negative.
3. Most conventional reference labs do not test for the breadth of antibodies associated with LD, so will miss patients who have Lyme-specific antibodies. If you don't look, you won't find it.
4. It can take up to 6 weeks to produce antibodies once someone has been bitten by a tick, so no reliable testing for acute cases.

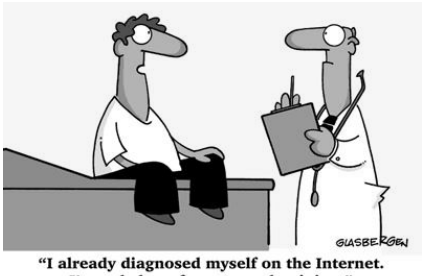
Diagnosis of Lyme Disease

The International Lyme and Associated Disease Society (ILADS) have established a different set of criteria for diagnosing LD and coinfections.

ILADS doctors often diagnose patients based on their clinical symptoms in conjunction with lab tests that shows that someone has had exposure to a particular organism(s).

Other inflammatory and autoimmune illnesses must be ruled out as well, since LD mimics many other conditions.

Diagnosis of Lyme Disease



"I already diagnosed myself on the Internet. I'm only here for a second opinion."

Diagnosis of Lyme Disease

Other Labs To Run

1. Coinfections: Bartonella, Babesia, Anaplasma, Ehrlichia, Mycoplasma, Rickettsia, Chlamydia pneumoniae, Strep
2. TFT's: TSH, free T3, free T4, thyroid antibodies
3. Adrenal function: AM cortisol, DHEA-S, aldosterone (if suspect POTS)
4. CBC with diff.
5. Iron panel: ferritin, serum iron, TIBC
6. Comprehensive Metabolic Panel
7. Immune markers: IgG/IgA/IgM, IgG subclasses, T and B cell quant., C4a, TGF-β (some of this is limited in Canada for ND's, but can refer to MD)
8. Inflammatory markers: CRP, ESR, cytokines
9. Nutritional status: vitamin D (25-OH), RBC Minerals, Amino acids

Treatment of Lyme Disease

CDC Recommendations: Based on IDSA Guidelines (2006)

1. Known deer tick bite: treat prophylactically with single dose of 200 mg of doxycycline for adults or children > 8 years old.
2. If someone is symptomatic, has erythema migrans or has a positive blood test for LD, treat with 14-21 days of doxycycline 100 mg 2 times a day for adults and children older than 8 years old and 500 mg 3 times per day of amoxicillin for children under 8 years old or pregnant women.
3. Cefuroxime (Ceftin™) 500 mg 2 times a day may be used for those allergic to amoxicillin.
4. Lyme meningitis: add IV ceftriaxone (Rocephin™) or IV cefotaxime.

Treatment of Lyme Disease

Antimicrobial Therapy: The Good, The Bad and The Ugly

The Good

- Many patients experience clinical benefit from these treatments are are symptomatically improved.
- Patients who have suffered for many years with LD or have been disabled start to function again.
- Even if a patient had been exposed to a tick many years prior, often these treatment regimens help.

Treatment of Lyme Disease

Antimicrobial Therapy: The Good, The Bad and The Ugly

The Bad

- Many patients also experience die-off reactions called Herxheimer reactions (aka "herxing"). These are flu-like symptoms that occur as the organism is being killed and can last days to weeks in some individuals.
- Combinations of antimicrobials can have undesired side effects, including nausea, loss of appetite, diarrhea, abdominal pain, headaches.
- Long-term antimicrobial use can cause liver or other organ damage, so blood count, liver and kidney function need to be monitored closely.

Treatment of Lyme Disease

Antimicrobial Therapy: The Good, The Bad and The Ugly

The Ugly

- Combination antimicrobials can wipe out your normal bacterial flora in the gut, causing *Clostridia difficile* or yeast infections, which then need to be treated with other stronger antimicrobials or antifungals.
- Some antimicrobials suppress your own immune system, making it more difficult for you to fight your own infections.
- We don't fully understand the consequences of long-term antibiotic use in LD and how it disrupts the normal gut microbiome.

Treatment of Lyme Disease

Diet for Lyme Disease

There are many diets out there that promote various health benefits. I find most people with Lyme disease do well when they consume an alkaline diet.

pH is tightly regulated by the body. Blood pH is between 7.2-7.4. With exception to the stomach, bladder and vagina, most of our tissues are alkaline. Our cells and receptors function best at an alkaline pH.

Diet for Lyme Disease

Foods that can be consumed often:

Vegetables (eat all you want):
- *Artichokes*
- *Asparagus*
- *Beets and beet greens*
- *Broccoli*
- *Brussels sprouts*
- *Cabbage*
- *Carrots*
- *Cauliflower*
- *Celery*
- *Chard*
- *Collard greens*
- *Cucumbers*
- *Endives*
- *Garlic*
- *Green beans*
- *Jerusalem artichokes (Sunchokes)*
- *Lettuces*
- *Mustard greens*
- *Okra*
- *Onions*
- *Parsley*
- *Parsnips*
- *Peas*
- *Rutabaga*
- *Seaweeds (Nori, Dulse, etc.)*
- *Scallions*
- *Spinach*
- *Sprouted grains*
- *Sprouts*
- *Tomatoes (raw only)*
- *Turnips*
- *Zucchini*

Vegetables (eat no more than 1 serving a day):
- *Sweet potato*
- *Squash*
- *Yams*

Fruits:
- *Avocado*
- *Grapefruit*
- *Lemon-Lime*
- *Pomegranates*
- *Watermelon*

Diet for Lyme Disease

Grains/Legumes:
- ***Amaranth***
- ***Buckwheat***
- ***Chia***
- ***Kamut***
- ***Lentils***
- ***Lima beans***
- ***Millet***
- ***Mung beans***
- ***Navy beans***
- ***Pinto beans***
- ***Red beans***
- ***Quinoa***
- ***Spelt***
- ***White beans***

Nuts/Seeds:
- ***Almonds***
- ***Brazil nuts***
- ***Coconut***
- ***Flax seeds***
- ***Pumpkin seeds***
- ***Sesame seeds***
- ***Sunflower seeds***

Oils:
- ***Avocado oil***
- ***Coconut oil***
- ***Flax oil***
- ***Olive oil***
- ***Safflower oil***

Beverages:
- ***Alkaline water***
- ***Herbal teas***
- ***Green drinks***
- ***Water***

Diet for Lyme Disease

Foods that may be eaten in less than 20% of your weekly dietary intake: (neutral pH or slightly acid-forming)

Fruits:
- *Apples*
- *Apricots*
- *Berries*
- *Cantaloupe*
- *Cherries*
- *Grapes*
- *Honeydew melon*
- *Mango*
- *Nectarines*
- *Oranges*
- *Peaches*
- *Papaya*
- *Pineapple*
- *Plums*

Nuts/Seeds:
- *Pecans*
- *Hazel nuts*

Grains/Legumes:
- *Brown rice*
- *White rice*
- *Oats*
- *Rye*
- *Hemp*
- *Soy (organic only)*

Oils:
- *Sunflower oil*
- *Grapeseed oil*

Meat, Fish, Eggs:
- *Beef*
- *Chicken*
- *Eggs*
- *Farmed-raised fish*
- *Pork*
- *Shellfish*
- *Turkey*

Fish (wild only):
- *Mackerel*
- *Perch*
- *Pike*
- *Roughy*
- *Salmon*
- *Sardines*
- *Sole, Tilapia*

Diet for Lyme Disease

Foods to avoid while on the program:

Dairy Products:
- *Cheese*
- *Ice cream*
- *Milk*
- *Sour cream*
- *Yogurt*

Fruits:
- *Dried fruits*

Nuts/Seeds:
- *Macadamia nuts*
- *Peanuts*
- *Pistachios*

Beverages:
- *Alcohol*
- *Black tea*
- *Coffee*
- *Fruit juice*

Refined, Processed and Simple carbohydrate Foods:
- *All additives*
- *Artificial dyes, flavorings and sweeteners*
- *Candy, cookies, doughnuts, crackers*
- *Canned foods (they tend to contain lots of preservatives and chemicals)*
- *Chocolate/Cocoa*
- *Corn and all corn products (corn syrup, corn starch, etc.)*
- *Chips*
- *Margarine*
- *Preservatives (Sulfites,Nitrites, etc.)*
- *Sugar*
- *Yeast*

Condiments:
- *Honey*
- *Jam*
- *Jelly*
- *Mustard*
- *Soy sauce*
- *Vinegar*

Oils:
- *Corn oil*
- *Cottonseed oil*
- *Soybean oil*
- *Vegetable oil*
- *All hydrogenated oils and trans fats*

Treatment of Lyme Disease

<u>Cowden Protocol</u>: developed by Dr. Lee Cowden

1. Amantilla
2. Banderol
3. Burbur
4. Cumanda
5. Enula
6. Houttuynia
7. Magnesium
8. Mora
9. Parsley
10. Pinella
11. Samento
12. Sealantro
13. Serrapeptase
14. Sparga

Treatment of Lyme Disease

<u>Modified Cowden Protocol</u>

Samento (Cat's claw)

- Rich in pentacyclic oxindole alkaloids (POA's), which help stimulate the immune system to fight infection
- Is a potent anti-inflammatory
- Useful for treating coinfections
- Little to no side effects
- Free of TOA's, which may inhibit action of POA's

Treatment of Lyme Disease

Modified Cowden Protocol

Banderol

- Derived from *Otaba* tree in South America
- Broad spectrum activity against Lyme and coinfections
- Is a potent anti-inflammatory
- Works well in conjunction with Samento. Dr. Eva Sapi at University of New Haven showed that Samento and Banderol were able to eliminate all 3 forms of *Borrelia*.

Treatment of Lyme Disease

Modified Cowden Protocol

Cumanda

- Derived from bark of *Campsiandra angustifolia* tree in South America.
- May be the most broad spectrum herb against Lyme and coinfections. Used locally to treat malaria.
- Is a potent anti-inflammatory. Used to treat arthritis and fever.
- Can produce significant Herxheimer reactions.

Treatment of Lyme Disease

Modified Cowden Protocol

Burbur

- Derived from leaves of *Desmodium molliculum,* an Amazonian plant.
- Used primarily for detoxification purposes, especially the liver, kidneys and lymphatics.
- Can protect against toxic effects of other medications.
- Beneficial to minimize or stop Herx reactions.
- Can use every 10 minutes if Herx reactions become intolerable for patients.

Treatment of Lyme Disease

Modified Cowden Protocol

Acute Lyme Disease:

- Start with Samento, Banderol and Cumanda
- Give 15-30 drops 2 times per day in 1 oz water of each for 30 days.
- May add Burbur if Herxheimer reaction is strong.
- If patient starts Herx reaction, keep dose the same. Only increase dose if there is no improvement or reaction.

Treatment of Lyme Disease

Modified Cowden Protocol

Persistent Lyme Disease:

- Start with Samento, Banderol, Cumanda and Burbur
- Give 2-4 drops 2 times per day in 1 oz water of each.
- Increase by 1 drop 2 times per day every 3-4 days if there is no reaction or improvement up to 30 drops twice a day.
- If patient starts Herx reaction, keep dose the same.
- Give 10 drops of Burbur every 10 minutes for severe Herx reaction.

Treatment of Lyme Disease

Cowden Protocol

Combinations of these products are used to help kill the microbes, support detoxification and clear heavy metals.

It is a 5 month protocol with the combination of herbs changing each month.

Since these are liquid extracts and drop doses are administered, it is possible to use in children. Dose can be altered based on body weight.

Treatment of Lyme Disease

Cowden Protocol

Advantages: easy to administer (relatively), clinically beneficial, reasonably cost-effective.

Disadvantages: Herx reactions common, long-term treatment, requires multiple bottles and dosing schedule (labor intensive).

Treatment of Lyme Disease

Let's take a break…….

Treatment of Lyme Disease

Zhang Protocol: developed by Dr. Qincao Zhang, LAc

1. Artemisiae
2. Houttuynia (HH Caps)
3. Circulation P
4. Coptis
5. Cordyceps
6. Pueraria
7. R-5081
8. AI#3
9. Allicin

Treatment of Lyme Disease

Zhang Protocol

Dr. Zhang's protocol helps eradicate the infections, improve circulation, reduce inflammation and improve detoxification. It is one of the most comprehensive herbal protocols to address each aspect of LD.

I use this protocol for 3-6 months, depending on patient's response.

Treatment of Lyme Disease

Zhang Protocol: Allicin Caps

- Allicin is one of the active ingredients in *Allium sativum* (garlic). Allicin Caps contain allitridi, which gets converted to allicin.
- Well-established anti-microbial, but also helps improve circulation and is mild anti-inflammatory.
- Time released caps, so allicin gets absorbed over a longer period of time.
- Patients will definitely excrete it through their skin, so may be socially problematic for some.

Treatment of Lyme Disease

Zhang Protocol: Artemisiae Caps

- Extract of wormwood (*Artemisiae annua*), containing artemisinin. Also contains astragalus (*Astragalus membranaceus*) and codonopsis (*Codonopsis pilosula*).
- Effective against *Babesia* mostly, but also against *Borrelia* as well.
- Helps suppress autoimmune reactions and has anti-inflammatory effects.
- This formula helps modulate the immune system and has adaptogenic properties.

Treatment of Lyme Disease

Zhang Protocol: Coptis Caps

- Extract of coptis (*Coptis chinensis*).
- Has broad anti-microbial activity and has been used to treat bacterial, viral, fungal and parasitic infections.
- In-vitro studies find it as effective as some antibiotics in eradicating bacterial infections.

Treatment of Lyme Disease

Zhang Protocol: Cordyceps

- Medicinal mushroom (*Cordyceps sinensis*) that has been used in TCM for more than 2000 years.
- Is a potent immune boosting herb.
- Helps improve circulation.
- Is useful for persistent fatigue.
- Has blood sugar lowering effects, so be careful with diabetics with LD.

Treatment of Lyme Disease

Zhang Protocol: R-5081

- 7 traditional Chinese herbs, including *Smilax* and *Scutellaria*.
- *Smilax* and *Scutellaria* have long history of treating spirochetes like *Leptospira* and *Treponema*.
- Other herbs in the formula help promote detoxification, reduce inflammation and enhance tissue repair.

Treatment of Lyme Disease

Zhang Protocol: Circulation P

- Combination of 2 TCM herbal formulas with 10 herbs.
- Promotes enhanced circulation by preventing platelet aggregation.
- Boosts immune function and improves clearing cellular debris of bacteria and viruses.

Treatment of Lyme Disease

Zhang Protocol: AI#3

- Combination of *Macunae caulis*, *Sargentodoxae caulis* and *Paederiae caulis*.
- Have anti-inflammatory and analgesic effects.
- Can have immune suppressive effects, so limit use to 3-4 months.
- May alter menstrual cycle in some women, so discontinue 3 months prior to conception.

Treatment of Lyme Disease

Zhang Protocol: Puerarin Caps

- Derived from he root of *Pueraria species*.
- Used to treat high fever, muscles spasms, headaches, stiff joints and diarrhea.
- Help improve blood flow to the heart and brain, so is particularly good for those suffering from brain fog or poor memory.
- Potent anti-inflammatory.

Lee, K.-H., Morris-Natschke, S., Qian, K., Dong, Y., Yang, X., Zhou, T., … Akiyama, T. (2012). Recent Progress of Research on Herbal Products Used in Traditional Chinese Medicine: the Herbs belonging to The Divine Husbandman's Herbal Foundation Canon (神農本草經 Shén Nóng Běn Cǎo Jīng). *Journal of Traditional and Complementary Medicine*, *2*(1), 6–26.

Treatment of Lyme Disease

Zhang Protocol

Acute Lyme Disease

- HH Caps, Coptis, Cordyceps: give 1 cap 3 times a day. May use Allicin if patient tolerates.
- Add AI#3 if joint/muscle pain: give 1 cap 3 times per day or 2 x 1 x 2 for 5 days loading dose.
- Add Puerarin Caps if has fever, myalgia or Raynaud's. Give 1 cap 3 times per day.

Treatment of Lyme Disease

Zhang Protocol

Persistent Lyme Disease

- HH Caps, Artemisiae, Circulation P, Cordyceps, R-5081: give 1 cap 2-3 times a day.
- Add AI#3 if joint/muscle pain: give 1 cap 2-3 times per day or 2 x 1 x 2 for 5 days loading dose.
- Add Puerarin Caps if has fever, myalgia or Raynaud's. Give 1 cap 2-3 times per day.

Treatment of Lyme Disease

Zhang Protocol: developed by Dr. Qincao Zhang, LAc

Advantages: clinically beneficial, Herx reactions not common, few side effects.

Disadvantages: difficult to administer if cannot swallow capsules, long-term treatment, expensive.

Treatment of Lyme Disease

Byron White Protocol: developed by Byron White

**May not be available in Canada*

1. AL-Complex
2. A-Bab
3. A-Bart
4. A-C
5. A-FNG
6. A-Myco
7. A-RMSF
8. Other specific formulas

Treatment of Lyme Disease

Byron White Protocol

Botanical formulas that are specific to the organism being treated (i.e. AL-Complex for Lyme, A-Bab for Babesia, etc.).

These are liquid extracts that use drop dosing, using even fewer drops than Cowden protocol. Extracts are highly concentrated.

Treatment of Lyme Disease

Byron White Protocol

Advantages: clinically beneficial, easy to administer.

Disadvantages: Herx reactions common, long-term treatment, expensive.

Treatment of Lyme Disease

Other Botanical Therapies

Buhner Protocol: protocol consists of Japanese knotwood (*Polygonum cuspidatum*), Cat's Claw (*Uncaria tomentosa*), Andrographis (*Andrographis paniculata*), Wireweed (*Sida acuta)* and Yellow Dye Root (*Cryptolepis Sanguinolenta*).

Other herbs that help support the immune system, have anti-microbial effects, anti-inflammatory and help improve circulation or reduce pain.

Treatment of Lyme Disease

Managing Herxheimer Reactions

- AI#3: take 1 cap 3-4 times per day before meals.
- Burbur: take 10 drops every 15-30 minutes in 1 ounce of water.
- Curcumin (*Curcuma longa*): use companies that have well-studied forms that are well absorbed. Take 2-3 capsules 3 times per day before meals.
- Boswellia (*Boswellia serrata*) 400 mg: this is an herb from India that has a long history of use as an anti-inflammatory. Take 1-2 caps 3 times per day before meals.
- White willow bark (*Salix alba*) 400 mg: this herb contains salicin, a component similar to that found in aspirin. Take 1-2 caps 3 times per day before meals.

Treatment of Lyme Disease

Managing Herxheimer Reactions

Alkalizing your body will also help keep Herxing under control. You can take a bicarbonate formula to help keep you more alkaline. I recommend taking:

- Alka Seltzer Gold: take 1 tablet 3-4 times per day in 2-4 ounces of water and drink.
- Tri-Salts: 2 capsules 3 times per day.
- Baking soda: ¼ tsp 3-4 times per day.

Treatment of Lyme Disease

Breaking Down Biofilm

Biofilm is produced by many bacteria, including Lyme and is composed of extracellular DNA, proteins and carbohydrates…AKA "slime".

Biofilm enhances microbial adhesion to host cells and to each other.

Biofilm protects the microbe against innate and humoral immune responses and can lead to antibiotic resistance.

Treatment of Lyme Disease

Breaking Down Biofilm

- Biofilm busting enzymes – there are several products that contain enzymes that will help digest the biofilm and break it down. I use serrapeptase a lot and find it works well. I give between 40,000-60,000 U per day away from food. Nattokinase is another enzyme derived from natto, a fermented soy product. I give 20,000 FU 2-3 times per day away from food. For more difficult patients, I often use lumbrokinase, an enzyme derived from a type of earthworm. The enzyme activity is about 10 times that of nattokinase, but is also significantly more expensive. I specifically use Boluoke, as it has the best research behind it. Take 1 capsule 2 times per day, which delivers 600,000 U per day in total.
- Interfase Plus: this product contains enzymes with the addition of disodium EDTA and chitosans that also help break down biofilm. Take 1-2 capsules twice a day between meals.

Treatment of Lyme Disease

Breaking Down Biofilm

- Lactoferrin: this molecule binds up iron, which effectively prevents the formation of biofilm. Be careful if patient is already iron deficient or anemic. It is also not be to be taken if they have a dairy allergy, as it is derived from dairy and could worsen symptoms. Take 600 mg 1-2 times per day.
- Xylitol: this is a low carbohydrate sweetener that is naturally found in low amounts in some fruits and vegetables. It has been shown to make the biofilm weaker in dental studies. Although it is safe for humans, it is extremely toxic to dogs, so avoiding keeping around pets. Give 1 tsp 3-4 times a day in water or juice to start and you can increase up to 1 Tbsp. 3-4 times a day. Some people get gas and bloating with xylitol, so you may have to ramp up the dose slowly.

Treatment of Lyme Disease

Breaking Down Biofilm

- Coconut oil (organic): coconut oil has been used to treat various infections, including bacterial and yeast infections and contains a compound called monolaurin. It also has the ability to disrupt biofilm formation. Give 1Tbsp twice a day in food.
- N-acetyl cysteine (NAC): this is an amino acid that has been used to help break up mucus in the body and has been shown in numerous studies to break up biofilm. Give 200-600 mg 3 times per day. NAC may deplete zinc and copper when used long-term, so I recommend supplementing with these minerals if you take NAC for more than 2 months. NAC can cause gastrointestinal distress in some individuals and should not be taken by anyone with an active stomach ulcer.

Treatment of Lyme Disease

Boosting Immune Function

1. Vitamin C: vitamin C helps with active infections and may help improve the effect of antibiotics. Test tube studies show large doses of vitamin C may inhibit the growth of bacteria or kill it altogether. Take 1000 mg 2-3 times per day.

1. Vitamin D: many Lyme patients are vitamin D deficient. Vitamin D is a hormone that helps modulate the immune system. Give 2000-4000 IU per day with food. Higher doses may be needed if serum 25- hydroxy vitamin D is still low after supplementation.

Treatment of Lyme Disease

Boosting Immune Function

3. Zinc: It is an effective anti-viral and anti-inflammatory nutrient. Give 30-50 mg per day with food. It is essential to take zinc with food or it can make patient nauseous if they take it on an empty stomach. Long-term use of zinc supplements can induce a deficiency of folate or copper.

4. Andrographis (*Andrographis paniculata*) is a potent anti-microbial and anti-inflammatory herb. I prefer using an encapsulated standardized extract. I recommend taking 300-400 mg twice a day of a 50% andrographolide product. Andrographis is not for people with autoimmune conditions that are not related to Lyme disease, such as lupus or rheumatoid arthritis as it may exacerbate their symptoms.

Treatment of Lyme Disease

Low Dose Naltrexone (LDN)

Naltrexone is an opioid antagonist, but at low doses appears to enhance endogenous opioid production.

Short term blocking of opioid receptors for 4-6 hours leads to increased levels of endogenous opioids for up to 20 hours.

Is used off label for numerous conditions, including cancer, fibromyalgia, MS, Crohn's disease, pain syndromes and autism.

Treatment of Lyme Disease

Low Dose Naltrexone (LDN)

Chronic pain

Younger, J., Parkitny, L., & McLain, D. (2014). The use of low-dose naltrexone (LDN) as a novel anti-inflammatory treatment for chronic pain. *Clinical Rheumatology*, *33*(4), 451–459. http://doi.org/10.1007/s10067-014-2517-2

Multiple Sclerosis

Rahn KA, McLaughlin PJ, Zagon IS. (2011). Prevention and diminished expression of experimental autoimmune encephalomyelitis by low dose naltrexone (LDN) or opioid growth factor (OGF) for an extended period: Therapeutic implications for multiple sclerosis. *Brain Res*., Mar 24;1381:243-53. doi: 10.1016/j.brainres.2011.01.036. Epub 2011 Jan 20.

Fibromyalgia

Younger, J., & Mackey, S. (2009). Fibromyalgia Symptoms Are Reduced by Low-Dose Naltrexone: A Pilot Study. *Pain Medicine (Malden, Mass.)*, *10*(4), 663–672. http://doi.org/10.1111/j.1526-4637.2009.00613.x

Treatment of Lyme Disease

Low Dose Naltrexone (LDN)

Immune Modulation

Bihari, B. (2013). Bernard Bihari, MD: low-dose naltrexone for normalizing immune system function. *Altern Ther Health Med*, Mar-Apr;19(2):56-65.

Quality of Life

Brown, N., Panskepp, J. (2009). Low-dose naltrexone for disease prevention and quality of life. *Med Hypotheses*, Mar;72(3):333-7. doi: 10.1016/j.mehy.2008.06.048. Epub 2008 Nov 28.

Crohn's Disease

Segal D, Macdonald JK, Chande N. (2014). Low dose naltrexone for induction of remission in Crohn's disease. *Cochrane Database Syst Rev*, Feb 21;(2):CD010410. doi: 10.1002/14651858.CD010410.pub2.

Treatment of Lyme Disease

Low Dose Naltrexone (LDN)

LDN has not been studied specifically in Lyme disease, but has been used by numerous practitioners with good clinical success.

It may help modulate the immune system and restore balance in Th1/Th2 system. It also help alleviate pain.

LDN has an excellent safety profile and is well tolerated. Changes in sleep pattern or dreams have been reported by some individuals taking LDN.

Treatment of Lyme Disease

Low Dose Naltrexone (LDN)

Dosing:

Start with 1 mg at bedtime. May increase by 1 mg every 2 weeks up to 6 mg.

Women: often do best at 3 mg

Men: often do best at 4.5 mg

Treatment of Lyme Disease

Pulsed Electro-Magnetic Frequencies (PEMF)

There is recognition that the cells of the body vibrate or "oscillate" and have their own unique resonant energy.

Think of pushing a child on a swing, then when you push in the direction the child is moving, they go higher. If you push in the opposite direction, it will slow or stop the child's motion.

Treatment of Lyme Disease

Pulsed Electro-Magnetic Frequencies (PEMF)

PEMF devices are designed to produce a series of very low electromagnetic frequencies that fall within a biological window that resonate with human cells.

There are over 1 million receptor on any given cell and applying the right EMF may help stimulate these receptors to alter cellular function.

Treatment of Lyme Disease

Pulsed Electro-Magnetic Frequencies (PEMF)

Our bodies are exposed to numerous EMF daily via WiFi, electrical wiring in home or office, cell phones, cordless phones, etc. Some of the frequencies can be damaging, while others are healing.

The goal is to find the right frequencies that help stimulate the body toward better health. Most of medicine focuses on the chemistry of the body and virtually ignores the physics of the body.

Treatment of Lyme Disease

Pulsed Electro-Magnetic Frequencies (PEMF)

Potential benefits include:

- ***Improved circulation***
- ***Decreased pain***
- ***Reduced inflammation***
- Faster recovery after injury or surgery
- Faster healing of skin wounds
- ***Acceleration of nerve regeneration***

Treatment of Lyme Disease

Pulsed Electro-Magnetic Frequencies (PEMF)

There are over 1600 studies on the use of PEMF devices and most devices are currently FDA approved in the US. Some devices are designed for home use and others for professional use.

I recommend 2 treatments per week. Each treatment can be short (8 minutes) to longer (75 minutes). This is a great, non-invasive approach that can be customized to the individual.

Treatment of Lyme Disease

Detoxification Therapies

- IR Sauna
- Constitutional hydrotherapy
- Drainage remedies (Unda, Pekana, Marco Pharma, Seroyal)
- Exercise (gentle): yoga, tai chi, stretching, etc.
- Colon hydrotherapy

Even the most difficult Lyme patient can respond to these therapies, even when others have failed!

Treatment of Lyme Disease

Low Dose Immunotherapy (LDI): developed by Dr. Ty Vincent

We recognize that many microorganisms can trigger an autoimmune reactions once someone has been exposed to that organism. Rheumatic fever following strep infection is well-known in the medical community as a consequence of having had strep, even once the infection is eradicated.

Molecular mimicry of a microbe can create an autoimmune reaction against our own tissues.

Treatment of Lyme Disease

Low Dose Immunotherapy (LDI)

If a microorganism is capable of turning on the immune system against our own tissues, how effective will antimicrobial therapy be?

Reducing the load of the microbe may certainly lessen the immune response, but does it completely stop an autoimmune reaction? Does this explain why people flare periodically, even though they have been undergoing antimicrobial therapy for months or years?

Treatment of Lyme Disease

Low Dose Immunotherapy (LDI)

The goal of LDI is to promote tolerance to the offending antigen using homeopathic doses of nosodes mixed with beta-glucuronidase.

Beta-glucuronidase is an enzyme that was found (by mistake) to help build immune tolerance to whatever coexisted with the enzyme. This enzyme has been used with low dose allergy (LDA) therapy for the treatment of allergies to foods, mold, pollens and chemicals.

Treatment of Lyme Disease

Low Dose Immunotherapy (LDI)

The antigen is selected by the doctor depending on what organism(s) are suspicious to be causing symptoms. The dose selected is dependent on the sensitivity of the individual.

Intradermal or sublingual doses are administered every 7-8 weeks depending on patient response. In many cases, clinical improvement has been observed within 24-48 hours. However, it can take a few weeks to see the full benefit of the treatment dose.

Treatment of Lyme Disease

Low Dose Immunotherapy (LDI): Case 1
15 year old girl with autism

Jill has been in treatment with autism since she was 2 years old doing various biomedical and immune modulating therapies, all of which have helped to varying degrees. Her current primary issues are scripting, hyperactivity and lack of focus. She has also has intermittent skin rashes.

Treatment of Lyme Disease

Low Dose Immunotherapy (LDI): Case 1
15 year old girl with autism

Jill had been tested for Lyme disease and coinfections, which none of the tests were positive. She had a history of candidiasis however and had been on antifungal therapy for many years.

I gave Jill Candida Mix 10C sublingually. The next day, her mother called and said that she was completely calm and more mentally "clear". The scripting was less and her skin was not as itchy. After 2 months, she is stable and has not regressed.

Treatment of Lyme Disease

Low Dose Immunotherapy (LDI): Case 2
9 year old boy with tics

John had been having vocal and neck tics for a few months when the mother brought him to our clinic. He was tested and treated for food allergies, which helped reduce his tics significantly. However, the tics had not completely resolved.

I tested him for PANDAS and he was positive for ASO and DNAse B antibodies, despite having had a negative throat culture. He had a history of Lyme disease when he was 3-4 years old, which was treated with antibiotics at the time.

Treatment of Lyme Disease

Low Dose Immunotherapy (LDI): Case 2
9 year old boy with tics

I gave John a Strep Mix 10C and the mother reported no noticeable changes. I gave him a Strep Mix 9C the following week and again, no noticeable changes in his tics.

I then tried the Lyme Mix 10C and that following day he had a severe headache. The following day, the headache dissipated and the tics completely stopped. He has now been tic-free for 3 months

Treatment of Lyme Disease

Low Dose Immunotherapy (LDI): Case 3
47 year old woman with Lyme disease

Susan had a h/o chronic neck and shoulder pain, fatigue and joint pain. She had seen several doctors, including a rheumatologist who ran many labs for autoimmune disease, which were all negative.

Went to a large autoimmune clinic in TX and was put on AI diet and Rx many supplements, which helped, but did not resolve her Sx.

Treatment of Lyme Disease

Low Dose Immunotherapy (LDI): Case 3
47 year old woman with Lyme disease

Susan was tested for Lyme and coinfections and found to have a + Lyme Western Blot IgG and IgM. She was referred to my office for Tx.

I started her on an alkaline diet, Dr. Zhang protocol and gave her LDI Lyme 12C. She reported the next day her neck pain had improved by 90%.

Treatment of Lyme Disease

Low Dose Immunotherapy (LDI): Case 3
47 year old woman with Lyme disease

Over the next month, her neck and joint pain almost completely resolved. Her energy was better and she was becoming more physically active again. She was doing well for about 6 months and then started to have RUQ pain.

She had U/S and MRCP which showed dilated common bile duct, but otherwise negative for cholecystitis or obstruction.

Treatment of Lyme Disease

Low Dose Immunotherapy (LDI): Case 3
47 year old woman with Lyme disease

Over the next month, her neck and joint pain almost completely resolved. Her energy was better and she was becoming more physically active again. She was doing well for about 6 months and then started to have RUQ pain. She denies irregular BM, constipation or diarrhea.

She had U/S and MRCP which showed dilated common bile duct, but otherwise negative for cholecystitis or obstruction. CDSA was unremarkable, except no yeast growth.

Treatment of Lyme Disease

Low Dose Immunotherapy (LDI): Case 3
47 year old woman with Lyme disease

I then gave her LDI Candida 12C and her abdominal pain was 50% improved within 48 hours. I saw her 2 weeks later and gave her a booster dose of Candida 13C, which continued to help her Sx.

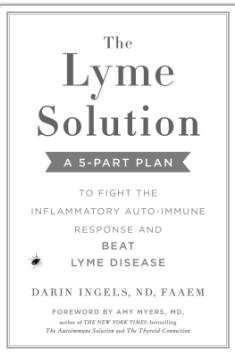
After a second dose of Candida 12C, her RUQ pain is gone. She is currently doing well and RUQ pain has not returned.

Treatment of Lyme Disease

The treatment of LD cannot be a single treatment approach. It is a complicated illness and the treatment needs to encompass many aspects of improving immune health.

1. Treat the organism(s) if it is acute.
2. Treat other immune distracters such as food allergies, environmental allergies, etc.
3. Detoxify the body. Eliminate heavy metals.
4. Fix endocrine dysregulation.
5. Get proper sleep.
6. Reduce inflammation.
7. Improve nutritional status.
8. Improve mitochondrial function.
9. Improve circulation.
10. Reduce autoimmunity.

The Lyme Solution



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The End

"You have Lyme's Disease. Do you spend any time in areas where there are a lot of deer?"

Lyme Paradox 2/3/18: Darin Ingels, ND

Common and Complicated Infections: When Antibiotics Fail

Darin Ingels, ND, FAAEM

AARM
Association for the Advancement of Restorative Medicine

Fundamentals of Infection

Questions to ask yourself when you have a patient who is prone to chronic infections:

1. What is it about this person that disposes him or her to these infections?
2. What is in their environment that may create imbalance in the body's ecosystem?
3. What lifestyle factors are harming the patient and setting them up for illness?
4. What microbes are normally present in the tissues where they have the most weakness and get ill?
5. Is the infectious agent truly foreign or part of us?
6. Do we need to treat the infection or just support the immune system?

Fundamentals of Infection

Infection is caused by the invasion and replication of microbes, the production of endogenous toxins produced by the microbe or the immune response to the microbe. Remember…there are 10X's as many microbes as cells in our bodies!

Symptoms may be precipitated by:
- Bacteria
- Viruses
- Fungi or yeasts
- Parasites
- Arthropods
- Prions
- Others?

Most of the symptoms associated with infection is the immune reaction to the infection.

Fundamentals of Infection

We are exposed to microbes ***all of the time***.

We get "infected" through eating food and drinking fluids, brushing our teeth, sexual activity, touching everything around us, breathing, etc.

Tissues one believed to be sterile, such as the bladder or small intestine are now known not to be sterile. Have we inadvertently become too sterile? Has loss of beneficial microbes actually predisposed toward persistent or chronic infections? Has the overuse of antibiotics wiped out our protective microbes?

Read "The Dirt Cure" by Dr. Shetreat-Klein.

Otitis Media

There are two main types of OM:
1. Acute Otitis Media (AOM)
2. Otitis Media with Effusion (OME)

AOM: sudden onset with acute ear pain. Typical ear infection that brings most patients to the office for treatment.

OME: pain is rarely part of the symptom picture, but patient describes fullness in ear. Can last weeks to months.

Chronic suppurative otitis media (CSOM) is when AOM lasts longer than 2 weeks.

Otitis Media

Causes of AOM:

1. Anatomy: horizontal Eustachian tubes do not allow for proper drainage. This is the most popular theory of why children get AOM.
2. ***Allergies:*** the accumulation of serous fluid in the middle ear allows for the growth of bacteria and viruses. Allergies to foods, mold, pollen, dust, animal danders and others can trigger inflammation in the middle ear.
3. Particulate inhalants: cigarette smoke, pollution, etc.
4. Other upper respiratory illnesses, such as colds, flu, etc.
5. Enlarged adenoids: block opening to Eustachian tube.

Otitis Media

Causes of AOM:

AOM is primarily caused by bacteria, including:
1. *Streptococcus pneumoniae*
2. *Haemophilus influenzae*
3. *Moraxella catarrhalis*
4. *Streptococcus pyogenes (Group A)*

Viruses may also cause AOM, but are usually a part of a larger URI. Common viruses that are associated with AOM include RSV, adenovirus, coronavirus, rhinovirus and parainfluenza virus.

Otitis Media

Naturopathic Treatment: Prevention

Prevention is the best medicine!

Find the cause…vast majority of AOM is related to allergy, so find the allergen and treat it. If you stop the fluid from accumulating, the ears stay dry and there is less liklihood of getting AOM in the first place.

Look at the patient's environment to identify triggers, including diet, home environment, school environment, family habits and hobbies.

Giving Xylitol chewing gum at a dose of 8.4-19 g per day has been shown to reduce the incidence of AOM in children attending day care.

Otitis Media

Naturopathic Treatment: Active Infection

1. ***Mullein oil ear drops with garlic***: warm bottle under warm water to heat oil. Place 2 drops in affected ear 3 times a day or as needed until ear pain subsides. Can add *Hypericum* to it for pain relief.

1. ***Vitamin A***: give 10,000 to 50,000 IU bid-tid with food for up to 7 days. Vitamin A increases secretory IgA, which lines all of the mucous membranes and supports immune function. Research suggests children more prone to AOM are deficient in vitamin A and then vitamin A supplementation may help treat AOM.[1]

[1] Lasisi AO. The role of retinol in the etiology and outcome of suppurative otitis media. Eur Arch Otorhinolaryngol. 2009 May;266(5):647-52.

Otitis Media

Naturopathic Treatment: Active Infection

3. ***Zinc***: give 15-50 mg daily with food. Research is mixed on preventing AOM and few studies on actively treating AOM with zinc supplementation.

3. ***Vitamin C***: give 500 -1000 mg 3 times a day to help support immune function. Research shows that children with AOM tend to have low antioxidant stores, so giving antioxidants may help reduce incidence of AOM. Vitamin C also helps boost immune function.[1]

[1]Yilmaz T1, Koçan EG, Besler HT, Yilmaz G, Gürsel B. The role of oxidants and antioxidants in otitis media with effusion in children. Otolaryngol Head Neck Surg. 2004 Dec;131(6):797-803.

Otitis Media

Naturopathic Treatment: Active Infection

5. ***Probiotics***: *Streptococcus salivarius* K12. Give 1 billion col/tab at night. Reduced AOM by almost 43%. [1] This has also been developed as a nasal spray and shown to be effective. Other studies found conflicting results with *Lactobacillus rhamnosus* GG and LC705, *Bifidobacterium breve* 99 and *Propionibacterium freudenreichii.,* but did find benefit with *Lactobacillus rhamnosus* GG when combined with *Bifidobacterium lactis* Bb-12.

5. ***Essential oils***: there is some anecdotal evidence that placing essential oils into the affected ear may help. These include thyme, eucalyptus and basil oils. Research has only been done on basil oil.[2] Essential oils should be mixed with a carrier oil to reduce irritation.

[1] DiPierro F, DiPasquale D, DiCicco M. Oral use of *Streptococcus* salivarius K12 in children with secretory otitis media: preliminary results of a pilot, uncontrolled study. Int J Gen Med. 2015: 8; 303-308.

[2] Kristinsson KG1, Magnusdottir AB, Petersen H, Hermansson A. Effective treatment of experimental acute otitis media by application of volatile fluids into the ear canal. J Infect Dis. 2005 Jun 1;191(11):1876-80. Epub 2005 Apr 29.

Otitis Media

Naturopathic Treatment: Active Infection

5. ***Botanical therapy***:

- *Echinacea angustifolia*: use 1:1 tincture. Give 9-15 ml per day in divided doses.
- *Lomatium dissectum*: use lomatium isolate as a resin in the whole plant can causes a measles-like rash. Give 6-12 drops twice a day in water.
- *Hydrastis canadensis:* contains alkaloids, like berberine, which have antimicrobial effects. Use 1:5 tincture. Give 15-30 drops 3 times a day. Very bitter.
- *Baptisia tinctoria* or *Galium aparine* for reducing tonsillar swelling. Use 1:3 tincture. Give 5-7 ml 3 times per day.

Otitis Media

Naturopathic Treatment: Active Infection

6. ***Homeopathic therapy***:

- Aconite 30C: pain, restless, irritable, skin dry and hot.
- Belladonna 30C: right side, rapid onset, redness, thirstless.
- Chamomilla 30C: worse at night, worse bending over, screaming and inconsolable. One cheek red, one white.
- Ferrum phos 30C: high fever, few other symptoms. Use when belladonna fails
- Hepar sulph 30C: left to right, thick pus, smelly, chilly.
- Kali mur 30C: lots of catarrh, hearing loss.
- Pulsatilla 30C: thick, green/yellow discharge, whining.

Otitis Media

Naturopathic Treatment: Active Infection

6. ***Physiotherapy***:

- Eustachian tube massage
- Wet sock treatment
- Onion "ear muffs"
- Cervical adjustment to C2/C3
- Lymphatic drainage
- Gua Sha

Urinary Tract Infections

UTI's are most common in women >children> men, mostly due to short urethra in women.

Infections are generally caused by bacteria, especially:

1. *Escherichia coli*
2. *Klebsiella pneumoniae*
3. *Proteus mirabilis*
4. *Pseudomonas aeruginosa*
5. *Any coliform bacteria*
6. *Ureaplasma urealyticum*
7. *Candidal infections rare (need to ask for specific culture)*

Urinary Tract Infections

The Urinary Microbiota

It has long been taught that the bladder is sterile, but emerging evidence shows that it is not. Standard urinary testing does not account for slow growing organisms, anaerobes or potential commensal non-bacterial microbes.

Newer quantitative technologies and DNA sequencing may provide better insight into what is "normal" in the bladder and may have some individual variance.[1]

[1] Brubaker L, Wolfe AJ. The new world of the urnianry microbiota in women. Am J Obstet Gynecol 2015;213:644-649.

Urinary Tract Infections

Naturopathic Treatment

1. ***D-mannose***: ONLY useful for *E.coli* infections. Can use powder or caps. Give 3 day dosing with higher doses on day 1 and tapering to day 3. D-mannose binds to fimbria on *E.coli* and prevents attachment to bladder wall.

1. ***Uva ursi***: *Arctostaphylos uva ursi.* Arbutin in uva ursi is activated in alkaline urine to make antispetic hydroquinone. Also contains tannins, which have astringent effect. Use standardized extract to 20% arbutin. Give 600 mg bid-tid. Use cautiously in pregnancy, since has mild oxytocic effects.

1. ***Tri-salts***: bicarbonate formula to alkalinize the urine. Bacteria generally like acid environment to thrive. Give 2 caps 3 times a day. Reduce dose if gets loose stool.

Urinary Tract Infections

Naturopathic Treatment

4. ***Cranberry juice extract***: many studies showing it is effective for prevention and treatment of UTI's. Can use unsweetened juice or capsules. Take 250-300 ml of juice tid or 200 mg bid of concentrated capsules. Does not kill bacteria, but inhibits growth and attachment to bladder wall.[1] Cranberry extract has also been shown to be effective in preventing UTI's in children, especially those with urogenital abnormalities.[2]

5. ***Vitamin C***: little research. May need very high oral doses to be effective. High dose vitamin C of up to 10g a day may be needed to be effective. It is bacteriostatic at high doses.[3]

[1] Stothers L. A randomized trial to evaluate effectiveness and cost effectiveness of naturopathic cranberry products as prophylaxis against urinary tract infection in women. Can J Urol 2002;9:1558-1562.

[2] Durham SH, Stamm PL, Eiland LS. Cranberry products for the prophylaxis of urinary tract infections in pediatric patients. Ann Pharmacother 2015;49:1349-1356.

[3] Gupta GCD, Guha BC. The effect of vitamin C and certain other substances on the growth of micro-organisms. Ann Biochem Exp Med 1941;1:14-26.

Urinary Tract Infections

Naturopathic Treatment

6. ***Probiotics***: *Lactobacillus acidophilus* LbK3, *Lactobacillus rhamnosus* GG, *Lactobacillus rhamnosus* GR-1 and *Lactobacillus reuteri* RC-14 have all been shown to help prevent and treat UTI's. A popular formula contains *L. rhamnosus* GR-1 and *L. reuteri* RC-14. Give 1 cap bid-tid or may use intravaginally at 1 cap hs. [1,2,3]

[1] Gardiner GE, Heinemann C, Bruce AW et al. Persistence of Lactobacillus fermentum RC-14 and Lactobacillus rhamnosus GR-1, but not L. rhamnosus GG in the human vagina as demonstrated by randomly amplified polymorphic DNA. Clin Diagn Lab Immunol 2002:9;92-96.

[2] Cadieux P, Burton J, Gardiner G et al. Lactobacillus strains and vaginal ecology. JAMA 2002:287;1940-1941.

[3] Reid G, Bruce AW. Selection of Lactobacillus strains for urogenital probiotic applications. J Infect Dis 2001:183(Suppl 1):S77-S80.

Urinary Tract Infections

Naturopathic Treatment

7. ***Zea mays (corn silk)***: contains flavones that inhibit the adherence of *E. coli* to the bladder wall.[1] Zea mays is traditionally used as a hot tea. The corn silk steeped in hot water for 10 minutes, strained and then drink the residua fluid. Have patients drink 3-6 cups per day.

[1] Rafsanjany N, Sendeker J, Lechtenberg M et al. Traditionally used medicinal plants against uncomplicated urinary tract infections: Are unusual, flavon-4-ol- and derhamnosylmaysin derivatives responsible for the antiadhesive activity of extracts obtained from the stigmata of Zea mays L. against uropathogenic E. coli and Benzethonium chloride as frequent contaminant faking potential antibacterial activities? Filoterapia 2015;105:246-253.

Urinary Tract Infections

Naturopathic Treatment

8. ***Green tea (Camilla sinensis)***: in-vitro studies show that many of the polyphenolic compounds in green tea have antimicrobial activity against uropathogens. The catechins also have a synergistic effect with many antibiotics, such as amoxicillin, sulfamethoxazole, azithromycin, methicillin, levofloxacin and ciprofloxacin. One cup of Japanese green tea provides 150 mcg of EGC and bactericidal activity is noted at microgram doses.

[1] Noormandi A, Dabaghzadeh F. Effects of green tea on *Escherichia coli* as a uropathogen. J Tradit Complement Med 2015;5:15-20.

Bronchitis

Naturopathic Prevention

1. **Avoid cigarette smoke.**
2. **Avoid pollutants.**

[1] Seibel J, Pergola C, Werz O, Kryshen K, Wosikowski K, Lehner MD, Haunschild J. Bronchipret® syrup containing thyme and ivy extracts suppresses bronchoalveolar inflammation and goblet cell hyperplasia in experimental bronchoalveolitis. Phytomedicine. 2015 Dec 1;22(13):1172-7.

Bronchitis

Naturopathic Treatment

1. ***Thyme and Ivy Extract*:** animal models shows that extracts of thyme and ivy leaf extract help reduce bronchitis by inhibiting 5-lipoxygenase and reducing leukocyte infiltration in the lungs. Also reduces goblet cell numbers, so decreases mucus formation.[1]

Give 1 tsp tid-qid for children and 1T tid-qid for adults.

[1] Seibel J, Pergola C, Werz O, Kryshen K, Wosikowski K, Lehner MD, Haunschild J. Bronchipret® syrup containing thyme and ivy extracts suppresses bronchoalveolar inflammation and goblet cell hyperplasia in experimental bronchoalveolitis. Phytomedicine. 2015 Dec 1;22(13):1172-7.

Bronchitis

Naturopathic Treatment

2. ***NAC (N-acetylcysteine)*:** a recent meta-analysis showed that giving >1200 mg per day of NAC helps prevent chronic bronchitis in those prone to airway obstruction, where 600 mg per day may be beneficial in those who get bronchitis and no airway obstruction. NAC is well tolerated with minimal side effects.[1] If using NAC long-term, give zinc as NAC can deplete zinc. NAC also has antiinflamatory effects.[2]

[1] Cazzola M, Calzetta L, Page C et al. Influence of N-acetylcysteine on chronic bronchitis or COPD exacerbations: a meta-analysis. Eur Respir Rev. 2015 Sep;24(137):451-61.

[2] Gillssen A. Anti-inflammatory efficacy of N-acetylcysteine and therapeutic usefulness. Pneumologie. 2011 Sep;65(9):549-57.

Bronchitis

Naturopathic Treatment

3. ***Inhaled glutathione***: it is known that environmental pollution causes oxidative damage that can exacerbate COPD and bronchitis. Although no specific human trials have been done on inhaled glutathione, it is postulated that using inhaled glutathione may reduce oxidative stress and protect against mucosal damage and modulate the immune response in the lungs.[1]

I have personally used inhaled glutathione with success in chronic bronchitis and asthma patients. Use 60 mg/ml daily in children up to 200 mg/ml in adults.

[1] Allen J. Inhaled glutathione for the prevention of air pollution-related health effects: a brief review. Altern Ther Health Med. 2008 May-Jun;14(3):42-4.

Bronchitis

Naturopathic Treatment

4. ***Magnesium***: research shows that infants with chronic bronchitis have low serum and RBC magnesium levels, while urine magnesium excretion is high.[1] Although it is unclear if the hypomagnesemia is causative of chronic bronchitis, supplementing is reasonable.

Give 200 mg bid to children and TBT to adults.

[1] Bednarek A, Pasternak K, Karska M. Evaluation of blood serum, erythrocyte and urine magnesium concentrations in babies with pneumonia or bronchial obstructive bronchitis. Magnes Res. 2003 Dec;16(4):271-80.

Bronchitis

Naturopathic Treatment

5. ***Elderberry***:

Elderberry (*Sambucus nigra*) has historical use for respiratory illnesses such as bronchitis, colds and flu. It has natural antiviral and antiinflamatory activity. It induces the release of infection-fighting cytokines. The antiinflamatory effects in the bronchioles make it useful for viral and bacterial infections of the lungs, including bronchioltitis, bronchitis, pneumonia and reactive airway disease.

Give 1 tsp tid-qid for children and 1T tid-qid for adults.

Bronchitis

Naturopathic Treatment

6. ***Andrographis paniculata***: in-vitro studies show andrographolide upregulates human β-defensin-2, an inducible antimicrobial peptide that is important in innate immunity. The result is an increase in NF-κB, which control cellular immunity and cytokine production.[1] One study found an extract of *andrographis* help reduce the duration of illness in uncomplicated URI by more than 2 days.[2]

Andrographis has known antiviral effects against HSV, influenza, campylobacter, skin yeast, Group B strep and other microbes. Because of its anti-inflammatory effects, it is used for other inflammatory conditions like RA and UC.

Give 200-500 mg qd-bid of a 5% standardized extract.

[1]Shao ZJ, Zheng XW, Feng T et al. Andrographolide exerted its antimicrobial effects by upregulation of human β-defensin-2 induced through p38 MAPK and NF-κB pathway in human lung epithelial cells. Can J Physiol Pharmacol. 2012 May;90(5):647-53.

[2] Saxena RC, Singh R, Kumar P et al. A randomized double blind placebo controlled clinical evaluation of extract of Andrographis paniculata (KalmCold) in patients with uncomplicated upper respiratory tract infection. Phytomedicine. 2010 Mar;17(3-4):178-85.

Bronchitis

Naturopathic Treatment

7. ***Vitamin C***: most of the research on vitamin C is with respect to the common cold, but one randomized study found vitamin C helped reduced severity and duration of bronchitis in elderly people who were hospitalized.[1] Of note, these patients were shown to have low serum vitamin C levels and were only supplemented with 200 mg per day.

It is generally recommended to give at least 1000 mg per day to adults, but higher doses may be helpful.

[1] Hemilä H, Douglas RM. Vitamin C and acute respiratory infections. Int J Tuberc Lung Dis. 1999 Sep;3(9):756-61.

Bronchitis

Naturopathic Treatment

8. ***Myers cocktail***: Dr. John Myers made this formula popular in the 1970's and has been used by thousands of physicians around the world since. The cocktail is a combination of vitamin C, magnesium chloride, calcium gluconate, thiamine, vitamin B6, vitamin B12, calcium pantothenate, vitamin B complex and dilute HCL.[1]

It is theorized that the higher doses of nutrients exert pharmacologic effects, including stimulating immune function.

Dr. Alan Gaby has treated over 1000 patients with this IV mix with clinical success and minimal side effects, mostly due to doing IV push too quickly and causing flushing or nausea.

[1] Gaby AR. Intravenous nutrient therapy: the "Myers' cocktail". Altern Med Rev. 2002 Oct;7(5):389-403.

Bronchitis

Naturopathic Treatment

Other possible treatments:

- Vitamin A : increases secretory IgA.
- Zinc: boosts immune function.
- Oral glutathione: raise tissue glutathione.
- Essential oils: thyme, oregano, artemisia
- Cupping: increase blood flow to chest
- Constitutional hydrotherapy: applying alternating hot and cold towels to chest and back.

Pediatric Diarrhea

Need to investigate cause of diarrhea as treatment varies depending on diagnosis. Most common causes of pediatric diarrhea include:

- Rotavirus
- Other enteric viruses, including enterovirus, adenovirus, coronavirus, Norwalk virus.
- Food poisoning (salmonella, shigella, campylobacter)
- IBS
- IBD
- Celiac disease
- Food allergies

Pediatric Diarrhea

Naturopathic Treatment: Diet

- Hydration: push fluids. Use electrolyte replacement formulas. Make into popsicles for small children and infants.
- B.R.A.T diet: keep diet simple and bland until diarrhea resolves. Bananas, applesauce, rice and toast (gluten-free).
- Avoid simple carbohydrates and junk food. This includes, milk, soda or juice of all kinds.
- Feed small, frequent meals if tolerated. Make sure foods are well cooked. No raw foods or legumes.

Pediatric Diarrhea

Naturopathic Treatment

1. ***Probiotics:*** Use the following probiotics for pediatric gastrointestinal conditions:

Prevention of acute infectious diarrhea: Bifidobacterium lactis, Lactobacillus rhamnosus GG (LGG), and L. reuteri.

Treatment of AID: Lactobacillus GG and S. boulardii or Lactobacillus reuteri.

Prevention of antibiotic-associated diarrhea: Lactobacillus GG and S. boulardii.

Prevention of traveler's diarrhea: S. boulardii. Give 1-2 caps bid with food.

Induction and maintenance of ulcerative colitis: VSL#3. Give 2 caps bid-tid with food.

Improving symptoms of irritable bowel syndrome: Lactobacillus GG and VSL#3.

Cruchet S, Furnes R, Maruy A et al. The use of probiotics in pediatric gastroenterology: a review of the literature and recommendations by Latin-American experts. Paediatr Drugs. 2015 Jun;17(3):199-216.

Pediatric Diarrhea

Naturopathic Treatment

2. ***Glutamine:*** glutamine powder can be useful in pediatric acute diarrhea as it is a fuel source for enterocytes and enteric lymphocytes. One study found that glutamine powder at 0.3g/kg/day helped shorten the duration of diarrhea by more than 24 hours.[1]

Glutamine dosing should be fairly high in acute diarrhea, so an 80 lb child would get 10g/day. Adults getting chemotherapy have received as high as 30g/day.

[1] Yalçin SS, Yurdakök K, Tezcan I, Oner L. Effect of glutamine supplementation on diarrhea, interleukin-8 and secretory immunoglobulin A in children with acute diarrhea. J Pediatr Gastroenterol Nutr. 2004 May;38(5):494-501.

Pediatric Diarrhea

Naturopathic Treatment

3. ***Carob:*** carob powder is a rich source of tannins, polyphenols and fiber and has long history of use for diarrhea. One study is infants between 3-21 months with acute diarrhea were given up to 15g/day of carob powder compared with placebo. The duration of diarrhea in those receiving carob powder was reduced by almost 2 days. Cessation of vomiting, weight loss and regulation of body temperature was also more quickly normalized in those taking carob powder.[1]

[1] Loeb H, Vandenplas Y, Würsch P, Guesry P. Tannin-rich carob pod for the treatment of acute-onset diarrhea. J Pediatr Gastroenterol Nutr. 1989 May;8(4):480-5.

Pediatric Diarrhea

Naturopathic Treatment

4. ***Zinc:*** supplementation with zinc can also be effective at reducing length and severity of diarrhea. Giving 10-20 mg/kg/day of zinc helped restore normal bowel habits in hospitalized children with diarrhea.[1] The effect was even greater when 1500 IU of vitamin A per day was added to the treatment regimen.

On a practical note, you must give zinc with food or it can make patient nauseous. Best to give in small doses with food.

[1] Wang Y, Gao Y, Liu Q, et al. Effect of vitamin A and Zn supplementation on indices of vitamin A status, haemoglobin level and defecation of children with persistent diarrhea. *Journal of Clinical Biochemistry and Nutrition*. 2016;59(1):58-64.

Pediatric Diarrhea

Naturopathic Treatment

5. ***Vitamin D:*** low serum levels of vitamin D have ben noted in children with acute diarrhea.[1] However, there are no good studies on supplementing with vitamin D as a preventive or treatment measurement for diarrhea in children.

Nonetheless, vitamin D deficiency has been indicated in numerous chronic illnesses, including IBD and IBS. It is reasonable to supplement vitamin D, especially in those with low serum vitamin D.

[1] Talachian E, Bidari A, Noorbakhsh S, Tabatabaei A, Salari F. Serum levels of vitamins A and D, and zinc in children with acute diarrhea: A cross-sectional study. *Medical Journal of the Islamic Republic of Iran*. 2015;29:207.

Pediatric Diarrhea

Naturopathic Treatment

6. *Botanicals*: there are no randomized studies on most botanicals for pediatric diarrhea, but these herbs have a long historical use and are GRAS. These herbs have astringent, demulcent and anti-inflammatory effects.

- ***Ulmus fulva*** **(Slippery Elm):** use cold infusion.
- ***Althea officinalis*** **(Marshmallow):** use cold infusion.
- ***Geranium maculatum*** **(Cranesbill):** use tincture.
- ***Achillea millefolium*** **(Yarrow):** use tea or tincture.
- ***Rubus macropetalus (*****Black raspberry root):** use tincture.
- ***Filipendula ulmaria*** **(Meadowsweet):** use tea or caps.

Pediatric Diarrhea

Naturopathic Treatment

7. ***Homeopathics:*** use low potency, 12C or 30C.

Podophyllum: Main remedy for acute diarrhea. Sudden urgency for a stool with profuse, offensive-smelling stools. Explosive diarrhea. Large thirst for cold liquids.

Arsenicum album: Main remedy for diarrhea caused by food poisoning or from viral diseases. The diarrhea is worse after eating or drinking, and is usually accompanied by nausea, vomiting, burning or cramping pains in the abdomen. Chilly. Thirsty, but sips fluids.

Aloe socotrina : Accidental leaking of stool after passing gas. Have a lot of sputtering during its release. Stools is very mucousy and like Jell-O.

Veratrum album: Profuse, painful diarrhea that is forcibly evacuated. Chilly people, but they crave ice and cold drinks. Profuse sweating with chills, with projectile vomiting.

Chamomilla: Diarrhea, in children with extreme irritability during their illness. Green, foul smelling diarrhea. Wants to be carried.

Calcarea carbonica: Most commonly given to infants. Pale, lethargic infants who sweat profusely on head. Desires eggs and indigestible things like chalk or dirt.

Cinchona officinalis: Diarrhea with great bloating, indigestion, and general weakness. The symptoms are noticeably worse at night, in hot weather, and after nursing.

** Adopted from Dana Ullman, MPH*

MRSA

Treatment of MRSA:

1. ***Manuka honey***: the hydrogen peroxide found in honey creates hydroxyl free radicals which inhibit growth of MRSA and also disrupt intact DNA. Studies also show in inhibits the growth of vancomycin-resistant enterococcus.[1]

The active ingredient in manuka honey is methylglyoxal (MG), a compound found in most types of honey, but usually only in small quantities. Medical grade Manuka honey has a higher concentration of methylglyoxal by up to 10X's more than regular honey.

This is a very safe, effective treatment for MRSA, especially for lesions around a child's mouth.

[1] Brudzynski K, Lannigan R. Mechanism of Honey Bacteriostatic Action Against MRSA and VRE Involves Hydroxyl Radicals Generated from Honey's Hydrogen Peroxide. Frontiers in Microbiology. 2012;3:36.

MRSA

Treatment of MRSA:

2. ***Ursolic acid-containing oils:*** ursolic acid is found in many plants and fruits, including the skin of apples, Holy Basil, bilberry, cranberry, elder flower, oregano, peppermint, rosemary, thyme, lavender and hawthorn.

Ursolic acid disrupts bacterial reproduction cycles in-vitro, so may help kill organism. There are no human studies on ursolic acid and MRSA, but concentrated essential oils have been used clinically with success.

Wang CM, Jhan YL, Tsai SJ, Chou CH. The Pleiotropic Antibacterial Mechanisms of Ursolic Acid against Methicillin-Resistant Staphylococcus aureus (MRSA). Molecules. 2016 Jul 7;21(7).

MRSA

Treatment of MRSA:

3. ***Licorice (Glycyrrhiza glabra):*** in-vitro and in-vivo studies show licorice has a synergistic effect with some β-lactam drugs and improved the MIC up to 16-fold. This suggests adding licorice to other antibiotic regimens may help improve the clinical outcome of the infection.[1]

Other mouse studies have demonstrated that using topical *Glycyrrhiza* is effective at reducing lesion size and inhibiting specific genes involved in bacterial reproduction.[2]

[1] Gaur R, Gupta VK, Singh P, et al. Drug Resistance Reversal Potential of Isoliquiritigenin and Liquiritigenin Isolated from Glycyrrhiza glabra Against Methicillin-Resistant Staphylococcus aureus (MRSA). Phytother Res. 2016 Jul 8.

[2] Long DR, Mead J, Hendricks JM, Hardy ME, Voyich JM. 18β-Glycyrrhetinic Acid Inhibits Methicillin-Resistant Staphylococcus aureus Survival and Attenuates Virulence Gene Expression. Antimicrobial Agents and Chemotherapy. 2013;57(1):241-247.

MRSA

Treatment of MRSA:

4. ***Berberine:*** in-vitro studies show berberine, in a dose dependent manner, inhibits MRSA amyloid fibrils formation (aka "biofilm"). Although berberine is not directly bactericidal, it can be an effective adjunctive therapy with antibiotics.[1]

Although this was an in-vitro study, the dose-dependent effect would suggest higher doses would be more effective than lower doses.

[1] Chu M, Zhang M, Liu Y, et al. Role of Berberine in the Treatment of Methicillin-Resistant Staphylococcus aureus Infections. Scientific Reports. 2016;6:24748.

MRSA

Treatment of MRSA:

5. ***Colloidal silver:*** nanoparticles of silver (less than 100 nm) have demonstrated in-vitro bactericidal activity against MRSA.[1] The MIC was found to be 100 ug/ml and almost all of the MRSA was completely killed at 4 hours post-inoculation. The study also showed nano-Ag inhibited the development of MRSA biofilm.[1]

It is important to note that Ag has a long history as an antimicrobial. Caution should be exercised when using orally as it could alter normal gut flora.

[1] Abdel Rahim KAA, Ali Mohamed AM. Bactericidal and Antibiotic Synergistic Effect of Nanosilver Against Methicillin-Resistant Staphylococcus aureus. Jundishapur Journal of Microbiology. 2015;8(11):e25867.

MRSA

Treatment of MRSA:

6. ***Tea tree oil (Melaleuca alternifolia):***

Most in-vitro studies have shown tea tree oil has anti-microbial effects against *S. aureus*. There have only been a few clinical studies in humans comparing tea tree oil with mupirocin. While tea tree oil was effective in eradicating MRSA, it was not as effective as mupirocin.[1]

However, using a 4% tea tree oil nasal ointment and a 5% tea tree oil body wash compared with a 2% mupirocin nasal ointment and triclosan body wash seemed to be more effective than standard treatment.[2]

[1] Dryden MS, Dailly S, Crouch M. A randomized, controlled trial of tea tree topical preparations versus a standard topical regimen for the clearance of MRSA colonization. J Hosp Infect. 2004 Apr;56(4):283-6.
[2] Caelli M, Porteous J, Carson CF, Heller R, Riley TV. Tea tree oil as an alternative topical decolonization agent for methicillin-resistant Staphylococcus aureus. J Hosp Infect. 2000 Nov;46(3):236-7.

Small Intestine Bacterial Overgrowth (SIBO)

SIBO is due to an overgrowth of bacteria in the small intestine that is still largely misunderstood. The two most common predisposing factors to SIBO are lack of gastric acid or disruptions in small bowel motility.

It is believed that SIBO arises from overgrowth of bacteria in the small bowel. However, which microbes are most to blame as obtaining small bowel flora is technically difficult, especially for anaerobes.

Lactulose breath test is the most common method of diagnosing SIBO. Lactulose makes it to the distal jejunum, so covers the entire small bowel. Glucose can be used as substrate to identify more proximal SIBO.

Small Intestine Bacterial Overgrowth (SIBO)

Risk Factors

1. PPI use
2. Pancreatitis
3. Non-alcoholic fatty liver disease
4. Hypochlorhydria
5. Dysmotility disorders
6. Diabetes
7. Elderly persons
8. Alcohol consumption
9. IBS
10. IBD/Celiac disease

Small Intestine Bacterial Overgrowth

Naturopathic Treatment

Diet

No specific diet has ever been studied, but many healthcare providers recommend following FODMAPs diet. These are **F**ermentable **O**ligosaccharides, **D**isaccharides, **M**onosaccharides **A**nd **P**olyols.

It is also advisable to have patients avoid gluten, casein and known food allergies/sensitivities.

Encourage fluids as constipation likely makes SIBO worse.

Small Intestine Bacterial Overgrowth

Naturopathic Treatment

1. ***Herbal therapies compared with Rifaximin™:***
- ***FC-Cidal™ and Dysbiocide™ (Biotics)***
- ***Candibactin-AR™ and Candibactin-BR™ (Metagenics)***

Participants with + LBT were given either 200 mg Rifaximin™ tid or 2 caps of each herbal formula bid for 4 weeks. At the conclusion of the study, 46% of those taking the herbal formulas had a negative LBT compared with 34% of those taking Rifaximin™.[1]

The authors did not publish the differences between the two herbal protocols, so it is unclear if one protocol is better than the other.

[1] Chedid V, Dhalla S, Clarke JO, et al. Herbal Therapy Is Equivalent to Rifaximin for the Treatment of Small Intestinal Bacterial Overgrowth. Global Advances in Health and Medicine. 2014;3(3):16-24.

Small Intestine Bacterial Overgrowth

Table 5

Herbal Preparations for the Treatment of Small Intestine Bacterial Overgrowth

FC Cidal	Dysbiocide	Candibactin-AR	Candibactin-BR
Proprietary blend - 500 mg: 1 capsule	Proprietary Blend 950 mg per 2 capsules	One Capsule contains:	Two Capsules contain:
Tinospora cordifolia (stem)	Dill seed	Red Thyme oil (thymus vulgaris, providing 30%-50% thymol) 0.2 mL	Coptis root and rhizome extract (coptis chinensis, containing berberine) 30 mg
Equisetum arvense (stem)	Stemona Sessilifolia powder and extract	Oregano Oil (origanum vulgare, providing 55% to 75% carvacrol) 0.1 mL	Indian Barberry root extract (berberis aristata, containing berberine) 70 mg
Pau D'Arco (inner bark)	Artemisia Absinthium shoots and leaves extract,	Sage leaf 5.5:1 extract (salvia officinalis) 75 mg	Berberine Sulfate 400 mg • Proprietary 4:1 Extract 300 mg: Coptis root and rhizome (coptis chinensis)
Thymus vulgaris (aerial part)	Pulsatilla Chinensis rhizome powder and extract	Lemon Balm leaf 5:1 extract (melissa officinalis) 50 mg	Chinese Skullcap root (scutellaria baicalensis)
Artemisia dracunculus (leaf)	Brucea Javanica powder and extract		Philodendron bark (phellodendron chinense)
Sida cordifolia (aerial part)	Picrasma Excelsa bark extract		Ginger rhizome (zingiber officinale)
Olea europaea (leaf)	Acacia Catechu stem extract		Chinese Licorice root (glycyrrhiza uralensis)
	Hedyotis Diffusa powder and extract		Chinese Rhubarb root and rhizome (rheum officinale)
	Yarrow leaf and flower extract (achillea millefolium).		Chinese Rhubarb root and rhizome (rheum officinale).

Small Intestine Bacterial Overgrowth

Naturopathic Treatment

2. ***Probiotics with FOS:*** a small pilot study found giving probiotics (*Bacillus coagulan*) with FOS in addition to minocycline for 6 months (15 days minocycline and 15 days probiotics) eliminated SIBO in 93% of cases compared with only 67% using minocycline alone.[1]

[1] Khalighi AR, Khalighi MR, Behdani R, et al. Evaluating the efficacy of probiotic on treatment in patients with small intestinal bacterial overgrowth (SIBO) - A pilot study. The Indian Journal of Medical Research. 2014;140(5):604-608.

Small Intestine Bacterial Overgrowth

Naturopathic Treatment

3. ***Probiotics without FOS:*** short-term probiotic use may be effective at eliminating SIBO in patients with chronic liver disease. A combination of *Bifidobacterium bifidum, Bifidobacterium lactis, Bifidobacterium longum, Lactobacillus acidophilus, Lactobacillus rhamnosus*, and *Streptococcus thermophilus* given for 4 weeks helped reduce symptoms of SIBO, but had no effect on liver disease.[1]

[1] Kwak DS, Jun DW, Seo JG, et al. Short-term probiotic therapy alleviates small intestinal bacterial overgrowth, but does not improve intestinal permeability in chronic liver disease. Eur J Gastroenterol Hepatol. 2014 Dec;26(12):1353-9.

Small Intestine Bacterial Overgrowth

Naturopathic Treatment

4. ***Guar gum:***. Giving 5g/day of guar gum with 1200 mg of Rifaximin™ for 10 days was more effective in eradicating SIBO than by just giving Rifaximin™ alone, by 87% and 62%, respectively. [1]

It is unknown whether guar gum by itself would provide any benefit.

[1] Furnari, M., Parodi, A., Gemignani, L., et al. Clinical trial: the combination of rifaximin with partially hydrolysed guar gum is more effective than rifaximin alone in eradicating small intestinal bacterial overgrowth. Alimentary Pharmacology & Therapeutics, 2010;32: 1000–1006.

Small Intestine Bacterial Overgrowth

Naturopathic Treatment

5. Digestive enzymes:

There is no research on the use of digestive enzymes of HCL in the treatment of SIBO, but if we believe that part of the problem is the inability to break down food products and dysfunctional digestion and/or fermentation, digestive enzymes may help provide symptomatic relief.

I recommend using digestive enzymes containing pancreatin and DPP-IV for those with gluten or casein intolerance.

Small Intestine Bacterial Overgrowth

Naturopathic Treatment

When its not SIBO…

There is some new evidence that patients who have SIBO-like symptoms and have a negative hydrogen and methane breath test may suffer from sucralase deficiency. This was previously believed to be a geentically inheirited condition, but it may affect some individuals who do not necessarily carry the gene.

You can test by doing a sucrose hydrogen breath test.

Sucraid® is an enzyme developed to help those who have this deficiency.

Clostridium difficile Infection

Clostridium difficile: Gram positive, anaerobic, spore forming and toxin producing (some strains) bacteria that can be infectious (fecal-oral route) or simply overgrow due to antibiotic use or other perturbations of the GI tract.

24% of HC workers had C. difficile spores on their hands after working with C. diff patients (0% for unexposed HC workers). http://www.ncbi.nlm.nih.gov/pubmed/24334792.

About 60% of young children carry C. diff asymptomatically. Only 3-5% of healthy adults carry C. diff.

Sensitivity of the EIA test for detection of C. diff toxin in stool is low (only about 50%), so the PCR test is replacing the EIA test.

Clostridium difficile Infection

Clostridia by themselves are generally harmless. The toxin produced by *Clostridium difficile* is what triggers symptoms.

By aware that testing for the toxin can be difficult as the toxins (A and B) are heat labile and breakdown easily if not kept at a cool temperature once outside of the body. Stability of toxin at room temperature is only 4 hours and up to 72 hours if refrigerated.

If you are going to have patient collect sample, make sure they refrigerate the sample immediately and take to lab on ice or cold pack to ensure the toxin remains intact if present.

Clostridium difficile Infection

Naturopathic Treatment

Diet

One study found patients with CDI has low RBC levels of Ω-3 Fatty acids and higher levels of RBC Ω-6 fatty acids.[1] While this was not an interventional study, other research has shown that Ω-3 fatty acids have anti-inflammatory effects. Adding Ω-3 FA's may help reduce inflammation associated with CDI.

Avoid known food allergies/sensitivities/intolerances.

[1] Czepiel J, Gdula-Argasińska J, Garlicki A. n-3 and n-6 Fatty Acid Changes in the Erythrocyte Membranes of Patients with 658240251 Clostridium difficile Infection. Folia Biol (Krakow). 2016;64(1):3-10.

Clostridium difficile Infection

Naturopathic Treatment

1. ***Probiotics:*** Evidence suggests taking probiotics can help prevent and treat active CDI. While several strains have been studies, a 2011 review found that probiotics that contained Saccharomyces boulardii and Lactobacillus species were most effective.[1]

Another meta-analysis found that probiotics reduced CDI by 66%.[2]

I have had good success using VSL#3®. It is a combination of *Streptococcus thermophilus, Bifidobacterium breve, Bifidobacterium longum, Bifidobacterium infantis, Lactobacillus acidophilus, Lactobacillus plantarum, Lactobacillus paracasei, Lactobacillus delbrueckii subsp.Bulgaricus.* Each capsule delivers 150 billion organisms. Give 2-4 caps bid-tid with food.

[1] Na X, Kelly C. Probiotics in clostridium difficile infection. J Clin Gastroenterol. 2011 Nov;45 Suppl:S154-8.

[2] Johnston BC, Ma SS, Goldenberg JZ, et al. Probiotics for the prevention of Clostridium difficile-associated diarrhea: a systematic review and meta-analysis. Ann Intern Med. 2012 Dec 18;157(12):878-88.

Clostridium difficile Infection

Naturopathic Treatment

2. Fecal microbiota transplant:

A recent meta-analysis showed that FMT was more effective at resolving CDI than antibiotics alone. More than 80% of patients with CDI improved with FMT, whereas only 31% of those with CDI improved with antibiotic therapy.[1]

However, FMT continues to have difficulties with adverse events. AE's were significantly higher in those who received transplants through upper GI methods (43.6%), compared with those who received their transplant through lower GI methods (17.7%).[2]

[1] Drekonja D, Reich J, Gezahegn S, et al. Fecal Microbiota Transplantation for Clostridium difficile Infection: A Systematic Review. Ann Intern Med. 2015 May 5;162(9):630-8.

[2] Wang S, Xu M, Wang W, et al. Systematic Review: Adverse Events of Fecal Microbiota Transplantation. Grivennikov S, ed. PLoS ONE. 2016;11(8):e0161174.

Clostridium difficile Infection

Naturopathic Treatment

3. Indole-3-carbinol:

A recent mouse study found that adding I3C to the diet helped reduce severity of CDI. The I3C appears to help upregulate T_{reg} cells, other T cells and neutrophils without increasing inflamation.[1]

Although there are no human studies for CDI, I3C has been used in clinical trials for prevention of cancer, particularly breast cancer.

[1] Julliard W, De Wolfe TJ, Fechner JH, Safdar N, Agni R, Mezrich JD. Amelioration of Clostridium difficile Infection in Mice by Dietary Supplementation With Indole-3-carbinol. Ann Surg. 2016 Jun 8.

Clostridium difficile Infection

Naturopathic Treatment

4. Vitamin A: research suggests vitamin A has immune enhancing effects. It is known to help reduce some diarrhea, HIV, measles, malaria and other infections in preschool children.[1] However, it is not clear by what mechanism it works.

It is also know that children with higher fecal SIgA are less likely to develop CDI compared with those who have lower SIgA levels.[2]

It is reasonable to try using high-dose vitamin A therapy (50,000 IU-200,000 IU) in CDI. Watch for vitamin A toxicity, including headaches, joint pain, muscle aches, fatigue and dry skin.

[1] Villamor E, Fawzi WW. Effects of vitamin a supplementation on immune responses and correlation with clinical outcomes. Clin Microbiol Rev. 2005 Jul;18(3):446-64.

[2] Bridgman SL, Konya T, Azad MB, et al. High fecal IgA is associated with reduced Clostridium difficile colonization in infants. Microbes Infect. 2016 Sep;18(9):543-9.

Clostridium difficile Infection

Naturopathic Treatment

5. Vitamin D: vitamin D deficiency has been associated with CDI. People with lower vitamin D (25-OH) levels were 60% more likely to develop CDI than those with sufficient vitamin D levels.[1]

Vitamin D also has a protective effect on the intestinal barrier and may help reduce intestinal permeability.[2]

Give enough vitamin D3 to restore serum levels to sufficient status (> 30 ng/ml). I try to get levels between 60-100 ng/ml.

[1] Furuya-Kanamori L, Wangdi K, Yakob L, et al. 25-Hydroxyvitamin D Concentrations and Clostridium difficile Infection: A Meta-Analysis. JPEN J Parenter Enteral Nutr. 2015 Dec 23.

[2] De Santis S, Cavalcanti E, Mastronardi M, Jirillo E, Chieppa M. Nutritional Keys for Intestinal Barrier Modulation. Frontiers in Immunology. 2015;6:612.

For More Information

Website: DarinIngelsND.com

Facebook: @DarinIngelsND or @LymeExpert

Instagram: @DarinIngelsND

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The End!

Questions?

Complicating Factors in Lyme Disease: Multiple Chronic Infectious Disease Syndrome (MCIDS) and the Cell Danger Response

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ASSOCIATION FOR THE ADVANCEMENT OF RESTORATIVE MEDICINE REGIONAL CONFERENCE

TORONTO, CA

FEBRUARY 3&4, 2018

AARM
Association for the Advancement of Restorative Medicine

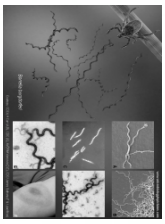
Disclosure Statement

I, Kelly K. McCann, MD, have no financial arrangements or affiliations with any commercial entities whose products, research or services may be discussed in these materials.

Objectives

- Discuss how chronic infections such as Lyme Disease and Co-infections lead to oxidative stress, chronic inflammation, and immune system dysfunction which manifests in physical and mental health symptoms.
- Review the Multiple Systemic Infectious Disease Syndrome (MSIDS) and the use of the questionnaire for suspected Lyme disease.
- Discuss the Cell Danger Response and its impact in chronic infections.
- Comprehensive treatment strategies addressing environmental exposures such as mold and toxicants.
- Utilizing case presentations to highlight teaching points.

Defining terms

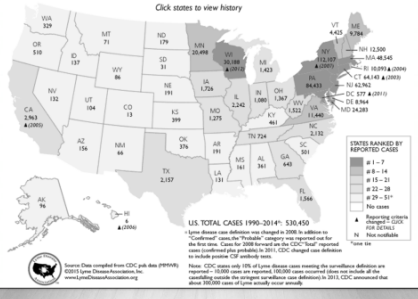


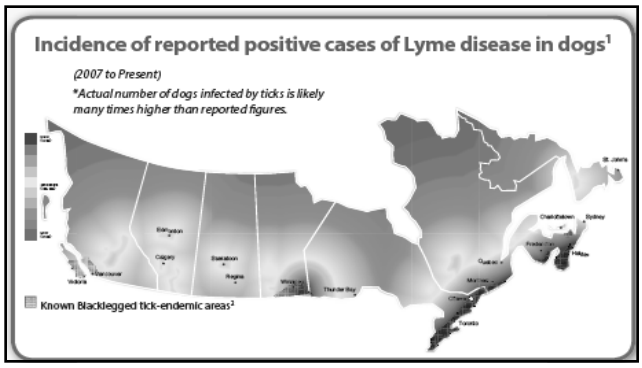
- **Lyme Disease** (interchangeable with Lyme): refers to the infection that includes not only *B. burgdorferi* but many co-infections.
- **Lyme Borreliosis**: Solo infection with *B. burgdorferi*.
- **Persistent Lyme Disease**: A patient with persistent and chronic Lyme disease has Borrelia infection and likely other infections, as well as; immune dysfunction, inflammation, opportunistic infections, deficient biological terrain, metabolic and hormonal imbalances, deconditioning, biotoxin illness or chronic inflammatory response syndrome (CIRS) or environmental toxicant burden, etc. that need to be addressed in order to bring the patient to wellness.

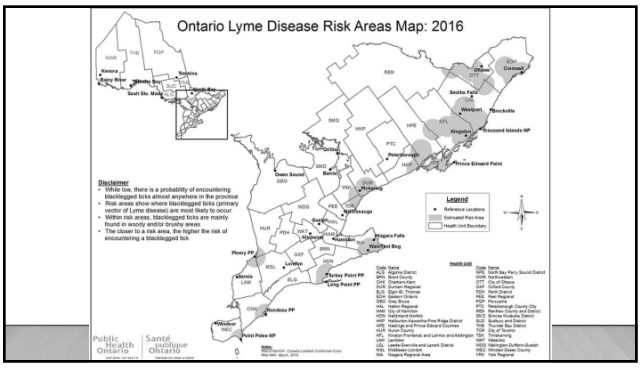
Meet Otzi the Iceman

- The autopsy of Otzi, a 5,300 year old mummy found in the Italian Alps in 2010, revealed the presence of *Borrelia burgdorferi* DNA.
- Earliest known human with Lyme disease.

Hall, SS. Iceman Autopsy: Unfrozen. National Geographic. 2011 Nov.







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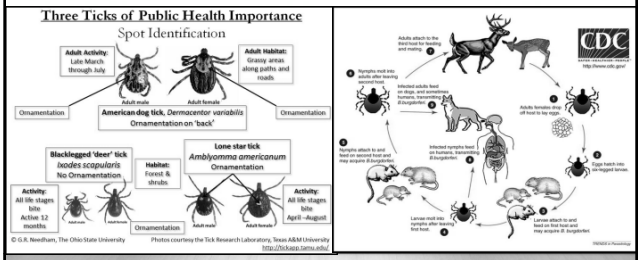
Relevant Lyme disease ticks and their life cycle



Kelly K. McCann, MD

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It's not just about the tick…

- Case reports of illness after mosquito bites and bird mite bites.
- *Borrelia burgdorferi* found in mosquitos, horse flies, and deer flies in endemic areas, but researchers claim those insects are unable to transmit infections to humans.
- Studies in Czech republic prove evidence of Borrelia in mites from wild rodents and in chigger mites from wild birds.
- Evidence to support sexual transmission of Lyme disease.
- Numerous case reports support evidence for congenital transmission of Lyme disease.
- Possible transmission via breast milk.

AGJ Infect Dis. 1986. Aug;154(2):355-8.
J Clin Microbiol. 1988 Aug; 26(8):1482-86.
Exp Appl Acarol. 2008 Apr; 44(4): 307-14.
Expert Rev Anti Infect Ther. 2015;13(11):1303-6.
Vector Borne Zoonotic Dis. 2005 Fall;5(3):277-32.
Ann Intern Med 1985; 103:67-8.
Rheum Dis Clin North Am. 1989 Nov; 15(4):657-77.
Diagn Microbiol Infect Dis 1995 Mar; 21(3):121-8.

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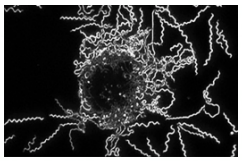
Chronic Lyme vs. Post Treatment Lyme Disease Syndrome



1. Inflammatory host response to antigenic debris
2. Autoimmune
3. Residual damage to tissues during infection
4. Co-infection
5. Secondary opportunistic infections
6. **Lyme Persisters**
   not killed by current Lyme antibiotics

Let's use the term…Persistent Lyme

Maloney. Controversies in Persistent (Chronic) Lyme Disease. Art Sci Infusion Nursing. 2016 Nov; 39(6): 369 375.
Marques. Chronic Lyme Disease: An appraisal. Infect Dis Clin North Am. 2008 Jun; 22(2): 341–360.

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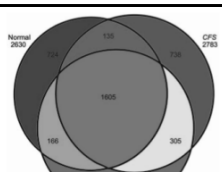

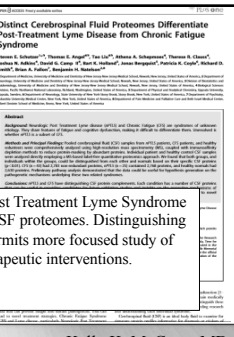

Chronic fatigue syndrome (CFS) and neurological Post Treatment Lyme Syndrome (nPTLS) are distinguishable disorders with distinct CSF proteomes. Distinguishing these conditions from each other and controls will permits more focused study of each condition and lead to novel diagnostics and therapeutic interventions.
Schutzer, 2011

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Neuropsychiatric symptoms of Lyme disease

Depression
Anxiety/Panic attacks
Mood swings
Irritability
Sleep disorders
Seizures
ADHD-like behavior
Autism-like behaviors
Schizophrenia
Bipolar disorder
Peripheral neuropathy

Obsessive –compulsive disorders
PANDAS/PANS
Chronic fatigue Syndrome
Fibromyalgia
Brain fog
Memory issues
Headaches/Migraines
Concentration issues
Dementia
Psychosis/ Paranoia
Eating disorders

Fallon, et al. The Neuropsychiatric Manifestations of Lyme Borreliosis. Psychiatric Quarterly, Vol63, No 1, Spring 1992

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Index of suspicion for Persistent Lyme Disease

Cognitive difficulties
Simple and complex attention
Slow processing – visual and auditory
Visual spatial difficulties
Sensory integration disorders
Short-term memory difficulties
Word-finding and communication difficulties
Decline in executive functioning
Confusion – overall decline in intellectual performance

Emotional/Behavioral Difficulties
Anxiety, with panic attacks
Depression
Irritability/rage/impulse control
Oppositional defiant disorders
Sleep disorders
Rapid mood swings (bipolar)
Obsessive compulsive disorder
Hyperactivity
Autism-like spectrum disorders
Antisocial disorders
Eating disorders

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Complicating Factors in Lyme disease as a Chronic Illness

BACTERIA FACTORS
1. Numerous strains of Borrelia
2. Different forms of Borrelia
3. Testing Challenges
4. Co-infections
5. Biofilms
6. Immune evasion and persistent infections
7. Various Treatment Guidelines

PATIENT FACTORS
1. Lyme disease and Co-infections
2. Immune Dysfunction
3. Inflammation
4. Environmental toxins – chemicals and mold
5. Nutritional deficiencies
6. Mitochondrial dysfunction
7. Endocrine abnormalities
8. Neurodegenerative disorders
9. Neuropsychiatric disorders
10. Sleep disorders
11. Autonomic nervous system dysfunction and POTS
12. Allergies
13. GI disorders
14. Liver dysfunction
15. Pain dis./addiction
16. Deconditioning

Patient list from Richard Horowitz, MD

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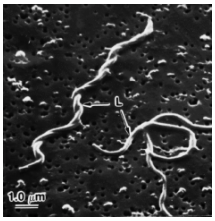
There are many pathogenic bacteria

B. burgdorferi
B. afzelli
B. garinii
B. spielmanii
B. lonestari
B. bissettii
B. carolinensis
B. americana
B. andersonii
B. kurtenbachii

B. lusitaniae
B. valaisiana
B. sinica
B. bavariensis
B. finlandensis
B. japonica
B. miyamoti
B. hermsii
B. yangtze
B. tanuki
B. turdi
Etc…



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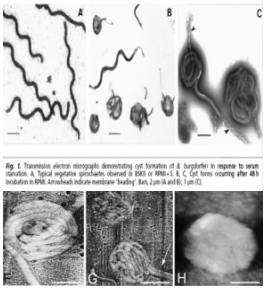
Pleomorphic bacteria

- Spirochete form
- Atypical forms
- Cyst, rolled, looped, ring
- Cell-less wall or L-form?
- Biofilms

Typical treatment regimens target these forms.



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Possible additional infections

- Anaplasmosis/Ehrlichiosis
- Babesia (B.microti, B. duncani)
- Bartonella (B. henselae, B. quintana, B. bacilliformis)
- Relapsing fever Borrelia (Borrelia miyamotoi, B. hermsii)
- Rickettsia (Rocky Mountain Spotted Fever, R. typhi)
- Coxiella burnetti (Q fever)
- Chlamydia infections
- Mycoplasma infections
- Tularemia
- Brucella
- Tick paralysis
- Colorado Tick fever
- STARI (Southern Tick Associated Rash Illness)

Viral infections
- Heartland Virus
- Powassan Encephalitis
- West Nile
- Human Herpes Virus-6 (HHV-6)
- Epstein Barr Virus (EBV)
- Cytomegalovirus (CMV)

Fungal Infections

Parasitic infections

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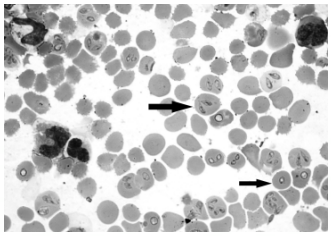
Seroprevalence of *Babesia microti* in Lyme patients

- 130 patients in New York
- Positive tests for Lyme disease
- 26.9% samples positive for *Babesia microti* IgG and IgM antibodies
- 6.7% of Lyme disease negative controls were positive



Curcio, SR et al. Seroprevalence of *Babesia microti*. Vector Borne Zoonotic Dis 2016 Dec; 16(12): 737-743.

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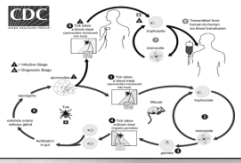
Babesia-like Organisms

Fever/ Chills
Fatigue
Headaches
Drenching sweats
Muscle aches
Chest pain
Cough
Loss of Appetite
Air hunger/ Shortness of breath
"Brain Fog" /Cognitive problems
Elevation of liver enzymes
Hemolytic anemia

20+ different species.
We can test for 2 species.
Babesia microti
Babesia duncani (Wa-1)
Can be transmitted via tick bite, blood transfusion and via placenta in utero



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Bartonella-like Organisms (Cat Scratch Fever)

Spread by ticks, other insects and in utero
Symptoms include:
Fatigue
Chronic pain
Pelvic pain/ interstitial cystitis
Pain on the soles of the feet
Chest pain/Palpitations
Headaches
Myalgias/ arthralgias
Abnormal liver enzymes
Encephalopathy
Endocarditis/myocarditis
Hemolysis with anemia
Hepato-splenomegaly
Lymphadenopathy
Papular or angiomatous rash
Weakened immune response
Anxiety/ Panic attacks
Striae
Sore throat
Fever

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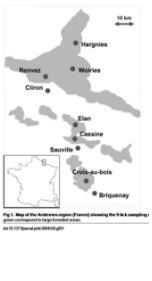
Co-infection of Ticks: The Rule Rather Than the Exception

Abstract



267 *Ixodes ricinus* female ticks tested
45% were co-infected
Carrying up to 5 pathogens

Including symbiont prevalences, all ticks were infected with at least one organism. Up to 8 pathogens in the same tick.

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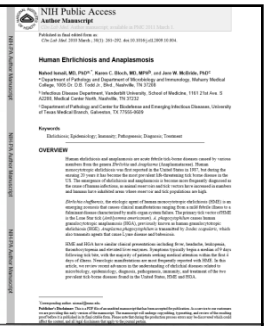
Ehrlichia (HME) /Anaplasma (HGA)

Ehrlichia Symptoms:
Fever 97%
Headaches 80%
Myalgias 57%
Arthralgia 41%
Rash 66% pediatric
Nausea/vomiting
Abdominal pain
Cough
Meningitis/meningo-encephatitis 20%
42% require hospitalization
3% case fatality

Anaplasma Symptoms:
Similar for fever, HA, myalgias, but less severe than HME
Rash 10%
CNS involvement 1%
PNS higher – peripheral neuropathy, cranial nerve palsies
Both have pancytopenias and elevated LFTs



NIH Public Access
Author Manuscript

Human Ehrlichiosis and Anaplasmosis

OVERVIEW

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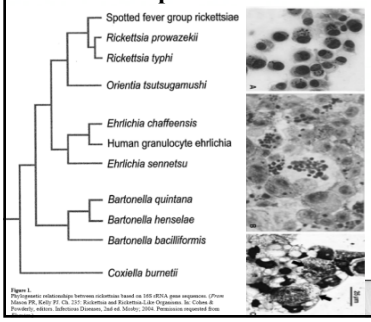
Ehrlichia/Anaplasma/Rickettsia



- Rickettsial infections are transmitted by fleas, mites, and ticks.
- Can be mild or life threatening.
- Rocky Mountain spotted fever presents as fever, headache, myalgias, petechial rash, and tick exposure.

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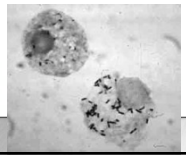
Diversity of Rickettsiae in Rural Northern California

DNA PCR of rickettsia species found in:
3% in humans
33% in grey foxes
42% in dogs
79% in cats
83% in bobcats
Found in fleas, ticks both Ixodes pacificus and Dermacentor varibilis species



Stephenson, et al. Diversity of rickettsiae in a rural community in northern California. Ticks tick Borne Dis. 2017. Feb. pii:s1877-959x(17)30110-3.

Kelly K. McCann, MD

Kelly K. McCann, MD

Case: MB

33 yr old woman presented in March 2014 with a number of chronic issues for which she wanted functional medicine approaches.

PMHx: Major depressive disorder
Borderline personality disorder
Hashimoto's thyroiditis
PCOS with infertility issues
Premenstrual syndrome
Chronic back pain from 3 herniated discs
History of SIBO treated with rifaximin.
Corn allergy

PSHx: none

Family Hx: Mom 66, depression
MGM deceased at 81, depression
PGF deceased 70s, psych disorder

Social history: Married, desired children, no drug or tobacco use, +Etoh use.

She had dissociative episodes in college and started therapy. Had a "breakdown" in the first semester of her MFT program. She is now mentally stable on Pristiq.

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Case: MB

3/13/14 labs:
Chol 188 mg/dL = 4.87 mmol/L
LDL 101mg/dL = 2.62 mmol/L
HDL 54 mg/dL = 1.4 mmol/L
trig 206H mg/dL = 2.33 mmol/L
Wbc 6.7 x103, hgb 13.9, plt 266
Glu 86 mg/dL = 4.77 mmol/L
cmp wnl, HgA1c 5.3%,
MTHFR C677t +/-, Celiac neg, ANA neg
Pregnenolone 71 ng/mL =225.8nmol/L
DHEA-S 253 µg/dL = 6.63µmol/L
Ferritin 43 ng/mL = 96 pmol/L
TSH 2.32 mIU/L
free t4 0.89 mg/dL = 11.46 pmol/L
free t3 2.9 pmol/L = 188.31 pg/dL
+thyroid antibodies
Hs CRP 6.79 mg/L = 64.67 nmol/L

Alletess food IgG sensitivities –reactions to gluten, dairy, egg

Comprehensive stool analysis - 4+ Candida glabrata. Calprotectin – 68 (<50 is normal)
Secretory IgA – 255 (51-204 normal)

Cd 57 was 34 (abs CD8-CD57 +lymph) (optimal >200)
Transforming Growth Factor Beta1 – 11,460 pg/mL (normal is <2382)

Vit D 25 OH - 18.9 ng/mL = 47.17 nmol/L
Vit D 1,25 OH - 64 pg/mL = 166 pmol/L

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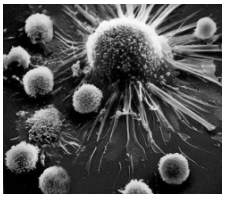
What is CD 57?

- CD57 is a subset of natural killer (NK) cells
- Distinct from CD 56 cells the major subset of NK cells
- Function is poorly understood
- May be suppressed in chronic infections including EBV, CMV, HIV and Lyme disease
- Associations with remission rates in cancers
- Downregulated by TH1 cytokines (IL2, IFN, TNF)
- CD57 marker is found on other cells (T-cells and nerve cells)



- Stricker RB, Burrascano J, Winger E. Longterm decrease in the CD57 lymphocyte subset in a patient with chronic Lyme disease. Ann Agric Environ Med. 2002;9(1):111-3.
- Marques A, et al. Natural killer cell counts are not different between patients with post-Lyme disease syndrome and controls. Clin Vaccine Immunol. 2009 Aug;16(8):1249-50.
- Nielsen, CM, et al. Functional Significance of CD57 Expression on Human NK Cells and Relevance to Disease. Front Immunol. 2013; 4: 422.

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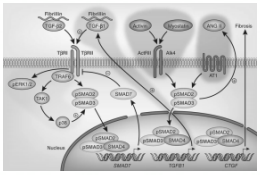
Transforming Growth Factor Beta1



Zhang, et al. TGF-β1 factor in the cerebrovascular diseases of Alzheimer's disease. Eur Rev Med Pharmacol Sci. 2016 Dec;20(24):5178-5185.
Schumann. TGFbeta1 of no avail as prognostic marker in Lyme disease. PeerJ2:e398; DOI 10.7717/peerj.398.

- TGF-beta 1 (Transforming Growth Factor Beta 1) (normal is <2382)
- Immunomodulatory cytokine, has pleiotropic effects.
- A marker of an overactive immune system. Directs immunity towards TH17, often results in autoimmunity.
- Also role in tumor suppression and promoting tolerance to allergens and self- antigens.
- Can be elevated in CIRS from mold or Lyme disease.
- Important in autoimmune hepatitis, IBD, hepatocellular carcinoma and RA

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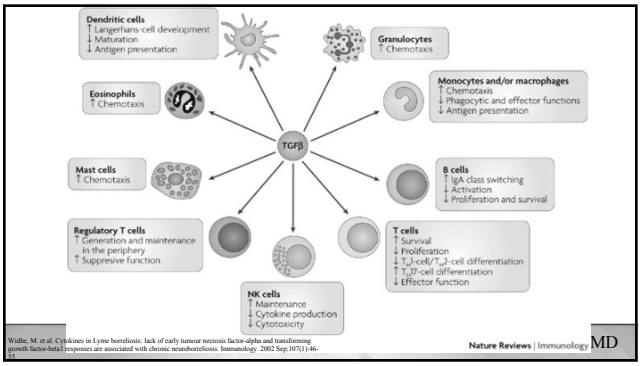

Widhe, M. et al. Cytokines in Lyme borreliosis: lack of early tumour necrosis factor-alpha and transforming growth factor-beta1 responses are associated with chronic neuroborreliosis. Immunology. 2002 Sep;107(1):46-55

Nature Reviews | Immunology

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***This Slide Enlarged on Page 138**

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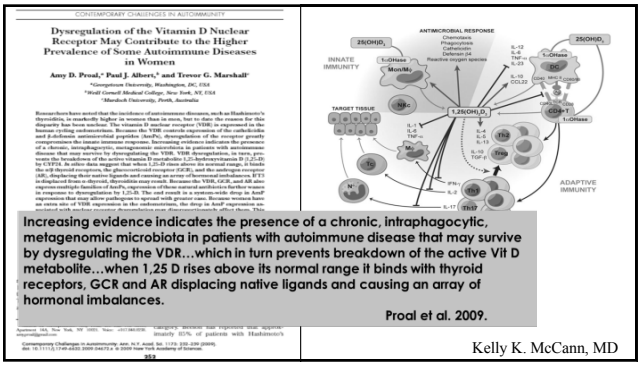

CONTEMPORARY CHALLENGES IN AUTOIMMUNITY

Dysregulation of the Vitamin D Nuclear Receptor May Contribute to the Higher Prevalence of Some Autoimmune Diseases in Women

Amy D. Proal,[a] Paul J. Albert,[b] and Trevor G. Marshall[c]

[a]Georgetown University, Washington, DC, USA
[b]Weill Cornell Medical College, New York, NY, USA
[c]Murdoch University, Perth, Australia

Increasing evidence indicates the presence of a chronic, intraphagocytic, metagenomic microbiota in patients with autoimmune disease that may survive by dysregulating the VDR…which in turn prevents breakdown of the active Vit D metabolite…when 1,25 D rises above its normal range it binds with thyroid receptors, GCR and AR displacing native ligands and causing an array of hormonal imbalances.

Proal et al. 2009.

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Vitamin D discrepancy

- Inflammatory disease processes appear to be due to alterations in the microbiome.
- Autoimmune diseases may be antibody generation against polymicrobial colonies and infections.
- Intracellular microbes slow innate immune system defense by dysregulating the vitamin D nuclear receptor (VDR).
- VDR affects transcription of at least 913 gene including the expression of key antimicrobial peptides.
- This dysregulation facilitates the ability of other pathogens to persist and slow the immune system further.

- VDR dysregulation prevents the breakdown of the active Vit D metabolite 1,25oh, thus it becomes elevated and 25-OH vit D remains low.
- Elevated 1,25OH – D can interfere with the expression of other nuclear receptors such as the androgen receptor, glucocorticoid receptor and thyroid receptors.

Proal. 2009. Ann NY Acad Sci 1173: 252-9.
Sun. 2010. Cur Opin GI 26(6): 591-595.
Proal. 2013. Curr Opin Rheumatol. Mar 25(2): 234-40.
Proal 2014. Discovery Medicine. 17(95):257-65.
Proal 2011. Cell & Mol Immunol 8: 213-225.

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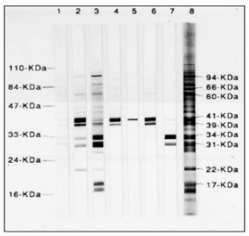

Significant Lyme disease antibodies detected on Western blot test, including 31- and 34-kilodalton bands. Courtesy of IGeneX, Inc.

Laboratory testing

- Stony Brook University
  IFA, Western blot plus bands 31 (OspA) and 34 (OspB)
- Igenex
  Lyme, relapsing fever borrelias IFA, western blot, PCR
  Bartonella henselae antibodies, Bartonella FISH
  Babesia microti and duncani antibodies, Babesia FISH
  Ehrlichia, Anaplasma, C. pneumonia, Rickesttia
  Immunoblot
- Fry Labs
  Advanced stains for Protomyxzoa rheumatic and other parasites
- Advanced Lab - Borrelia culture
- Medical Diagnostic Labs (MDL)
  Bacteria, vectors, viral antibodies and PCR
- Galaxy Labs
  Bartonella species testing
- Armin Labs (Germany)– Lyme and co-infection urine testing
- Mayo Medical Laboratory – Lyme serology and Immunoblot

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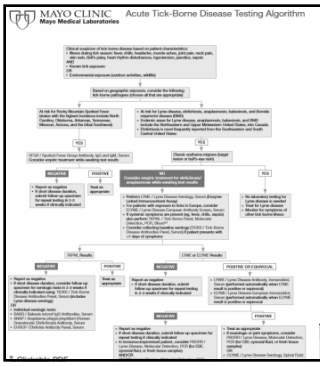


https://www.mayomedicallaboratories.com/it-mmfiles/Acute_Tick-Borne_Disease_Testing_Algorithm.pdf

Case: MB Lyme western blot through Stonybrook

11/16/15
IFA – nonreactive
IgM – positive for bands 23, 41 and (62 and 93) – positive by CDC criteria
IgG – 41+ band only

2/29/16
IFA – nonreactive
IgM - positive for bands 23, 41 and (36, 62, and 93) – positive by CDC criteria
IgG – positive for 41, 66 and 25

She couldn't afford any co-infection testing other than commercial labs and those tests were all negative.

Case: MB Follow up

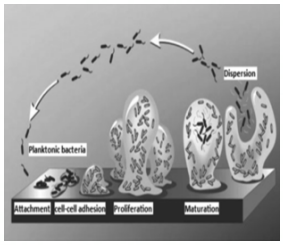
- She did antibiotics for 1 year and then had an embryo transfer.
- Continued on a single antibiotic Augmentin as the other antibiotics caused diarrhea during her pregnancy.
- Plus a Chrysanthemum morifolium product as additional antimicrobial.
- Had healthy baby girl. All infant tests so far have been negative for Lyme.

Complicating Factors in Lyme disease as a Chronic Illness

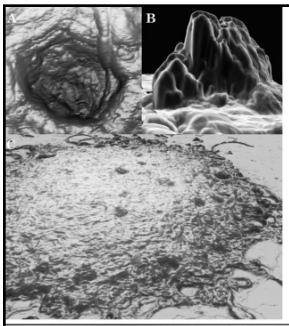
BACTERIA FACTORS
1. Numerous strains of Borrelia
2. Different forms of Borrelia
3. Testing Challenges
4. Co-infections
5. Biofilms
6. Immune evasion and persistent infections
7. Various Treatment Guidelines

What's a biofilm?

- Bacterial biofilms are microbial communities held together by an extracellular polymeric substance matrix predominantly composed of polysaccharides, proteins and nucleic acids.
- Biofilms protect the bacteria complicating treatment.



Sapi, E, et al. Characterization of Biofilm Formation by Borrelia burgdorferi In Vitro. PLoS One. 2012; 7(10): e48277.
Sapi, E, et al. Evidence of In Vivo Existence of Borrelia Biofilm in Borrelial Lymphocytomas. Eur J Microbiol Immunol (Bp). 2016 Feb 9;6(1):9-24



Biofilms in 3D

- Biofilms protect the resident individuals from the hostile environment of the host immune system attack or antibiotics or other targeted phytonutrient therapies.
- Dr. Sapi states, "It was demonstrated that pathogenic biofilms possess as much as 1000 fold increased tolerance to antimicrobial agents, making them very difficult to eradicate."
- Borrelia biofilms have been demonstrated in vitro and in tissue biopsy specimen.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3480481/

Lyme evades immune system responses

- Lyme causes immune system dysfunction and immune suppression
  - Tick salivary proteins delay early host immune response
  - Atypical morphologies evade immune response
- The spirochete has form changes and antigenic variation
  - Deceives alternative complement pathways
  - Antigenic variation challenges the humoral immune responses
- Physical seclusion to Intracellular and extracellular sites
  - Unique motility skills
  - Seeks niches to evade host immune system.
- Biofilms
- Persister cells

Berndtson, K. Inter Jour Gen med 2013;6: 291-306.
Embers, Microbes Infect 2004;6:312-8.

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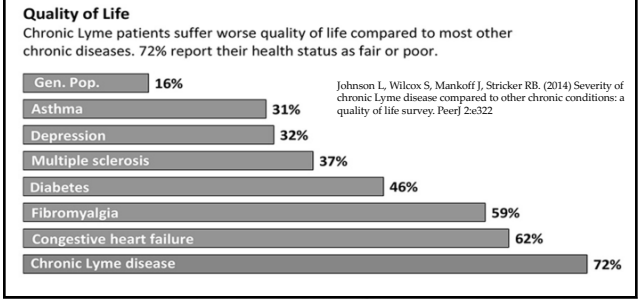
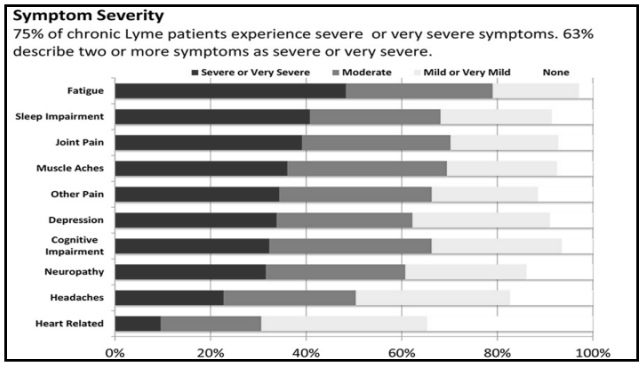
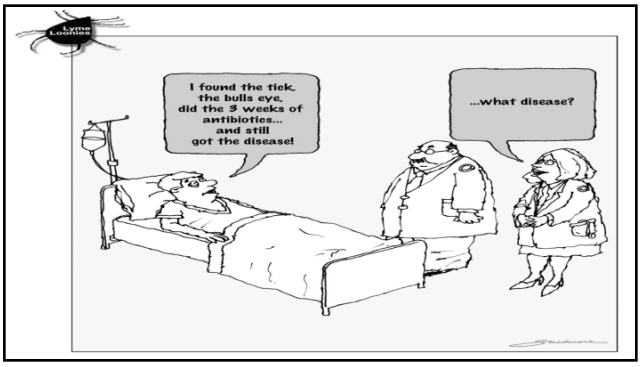
Lyme patients can become chronically ill patients



Johnson L, Wilcox S, Mankoff J, Stricker RB. (2014) Severity of chronic Lyme disease compared to other chronic conditions: a quality of life survey. PeerJ 2:e322





Complicating Factors in Lyme disease as a Chronic Illness

PATIENT FACTORS

1. Lyme disease and Co-infections
2. Immune Dysfunction
3. Inflammation
4. Environmental toxins – chemicals and mold
5. Nutritional deficiencies
6. Mitochondrial dysfunction
7. Endocrine abnormalities
8. Neurodegenerative disorders
9. Neuropsychiatric disorders
10. Sleep disorders
11. Autonomic nervous system dysfunction and POTS
12. Allergies
13. GI disorders
14. Liver dysfunction
15. Pain disorders/addiction
16. Deconditioning

Patient list from Richard Horowitz, MD

Kelly K. McCann, MD

Horowitz Lyme-MSIDS Questionnaire

The Horowitz Lyme-MSIDS Questionnaire is not intended to replace the advice of your own physician or other medical professional. You should consult a medical professional in matters relating to health, and individuals are solely responsible for their own health care decisions regarding the use of this questionnaire. It is intended for informational purposes only and not for self-treatment or diagnosis.

SECTION 1: SYMPTOM FREQUENCY SCORE

0 None 1 Mild 2 Moderate 3 Severe

1. Unexplained fevers, sweats, chills, or flushing	
2. Unexplained weight change; loss or gain	
3. Fatigue, tiredness	
4. Unexplained hair loss	
5. Swollen glands	
6. Sore throat	
7. Testicular or pelvic pain	
8. Unexplained menstrual irregularity	
9. Unexplained breast milk production; breast pain	
10. Irritable bladder or bladder dysfunction	
11. Sexual dysfunction or loss of libido	
12. Upset stomach	
13. Change in bowel function (constipation or diarrhea)	
14. Chest pain or rib soreness	
15. Shortness of breath or cough	
16. Heart palpitations, pulse skips, heart block	
17. History of a heart murmur or valve prolapse	
18. Joint pain or swelling	
19. Stiffness of the neck or back	
20. Muscle pain or cramps	
21. Twitching of the face or other muscles	
22. Headaches	
23. Neck cracks or neck stiffness	

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Horowitz Lyme-MSIDS Questionnaire

24. Tingling, numbness, burning, or stabbing sensations	
25. Facial paralysis (Bell's palsy)	
26. Eyes/vision: double, blurry	
27. Ears/hearing: buzzing, ringing, ear pain	
28. Increased motion sickness, vertigo	
29. Light-headedness, poor balance, difficulty walking	
30. Tremors	
31. Confusion, difficulty thinking	
32. Difficulty with concentration or reading	
33. Forgetfulness, poor short-term memory	
34. Disorientation: getting lost; going to wrong places	
35. Difficulty with speech or writing	
36. Mood swings, irritability, depression	
37. Disturbed sleep: too much, too little, early awakening	
38. Exaggerated symptoms or worse hangover from alcohol	
TOTAL Section 1	

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SECTION 2: MOST COMMON LYME SYMPTOMS SCORE

If you rated a 3 for each of the following in section 1, give yourself 5 additional points:	
39. Fatigue	
40. Forgetfulness, poor short-term memory	
41. Joint pain or swelling	
42. Tingling, numbness, burning, or stabbing sensations	
43. Disturbed sleep: too much, too little, early awakening	
TOTAL Section 2	

SECTION 3: LYME INCIDENCE SCORE

Now please circle the points for each of the following statements you can agree with:	If true, transpose points here:
44. You have had a tick bite with no rash or flulike symptoms. *3 points*	
45. You have had a tick bite, an erythema migrans, or an undefined rash, followed by flulike symptoms. *5 points*	
46. You live in what is considered a Lyme-endemic area. *2 points*	
47. You have a family member who has been diagnosed with Lyme and/or other tick-borne infections. *1 point*	
48. You experience migratory muscle pain. *4 points*	
49. You experience migratory joint pain. *4 points*	
50. You experience tingling/burning/numbness that migrates and/or comes and goes. *4 points*	
51. You have received a prior diagnosis of chronic fatigue syndrome or fibromyalgia. *3 points*	
52. You have received a prior diagnosis of a specific autoimmune disorder (lupus, MS, or rheumatoid arthritis), or of a nonspecific autoimmune disorder. *3 points*	
53. You have had a positive Lyme test (IFA, ELISA, Western blot, PCR, and/or borrelia culture). *5 points*	
TOTAL Section 3	

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Horowitz Lyme-MSIDS Questionnaire

SECTION 4: OVERALL HEALTH SCORE

	Transpose the points from column A here:
54. Thinking about your overall physical health, for how many of the past thirty days was your physical health not good?_____ days Award yourself the following points based on the total number of days: 0–5 days = 1 point 6–12 days = 2 points 13–20 days = 3 points 21–30 days = 4 points	
55. Thinking about your overall mental health, for how many days during the past thirty days was your mental health not good?_____ days Award yourself the following points based on the total number of days: 0–5 days = 1 point 6–12 days = 2 points 13–20 days = 3 points 21–30 days = 4 points	
TOTAL Section 4	

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SCORING:

Record your total scores for each section below and add them together to achieve your final score:

Section 1 Total:	
Section 2 total:	
Section 3 total:	
Section 4 total:	
FINAL SCORE	

If you scored 46 or more, you have a high probability of a tick-borne disorder and should see a health-care provider for further evaluation.
If you scored between 21 and 45, you possibly have a tick-borne disorder and should see a health-care provider for further evaluation.
If you scored under 21, you are not likely to have a tick-borne disorder.

Interpreting the Results
We see a high frequency of Section 1 symptoms in our patients, including fatigue, joint and muscle pain that often migrates, sleep disorders, as well as memory and concentration problems, and a high frequency of Section 3 symptoms, especially neuropathic pain that comes and goes and migrates (tingling, numbness, burning, etc.). These form a cluster of presenting symptoms that are characteristic of those with a high probability of having Lyme-MSIDS.
In one recent study conducted in our office of 100 consecutive patients, we found that more than 25 percent reported that the following symptoms were present most or all of the time in the month preceding their office visit. Many of these patients reported that these symptoms affected their quality of life: 71 percent reported that their physical health was not good and 47 percent reported that their mental health was not good on at least fifteen days in the previous month.

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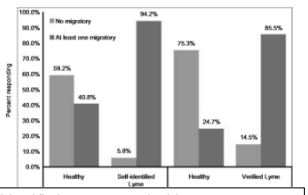
International Journal of General Medicine
Dovepress
ORIGINAL RESEARCH

Empirical validation of the Horowitz Multiple Systemic Infectious Disease Syndrome Questionnaire for suspected Lyme disease

Maryalice Citera[1]
Phyllis R Freeman[2]
Richard I Horowitz[2]

[1]Department of Psychology, State University of New York at New Paltz, New Paltz, NY, USA; [2]Hudson Valley Healing Arts Center, Hyde Park, NY, USA



Paper includes 3 studies. 6 factors were identified to correspond with Lyme symptoms including tingling, numbness, burning or stabbing sensations, forgetfulness and poor short term memory, joint pain or swelling, fatigue, disturbed sleep; plus dysautonomia and cardio/respiratory symptoms. 85% of Lyme patients had at least one migratory symptom, only 24% of healthy individuals possessed. Focus on migratory joint pain, muscle pain and neuropathic pains. Citera, 2017

MD

Pathophysiology of Lyme and Chronic Illness

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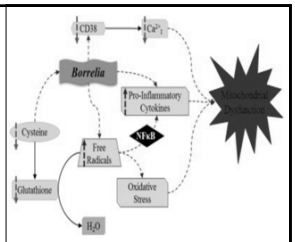
Autoimmunity
Molecular mimicry
Mitochondrial dysfunction
IDO upregulation
Increased kynurenic acid
Microglial activation
Gastrointestinal disturbances
Endocrine dysfunction
Mineral imbalance – zinc and manganese

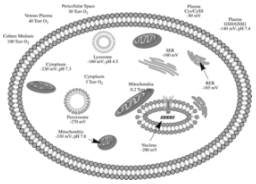
Lyme disease – inflammation and oxidative stress

- Significant rise in mitochondrial superoxide and decrease in ionized calcium indicate oxidative stress, mitochondrial membrane instability and release of pro-inflammatory cytokines in Lyme borreliosis patients.
- Activation of Inflammation and host immune responses cause damage leading to hallmarks of neurodegeneration. Misfolded proteins, oxidative stress, deficient apoptosis, cell death.
- Dexamethasone reverses inflammatory cascade, both lower inflammatory markers and preventing pathological changes in animal neuroborreliosis.



DeChiara, etal. 2012. Mol Neurobiol 46:614-38.
Peacock 2015. Redox Biology 5:66-70.
Ramesh. Amer Journ of Pathology. 2015. 185 (5): 1344-60.

Oxidative shielding rather than oxidative stress

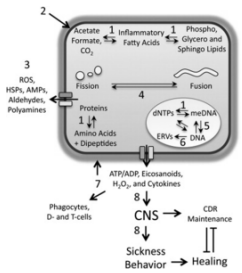


Naviaux. Journal of Pharmacology and Experimental Therapeutics. 2012, 342(3):608-18.

- When mitochondria nutrients and substrates are perturbed by viral or microbial infection or toxins, there is a metabolic mismatch.
- Electrons are diverted, oxygen consumption falls, assembly of DNA, RNA, lipids, proteins and carb synthesis stops. ROS/RNS rise and there is a limit to the replication of the invading pathogen.
- Oxidative changes are the symptoms of the disease, not the cause.

The Cell Danger Response

- The cell danger response (CDR) is an evolutionarily conserved cellular metabolic response that is activated when a cell encounters a chemical, physical, or microbial threat that could injure or kill the cell.
- Psychological trauma, particularly during childhood, can also activate the cell danger response, produce chronic inflammation, and increase the risk of many disorders.



Naviaux. Mitochondrion. 2014. 16:7–17

The Cell Danger Response

The acute CDR produces at least 8 functional changes:

1) It shifts cellular metabolism to prevent the hijacking and assembly of cellular resources by intracellular pathogens.
2) It stiffens the membranes of the cell
3) Releases antiviral and antimicrobial chemicals into the pericellular environment
4) Increases autophagy and mitochondrial fission to remove intracellular pathogens

The Cell Danger Response

5) Changes DNA methylation and histone modification to alter gene expression
6) Mobilizes endogenous retroviruses and other mobile genetic elements like the long interspersed nuclear elements (LINEs) to produce genetic variations
7) Warns neighboring cells and distant effector cells of the danger
8) Alters the behavior of the host to prevent the spread of infection to kin and sleep patterns to facilitate healing

Metabolic features of chronic fatigue syndrome

Robert K. Naviaux, Jane C. Naviaux, Kefeng Li, A. Taylor Bright, William A. Alaynick, Lin Wang, Asha Baxter, Neil Nathan, Wayne Anderson, and Eric Gordon

Features of CFS

- Metabolomics of chronic fatigue indicate a hypometabolic state in response to pathologically persist or recurrent cell danger signaling, as in the case of persistent viral or bacterial infections.
- Dauer, which means persistent or long-lived in German, is a hypometabolic state capable of living efficiently by altering basic mitochondrial functions to confer a survival advantage.
- Both males and females with Chronic Fatigue Syndrome had chemical signature that was distinct from healthy controls.

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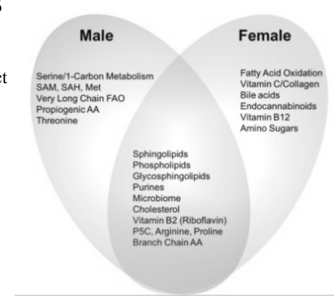
Metabolic Features of CFS

- Both males and females with Chronic Fatigue Syndrome had chemical signature that was distinct from healthy controls.
- 9 common pathways, 11 showed gender differences.
- Dominant abnormalities in sphingolipids constituted close to 50% of all metabolic changes.
- Phospholipids changes 16% in males, 26% in females.



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Pathophysiology of Lyme and Chronic Illness

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Microglial activation
Gastrointestinal disturbances
Endocrine dysfunction
Mineral imbalance – zinc and manganese

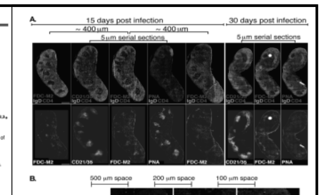
Kelly K. McCann, MD

PLOS PATHOGENS

RESEARCH ARTICLE

Suppression of Long-Lived Humoral Immunity Following *Borrelia burgdorferi* Infection

Rebecca A. Elsner, Christine J. Hastey, Kimberly J. Olsen, Nicole Baumgarth



Following the infection of mice with Borrelia burgdorferi, the germinal centers are structurally abnormal and long-lived plasma cells and B memory cells, which are normal immune responses, fail to develop for months after the infection…Also when infected, vaccination with influenza fails to induce protective anti-viral immunity.
Elsner, et al. 2014

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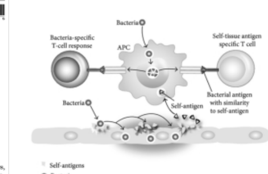
Review — Cell

Autoimmunity and the environment

Infections and autoimmunity – friends or foes?

Shaye Kivity, Nancy Agmon-Levin, Miri Blank and Yehuda Shoenfeld



Most infectious agents can induce autoimmunity disease in genetic susceptible hosts, which in turn increases their risks of additional infections. Post-infectious autoimmunity can be induced by a variety of mechanisms including molecular mimicry, bystander activation, persistent infections and polyclonal activation. Burden of infections are cumulative over lifetime to a breakthrough point. Kivity, et al. 2009

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Ten principles of the relationship between infection and autoimmunity

1. Infections can cause autoimmune diseases.
2. Different infectious agents (viruses, bacteria, fungus and parasites) can trigger autoimmunity.
3. An infection can trigger an individual with an underlying immune dysregulation to express an overt autoimmune disease.
4. Infectious agents can determine the presence of disease-specific auto-antibodies and clinical manifestations.
5. In many cases, it is not a single infection, but rather the ‘burden of infections’ during life that is responsible for induction of autoimmunity.

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Ten principles of the relationship between infection and autoimmunity

6. Infections during childhood can be implicated in the development of autoimmune diseases in adulthood.
7. Infections can protect individuals from some autoimmune diseases.
8. The same infectious agent can induce one specific autoimmune disease and protect from another autoimmune disease.
9. Molecular mimicry, epitope spreading, bystander activation and polyclonal activation can induce autoimmunity after infections via innate and adaptive immune responses.
10. Genetic susceptibility might explain why only a subgroup of individuals will develop autoimmunity after infections.

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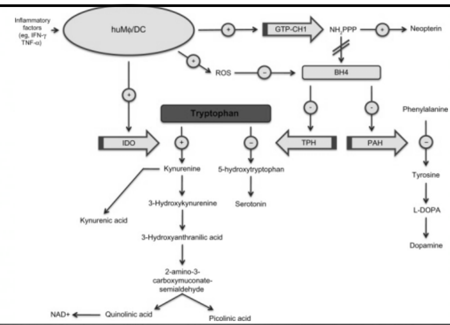
Tryptophan metabolism
- Lyme and serotonin



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Tryptophan metabolism
- Lyme and serotonin

- IDO is induced by interferon (IFN)γ, interleukin-6 and tumor necrosis factor-α, lipopolysaccharides and oxidative stress, factors that play a role in the pathophysiology of depression.
- TRYCATs, like kynurenine and quinolinic acid, are depressogenic and anxiogenic; activate oxidative pathways; cause mitochondrial dysfunctions; and have neuroexcitatory and neurotoxic effects that may lead to neurodegeneration.


INSTITUT PASTEUR

Review

Indoleamine 2,3-dioxygenase in infection: the paradox of an evasive strategy that benefits the host

Teresa Zelante*, Francesca Fallarino, Francesco Bistoni, Paolo Puccetti, Luigina Romani

Kelly K. McCann, MD


JOURNAL OF LEUKOCYTE BIOLOGY

Induction of indoleamine 2,3-dioxygenase by *Borrelia burgdorferi* in human immune cells correlates with pathogenic potential

Abstract

- Certain strains of *B. burgdorferi* induce IDO as a mechanism to evade the immune system and promote dissemination of the infection.
- Cytokines stimulate release of neopterin and induce IDO to degrade tryptophan.
- Increased concentrations of neopterin and l-kynurenine have been detected in the cerebrospinal fluid of patients with Lyme neuroborreliosis and Lyme encephalopathy.

Gasse, et al. Eur J Clin Chem Clin Biochem. 1994 Sep;32(9):685-9.
Widner, B, et al. Brain Behav Immun. 2002 Oct;16(5):590-5.

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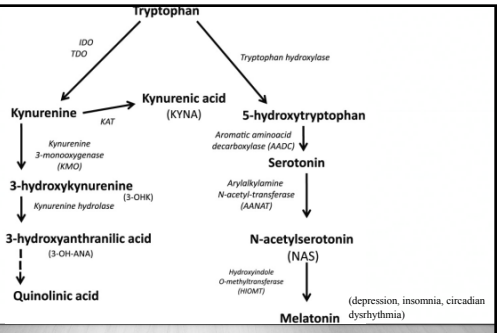
Neuroactive Kynurenines (anxiety, cognitive impairment



(depression, insomnia, circadian dysrhythmia)

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Doi: 10.1186/1742-2094-6-23
http://www.dr-w-klemann.de

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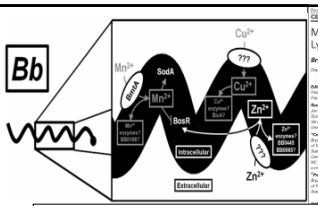

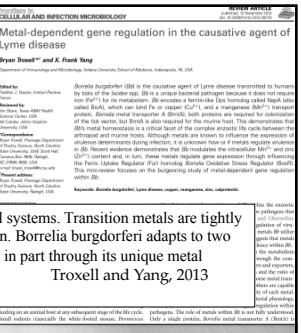
REVIEW ARTICLE
CELLULAR AND INFECTION MICROBIOLOGY
Metal-dependent gene regulation in the causative agent of Lyme disease
Bryan Troxell*† and X. Frank Yang

Metalloenzymes are essential for biological systems. Transition metals are tightly regulating and important for gene regulation. Borrelia burgdorferi adapts to two diverse niches, vector and mammalian host in part through its unique metal utilization, thus altering virulence factors. Troxell and Yang, 2013

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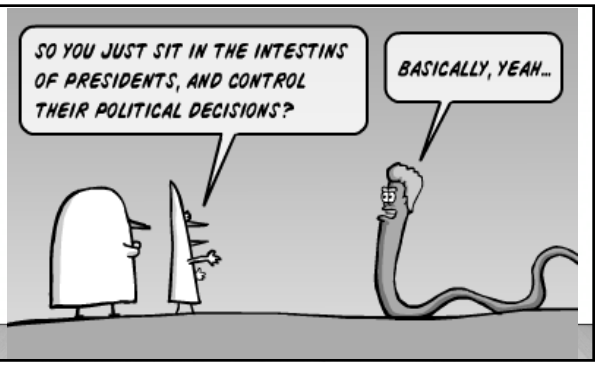

Complicating Factors in Lyme disease as a Chronic Illness

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Patient list from Richard Horowitz, MD

Kelly K. McCann, MD

Case: KF 53 year old woman – May 2015

- Life-time of good health until 2014 during menopause.
- Ran 17 marathons from age 15-46, then ran 25-30 miles a week until 2014
- Vegetarian for 30 years
- On HRT but wanting to optimize. She thought she wasn't on high enough doses.
- Presented with fatigue, decreased stamina and motivation, which she attributed to stress and hormonal imbalances.
- Also complained of night sweats, brain fog, abdominal pain and bloating, back pain and stiffness, leg weakness, new headaches, mood swings, depression, anxiety, sleep issues and a chronic cough.

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Case: KF 53 year old woman – May 2015

Past medical history significant for tinnitus, hypothyroidism, chronic sinusitis, and migraines.

Routine labs:

chol 213mg/dL = 5.52mmol/L, LDL 138 mg/dL = 3.57 mmol/L, HDL 85 mg/dL = 2.2mmol/L, pattern A

estradiol - not detectible

hs CRP <0.3mg/dL, HgA1c 5.4%, thyroid wnl. CBC wnl, CMP wnl.

TPO and anti-thyroglobulin were elevated.

- **Vit D25oh 44ng/mL = 109 nmol/L**
- **Vit D1,25oh was 147H = 382 pmol/L**

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Case: KF September 2015

- During a return visit review labs, she described an episode when she drank a glass of wine after work and became profoundly exhausted, nauseated with abdominal pain, fever, diarrhea and limb pain.
- The month prior had had increasing fatigue and limb achiness.
- The nausea dissipated over 6 days, but she was left weak with achy arms and legs and brain fog.
- She worked as a college professor and was challenged to organize her thoughts. She describes brain fog and dizziness. She was short of breath.
- She had dental pain and a herpes outbreak in her mouth.
- The college library was under remediation for mold.

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Case: KF September 2015

- **Differential diagnosis included:**
- Mold exposure and environmentally acquired illness (previously known as CIRS - chronic inflammatory response syndrome)
- New onset of neurodegenerative disease like Multiple sclerosis or ALS
- Psychosomatic manifestions of depression
- Cardiovascular disease
- Lyme disease and co-infections
- Viral infections
- Toxic exposures – heavy metals
- Small intestinal bacterial overgrowth or profound dysbiosis
- Parasites infestation
- Cancer

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Is it Lyme or mold? Could it be both?

Lyme symptoms		**Mold symptoms**	
Fatigue	**Joint pain**	**Fatigue**	Tingling
Fevers	**Myalgias**	Weakness	Tremors
Rashes	Joint swelling	Decreased assimilation of new knowledge	**Unusual pain**
Sweats	**Back pain**	**Myalgias**	**Shortness of breath**
Hair loss	**Neck stiffness**	**Headaches**	Sinus congestion
Swollen lymph nodes	TMJ pain	**Memory impairment**	**Cough**
Sore throat	**Headaches**	**Word finding problems**	Excessive thirst
Chest pain	**Muscle twitching**	**Decreased concentration**	**Confusion**
Shortness of breath	Neurological sensations of tingling, burning or stabbing	Light sensitivity	**Appetite swings**
Heart palpitations	Increased motion sickness	**Joint pains**	Temperature regulation
Nausea or vomiting	Vision changes	**Morning stiffness**	Increased urinary frequency
Difficulty eating	Hearing changes	Red eyes	Nocturia
Constipation/diarrhea	Hypotension	Tearing eyes	**Abdominal pain**
Bladder dysfunction	**Disturbed sleep**	Blurred vision	Numbness
Cystitis	**Memory loss**	**Vertigo**	Disorientation
Dizziness	**Confusion**	**Aches**	Metallic taste
Balance problems	**Difficulty concentrating**		Static shocks
Tremor			**Sweats (esp night sweats)**
Psychiatric disorders			Skin sensitivity/rashes
			Ice pick pain
			Gluten sensitivity

***This Slide Enlarged on Page 138**

KF specialty labs

- Natural Killer Cell - CD 57 is 34. (nl 60-360)
- Transforming Growth Factor beta1 (TGFBeta1) was 16,140 pg/mL. (nl <2382)
- C4a at quest was 7990 ng/mL (nl <2830)
- Vascular endothelial growth factor (VEGF) <31 pg/mL (nl 31-86)
- Vasointestinal active peptide (VIP) 39.1 pg/mL(nl 23-63)
- Melanocyte Stimulating Hormone (MSH) <8 pg/mL (nl 35-81)

HLA DR - 1-5 low MSH haplotype,
- 7-2-53 mold susceptible haplotype
- She failed her visual contrast test
- Nasal swab was positive for MARCONS

Igenex test result
IFA <40
IgM - 18 kDa++, 30 kDa+, 34 kDa+, 39 kDa IND, 41+, 58+, 83 IND – positive by Igenex criteria
IgG – 41+

Kelly K. McCann, MD

Seven Rules of Lyme Disease Action Plan

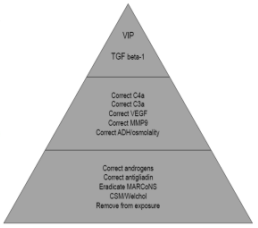
1. Symptoms Drive Diagnosis and Treatment
2. Lower Inflammation
3. Detox, Detox, Detox
4. Repair the Damage
5. Provide Internal Balance
6. Master the Big 3: Sleep, Food and Exercise
7. Heal your Emotional Wounds

Kelly K. McCann, MD

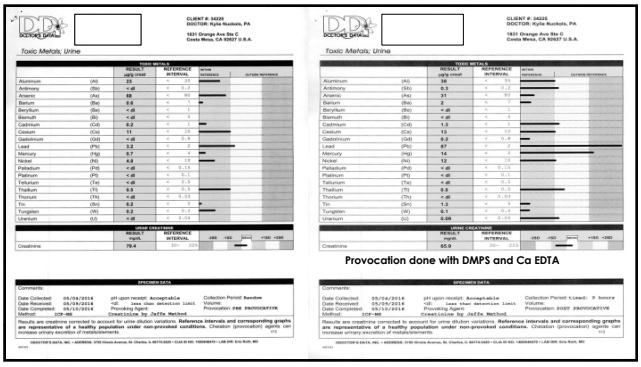
KF treatment plan

- For the environmentally acquired illness (CIRS) inflammation she needs binders activated charcoal, bentonite clay and short term use of Cholestyramine for lowering biotoxin inflammation due to mold and lyme.
- Then BEG spray for MARCONS
- Short course of antibiotics per patient's choice. Continuation of herbal treatments with Byron White Formulas.
- Biofilm buster – Lumbrokinase added
- Heavy metal retention assessment
- Her partner is a dentist!!

Shoemaker's CIRS treatment protocol



Kelly K. McCann, MD



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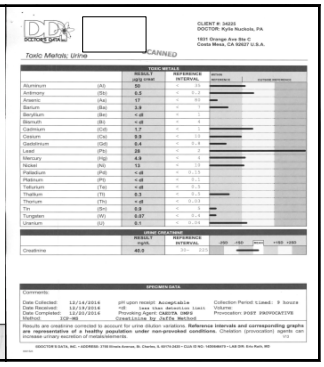
KF: treatment plan

- She completed 10 rounds of IV chelation with DMPS and CA EDTA.
- Far infrared sauna 2-4 times per week
- Weekly colonics
- Methylation, detox and nutritional support throughout



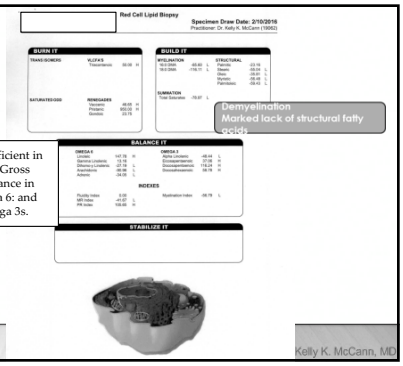
Complicating Factors in Lyme disease as a Chronic Illness

PATIENT FACTORS

1. Lyme disease and Co-infections
2. Immune Dysfunction
3. Inflammation
4. Environmental toxins – chemicals and mold
5. Nutritional deficiencies
6. Mitochondrial dysfunction
7. Endocrine abnormalities
8. Neurodegenerative disorders
9. Neuropsychiatric disorders
10. Sleep disorders
11. Autonomic nervous system dysfunction and POTS
12. Allergies
13. GI disorders
14. Liver dysfunction
15. Pain disorders/addiction
16. Deconditioning
17. **Membrane stability/ Fatty acid composition**

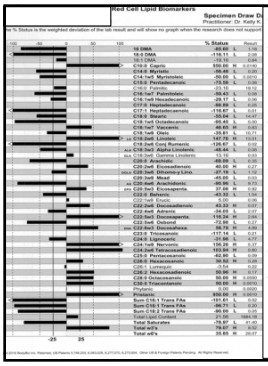
Patient list from Richard Horowitz, MD Kelly K. McCann, MD

RBC fatty acid analysis



90% deficient in AA. Gross imbalance in Omega 6: and Omega 3s.

Kelly K. McCann, MD



- Add eggs to diet.
- Add more flax seeds, chia seeds, hemp seeds and nuts
- Phosphatidylcholine 1 tbsp or 8 caps daily = 9 grams or more if tolerated
- Sodium/potassium Butyrate 2 caps twice daily =500mg butyric acid/cap
- Evening primrose oil 1000mg daily
- Balance oil 4:1 mixture of Omega6:omega3 – 6 tbsp daily
- High dose B vitamins for methylation and detox support
- Bile salts to assist with fat absorption
- Fatty alcohols to repair demyelination along with uridine

Membrane Stabilizing Diet: Modified Ketogenic Diet for Optimal Neurometabolic Health

Permitted foods

Protein at every meal
Raw, organic ground seeds and nuts
Nut and seed butters
Free range eggs
Lentils and legume pastas
Paleo breads and wraps
Limited starchy vegetables
Organic ghee, butters and cheeses if tolerated
Fruits – mostly berries, kiwi
Veggies
Bone Broths
Cook foods in coconut oil or ghee

Kelly K. McCann, MD

Membrane Stabilizing Diet: Modified Ketogenic Diet for Optimal Neurometabolic Health

Omitted foods

All grains, esp gluten
No corn or rice
No peanuts or peanut butter
No mustard (often contaminated with molds and contain VLCFA)
Avoid commercial oils extracted under heat such as canola oil
No sodas or diet drinks
No hybridized oleic oils (olive)
No GMO foods
No dried fruits, high sugar fruits
NO fast food
NO Kombucha, No mushrooms
NO moldy or contaminated foods
No sugar or sweeteners

Kelly K. McCann, MD

KF follow up

- **Clinically she is doing well. Minimal fatigue and lower extremity heaviness. Still has occasional "crash days" as of 2/17. She is back running again. But as of 11/17, she is back to normal.**
- **Off antibiotics and binders.**
- **Continuing the Byron White formulas and biofilm busters.**
- **Doing LDI for lyme**
- **Getting dental work done as we determined she had resistant MARCONS due to dental reservoir.**
- **Maintaining Oral membrane stabilizing protocol**
- **Getting IV Phosphatidyl choline. Is up to 0.8 g/kg as of 6/17.**

- **LABS: 9/26/17**
- **C4a - 707 ng/mL (nl <2830)**
- **TGFBeta 1 – 1566 pg/mL (nl <2382)**
- **VIP – 42 pg/mL (nl 31-86 pg/mL)**
- **MSH <8 pg/mL (nl 35-81 pg/mL)**
- **CD 57 – 128 (optimal >300)**
- **Vit D 25oh is 70 ng/mL = 174 nmol/L**
- **Vit D1,25oh is 64 pg/mL = 166.4 pmol/L**

Kelly K. McCann, MD

Case: SD 16 year old with complicated past medical history presented in 2/15. Well until 2 years ago when she got the "flu" for 24 hour and never recovered. Saw ENTs, Neurologists, 3 different rheumatologists, endocrinologist, hematologist, several "holistic" practitioners, pain doctors.

Constant HA
Dizziness
Migraines
Vision Changes
Chronic Fatigue
Joint Pains
Tingling/ shooting pains
Fevers/Chills
Heart palpitations
Chest pains
Constipation
Ovarian cysts
Hashimoto's thyroiditis
Insulin resistance
Asthma
Bloating
Dysmenorrhea
Sleeping disturbance

Kelly K. McCann, MD

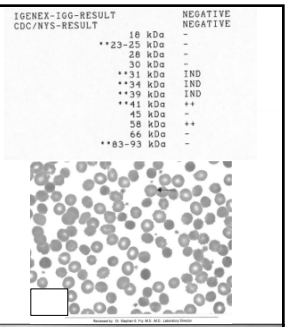
Case: SD 16 year old

Was told she had parasites and Lyme disease by a "holistic" practitioner based on Applied kinesiology testing.
Diagnosed with undifferentiated mixed connective tissue disorder and complex migraines but no medications helped.
Symptoms had waxed and waned over the 2 years prior to her initial appt. Hospitalization with lumbar puncture in mid 2014, ended up in a wheelchair for several months due to extreme joint pains. She was walking when she came into our clinic.

Kelly K. McCann, MD

Case: SD

Labs:
2/4/15. wbc 3.1 x10_3, hgb 10.4 g/L, mcv 70, plt 305 x10_3, cd 57 is 24 (low)
Ferritin 9 ng/mL = 20 pmol/L
IgA 62mg/dL (low), IgM 236mg/dL wnl, IgG3 subclass low 16mg/dL (low) rest wnl.
ANA neg. thyroid antibodies+
Vit D25oh 32 ng/mL = 79.87nmol/L
HLA DR 13-6-52A mold susceptible,
14-5-52B multi susceptible
TGFbeta1 9680pg/mL, VIP<16.8pg/mL, MSH 21pg/mL, Homocysteine 14.8µmol/L, hs CRP 1.1mg/L
Igenex –Lyme PCR neg, Indeterminate for Anaplasma, Bartonella.



Kelly K. McCann, MD

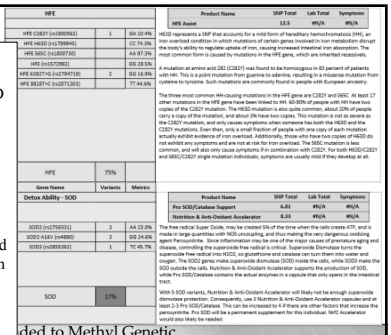
Case: SD

- The hematologist gave her Iron infusion weekly for 10 weeks until 1/16 and her energy improved. Joint pains persisted in hands, feet, back.
- Started on LDN. Supplements for sleep. Probiotics helped her GI tract.
- Started on Herbals immediately for Lyme and Bartonella. MC-BB1 and MC-BAR1
- Layered in antibiotics for Lyme and Bart including plaquenil, rifampin, doxycycline and azithromax.
- Stopped doxy due to intolerance

- 8 weeks post infusions her ferritin was 345, hgb 13.7.
- Repeat labs show persistent ferritin levels in the 200s-300s.
- By 4/16 cd 57 was still only 27, wbc 5.3, hgb 15.1, tgfbeta1 1724, vit D 33.5, Vit D1,25oh 36.6, hs CRP 2.38
- She stopped the rifampin and zithro. Continue plaquenil, LDN, herbals.
- Started an essential oil protocol for infections.
- 9/16 labs showed **ferritin 266**, %iron sat 78%, total iron 188, TIBC 240L, hgb 14.1. **Homocysteine 27.3,** folate level was 2.4. Clinically energy is ok. Joints are fine. No HA. Feels Lyme is under control. Iron/minerals off. Why?

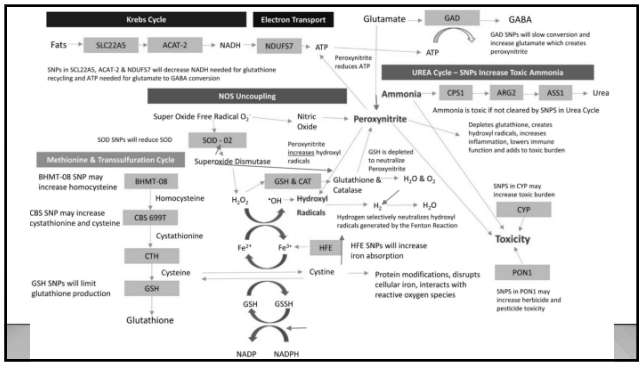
Case: SD

- She is heterozygous for HFE C282Y plus another HFE gene.
- She has significant variants in SOD expression which is critical for dealing with oxidative stress.
- She also variants in Catalase enzymes and glutathione enzymes systems.
- WHO published statement that a serum ferritin above 300mcg/L in men and 200mcg/L in women could be considered at risk for severe iron overload.
- She was experiencing Fenton reactions!



ded to Methyl Genetic tion.com

Kelly K. McCann, MD



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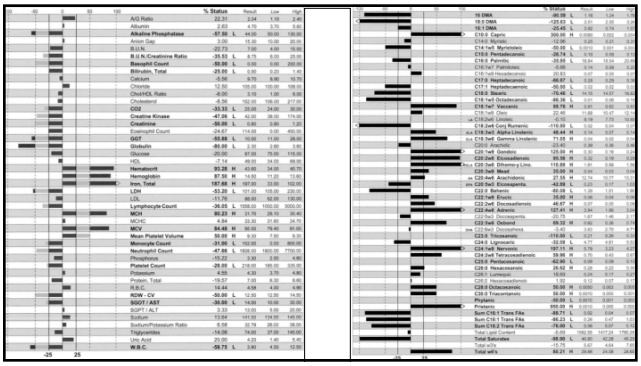

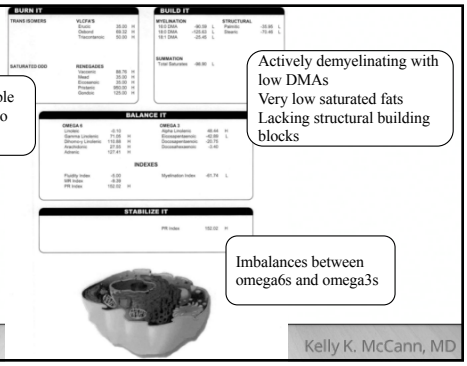

Lots of undesirable fats which need to be removed

Actively demyelinating with low DMAs
Very low saturated fats
Lacking structural building blocks

Test performed by Kennedy Krieger at John Hopkins and then analyzed and report generated by Body Bio.

Imbalances between omega6s and omega3s

Kelly K. McCann, MD

Case: SD

Treatment Plan:
- Phosphatidyl choline 1 tbsp
- SR3 oil which is sunflower omega6:flax omega3 in a 4:1 ratio 3-6 tbsp. daily
- Evening primrose oil
- high EPA fish oil
- methylated B vitamins
- Butryate for breaking down the VLCFA
- Prometol fatty alcohol for myelin support
- **IV phosphatidyl choline infusions**

HFE Assist

- HFE Assist brought her ferritin down from 230-250s to 79
- Next treatment, LDI – low dose immunotherapy!

Kelly K. McCann, MD

Case: KK

17 yr old adolescent with OCD on Prozac, Wellbutrin, Effexor, autism spectrum disorder, common variable immunodeficiency on IVIG, growth hormone deficiency, scoliosis, anxiety, hypothyroidism, chronic constipation, intestinal yeast overgrowth, sleep disturbance, cystic acne, chronic viral infections with emotional stability of acyclovir.

PMHx: Mom was sick with "cold" in the 3rd trimester.
No antibiotics given.
Full term. Traumatic birth.
Vacuum extraction.
Apgars 7/9. O2 given at birth.
He has been "sick" since birth.

Kelly K. McCann, MD

Case: KK

17 yr old adolescent with OCD on Prozac, Wellbutrin, Effexor, autism spectrum disorder, common variable immunodeficiency on IVIG, growth hormone deficiency, scoliosis, anxiety, hypothyroidism, chronic constipation, intestinal yeast overgrowth, sleep disturbance, cystic acne, chronic viral infections with emotional stability of acyclovir. PMHx: Mom was sick with "cold" in the 3rd trimester. No antibiotics given. FT, traumatic birth, apgars7/9. vacuum extraction. O2 at birth. He has been "sick" since birth.

PSHx: 2003 eye surgery for strabismus
2004 – PE tube placement
2005 – adenoidectomy
2006 – eye surgery for strabismus

IGENEX-IGG-RESULT CDC/NYS-RESULT	POSITIVE NEGATIVE
18 kDa	-
**23-25 kDa	-
28 kDa	-
30 kDa	-
**31 kDa	-
**34 kDa	-
**39 kDa	+
**41 kDa	+++
45 kDa	+
58 kDa	-
66 kDa	-
**83-93 kDa	-

Kelly K. McCann, MD

Relationship of Gestational Lyme and Chronic Infections

Dr. Jones performed chart reviews on 102 gestational borrelia cases.
14% Babesia, 7% Strep,
6% Ehrlichiosis
9% autism
56% attention deficit disorder

Psychological symptoms:
Mood swing 54%
Anger 23%
Anxiety 21%
Depression 13%
OCD 11%, Suicidal thoughts 7%

Neurological symptoms:
HA 50%, Vertigo 30%
Developmental delay 18%
Tic disorders 14%, seizure disorders 11%
Photophobia 43%, hyperacuity 36%
Poor memory 39%
Cognitive impairments 27%, speech delays 21%, read/writing delays 19%, auditory/visual processing 13%,
dyslexia 18%
Physical symptoms:
GERD 27%, abd pain 29%, diarrhea or constipation 32%, nausea 23%

Jones, et al. Case studies of 102 Live births. Lyme Times 2005:34-6. summer

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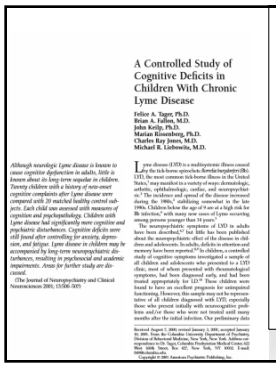

A Controlled Study of Cognitive Deficits in Children With Chronic Lyme Disease

Felice A. Tager, Ph.D.
Brian A. Fallon, M.D.
John Keilp, Ph.D.
Marian Rimoldzy, Ph.D.
Charles Ray Jones, M.D.
Michael R. Liebowitz, M.D.

Although neurologic Lyme disease is known to cause cognitive dysfunction in adults, little is known about its long-term sequelae in children. Twenty children with a history of new-onset cognitive complaints after Lyme disease were compared with 20 matched healthy control subjects. Each child was assessed with measures of cognition and psychopathology. Children with Lyme disease had significantly more cognitive and psychiatric disturbances. Cognitive deficits were still found after controlling for anxiety, depression, and fatigue. Lyme disease in children may be accompanied by long-term neuropsychiatric disturbances, resulting in psychosocial and academic impairments. Areas for further study are discussed.

(The Journal of Neuropsychiatry and Clinical Neurosciences 2001; 13:507–515)

Neurocognitive testing revealed:

Headaches (100%)
Brain fog (88%)
Short term memory loss (94%)
Word finding problems (82%)
Distractibility (82%)
School work deterioration (94%)
Irritability/depression (94%)
Insomnia (82%)
Sensitivity to sound (58%)
Sensitivity to light (74%)

Tager FA, et al. A controlled study of cognitive deficits in children with chronic Lyme disease. J Neuropsychiatry Clin Neurosci. 2001;13(4):500–507.

Kelly K. McCann, MD

Children and Lyme and Cognitive functioning

Pilot study: 8 children with Lyme age 7-13
Completed 1-5 months of antibiotics

Initial evaluation symptoms: fatigue, joint pains, headache, irritability, Trouble with schoolwork, Concentration, Memory, Sleep disturbance, Sensory sensitivity, Mood swings, Impulsivity, Depressed mood, Anxiety, Motor tics, Word retrieval difficulty, Balance problems, temper outbursts

Cognitive defects: Deficient in Performance IQ and verbal IQ, Scores were lowest on processing speed, visual scanning, sequencing, and causal reasoning; attention deficits, visual and sustained

http://www.neuro-lyme.com/Psychological_Evaluation_of_Pediatric_Neurologic_Lyme_Disease.html

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Children and Lyme and Cognitive functioning

Re-eval after antibiotics, (10-32 months)

All improved, 1 had HA, another sleep issues. 5/8 had improvements in cognition and academics, but 4 had cognitive, 5 had emotional, 2 had both and 1 had physical and emotional symptoms.

Cognitive testing showed global improvements

http://www.neuro-lyme.com/Psychological_Evaluation_of_Pediatric_Neurologic_Lyme_Disease.html

Kelly K. McCann, MD

Pilot studies of ASD and Lyme

Vojdani identified 22% of ASD patients via CDC criteria +Lyme

LIAF study found 26% of ASD children positive for Lyme vs 0 controls

Levine tests 9 ASD children. All had Igenex positive WB.

Nicholson tested 48 ASD patients found 20-30% PCR or southern blot positive and 68% co-infection with Mycoplasma, Bartonella, Ehrlichia and Babesia. 29% positive for HHV-6

Bransfield, et al. Association between tick-borne infections, Lyme borreliosis and autism spectrum disorders. Medical Hypotheses 2008 7, 967-974.

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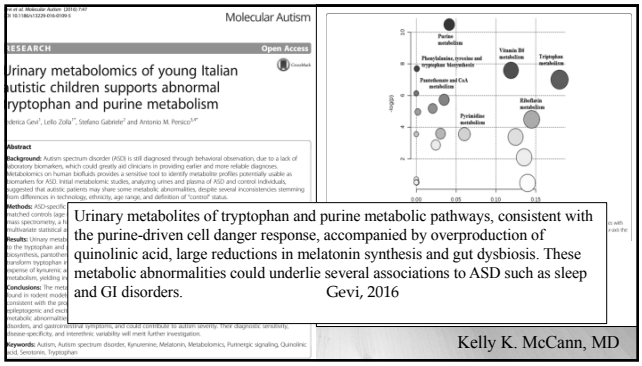

Molecular Autism

RESEARCH Open Access

Urinary metabolomics of young Italian autistic children supports abnormal tryptophan and purine metabolism

Abstract

Background: Autism spectrum disorder (ASD) is still diagnosed through behavioral observation, due to a lack of laboratory biomarkers, which could greatly aid clinicians in providing earlier and more reliable diagnoses. Metabolomics on human biofluids provides a sensitive tool to identify metabolite profiles potentially usable as biomarkers for ASD. Initial metabolomic studies, analyzing urines and plasma of ASD and control individuals, suggested that autistic patients may share some metabolic abnormalities, despite several inconsistencies stemming from differences in technology, ethnicity, age range, and definition of "control" status.

Methods: ASD-specific matched controls (age, mass spectrometry, a multivariate statistical a

Results: Urinary metab to the tryptophan and biosynthesis, pantothe transform tryptophan a reserve of kynurenic a metabolism, yielding in

Conclusions: The meth found in rodent model consistent with the pat epileptogenic and exci metabolic abnormalities disorders, and gastrointestinal symptoms, and could contribute to autism severity. Their diagnostic sensitivity, disease specificity, and intensities' variability will merit further investigation.

Keywords: Autism, Autism spectrum disorder, Kynurenine, Melatonin, Metabolomics, Purinergic signaling, Quinolinic acid, Serotonin, Tryptophan

Urinary metabolites of tryptophan and purine metabolic pathways, consistent with the purine-driven cell danger response, accompanied by overproduction of quinolinic acid, large reductions in melatonin synthesis and gut dysbiosis. These metabolic abnormalities could underlie several associations to ASD such as sleep and GI disorders. Gevi, 2016

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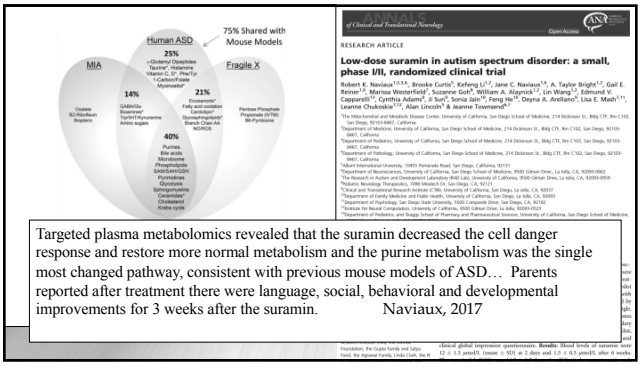

ANNALS of Clinical and Translational Neurology

RESEARCH ARTICLE

Low-dose suramin in autism spectrum disorder: a small, phase I/II, randomized clinical trial

Targeted plasma metabolomics revealed that the suramin decreased the cell danger response and restore more normal metabolism and the purine metabolism was the single most changed pathway, consistent with previous mouse models of ASD… Parents reported after treatment there were language, social, behavioral and developmental improvements for 3 weeks after the suramin. Naviaux, 2017

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Case: KK

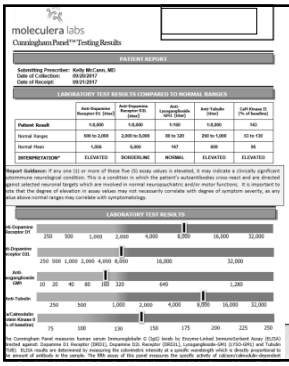
Odd chain fats created by viruses. Needs butyrate to break up the VLCFA and renegade fats

Needs better dietary fats, phosphatidyl choline and fatty alcohol to support remyelination

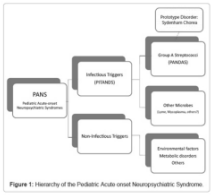
Needs sources of ALA (flax, chia, hemp) Evening primrose oil (GLA) and more fish oil Omega3s

Herbal protocols for Lyme were also instituted

Kelly K. McCann, MD



This patient has PANS – Pediatric Autoimmune encephalitis likely due to post natal trigger on top of possible gestational Lyme.



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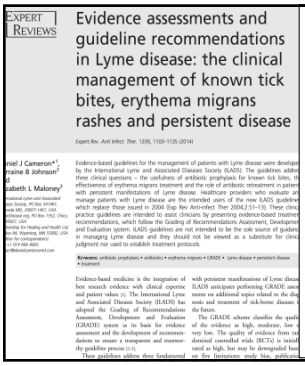
Complicating Factors in Lyme disease as a Chronic Illness

BACTERIA FACTORS
1. Numerous strains of Borrelia
2. Different forms of Borrelia
3. Testing Challenges
4. Co-infections
5. Biofilms
6. Immune evasion and persistent infections
7. **Various Treatment Guidelines**

Kelly K. McCann, MD



Evidence assessments and guideline recommendations in Lyme disease: the clinical management of known tick bites, erythema migrans rashes and persistent disease

The guidelines address 3 treatment questions:
1. Usefulness of antibiotics for known tick bites.
2. The effectiveness of erythema migrains (EM) treatment.
3. The role of antibiotic treatment in patients with persistent manifestation of Lyme disease.

With regard to the 3rd question, reassess diagnosis, screen for co-infections, evaluate for other causes, and start with 4-6 weeks of antibiotics if so agreed.

Extensive treatment options exist. Consider previous responsiveness, progression of illness, patient impairments.

Phytochemicals and Micronutrients for anti-borrelia efficacy

Dipsacus Sylvestris (Teasel root)
Grapefruit Seed Extract
Uncaria tomentosa
Otoba parvifolia
Stevia rebaudiana
Wild cherry
Black walnut green hull

Apricot seed
Anise
Vitamin B- complex
Vitamin C
Vitamin D3
Kelp (iodine)
Serrapeptase

Teasel root

Goc, et al. Ther Adv Infectious Dis 2016. 3(3-4): 75-82.
Goc, et al. Int Jour Bio Sci. 2016. 12(9): 1093-1103.

Kelly K. McCann, MD

Table 3. Efficacy of phytochemicals against *Borrelia sp.*

Phytochemicals	Spirochetes (µg/ml)	Rounded forms (µg/ml)	Biofilm (µg/ml)
Apigenin	MIC_{40} at 125	NS	NS	NS
Malvidin	MIC_{45} at 75	NS	NS	NS
Quercetin	MIC_{70} at 75	MBC_{45} at 125	MBC_{40} at 250	NS
E-viniferin	MIC_{70} at 75	MBC_{40} at 125	MBC_{40} at 250	NS
Resveratrol	MIC_{70} at 125	MBC_{40} at 250	MBC_{40} at 300	NS
Ellagic acid	MIC_{70} at100	MIC_{65} at 250	NS	NS
Oleuropein	MIC_{45} at 250	NS	MBC_{30} at 500	NS
Nordihydrogualaretic acid	MIC_{40} at 125	NS	NS	NS
Amygdalin	MIC_{90} at 75	MBC_{65} at 100	MBC_{50} at 150	NS
Fucoidan	NS	NS	NS	NS
Berberine sulfate	MIC_{90} at 100	MBC_{80} at 150	MBC_{50} at 250	NS

BSH medium, Buffered Schamm and Hestrin's; BSK; Barbour–Stoenner–Kelly; EC, effective concentration eradicating biofilm; MBC, minimal bactericidal concentration; MIC, minimal inhibitory concentration; NS, not susceptible.
Testing was performed with two species such as *Borrelia burgdorferi* and *Borrelia garinii*. Subscript index at the MIC value indicates the percent of inhibition at the provided concentration expressed as µg/ml in 1.5ml of BSK complete medium at 33°C after 72h; the MBC value indicates the percent of killing at the provided concentration expressed as µg/ml in 1.5ml of BSH complete medium at 33°C after 72h, according to [Goc *et al.* 2015].

Table 1. CAM treatment of Lyme disease with a combination of different antibiotics, herbal remedies, and nutritional supplements, with pertinent references

Antibiotics used for treatment of Lyme disease (Refs 6–8, 10, 11)	Herbal remedies	Ref	Nutritional supplements	Ref
Doxycycline	Samento	(24)	Omega-3 Fatty Acids	(26)
Minocycline	Cumada	(24)	Coenzyme-Q10	(26)
Amoxicillin	Burbur	(24)	S-Adenosylmethionine	(8, 24, 25)
Augmentin	Allicin	(25)	Grapeseed Extract	(26)
Azithromycin	Dragon's blood	(25)	Magnesium	(24)
Biaxin	Cat's claw	(25)	L-Carnitine	(4, 8)
Erythromycin	Devil's claw	(24)	α-Lipoic acid	(14, 15)
Vaucomycin	Echinacea	(25–28)	Dimethylglycine	(27)
Clarithromycin (biaxin)	Citriodiol (lemon eucalyptus extract)	(9)	Vitamin B-complex	(4, 8)
Cefuroxime axetil	Astragallus	(29)	Methylcobalamin	(4, 8)
Penicillin	Nettle	(24)	Vitamin C and D	(12, 13)
Ceftriaxone	Ginkgo biloba	(4, 8)	Hydrolytic enzymes	(16, 17)
Rifampin	Curcumin	(19–20)	Mushroom extracts and Beta-glucan	(22)
Flagyl	Oregano tea	(25)	Thymic peptides	(29)
Plaquenil	Boswellia	(26)	Pycnogenol	(27)
Taurox SB™	Parsley extract	(24)	*N*-Acetylcysteine and glutathione	(26)
Colloidal silver	Red chili pepper (capsaicin)	(18)	Probiotics	(23)
Imipinem	Quercetin	(21)	Dehydroepiandrosterone	(12)
			Royal Jelly	(26)

Doi:10.1093/ecam/nem138

Beyond Balance Products for Lyme and Co-infections

Core Immune Support
MC-BB1 - for Lyme
MC-BB2 – stronger formula for relapsing fever Borrelia, Erhlichia
MC-BAR-1 – for Bartonella
MC-BAR-2 – stronger formula for bartonella
MC-BAB-1 – for Babesia microti
MC-BAB-2 – for Babesia duncani and Protomyxoma rheumatica
MC-BAB-3 –broad spectrum blood parasites

MC-BB1

Supplement Facts
Serving size 1 ml
Servings per container 30

Amount Per Serving	%DV
Proprietary Blend	
Queen's Root (Root) *(Stillingia sylvatica)*	*
Motherwort (Tops) *(Leonurus cardiaca)*	*
Plantain Leaf (Tops) *(Plantago lanceolata)*	*
Black Walnut (Green Hull) *(Juglans nigra)*	*
Licorice (Root) *(Glycyrrhiza glabra)*	*
Calendula (Flower) *(Calendula officinalis)*	*

* Daily Value Not Established

Other Ingredients: Kosher vegetable glycerin (80% by volume), Filtered water

Allergens: This product contains no soy, corn, or any other known allergens. Free from preservatives, artificial colorings, or flavorings.

Warning: If pregnant, nursing, or taking medications, consult your healthcare professional before use.

Beyond Balance Products for Lyme and Co-infections

Tox-Ease GL

Supplement Facts
Serving size 1 ml
Servings per container 59

Amount Per Serving 100 mg	%DV
Proprietary Blend	
Slippery Elm (Bark) *(Ulmus fulva)*	*
Bilberry (Berry) *(Vaccinium myrtillus)*	*
Grape Seed (Seed) Extract *(Vitis vinifera)*	*
Mullein (Leaf) *(Verbascum thapsus)*	*
Elder (Berry) *(Sambucus nigra)*	*
Rosehips (Bud) *(Rosa canina)*	*
Red Clover (Blossom) *(Trifolium pratense)*	*
Licorice (Root) *(Glycyrrhiza glabra)*	*
Dandelion (Leaf) *(Taraxacum officinale)*	*
Rhubarb (Root) *(Rheum spp.)*	*
Fresh Skullcap (Flowering tops) *(Scutellaria lateriflora)*	*
Milk Thistle (Seed) *(Silybum marianum)*	*
Cayenne (Fruit) *(Capsicum annum)*	*

* Daily Value Not Established

Detox support
Tox-Ease – general detox/digest aid
Tox-Ease II – heavy metal detox
Tox-Ease GL –gentle cellular detox
Cognease Detox

Biofilm Breakdown
MC-BFM-1 – made from Guggul
MC-BFM-P – pediatric doses

Fungal Products
Pro-Myco
Mycoregen

Parasite Products
MC-PZ
Parazomin

Beyond Balance Products for Lyme and Co-infections

Immune Support Products
IMN-B – guard against bacteria
IMN-GI – support GI immunity
IMN-R –Immune modulatory
IMN-V – guard against viruses
IMN-V-III – for neurological viral symptoms

Environmental Detox Support
ENL-BT-1 – for Biotoxins
ENL-MC – for Mycoplasma
ENL-NM - for environmental toxins
ENL-RD – for radiation exposure

Inflammation
Cyflacalm
Cyflacalm II- for vascular/nervous inflammation

IMN-V-III

Supplement Facts
Serving size 1 ml
Servings per container 60

Amount Per Serving 100 mg	%DV
Proprietary Blend	
Cat's Claw (Bark) *(Uncaria tomentosa)*	*
Licorice (Root) *(Glycyrrhiza glabra)*	*
Skullcap (Flowering Tops) *(Scutellaria lateriflora)*	*
Rosehips (Hip) *(Rosa canina)*	*
Coptis (Rhizome) *(Coptis chinensis)*	*
Cleavers (Tops) *(Galium aparine)*	*
Dandelion (Whole Plant) *(Taraxacum officinale)*	*
Kelp (Thallus) *(Laminaria digitata)*	*
Elderberry (Berry) *(Sambucus nigra)*	*
Mistletoe (Leaf) *(Viscum album)*	*
Valerian (Root) *(Valeriana officinalis)*	*
Wild Lettuce (Leaf) *(Lactuca spp.)*	*
Cornsilk (Green Silk) *(Zea Mays)*	*
Grape Seed (Seed) *(Vitis vinifera)*	*
Horsetail (Spring Shoots) *(Equisetum arvense)*	*
Rosemary (Leaf) *(Rosmarinus officinalis)*	*
Gotu Kola (Leaf) *(Centella asiatica)*	*
Thyme (Leaf) *(Thymus vulgaris)*	*
Marshmallow (Root) *(Althaea officinalis)*	*
White Willow (Bark) *(Salix alba)*	*

* Daily Value Not Established

Beyond Balance Products for Lyme and Co-infections

Begin by Layering Formulas
1. Start with Detox of the terrain first
2. Antimicrobial treatment
3. Ensure solid nutritional support
4. Support reduction of inflammation
5. Address biofilm
6. Continue detox support
7. Continue evaluating and supporting as clinical indicated.

Sample protocol for multiply infected patient with brain fog:
1. Start **Tox-Ease GL** 3 drops BID, gradually increase by 1 drop BID up to 12-15 drops 2-3 times per day.
2. Add **MC-BB-1** 1 drop BID. Slowly increase as tolerated up to 10-12 drops BID
3. **Cyflacalm II** 3-4 drops BID
4. Next **MC-BAR-1** for bartonella. (adjust like MC-BB-1)
5. Add **MC-BFM-P** –pinch once daily, then ½ cap once daily, work up to 1 cap BID.
6. **Cognease Detox** 1 drop BID, increase up to 10-15 drops 2-3 times daily.

Integrative and Functional approaches to Lyme disease and chronic infections

- Identify infections
- Determine all areas of dysfunction
- Lifestyle Modifications
- Dietary adjustments
- Detoxification and reduction of exposures to toxins/molds/EMF
- Nutritional supplementation
- Immune support
- Genetic analyses and appropriate support
- Gastrointestinal assessments and support
- Mitochondrial support
- Adrenal/endocrine support
- Methylation support
- Membrane stabilizing therapies

Integrative and Functional approaches to Lyme disease and chronic infections

- Low dose immunotherapy
- Emotional and psychological issues/Trauma
- Structural dysfunctional support
- Physical therapy
- OMT/craniosacral therapy
- Chiropractic manipulation
- Visceral manipulation
- Acupuncture/TCM referrals
- Energy medicine/Rife
- Movement/exercise
- Spiritual counseling
- Family counseling

Kelly K. McCann, MD

"According to my research, laughter is the best medicine, giggling is good for mild infections, chuckling works for minor cuts and bruises, and snickering only makes things worse."

Kelly K. McCann, MD

How to manage a patient whom you suspect has Lyme disease

- Patients often need a team approach to their care.
- Locate and meet with Lyme literate practitioners in your area.
- Check out www.ILADS.org or your state or local Lyme advocacy groups for referrals.
- Begin the work up, if comfortable. If not, refer.
- You may also need functional and integrative medicine practitioners with whom to partner, if you can't find a Lyme literate, functional practitioner.
- Know that these patients have often been neglected and dismissed by the medical system. They need your support and acknowledgment that you believe them, even if you can't explain all their symptoms.
- If the psychological and emotional and even spiritual aspects don't get addressed, they will continue to struggle.
- Metaphor of immune system – boundary issues

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