Moldy: Identification and Treatment of Mold and Fungal-Related Illness

KELLY K. MCCANN, MD, MPH&TM, FACP, FABP, ABHIM, IFMCP

FEBRUARY 4, 2018

ASSOCIATION FOR THE ADVANCEMENT OF RESTORATIVE MEDICINE

TORONTO, ONTARIO, CA

Disclosure

- I, Kelly McCann, have nothing to disclose. I have NO financial ties to any laboratory, medication, or supplement product to be discussed in this presentation.

Objectives

- Discuss the scope of the problem of mold and mycotoxins
- Health impacts of mold from allergies to digestive issues
- Review definition and diagnostic criteria for Environmentally Acquired Illness (formerly known as CIRS – Chronic Inflammatory Response Syndrome)
- Highlight interventions and treatment strategies both from the Shoemaker and Brewer protocols
- Introduce concepts of the mycobiome and fungal biofilms and the emerging literature on health impacts
- Brief exploration of Mast Cell Activation Disease; diagnosis, testing and treatment
- Review literature on phosphatidyl choline and membrane stabilizing therapies
- Discuss specific patient teaching points

Mold and Fungi

- Over 200,000 species of fungi, including mold, yeast, and mushrooms. More than 100,000 mold species have been identified.
- Molds are ubiquitous outside and live on many plants and food. They spread and reproduce by producing spores.
- Fungus and mold comprise 25% of the world's biomass.
- Exposure to molds can also occur by ingestion, inhalation of contaminated air and dermal contact
- Indoor molds proliferate in environments that contain excessive moisture, such as from leaks in plumbing, roofs, walls, and potted plants.
- The most common molds found indoors are Cladosporium, Penicillium, Aspergillus, and Alternaria,

  Stachybotrys and Trichoderma species.

Daschner A. An Evolutionary-Based Framework for Analyzing Mold and Dampness-Associated Symptoms in DMHS. Front. Immunol. 2017; 7:672.

Beneficial uses of molds

- Koji mold, an aspergillus species is used in the making of **soy sauce**
- Koji molds also break down the starch in rice, barley, sweet potatoes in the production of **sake and other distilled spirits**.
- Some **sausages** incorporate starter cultures of molds to improve flavor and reduce bacterial spoilage during curing.
- Geotrichum candidum and Penicillium species are used in the production of various **cheeses** including Brie and Blue cheese.
- Derived from Penicillin notatum, Alexander Fleming's discovery of **Penicillin** in 1928 transformed medicine.
- Used for centuries in China as both food and medicine, **red yeast rice** is made by fermenting a type of yeast called Monascus purpureus over red rice> it is used today for lowering cholesterol as it contains a chemical called monacolin K, has the same makeup as the drug lovastatin.
- Discovered in 1971, **Cyclosporine** immunosuppresses T cells without excessive toxicity. Cyclosporine was isolated from the fungus Tolypocladium inflatum by J. F. Borel.
- Decomposition of living matter.

Negative health effects of molds and fungus

- Mold and fungal allergy or hypersensitivity reactions – IgE, IgG
- Susceptibility to infections
- Mycotoxicoses
- Consequences of ingestion of molds and mycotoxins
  - Alimentary Toxic Aleukia
  - Environmental Enteropathy
- Environmentally Acquired Illness (CIRS – Chronic Inflammatory Response Syndrome)
- Mycobiome and Fungal biofilms
- Systemic mycoses - Fungal infections

Fungal Allergy and Asthma

- Many fungi, esp Alternaria, Penicillium, Aspergillus and Cladosporium spp., is strongly associated with type 1 allergic (IgE) responses
- Fungi are also well-known sources of type III (or IgG-inducing) antigens.
- At high concentrations, fungi may also be involved in combined type III and IV hypersensitivity reactions, including hypersensitivity pneumonitis.
- Numerous studies correlating asthma with fungal exposure and elevated ERMI scores
- Exposure to fungi, dust mites and endotoxins increase risk of eczema, allergy and asthma.

Baxi, SN. et al. Exposure and Health Effects of Fungi on Humans. J Allergy Clin Immunol Prac. 2016 4(3):396-404.
Vesper S, Wymer L. Relationship between ERMI and asthma. Int J Hyg Envirn Health 2016. 219(3): 233-8.
McSharry C, et al. Decreased FEV1% in asthmatic adults with high ERMI values. Clin Exp Allergy 2015. 45(5):902-7.
Sharpe, RA, et al. Risk of atopic disease due to indoor fungal exposure. Clin Exp Allergy 2015. 45(10): 1566-78.

Kelly K. McCann, MD

Alimentary Toxic Aleukia (ATA)

- Associated with eating grains (corn and wheat) which have been under snow the previous winter.
- Grains are contaminated with Fusarium and Stachybotrys
- First appeared in 1913 in eastern Siberia
- >100,000 Russians died between 1942-1948. 60% mortality rate.
- Necrotic ulcers in mouth, throat, nose, stomach and intestines
- Bleeding from nose, mouth, GI tract and kidneys
- Anemia, Leukopenia, Agranulocytosis due to bone marrow suppression
- Microscopic observations of the alimentary tract showed erosion of the gastric epithelium, frequently with bacterial invasion and cryptitis
- Pulmonary hemosiderosis, congestion and edema

Drobotko. Stachybotryotoxicosis. Am Review of Soviet Med 1945, 2:238-42.
Lutsky and Mor. Alimentary Toxic Aleukia. Am J Path 1981. 104(2):189-191.
Mayer, CF. Endemic panmyelotoxicosis in the Russian Grain Belt. 1953, 113:173-89.

Kelly K. McCann, MD

Environmental Enteropathy

- Condition characterized by increased intestinal permeability, villous atrophy, impaired gut immune function, malabsorption, growth faltering, and oral vaccine failure without overt diarrhea.
- Pathology changes similar to celiac disease, but not tropical sprue.
- Unclear etiology. Possibly related to fecal-oral contamination or mycotoxin contamination.
- Maize and groundnuts common in developing world diet. Often contaminated with Aspergillus and Fusarium.
- Mycotoxins aflatoxin (AF), fumonisin (FUM) and deoxynivaenol (DON) mediate intestinal damage
- Aspergillus strains can produce AF and ochratoxin and Fusarium mold strains can produce FUM, DON, and zearalenone.

Korpe and Petri. Environmental Enteropathy. Trends Mol Med. 2012 June ; 18(6): 328–336.
Smith. Food chain mycotoxin exposure, gut health, and impaired growth. Adv Nutr. 2012 Jul 1;3(4):526-31.

Kelly K. McCann, MD

Mycotoxins and Mycotoxicoses

- Mycotoxins are secondary metabolites produced by many molds.
- Between 350-400 known mycotoxins, about a dozen with health effects.
- Some Aspergillus, Penicillium, Fusarium, Alternaria and Stachybotrys genera are known to produce mycotoxins.
- **Mycotoxins are NOT ALIVE!**
- Aflatoxins
  Ochratoxins
- Tricothecenes Gliotoxin
- Ergot AlkaloidsFumonisins
- Patulin
  Zearalenone
- Deoxynivalenol (DON)

Numerous Health Effects

- Inhibition of protein synthesis
- Anemia Nephropathy
- Hepatotoxicity Carcinogenic
- Allergies Headaches
- Myalgias Fatigue
- Neurological damage
- Neural tube defects Visual disturbances
- Cognitive changes Respiratory illnesses
- Pulmonary hemorrhage
- Immunosuppression Depression
- Systemic inflammation
- Increased intestinal permeability

Bennett, JW and Klich, M. Mycotoxins. Clinical Microbiology Review, July 2003; 497-516.

Kelly K. McCann, MD

Mycotoxins in food

Mycotoxin	Major Foods	Species	Health Effect	LD50 (mg/kg)
Penitrem	Walnuts	Penicillum aurantiogriseum	Tremors	1.05 (mouse)
T-2 toxin	Cereals	Fusarium sporotrichioides	Alimentary toxic aleukia	4 (rat)
Ergotamine	Rye	Claviceps purpurea	Neurotoxin	
Zearolenone	Maize, barley, wheat	Fusarium graminearum	Estrogenic	Not acutely toxic?

Peraica, M, et al. Toxic Effects of Mycotoxins in humans. Bulletin of the WHO. 1999; 77(9): 754-765.

Kelly K. McCann, MD

Mycotoxin	Major Foods	Species	Health Effect	LD50 (mg/kg)
Aflatoxin	Maize, groundnuts, figs, tree nuts, milk, milk products	Aspergillus flavus Aspergillus parasiticus	Hepatotoxic, carcinogenic	0.5 (dog) 9.0 (mouse)
Cyclopiazonic acid	Cheese, maize, groundnuts, Rodo millet	Aspergillus flavus Penicillium aurantiogriseum	Convulsions	36 (rat)
Deoxynivalenol	Cereals	Fusarium graminearum	Vomiting, food Refusal, DNA damage	70 (mouse)
Fumonisin	Maize	Fusarium moniliforme	Esophageal Cancer	?
Ochratoxin	Maize, cereals, coffee beans	Penicillium verrucosum Aspergillus ochraceus	Nephrotoxic	20-30 (rat)
Patulin	Apple juice, damaged apples	Penicillium expansum	Edema, hemorrhage, cancer	35 (mouse)

***This Slide Enlarged on Page 144**

Effects of Mycotoxins

T2 toxin, DON, AFB
gastroenteritis
intestinal hemorrhages
impaired rumen function
diarrhea
ketosis

Ergots
impaired thermoregulation
convulsions

DON – Deoxynivalenol
ZEN – Zearalenone
AFB_1 – Aflatoxin B_1
T-2 Toxin
Ergots - Ergot Alkaloids
Endotoxins

Zen, Ergots
irregular heats
low conception rates
ovarian cysts
embryonic loss
abortions
low testicular development
low sperm production

T2 toxin, DON, Ergots
decreased feed intake
decreased feed efficiency

AFB, T2 toxin, DON
milk contamination
decreased milk production
mastitis

DON, Ergots, Endotoxins
Laminitis (lameness)

Kelly K. McCann, MD

Effects of Mycotoxins

Zen, T2, DON, Ergots
Irregular heats
abortion
pseudo pregnancy
low conception rates
embryonic loss
tail necrosis
nymphomania
uterine hypertrophy
shrunken udder
stillbirths

T2, DON, AFB, OTA, FUM
intestinal hemorrhage
kidney damage
fatty liver
pulmonary edema
increased water intake

DON – Deoxynivalenol
ZEN – Zearalenone
AFB_1 – Aflatoxin B_1
T-2 – T-2 Toxin
FUM – Fumonisins
OTA – Ochratoxin A
Ergots – Ergot Alkaloids
Endotoxins

T2, DON, Ergots
Decreased feed intake
Dermal/ oral lesions
Feed refusal
vomiting
vasoconstriction
necrosis
impaired growth

AFB, T2, OTA
diarrhea
blood in feces and urine
bladder and kidney inflammation

T2, DON, AFB, OTA, FUM
decreased performance
immunosuppression
pancreatic necrosis

Kelly K. McCann, MD

Not just a developing world problem

- Food and Agricultural Organization (FAO) estimates 25% of crops are contaminated with molds, though multi-analyte methods show almost 100% of grain crops are contaminated.
- Climate change will continue to impact food mold and mycotoxin contamination.
- Mycotoxins can be found in coffee. Spanish study 21 mycotoxins. Only 11% of coffee was mycotoxin free.
- Ochratoxin A in coffee samples was 71.5% and 93.3% at 1ng/mL and 10ng/mL concentrations.

- De Saeger, S. et al. Report from the 5th International Symposium on Mycotoxins and Toxigenic Moulds. Toxins 2016, 8, 146.
- García-Moraleja, et al. Analysis of mycotoxins in coffee and risk assessment in Spanish adolescents and adults. Food Chem Toxicol. 2015 Dec;86:225-33.
- Jo, EJ, et al. Detection of ochratoxin A (OTA) in coffee using chemiluminescence resonance energy transfer (CRET) aptasensor. Food Chem. 2016 Mar 1;194:1102-7.
- Peraica, M, et al. Toxic Effects of Mycotoxins in humans. Bulletin of the WHO. 1999; 77(9): 754-765.

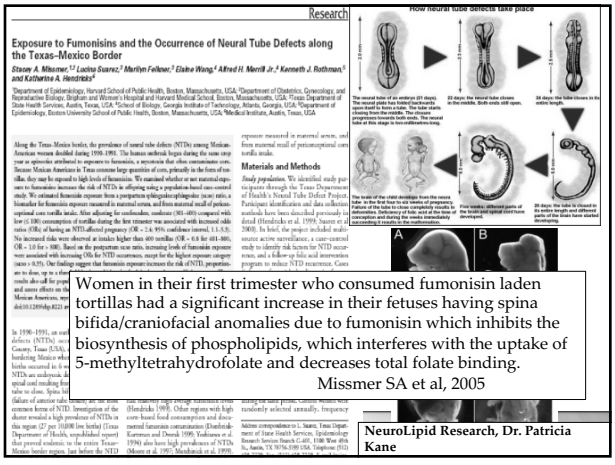
Kelly K. McCann, MD

No Pizza for you!

- 60 samples of pizza dough
- 9 mycotoxins detected
- 100% samples contaminated with at least 3 mycotoxins
- 12% exceeded EU limits
- Cow feed of maize contaminated with Aflatoxin B1 shows up in milk as aflatoxin M1

Quiles, JM et al. Occurrence of mycotoxins in refrigerated pizza dough and risk assessment of exposure for the Spanish population. Food Chem Toxicol. 2016 May 21;94:19-24
Van de Fels-Klerx. Presented at 5th International Symposium on Mycotoxins and Toxigenic Moulds. May 2016.

Kelly K. McCann, MD



Research

Exposure to Fumonisins and the Occurrence of Neural Tube Defects along the Texas–Mexico Border

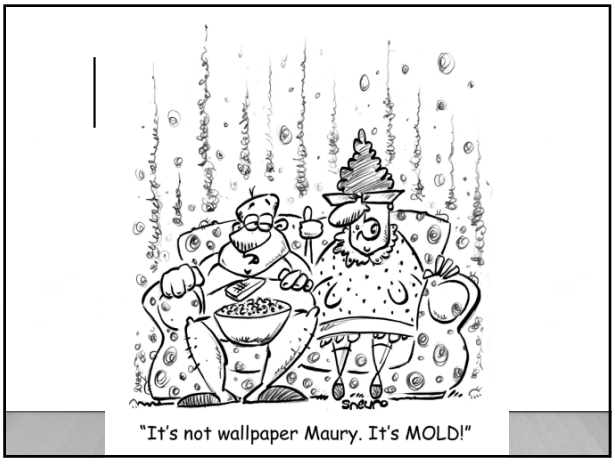
Stacey A. Missmer,[1,2] Lucina Suarez,[3] Marilyn Felkner,[3] Elaine Wang,[4] Alfred H. Merrill Jr.,[4] Kenneth J. Rothman,[5] and Katharine A. Hendricks[6]

How neural tube defects take place

Materials and Methods

Women in their first trimester who consumed fumonisin laden tortillas had a significant increase in their fetuses having spina bifida/craniofacial anomalies due to fumonisin which inhibits the biosynthesis of phospholipids, which interferes with the uptake of 5-methyltetrahydrofolate and decreases total folate binding.
Missmer SA et al, 2005

NeuroLipid Research, Dr. Patricia Kane



"It's not wallpaper Maury. It's MOLD!"

Water Damage and Dampness

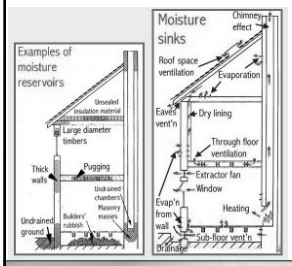
- Dampness in buildings ranges from 20% in studies in Europe and Canada to 50-60% in USA and parts of Asia.
- Case control studies of asthma in West bank and Gaza reveal 56-78% damp problems, leaks or indoor mold.
- Lower income and lower education associated with higher likelihood of dampness and mold.
- Lawrence Berkeley report from 2009. 47% of US homes with dampness or water damage. 85% percent of other buildings had past water damage and 45% had current water leaks.

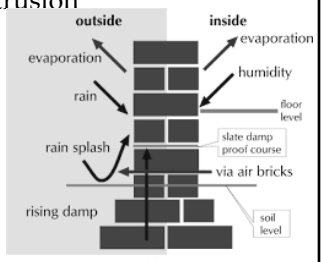
- WHO guidelines for indoor air quality: dampness and mould 2009, **http//www.who.int/indoorair/publications/7989289041683/en/**
- https://iaqscience.lbl.gov/dampness-prevalence

Kelly K. McCann, MD

Let's talk about indoor molds and water intrusion

- **Many sources of moisture are hidden.**





- **Remember that what is in the wall spaces travels throughout the building.**

Kelly K. McCann, MD

Other ingredients in the Indoor mold toxic soup

- Gram negative bacteria
- Gram positive bacteria
- Cell fragments
- Beta Glucans
- Mannans
- Hemolysins
- Proteinases
- Chitinases
- Endotoxins
- Mycobacteria
- Lipopolysaccharides
- Hyphal fragments
- Actinomycetes
- Nocardia
- Microbial VOCs
- Building material VOCs
- Coarse particulates
- Fine and ultrafine particulates
- Nano-sized particulates
- Mycoplasma
- Protozoa
- Dust mites

Kelly K. McCann, MD

- Bloom E, Nyman E. Molds and mycotoxins in indoor environments--a survey in water-damaged buildings. J Occup Environ Hyg. 2009 Nov;6(11):671-8.
- Rasimus, ,et al. Amylosin of Bacillus from moisture-damaged buildings is immunotoxic. Appl. Environ Microbiol. 2015 Apr; 81(8): 2939-49
- Thrasher JD, Crawley S. The biocontaminants and complexity of damp indoor spaces: more than what meets the eyes. Toxicol Ind Health. 2009 Oct-Nov;25(9-10):583-615.

Microbial Volatile Organic Compounds (mVOCs)

- Fungi emit numerous VOCs as alcohols, esters, ketones, aldehydes, terpenoids, etc.
- Exposure to mVOCs has been linked to symptoms such as headaches, nasal irritation, dizziness, fatigue, and nausea.
- Human health effects will require more study.
- mVOCs may be used for early mold detection.
- In animal model Drosophila melanogaster, mVOCs had greater toxic effect than formaldehyde, xylene, benezene and toluene.
- Specific VOC 1-octen-3-ol caused neurotoxicity, shortened lifespan, developmental defects, and various other toxicities.

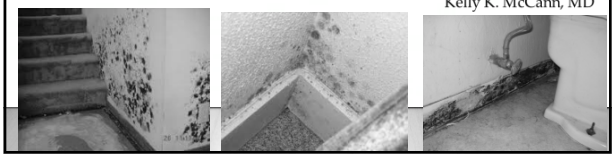
Inamdar, et al. Drosphila as a model to characterize fungal VOCs. Environ. Toxic 2014 May:29(7):829-36.
Bennett, JW. Silver linings. Front Microbiol. 2015 Mar 18;6:206.
Betancourt, et al. Microbial VOCs from Stacybotrys. BMC Microbiol. 2013 Dec5:13:283.

Kelly K. McCann, MD

Exposure history

- Do you live or work in a building that has any water damage such as roof leaks, floods, plumbing problems, slab leaks?
- Do you have a flat roof? Crawl space? Damp basement? Humidity problems? Window condensation?
- How old is the building? Has there been recent construction?
- Visible mold? Moldy or musty smells?
- Development of illness after change in buildings?
- Do you feel better being in fresh air locations?

Kelly K. McCann, MD



Other Mold Toxicity Manifestations

- Fatigue
- Weakness
- Headaches
- Chemical sensitivity
- EMR and Electrical sensitivity
- Adrenal dysfunction
- Endocrine dysfunction
- Dysautonomia
- Nutritional depletion
- Hypoxia
- Confusion/Memory Problems
- Chronic pain
- Insomnia
- Celiac disease or gluten sensitivity
- Weight gain
- Respiratory and sinus problems
- Chronic infections
- Poor wound healing
- Myalgias
- Reduced exercise tolerance

Etzel RA. Mycotoxins. JAMA 2002; 287;425-427.
Shoemaker.

Kelly K. McCann, MD

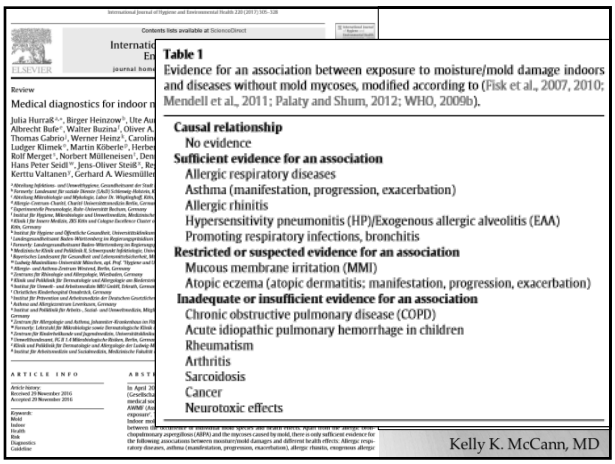


Table 1
Evidence for an association between exposure to moisture/mold damage indoors and diseases without mold mycoses, modified according to (Fisk et al., 2007, 2010; Mendell et al., 2011; Palaty and Shum, 2012; WHO, 2009b).

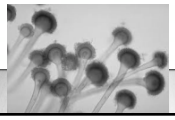
Causal relationship
No evidence
Sufficient evidence for an association
Allergic respiratory diseases
Asthma (manifestation, progression, exacerbation)
Allergic rhinitis
Hypersensitivity pneumonitis (HP)/Exogenous allergic alveolitis (EAA)
Promoting respiratory infections, bronchitis
Restricted or suspected evidence for an association
Mucous membrane irritation (MMI)
Atopic eczema (atopic dermatitis; manifestation, progression, exacerbation)
Inadequate or insufficient evidence for an association
Chronic obstructive pulmonary disease (COPD)
Acute idiopathic pulmonary hemorrhage in children
Rheumatism
Arthritis
Sarcoidosis
Cancer
Neurotoxic effects

Kelly K. McCann, MD

***This Slide Enlarged on Page 145**

Environmentally Acquired Illness due to Biotoxins (formering CIRS)

- Dr. Ritchie Shoemaker
- Environmentally Acquired Illness is caused by poor clearance of biotoxins produced by dinoflagellates, algae and mold.
- Genomic, multi-system, multi-symptom illness
- Chronic illness will perpetuate if no intervention
- Normal innate immune response allows for the production of antibodies by the adaptive system to remove the biotoxin.
- Defective antigen presentation in dysregulated innate immune system results in chronic inflammation



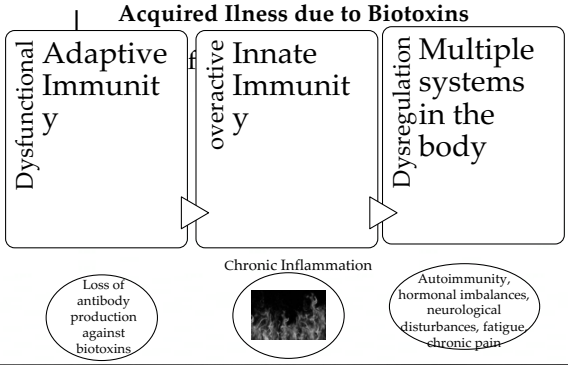
Kelly K. McCann, MD

EAI due to Biotoxins- Case definition

- 1. History, signs and symptoms consistent with biotoxin exposure. In the case of Mold-related illness, must have history of exposure to water damaged building with amplified microbial growth evidenced by:
  - A. Presence of visible mold
  - B. Musty odor
  - C. Commercial testing verifying mold growth
- 2. Genetic predisposition to biotoxin-related illness based on HLA haplotype.
- 3. Abnormalities documented by Visual Contrast Sensitivity (VCS) testing.
- 4. Biomarkers consistent with Biotoxin abnormalities and favorable response to treatment in 5 out of 8 biomarkers.

Kelly K. McCann, MD

Causes of Environmentally Acquired Illness due to Biotoxins



Kelly K. McCann, MD

Environmental Acquired Illness Diagnosis – Symptoms

Age <19 – 19/37 Symptoms
Age > 19 – 25/37 symptoms

- Fatigue
- Myalgias
- Joint pains
- Red eyes
- Blurred vision
- Decreased assimilation of new knowledge
- Word finding problems
- Shortness of breath
- Tingling
- Unusual pain
- Sinus congestion
- Excessive thirst
- Appetite swings
- Abdominal pain
- Disorientation
- Sweats (esp night sweats)
- Skin sensitivity/rashes

Kelly K. McCann, MD

Environmental Acquired Illness Diagnosis – Symptoms

Age <19 – 19/37 Symptoms
Age > 19 – 25/37 symptoms

- Weakness
- Headaches
- Morning stiffness
- Tearing eyes
- Vertigo
- Gluten sensitivity
- Muscle Aches
- Light sensitivity
- Memory impairment
- Decreased concentration
- Tremors
- Metallic taste
- Cough
- Confusion
- Nocturia
- Numbness
- Static shocks
- Temperature regulation issues
- Increased urinary frequency

Kelly K. McCann, MD

Cluster analyses

Cluster analyses: Give 1 point for any or all symptoms in a category. 6 or more points for children. 8 or more teens and adults. Circle any that apply

- **Fatigue**
- **Weakness, difficulty assimilating new information, muscle aches, headaches, light sensitivity**
- **Memory problems, word finding difficulties**
- **Problems with Concentration**
- **Joint pains, morning stiffness, muscle cramps**
- **Unusual skin sensations, tingling**
- **Shortness of breath, sinus congestion or nasal drainage**

Kelly K. McCann, MD

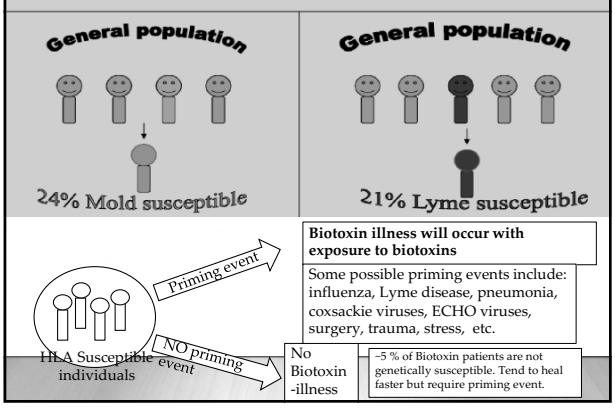
Cluster analyses

Cluster analyses: Give 1 point for any or all symptoms in a category. 6 or more points for children. 8 or more teens and adults. Circle any that apply

- **Cough, increased thirst, confusion**
- **Appetite swings, body temperature regulation, urinary frequency/urgency**
- **Red eyes, blurred vision, excessive or nighttime sweating, mood swings, unusual pains esp. "ice pick pains"**
- **Abdominal tenderness or pain, diarrhea or loose stools, numbness**
- **Eye tearing, disorientation, metallic taste**
- **Static shocks, vertigo**
    - **Total number:**

Kelly K. McCann, MD

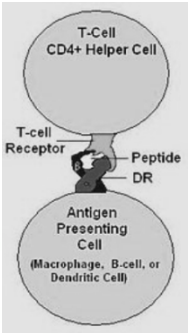
Statistics Based on International Gene Registries



***This Slide Enlarged on Page 144**

HLA-DR

- HLA-DR is a major histocompatibility (MHC) class II cell surface receptor.
- Graft vs host compatibility
- Involved in immune responses, autoimmune conditions
- Extensive genetic polymorphisms
- Found on macrophages, B-cells and dendritic cells
- Presents antigens to T cells
- Stimulation of T cells through HLA-DR, leads to antibody production by B cells



Kelly K. McCann, MD

HLA Susceptibility

Susceptibility	DRB1	DQ	DRB3	DRB4	DRB5
Multisusceptible	4	3		53	
	11/12	3	52B		
	14	5	52B		
Mold Susceptible	7	2/3		53	
	13	6	52A, B, C		
	17	2	52A		
	18*	4	52A		
Borrelia, post Lyme Syndrome	15	6			51
	16	5			51
Dinoflagellates (Pfiesteria, ciguatera)	4	7/8		53	
Multiple Antibiotic Resistant Staph Epidermis (MARCoNS)	11	7	52B		
Low MSH	1	5			
No recognized significance	8	3, 4, 6			
Low-risk Mold	7	9		53	
	12	7	52B		
	9	9		53	

Shoemaker R. Linkage disequilibrium in alleles of HLA DR: differential association with susceptibility to chronic illness following exposure to biologically produced neurotoxins. American Society of Microbiology 2003. (conference peer review).

***This Slide Enlarged on Page 147**

Interpreting the HLA Haplo-type

- **HLA Lab Corp –Code 167120 (HLA DRB1, DQ, DRB3, 4, 5)**

- DRB1 *03 ⇨ 17
- DRB1 *04
- DRB3 *01 ⇨ 52A
- DRB3 * -
- DRB4 *01
- DRB4 * - ⇨ 53
- DRB5 * -
- DRB5 * - ⇨ 51
- DQB1 *02
- DQB1 *03

- DRB1 is always first. Followed by DQ which is then linked to one of the DRB 3,4 or 5.
- Ignore any extra letters after the numbers.
- Dashes mean no genes.
- On DRB3 *01 =A, *02 =B, *03 =C
- There is a low MSH. 1-5

DRB1 *01

DQB1 *05

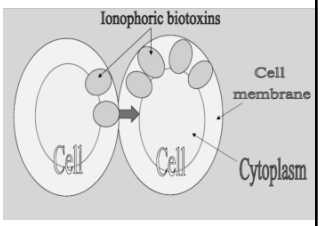
- This person is:
- HLA DR 17-2-52A mold susceptible
- HLA DR 4-3-53 multi-susceptible

http://www.myhousemakesmesick.com/hlacalc/

Kelly K. McCann, MD

Ionophoric Biotoxins

- Ionophoric biotoxins are very small and easily move in and out of cells
- They are not easily detected in the blood
- Secreted by liver into the bile and reabsorbed into the body unless tagged by the immune system.
- In genetically susceptible individuals since unable to tag the biotoxins, they are not removed which leads to chronic inflammation.



Kelly K. McCann, MD

Biotoxin	Microorganism Souce	Route of transmission
Ciguatera	*Gambierdiscus toxicus* (dinoflagellate algae)	Ingestion of contaminated fish
Possible estuarine-associated syndrome (PEAS)	*Pfiesteria piscicida*	Direct contact with contaminated water or inhalation of aerosolized toxins, esp in the area of fish kills.
Lyme Biotoxin	*Borrelia burdorferi* spirochete	Tick bite
Brown Recluse Spider toxin		Spider bite
Babesiosis	*Babesia microti* or *duncani* or BLO	Tick bite

(Information for table taken from (Shoemaker, 2011, June 27, DVD))

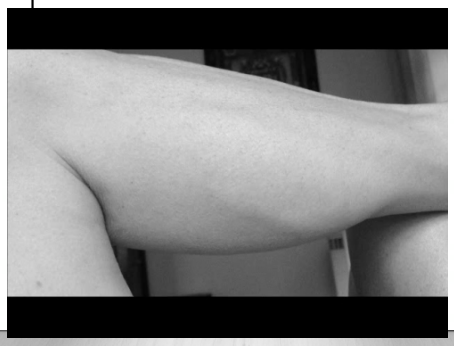
Kelly K. McCann, MD

Case 1: December 2013

- 45 year old woman with history of seasonal allergies and mild PMS presents with depression, new onset insomnia, worsening food sensitivities, lower leg muscle fasciculations, and urinary frequency.
- PSHx: tonsillectomy age 18
- Medications: none
- Family history: Mom 70 –celiac, glaucoma, peripheral neuropathy; Dad 72 – htn, hyperlipidemia, carpal tunnel; sister 38 – htn
- Social Hx: no tobacco, social Etoh
- Location: Recently moved into an older home with moldy smell in the master bathroom

Kelly K. McCann, MD

Case 1: Physical Exam



Kelly K. McCann, MD

Case 1: PE and Labs

PE – Wt 114Lb, Ht 5'4"
BP 108/68, HR 74

- Rest of physical exam unremarkable except for allergic shiners and intermittent muscle fasciculations on left calf

LABS: hs crp 0.3 mg/L =2.86nmol/L
thyroid wnl
Chol 208 mg/dL = 5.38 mmol/l
LDL 107 mg/dL= 2.77 mmol/l
HDL 85 mg/dL= 2.19 mmol/l
trig 80 mg/dL = 0.9032 mmol/l
pattern A
wbc 4.9, hgb 13.3
Cmp wnl, GGT 14
HgA1c 5.6 %
ANA neg
Vit D25oh 65 ng/mL= 162.5nmol/L

- **MTHFR** – C677t++

Kelly K. McCann, MD

Case 1: Labs

- **HLA DR** 4-3-53 multi-susceptible, 17-2-52A mold susceptible
- **Transforming Growth Factor Beta 1** - 9520 pg/mL (344-2382)
- **VasoIntestinal Active Peptide (VIP)** <16.8 (23-63 pg/mL)
- **Melanocyte Stimulating Hormone (MSH)** <8 (35-81pg/mL)
- **VEGF** <31 (31-86 pg/mL)
- **C4a** – 1672 (0-2830 ng/mL)
- **ADH** – <1.0 (1.0-13.3 pg/mL)
- **Osm** – 293 (278-305 mOsm/kg)
- **MMP-9** – 928 (<332)

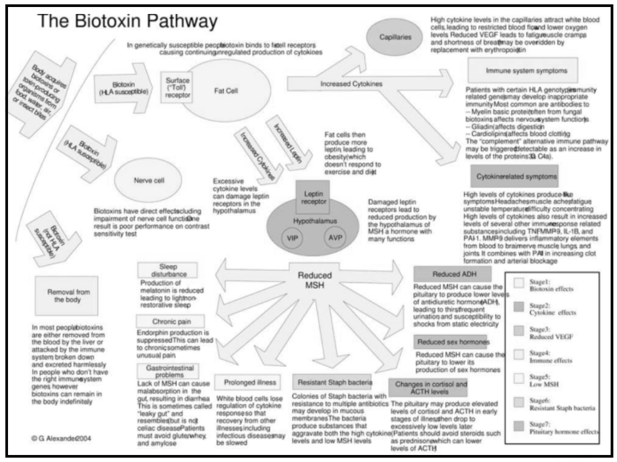
- Cyrex array 5 – numerous predictive autoantibodies.
- IgG Food sensitivity testing – highly reactive to all dairy, gluten, almonds, rice, peas, eggs, mushrooms, yeast.
- CDSA Stool test – low pancreatic elastase, low diversity, no fungal growth.

Kelly K. McCann, MD

Other Labs to be Considered

- Routine labs – CBC, CMP, ferritin, iron/TIBC
- Hormones - thyroid, adrenal, aldosterone, sex hormones
- Autoimmunity, ANA, RF, Antibody sub-fractions
- Predictive autoantibodies
- Gluten sensitivity/celiac panel
- Food sensitivity testing
- Chronic infection work- up – Lyme and co-infections, viral infections
- Toxicant testing
- Heavy metal testing
- Inflammatory markers – CRP, ESR will be normal in CIRS
- Immune system dysfunction – Immunoglobulin panel, T&B cells, NK cell panel, complement levels, IgE
- Von Willebrands
- Hypercoagulability through Esoterix labs
- Cultures for nasal bacteria/fungus and stool studies
- Mold allergy and sensitivity testing
- Nutritional analysis
- Genomic analysis

Kelly K. McCann, MD



The Biotoxin Pathway
In genetically susceptible peoplebiotoxin binds to fat cell receptors causing continuing unregulated production of cytokines
Body acquires biotoxins or toxin-producing organisms from food, water, air, or insect bites
Biotoxin (HLA susceptible)
Surface ("Toll") receptor
Fat Cell
Increased Cytokines
Capillaries
High cytokine levels in the capillaries attract white blood cells, leading to restricted blood flow and lower oxygen levels. Reduced VEGF leads to fatigue, muscle cramps and shortness of breath (may be overidden by replacement with erythropoietin)
Immune system symptoms
Patients with certain HLA genotypes (immunity related genes) may develop inappropriate immunity. Most common are antibodies to
-- Myelin basic protein (often from fungal biotoxins; affects nervous system functions)
-- Gliadin (affects digestion)
-- Cardiolipins (affects blood clotting)
The "complement" alternative immune pathway may be triggered (detectable as an increase in levels of the proteins C3a, C4a).
Cytokine-related symptoms
High levels of cytokines produce flu-like symptoms: Headaches, muscle aches, fatigue, unstable temperature, difficulty concentrating. High levels of cytokines also result in increased levels of several other immune response related substances including TNF, MMP-9, IL-1B, and PAI-1. MMP-9 delivers inflammatory elements from blood to brain, nerve, muscle, lungs, and joints. It combines with PAI-1 in increasing clot formation and arterial blockage
Biotoxin (HLA susceptible)
Nerve cell
Biotoxins have direct effects including impairment of nerve cell function. One result is poor performance on contrast sensitivity test
Increased Cytokines
Increased Leptin
Excessive cytokine levels can damage leptin receptors in the hypothalamus
Fat cells then produce more leptin, leading to obesity (which doesn't respond to exercise and diet)
Leptin receptor
Hypothalamus
VIP
AVP
Damaged leptin receptors lead to reduced production by the hypothalamus of MSH, a hormone with many functions
Biotoxin (not HLA susceptible)
Removal from the body
In most people, biotoxins are either removed from the blood by the liver or attacked by the immune system, broken down and excreted harmlessly. In people who don't have the right immune system genes, however, biotoxins can remain in the body indefinitely
Reduced MSH
Sleep disturbance
Production of melatonin is reduced, leading to light, non-restorative sleep
Chronic pain
Endorphin production is suppressed. This can lead to chronic, sometimes unusual pain.
Gastrointestinal problems
Lack of MSH can cause malabsorption in the gut, resulting in diarrhea. This is sometimes called "leaky gut" and resembles (but is not) celiac disease. Patients must avoid gluten, whey, and amylose
Prolonged illness
White blood cells lose regulation of cytokine response so that recovery from other illnesses including infectious diseases may be slowed
Resistant Staph bacteria
Colonies of Staph bacteria with resistance to multiple antibiotics may develop in mucous membranes. The bacteria produce substances that aggravate both the high cytokine levels and low MSH levels
Changes in cortisol and ACTH levels
The pituitary may produce elevated levels of cortisol and ACTH in early stages of illness, then drop to excessively low levels later (Patients should avoid steroids such as prednisone, which can lower levels of ACTH)
Reduced ADH
Reduced MSH can cause the pituitary to produce lower levels of anti-diuretic hormone (ADH), leading to thirst, frequent urination and susceptibility to shocks from static electricity
Reduced sex hormones
Reduced MSH can cause the pituitary to lower its production of sex hormones
Stage1: Biotoxin effects
Stage2: Cytokine effects
Stage3: Reduced VEGF
Stage4: Immune effects
Stage5: Low MSH
Stage6: Resistant Staph bacteria
Stage7: Pituitary hormone effects
© G Alexander 2004

This Slide Enlarged on Page 148

Physician Order Sheet

Please Draw	Test	Lab to Use		Code #	DX Codes	CPT codes
	HLA DR by PCR	LabCorp	Spec	167120	D84.1 D83.1 D89.89	81375
	VIP	Quest	Lavender, room temp	929	D84.1 D89.89	84586
	MSH	Lab Corp only	Lav - freeze-trasylol	010421	E23.0 R65.10	83519
	Leptin	LabCorp	Lav - freeze-trasylol	146712	E23.0 R65.10	82397
		Quest	Lav - freeze-trasylol	90367	E23.0 R65.10 995.93	83520
	ADH	LabCorp	SST - freeze	10447	E23.0 R65.10 995.93	84588
		Quest	SST - freeze	252	995.93 R65.10	83930 84588
	Osmo	Labcorp	LAV freeze	2071	E23.2	83930
		Quest	LAV freeze	677	R65.10 995.93	83930
	ACTH	Labcorp	SST - freeze	004440	E27.4	82024
		Quest	SST - freeze	211	E27.40 255.41	82024
	Cortisol	LabCorp	Lav - freeze	004051	E27.40 255.41	82533
		Quest	Lav - freeze	4212	E27.40 255.41	82533
	DHEAS	LabCorp	SST freeze	004020	E27.40 255.41	82627
		Quest	SST freeze	402	E27.40 255.41	82627
	Testosterone	LabCorp	SST - freeze	140103	E29.1	84402 84403
		Quest	SST - freeze	873	E29.1	84402 84403
	Androstenedione	LabCorp	red top - room temp	500171	E27.40 255.41	82157
		Quest	red top - room temp	17182x	E27.40 255.41	82157
	CRP	LabCorp	SST - freeze	120766	R79.82	86141
		Quest	SST - freeze	17182x	R79.82	86141
	ESR	LabCorp	SST - room temp	5215	D89.89 279.49	85652
		Quest	SST - room temp	809	D89.89 279.49	85652
	TGF-B1	LabCorp	Lav	905006	D84.1 D83.1	83520
		Quest	Lav	01238	D84.1 D83.1	83520
	MMP-9	LabCorp	Lav freeze (platelet poor plasma)	500124	D89.89 R53.81	83520
	PAI-1	LabCorp	SST - freeze	146787	I27.5	85415
		Quest	SST - freeze	36555	D68.9 286.9 I67.5	85415
	CBC	Quest	Lav - room temp	17182x	E27.40 255.41	85025
		LabCorp	Lav - room temp	5009	E27.40 255.41	85025
	CMP	LabCorp	SST - room temp	322000	E27.40 255.41	80053
		Quest	SST - room temp	10231x	E27.40 255.41	80053
	GGT	LabCorp	SST - room temp	001958	E27.40 255.41	82977
		Quest	SST - room temp	10231x	E27.40 255.41	82977
	VEGF (not sen.m)	LabCorp	Rm temp	117006	E23.0 R65.10	83520
		Quest	Rm temp	14512	995.93 R65.10	83520
	Erythropoietin	LabCorp	Red- freeze	140277		82668
		Quest	Red - freeze	477x		82668
	Anticardiolipins	LabCorp	Red - freeze	161950	M32.1	86147
		Quest	Red - freeze	7552	289.9 D68.9	86147
	Antigliadin, IgA, IgG	LabCorp	SST - freeze	161646/131667	K90.0	83516
		Quest	SST - freeze	8865x	279.8/D89.89	83516
	C3a RIA (not Fulham)	Quest only	SST - freeze	17689	279.8/D89.89	86160
	C4a RIA (not Fulham)	Quest only	Lav - freeze	19866	279.8 / D89.89	86160
	IgE	Quest	Lav - freeze	542x	279.05 D80.3	82785
		LabCorp	Lav - freeze	002295	279.05 D80.3	82784
	Lyme WB	Quest	SST - freeze	6593	088.81/A69.20	86617
	TSH	LabCorp	SST - freeze	004259	244.8	84443
		Quest	SST - freeze	899x	244.8	84443
	von Willebrand's profile	Quest	SST - freeze	15640x	286.9 D68.9	85240
	Fe/TIBC	Quest	Blue freeze - 3 aliquots	7573x	R53.81	83540
		LabCorp	Blue freeze - 3 aliquots	001321	R53.81	83540

- **Lab Corp**

HLA DR, MMP-9, MSH, VIP, cd 57 – if desired

- **QUEST**

VEGF, ADH, OSM, and C4a – if able

- **TGfbeta1 needs to go to Cambridge Biomedical**
- **C4a needs to go to National Jewish on dry ice**

Kelly K. McCann, MD

Case Definition Specific Labs

- HLA haplotype
- MARCONS
- ADH/osmolality 4 abnl tests <11 yrs +diagnostic for CIRS
- ACTH/Cortisol 5 abnl tests >11 yrs +diagnostic for CIRS
- MMP-9
- MSH
- VIP
- TGF beta 1
- C4a
- Anticardiolipin antibodies
- Anti-gliadin antibodies
- Also check VCS. Use handheld device rather than online.

Kelly K. McCann, MD

Environmentally Acquired Illness Labs

TGF-beta 1 (Transforming Growth Factor Beta 1)

- A marker of an overactive immune system. Directs immunity towards TH17, often results in autoimmunity.
- Potent immune suppressor, leading to chronic infections.
- Also role in tumor suppression and promoting tolerance to allergens and self- antigens.

C4a level (complement cascade)

- Split product of complement activation. Increased vascular permeability, capillary hypoperfusion.
- Represent an excessive innate immune response to biotoxins.
- High C4a levels may also be seen in Lupus and Lyme disease.

Kelly K. McCann, MD

Environmentally Acquired Illness Labs

MMP-9 (Matrix metalloproteinase-9) level

- Zinc-dependent enzyme involved in remodeling extracellular matrix
- Correlates with high toxin load. Marker for disease progression.
- Associated with increased permeability in the blood brain barrier
- Implicated in pathogenesis COPD by destruction of lung elastin, in rheumatoid arthritis, atherosclerosis, cardiomyopathy, demyelinating diseases and abdominal aortic aneurysm.

VEGF (vascular endothelial growth factor) level

- A marker of capillary hypo-perfusion.
- A low level of skeletal muscle VEGF is associated with decreased muscle endurance. Other symptoms include persistent fatigue, cognitive difficulties, difficulty recovering from even mild activity
- Early in biotoxin illness, VEGF can run high, a sign that it is trying to help compensate for low oxygen delivery to issues.

Kelly K. McCann, MD

Environmentally Acquired Illness Labs

VIP (vasointestinal active peptide) level

- Neuroregulatory hormone, regulates cytokines and inflammatory responses.
- Marker of blood flow regulation and distribution.
- Low levels are associated with capillary hypo perfusion and abnormal pulmonary artery pressure at rest or in response to exercise.

MSH (melanocyte stimulating hormone) level

- Marker of neuropeptide control of multiple functions.
- Alpha MSH binding to receptors in the brain and on white blood cells reduces inflammatory responses, including decreased production of pro-inflammatory cytokines.
- Symptoms often include fatigue and unusual pain syndromes.

Kelly K. McCann, MD

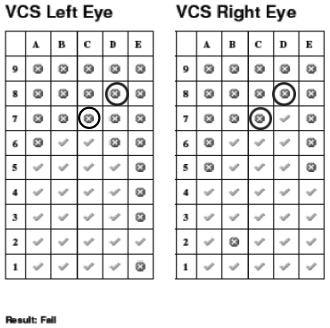
My lab recommendations

- TGFbeta 1 through Cambridge Biomedical
- C4a through National Jewish
- MMP9 through Lab Corp
- VEGF through Quest
- MSH at baseline only
- VIP initially and follow only if low
- ADH/OSM if symptoms
- ACTH/Cortisol and other hormones if symptoms
- HLA DR only if desired by patient
- Urine Mycotoxins if desired

Kelly K. McCann, MD

Visual Contrast Sensitivity (VCS) test

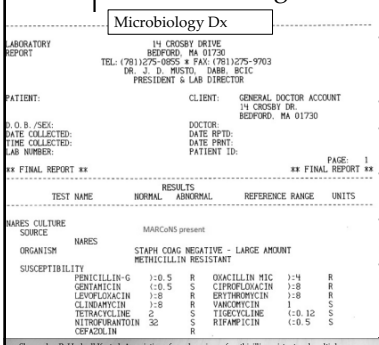
- The nerve fibers in the upper/outer portions of the optic nerve carry "edge detection" information, ability to discern visual contrast.
- Test is designed to distinguish differences in shading, thickness and separation of grey on grey lines.
- To pass the VCS screen, must be correct for row 7, column C and row 8, column D (see blue circles)
- Patients with CIRS, 92% will fail and 8% will pass.
- Must have 20/50 acuity to test.



Online screening or purchase of handheld device: www.survivingmold.com or www.vcstest.com

Kelly K. McCann, MD

MaRCoNS – Multidrug Antibiotic Resistant Coagulase Negative Staph


Microbiology Dx

LABORATORY REPORT
14 CROSBY DRIVE
BEDFORD, MA 01730
TEL: (781)275-8855 x FAX: (781)275-9703
DR. J. D. MUSTO, DABB, BCIC
PRESIDENT & LAB DIRECTOR

PATIENT:
CLIENT: GENERAL DOCTOR ACCOUNT
14 CROSBY DR.
BEDFORD, MA 01730
D.O.B./SEX:
DATE COLLECTED:
TIME COLLECTED:
LAB NUMBER:
DOCTOR:
DATE RPTD:
DATE PRNT:
PATIENT ID:
PAGE: 1
** FINAL REPORT ** ** FINAL REPORT **

RESULTS

TEST NAME	NORMAL	ABNORMAL	REFERENCE RANGE	UNITS

NARES CULTURE
SOURCE
NARES
ORGANISM
STAPH COAG NEGATIVE - LARGE AMOUNT
METHICILLIN RESISTANT
SUSCEPTIBILITY

PENICILLIN-G	>0.5	R	OXACILLIN MIC	>4	R
GENTAMICIN	<0.5	S	CIPROFLOXACIN	>8	R
LEVOFLOXACIN	>8	R	ERYTHROMYCIN	>8	R
CLINDAMYCIN	>8	R	VANCOMYCIN	1	S
TETRACYCLINE	2	S	TIGECYCLINE	<0.12	S
NITROFURANTOIN	32	S	RIFAMPICIN	<0.5	S
CEFAZOLIN		R			

MARCoNS present

- Bacterial colonizer in the nasal passages and possibly dental reservoirs.
- Creates biofilms
- Releases exotoxins that suppress alpha MSH.
- Differentially activates gene expressions
- Fungal nasal cultures available
- Company now tests strength of biofilms

Shoemaker R, Hudnell K, et al. Association of nasal carriage of methicillin resistant and multiple antibiotic resistant coagulase negative staphylococci species with deficiency of alpha melanocyte stimulating hormone in Chronic Fatigue Syndrome. American Society of Microbiology 2003. (conference peer review)

Kelly K. McCann, MD

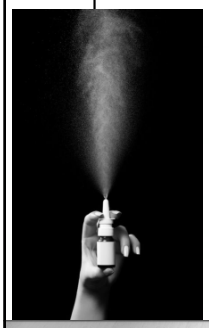
***This Slide Enlarged on Page 146**

MaRCoNS – Multidrug Antibiotic Resistant Coagulase Negative Staph

- Rarely found in nature
- Reservoirs in dogs, but not cats
- In family members with low MSH.
- Found in Chronic Fatigue Syndrome and chronic facial pain patients
- Kids rarely have MARCoNS
- No eradication of MARCoNS, there was no improvement
- 80% patients with low MSH have MARCoNS.
- 60% had methicillin resistances.
- If a patient has low MSH, do a nasal swab.
- If one round of treatment doesn't eradicate, MARCoNS, consider sending to biological dentist to evaluate for cavitations.

Kelly K. McCann, MD

BEG/BEC spray

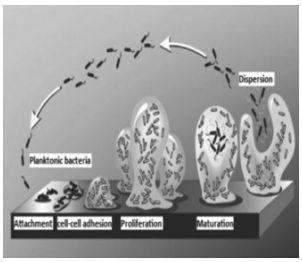


- BEG spray – Bactroban, EDTA, Gentamicin
- BEC – Substitute Clindamycin
- Available through compounding pharmacis
- Choice depends of resistance and tolerability
- 2 sprays each nostril 3 times daily for 1 month
- Reculture. Must confirm eradication.
- Do not use rifampin.
- Pretreatment with xylitol nasal spray may improve tolerability.
- Can also use Silver and EDTA

Kelly K. McCann, MD

Nasal Fungal Culture and Intranasal Treatments

- Mold exposed patients may have both MARCoNs and fungal colonizers.
- Treatment with intranasal antifungals may help
- Amphotericin B, nystatin, ketoconazole, or itraconazole



Brewer JH, Thrasher JD, et al. Chronic illness associated with mold and mycotoxins: is naso-sinus fungal biofilms the culprit? Toxins 2013; 6(1) :66-80. PMID: 24368325

Brewer JH, Hooper D, et al. Intranasal antifungal therapy inpatients with chronic illness associated with mold and mycotoxins. GJMR 2015 Vol 15 2:29-33.

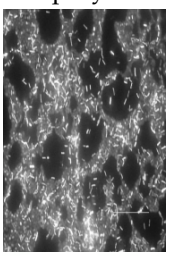
Brewer, JH, Hooper, D, et al. Intranasal nystatin Therapy in patients with Chronic Illness. GJMR 2015. 15(5).

Antifungal Nasal Sprays

- Nystatin 50,000 units/spray BID
- Itraconazole 40mg/spray BID
- Ketoconazole – not recommended
- Amphotericin B 5mg/spray BID

Addressing Biofilms

- Polysorbate 80 - nonionic surfactant
- Xylitol - variable effectiveness
- Mupirocin – ENT gold standard
- EDTA



- Sloup RE, et al. Polysorbates prevent biofilm formation and pathogenesis of Escherichia coli O104:H4. Biofouling. 2016 Oct;32(9):1131-1140.
- Jain R, etal. The in vitro effect of xylitol on chronic rhinosinusitis biofilms. Rhinology. 2016 Jul 10.
- Smith A, Buchinsky FJ, Post JC. Eradicating chronic ear, nose, and throat infections: a systematically conducted literature review of advances in biofilm treatment. Otolaryngol Head Neck Surg. 2011 Mar;144(3):338-47
- Drilling A, et al. Safety and efficacy of topical bacteriophage and ethylenediaminetetraacetic acid treatment of Staphylococcus aureus infection in a sheep model of sinusitis. Int Forum Allergy Rhinol. 2014 Mar;4(3):176-86

Atomizer versus Nasal Rinse

- Nasal Touch Atomizer
- Anecdotal evidence
- Less dilution of medication
- Costs $85

- Evidence based
- Readily available
- Inexpensive
- Contraindicated in ear issues
- Rinse can get into sinuses

- http://www.neilmed.com/usa/articles_nasalirrigation.php
- Brown and Graham. Current Opinion in Otolaryngology & Head and Neck Surgery 2004, 12:9–13

This is a marathon…..

- Treating for intranasal fungus is a marathon.
- Anticipate at least 6, if not 12 months of treatment.

- Must rinse out the nasal passages with saline after the medications
- If live in humid or highly polluted areas may need to treat longer.
- Can continue every other day indefinitely

"Honey, do we have a problem with mold in our house?"

Case 1:

Urine test fo
mycotoxins

Aflatoxin
Ochratoxin
Tricothecene
Gliotoxin

Research on urine mycotoxin testing

- Validated exposure biomarkers for aflatoxin were established 20 years ago.
- Urinary deoxynivalenol (DON) zearalenone, ochratoxin A (OTA), fumonisin B1 (FB1) found in farmers in South Africa.
- Belgian study in 2015 determined 100% of 394 study participants had DON urine mycotoxins.

- 93% of 112 CFS patients had one urine mycotoxin. 30% had numerous.
- OTA most common 83%, tricothecenes 44%
- 90% case histories indicate current or past exposure to WDB.
- 55 healthy controls = 0 mycotoxins

Brewer, et al. Detection of mycotoxins in CFS patients. Toxins (basel) 2013 April 11;5(4):605-17.
De Saeger, S. et al. Report from the 5th International Symposium on Mycotoxins and Toxigenic Moulds. Toxins 2016, 8, 146.
Shephard, etal. Multiple Mycotoxins exposure determined by urinary biomarkers in susbsistence farmers in South Africa. Food Chem Toxicol 2013 Dec;62:217-25.
Turner, PC, et al. Role of Biomarkers in human health concerns from fungal contaminants in food. Nutr Res Rev 2012 Jun;25(1): 162-179.

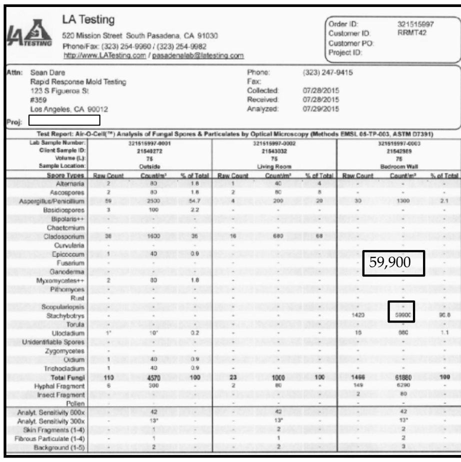
Kelly K. McCann, MD

Cases 2 and 3

- Wife – 41 year old presented in 5/2012
- Fatigue, Depression, Dysmenorrhea
- Gallbladder resected
- Chronic Headaches
- Chronic diarrhea
- Intermittent SOB, sweats, shaking, dizziness
- Developed joint pains, difficulty walking
- Foot drop (mom has Charcot-Marie-Tooth)
- +numerous symptoms also c/w Lyme disease. +positive IgM Lab corp test

- Husband – 44 year old presented in November 2015
- Mild depression – life long
- Increased fatigue
- Increased anxiety and fear of children
- Developed high blood pressure
- Headaches
- Glass sensations in his eyes
- Problems with focus
- Increased urination

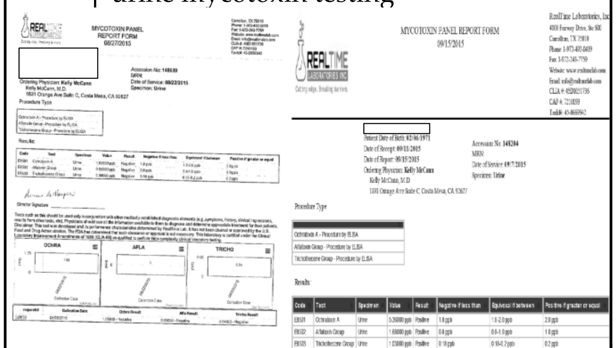
Kelly K. McCann, MD



Outside test is an air trap sample. The other samples are spore counts taken from a wall sample.

Kelly K. McCann, MD

Cases 2 and 3: Potential flaws in urine mycotoxin testing



Kelly K. McCann, MD

New Urine Mycotoxin test option

Mycotoxins

- Aflatoxin M1 (AFM1)
- Ochratoxin A (OTA)
- Sterigmatocystin (STG)
- Roridin E
- Verrucarin A
- Enniatin B1
- Zearalenone (ZEA)

Molds

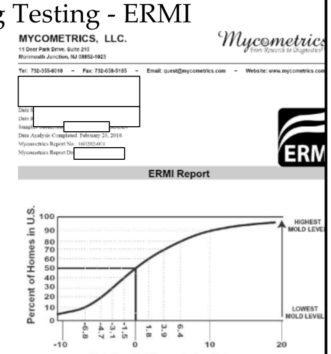
- Aspergillus
- Penicillum
- Stachybotrys
- Fusarium

Kelly K. McCann, MD

*This Slide Enlarged on Page 145

Building Testing - ERMI

- ERMI – Environmental Relative Mold Index (Use Mycometrics)
- Looks for mold DNA 26 from toxin producing species and compares that to DNA from non-toxic molds.
- EPA holds patent on ERMI testing which uses vacuum canister attachment to collect dust. Swiffer cloth is used for surfaces.



Kelly K. McCann, MD

*This Slide Enlarged on Page 146

Location	
	Spore E./mg
Fungal ID \ Sample ID	EC4275 Kit, LR, MBR
Aspergillus flavus/oryzae	<1
Aspergillus fumigatus	1
Aspergillus niger	14
Aspergillus ochraceus	ND
Aspergillus penicillioides	7
Aspergillus restrictus*	ND
Aspergillus sclerotiorum	ND
Aspergillus sydowii	ND
Aspergillus unguis	<1
Aspergillus versicolor	ND
Aureobasidium pullulans	15
Chaetomium globosum	<1
Cladosporium sphaerospermum	37
Eurotium (Asp.) amstelodami*	3
Paecilomyces variotii	<1
Penicillium brevicompactum	5
Penicillium corylophilum	ND
Penicillium crustosum*	ND
Penicillium purpurogenum	1
Penicillium spinulosum*	ND
Penicillium variabile	ND
Scopulariopsis brevicaulis/fusca	1
Scopulariopsis chartarum	<1
Stachybotrys chartarum	<1
Trichoderma viride*	<1
Wallemia sebi	5
Sum of the Logs (Group I):	**6.63**
Acremonium strictum	ND
Alternaria alternata	8
Aspergillus ustus	<1
Cladosporium cladosporioides 1	96
Cladosporium cladosporioides 2	80
Cladosporium herbarum	130
Epicoccum nigrum	150
Mucor amphibiorum*	1
Penicillium chrysogenum	23
Rhizopus stolonifer	<1
Sum of the Logs (Group II):	**10.43**
ERMI (Group I - Group II):	**-3.80**

ERMI

ERMI score = Group I- Group II

In environmentally acquired illness cases;

- A score < 2 is considered mold-safe if MSH is normal.
- If MSH is <35 and C4a >20,000, ERMI must be <-1 to be considered safe.
- A score of > 2 is consider mold-unsafe.

Kelly K. McCann, MD

Building Testing - HERTSMI 2

- **HERTSMI 2 – DNA analysis of the 5 toxin producing molds**

Points	**4**	**6**	**10**
Aspergillus penicilloides	**10-99**	**100-499**	**500+**
Aspergillus versicolor	**10-99**	**100-499**	**500+**
Chaetomium globosum	**5-24**	**25-124**	**125+**
Stachybotrys	**5-24**	**25-124**	**125+**
Wallemia	**100-499**	**500-2499**	**2500+**

- **Interpretation:**
- **<11 statistically safe to enter for those with CIRS**
- **11-15 Borderline, clean first and then recheck**
- **>15 Dangerous for those with CIRS**
- **Disclaimer: HERTSMI-2 is a building index and doesn't replace careful observation and lab markers.**

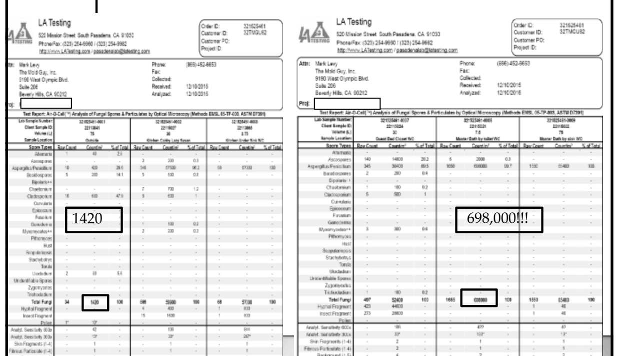
Kelly K. McCann, MD

Other environmental testing options

- The RealTime Laboratories Environmental Mycotoxin Test will determine the presence or absence of 15 of the most common and most toxic mycotoxins, including 9 Macrocyclic Trichothecenes produced by the "Black Mold", Stachybotrys. Testing is simple, only requiring small amounts of dust or material from AC or heater filters. $299. can be order directly by patient.

Kelly K. McCann, MD

Case 1: House Mold Testing



Kelly K. McCann, MD

Testing and remediation

- The test is only as good as the sample collection.
- If the musty smell is in the bathroom, sampling in the living room may not reflect the full extent of the problem.
- Utilize an qualified inspector who will use the appropriate testing methods available, including ERMI or HERSTMI2, air samples and wall samples when indicated.
- Certified Indoor Environmental Professional
- Read the Consensus Statement for indoor environmental professional (IEP) on inspection and remediation. https://www.survivingmold.com/docs/IEP_CONSENSUS_04_12_16.pdf
- An inspector should never be the remediator. Often the remediator is not the contractor to repair the work. Some situations require plumbers and general contractors.
- Patients and health care practitioners need to advocate for themselves. Very few IEPs, remediators or contractors understand the level of remediation required for HLA susceptible persons.

Kelly K. McCann, MD

Treatment of Mold Exposure

Get in your car and drive away! (although often the car is contaminated as well)

- Remediate the house or move.
- Test the new house, if able.
- Focus on healing the body.

- GET AWAY FROM THE MOLDY ENVIRONMENT!!
- Avoid other moldy environments.
- Avoid other environmental toxins; such as pesticides, formaldehyde, fragrances, plastics, chemicals, heavy Metals, EMR
- Leave any belongings that can't be cleaned. All cloth and porous surfaced materials will be difficult to clean.
- Any items kept, should be cleaned and placed in storage for several months to ensure no mold growth.
- Use High Quality HEPA Air filters and be sure to change out the filters after the mold/remediation

Kelly K. McCann, MD

Mold Removing Options

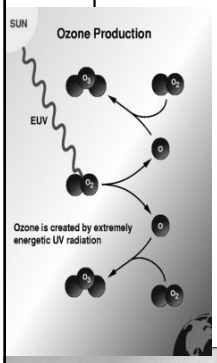
- Bleach
- Ethanol
- Vinegar
- Ammonia
- Hydrogen peroxide
- Detergent
- Baking soda
- Tea tree oil
- Grapefruit seed extract

Rogawansamy, et al. Evaluation of antifungal agents for the treatment of fungal contamination in indoor air environments. In J Environ Res Public Health 2015 June 2;12(6): 6319-32.

LOE: B

Kelly K. McCann, MD

What about Ozone?



- Used to disinfect by inactivating bacteria, viruses, fungi, yeast and protozoa
- Ozone used to treat contaminated grains, including wheat, maize, grapes, peanuts, sausages, cheeses by reducing mold and mycotoxins.
- Used in dental medicine and wound care

PMID: 22470237, 20477724, 26812055, 27287337, 26041242, 24982899, 24374809, 24282818

LOE: A

Kelly K. McCann, MD

Effect of Ozonation on Furniture Dust

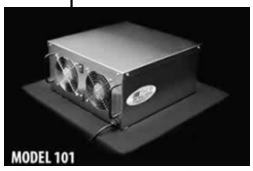
- Furniture from 46 moisture-damaged sites totaling 73 sample pairs
- Ozone vs. steam clean plus ozone – not statistically different
- Assessed microbes in dust via DNA PCR and immunotoxic effects in vitro.
- Overall viable microbes decreased with both methods, with some persistence of fungal materials.
- Nitric oxide, Cytokines TNF alpha and IL-6 were lower after treatment.

- Huttunen, et al. The Effect of ozonation on furniture dust. Science of the otal Environment 408 (2010) 2305-11.

Kelly K. McCann, MD

UV light /Air reactors

- HOW THE AIR REACTOR WORKS



- www.hitechairsolutions.com
- www.airoasis.com
- The Molecules that it destroys are ALL organic matter, Viruses, Bacteria, Mold, Mildew, Odors, off gasses, formaldehyde, as well as many others.

- "We use UV lighting (not to kill with) but to separate the light rays into different colors. What we have found with our research is that once the light rays are separated into different colors, different molecules attach to different color of light rays. We then developed a reactor pad, for these Molecules to travel through. While they are attached to different colors of light rays and travel through our specially designed reactor pad, it actually changes the molecular structure of that Molecule so that it is not what it was. Basically it implodes the molecule so that it does not exist as the molecule that it once was." - from the website…

LOE: C

Kelly K. McCann, MD

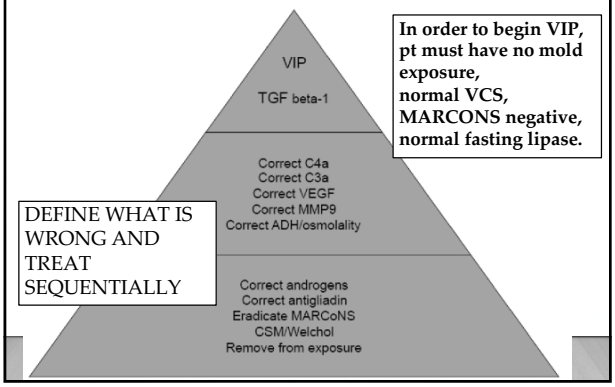
"How damp is this place?
Let me put it this way: I use mold and mildew remover as a skin care product."

Mold and Mycotoxin Treatment Principles

- Reduce inflammation
- Detoxify - Remove the toxins
- Repair the gastrointestinal tract
- Correct cellular immune dysfunct
- Deal with autoimmunity
- Reduce colonization/ infection
- Rebuild mitochondria
- Restore the nervous system
- Improve hypoperfusion
- Balance hormones and adrenals
- Replenish nutrients
- Optimize Methylation
- Reset limbic system
- Foster healthy lifestyle choices

Kelly K. McCann, MD

Shoemaker Treatment Protocol



In order to begin VIP, pt must have no mold exposure, normal VCS, MARCONS negative, normal fasting lipase.

DEFINE WHAT IS WRONG AND TREAT SEQUENTIALLY

Cholestyramine (CSM)

Cholestyramine– Insoluble quaternary ammonium exchange bile acid resin binder FDA approved for > 50 years to lower cholesterol. It is a long polystyrene chain with side groups. Positively charged, it binds to the mycotoxins which are ionophores containing both hydrophilic and hydrophobic aspects.

Off-label use of CSM. Consider informed consent.

- 4 grams four times daily. 30 minutes before fatty meal.
- Wait 90 minutes after eating. Mix in water or juice
- Start low and go slow with sensitive patients
- GI side effects include bloating, constipation
- Commercially available product contains

aspartame. Compounding pharmacies can make alternatives.

Cholestyramine Evidence

Cholestyramine has been shown in studies to bind to:

- Cyanobacteria
- Dinoflagellates
- Clostridia Difficile toxin
- Borrelia burdorferi
- Babesia microti
- Ochratoxin A
- Fumonisins (mycotoxins)
- Helicobacter pylori

- Falsafi T, et al. Culture of Helicobacter pylori from stool samples in children. Can J Microbiol. 2007 Mar;53(3):411-6.
- Hope JH, Hope BE. A review of the diagnosis and treatment of Ochratoxin A inhalational exposure associated with human illness and kidney disease including focal segmental glomerulosclerosis. J Environ Public Health. 2012;2012:835059.
- Puri BK, et al. The potential use of cholestyramine to reduce the risk of developing Clostridium difficile-associated diarrhoea in patients receiving long-term intravenous ceftriaxone. Med Hypotheses. 2015 Jan;84(1):78-80.
- Rankin KA, etal. Treatment of cyanobacterial (microcystin) toxicosis using oral cholestyramine: case report of a dog from Montana. Toxins (Basel). 2013 Jun;5(6):1051-63.
- Shoemaker RC, Hudnell HK, et al. Atovaquone plus cholestyramine in patients coinfected with Babesia microti and Borrelia burgdorferi refractory to other treatment. Adv Ther. 2006 Jan-Feb;23(1):1-11.
- Solfrizzo M, etal. In vitro and in vivo studies to assess the effectiveness of cholestyramine as a binding agent for fumonisins. Mycopathologia. 2001;151(3):147-53.

Welchol

- Welchol (Colesevelam) – 625mg tab 3 tabs twice daily with meals.
- Bile acid sequestrant
- Due to the structure, Welchol is only 25% as effective at binding mycotoxins.
- Contraindications include gastroparesis, bowel obstructions, triglycerides >500, history of hypertriglyceridemia-induced pancreatitis
- Be wary in patients with diabetes on insulin, triglycerides >300, or patients at risk for fat soluble vitamin deficiencies.
- Side effects include constipation 3-11%, dyspepsia 3-8%, headaches 4-8%, fatigue 4%, hypertriglyceridemia 4-5%, diarrhea 3%, weakness 3% , elevated CRP 3%

Information obtained from UpToDate

Sequestering Agents

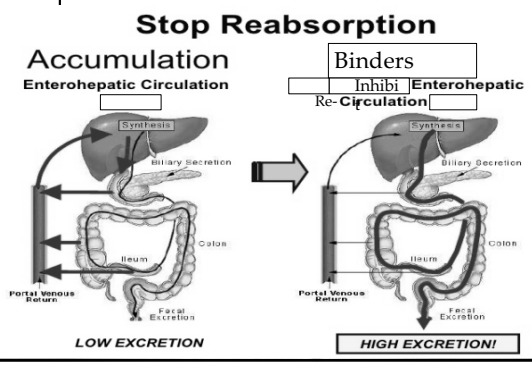
- These non-absorbable agents bind the mycotoxins and prevent them from entering the enterohepatic circulation, eventually lowering the total load. These need to be taken on an empty stomach away from food and supplements. Ideally 30-60 minutes before and 90+ minutes after.
- **Activated charcoal** – 2-3 caps once or twice daily. Build up dose slowly to avoid side effects. May bind aflatoxins, zearalenone and DON, and more effective for trichothecenes.
- **Bentonite Clay** – 2-3 caps once or twice daily. Can take liquid. Build up slowly. More drying and constipation inducing. Give adequate magnesium to soften stools. More effective for aflatoxins.

Sequestering agents

- **Chlorophyll-Chlorella** – Some practitioners have found helpful. 20 tabs three times daily 30 minutes before a meal.
- **Diatomaceous earth** – appears to bind aflatoxin, T-2 toxin, zearalenone and ochratoxin in vitro and in vivo in animal studies. Start 1 tsp once daily and work up to 1 tbsp TID

Denli M, et al. Efficacy of activated diatomaceous clay in reducing the toxicity of zearalenone in rats and piglets. J Anim Sci. 2015 Feb;93(2):637-45.
Bhatti SA, Comparative efficacy of Bentonite clay, activated charcoal and Trichosporon mycotoxinivorans in regulating the feed-to-tissue transfer of mycotoxins. J Sci Food Agric. 2017 Jul 11.
Dalie, et al. Lactic acid bacteria-Potential for control of mold growth and mycotoxins. Food Control 2010. 21(4) 370-80.
Del Pilar, et al. Activated carbons as potentially useful non-nutritive additives to prevent the effect of fumonisin B1 on sodium bentonite activity against chronic aflatoxicosis. Food Addit Contam Part A. 2016 May 31:1-10.
Kolosova. Substances for the reduction of the contamination of feed by mycotoxins. World Mycotoxin Journal 2011. 4(3): 225-56
Pappas, et al. Role of bentonite binders in mycotoxins in chicken diets. Br Poult Sci 2016 May 12.

Enterohepatic Circulation



Shoemaker Protocol Steps

- 1. **Remove from mold exposure**
- 2. Perform **ERMI** testing
- 3. Treat with **Cholestyramine** (CSM) 4 grams 4 times daily or Welchol 2 tabs TID or 3 tabs BID with meals. Start slow and work up. Treat constipation! TAKE AWAY FROM FOOD AND SUPPLEMENTS.
- Treat for 1 month and then move on to step 4. Continue CSM.
- 4. Treat **MARCONS** with BEG nasal spray (Bacitracin/EDTA/Gentamycin) or BEC spray (Clindamycin) 2 sprays TID for 4-6 weeks. Or Silver and EDTA. Repeat test for cure. If persists, consider dental cavitation source, canine or close contact source or ongoing mold exposure. Ramp up slowly and support detox.
- Obtain BEG spray from Hopkinton Drug in Hopkinton, MA

Shoemaker RC, House DE. Sick building syndrome (SBS) and exposure to water-damaged buildings: time series study, clinical trial and mechanisms.
Neurotoxicol Teratol. 2006 Sep-Oct;28(5):573-88.

Kelly K. McCann, MD

Shoemaker treatment protocol

- 5. **Correct anti-gliadin**, anti-cardiolipin ab. Eliminate gluten when warranted. Treat hypercoagulability.
- 6. **Correct androgens**. If estradiol levels too high, consider aromatase inhibitor. Inflammation and low VIP drives aromatase shunting testosterone to estradiol. Can support with DHEA. Androgens tend to self correct with toxin clearance. Testosterone replacement, in these patients, often causes more problems than it solves.
- 7. **Correct ADH.** Replete minerals when osmolality is low (<280) if ADH is low and osmolality high >295, consider DDAVP (vasopressin) with close supervision.
- 8. **Correct MMP-9 and VEGF.** Amylose-free diet and 2.4g EPA +1.8g DHA divided BID. Actos 15-45 mg was recommended previously.

Chaturvedi S, McCrae KR. Diagnosis and management of the antiphospholipid syndrome. Blood Rev. 2017 Jul 30.

Kelly K. McCann, MD

Shoemaker treatment protocol

- 9. **Correct C4a.** Off-label treatment includes Procrit (Epogen) Has black box warnings.
- 10. **Correct TGF beta1**. Losartan increases a patient's T reg cells by slowing conversion of T reg into Th17 cytotoxic T cells, which in turn lowers TGF beta-1 levels. This is off label use.
- 11. **Replace VIP.** Ensure no exposure and no MARCONS. Check pre and post treatment labs in office.
- VIP nasal spray 50 mcg.
- One nasal spray - alternating nostrils -4 times daily.
- Obtain from Hopkinton Drug

Internal Medicine Review- Intranasal VIP safely restores volume to multiple grey matter nuclei in patients with CIRS- April 2017 Shoemaker, R., Katz, D., Ackerley, M., Rapaport, S., McMahon, S., Berndtson, K., Ryan, J.

Shoemaker R, House D, Ryan J. Vasoactive intestinal polypeptide (VIP) corrects chronic inflammatory response syndrome (CIRS) acquired following exposure to water-damaged buildings. Health 2013; 3: 396-401.

"You've got a real fungus problem. You'll have to move out until it's taken care of."

Nutrient Supportive Treatments

- **Quercetin ameliorate Ochratoxin A toxicity in cell cultures.**
- **N-Acetyl Cysteine (NAC) 1800mg can lower TGF beta1 and protect intestinal barrier function.**
- **Liposomal glutathione - different formulations available.**
- **Co Q 10 100mg once or twice daily**
- **Methyl B12, methylfolate or folinic acid for methylation support**

Berk M. Biol Psychiatry 2008 Sep 1;64(5):361-8.
Berk M. Biol Psychiatry. 2008 Sep 15;64(6):468-75.
El Golli. Induction of Hsp 70 in Vero Cells in response to mycotoxins: Cytoprotection by Vitamin E. Toxicology letters 2006. 166(2): 122-130.
Guilford FT, Hope J. Deficient glutathione in the pathophysiology of mycotoxin-related illness. Toxins (Basel). 2014 Feb 10;6(2):608-23.
Raghubeer, et al. Resveratrol ameliorates OTA toxicity kidney cells. J Cell BioChem.2015 Dec;116(12):2947-55.
Ramyaa, et al. Quercetin modulate OTA-induced oxidative stress. BiochimBiophysActa.2014Jan;1840(1):681-92
Ranaldi. Intracellular zinc stores protect the intestinal epithelium from Ochratoxin A toxicity. Toxicology in vitro. 2009. 23(8): 516-21.
Speight,Neal. htttps://www.crcpress.com/Advancing-Medicine-with-Food-and-Nutrients-Secondedition/

Kelly K. McCann, MD

Nutrient Supportive Treatments

- **Zinc – must balance with copper if given in high amounts**
- **Vitamin E – 400 iu daily**
- **Butyrate inhibits yeast and yeast biofilms, inhibits tumorigenesis, improves gut integrity**
- **Curcumin 1000mg twice daily or more to reduce inflammation and break down biofilms.**
- **Green tea polyphenol extract or green tea 2-5 cups daily has been shown in a number of trials to reduce MMP9.**

Kelly K. McCann, MD

Nutrient Supportive therapies

- **Pterostibene has also been shown to lower MMP9.**
- **Resveratrol 100mg BID. Lowers TGFbeta1, Alters Treg/TH17.**
- **Taurine 1-2 grams/day. Taurine has anti-inflammatory and immunomodulatory activity.**

- Abrigo J, etal. Transforming growth factor type beta (TGF-β) requires reactive oxygen species to induce skeletal muscle atrophy. Cell Signal. 2016 May;28(5):366-76.
- Chakraborty A, et al. In vitro evaluation of the cytotoxic, anti-proliferative and anti-oxidant properties of pterostilbene isolated from Pterocarpus marsupium. Toxicol In Vitro. 2010 Jun;24(4):1215-28.
- Roomi MW, et al. Repression of matrix by a nutrient mixture, containing ascorbic acid, lysine, proline, and green tea extract on human Fanconi anemia fibroblast cell lines. Exp Oncol. 2013 Mar;35(1):20-4.
- Park JW, et al. Green tea polyphenol (-)-epigallocatechin gallate reduces matrix metalloproteinase-9 activity following transient focal cerebral ischemia. J Nutr Biochem. 2010 Nov;21(11):1038-44.
- Shahahzad, M. Utilising polyphenols for the clinical management of Candida albicans biofilms. Int J Antimicrob Agents. 2014 Sep;44(3):269-73.
- Yao J, etal. Effect of resveratrol on Treg/Th17 signaling and ulcerative colitis treatment in mice. World J Gastroenterol. 2015 Jun 7;21(21):6572-81.

Kelly K. McCann, MD

Supportive Treatment of Mycotoxicosis

- Create a bedroom sanctuary
- Sauna – far infrared or traditional
- Epsom salt baths
- Body washes with charcoal or clay for itchy skin
- Sleep support
- Physical therapy and massage
- Colon hydrotherapy and coffee enemas
- "Bottoms Up" therapy
- Oxygen therapy
- Low Dose Naltrexone for immune dysregulation
- Phosphatidyl Choline – oral and IV forms

Kane. Detoxx
Rea, WJ. Treatment of patients with mycotoxin disease. Toxicol Ind Health. 2009 Oct-Nov;25(9-10):711-4.

Kelly K. McCann, MD

Sauna

Compounds released in sweat

- Bromide, Chloride, Chromium, Copper, Iron
- Potassium, Sodium, Magnesium Manganese, Zinc, Copper, Cobalt
- Antimony, Cadmium, Lead, Mercury, Nickel
- Medications
- PCBs
- Mycotoxins

Genuis SJ, et al. Blood, urine, and sweat (BUS) study: monitoring and elimination of bioaccumulated toxic elements. Arch Environ Contam Toxicol. 2011 Aug;61(2):344-57.

Kelly K. McCann, MD

Membrane Stabilizing Diet: Modified Ketogenic Diet for Optimal Neurometabolic Health

Permitted foods

- Protein at every meal
- Raw, organic ground seeds and nuts and 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

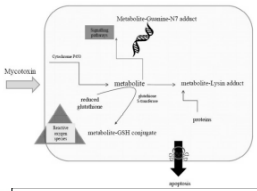
Omitted foods

- 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 sugar or sweeteners, No sodas or diet drinks
- No hybridized oleic oils (olive)
- No moldy foods, No GMO foods
- No dried fruits, high sugar fruits
- NO fast food
- NO Kombucha, No mushrooms

Kelly K. McCann, MD

Mold and Mycotoxins Induce Oxidative Stress and Inflammation

- Chronic mold exposures induce changes in inflammatory and immune responses to specific mold and mycotoxin challenges.
- Mold exposed patients had different cytokine and chemokine profiles when their peripheral blood mononuclear cells (PBMCs) were exposed to mold vs non-exposed controls.



- ROS are cleared from the cell by the action of superoxide dismutase (SOD), catalase (CAT), or glutathione peroxidase (GPx). The main damage to cells results from the ROS-induced alteration of macromolecules such as polyunsaturated fatty acids in membrane lipids, proteins, and DNA.

Hossam El-Din M. Mycotoxins-Induced Oxidative Stress and Disease DOI: 10.5772/51806
Rosenblum Litchenstein. PloS one 2015 May; 10(5).

Kelly K. McCann, MD

Mold and Mycotoxins Induce Oxidative Stress and Inflammation

- Mold toxins may suppress the immune system through a balance of cytotoxicity and altered Th1/Th2 balance, with increase Th1. The alteration of immune responses due to chronic mold exposures may also adversely affect the ability of the immune system to fight infections and other environmental challenges.
- This may explain patient complaints of concurrent susceptibility to infectious organisms and enhanced responses to chemical irritants.

Hossam El-Din M. Mycotoxins-Induced Oxidative Stress and Disease DOI: 10.5772/51806
Rosenblum Litchenstein. PloS one 2015 May; 10(5).

Kelly K. McCann, MD

Mold, Mycotoxin, Fungal Infections and the Mycobiome

- **Mycotoxins (ingested or inhaled) in the GI tract**
  - **Affect regeneration and repair of intestinal epithelial cells**
  - **Increase intestinal mucosal permeability**
  - **Alter immune system response**
  - **Changes the composition of intestinal bacterial communities (and possibly the fungal mycobiome)**
  - **Are carcinogens in hepatocellular and esophagogastric cancers**
- **Commensal mycobiota may turn pathogenic**
- **Fungal pathogens elicit complex innate and adaptive immune responses**
- **Some genetic polymorphisms/predispositions increasing susceptibility to systemic fungal infections and induce chronic inflammation resulting in IBD colitis.**

Sam, QH, et al. The Fungal Mycobiome and its Interaction with the Gut Bacteria in the Host. Int J. Mol. Sci 2017; 18, 330.
Wang, 2014.

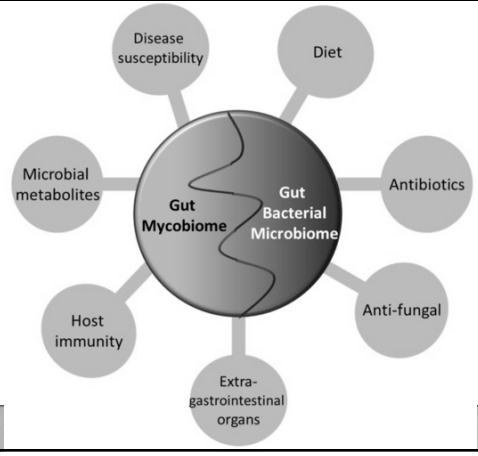
Kelly K. McCann, MD

Fungal mycobiome

- **Fungal mycobiota important in GI tract**
- **70% of health adults have fungal organisms in GI tract**
- **Fungi also found in vagina, oral cavity, lungs, skin – intense research area**
- **Metagenomic analysis – only 0.1% of fecal microbial DNA was eukaryotic.**
- **Mycobiome affected similarly to microbiome. (age, BMI, birth circumstance, diet, geography, toxicants, tobacco, antibiotic usage, etc.)**
- **Some mycobiome from food sources**
- **Fungal-bacterial interactions very complex. Synergistic and antagonist**
- **Fungus as pathogen. Fungus as commensal perhaps not as clear cut as once assumed.**

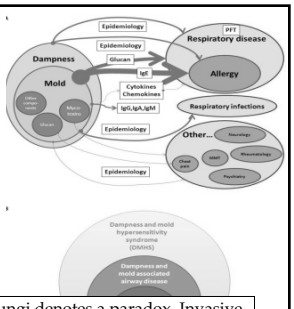
Wang, ZK et al. Review article: fungal microbiota and digestive diseases. Aliment Pharmacol Ther 2014; 39:751-66.

Kelly K. McCann, MD



frontiers in Immunology

An Evolutionary-Based Framework for Analyzing Mold and Dampness-Associated Symptoms in DMHS



Relationship between humans and fungi denotes a paradox. Invasive fungal infections are rare…(but) the absence of a host-parasite relationship is associated with higher pathogenicity. Humans have a higher investment in prevention and elimination of these potential invaders, thus the pro-inflammatory response of the host is magnified.

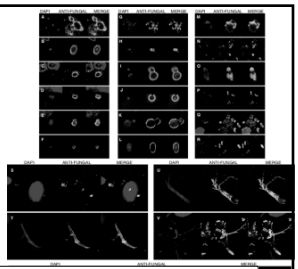
Daschner 2017

www.nature.com/scientificreports

SCIENTIFIC REPORTS

OPEN

Different Brain Regions are Infected with Fungi in Alzheimer's Disease



Fungal proteins and polysaccharides are present in the blood and fungal proteins and DNA was detected in the brain tissue of 100% of AD patients. Direct visualization of intracellular fungal infection in the neurons from the frontal cortex was demonstrated with fungal-specific antibodies, all of which were absent in controls. Fungal cells and hyphae were detected inside capillaries and blood vessels. Pisa 2015

Int J Biol Sci 2015, Vol. 11 546

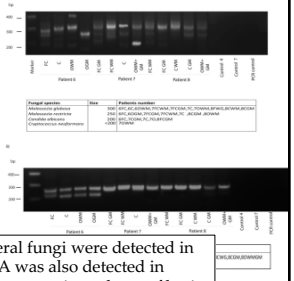
IVYSPRING INTERNATIONAL PUBLISHER

International Journal of Biological Sciences

2015; 11(5): 546-558. doi: 10.7150/ijbs.11064

Research Paper

Evidence for Fungal Infection in Cerebrospinal Fluid and Brain Tissue from Patients with Amyotrophic Lateral Sclerosis



Fungal antigens and DNA from several fungi were detected in the CFS of ALS patients. Fungal DNA was also detected in brain tissue using PCR analysis and proteomic analyses of brain tissue demonstrated with occurrence of several fungal peptides. In familial ALS, the most common gene mutation is of Cu/Zn superoxide dismutase (SOD1) which is an antioxidant defense gene involved in innate immune response to a number of pathogens, including fungi.

Alonso, et al 2015

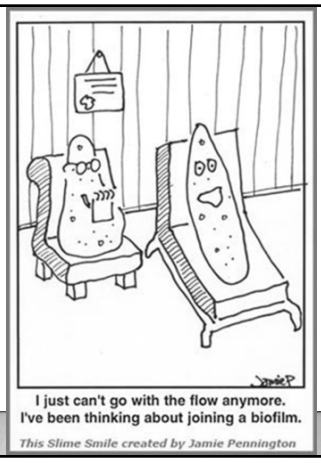
Inhalational Alzheimer's disease

- **Three subtypes of AD**
- **1. Systemic inflammation**
- **2. Atrophic – often with hyperhomocysteine and insulin resistance**
- **3. CIRS type**
  - **Younger age (40-60 yrs)**
  - **APO E3/3, rather than APOE4**
  - **Onset following stress, menopause, surgery, trauma**
  - **Dyscalculia, executive dysfunction is neuro dysfunction**
  - **Preceded by depression**
  - **Treated with CIRS protocols**

Table 2. Symptoms, signs, and laboratory values suggestive of type 3 Alzheimer's disease.

Characteristic	Comment
Age at symptom onset less than 65 years	Symptoms often begin in the 50s or late 40s.
ApoE ε4-negative genotype.	Typically ApoE3/3 unless there are other risk factors.
Negative family history or family history positive with symptom onset only in much older individuals than the patient.	
Symptom onset in association with menopause or andropause.	
Depression as a preceding or significant accompaniment of the cognitive decline.	
Headache as an early or preceding symptom.	
Atypical presentation, in which memory consolidation is not the initial and dominant characteristic.	Typical deficits include executive deficits, dyscalculia, paraphasias, or aphasia.
Precipitation or exacerbation by a period of great stress (e.g., loss of employment or marriage dissolution or family change) and sleep loss.	The degree of dysfunction is also markedly affected by stress and sleep loss.
Exposure to mycotoxins or metals (e.g., inorganic mercury via amalgams, or organic mercury via the consumption of large fish such as tuna) or both.	
Diagnosis of CIRS with cognitive decline.	Cognitive decline is common with CIRS.
Imaging suggestive of more than typical Alzheimer's involvement.	FDG-PET may show frontal as well as temporoparietal reductions in glucose utilization, even early in the course of the illness; MRI may show generalized cerebral and cerebellar atrophy, especially with mild FLAIR (fluid-attenuated inversion recovery) hyperintensity.
Low serum triglycerides or triglyceride:total cholesterol ratio.	Triglycerides are often in the 50s.
Low serum zinc (<75mcg/dl) or RBC zinc, or high copper:zinc ratio (>1.1).	
HPA axis dysfunction, with low pregnenolone, DHEA-S, and/or AM cortisol.	
High serum C4a, TGF-β1, or MMP9; or low serum MSH (melanocyte-stimulating hormone). Positive deep naso-pharyngeal culture for MARCoNS.	See reference 5.
HLA-DR/DQ associated with multiple biotoxin sensitivities or pathogen-specific sensitivity.	See reference 5.

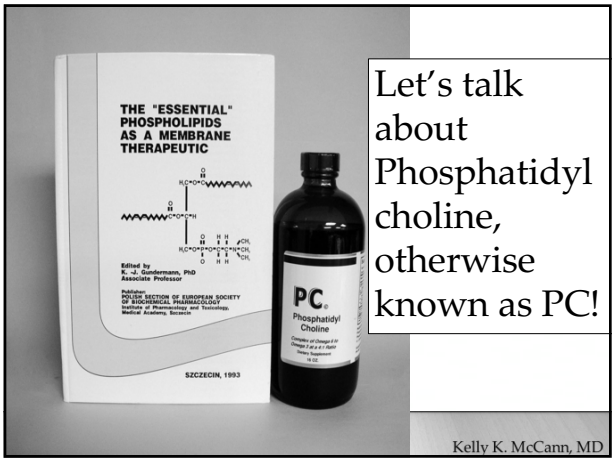
Bredesen. Aging.Feb 2016; 8(2): 304-313.



Do Mycotoxins Alter Phospholipids?

- **Stachybotrys chartarum mycotoxin reduces phosphatidylcholine enzyme synthesis in lung by 50%**
- **Fumonisin B1 disrupt membrane structure, enhances lipid oxidation leading to cell death.**
- **Fumonisin B1 in hepatocyte cultures changes to more rigid membrane structure by altering phospholipids**
- **Fumonisin B1 alters of lipid constituents of cellular membranes, and is a possible mechanism for hepatic cancer promotion and immunotoxicology**
- **Mushroom toxin phallolysin damages liposomes and phospholipid membranes**
- **Ochratoxin A is nephrotoxic, immunotoxic and carcinogenic, possibly by altering phospholipids.**

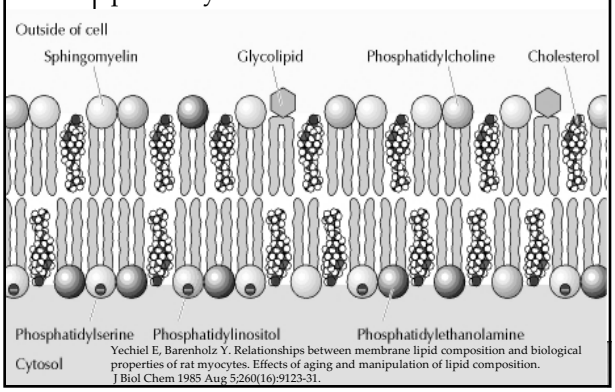
Hastings, C. et al. Toxicolo Sci 2005. Mar 84(1):186-94.
Yin, JJ. Biochim Biophys Acta. 1998. Apr 22;1371(1):134-42.
Buhring, HJ. Biochim Biophys Acta. 1983. Aug 24;733(1):117-23.
Burger HM. Lipids. 2007 Apr;42(3):249-61.
Hope. Jour Environ and Pub Health 2012. art ID 835059



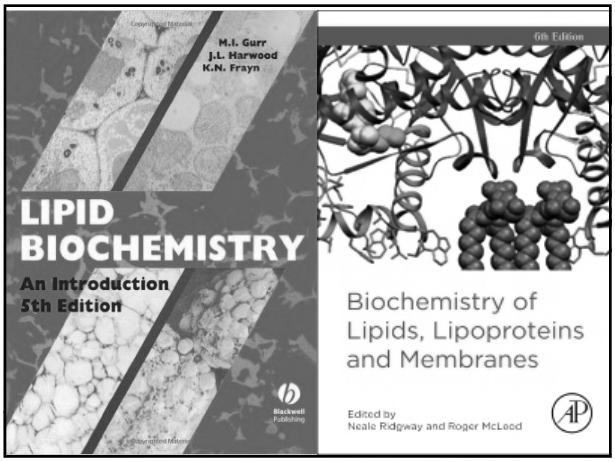
Let's talk about Phosphatidylcholine, otherwise known as PC!

Kelly K. McCann, MD

The Lipid Bilayer



Yechiel E, Barenholz Y. Relationships between membrane lipid composition and biological properties of rat myocytes. Effects of aging and manipulation of lipid composition. J Biol Chem 1985 Aug 5;260(16):9123-31.

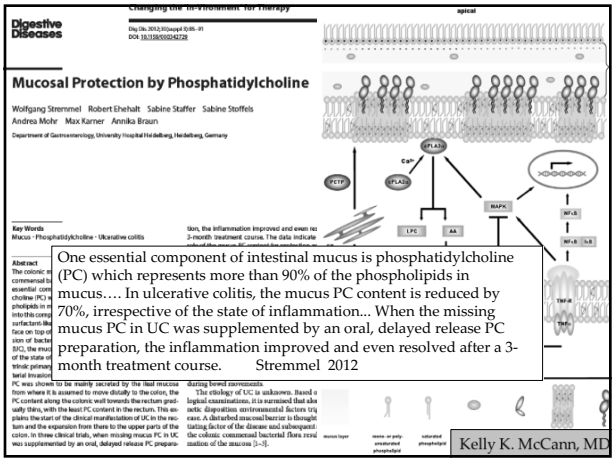


Clinical Indications for use of Phosphatidylcholine

- Acute and chronic hepatitis
- Fatty liver
- Toxic liver damage
- Cirrhosis of the Liver
- Prevention gallstones
- Renal insufficiency
- Hyperemesis gravidarum
- Dyslipidemia
- Atherosclerosis
- Circulatory problems
- Angina pectoris
- Hypertension
- Gastrointestinal inflammation
- Dementia
- Multiple sclerosis
- Headache
- Insomnia
- Psoriasis
- Any Inflammatory condition

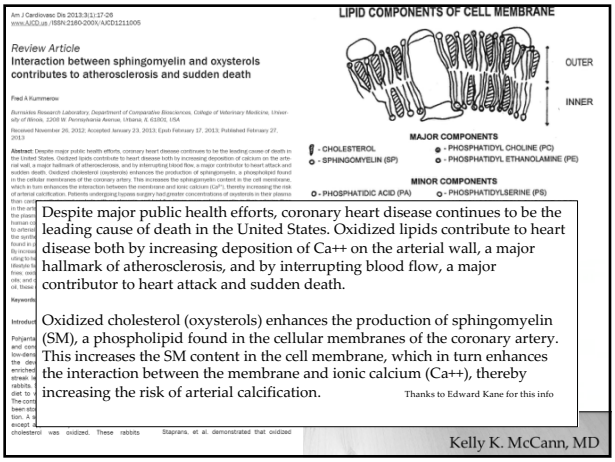
Sunderman. Essential Phospholipids.1993.
https://www.bodybio.com/BodyBio/docs/PC-Phosphatidylcholine-Fountain-of-Health.pdf
PhosChol monograph; http://www.phoschol.com/prescribing_information/PhosCholPrescribing.pdf

Kelly K. McCann, MD



One essential component of intestinal mucus is phosphatidylcholine (PC) which represents more than 90% of the phospholipids in mucus…. In ulcerative colitis, the mucus PC content is reduced by 70%, irrespective of the state of inflammation... When the missing mucus PC in UC was supplemented by an oral, delayed release PC preparation, the inflammation improved and even resolved after a 3-month treatment course. Stremmel 2012

Kelly K. McCann, MD

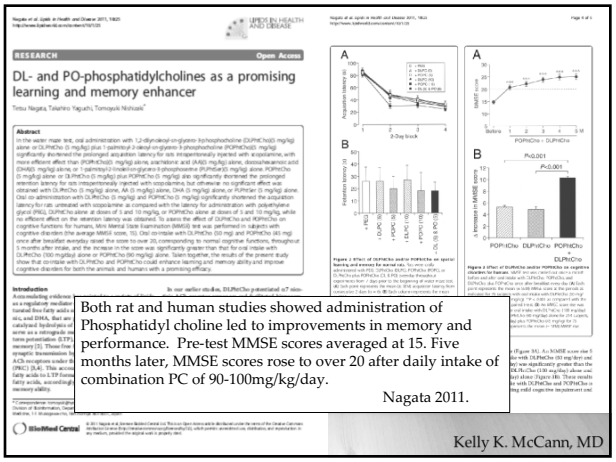


Despite major public health efforts, coronary heart disease continues to be the leading cause of death in the United States. Oxidized lipids contribute to heart disease both by increasing deposition of Ca++ on the arterial wall, a major hallmark of atherosclerosis, and by interrupting blood flow, a major contributor to heart attack and sudden death.

Oxidized cholesterol (oxysterols) enhances the production of sphingomyelin (SM), a phospholipid found in the cellular membranes of the coronary artery. This increases the SM content in the cell membrane, which in turn enhances the interaction between the membrane and ionic calcium (Ca++), thereby increasing the risk of arterial calcification.

Thanks to Edward Kane for this info

Kelly K. McCann, MD

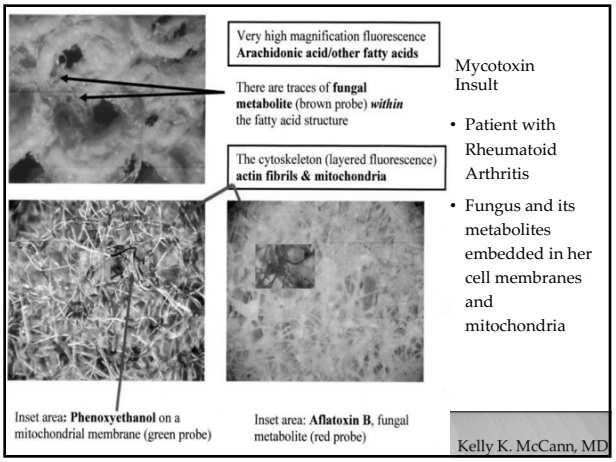


DL- and PO-phosphatidylcholines as a promising learning and memory enhancer

Both rat and human studies showed administration of Phosphatidyl choline led to improvements in memory and performance. Pre-test MMSE scores averaged at 15. Five months later, MMSE scores rose to over 20 after daily intake of combination PC of 90-100mg/kg/day.

Nagata 2011.

Kelly K. McCann, MD



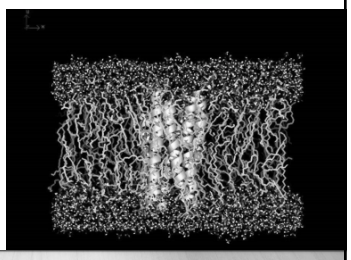
Mycotoxin Insult

- Patient with Rheumatoid Arthritis
- Fungus and its metabolites embedded in her cell membranes and mitochondria

Kelly K. McCann, MD

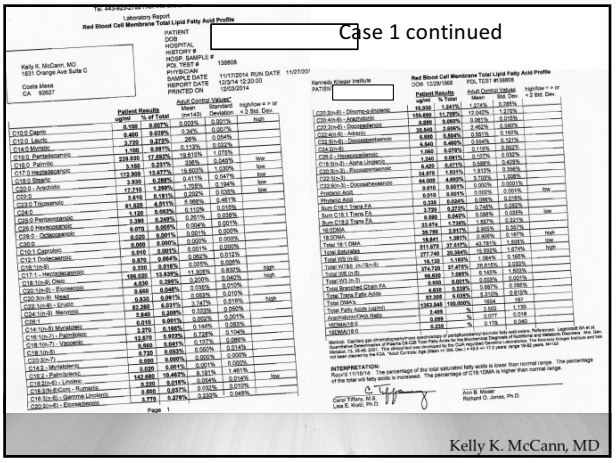
Assessing RBC fatty acid content

- Kennedy Krieger Institute Peroxisomal Laboratory at Johns Hopkins University
- Body Bio Assessment



Kelly K. McCann, MD

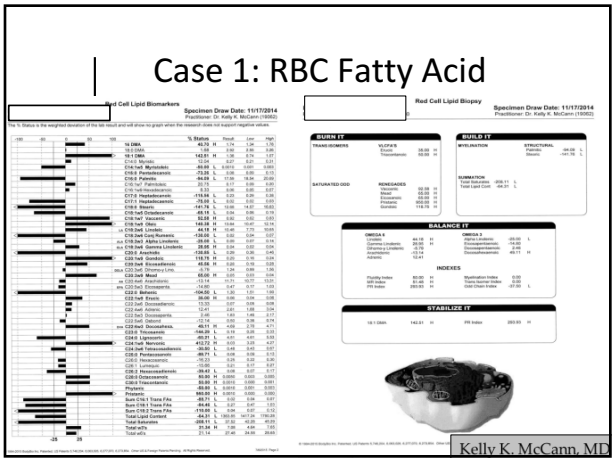
Case 1 continued



Kelly K. McCann, MD

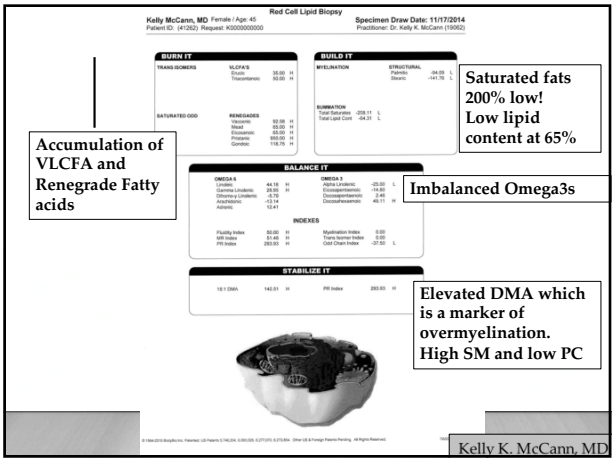
***This Slide Enlarged on Page 150**

Case 1: RBC Fatty Acid



Kelly K. McCann, MD

***This Slide Enlarged on Page 151**



Kelly K. McCann, MD

Oral Protocol for Case 1

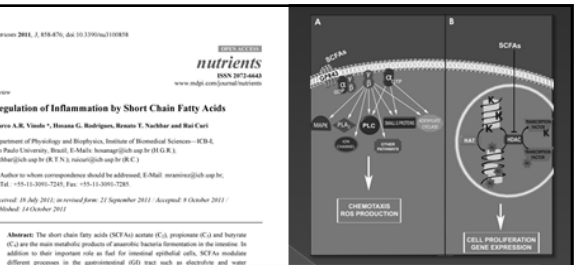
- Phosphatidylcholine 1 tbsp or 14 caps daily = 9 grams or more if tolerated
- Sodium/potassium Butyrate 2 caps twice daily =500mg butyric acid/cap
- E'lyte solution – can give up to ½ bottle daily in severe fasciculations
- Evening primrose oil 1000mg daily
- Fish in the form of caviar or small fish
- Balance oil 4:1 mixture of Omega6:omega3 – 4-6 tbsp daily

Kelly K. McCann, MD

Membrane Stabilizing Protein Drink

- Protein powder
- Phosphatidylcholine 1 tbsp
- E'lyte 1 tbsp or more
- Body Bio Balance Oil 2 tbsp
- Evening primrose oil 1 tbsp = 1000mg
- Trace minerals
- Can add coconut, almond or sheep milk kefir
- Organic seeds, nuts can be soaked and blended and added
- Berries to taste

Kelly K. McCann, MD



Butyrate, a short chain fatty acid, modulates gene expression by activation of GPCRs and inhibition of histone deacetylase (HDAC) activity but its effects are far reaching in modulating inflammatory mediators, modifying lipid metabolism as stimulating the production of resolvins/protectins and having a CNS protective aspect in neurological disease including reduction in brain infarct volume.

Vinolo MA et al. 2011

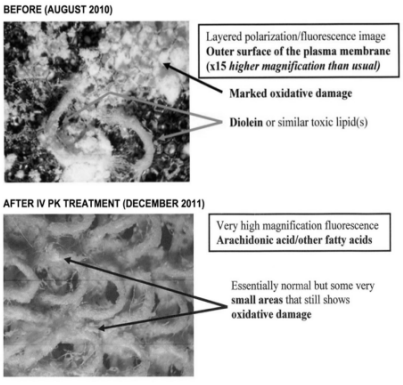
Kelly K. McCann, MD

Butyrate

- Butyrate may be anti-atherogenic and antioxidant effects on glutathione production
- Butyrate reduces inflammation in shigellosis
- Modulates gene expression
- Butyrate decreases proinflammatory expression via inhibition of NFκB activation in Crohn's
- Must be used with PC and lipids
- Butyrate protects mice from NASH by reducing inflammation
- Phenylbutyrate is a histone deactylator and breaks up VLCFA and has indications in spinal muscle atrophy, ALS, ischemia, urea cycle defects, sickle cell, Cystic fibrosis and Huntington's disease

Omana, P. Pharmaceuticals (Basel). 2014 Nov; 7(11): 1008–1027.
Johannes J. Immunology. 2013 Jul; 139(3): 395–405.
Rubhana. BMC Infect Dis. 2012; 12: 111.
Tan, J. Adv Immunol. 2014;121:91-119.
Vinolo. Nutrients. 2011 Oct; 3(10): 858–876.
Segain JP. Gut. 2000;47:397–403.
Iannitti and Palmier. Drugs RD 2011; 11(3):227-249

Kelly K. McCann, MD



- Research lab in the UK/ Germany
- Not currently available for most clinicians

Kelly K. McCann, MD

NEUROLIPID RESEARCH FOUNDATION

Amount of Essentiale-PC Required to Clear Toxicity

At the International Phospholipid conference in London November 12-13, 2010 physicians Katrin Bieber and Meinrad Milz (oncologist) presented their extensive biostatistical analysis of their patients' cellular toxicity status from repeat blood analyses from Acumen research laboratory that the amount of Essentiale-PC in the IV PK Membrane Stabilizing Protocol required to clear toxins adducted to the nuclear and mitochondrial DNA, normalize test results and note improvement in clinical presentation is the following.

The amount of PC required to clear DNA adducts and stabilize patient:

0.5 to 1.2 grams of PC per kg of body weight
quantity of PC required to clear DNA adducts,
normalize cell membranes and stabilize patient
Bieber K and Milz M 2010
per biostatistical analysis at the University of Ulm in Germany working with Dr. Meinrad Milz and Dr. Katrin Bieber

Example:

Requirement of Essentiale is 2 to 5 vials per kg body wt
For a 50 kg female this equals 100 to 250 vials
At 8 vials per treatment would equate to 12 to 32 treatments.

The Membrane Stabilizing IV Protocol is initiated with a phospholipid exchange or bolus phospholipid drip followed by IV folinic acid (Leucovorin or Fusilev) to support methylation. In the last step of the protocol reduced glutathione (diluted with sterile H_2O, not saline) is infused to support sulfation. In administering glutathione with PC we are attempting to achieve a lipid-soluble glutathione to clear numerous toxins and to chelate heavy metals bound to the peptide metallothionein, (which binds heavy metals), support immune function, and suppress PLA2, thereby stabilizing the phospholipids in the membrane. Glutathione can form metal complexes via nonenzymatic reactions and is a versatile and pervasive metal-binding ligand. The sulfhydryl group of the cysteine moiety of glutathione has a strong affinity for mercury, silver, cadmium, arsenic, lead, gold, zinc, and copper. Glutathione, however, is not lipid soluble and cannot penetrate the membrane of blood brain barrier without the 'drug delivery system' effect of Essentiale Phosphatidylcholine. Thus the infusion of Essentiale precedes the administration of glutathione so that it is 'lipid soluble' and can penetrate the cell membrane.

The cellular impact of toxic burdens can result in disturbed prostaglandin synthesis, poor cellular integrity, increased cytokine release, decreased glutathione levels, suppression of omega-6 arachidonic and linoleic acids, and marked elevation of renegade fats. Our clinical recourse is to address cellular derangement with PC, both orally and by infusion, to potentially offset the accumulation of ceramides, influence membrane fluidity, clear neurotoxins from the nuclear and mitochondrial DNA, and stabilize the integrity of the lipid mitochondrial cardiolipin based inner membrane and plasma membrane leaflets.

Kelly K. McCann, MD

Case 1: follow up

- She received 0.5g/kg of IV PC so far.
- Patient relocated to a mold-free house.
- She got rid of ALL her soft furniture items including her mattress, sofa, chairs, dining room chairs, carpets, lamps
- She dry cleaned or washed with the mold laundry additive her absolute favorite clothes and put them in storage to see if mold would grow after several months.
- She wiped down and stored all her wood furniture for 2 months.
- And repeated her labs….
- TGFbeta1 2300 pg/mL (<2382) down from 9800+
- MMP9 368 ng/mL (<332) down from 900+
- VIP 26.6 pg/mL (23-63) up from <16
- MSH <8 pg/mL, unchanged

Kelly K. McCann, MD

Case 5: September 2016

- **48 yr old woman came in with multiple medical problems and a long history of not feeling well for the past 7-8 years. She complained of:**
- **Joint pains, Fatigue**
- **Brain fog**
- **Muscle tightness and twitches**
- **Chemical sensitivities**
- **Food sensitivities - only 5 foods**
- **Flushing, Voice hoarseness**
- **Mouth pain**
- **Irritable bowel symptoms**
- **Burning eyes, Dizziness**
- **Adrenal fatigue on Cortef**
- **Tick bit in Orange County, CA 2 ½ years prior, then developed bronchitis requiring steroids and antibiotics, then 2 weeks later a cellulitis on her Great toe, in another 2 weeks had an eye infection and recurrent rashes.**
- **Igenex lyme test was equivocal but 31 epitope test was negative.**
- **Current house and work environment are both moldy.**

Kelly K. McCann, MD

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	Light sensitivity	**Appetite swings**
Heart palpitations	burning or stabbing	**Joint pains**	Temperature regulation issues
Nausea or vomiting	Increased motion sickness	**Morning stiffness**	Increased urinary frequency
Difficulty eating	Vision changes	Red eyes	Nocturia
Constipation	Hearing changes	Tearing eyes	**Abdominal pain**
Diarrhea	Hypotension	Blurred vision	Numbness
Bladder dysfunction	**Disturbed sleep**	**Vertigo**	Disorientation
Cystitis	**Memory loss**	**Aches**	Metallic taste
Dizziness	**Confusion**	Ice pick pain	Static shocks
Balance problems	**Difficulty concentrating**		**Sweats (esp night sweats)** Skin sensitivity/rashes
Tremor			

***This Slide Enlarged on Page 138**

CLUSTER ANALYSES. Give 1 point for any or all symptoms in a category. 6 or more points for children. 8 or more teens and adults. Circle any that apply

- **Fatigue**
- **Weakness, difficulty assimilating new information, muscle aches, headaches, light sensitivity**
- **Memory problems, word finding difficulties**
- **Problems with Concentration**
- **Joint pains, morning stiffness, muscle cramps**
- **Unusual skin sensations, tingling**
- **Shortness of breath, sinus congestion or nasal drainage**
- **Cough, increased thirst, confusion**
- **Appetite swings, body temperature regulation, urinary frequency/urgency**
- **Red eyes, blurred vision, excessive or nighttime sweating, mood swings, unusual pains esp. "ice pick pains"**
- **Abdominal tenderness or pain, diarrhea or loose stools, numbness**
- **Eye tearing, disorientation, metallic taste**
- **Static shocks, vertigo** **Total number:**

Kelly K. McCann, MD

Case 5

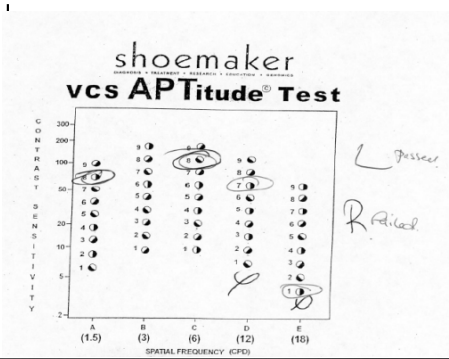
- PMHx: hyperlipidemia, tinnitus, CFS, fibromyalgia, hypothyroidism, IBS, insomnia, GERD, +RF, depression, anxiety, osteopenia, metabolic syndrome perimenopausal, recurrent hives, mast cell activation syndrome, Multiple Chemical Sensitivity
- PSHx: uterine ablation 2015

LABS: HLA DR 1-5 low MSH, 13-6-52C mold susceptible

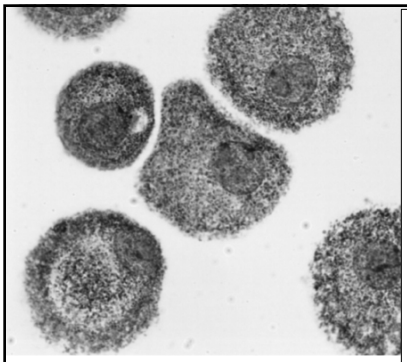
- MSH 17 pg/mL (nl 35-81)
- VIP 48.8pg/mL (nl 23-63)
- TGFBeta1 5623 pg/mL H (<2382)
- C4a 14,043ng/mL H (<2830)
- MMP9 766 ng/mL H (<332)
- VEGF 53 pg/mL (nl 31-86)
- MARCONS +large amount
- RF 177 IU/mL H
- antiCCP<1 U/mL
- hs CRP 3.45mg/dL = 32.86 nmol/L

Kelly K. McCann, MD

Case 5



Kelly K. McCann, MD



Mast Cells: Laboratory of Allergic Diseases, National Institute of Allergy and I
Diseases, National Institutes of Health (LAD/NIAID/NIH)

What are Mast Cells?
Mast cells are type of white blood cells, specifically, granulocytes derived from myeloid stem cell that is part of the immune and neuroimmune system. Each mast cell contains secretory granules (storage sacs), each containing powerful biologically active molecules called mediators, like histamine and heparin. These can be secreted when mast cells are triggered, leading to allergic and inflammatory diseases.

Kelly K. McCann, MD

Classification of mast cell disorders

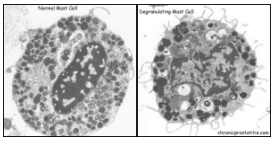
Primary mast cell disorders
Mastocytosis (systemic and cutaneous)
Monoclonal mast cell activation syndrome
Secondary mast cell disorders
Allergic disorders
Physical urticarias
Mast cell activation associated with chronic inflammatory or neoplastic disorders
Idiopathic mast cell disorders
Idiopathic anaphylaxis
Idiopathic urticaria
Idiopathic histaminergic angioedema
Idiopathic mast cell activation syndrome

Kelly K. McCann, MD

Table 3 Frequent signs and clinical symptoms ascribed to episodic unregulated release of mast cell mediators (modified from [12]; further references therein; an exhaustive survey is given in [50])

Signs and Symptoms	
Abdominal	abdominal pain, intestinal cramping and bloating, diarrhea and/or obstipation, nausea, non-cardiac chest pain, Helicobacter pylori-negative gastritis, malabsorption
Oropharyngeal	burning pain, aphthae
Respiratory	cough, asthma-like symptoms, dyspnea, rhinitis, sinusitis
Ophthalmologic	conjunctivitis, difficulty in focusing
Hepatic	splenomegaly, hyperbilirubinemia, elevation of liver transaminases, hypercholesterolemia
Splenomegaly	
Lymphadenopathy	
Cardiovascular	tachycardia, blood pressure irregularity (hypotension and/or hypertension), syncope, hot flush
Neuropsychiatric	headache, neuropathic pain, polyneuropathy, decreased attention span, difficulty in concentration, forgetfulness, anxiety, sleeplessness, organic brain syndrome, vertigo, lightheadedness, tinnitus
Cutaneous	urticaria pigmentosa, hives, efflorescences with/without pruritus, telangiectasia, flushing, angioedema
Abnormal bleeding	
Musculoskeletal	muscle pain, osteoporosis/osteopenia, bone pain, migratory arthritis
Interstitial cystitis	
Constitutional	fatigue, asthenia, fever, environmental sensitivities

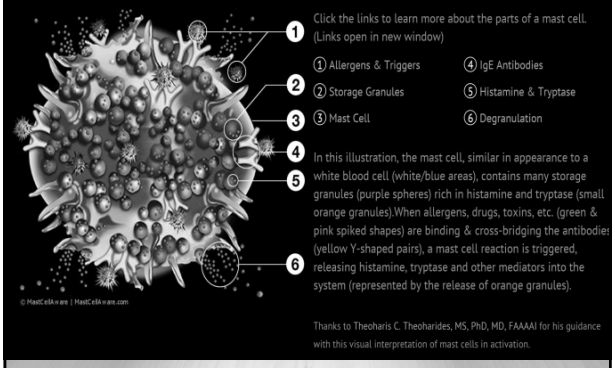
Mast Cell Activation Syndrome (MCAS)



Kelly K. McCann, MD

***This Slide Enlarged on Page 152**

Mast Cells In Activation



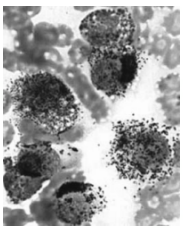
Kelly K. McCann, MD

***This Slide Enlarged on Page 153**

Testing for Mast cell Activation Syndrome

Must stop all NSAIDS, aspirin or other salisylates and all PPIs 5 days prior to testing. It is ok to continue H2 blockers like zantac or pepcid or other histamine blockers such as bendaryl, zyrtec or Claritin if necessary. If at all possible, stop these.

1. **Chilled serum trypase**
2. **Chromogranin A**
3. **Plasma prostaglandin D2**
4. **Histamine**
5. **Heparin**
6. **Random urine N-methylhistamine**
7. **Random urine Leukotriene E4**
8. **24-hour urine prostaglandin D2**



Kelly K. McCann, MD

Testing for Mast cell Activation Syndrome

9. **24-hour urine N-methylhistamine**
10. **24-hour urine leukotriene E4**
11. **24-hour urine 2,3-dinor-11beta-prostaglandin F2 alpha**
12. **Anti-IgE IgG (define autoimmunity)**
13. **Anti-IgE-receptor antibody testing (define autoimmune urticaria)**

- All blood tests must be collected on ice, spun down in the cold centrifuge, and sent frozen.
- For random urine collections, they must be kept cold (either on ice or in the refrigerator) until they are processed in the Reference lab, and then sent frozen.
- For 24 hour urine collections, they must be kept refrigerated during collection (as usual), and sent frozen.

Kelly K. McCann, MD

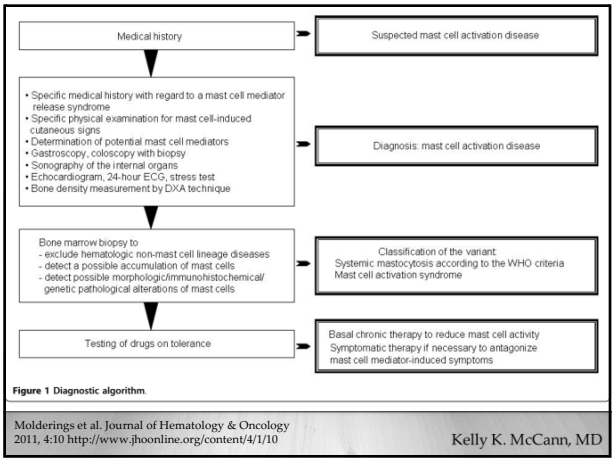
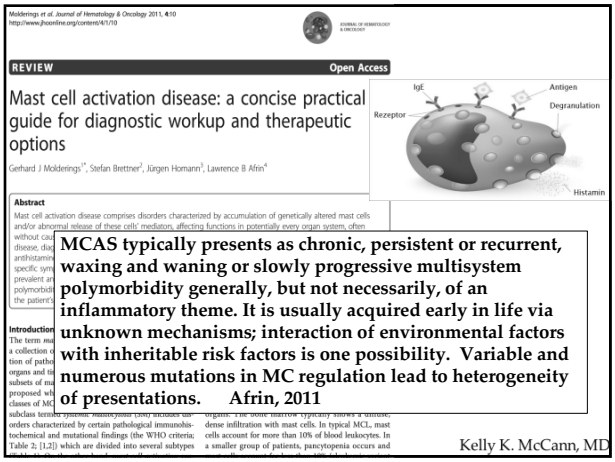


Figure 1 Diagnostic algorithm.

Molderings et al. Journal of Hematology & Oncology 2011, 4:10 http://www.jhoonline.org/content/4/1/10

Kelly K. McCann, MD

***This Slide Enlarged on Page 149**



Molderings et al. Journal of Hematology & Oncology 2011, 4:10
http://www.jhoonline.org/content/4/1/10

REVIEW Open Access

Mast cell activation disease: a concise practical guide for diagnostic workup and therapeutic options

Gerhard J Molderings[1*], Stefan Brettner[2], Jürgen Homann[3], Lawrence B Afrin[4]

Abstract

Mast cell activation disease comprises disorders characterized by accumulation of genetically altered mast cells and/or abnormal release of these cells' mediators, affecting functions in potentially every organ system, often

MCAS typically presents as chronic, persistent or recurrent, waxing and waning or slowly progressive multisystem polymorbidity generally, but not necessarily, of an inflammatory theme. It is usually acquired early in life via unknown mechanisms; interaction of environmental factors with inheritable risk factors is one possibility. Variable and numerous mutations in MC regulation lead to heterogeneity of presentations. Afrin, 2011

Kelly K. McCann, MD

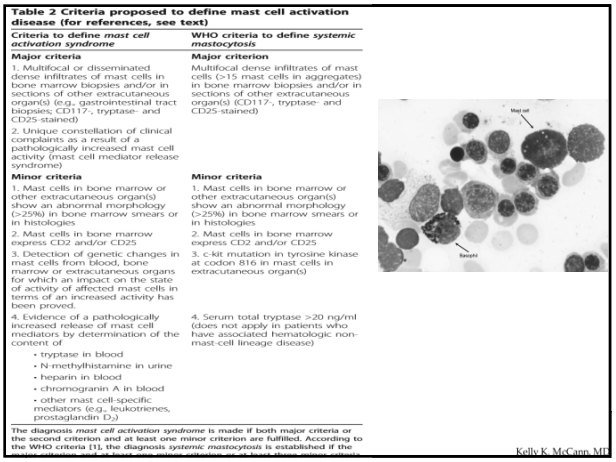


Table 2 Criteria proposed to define mast cell activation disease (for references, see text)

Criteria to define *mast cell activation syndrome*	WHO criteria to define *systemic mastocytosis*
Major criteria	**Major criterion**
1. Multifocal or disseminated dense infiltrates of mast cells in bone marrow biopsies and/or in sections of other extracutaneous organ(s) (e.g., gastrointestinal tract biopsies; CD117-, tryptase- and CD25-stained)	Multifocal dense infiltrates of mast cells (>15 mast cells in aggregates) in bone marrow biopsies and/or in sections of other extracutaneous organ(s) (CD117-, tryptase- and CD25-stained)
2. Unique constellation of clinical complaints as a result of a pathologically increased mast cell activity (mast cell mediator release syndrome)	
Minor criteria	**Minor criteria**
1. Mast cells in bone marrow or other extracutaneous organ(s) show an abnormal morphology (>25%) in bone marrow smears or in histologies	1. Mast cells in bone marrow or other extracutaneous organ(s) show an abnormal morphology (>25%) in bone marrow smears or in histologies
2. Mast cells in bone marrow express CD2 and/or CD25	2. Mast cells in bone marrow express CD2 and/or CD25
3. Detection of genetic changes in mast cells from blood, bone marrow or extracutaneous organs for which an impact on the state of activity of affected mast cells in terms of an increased activity has been proved.	3. c-kit mutation in tyrosine kinase at codon 816 in mast cells in extracutaneous organ(s)
4. Evidence of a pathologically increased release of mast cell mediators by determination of the content of • tryptase in blood • N-methylhistamine in urine • heparin in blood • chromogranin A in blood • other mast cell-specific mediators (e.g., leukotrienes, prostaglandin D_2)	4. Serum total tryptase >20 ng/ml (does not apply in patients who have associated hematologic non-mast-cell lineage disease)

The diagnosis *mast cell activation syndrome* is made if both major criteria or the second criterion and at least one minor criterion are fulfilled. According to the WHO criteria [1], the diagnosis *systemic mastocytosis* is established if the

Kelly K. McCann, MD

***This Slide Enlarged on Page 154**

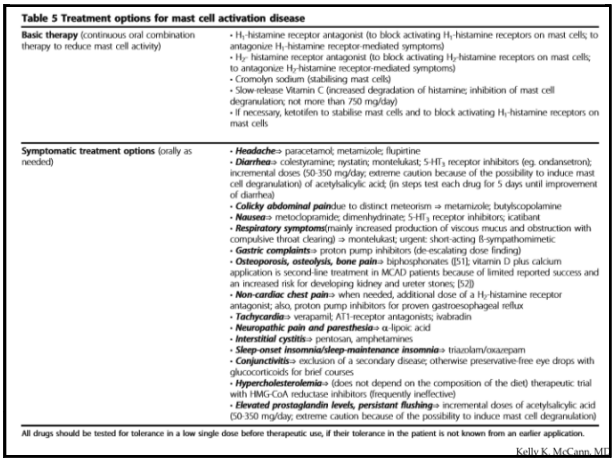


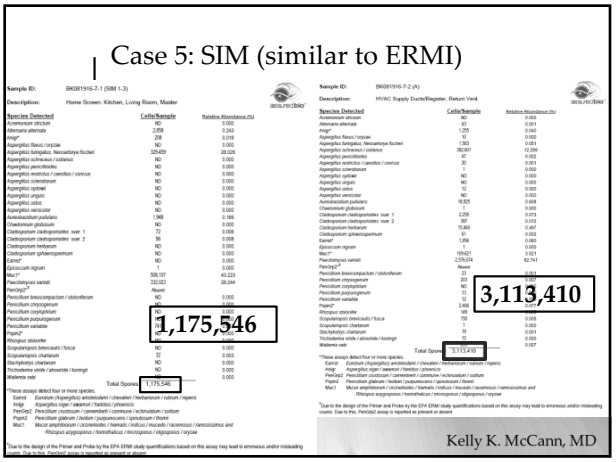
Table 5 Treatment options for mast cell activation disease

Basic therapy (continuous oral combination therapy to reduce mast cell activity)	• H_1-histamine receptor antagonist (to block activating H_1-histamine receptors on mast cells; to antagonize H_1-histamine receptor-mediated symptoms) • H_2- histamine receptor antagonist (to block activating H_2-histamine receptors on mast cells; to antagonize H_2-histamine receptor-mediated symptoms) • Cromolyn sodium (stabilising mast cells) • Slow-release Vitamin C (increased degradation of histamine; inhibition of mast cell degranulation; not more than 750 mg/day) • If necessary, ketotifen to stabilise mast cells and to block activating H_1-histamine receptors on mast cells
Symptomatic treatment options (orally as needed)	• ***Headache***⇒ paracetamol; metamizole; flupirtine • ***Diarrhea***⇒ colestyramine; nystatin; montelukast; 5-HT_3 receptor inhibitors (eg. ondansetron); incremental doses (50-350 mg/day; extreme caution because of the possibility to induce mast cell degranulation) of acetylsalicylic acid; (in steps test each drug for 5 days until improvement of diarrhea) • ***Colicky abdominal pain***due to distinct meteorism ⇒ metamizole; butylscopolamine • ***Nausea***⇒ metoclopramide; dimenhydrinate; 5-HT_3 receptor inhibitors; icatibant • ***Respiratory symptoms***(mainly increased production of viscous mucus and obstruction with compulsive throat clearing) ⇒ montelukast; urgent: short-acting ß-sympathomimetic • ***Gastric complaints***⇒ proton pump inhibitors (de-escalating dose finding) • ***Osteoporosis, osteolysis, bone pain***⇒ biphosphonates ([51]; vitamin D plus calcium application is second-line treatment in MCAD patients because of limited reported success and an increased risk for developing kidney and ureter stones; [52]) • ***Non-cardiac chest pain***⇒ when needed, additional dose of a H_2-histamine receptor antagonist; also, proton pump inhibitors for proven gastroesophageal reflux • ***Tachycardia***⇒ verapamil; AT1-receptor antagonists; ivabradin • ***Neuropathic pain and paresthesia***⇒ α-lipoic acid • ***Interstitial cystitis***⇒ pentosan, amphetamines • ***Sleep-onset insomnia/sleep-maintenance insomnia***⇒ triazolam/oxazepam • ***Conjunctivitis***⇒ exclusion of a secondary disease; otherwise preservative-free eye drops with glucocorticoids for brief courses • ***Hypercholesterolemia***⇒ (does not depend on the composition of the diet) therapeutic trial with HMG-CoA reductase inhibitors (frequently ineffective) • ***Elevated prostaglandin levels, persistent flushing***⇒ incremental doses of acetylsalicylic acid (50-350 mg/day; extreme caution because of the possibility to induce mast cell degranulation)

All drugs should be tested for tolerance in a low single dose before therapeutic use, if their tolerance in the patient is not known from an earlier application.

Kelly K. McCann, MD

***This Slide Enlarged on Page 155**



Kelly K. McCann, MD

CASE 5: Gentle Detox support

- For sensitive patients who can't tolerate binders consider starting:
- **Homeopathic detox** *(Pekana Detox Kit*– Itires, Apo-hepat, Renelix) – start 1-2 drops once or twice daily and can work up to 15 drops of each in glass water bottle and drink throughout the day.
- *Pekana* – Mucan – cleanses the extracellular matrix but mildly provocative so use later in the case
- Takesumi Supreme by *Supreme Nutritionals* is a bamboo charcoal that can be used as a generalized binder. 1 scoop or ¼ tsp 2-3 times per day.

Kelly K. McCann, MD

Herbal Mold/Fungal Treatment options

- *Beyond Balance* – ToxEase GL – 1-2 drops once or twice daily
- *Beyond Balance* – Pro-MYCO – assist against mold and mycotoxins. Start 1-2 drops BID and work up to 10 drops BID
- *Beyond Balance* – MycoRegen -guard against fungal issues (more potent) Start 1-2 drops 2 times daily and work up to 8-10 drops 2 times daily. Some may have to use very small doses.
- *Beyond Balance* – ENL-BT for biotoxins 1-2 drops 1-2 times daily. Don't exceed 8-10 drops three times daily.
- *Research Nutritionals* – Transfer Factor Enviro for mold. Intended to help against Penicillium, Fusarium, Aspergillus, Cladosporium and Candida sp. Start 1 cap daily away from food and supplements. Can increase to 2 or higher. Can take with Transfer Factor Multi Immune.

Kelly K. McCann, MD

MCAS treatments

- Treat her Mast Cell Activation Syndrome – Quercetin, DAO enzymes, NeuroproTek, Allqlear, Perimine as herbal options
- Mast Cell pharmaceutical options – H1 and H2 blockers (Pepcid or Zantac and Zyrtec or Clairitin) Ketotifen or Cromolyn.
- Lawrence Afrin, MD ***Never Bet Against Occam*** book on MCAS
- Theo Theoharides, MD, PhD has written a number of articles http://mastcellmaster.com/

Kelly K. McCann, MD

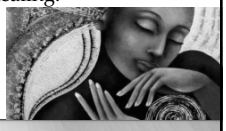
Moldy Recap

1. **Get patients to a safe, mold free environment. Including home, work, car and mold-free belongings**
2. **Differential diagnosis. Consider underlying chronic infections and chemical toxicant burdens**
3. **Do a thorough history and complete lab evaluations, if able**
4. **Begin binders – charcoal, clay, chlorella, takesumi, CSM**
5. **Begin Phosphatidyl choline to begin healing cellular membranes**
6. **Begin Butryate to break up VLCFA and other deleterious fatty acids.**
7. **Address nasal and GI colonizations and mycobiome disruption with antifungals and biofilm busters**
8. **Restore nutrients, hormones**
9. **Apply Naturopathic and functional medicine tools for healing**

Kelly K. McCann, MD

Final Notes

- These patients are complicated and sensitive. They often know what they need and can tolerate, so listen to them and devise an individualized plan to address their issues.
- www.retrainingthebrain.com – Dynamic Neural Retraining System by Annie Hopper
- Must address emotional, psychological and even spiritual issues to get these patients to a place of healing.
- Trust your clinical judgement



Kelly K. McCann, MD

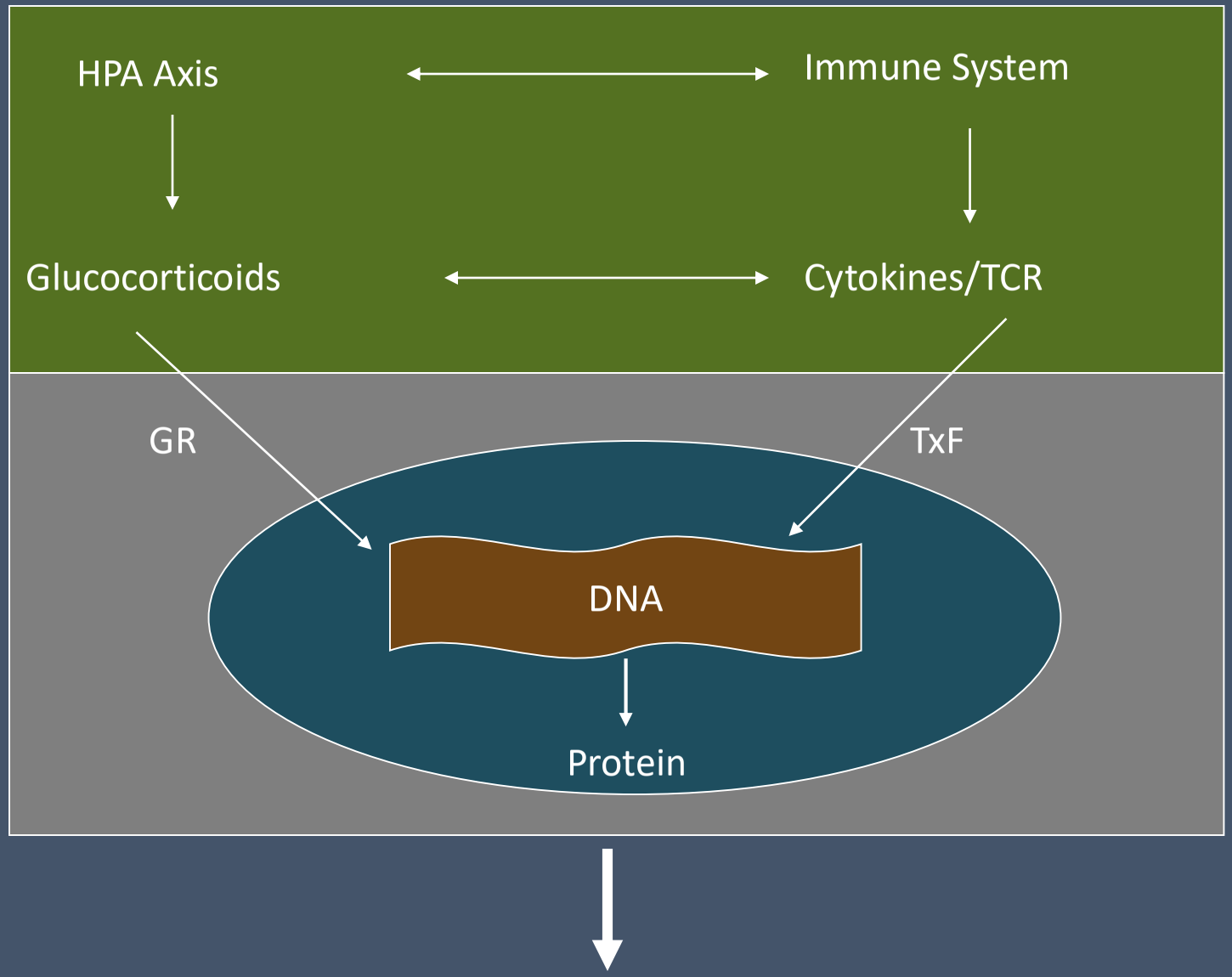
Contact information

Kelly K. McCann, MD, MPH & TM
The Spring Center
1831 Orange Avenue
Suite C
Costa Mesa, CA 92627
(949) 574.5800 phone
(949) 612.2715 fax
www.thespringcenter.com
drkelly@thespringcenter.com

Kelly K. McCann, MD

Systemic

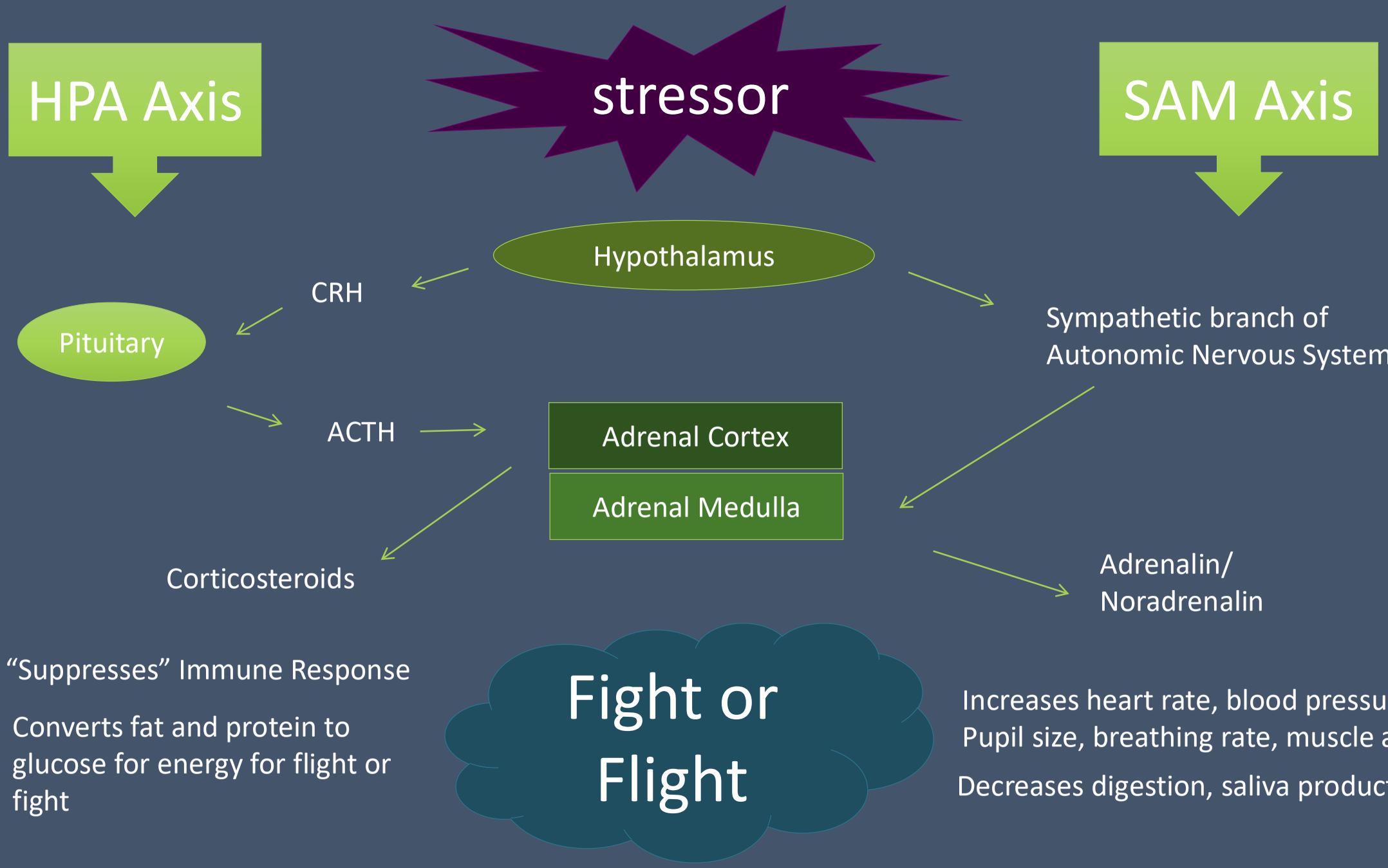
Cellular and Molecular



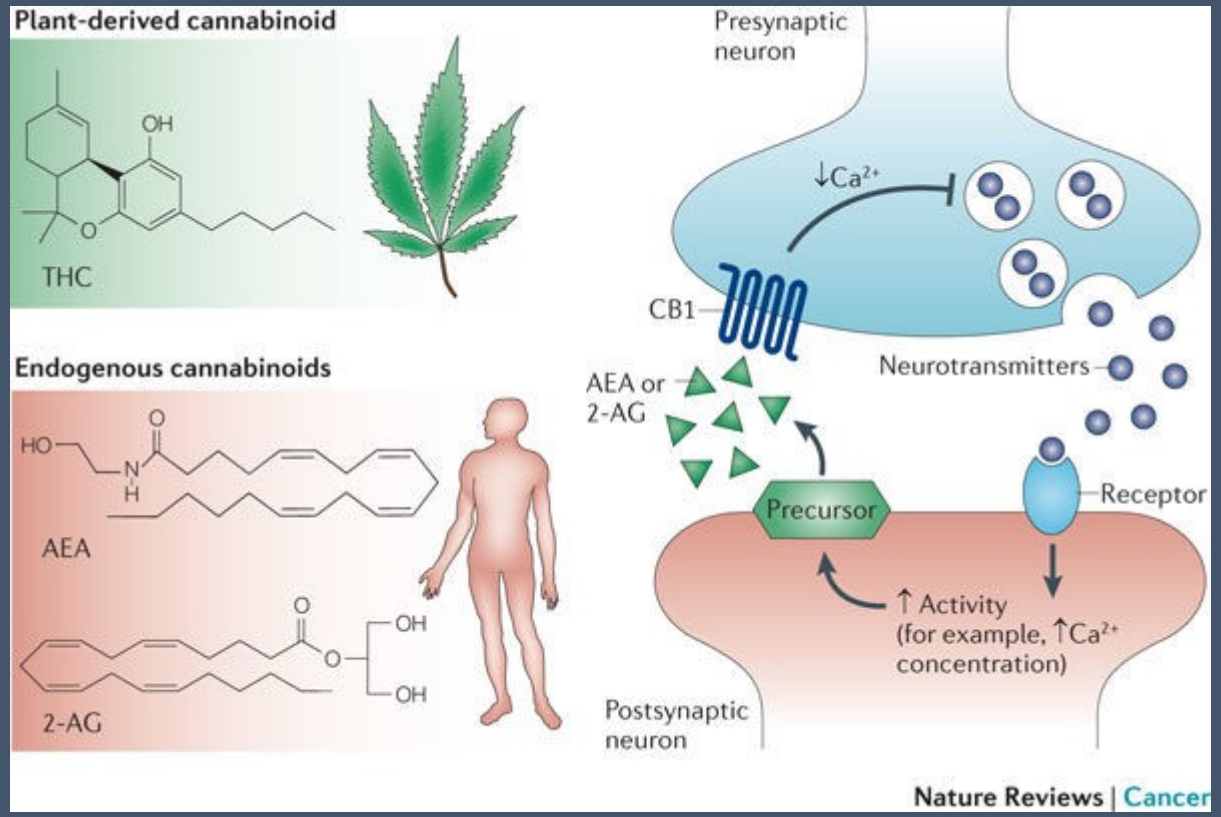
Adapted from Arzt et al. 2001

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


HPA Axis
stressor
SAM Axis
Hypothalamus
CRH
Pituitary
Sympathetic branch of
Autonomic Nervous System
ACTH
Adrenal Cortex
Adrenal Medulla
Corticosteroids
Adrenalin/
Noradrenalin
"Suppresses" Immune Response
Converts fat and protein to glucose for energy for flight or fight
Fight or Flight
Increases heart rate, blood pressure, Pupil size, breathing rate, muscle activity
Decreases digestion, saliva production

Endocannabinoids ≠ Cannabis



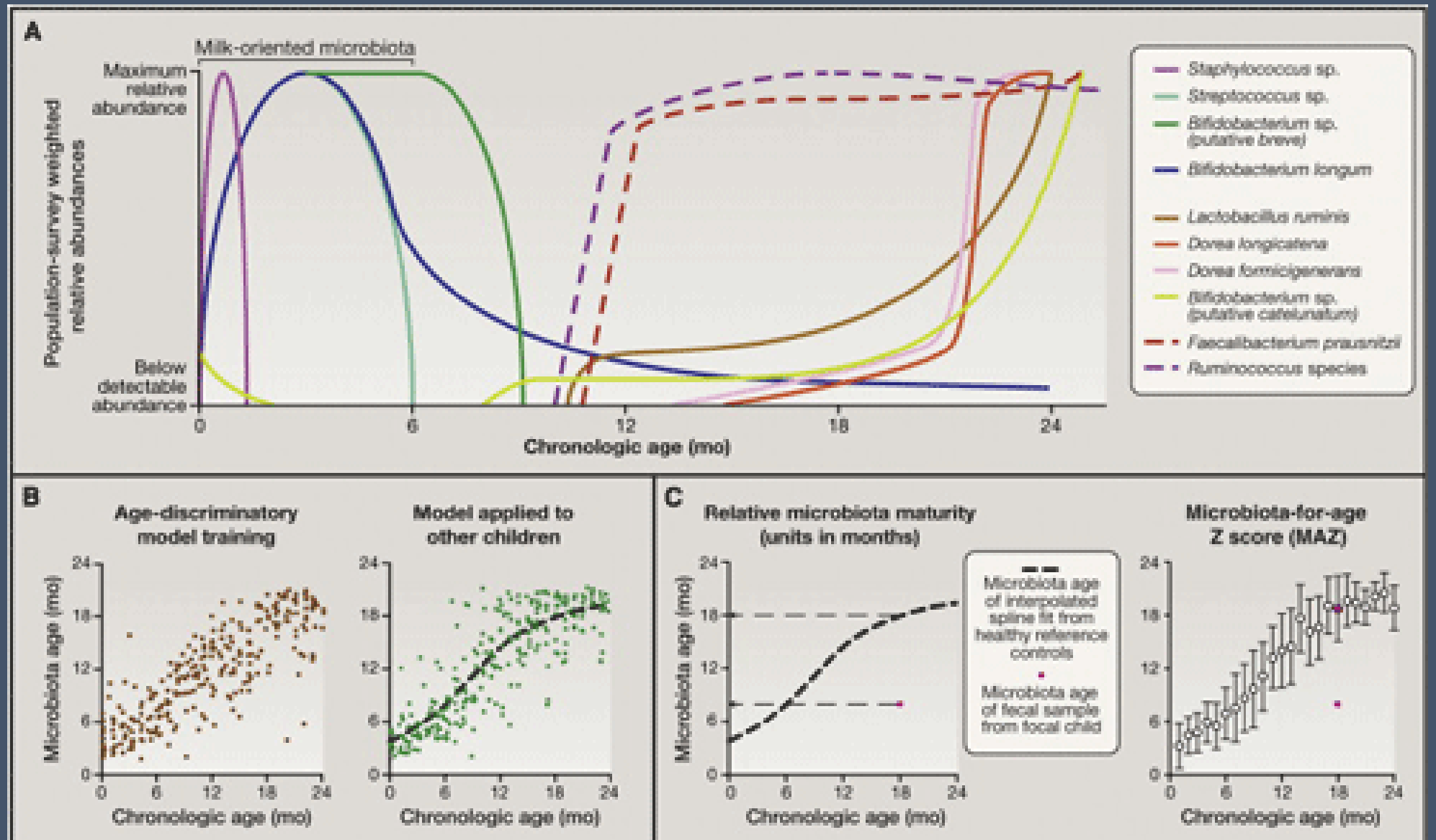
Endo

- Endocannabinoids modulate Th1 and Th2

Plant

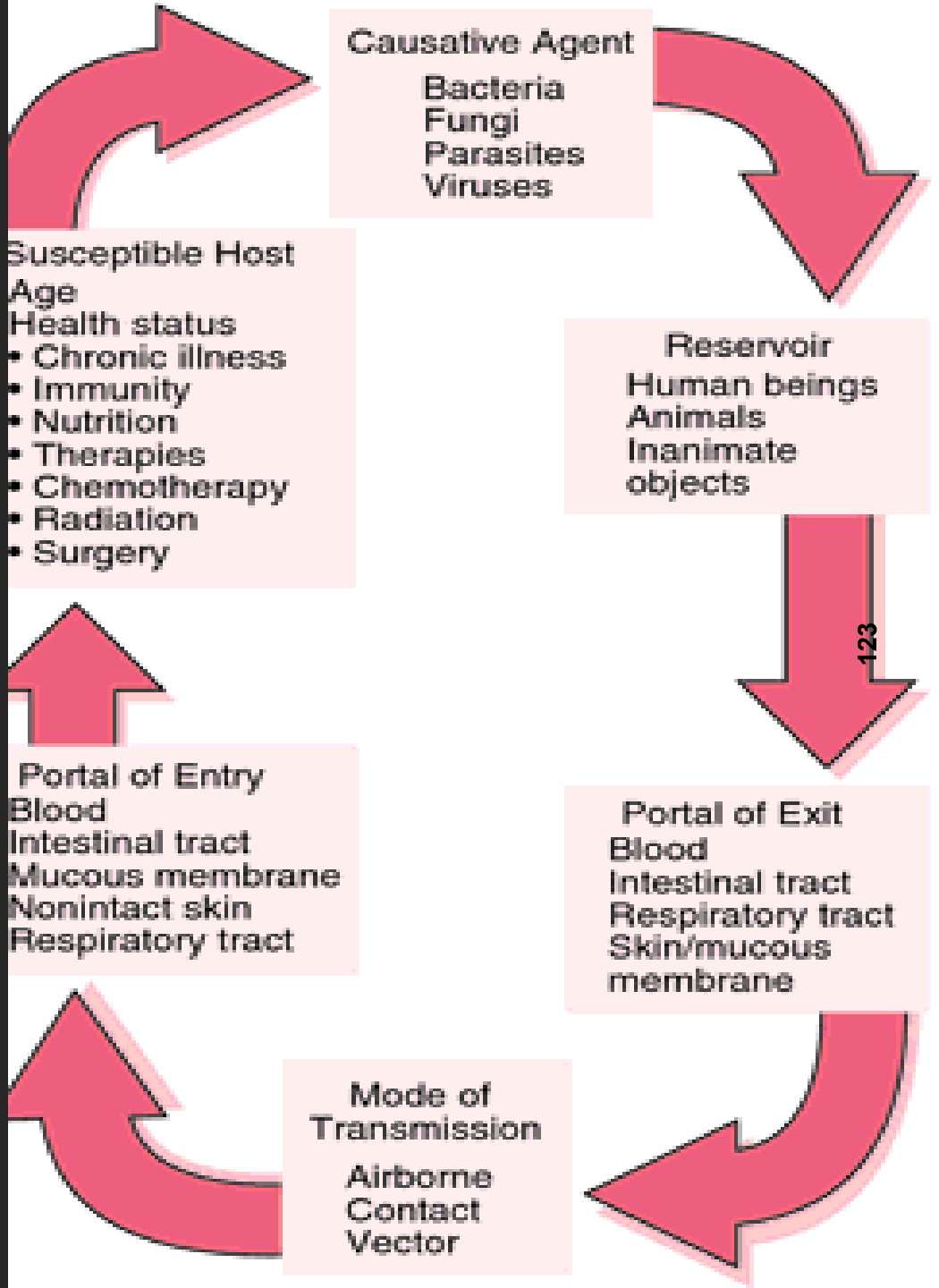
- Plant derived cannabinoids increase Th2

Microbiome Development

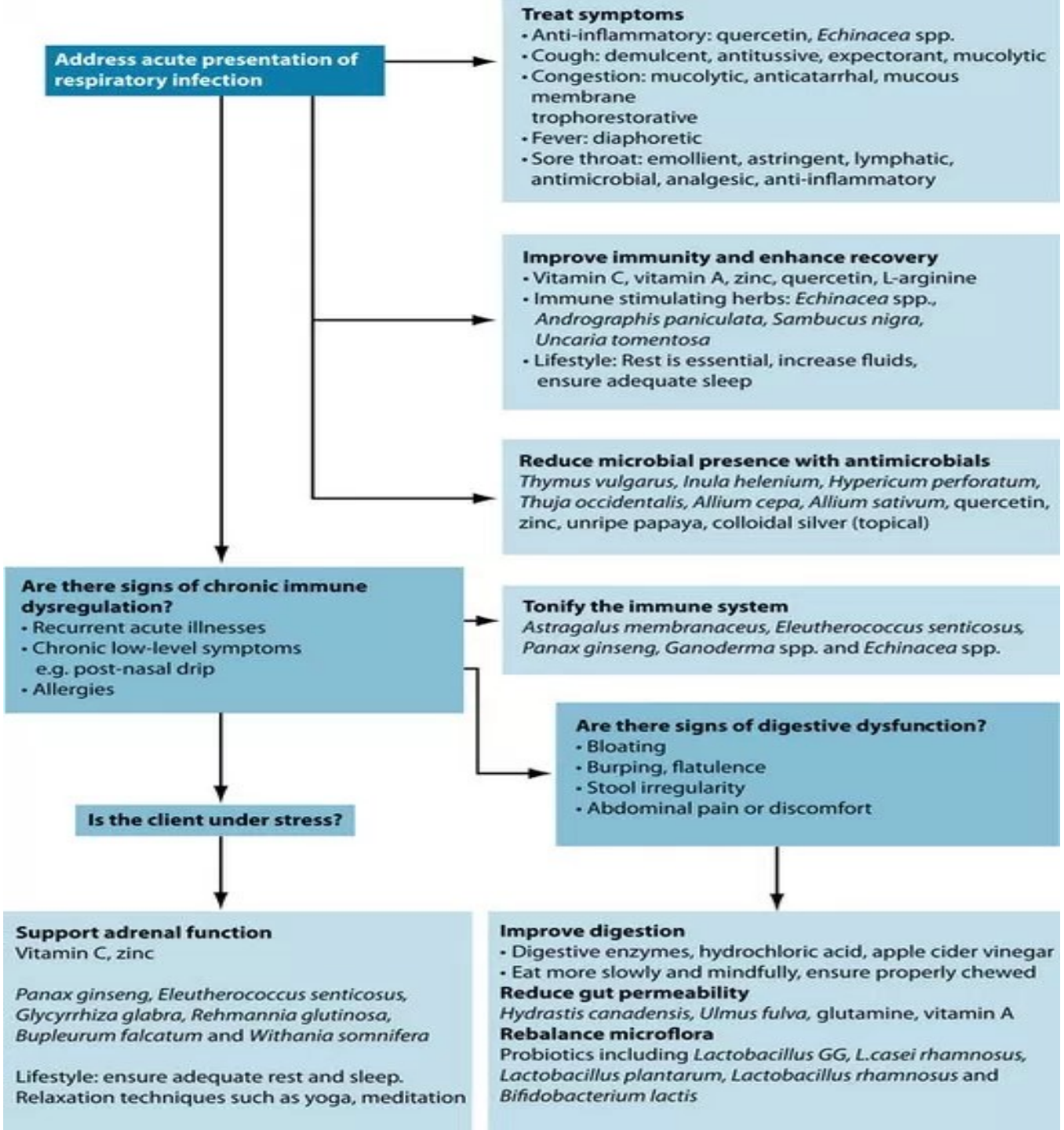


CONTRIBUTORS TO CHRONIC INFECTIONS

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



TREATMENT PROTOCOLS FOR RESPIRATORY INFECTION

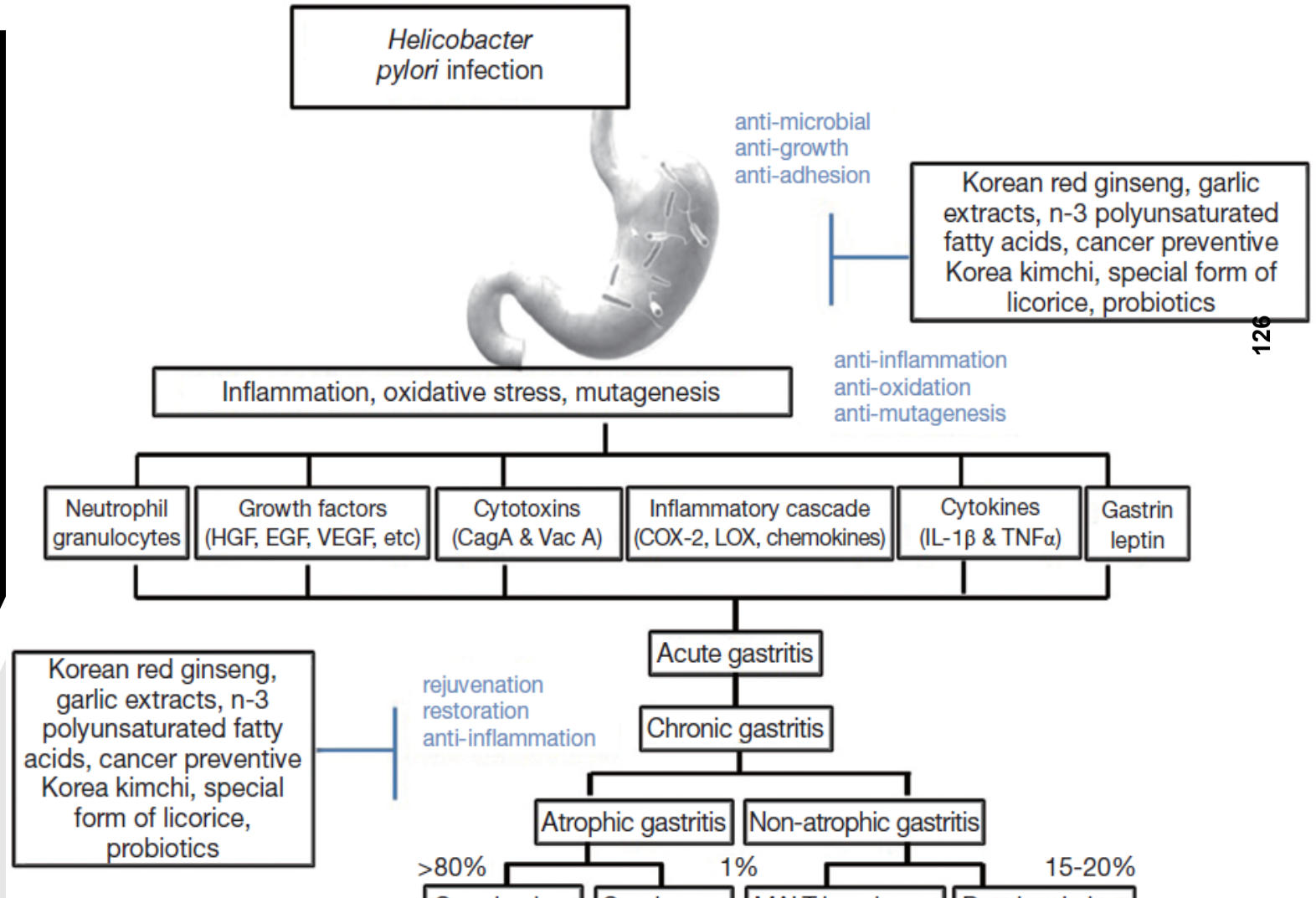


Bioregional Adaptogens

	Bioregion	Adaptogen	Notable Features
	Pacific Northwest U.S., Western Canada	*Oplopanax horridum* (devil's club) root bark	Little used for this purpose. Long revered as protective medicine.
	Northern California, Northern Asia, Northeastern North America	*Aralia californica* (California spikenard), *A. elata* (Manchurian spikenard), *A. racemosa* (spikenard) root	Greatly overlooked. Quite spicy, lung affinity.
	Southeast Asia	*Panax ginseng* (Asian ginseng) root	Widely cultivated. Tends to be fairly heating and somewhat more specific to men. Relatively well researched.
	Southeast Asia	*Panax notoginseng* (tienchi ginseng) root	Also widely used to staunch bleeding.
	Southeast Asia	*Schisandra chinensis* (schisandra) fruit	Also hepatoprotective. Relatively tasty.
	Southeast Asia	*Astragalus membranaceus* (astragalus) root	Pleasant, mild taste.
	Southeast Asia	*Codonopsis pilosula* (codonopsis) root	Commonly substituted for P. ginseng in modern TCM.
	Southeast Asia	*Gynostemma pentaphylla* (jiaogulan) root	Saponins very similar to P. ginseng. Easier to cultivate. Not yet cultivated in North America.
	China, Japan	*Lentinula edodes* (shiitake) fruiting body	Cultivated.
	Siberia, Northern China	*Eleutherococcus senticosus* (eleuthero) root	Moderately heating.
	Eurasia	*Glycyrrhiza glabra* (licorice); *G. uralensis* (gan cao) root	Very tasty. Also demulcent and hepatoprotective.
	India	*Withania somniferum* (ashwagandha) root	The most calming and anxiolytic of the adaptogens.
	Siberia	*Rhodiola rosea* (goldenroot) root	Also hypotensive. Cultivated.
	Globally in temperate areas	*Ganoderma lucidum* (reishi) fruiting body	Immunomodulating effects well documented in humans.
	Eastern U.S. and Canada	*Panax quinquefolius* (American ginseng) root	Available from wild-simulated cultivation.
	Northern U.S., Southern Canada	*Dicentra formosa* or *D. canadensis* (turkey corn) tuber (low ethanol/water extract)	Tonic formerly favored by the Eclectics.
	Eastern U.S. and Canada	*Podophyllum peltatum* (mayapple) root, water extract	Not to be confused with resin extracts of the root, which are quite toxic, the Eclectics describe this as one of the best restorative tonics they had, particularly when tissue were "full."

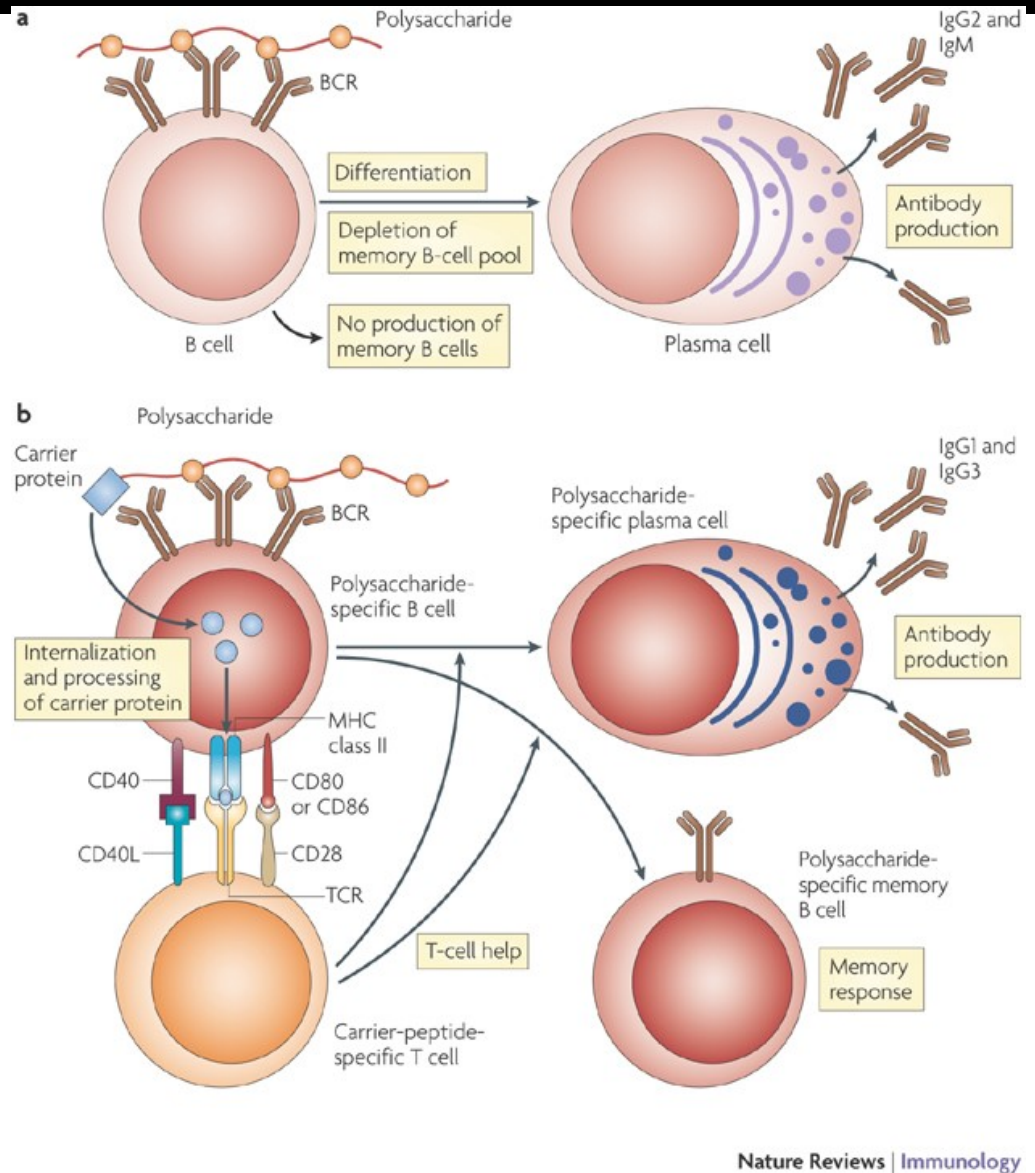
LICORICE
Glycyrrhiza glabra

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



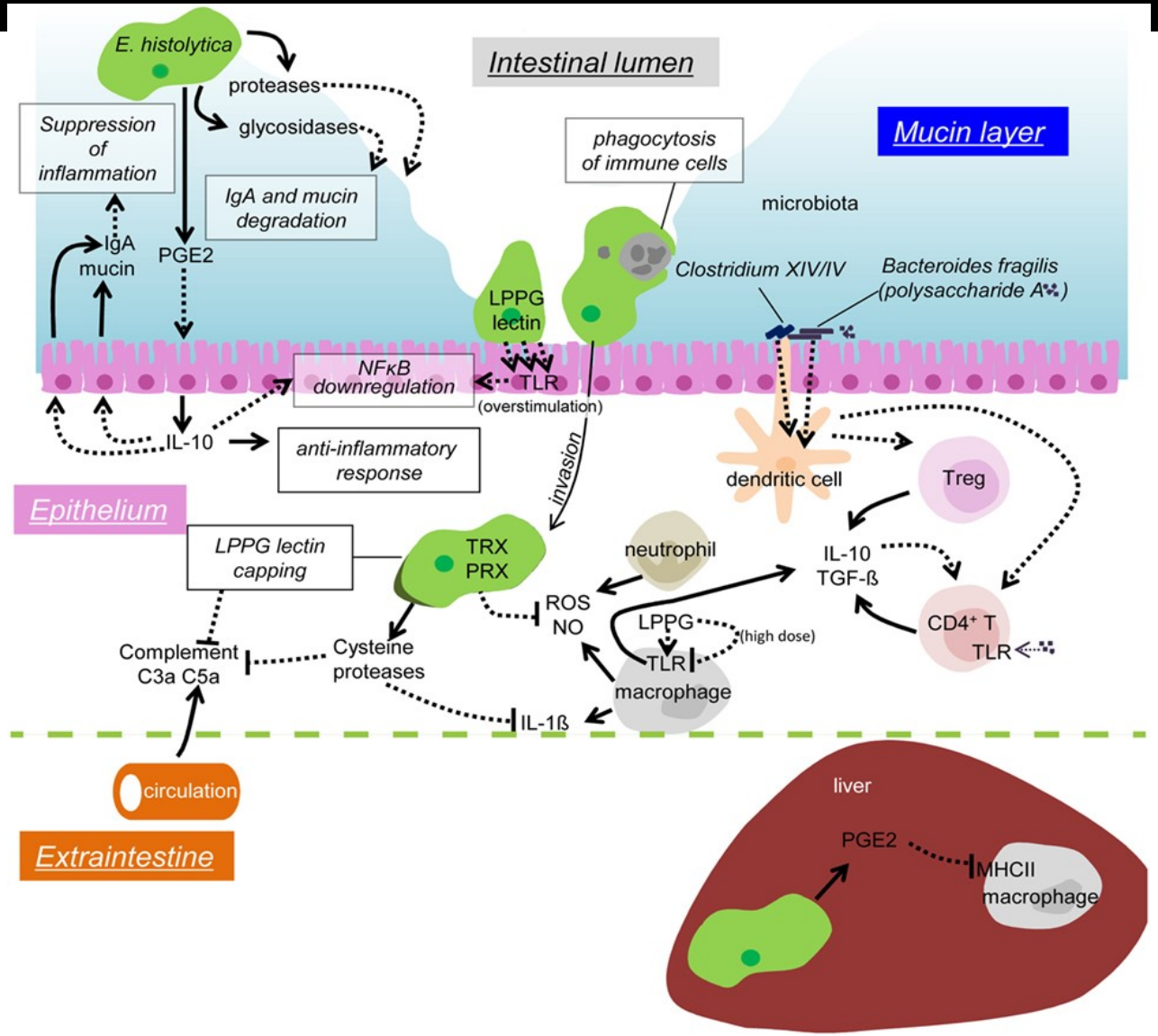
IMMUNE POLYSACCARHIDES

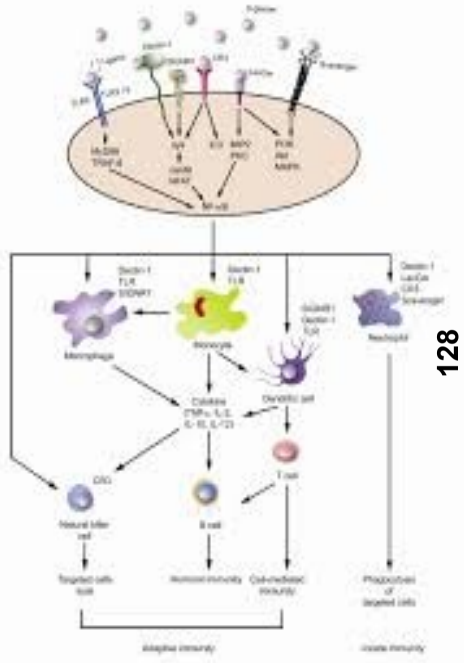
- **"Immune Polysaccarides" are large molecules known to enhance immune responses.**
- **One mechanism may be via local effects in the gut that triggers immune response via the carbohydrate aspect of the cytoskeleton.**



HERBS WITH IMMUNE POLYSACCARHIDES

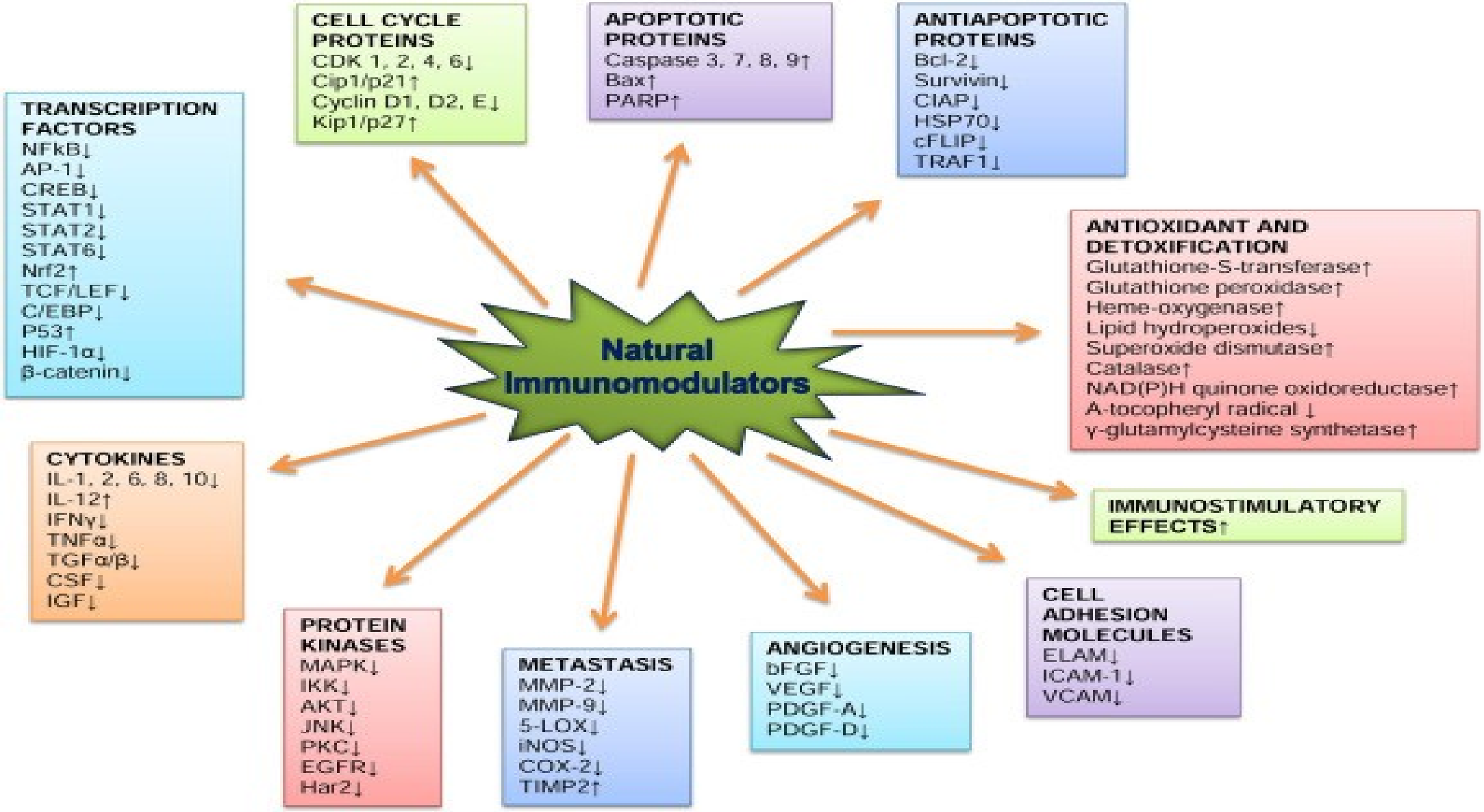
- Echinacea
- Astragalus
- Glycyrrhiza
- Ganoderma
- Lentinula
- Baptisia
- Seaweed
- Panax ginseng
- Aloe vera





128

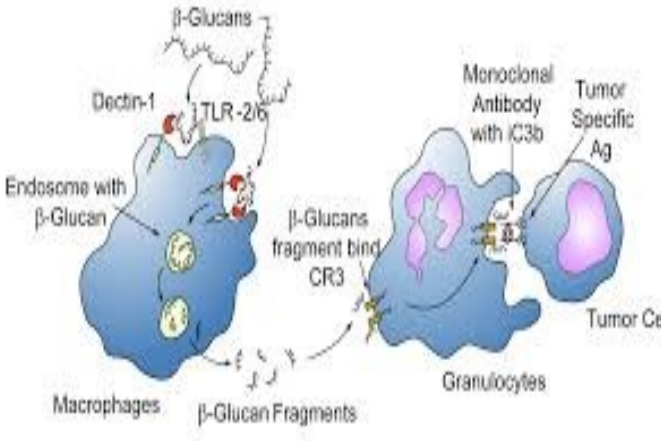
VARIED EFFECTS OF IMMUNE MODULATORS



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

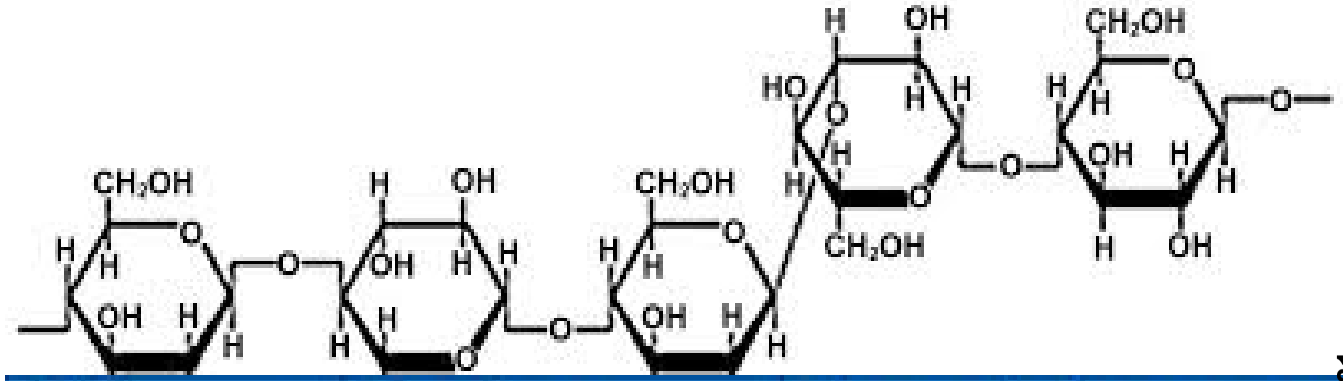
1. Production of white blood cells
2. Cellular mobilization
3. Phagocytic capacity
4. Production of reactive oxygen intermediates
5. Help shift from an overstimulated TH2 to a TH1 cell mediated immune response.

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.



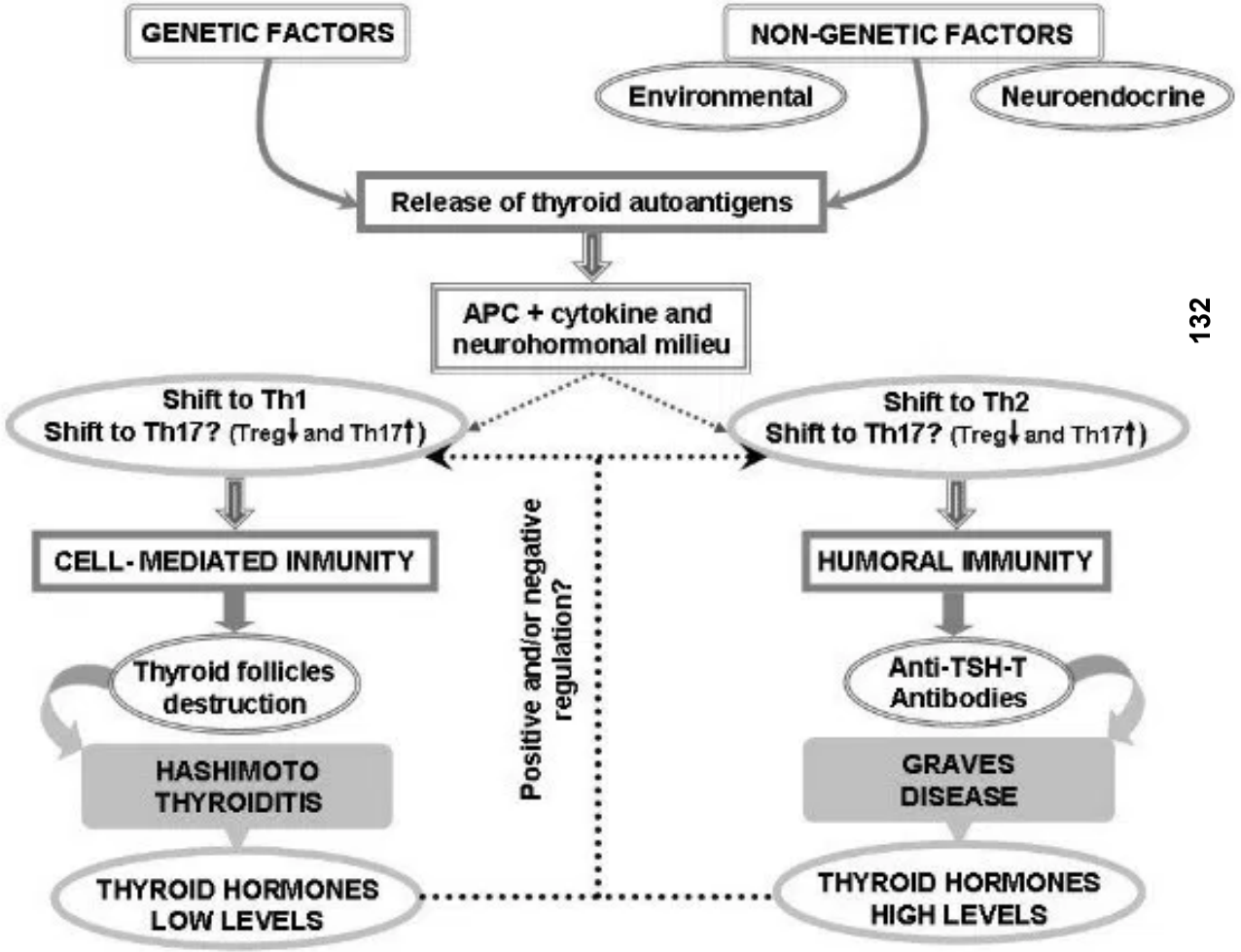
131

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)	—

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**



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**

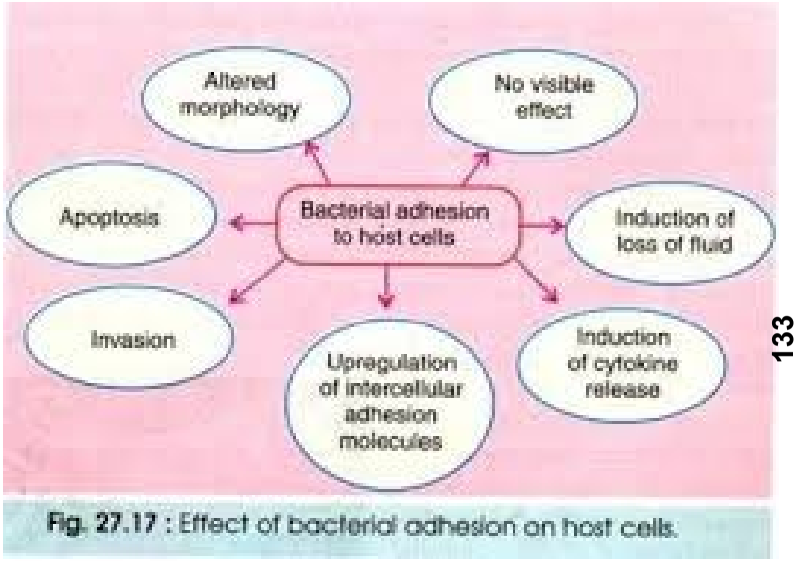
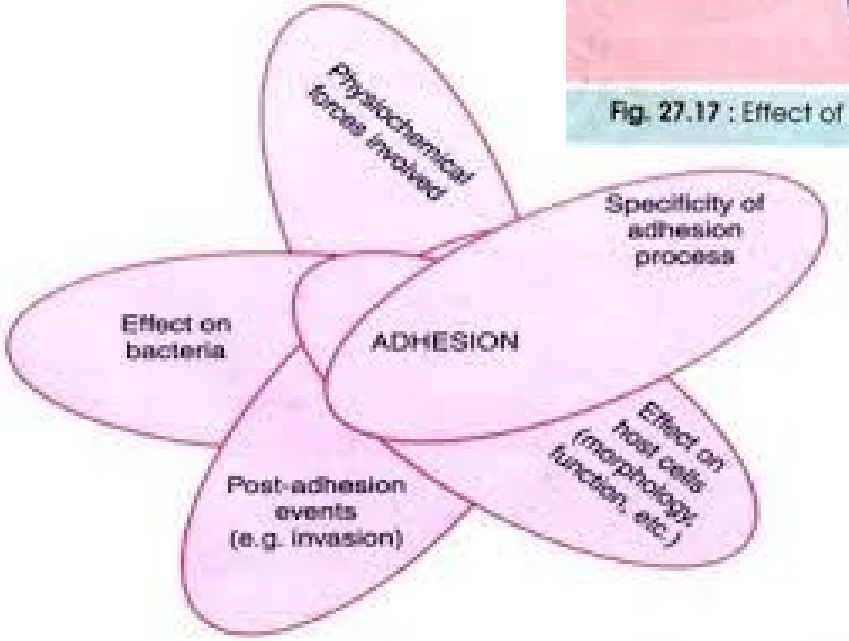


Fig. 27.17 : Effect of bacterial adhesion on host cells.



Herbs with Anti-Microbial Effects Via Mitochondrial Membrane Disruption

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

NUTRIENTS THAT SUPPORT MITOCHONDRIAL HEALTH

COENZYME Q10
Acts as an electron carrier between complexes I, II, and III of the mitochondrial respiratory chain. Deficiency causes a decline in activities of complex II + III, complex III and complex IV, reduced expression of mitochondrial proteins involved in oxidative phosphorylation, decreased mitochondrial membrane potential, increased production of reactive oxygen species, increased mitophagy of dysfunctional mitochondria, and reduced growth rates.

QUERCETIN
Restores mitochondrial membrane potential and enhances ATP levels.

ALPHA-LIPOIC ACID
Significantly improves mitochondrial content and size in the liver during animal studies.

GREEN TEA (EPICATECHIN)
Protects the cardiac mitochondria from damage.

OMEGA-3 FATTY ACIDS
Rats with mitochondrial heart damage fed omega-3 fatty acids experienced significant restoration of the respiration rate of mitochondria.

NICOTINAMIDE RIBOSIDE
Oral administration of nicotinamide riboside increases NAD+ levels in mice and stimulates mitochondrial biogenesis. Delays early- and late-stage mitochondrial myopathy disease progression in mice.

GLUCOSAMINE
A preliminary study in nematodes and aging mice indicates glucosamine stimulates mitochondrial biogenesis and extends lifespan.

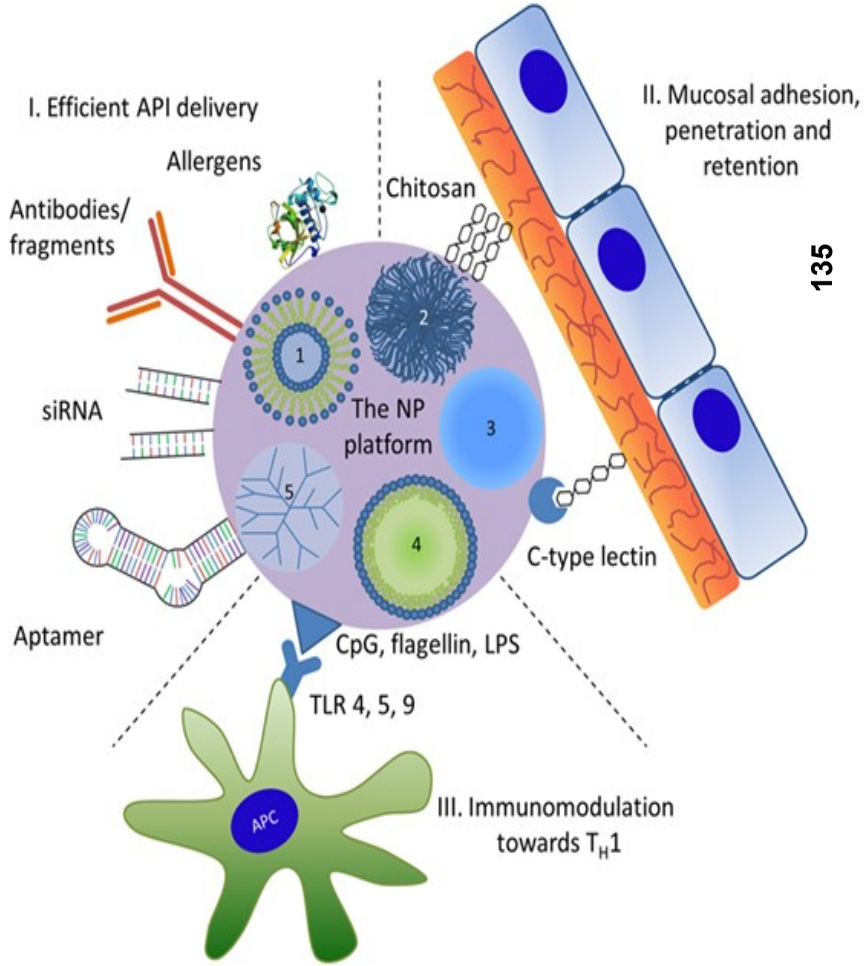
ACETYL L-CARNITINE
Improves mitochondrial content and size in the liver. Acetyl L-carnitine given to old rats promotes the development of new mitochondria in the liver, which can contribute to the reduction of cellular oxidative stress. Protects against mitochondrial dysfunction in models of stroke, ischemia, and neurodegenerative disorders.

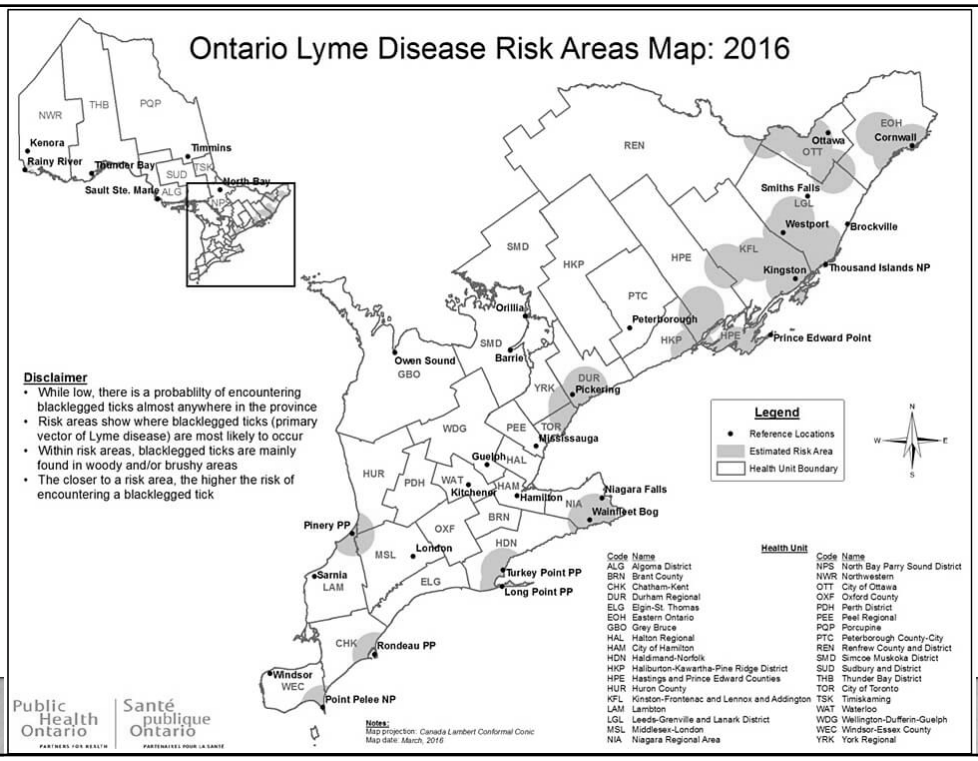
N-ACETYL CYSTEINE (NAC)
Significantly improves compromised total mitochondrial bioenergetics in a dose-dependent manner in a rat model of spinal cord injury. Inhibits the inflammatory response that occurs in cultured human synoviocytes due to mitochondrial damage.

RESVERATROL
In fibroblasts from early-onset Parkinson's disease, increases complex I activities and mitochondrial ATP production. Stops the development of diabetic cardiomyopathy in diabetic rats, partially through beneficial effects on the mitochondria.

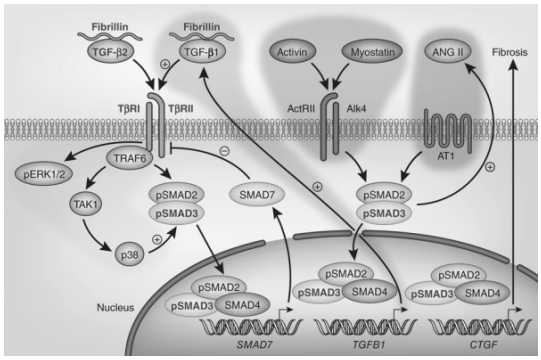
CREATINE MONOHYDRATE
Together with coenzyme Q10 and alpha-lipoic acid improves the health of patients who have mitochondrial cytopathies by reducing lactate and markers of oxidative stress. In people who have mitochondrial encephalomyopathies, creatine improves aerobic oxidative function of the mitochondria.

RICINIS CASTORIS
TOPICALLY FOR IMMUNE-MODULATING EFFECTS





Transforming Growth Factor Beta1



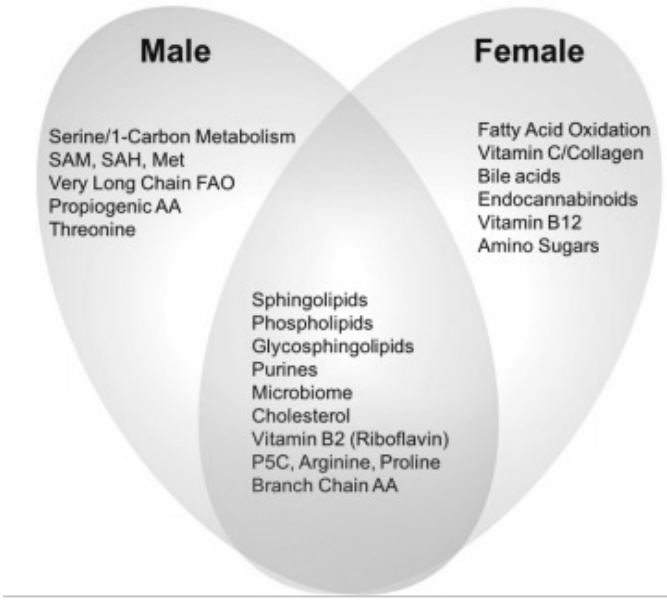
Zhang, et al. TGF-β1 factor in the cerebrovascular diseases of Alzheimer's disease. Eur Rev Med Pharmacol Sci. 2016 Dec;20(24):5178-5185.
Schumann. TGFbeta1 of no avail as prognostic marker in Lyme disease. PeerJ2:e398; DOI 10.7717/peerj.398.

- 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

Kelly K. McCann, MD

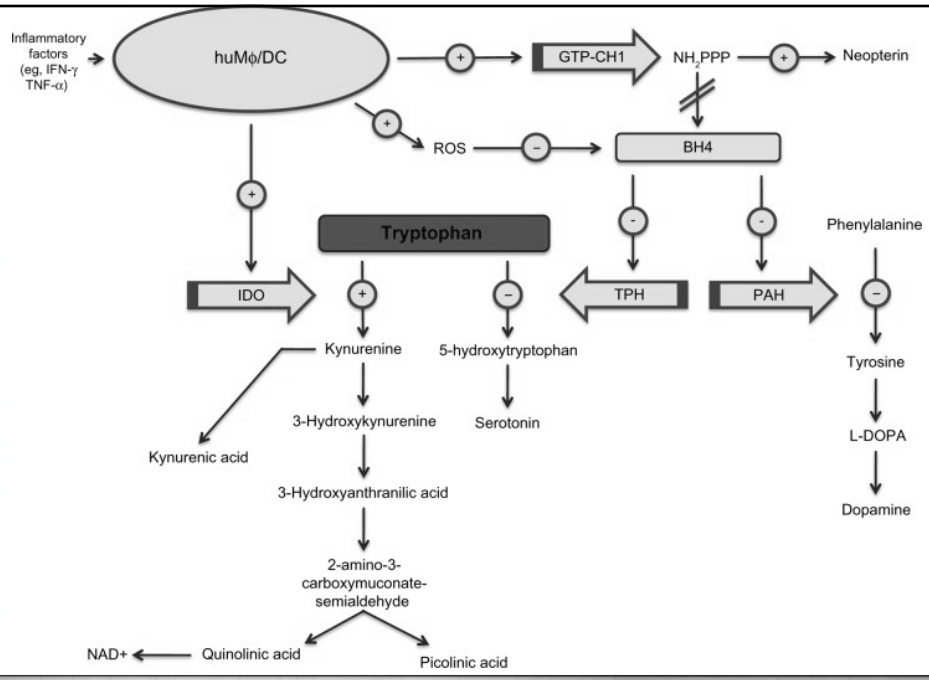
Metabolic Features of CFS

- 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.



Kelly K. McCann, MD

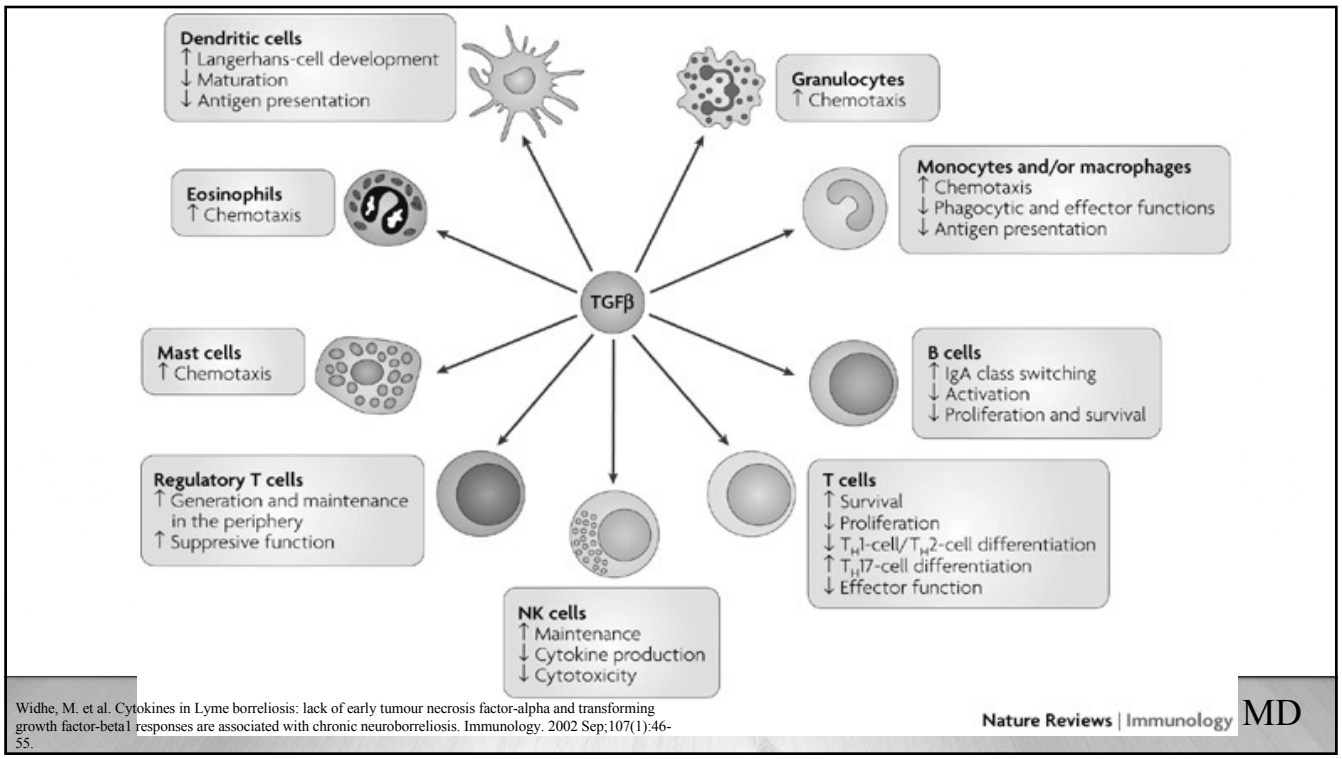
Tryptophan metabolism - Lyme and serotonin



Kelly K. McCann, MD

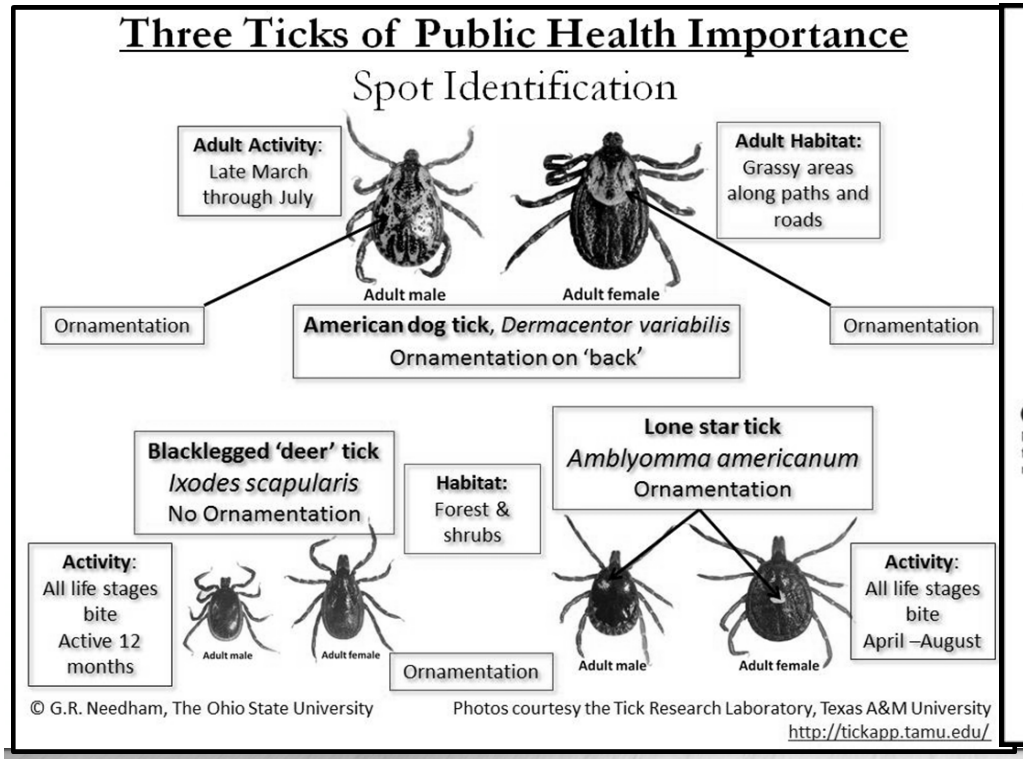
Is it Lyme or mold? Could it be both?

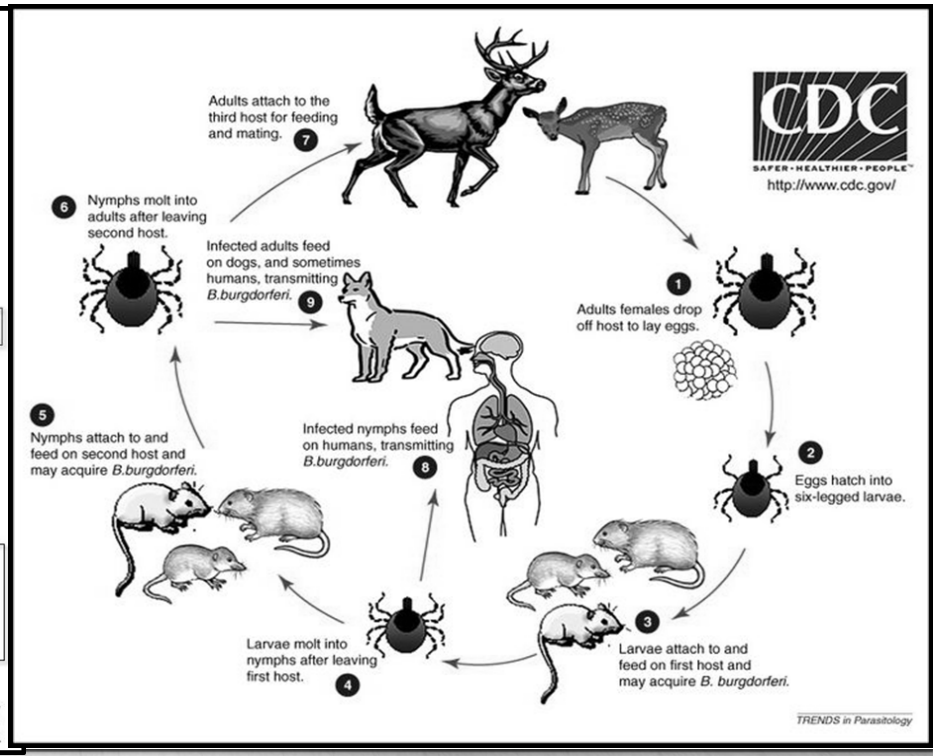
Lyme symptoms		Mold symptoms	
Fatigue	**Joint pain**	**Fatigue**	Tingling
Fevers	**Myalgias**	Weakness	Tremors
Rashes	Joint swelling	Decreased assimilation of new knowledge	**Unusual pain**
Sweats	**Back pain**	**Myalgias**	**Shortness of breath**
Hair loss	**Neck stiffness**	**Headaches**	Sinus congestion
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



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.

Relevant Lyme disease ticks and their life cycle





Kelly K. McCann, MD

DOCTOR'S DATA INC

CLIENT #: 34225
DOCTOR: Kylie Nuckols, PA

1831 Orange Ave Ste C
Costa Mesa, CA 92627 U.S.A.

Toxic Metals; Urine

TOXIC METALS		RESULT µg/g creat	REFERENCE INTERVAL	WITHIN REFERENCE / OUTSIDE REFERENCE
Aluminum	(Al)	23	< 35	
Antimony	(Sb)	< dl	< 0.2	
Arsenic	(As)	68	< 80	
Barium	(Ba)	0.6	< 7	
Beryllium	(Be)	< dl	< 1	
Bismuth	(Bi)	< dl	< 4	
Cadmium	(Cd)	0.2	< 1	
Cesium	(Cs)	11	< 10	
Gadolinium	(Gd)	< dl	< 0.8	
Lead	(Pb)	3.2	< 2	
Mercury	(Hg)	0.7	< 4	
Nickel	(Ni)	4.8	< 10	
Palladium	(Pd)	< dl	< 0.15	
Platinum	(Pt)	< dl	< 0.1	
Tellurium	(Te)	< dl	< 0.5	
Thallium	(Tl)	0.5	< 0.5	
Thorium	(Th)	< dl	< 0.03	
Tin	(Sn)	0.2	< 5	
Tungsten	(W)	0.2	< 0.4	
Uranium	(U)	< dl	< 0.04	

URINE CREATININE	RESULT mg/dL	REFERENCE INTERVAL	-2SD -1SD MEAN +1SD +2SD
Creatinine	79.4	30- 225	

SPECIMEN DATA

Comments:

Date Collected: 05/04/2016
Date Received: 05/09/2016
Date Completed: 05/10/2016
Method: ICP-MS

pH upon receipt: Acceptable
<dl: less than detection limit
Provoking Agent:
Creatinine by Jaffe Method

Collection Period: Random
Volume:
Provocation: PRE PROVOCATIVE

Results are creatinine corrected to account for urine dilution variations. **Reference intervals and corresponding graphs are representative of a healthy population under non-provoked conditions.** Chelation (provocation) agents can increase urinary excretion of metals/elements. V13

DOCTOR'S DATA INC

CLIENT #: 34225
DOCTOR: Kylie Nuckols, PA

1831 Orange Ave Ste C
Costa Mesa, CA 92627 U.S.A.

Toxic Metals; Urine

TOXIC METALS		RESULT µg/g creat	REFERENCE INTERVAL	WITHIN REFERENCE / OUTSIDE REFERENCE
Aluminum	(Al)	38	< 35	
Antimony	(Sb)	0.3	< 0.2	
Arsenic	(As)	31	< 80	
Barium	(Ba)	2	< 7	
Beryllium	(Be)	< dl	< 1	
Bismuth	(Bi)	< dl	< 4	
Cadmium	(Cd)	1.3	< 1	
Cesium	(Cs)	13	< 10	
Gadolinium	(Gd)	0.2	< 0.8	
Lead	(Pb)	87	< 2	
Mercury	(Hg)	14	< 4	
Nickel	(Ni)	12	< 10	
Palladium	(Pd)	< dl	< 0.15	
Platinum	(Pt)	< dl	< 0.1	
Tellurium	(Te)	< dl	< 0.5	
Thallium	(Tl)	0.8	< 0.5	
Thorium	(Th)	< dl	< 0.03	
Tin	(Sn)	1.3	< 5	
Tungsten	(W)	0.1	< 0.4	
Uranium	(U)	0.09	< 0.04	

URINE CREATININE	RESULT mg/dL	REFERENCE INTERVAL	-2SD -1SD MEAN +1SD +2SD
Creatinine	65.9	30- 225	

Provocation done with DMPS and Ca EDTA

SPECIMEN DATA

Comments:

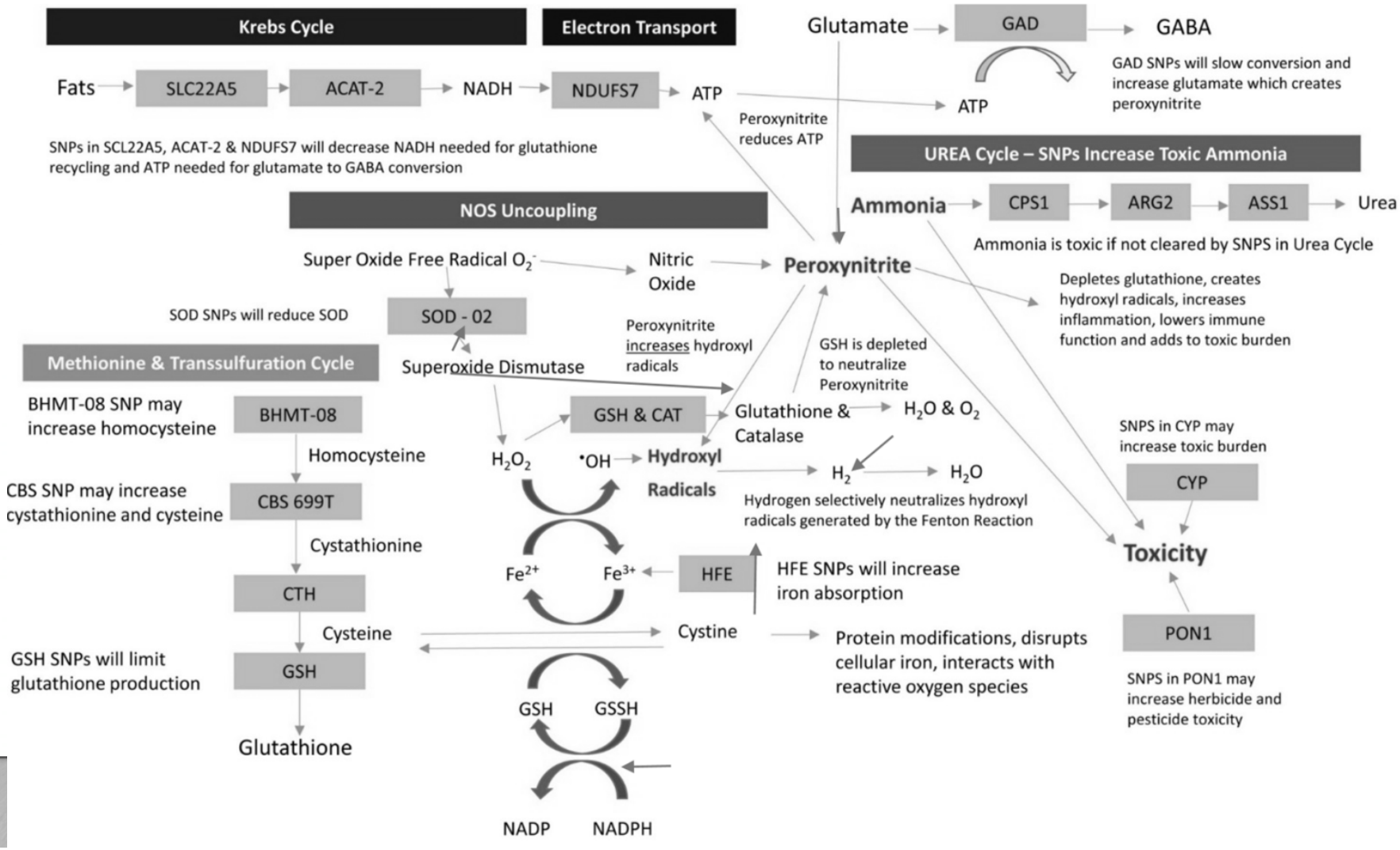
Date Collected: 05/04/2016
Date Received: 05/09/2016
Date Completed: 05/10/2016
Method: ICP-MS

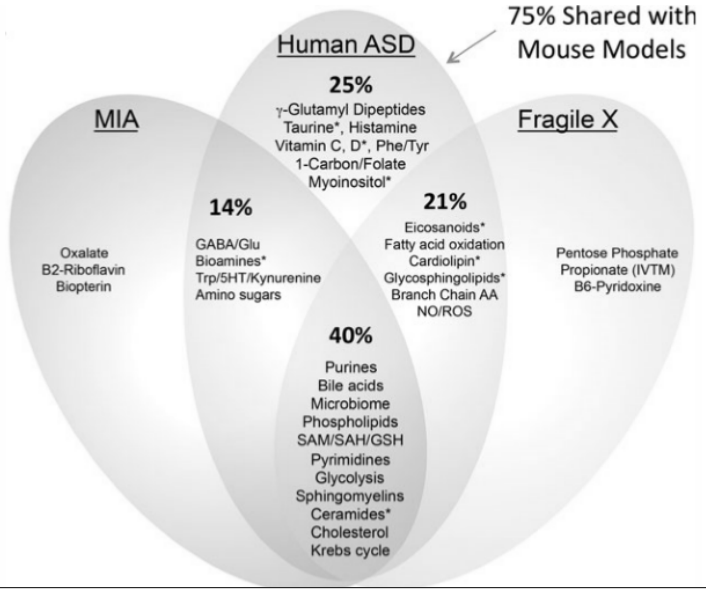
pH upon receipt: Acceptable
<dl: less than detection limit
Provoking Agent:
Creatinine by Jaffe Method

Collection Period: timed: 9 hours
Volume:
Provocation: POST PROVOCATIVE

Results are creatinine corrected to account for urine dilution variations. **Reference intervals and corresponding graphs are representative of a healthy population under non-provoked conditions.** Chelation (provocation) agents can increase urinary excretion of metals/elements. V13

©DOCTOR'S DATA, INC. • ADDRESS: 3755 Illinois Avenue, St. Charles, IL 60174-2420 • CLIA ID NO: 14D0646470 • LAB DIR: Erlo Roth, MD
0001523


Krebs Cycle
Electron Transport
Fats
SLC22A5
ACAT-2
NADH
NDUFS7
ATP
SNPs in SCL22A5, ACAT-2 & NDUFS7 will decrease NADH needed for glutathione recycling and ATP needed for glutamate to GABA conversion
Peroxynitrite reduces ATP
Glutamate
GAD
GABA
ATP
GAD SNPs will slow conversion and increase glutamate which creates peroxynitrite
UREA Cycle – SNPs Increase Toxic Ammonia
Ammonia
CPS1
ARG2
ASS1
Urea
Ammonia is toxic if not cleared by SNPS in Urea Cycle
NOS Uncoupling
Super Oxide Free Radical O_2^-
Nitric Oxide
Peroxynitrite
Depletes glutathione, creates hydroxyl radicals, increases inflammation, lowers immune function and adds to toxic burden
SOD SNPs will reduce SOD
SOD - 02
Superoxide Dismutase
Peroxynitrite increases hydroxyl radicals
GSH is depleted to neutralize Peroxynitrite
Methionine & Transsulfuration Cycle
BHMT-08 SNP may increase homocysteine
BHMT-08
Homocysteine
CBS SNP may increase cystathionine and cysteine
CBS 699T
Cystathionine
CTH
Cysteine
GSH SNPs will limit glutathione production
GSH
Glutathione
GSH & CAT
Glutathione & Catalase
H_2O & O_2
H_2O_2
•OH
Hydroxyl Radicals
H_2
H_2O
Hydrogen selectively neutralizes hydroxyl radicals generated by the Fenton Reaction
SNPS in CYP may increase toxic burden
CYP
Toxicity
Fe^{2+}
Fe^{3+}
HFE
HFE SNPs will increase iron absorption
Cystine
Protein modifications, disrupts cellular iron, interacts with reactive oxygen species
PON1
SNPS in PON1 may increase herbicide and pesticide toxicity
GSH
GSSH
NADP
NADPH



ANNALS of Clinical and Translational Neurology
Open Access
RESEARCH ARTICLE

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

Robert K. Naviaux[1,2,3,4], Brooke Curtis[5], Kefeng Li[1,2], Jane C. Naviaux[1,6], A. Taylor Bright[1,2], Gail E. Reiner[1,6], Marissa Westerfield[7], Suzanne Goh[8], William A. Alaynick[1,2], Lin Wang[1,2], Edmund V. Capparelli[13], Cynthia Adams[9], Ji Sun[9], Sonia Jain[10], Feng He[10], Deyna A. Arellano[9], Lisa E. Mash[7,11], Leanne Chukoskie[7,12], Alan Lincoln[5] & Jeanne Townsend[6,7]

[1]The Mitochondrial and Metabolic Disease Center, University of California, San Diego School of Medicine, 214 Dickinson St., Bldg CTF, Rm C102, San Diego, 92103-8467, California
[2]Department of Medicine, University of California, San Diego School of Medicine, 214 Dickinson St., Bldg CTF, Rm C102, San Diego, 92103-8467, California
[3]Department of Pediatrics, University of California, San Diego School of Medicine, 214 Dickinson St., Bldg CTF, Rm C102, San Diego, 92103-8467, California
[4]Department of Pathology, University of California, San Diego School of Medicine, 214 Dickinson St., Bldg CTF, Rm C102, San Diego, 92103-8467, California
[5]Alliant International University, 10455 Pomerado Road, San Diego, California, 92131
[6]Department of Neurosciences, University of California, San Diego School of Medicine, 9500 Gilman Drive., La Jolla, CA, 92093-0662
[7]The Research in Autism and Development Laboratory (RAD Lab), University of California, 9500 Gilman Drive, La Jolla, CA, 92093-0959
[8]Pediatric Neurology Therapeutics, 7090 Miratech Dr, San Diego, CA, 92121
[9]Clinical and Translational Research Institute (CTRI), University of California, San Diego, La Jolla, CA, 92037
[10]Department of Family Medicine and Public Health, University of California, San Diego, La Jolla, CA, 92093
[11]Department of Psychology, San Diego State University, 5500 Campanile Drive, San Diego, CA, 92182
[12]Institute for Neural Computation, University of California, 9500 Gilman Drive, La Jolla, 92093-0523
[13]Department of Pediatrics, and Skaggs School of Pharmacy and Pharmaceutical Sciences, University of California, San Diego School of Medicine,

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

Research Institute (ARI), the Lennox Foundation, the Gupta Family and Satya Fund, the Agrawal Family, Linda Clark, the N of One Autism Research Foundation, the

clinical global impression questionnaire. **Results**: Blood levels of suramin were 12 ± 1.5 μmol/L (mean ± SD) at 2 days and 1.5 ± 0.5 μmol/L after 6 weeks. The terminal half-life was 14.7 ± 0.7 days. A self-limited, asymptomatic rash

moleculera labs

Cunningham Panel™ Testing Results

PATIENT REPORT

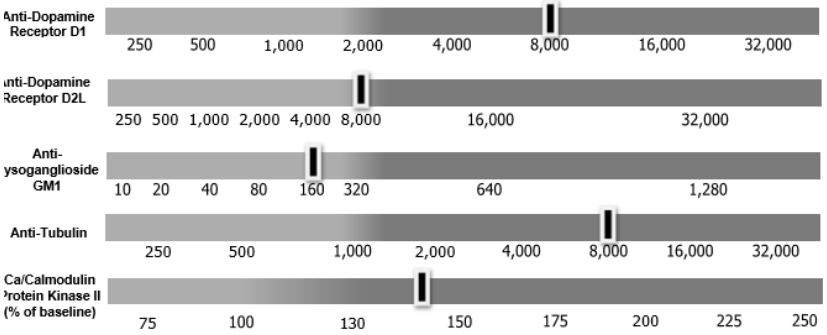
Submitting Prescriber: Kelly McCann, MD
Date of Collection: 09/20/2017
Date of Receipt: 09/21/2017

LABORATORY TEST RESULTS COMPARED TO NORMAL RANGES

	Anti-Dopamine Receptor D1 (titer)	Anti-Dopamine Receptor D2L (titer)	Anti-Lysoganglioside GM1 (titer)	Anti-Tubulin (titer)	CaM Kinase II (% of baseline)
Patient Result	1:8,000	1:8,000	1:160	1:8,000	143
Normal Ranges	500 to 2,000	2,000 to 8,000	80 to 320	250 to 1,000	53 to 130
Normal Mean	1,056	6,000	147	609	95
INTERPRETATION*	ELEVATED	BORDERLINE	NORMAL	ELEVATED	ELEVATED

***Report Guidance:** If any one (1) or more of these five (5) assay values is elevated, it may indicate a clinically significant autoimmune neurological condition. This is a condition in which the patient's autoantibodies cross-react and are directed against selected neuronal targets which are involved in normal neuropsychiatric and/or motor functions. It is important to note that the degree of elevation in assay values may not necessarily correlate with degree of symptom severity, as any value above normal ranges may correlate with symptomatology.

LABORATORY TEST RESULTS



The Cunningham Panel measures human serum Immunoglobulin G (IgG) levels by Enzyme-Linked ImmunoSorbent Assay (ELISA) directed against: Dopamine D1 Receptor (DRD1), Dopamine D2L Receptor (DRD2L), Lysoganglioside-GM1 (LYSO-GM1) and Tubulin (TUB). ELISA results are determined by measuring the colorimetric intensity at a specific wavelength which is directly proportional to the amount of antibody in the sample. The fifth assay of this panel measures the specific activity of calcium/calmodulin-dependent protein kinase II (CaM KII) induced by the patient serum in cultured human neuronal cell lines compared to controls. This panel

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

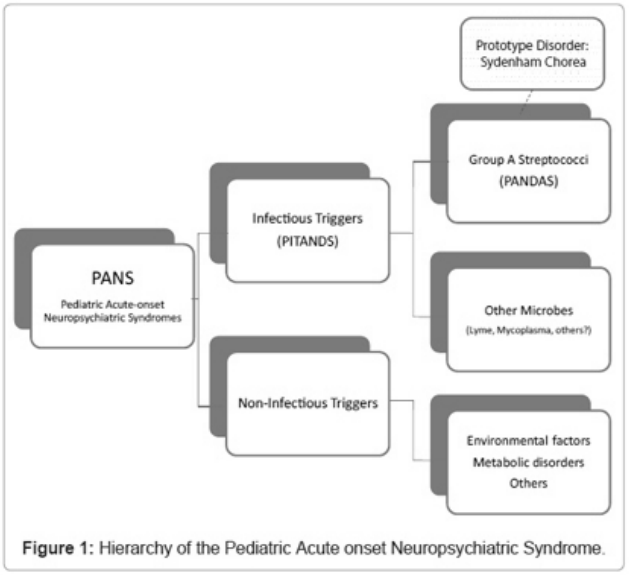
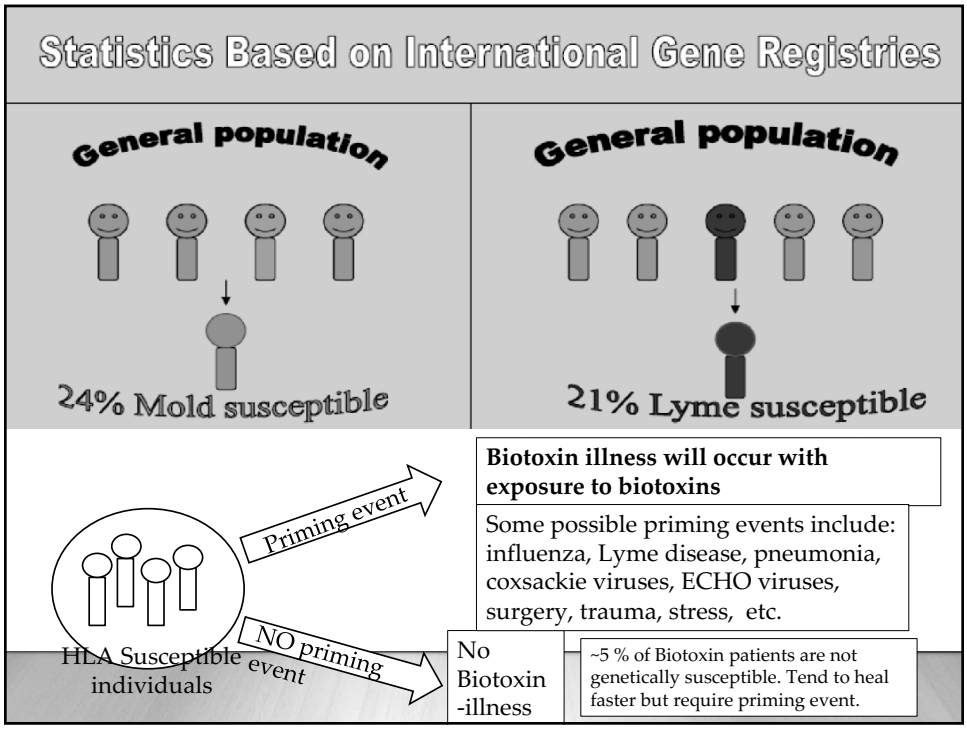


Figure 1: Hierarchy of the Pediatric Acute onset Neuropsychiatric Syndrome.

Image borrowed from "From Research Subgroup to Clinical Syndrome: Modifying the PANDAS Criteria to Describe PANS (Pediatric Acute-onset Neuropsychiatric Syndrome)"

Mycotoxin	Major Foods	Species	Health Effect	LD50 (mg/kg)
Aflatoxin	Maize, groundnuts, figs, tree nuts, milk, milk products	Aspergillus flavus Aspergillus parasiticus	Hepatotoxic, carcinogenic	0.5 (dog) 9.0 (mouse)
Cyclopiazonic acid	Cheese, maize, groundnuts, Rodo millet	Aspergillus flavus Penicillium aurantiogriseum	Convulsions	36 (rat)
Deoxynivalenol	Cereals	Fusarium graminearum	Vomiting, food Refusal, DNA damage	70 (mouse)
Fumonisin	Maize	Fusarium moniliforme	Esophageal Cancer	?
Ochratoxin	Maize, cereals, coffee beans	Penicillium verrucosum Aspergillus ochraceus	Nephrotoxic	20-30 (rat)
Patulin	Apple juice, damaged apples	Penicillium expansum	Edema, hemorrhage, cancer	35 (mouse)
Penitrem	Walnuts	Penicillum aurantiogriseum	Tremors	1.05 (mouse)
T-2 toxin	Cereals	Fusarium sporotrichioides	Alimentary toxic aleukia	4 (rat)
Ergotamine	Rye	Claviceps purpurea	Neurotoxin	
Zearolenone	Maize, barley, wheat	Fusarium graminearum	Estrogenic	Not acutely toxic



International Journal of Hygiene and Environmental Health 220 (2017) 305–328

Contents lists available at ScienceDirect

Review

Medical diagnostics for indoor m

Julia Hurraß[a,*], Birger Heinzow[b], Ute Au
Albrecht Bufe[c], Walter Buzina[f], Oliver A.
Thomas Gabrio[j], Werner Heinz[k], Carolin
Ludger Klimek[o], Martin Köberle[p], Herbe
Rolf Merget[s], Norbert Mülleneisen[t], Den
Hans Peter Seidl[w], Jens-Oliver Steiß[x], Re
Kerttu Valtanen[y], Gerhard A. Wiesmülle

Table 1
Evidence for an association between exposure to moisture/mold damage indoors and diseases without mold mycoses, modified according to (Fisk et al., 2007, 2010; Mendell et al., 2011; Palaty and Shum, 2012; WHO, 2009b).

Causal relationship
No evidence
Sufficient evidence for an association
Allergic respiratory diseases
Asthma (manifestation, progression, exacerbation)
Allergic rhinitis
Hypersensitivity pneumonitis (HP)/Exogenous allergic alveolitis (EAA)
Promoting respiratory infections, bronchitis
Restricted or suspected evidence for an association
Mucous membrane irritation (MMI)
Atopic eczema (atopic dermatitis; manifestation, progression, exacerbation)
Inadequate or insufficient evidence for an association
Chronic obstructive pulmonary disease (COPD)
Acute idiopathic pulmonary hemorrhage in children
Rheumatism
Arthritis
Sarcoidosis
Cancer
Neurotoxic effects

ARTICLE INFO

Article history:
Received 29 November 2016
Accepted 29 November 2016

Keywords:
Mold
Indoor
Health
Risk
Diagnostics
Guideline

Kelly K. McCann, MD

The Great Plains Laboratory, Inc.

William Shaw, Ph.D Director 11813 W. 77th Street, Lenexa, KS 66214 (913) 341-8949 Fax (913) 341-6207

GPL-MYCOTOX

Metabolite	Results (ng/g creatinine)	Common Range of Positive Results
Ochratoxin A	7.32	1.2 - 7.5

1.2 7.5

Ochratoxin A (OTA) is a nephrotoxic, immunotoxic, and carcinogenic mycotoxin. This chemical is produced by molds in the Aspergillus and Penicillium families. Exposure is primarily through contaminated foods such as cereals, grape juices, dairy, spices, wine, dried vine fruit, and coffee. Exposure to OTA can also come from inhalation exposure in water-damaged buildings. OTA can lead to kidney disease and adverse neurological effects. Studies have shown that OTA can lead to significant oxidative damage to multiple brain regions and is highly nephrotoxic. Dopamine levels in the brain of mice have been shown to be decreased after exposure to OTA. Some studies have hypothesized that OTA may contribute to the development of neurodegenerative diseases such as Alzheimer's and Parkinson's. Treatment should be aimed at removing the source of exposure. Agents such as oral cholestyramine, charcoal, and phenylalanine can help prevent the absorption of these toxins from food. Antioxidants such as vitamins A, E, C, NAC, rosmarinic acid, and liposomal glutathione alone or in combination have been shown to mitigate the oxidative effects of the toxin. Bentonite or zeolite clay is reported to reduce the absorption of multiple mycotoxins found in food, including OTA. Studies have also shown that OTA is present in sweat, which supports the use of sauna as a treatment to increase the excretion of OTA. (PMID 17195275, 16621780, 16293235, 27521635, 22069626, 24792326, 22253638, 16140385, 2467220, 16844142, 19148691, 22069658, 16019795, 18286403, 15781206, 11439224, 17092826, 32710148)

Sterigmatocystin	0	0.1 - 2.25

0.1 2.25

Sterigmatocystin (STC) is a mycotoxin that is closely related to aflatoxin. STC is produced from several species of mold such as Aspergillus, Penicillium, and Bipolaris. STC is considered to be carcinogenic, particularly in the cells of the GI tract and

New Urine Mycotoxin test option

Mycotoxins

- Aflatoxin M1 (AFM1)
- Ochratoxin A (OTA)
- Sterigmatocystin (STG)
- Roridin E
- Verrucarin A
- Enniatin B1
- Zearalenone (ZEA)

Molds

- Aspergillus
- Penicillum
- Stachybotrys
- Fusarium

Kelly K. McCann, MD

MaRCoNS – Multidrug Antibiotic Resistant Coagulase Negative Staph

Microbiology Dx

LABORATORY REPORT
14 CROSBY DRIVE
BEDFORD, MA 01730
TEL: (781)275-0855 * FAX: (781)275-9703
DR. J. D. MUSTO, DABB, BCIC
PRESIDENT & LAB DIRECTOR

PATIENT:
CLIENT: GENERAL DOCTOR ACCOUNT
14 CROSBY DR.
BEDFORD, MA 01730

D.O.B./SEX:
DOCTOR:
DATE COLLECTED:
DATE RPTD:
TIME COLLECTED:
DATE PRNT:
LAB NUMBER:
PATIENT ID:

PAGE: 1

** FINAL REPORT **
** FINAL REPORT **

RESULTS

TEST NAME	NORMAL	ABNORMAL	REFERENCE RANGE	UNITS

NARES CULTURE
SOURCE NARES
MARCoNS present
ORGANISM STAPH COAG NEGATIVE - LARGE AMOUNT
METHICILLIN RESISTANT

SUSCEPTIBILITY

PENICILLIN-G	)=0.5	R	OXACILLIN MIC	)=4	R
GENTAMICIN	(=0.5	S	CIPROFLOXACIN	)=8	R
LEVOFLOXACIN	)=8	R	ERYTHROMYCIN	)=8	R
CLINDAMYCIN	)=8	R	VANCOMYCIN	1	S
TETRACYCLINE	2	S	TIGECYCLINE	(=0.12	S
NITROFURANTOIN	32	S	RIFAMPICIN	(=0.5	S
CEFAZOLIN		R			

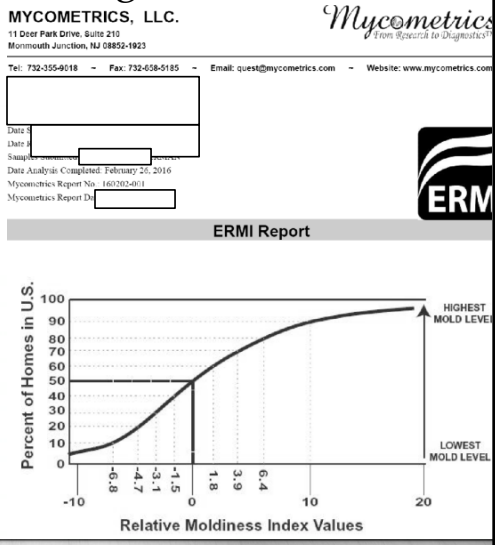
- Bacterial colonizer in the nasal passages and possibly dental reservoirs.
- Creates biofilms
- Releases exotoxins that suppress alpha MSH.
- Differentially activates gene expressions
- Fungal nasal cultures available
- Company now tests strength of biofilms

Shoemaker R, Hudnell K, et al. Association of nasal carriage of methicillin resistant and multiple antibiotic resistant coagulase negative staphylococci species with deficiency of alpha melanocyte stimulating hormone in Chronic Fatigue Syndrome. American Society of Microbiology 2003. (conference peer review)

Kelly K. McCann, MD

Building Testing - ERMI

- ERMI – Environmental Relative Mold Index (Use Mycometrics)
- Looks for mold DNA 26 from toxin producing species and compares that to DNA from non-toxic molds.
- EPA holds patent on ERMI testing which uses vacuum canister attachment to collect dust. Swiffer cloth is used for surfaces.



Kelly K. McCann, MD

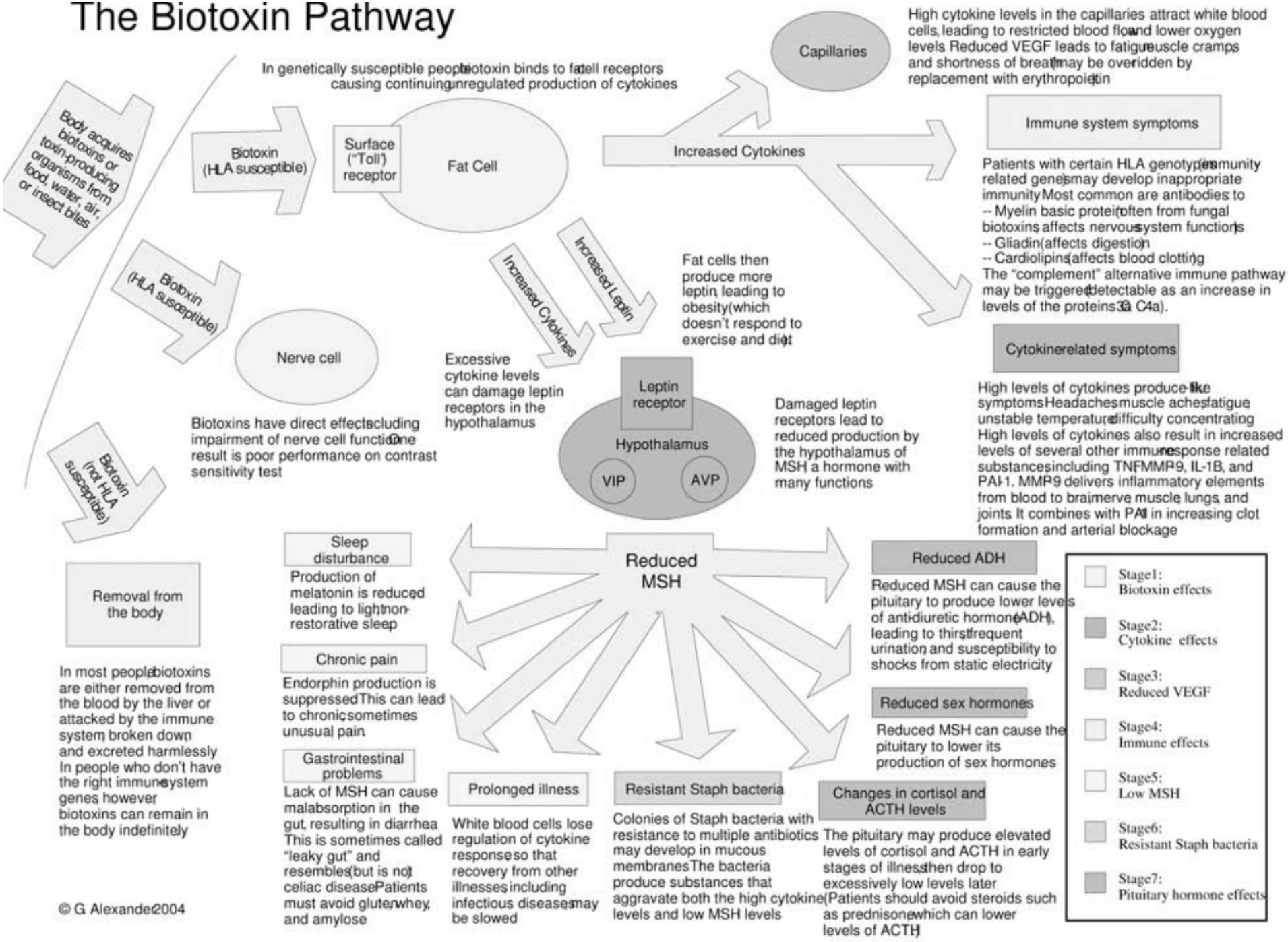
HLA Susceptibility

Dr. Shoemaker's HLA Rosetta Stone

Susceptibility	DRB1	DQ	DRB3	DRB4	DRB5
Multisusceptible	4	3		53	
	11/12	3	52B		
	14	5	52B		
Mold Susceptible	7	2/3		53	
	13	6	52A, B, C		
	17	2	52A		
	18*	4	52A		
Borrelia, post Lyme Syndrome	15	6			51
	16	5			51
Dinoflagellates (Pfiesteria, ciguatera)	4	7/8		53	
Multiple Antibiotic Resistant Staph Epidermis (MARCoNS)	11	7	52B		
Low MSH	1	5			
No recognized significance	8	3, 4, 6			
Low-risk Mold	7	9		53	
	12	7	52B		
	9	9		53	

Shoemaker R. Linkage disequilibrium in alleles of HLA DR: differential association with susceptibility to chronic illness following exposure to biologically produced neurotoxins. American Society of Microbiology 2003. (conference peer review).

The Biotoxin Pathway



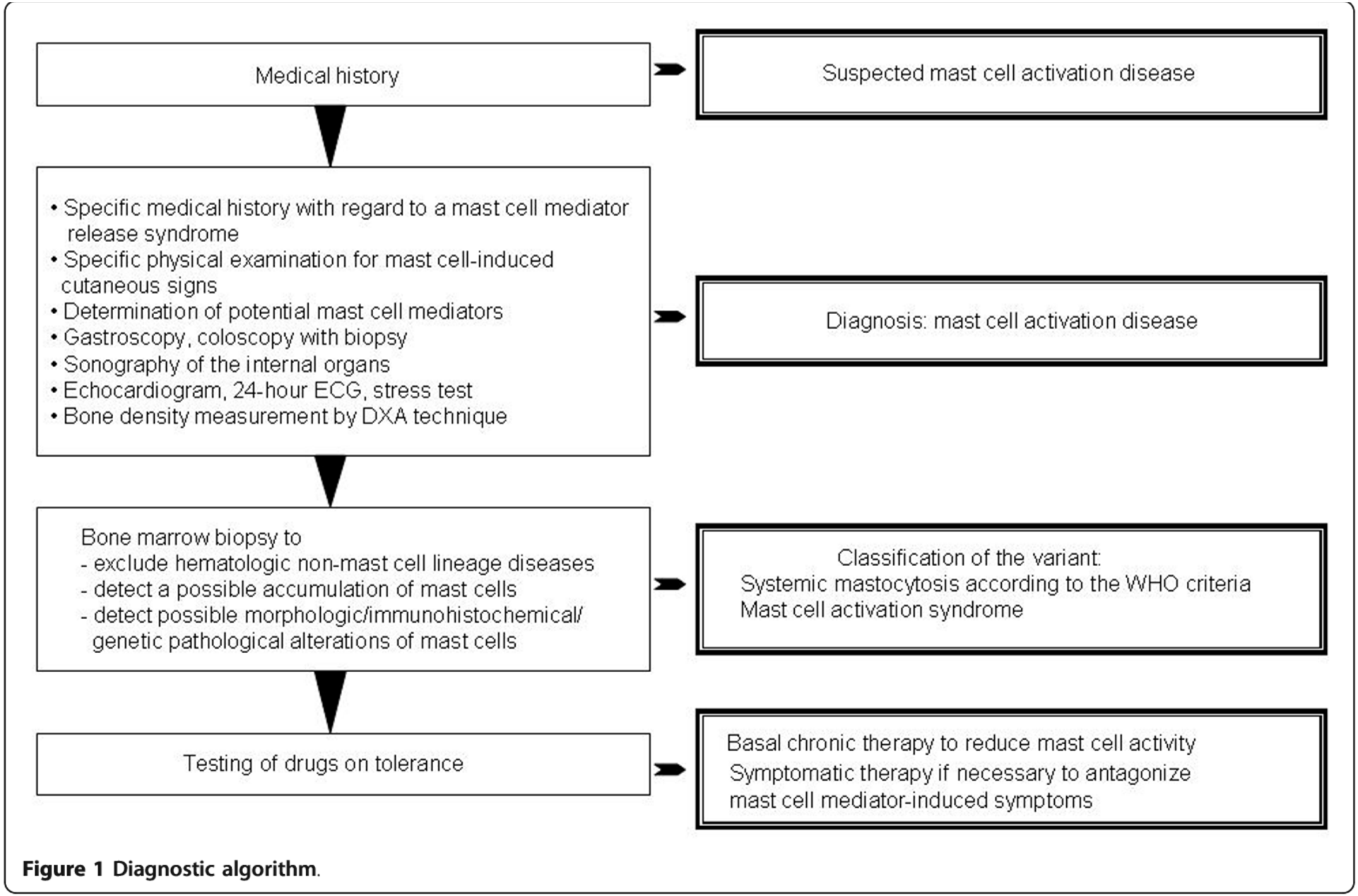
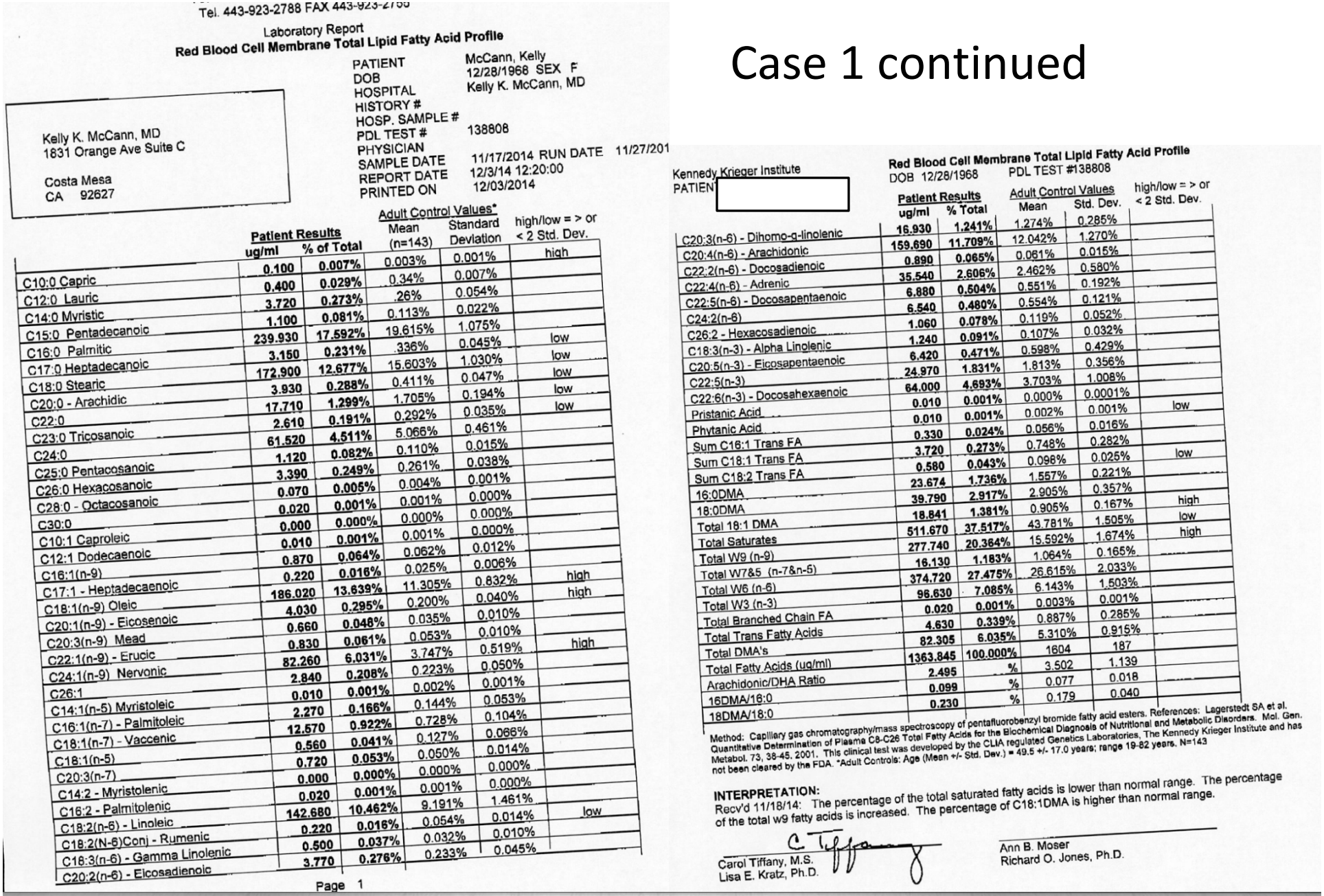


Figure 1 Diagnostic algorithm.

Case 1 continued



Tel. 443-923-2788 FAX 443-923-2755

Laboratory Report

Red Blood Cell Membrane Total Lipid Fatty Acid Profile

Kelly K. McCann, MD
1831 Orange Ave Suite C

Costa Mesa
CA 92627

PATIENT McCann, Kelly
DOB 12/28/1968 SEX F
HOSPITAL Kelly K. McCann, MD
HISTORY #
HOSP. SAMPLE #
PDL TEST # 138808
PHYSICIAN
SAMPLE DATE 11/17/2014 RUN DATE 11/27/201
REPORT DATE 12/3/14 12:20:00
PRINTED ON 12/03/2014

	Patient Results ug/ml	% of Total	Adult Control Values* Mean (n=143)	Standard Deviation	high/low = > or < 2 Std. Dev.
C10:0 Capric	0.100	0.007%	0.003%	0.001%	high
C12:0 Lauric	0.400	0.029%	0.34%	0.007%	
C14:0 Myristic	3.720	0.273%	.26%	0.054%	
C15:0 Pentadecanoic	1.100	0.081%	0.113%	0.022%	
C16:0 Palmitic	239.930	17.592%	19.615%	1.075%	
C17:0 Heptadecanoic	3.150	0.231%	.336%	0.045%	low
C18:0 Stearic	172.900	12.677%	15.603%	1.030%	low
C20:0 - Arachidic	3.930	0.288%	0.411%	0.047%	low
C22:0	17.710	1.299%	1.705%	0.194%	low
C23:0 Tricosanoic	2.610	0.191%	0.292%	0.035%	low
C24:0	61.520	4.511%	5.066%	0.461%	
C25:0 Pentacosanoic	1.120	0.082%	0.110%	0.015%	
C26:0 Hexacosanoic	3.390	0.249%	0.261%	0.038%	
C28:0 - Octacosanoic	0.070	0.005%	0.004%	0.001%	
C30:0	0.020	0.001%	0.001%	0.000%	
C10:1 Caproleic	0.000	0.000%	0.000%	0.000%	
C12:1 Dodecaenoic	0.010	0.001%	0.001%	0.000%	
C16:1(n-9)	0.870	0.064%	0.062%	0.012%	
C17:1 - Heptadecaenoic	0.220	0.016%	0.025%	0.006%	
C18:1(n-9) Oleic	186.020	13.639%	11.305%	0.832%	high
C20:1(n-9) - Eicosenoic	4.030	0.295%	0.200%	0.040%	high
C20:3(n-9) Mead	0.660	0.048%	0.035%	0.010%	
C22:1(n-9) - Erucic	0.830	0.061%	0.053%	0.010%	
C24:1(n-9) Nervonic	82.260	6.031%	3.747%	0.519%	high
C26:1	2.840	0.208%	0.223%	0.050%	
C14:1(n-5) Myristoleic	0.010	0.001%	0.002%	0.001%	
C16:1(n-7) - Palmitoleic	2.270	0.166%	0.144%	0.053%	
C18:1(n-7) - Vaccenic	12.570	0.922%	0.728%	0.104%	
C18:1(n-5)	0.560	0.041%	0.127%	0.066%	
C20:3(n-7)	0.720	0.053%	0.050%	0.014%	
C14:2 - Myristolenic	0.000	0.000%	0.000%	0.000%	
C16:2 - Palmitolenic	0.020	0.001%	0.001%	0.000%	
C18:2(n-6) - Linoleic	142.680	10.462%	9.191%	1.461%	
C18:2(N-6)Conj - Rumenic	0.220	0.016%	0.054%	0.014%	low
C18:3(n-6) - Gamma Linolenic	0.500	0.037%	0.032%	0.010%	
C20:2(n-6) - Eicosadienoic	3.770	0.276%	0.233%	0.045%	

Page 1

Kennedy Krieger Institute
PATIEN

Red Blood Cell Membrane Total Lipid Fatty Acid Profile
DOB 12/28/1968 PDL TEST #138808

	Patient Results ug/ml	% Total	Adult Control Values Mean	Std. Dev.	high/low = > or < 2 Std. Dev.
C20:3(n-6) - Dihomo-g-linolenic	16.930	1.241%	1.274%	0.285%	
C20:4(n-6) - Arachidonic	159.690	11.709%	12.042%	1.270%	
C22:2(n-6) - Docosadienoic	0.890	0.065%	0.061%	0.015%	
C22:4(n-6) - Adrenic	35.540	2.606%	2.462%	0.580%	
C22:5(n-6) - Docosapentaenoic	6.880	0.504%	0.551%	0.192%	
C24:2(n-6)	6.540	0.480%	0.554%	0.121%	
C26:2 - Hexacosadienoic	1.060	0.078%	0.119%	0.052%	
C18:3(n-3) - Alpha Linolenic	1.240	0.091%	0.107%	0.032%	
C20:5(n-3) - Eicosapentaenoic	6.420	0.471%	0.598%	0.429%	
C22:5(n-3)	24.970	1.831%	1.813%	0.356%	
C22:6(n-3) - Docosahexaenoic	64.000	4.693%	3.703%	1.008%	
Pristanic Acid	0.010	0.001%	0.000%	0.0001%	
Phytanic Acid	0.010	0.001%	0.002%	0.001%	low
Sum C16:1 Trans FA	0.330	0.024%	0.056%	0.016%	
Sum C18:1 Trans FA	3.720	0.273%	0.748%	0.282%	
Sum C18:2 Trans FA	0.580	0.043%	0.098%	0.025%	low
16:0DMA	23.674	1.736%	1.557%	0.221%	
18:0DMA	39.790	2.917%	2.905%	0.357%	
Total 18:1 DMA	18.841	1.381%	0.905%	0.167%	high
Total Saturates	511.670	37.517%	43.781%	1.505%	low
Total W9 (n-9)	277.740	20.364%	15.592%	1.674%	high
Total W7&5 (n-7&n-5)	16.130	1.183%	1.064%	0.165%	
Total W6 (n-6)	374.720	27.475%	26.615%	2.033%	
Total W3 (n-3)	96.630	7.085%	6.143%	1.503%	
Total Branched Chain FA	0.020	0.001%	0.003%	0.001%	
Total Trans Fatty Acids	4.630	0.339%	0.887%	0.285%	
Total DMA's	82.305	6.035%	5.310%	0.915%	
Total Fatty Acids (ug/ml)	1363.845	100.000%	1604	187	
Arachidonic/DHA Ratio	2.495	%	3.502	1.139	
16DMA/16:0	0.099	%	0.077	0.018	
18DMA/18:0	0.230	%	0.179	0.040	

Method: Capillary gas chromatography/mass spectroscopy of pentafluorobenzyl bromide fatty acid esters. References: Lagerstedt SA et al. Quantitative Determination of Plasma C8-C26 Total Fatty Acids for the Biochemical Diagnosis of Nutritional and Metabolic Disorders. Mol. Gen. Metabol. 73, 38-45. 2001. This clinical test was developed by the CLIA regulated Genetics Laboratories, The Kennedy Krieger Institute and has not been cleared by the FDA. *Adult Controls: Age (Mean +/- Std. Dev.) = 49.5 +/- 17.0 years; range 19-82 years. N=143

INTERPRETATION:
Recv'd 11/18/14: The percentage of the total saturated fatty acids is lower than normal range. The percentage of the total w9 fatty acids is increased. The percentage of C18:1DMA is higher than normal range.

Carol Tiffany, M.S.
Lisa E. Kratz, Ph.D.

Ann B. Moser
Richard O. Jones, Ph.D.

Kelly K. McCann, MD

Case 1: RBC Fatty Acid

[redacted]

Red Cell Lipid Biomarkers

Specimen Draw Date: 11/17/2014
Practitioner: Dr. Kelly K. McCann (19062)

The % Status is the weighted deviation of the lab result and will show no graph when the research does not support negative values.

	% Status		Result	Low	High
16 DMA	**40.70**	H	1.74	1.34	1.78
18:0 DMA	1.68		2.92	2.55	3.26
18:1 DMA	**142.51**	H	1.38	0.74	1.07
C14:0 Myristic	12.04		0.27	0.21	0.31
C14:1w5 Myristoleic	**-50.00**	L	0.0010	0.001	0.003
C15:0 Pentadecanoic	**-73.26**	L	0.08	0.09	0.13
C16:0 Palmitic	**-94.09**	L	17.59	18.54	20.69
C16:1w7 Palmitoleic	20.75		0.17	0.09	0.20
C16:1w9 Hexadecanoic	8.33		0.06	0.05	0.07
C17:0 Heptadecanoic	**-115.56**	L	0.23	0.29	0.38
C17:1 Heptadecaenoic	**-75.00**	L	0.02	0.02	0.03
C18:0 Stearic	**-141.76**	L	12.68	14.57	16.63
C18:1w5 Octadecanoic	**-65.15**	L	0.04	0.06	0.19
C18:1w7 Vaccenic	**92.58**	H	0.92	0.62	0.83
C18:1w9 Oleic	**140.38**	H	13.64	10.47	12.14
LA **C18:2w6 Linoleic**	**44.18**	H	10.48	7.73	10.65
C18:2w6 Conj Rumenic	**-130.00**	L	0.02	0.04	0.07
ALA **C18:3w3 Alpha Linolenic**	**-25.00**	L	0.09	0.07	0.14
GLA **C18:3w6 Gamma Linolenic**	**28.95**	H	0.04	0.02	0.04
C20:0 Arachidic	**-130.85**	L	0.29	0.36	0.46
C20:1w9 Gondoic	**118.75**	H	0.29	0.16	0.24
C20:2w6 Eicosadienoic	**45.56**	H	0.28	0.19	0.28
DGLA C20:3w6 Dihomo-y Lino.	-5.79		1.24	0.99	1.56
C20:3w9 Mead	**65.00**	H	0.05	0.03	0.04
AA C20:4w6 Arachidonic	-13.14		11.71	10.77	13.31
EPA C20:5w3 Eicosapenta.	-14.80		0.47	0.17	1.03
C22:0 Behenic	**-104.50**	L	1.30	1.51	1.90
C22:1w9 Erucic	**35.00**	H	0.06	0.04	0.06
C22:2w6 Docosadienoic	13.33		0.07	0.05	0.08
C22:4w6 Adrenic	12.41		2.61	1.88	3.04
C22:5w3 Docosapenta.	2.46		1.83	1.46	2.17
C22:5w6 Osbond	-12.14		0.50	0.36	0.74
DHA **C22:6w3 Docosahexa.**	**49.11**	H	4.69	2.70	4.71
C23:0 Tricosanoic	**-144.29**	L	0.19	0.26	0.33
C24:0 Lignoceric	**-60.21**	L	4.51	4.61	5.53
C24:1w9 Nervonic	**412.72**	H	8.03	3.23	4.27
C24:2w6 Tetracosadienoic	**-30.50**	L	0.48	0.43	0.67
C25:0 Pentacosanoic	**-88.71**	L	0.08	0.09	0.13
C26:0 Hexacosanoic	-16.23		0.25	0.22	0.30
C26:1 Lumequic	-15.66		0.21	0.17	0.27
C26:2 Hexacosadienoic	**-39.42**	L	0.08	0.07	0.17
C28:0 Octacosanoic	**50.00**	H	0.0050	0.003	0.005
C30:0 Triacontanoic	**50.00**	H	0.0010	0.000	0.001
Phytanic	**-50.00**	L	0.0010	0.001	0.003
Pristanic	**950.00**	H	0.0010	0.000	0.000
Sum C16:1 Trans FAs	**-88.71**	L	0.02	0.04	0.07
Sum C18:1 Trans FAs	**-84.46**	L	0.27	0.47	1.03
Sum C18:2 Trans FAs	**-110.00**	L	0.04	0.07	0.12
Total Lipid Content	**-64.31**	L	1363.85	1417.24	1790.28
Total Saturates	**-208.11**	L	37.52	42.28	45.29
Total w3's	**31.34**	H	7.08	4.64	7.65
Total w6's	21.14		27.48	24.58	28.65

[redacted]

Red Cell Lipid Biopsy

Specimen Draw Date: 11/17/2014
Practitioner: Dr. Kelly K. McCann (19062)

BURN IT

TRANS ISOMERS	**VLCFA'S**		
	Erucic	35.00	H
	Triacontanoic	50.00	H
SATURATED ODD	**RENEGADES**		
	Vaccenic	92.58	H
	Mead	65.00	H
	Eicosanoic	65.00	H
	Pristanic	950.00	H
	Gondoic	118.75	H

BUILD IT

MYELINATION			**STRUCTURAL**		
			Palmitic	-94.09	L
			Stearic	-141.76	L
SUMMATION					
Total Saturates	-208.11	L			
Total Lipid Cont	-64.31	L			

BALANCE IT

OMEGA 6			**OMEGA 3**		
Linoleic	44.18	H	Alpha Linolenic	-25.00	L
Gamma Linolenic	28.95	H	Eicosapentaenoic	-14.80	
Dihomo-y Linolenic	-5.79		Docosapentaenoic	2.46	
Arachidonic	-13.14		Docosahexaenoic	49.11	H
Adrenic	12.41				

INDEXES

Fluidity Index	50.00	H	Myelination Index	0.00	
MR Index	51.48	H	Trans Isomer Index	0.00	
PR Index	293.93	H	Odd Chain Index	-37.50	L

STABILIZE IT

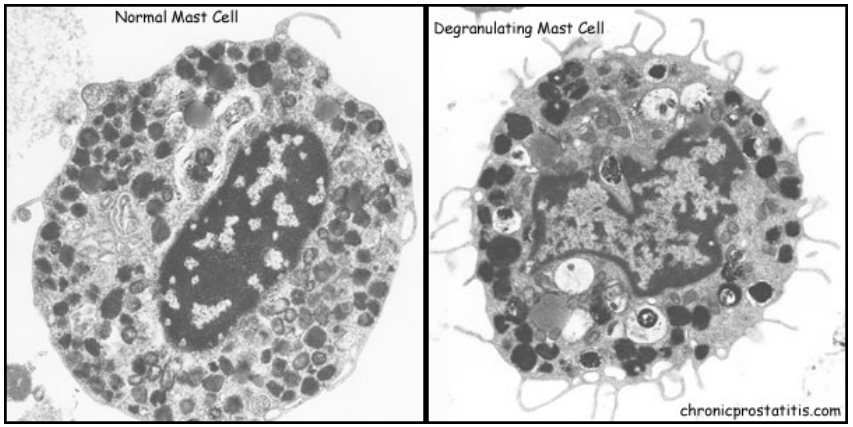
18:1 DMA	142.51	H	PR Index	293.93	H

Kelly K. McCann, MD

Table 3 Frequent signs and clinical symptoms ascribed to episodic unregulated release of mast cell mediators (modified from [12]; further references therein; an exhaustive survey is given in [50])

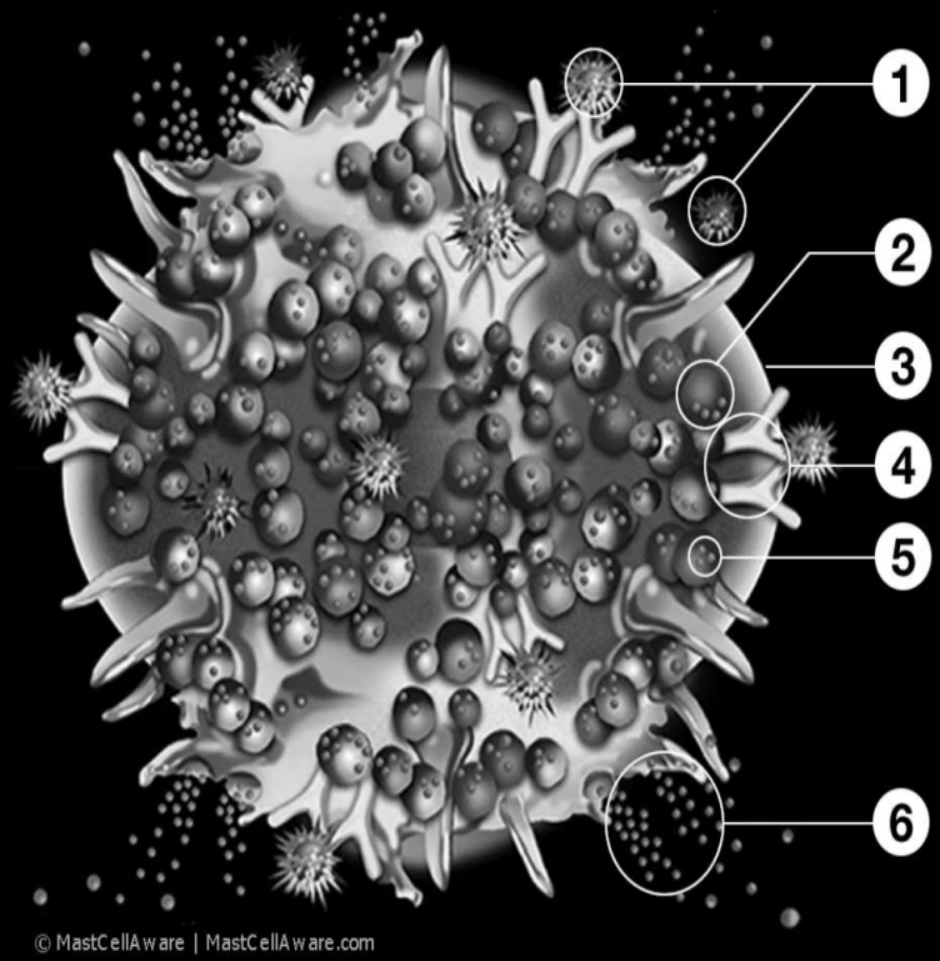
Signs and Symptoms	
Abdominal	abdominal pain, intestinal cramping and bloating, diarrhea and/or obstipation, nausea, non-cardiac chest pain, Helicobacter pylori-negative gastritis, malabsorption
Oropharyngeal	burning pain, aphthae
Respiratory	cough, asthma-like symptoms, dyspnea, rhinitis, sinusitis
Ophthalmologic	conjunctivitis, difficulty in focusing
Hepatic	splenomegaly, hyperbilirubinemia, elevation of liver transaminases, hypercholesterolemia
Splenomegaly	
Lymphadenopathy	
Cardiovascular	tachycardia, blood pressure irregularity (hypotension and/or hypertension), syncope, hot flush
Neuropsychiatric	headache, neuropathic pain, polyneuropathy, decreased attention span, difficulty in concentration, forgetfulness, anxiety, sleeplessness, organic brain syndrome, vertigo, lightheadedness, tinnitus
Cutaneous	urticaria pigmentosa, hives, efflorescences with/without pruritus, telangiectasia, flushing, angioedema
Abnormal bleeding	
Musculoskeletal	muscle pain, osteoporosis/osteopenia, bone pain, migratory arthritis
Interstitial cystitis	
Constitutional	fatigue, asthenia, fever, environmental sensitivities

Mast Cell Activation Syndrome (MCAS)



Kelly K. McCann, MD

Mast Cells In Activation



Click the links to learn more about the parts of a mast cell. (Links open in new window)

① Allergens & Triggers

② Storage Granules

③ Mast Cell

④ IgE Antibodies

⑤ Histamine & Tryptase

⑥ Degranulation

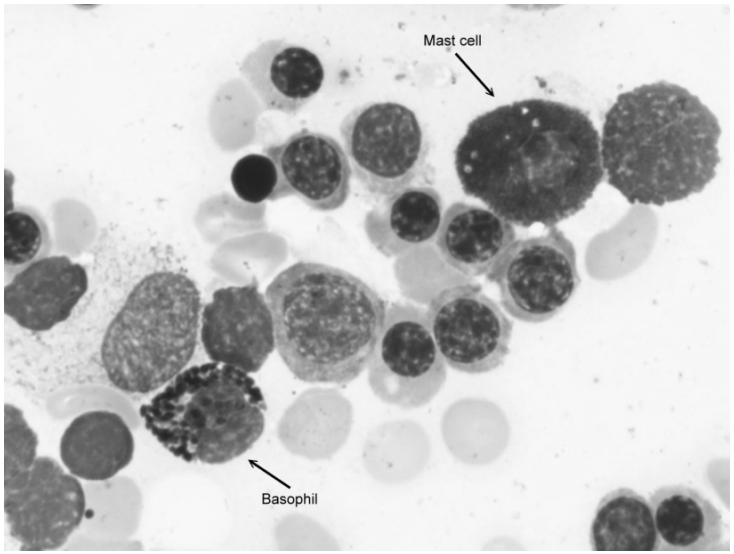
In this illustration, the mast cell, similar in appearance to a white blood cell (white/blue areas), contains many storage granules (purple spheres) rich in histamine and tryptase (small orange granules).When allergens, drugs, toxins, etc. (green & pink spiked shapes) are binding & cross-bridging the antibodies (yellow Y-shaped pairs), a mast cell reaction is triggered, releasing histamine, tryptase and other mediators into the system (represented by the release of orange granules).

Thanks to Theoharis C. Theoharides, MS, PhD, MD, FAAAAI for his guidance with this visual interpretation of mast cells in activation.

Table 2 Criteria proposed to define mast cell activation disease (for references, see text)

Criteria to define *mast cell activation syndrome*	WHO criteria to define *systemic mastocytosis*
Major criteria	**Major criterion**
1. Multifocal or disseminated dense infiltrates of mast cells in bone marrow biopsies and/or in sections of other extracutaneous organ(s) (e.g., gastrointestinal tract biopsies; CD117-, tryptase- and CD25-stained)	Multifocal dense infiltrates of mast cells (>15 mast cells in aggregates) in bone marrow biopsies and/or in sections of other extracutaneous organ(s) (CD117-, tryptase- and CD25-stained)
2. Unique constellation of clinical complaints as a result of a pathologically increased mast cell activity (mast cell mediator release syndrome)	
Minor criteria	**Minor criteria**
1. Mast cells in bone marrow or other extracutaneous organ(s) show an abnormal morphology (>25%) in bone marrow smears or in histologies	1. Mast cells in bone marrow or other extracutaneous organ(s) show an abnormal morphology (>25%) in bone marrow smears or in histologies
2. Mast cells in bone marrow express CD2 and/or CD25	2. Mast cells in bone marrow express CD2 and/or CD25
3. Detection of genetic changes in mast cells from blood, bone marrow or extracutaneous organs for which an impact on the state of activity of affected mast cells in terms of an increased activity has been proved.	3. c-kit mutation in tyrosine kinase at codon 816 in mast cells in extracutaneous organ(s)
4. Evidence of a pathologically increased release of mast cell mediators by determination of the content of • tryptase in blood • N-methylhistamine in urine • heparin in blood • chromogranin A in blood • other mast cell-specific mediators (e.g., leukotrienes, prostaglandin D_2)	4. Serum total tryptase >20 ng/ml (does not apply in patients who have associated hematologic non-mast-cell lineage disease)

The diagnosis *mast cell activation syndrome* is made if both major criteria or the second criterion and at least one minor criterion are fulfilled. According to the WHO criteria [1], the diagnosis *systemic mastocytosis* is established if the major criterion and at least one minor criterion or at least three minor criteria



Kelly K. McCann, MD

Table 5 Treatment options for mast cell activation disease

Basic therapy (continuous oral combination therapy to reduce mast cell activity)	• H_1-histamine receptor antagonist (to block activating H_1-histamine receptors on mast cells; to antagonize H_1-histamine receptor-mediated symptoms) • H_2- histamine receptor antagonist (to block activating H_2-histamine receptors on mast cells; to antagonize H_2-histamine receptor-mediated symptoms) • Cromolyn sodium (stabilising mast cells) • Slow-release Vitamin C (increased degradation of histamine; inhibition of mast cell degranulation; not more than 750 mg/day) • If necessary, ketotifen to stabilise mast cells and to block activating H_1-histamine receptors on mast cells
Symptomatic treatment options (orally as needed)	• ***Headache***⇒ paracetamol; metamizole; flupirtine • ***Diarrhea***⇒ colestyramine; nystatin; montelukast; 5-HT_3 receptor inhibitors (eg. ondansetron); incremental doses (50-350 mg/day; extreme caution because of the possibility to induce mast cell degranulation) of acetylsalicylic acid; (in steps test each drug for 5 days until improvement of diarrhea) • ***Colicky abdominal pain***due to distinct meteorism ⇒ metamizole; butylscopolamine • ***Nausea***⇒ metoclopramide; dimenhydrinate; 5-HT_3 receptor inhibitors; icatibant • ***Respiratory symptoms***(mainly increased production of viscous mucus and obstruction with compulsive throat clearing) ⇒ montelukast; urgent: short-acting ß-sympathomimetic • ***Gastric complaints***⇒ proton pump inhibitors (de-escalating dose finding) • ***Osteoporosis, osteolysis, bone pain***⇒ biphosphonates ([51]; vitamin D plus calcium application is second-line treatment in MCAD patients because of limited reported success and an increased risk for developing kidney and ureter stones; [52]) • ***Non-cardiac chest pain***⇒ when needed, additional dose of a H_2-histamine receptor antagonist; also, proton pump inhibitors for proven gastroesophageal reflux • ***Tachycardia***⇒ verapamil; AT1-receptor antagonists; ivabradin • ***Neuropathic pain and paresthesia***⇒ α-lipoic acid • ***Interstitial cystitis***⇒ pentosan, amphetamines • ***Sleep-onset insomnia/sleep-maintenance insomnia***⇒ triazolam/oxazepam • ***Conjunctivitis***⇒ exclusion of a secondary disease; otherwise preservative-free eye drops with glucocorticoids for brief courses • ***Hypercholesterolemia***⇒ (does not depend on the composition of the diet) therapeutic trial with HMG-CoA reductase inhibitors (frequently ineffective) • ***Elevated prostaglandin levels, persistant flushing***⇒ incremental doses of acetylsalicylic acid (50-350 mg/day; extreme caution because of the possibility to induce mast cell degranulation)

All drugs should be tested for tolerance in a low single dose before therapeutic use, if their tolerance in the patient is not known from an earlier application.

AARM

Association for the Advancement
of Restorative Medicine

AARM

P.O. Box 874

Montpelier, VT 05601

(866) 962-2276

www.RestorativeMedicine.org