IVIT Intensive: Tackling Complex Cases in the Post-Pandemic Era

Dr. Eric Marsden ND

Disclosure

- I own and operated an integrative healthcare facility offering some of these therapies
- Most of these therapies are presented for off-label use in Canada
- Many of these intravenous infusion therapies are not currently a part of the allowed substances for administration by injection for NDs in Ontario by CONO
  - They are presented for informational purposes or for those operating in a collaborative care environment with other providers

Outline

- Pathophysiology of Acute and Chronic Infections and long-term sequelae
- Review of Critical Nutrients for infection support
  - Ascorbic Acid
  - Zinc
  - Selenium
  - Glutathione
  - HCl
  - Artesunate
  - Glycyrrhizic Acid
- Clinical decision making on when/how to administer therapeutics in acute/chronic infections
- Review Alpha Lipoic Acid intravenous administration

Long-Haul Infections

It’s not just about SARS-CoV-2

Scope of the Problem: Ontario

- Early in pandemic, estimates were 40% of people experience symptoms beyond 4 weeks
- Newer evidence estimates 2-10% of vaccinated and 10-20% of unvaccinated people experience long-term symptoms
- It is estimated that 57,000-78,000 Ontarians are experiencing long-haul symptoms

Vaccination Impact

- This review of 17 studies looked at the effect of vaccination on long-covid
  - 6 looked at impact of vaccination pre-infection and 11 post infection

ARTICLES | VOLUME 53, 101624, NOVEMBER 2022 Download Full Issue

Impact of COVID-19 vaccination on the risk of developing long-COVID and on existing long-COVID symptoms: A systematic review

Kin Israel Notarte • Jesus Alfonso Catahay • Jacqueline Veronica Velasco • Adriel Pastrana • Abbygail Therese Ver • Flos Carmeli Pangilinan • et al. Show all authors

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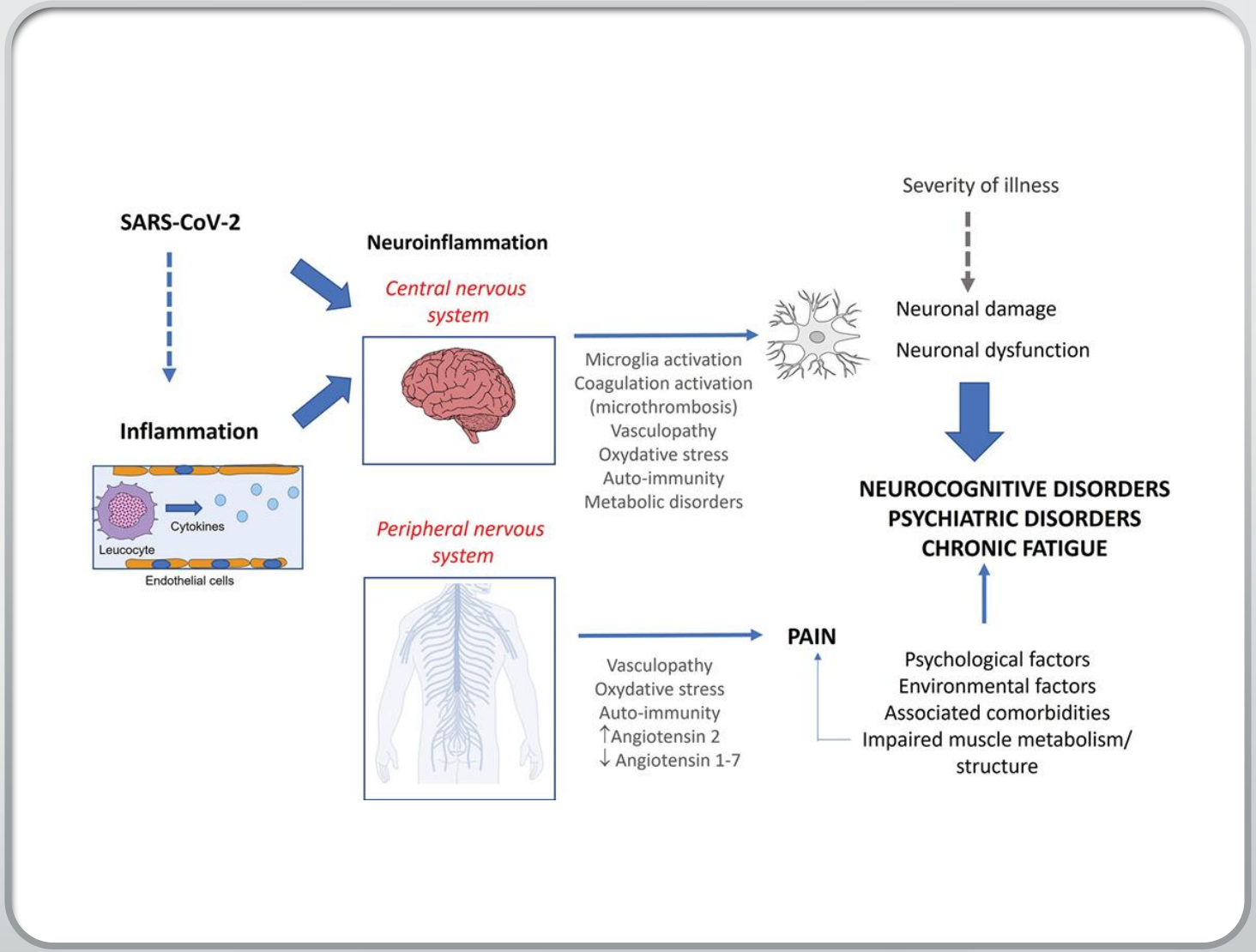
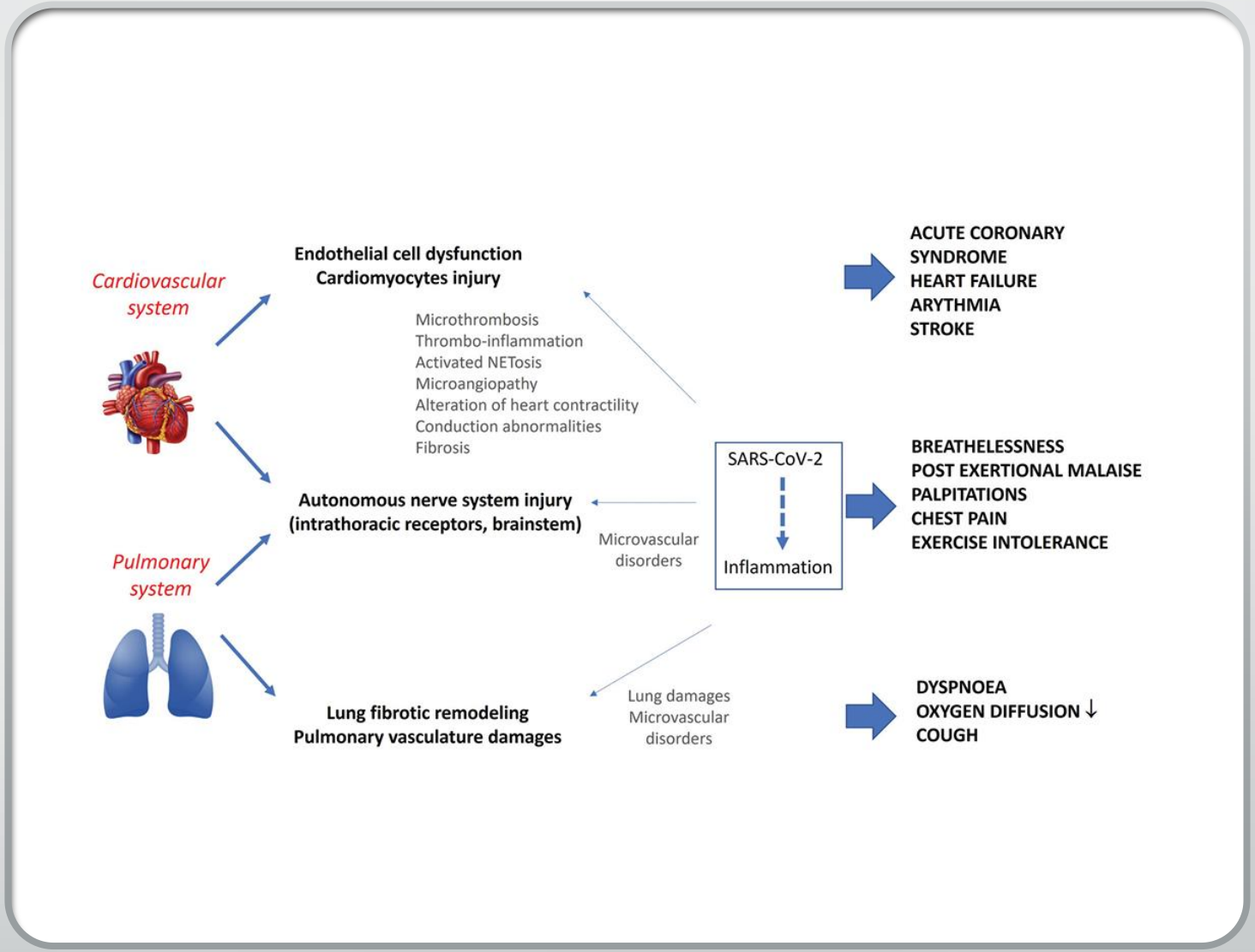
Study Conclusions

- Pre-infection vaccination
  - Significant heterogeneity in the studies (timing of vaccination relative to infection, number of doses, etc.)
  - All 6 studies agreed it reduced the risk
  - mRNA was superior to non-mRNA
  - Some studies showed 2 doses better than 1
  - Magnitude of effect 20-80% risk reduction
- Post long-haul vaccination
  - 7/11 studies showed improvement with single dose and 2 showed 2 doses lead to full restoration to baseline
  - 4/11 reported no improvement
  - Seems to have association between anti-body titers and severity of symptoms

Mechanisms of Long-Haul SARS-CoV-2 Neuroinflammation



Mechanism of Long-Haul SARS CoV-2: Cardiovascular/ Pulmonary



Additional mechanisms of SARS-CoV-2

- Immune:
  - Chronic multi-system inflammation (n.b. children with MIS-C)
  - Mast Cell Activation Syndrome
  - Persistent Infection
  - Autoimmunity (mimicry)
- Endocrine (direct viral invasion/immune dysregulation)
  - Sub-acute thyroiditis
  - Pancreatic dysfunction
- GI/Hepatobiliary
  - Microbiome alterations
  - Hepatobiliary damage
  - Autonomic GI dysregulation

Primary Symptoms

- increased malaise (extreme exhaustion and sickness) following physical activity or mental exertion
- problems with sleep
- difficulties with memory and concentration
- persistent muscle pain
- joint pain (without redness or swelling)
- headache
- tender lymph nodes in the neck or armpit
- sore throat

http://www.cdc.gov/cfs/symptoms/index.html

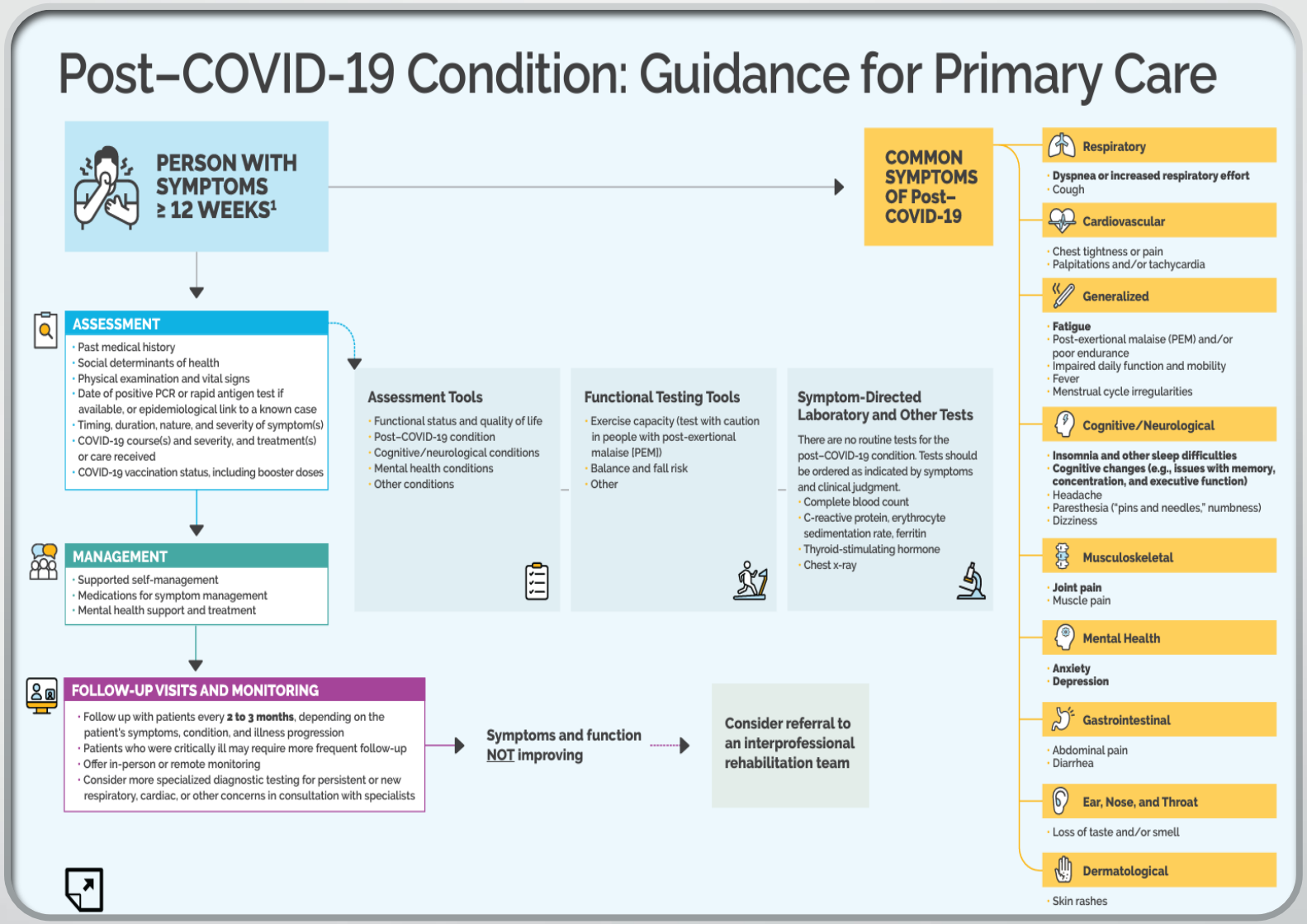
Secondary Symptoms

- brain fog (feeling like you're in a mental fog)
- difficulty maintaining an upright position, dizziness, balance problems or fainting
- allergies or sensitivities to foods, odors, chemicals, medications, or noise
- irritable bowel
- chills and night sweats
- visual disturbances (sensitivity to light, blurring, eye pain)
- depression or mood problems (irritability, mood swings, anxiety, panic attacks)

http://www.cdc.gov/cfs/symptoms/index.html

Sound Familiar?

Myalgic Encephalomyelitis/Chronic Fatigue Syndrome



Ontario Guidance

Diagnosis

- No definitive definition but there is some consensus on key features of post covid syndrome:
  - Hx of SARS Cov-2 infection, laboratory confirmed
  - Minimum time for onset of symptoms 3 months and duration of symptoms of at least 2 months and cannot be explained by other diagnoses
  - Symptoms must be new after infection or persistent from infection
  - Symptoms have an impact on ADLs
  - Symptoms can fluctuate and relapse

Symptom Profile

- Fatigue
- Shortness of breath
- Cognitive dysfunction
- Abdominal pain
- Menstrual irregularities
- Anxiety
- Altered vision
- Depression
- Altered taste and smell
- Intermittent fever
- Gastrointestinal dysfunction
- New onset allergies
- Neuropathy
- Etc.

Recommended Basic Testing

- CBC (check neut/lymph/ratio)
  - Consider flow cytometry
  - Globulin (consider electrophoresis)
- Autoimmune screen/Inflammatory status:
  - C-reactive protein
  - ESR
  - Complement
  - ANA
  - RF
- Liver function test
- Renal function test
  - Urinalysis
  - All electrolytes (Ca (with albumin), Mg, zinc)
- Endocrine
  - Thyroid function tests (thyroid stimulating hormone and free T_4).
  - Reproductive hormones as appropriate
  - AM/PM cortisol or other cortisol assessment

If Not Chronic Infection, What is Going on?

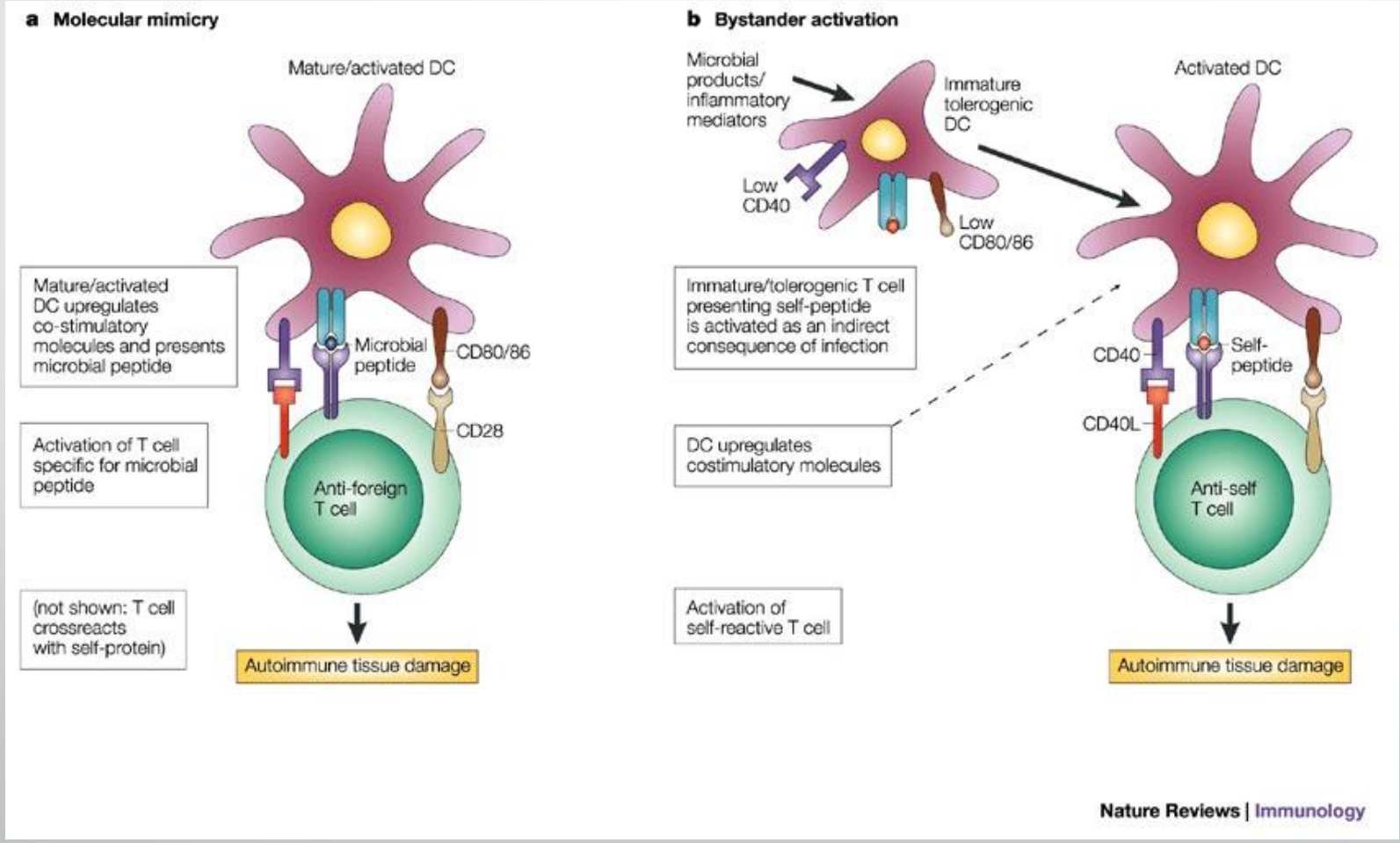
Cofactors – Peeling the Onion

- Immunological alterations
  - Mimicry
  - Role of microbiome
- Malnutrition
- Stress/Trauma
- Environmental Factors

Immune Alterations

- Abnormal natural killer cell cytotoxicity, increase immune activation markers, greater numbers of CD16+/CD3–natural killer cells, and the presence of interferon in serum and cerebrospinal fluid in CFS patients have been identified.
- Staines suggested the loss of immunologic tolerance to vasoactive neuropeptides or their receptors following infection, other events, or de novo as a mechanism.

Molecular Mimicry

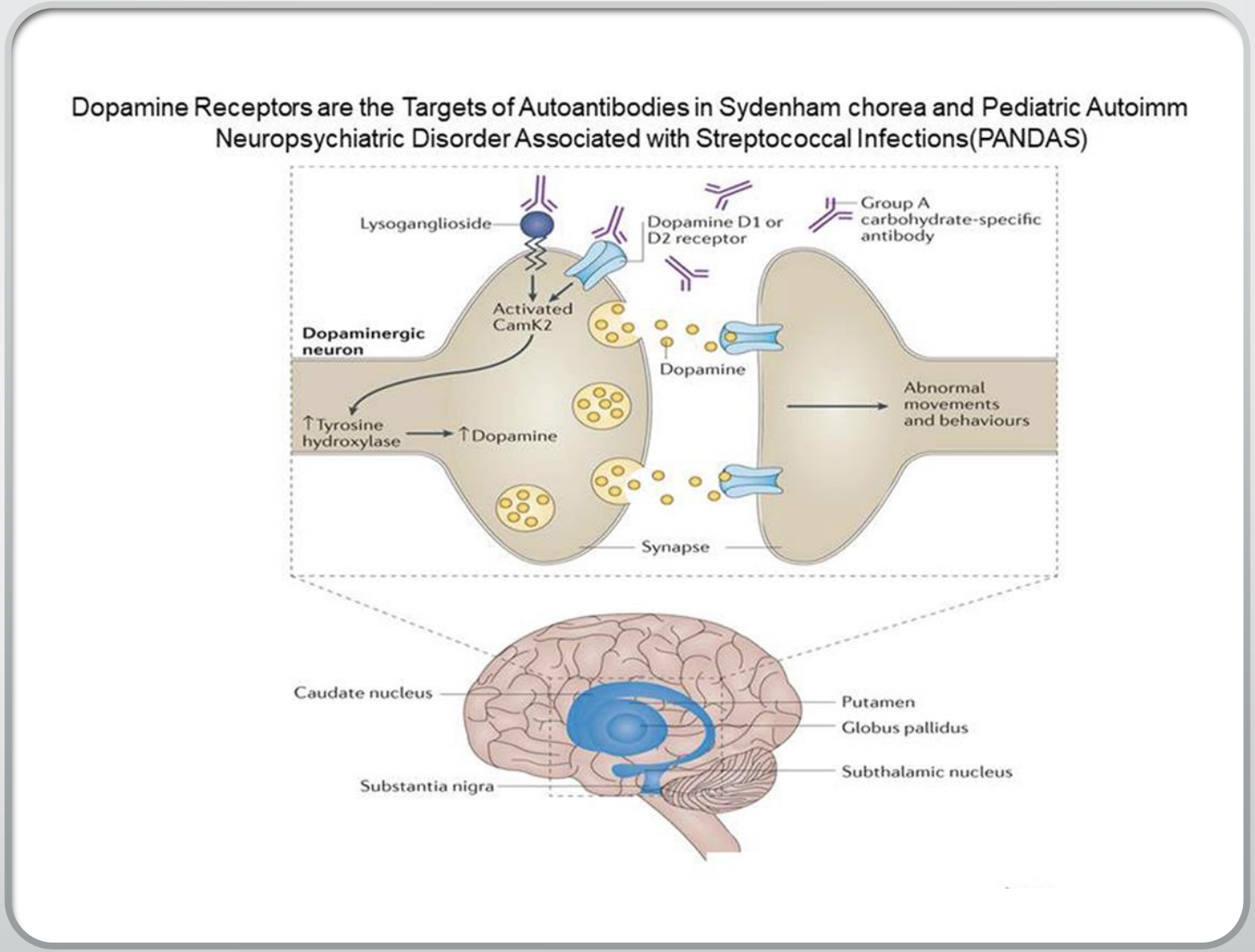


Molecular Mimicry and Autoimmunity

AUTOIMMUNE DISEASE	SELF ANTIGEN	PATHOGEN MIMETIC
Rheumatic fever	Cardiac myosin, tropomyosin laminin, vimentin, actin, keratin, *N*-acetyl-glucosamine	*Streptoccocus pyogenes* M protein and N-acetyl-glucosamine
Guillain-Barre'	Gangliosides	lipo-oligosaccharide of *Campylobacter jejuni*
Multiple sclerosis	Myelin basic protein (MBP)	Corona, measles, mumps, EBV, human herpes Semliki Forest Virus (SFV) E2 peptide 115–129 Acanthamoeba castellanii (ACA)
Experimental autoimmune encephalomyelitis	Myelin oligodendrocyte glycoprotein (MOG) 18–32	
	Myelin proteolipid protein (PLP)peptide 139–151; MBP89-101	
Myasthenia gravis	Acetylcholine receptor, neurofilaments	Herpes virus, *Hemophilus influenzae*
Chagas' cardiomyopathy	Human beta 1-adrenergic receptor; Cardiac myosin, Cha antigen Common glycolipid antigenson nervous tissue	*Trypanosoma cruzi*-Ribosomal P0; B13 protein; -shed acute-phase antigen (SAPA) ; 160-kDa flagellum; -trypomastigote stage-specific glycoprotein
Systemic lupus erythematosus	Ro 60 kD, Sm, NMDA, dsDNA	EBV,HERV, pneumococcal polysaccharide
Antiphospholipid syndrome	β2-glycoprotein-I	*Hemophilus influenza*, *Neisseria gonorea*, Tetanus toxin, CMV
Ankylosing spondylitis	HLA-B27, type I, II, IV collagen	*Klebsiella pneumoniae*, chlamydia
Lyme arthritis	*DRB1*0401* or *HLA-DRB1*0101* alleles. Human leukocyte function–associated antigen1α (hLFA-1)	*Borrelia burgdorferi* (outer surface protein A - OspA)

Molecular Mimicry Strep

- Auto-antibodies against brain tissues in Sydenham chorea and PANDAS with piano-playing choreiform movements cross-react with the group A streptococcal carbohydrate, lysoganglioside, and dopamine receptors D1R and D2R.



Molecular Mimicry SARS-COV-2

Table 1. Molecular mimicry of the S-protein with autoantigens of type 1 diabetes mellitus.

Langerhans' Islets β-Cell Autoantigens	Shared Pentapeptides
PTPRN (Q16849)	LPPLL
Islet cell autoantigen 1 (Q05084)	GYQPY, LDPLS
GAD67 (Q99259)	AGAAL, VGYQP
Carboxypeptidase H (P16870)	SALLA

Table 2. Molecular mimicry of the S-protein with the Addison's disease autoantigen.

Autoantigen of Adrenocorticocytes	Shared Pentapeptides
CYP21A2 (P08686)	LQDVV

Table 3. Molecular mimicry of the S-protein with the autoantigens of autoimmune thyroid disease.

Thyroid Autoantigens	Shared Pentapeptides
Thyroid peroxidase (P07202)	RAAEI
Thyrotropin receptor (P16473)	ICGDS, LLPLV
Thyroglobulin (P01266)	FNFSQ, SAIGK, LDSKT

Table 4. Molecular mimicry of the S-protein with a pituitary autoantigen.

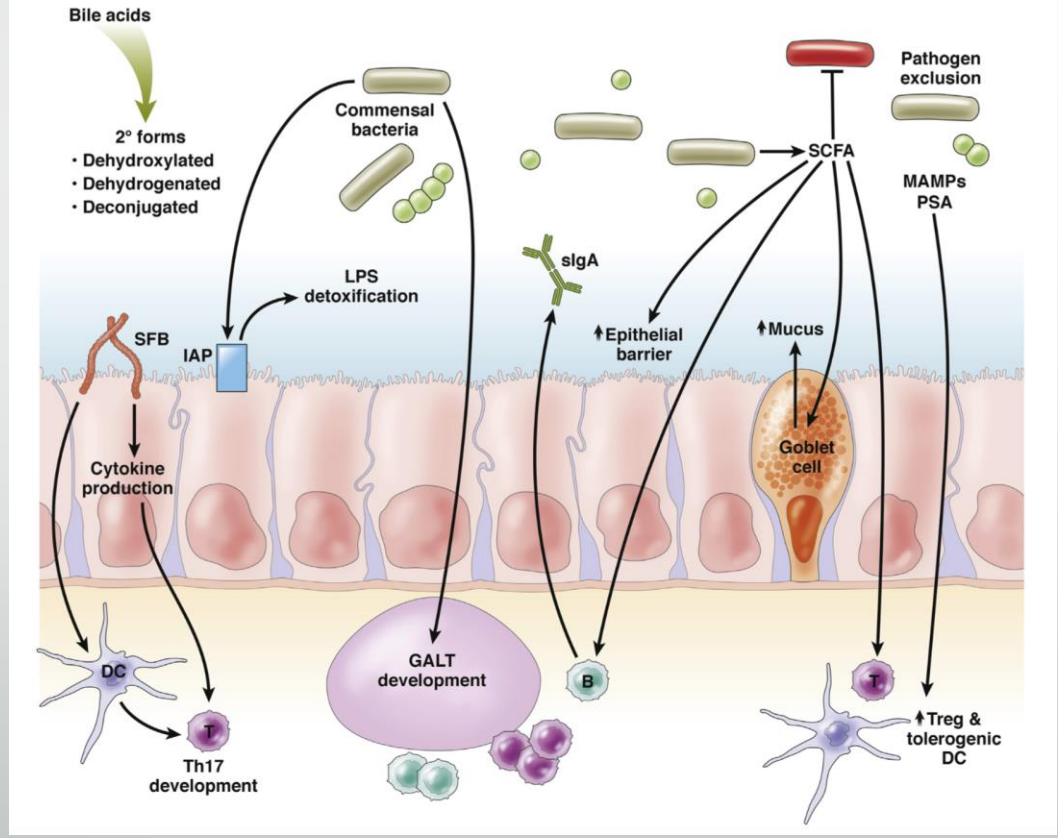
Pituitary Autoantigen	Shared Pentapeptide
Prolactin (P01236)	SNLLL

Other tasted pituitary autoantigens did not share any pentapeptides with the SARS-CoV-2 S-protein.

Table 5. Immunoreactive SARS-CoV-2 spike glycoprotein-derived epitopes containing pentapeptides shared between the S-protein and human endocrinocytes proteins.

IEDB ID of an Immunoreactive Epitope	Epitope Sequence
1125063	gltv**LPPLL**
1309589	sygfqptngv**GYQPY**rvvvl
1074866	ca**LDPLS**etk
531783	g**AGAAL**qipfamqma
1310448	gk**LQDVV**nqnaqaln
100428	qli**RAAEI**rasanlaatk
1310877	vdctmy**ICGDS**tecs
1071273	**LLPLV**ssqcvnlttr
1087679	pikdfgg**FNFSQ**ilpdps
1071651	nqfn**SAIGK**iqdsls
1075075	t**LDSKT**qsl
1069347	dstec**SNLLL**qygsf
1496254	qyt**SALLA**gtit
1309589	sygfqptng**VGYQP**yrvvvl

Bowel and Immune Tolerance

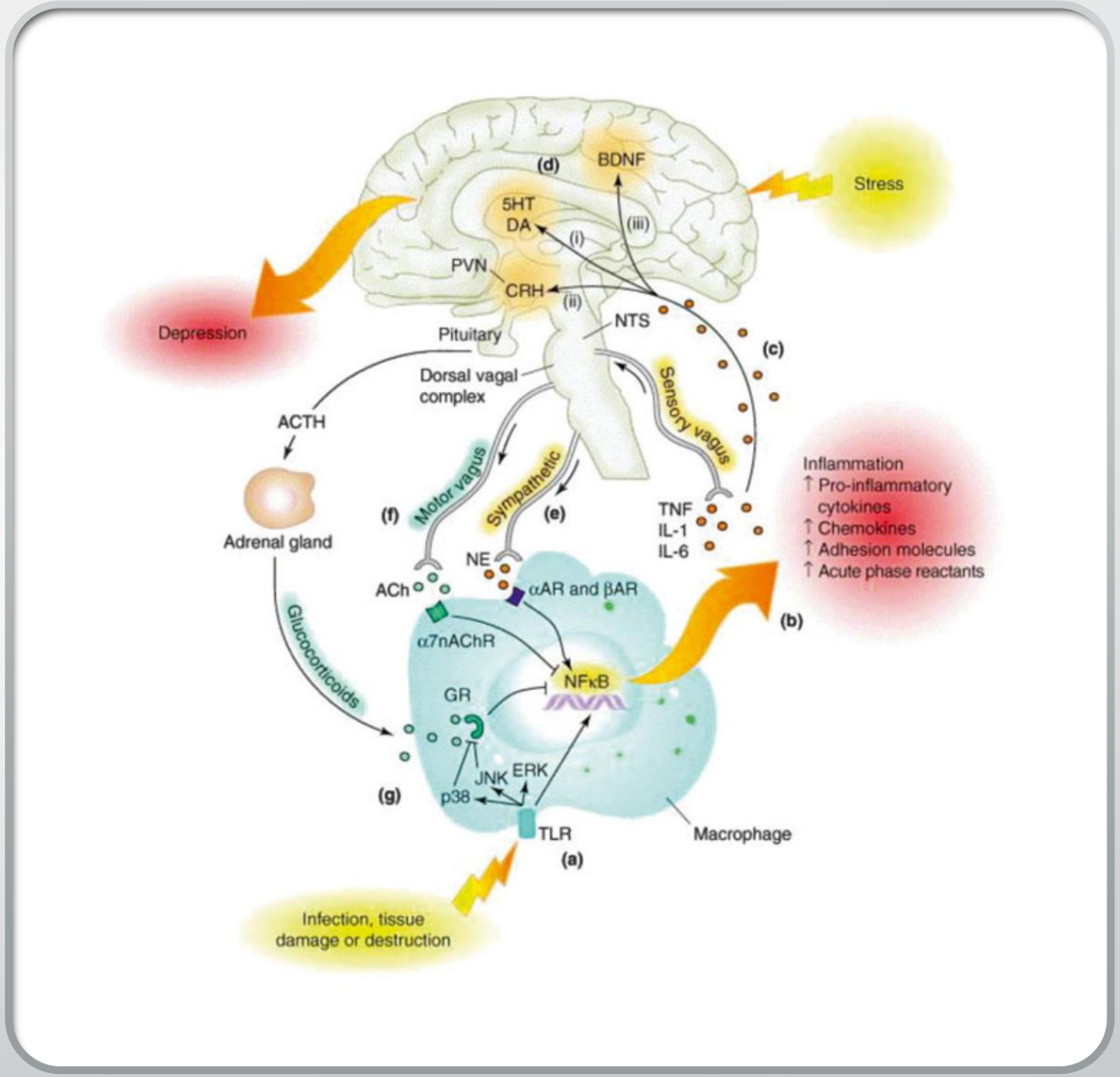


Causes

- Insufficient nutritional intake
- Insufficient absorption
- Increased demands due to:
  - Infection
  - Immune activation
  - Altered oxidation status

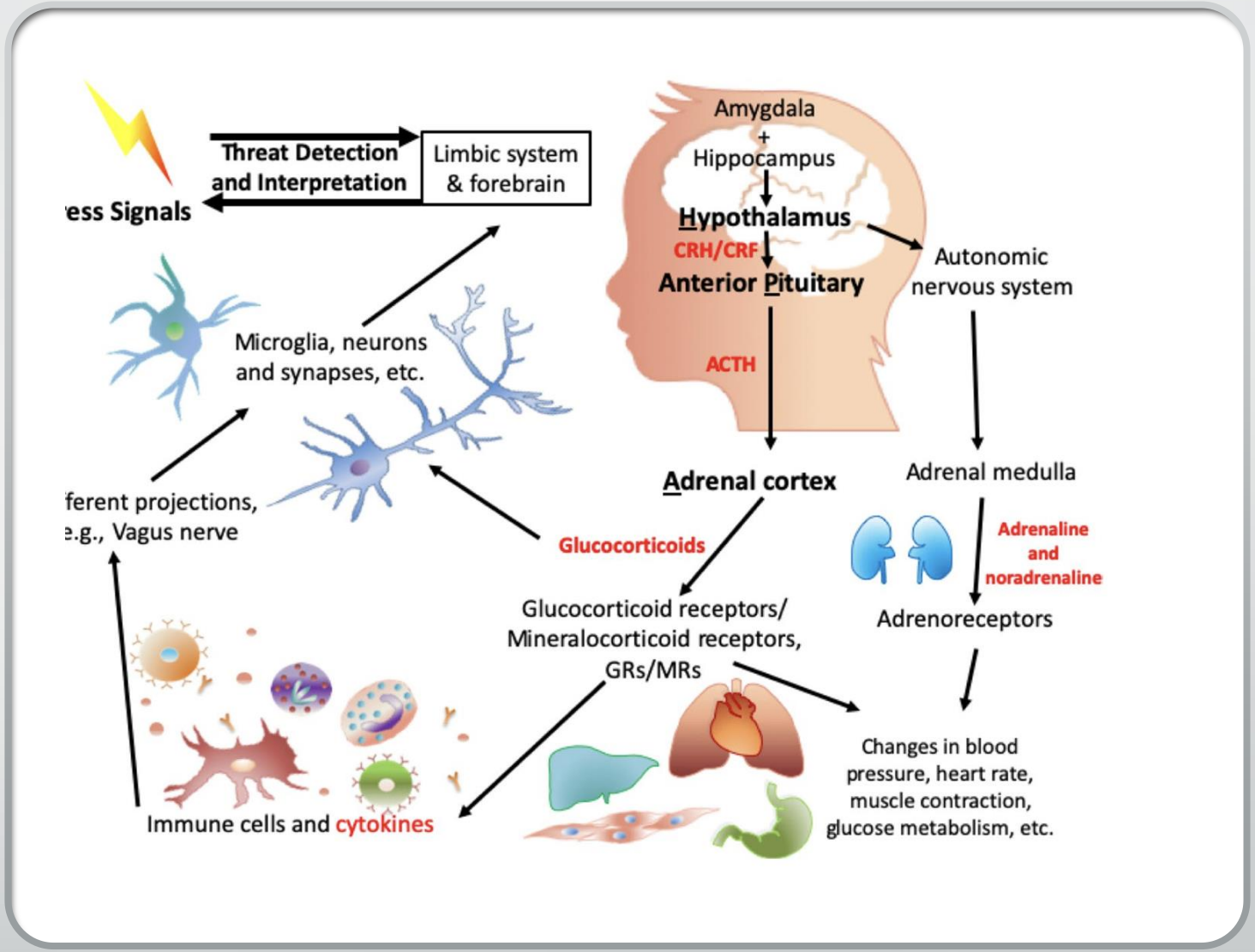
Stress and Immunity

- Chronic stress leads to:
  - Increase in pro-inflammatory cytokines
  - Increased chemokines
  - Increase in acute phase reactants
- Increases potential for overactive immune responses



Epigenetic Effects of Trauma

- FKBP5 – HSP90
- NR3C1 – GR
- HTR – Serotonin receptors
- BDNF



Assessments

- Cortisol am/pm serum
- Salivary (I prefer serum)
- DHEAS
- TSH, T_3, T_4
- Reproductive Hormones (including androgens)

Role of Co-Infection in long-haul illnesses Think CFS/ME

- Possible infectious etiologies have generated the most interest among CFS researchers.
- infectious agents have been linked to ME/CFS, including Borna disease virus, parvovirus B19 glandular fever, Enterovirus, human herpesviruses 4, 6, and 7, infectious mononucleosis, Nipah virus encephalitis, and fever
- Mycoplasma can lead to worsening/lengthened illness with SARS-Cov-2 and Sars COV-2 can reawaken preexisting viral illnesses
- Infections have not only played important etiologic roles, but also have been considered predictors of better prognoses when compared to noninfectious CFS cases
- Human herpesvirus 6 reactivation has been suggested as an objective biomarker for fatigue.

Coinfection Assessments

- Laboratory:
  - Measurements of Ab's (prior infection likely stealth incubation)
  - Western Blot (lyme) + other Armin/Igenx
  - RT PCR for identification of active infection
  - Stool PCR testing

Nutritional Deficiency

- Zinc and Selenium deficiency seem to predispose to long-haul illness
- Common nutritional deficiencies found in Chronic infection/Long-haul patients:
  - B Vitamins: **pyridoxine**, **cobalamin**, riboflavin and thiamine
  - Vitamin C
  - Vitamin D
  - Magnesium
  - Carnitine
  - Coenzyme Q10

Assessment

- Diet Diary
- Assume deficiency
- Serum/RBC elements/Urine (accuracy is questionable)

Environmental Aspects of Fatigue

Mercury

- Mercury is well known to be a neuro, immuno, cardio and endocrine disruptor
- Mercury increases ROS in the nervous system
- It can also alter the release of neurotransmitters like dopamine, acetylcholine, norepinephrine and serotonin
- Methyl mercury is a main cause of this
- Mercury can also lead to increased ROS in the cardiovascular system and is associated with increased risk of CVD

Mercury Tissue Effects

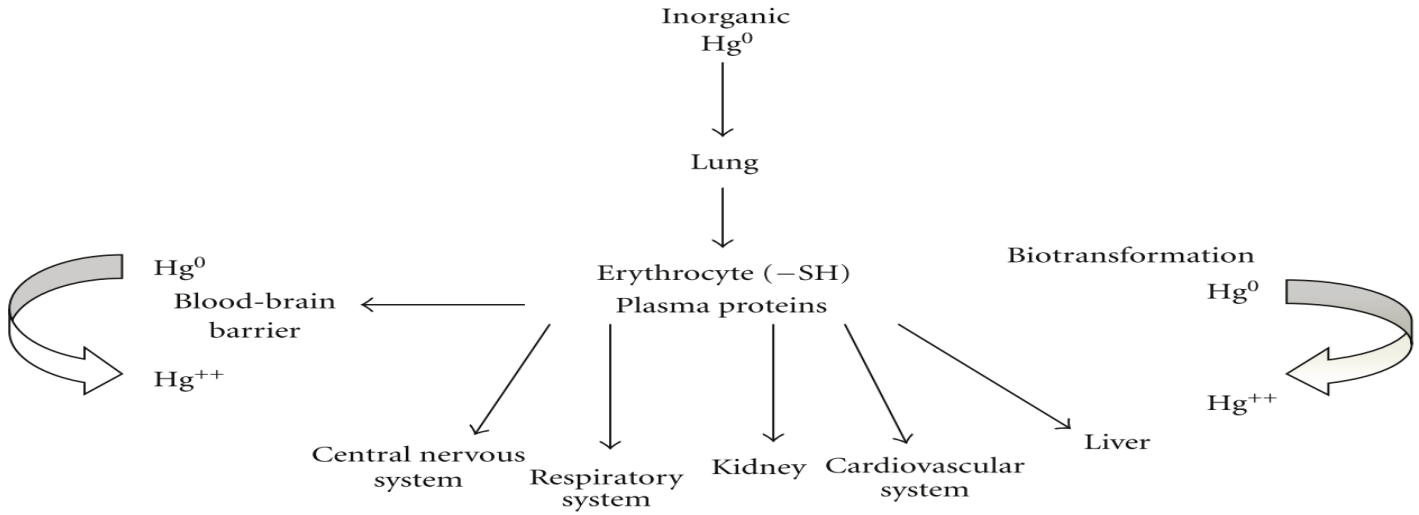


FIGURE 1: Scheme showing the entry of elemental mercury in organisms and their distribution in different organs.

Mercury Effects

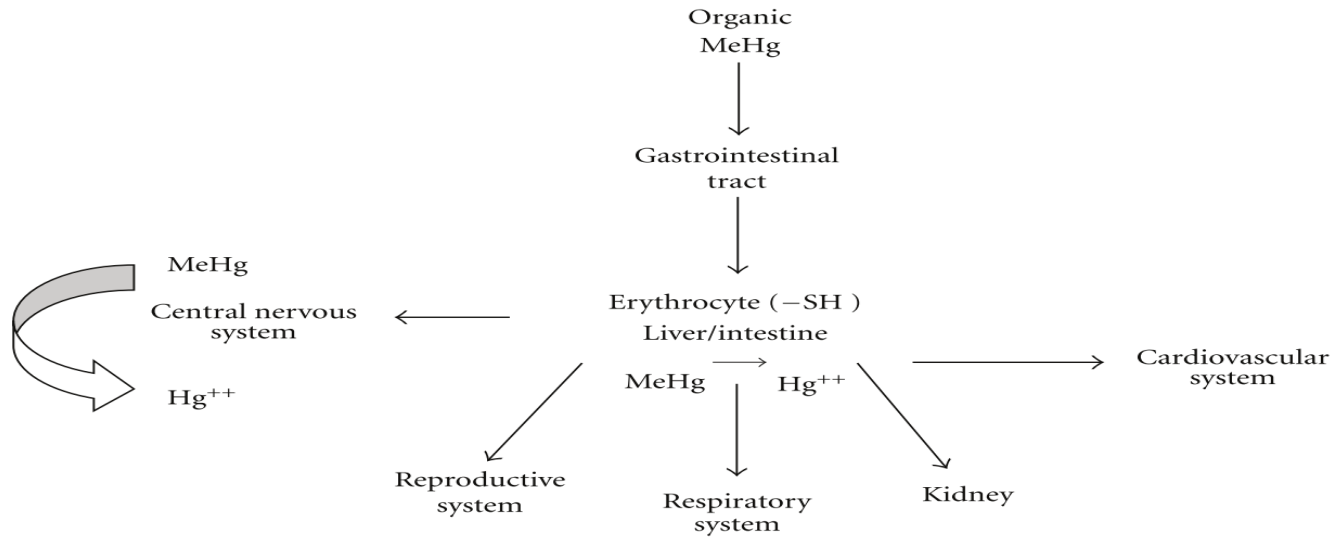


FIGURE 2: Scheme showing the entry of organic mercury in organisms and their distribution in different organs.

Lead Effects

- Encephalopathy is a known consequence of lead exposure. Symptoms include:
  - symptoms include dullness, irritability, poor attention span, headache, muscular tremor, loss of memory and hallucinations

Table 1. Types of lead poisoning.

	Exposure	Lead levels (µg/dl)	Clinical symptoms
Acute poisoning	Intense exposure of short duration	100–120	Muscle pain, fatigue, abdominal pain, headache, vomiting, seizures and coma
Chronic poisoning	Repeated low-level exposure over a prolonged period	40–60	Persistent vomiting, encephalopathy, lethargy, delirium, convulsions and coma

Lead Effects

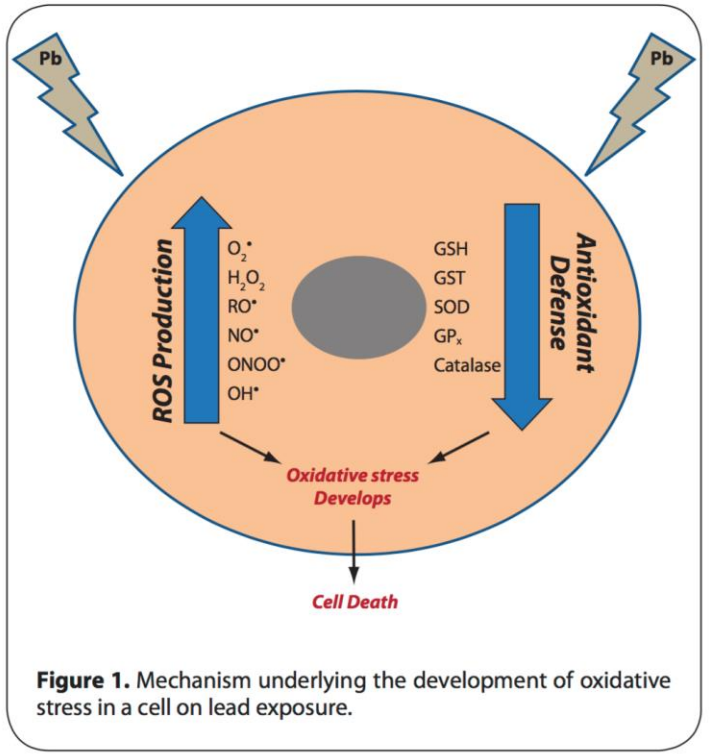


Figure 1. Mechanism underlying the development of oxidative stress in a cell on lead exposure.

Cadmium Effects

- Similar to Hg and Pb, Cd increases neuronal death through ROS induced apoptic and necrotic pathways
- Fatigue and lassitude is a common symptoms expressed in worker with high exposure to cadmium containing metal alloys
- Association studies are currently being done to elucidate a potential link

Exposure: Mercury

- electrical equipment (thermostats, switches), electrical lamps, thermometers, sphygmomanometers, barometers, dental amalgams, CFLs
- pharmaceutical applications – used as preservatives (eg. thimerosal, phenylmercuric acetate), topical antiseptics (eg. merbromin)
- cosmetic skin creams (skin lightening creams) from other countries other than US
- folk medicines
- released into the air from combustion of fossil fuels (primarily coal), solid-waste incineration, mining and smelting
- dietary sources: fish and seafood, HFCS, agave
- red ink tattoos
- wild fires

Exposure: Lead

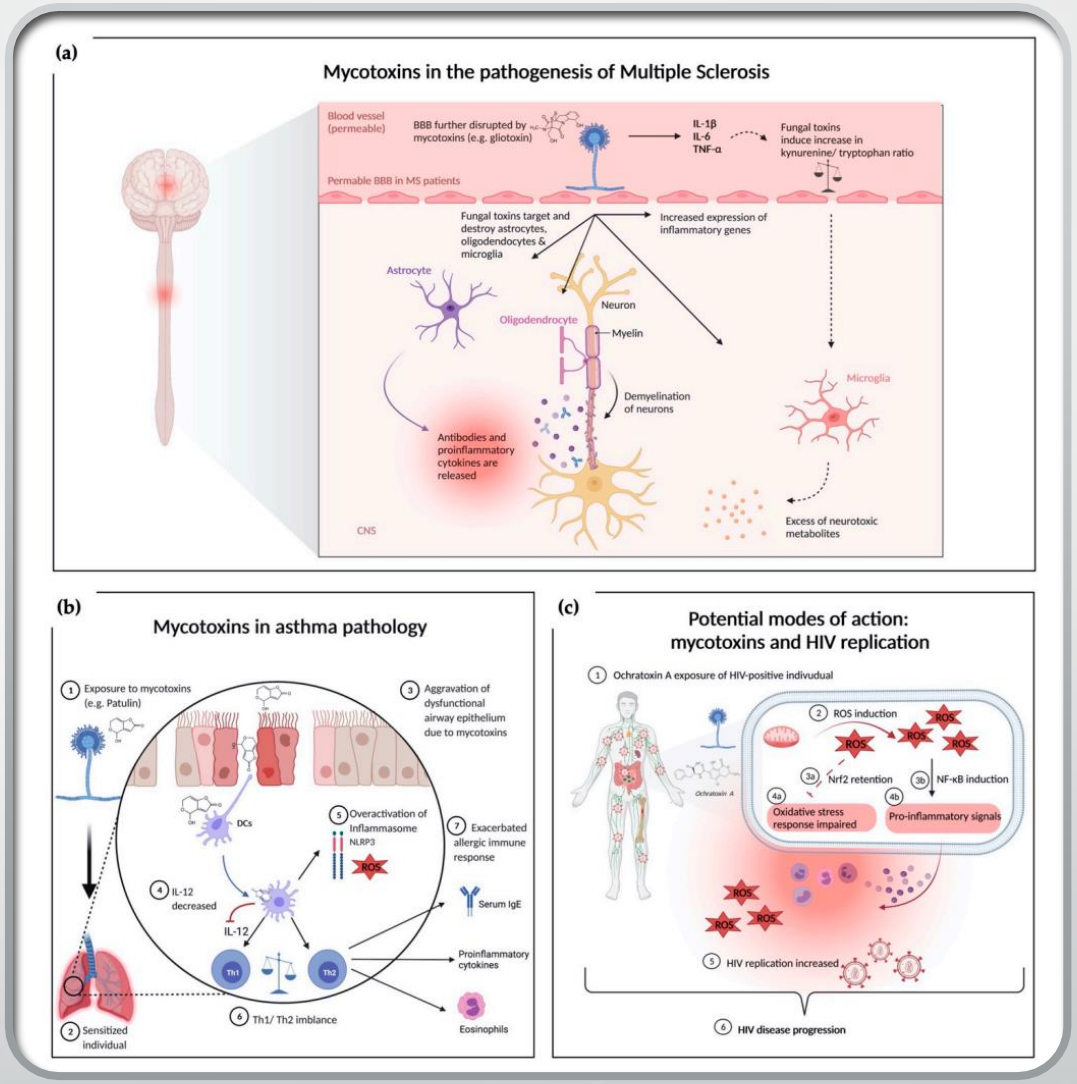
- manufacture of storage batteries, solders (esp. electrical components and automobile radiators), metal alloys (incl. brass, bronze, and certain types of steel), plastics, leaded glass, ceramic pottery glazes, ammunition; antique-molded or cast ornaments, shielding used as protection from radiation sources
- metallic-coated tableware, mugs, lead crystal
- in the past, lead was added to residential paints (before 1978) and gasoline (before late 1970's), used in plumbing for centuries
- burning fossil fuels
- deteriorated lead based paints → dust and soil contamination
- pewter utensils and drinking vessels
- plumbing systems with lead-soldered joints
- lead containing Chinese and Ayruvedic medicines
- bullet fragments retained in human tissue
- lead contaminated dust in indoor firing ranges
- cosmetics – lipstick (61% of lipsticks)
- soft vinyl lunch boxes
- mini-blinds from Mexico before 1996
- imported wines
- soldered joints in kettles
- printing industry

Exposure: Cadmium

- By-product during processing of zinc-containing ores, and to lesser extent during refining of lead and copper from sulfide ore
- Predominant commercial use of cadmium is the manufacture of batteries (78%); pigments (12%); coatings and platings (8%); stabilizers for plastic (PVC products (1.5%)
- from 2001-2004 commercial emissions from secondary lead smelting, primary lead production, hazardous and municipal waste incineration, petroleum refining
- cigarette smoke
- phosphate fertilizers
- gutta perch used to seal main canals after nerves removed in root canals
- cereal grains, wheat, rice, potatoes, various seeds

Mold – a hidden primer

- Neuroinflammation and increased porosity of BBB
- Induction of proinflammatory cytokines
- Increased ROS through upregulation of Nrf2 and NFKB
  - Increased viral load



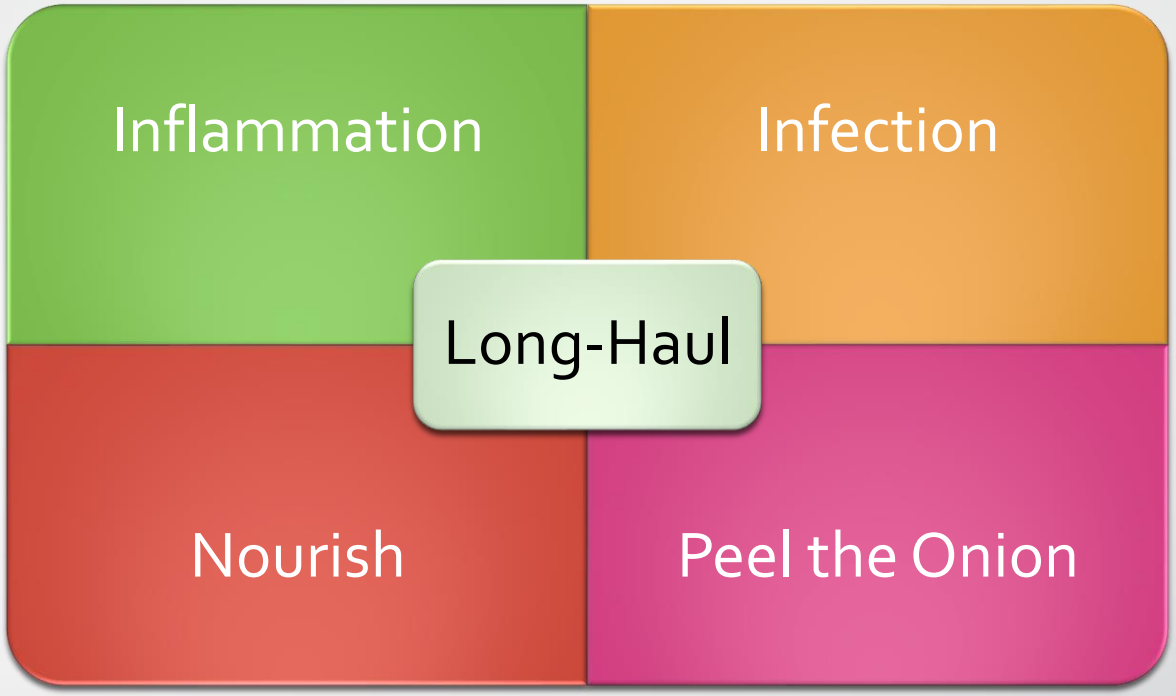
Assessment

- Exposure history assessment
- Random and provoked toxic metal urinalysis
- Hair toxic metal analysis

Treatment of Infectious Long-Haul Disease/Post Covid Syndrome with IVIT

Long-Haul Treatment Strategy

- Modulate inflammation
- Clear/Resolve persistent infections/co-infections
- Address underlying factors
  - Intestinal dysfunction
  - Environmental exposures
  - Neural dysregulation
- Restore adequate nutrition



Treatment of CFS Long-Haul with IVIT

- IVIT is a treatment option for Chronic Sequelae of Infectious illness as a component of a comprehensive program including:
  - Diet
  - Physical Activity
  - CBT Treatment
  - Off-label medications
  - Oral supplementation
  - Etc.

IV Therapeutics

Vitamin C

Immune Effects of Ascorbic Acid

- AA deficiencies result in well known immune alterations
- Increase in NK Cell activity (at 60 mg/kg) for up to 48 hours post infusion in healthy subjects
- Increased phagocytic activity of macrophages
- AA enhances immunoglobulin production increasing humoral immunity

Anti-Viral Effects of Vitamin C

- Vitamin C had been used with some success, prior to the advent of antibiotics and vaccines, for infections like polio, diptheria, coxsackie, etc.
- ROS generated by higher dose vitamin C are the main potentials for anti viral effects

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High Dose Intraveneous Vitamin C and Chikungunya Fever: A Case Report

Michael J. Gonzalez, NMD, DSc, PhD, FANMA, FACN[1], **Jorge R. Miranda-Massari, PharmD**[2], **Miguel J. Berdiel, MD**[3], **Jorge Duconge, PhD**[2], **Joshua L. Rodríguez-López, BS**[4], **Ron Hunninghake, MD**[5], and **Vicente J. Cobas-Rosario, BS**[6]

[1]University of Puerto Rico Medical Sciences Campus, School of Public Health

[2]School of Pharmacy

[3]Pontifical Catholic University of Puerto Rico, Biology Department

[4]Ponce School of Medicine

[5]Riordan Clinic

[6]Rio Piedras Campus, Biology Department, Ponce School of Medicine

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CASE REPORT

Intravenous vitamin C as adjunctive therapy for enterovirus/rhinovirus induced acute respiratory distress syndrome

Alpha A Fowler Ⅲ, Christin Kim, Lawrence Lepler, Rajiv Malhotra, Orlando Debesa, Ramesh Natarajan, Bernard J Fisher, Aamer Syed, Christine DeWilde, Anna Priday, Vigneshwar Kasirajan

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Effect of high dose vitamin C on Epstein-Barr viral infection

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Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

ACDE **Nina A. Mikirova**
A **Ronald Hunninghake**

Bio-Communication Research Institute, Riordan Clinic, Wichita, KS, U.S.A.

Corresponding Author: Nina A. Mikirova, e-mail: nmikirova@riordanclinic.org
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RESEARCH Open Access

Phase I safety trial of intravenous ascorbic acid in patients with severe sepsis

Alpha A Fowler III[1*], Aamer A Syed[1], Shelley Knowlson[2], Robin Sculthorpe[3], Don Farthing[4], Christine DeWilde[1], Christine A Farthing[4], Terri L Larus[4], Erika Martin[5], Donald F Brophy[5], Seema Gupta[6], Medical Respiratory Intensive Care Unit Nursing[2], Bernard J Fisher[1] and Ramesh Natarajan[1]

Effects of IV Vitamin C in Sepsis

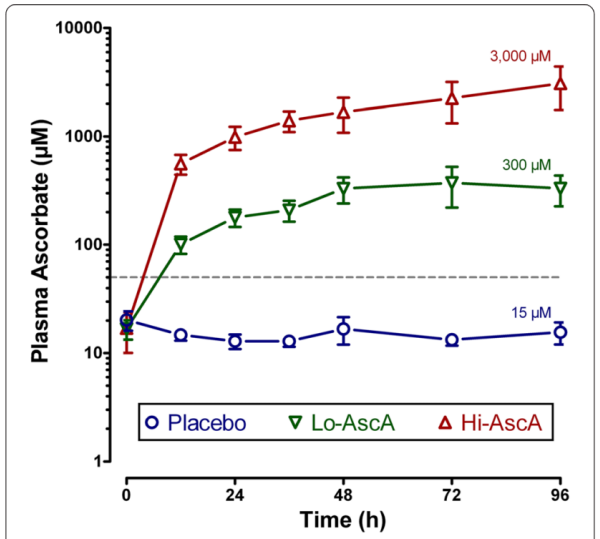


Figure 1 Plasma ascorbic acid levels following intravenous infusion of ascorbic acid. Plasma ascorbic acid levels were subnormal at entry (<50 μM, dotted line). Ascorbic acid levels rose rapidly in the two treatment groups and were significantly higher than placebo within twelve hours (Lo-AscA vs. placebo $p < 0.005$, Hi-AscA vs. placebo $p < 0.0005$) remaining consistently elevated for 96 hours. Ascorbic acid levels in the Hi-AscA group were significantly higher than the Lo-AscA group from the 12 hour point forward. These data show that an intermittent ascorbic acid infusion protocol (every 6 hours) produces sustained steady state levels in patients with severe sepsis. Placebo (O), Lo-AscA (▼), Hi-AscA (▲).

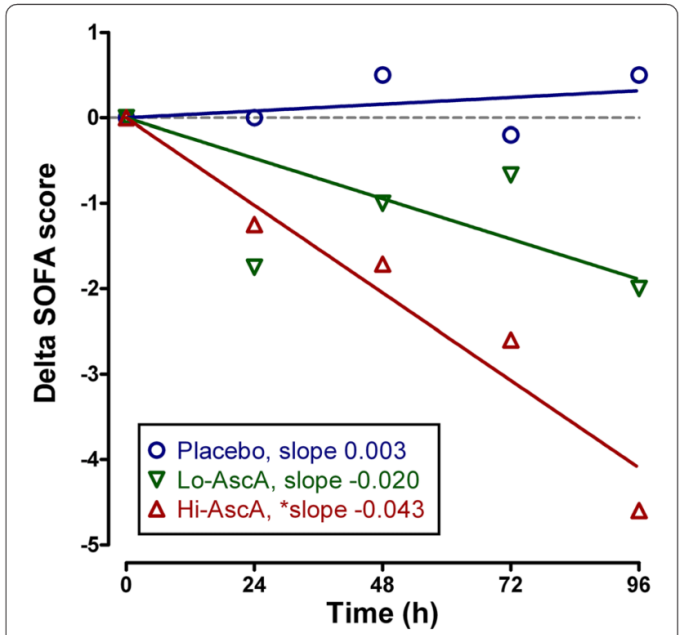


Figure 2 Effect of ascorbic acid infusion on Sequential Organ Failure Assessment (SOFA) score (days 0–4). Daily mean SOFA scores decreased over time with both doses of ascorbic acid infusion ($p < 0.05$ significantly non-zero) with the higher dose significantly less than placebo (Hi-AscA vs. placebo $p < 0.01$). Placebo (O), Lo-AscA (▼), Hi-AscA (▲).

IV Vitamin C Protocols for Infection

- There are 2 strategies for using IV Vitamin C for infection support
  - Antimicrobial (reduce infectious agent load)
  - Antioxidant (reduce infection agent/immune response impact on body systems)
- Antimicrobial - Higher vitamin c dose strategy 10-50 g/session
- Antioxidant lower dose vitamin c strategy 1-10 g per session
- Use functional status as an indicator for choice of strategy
  - e.g. patients with poorer functional status start with antioxidant protocol

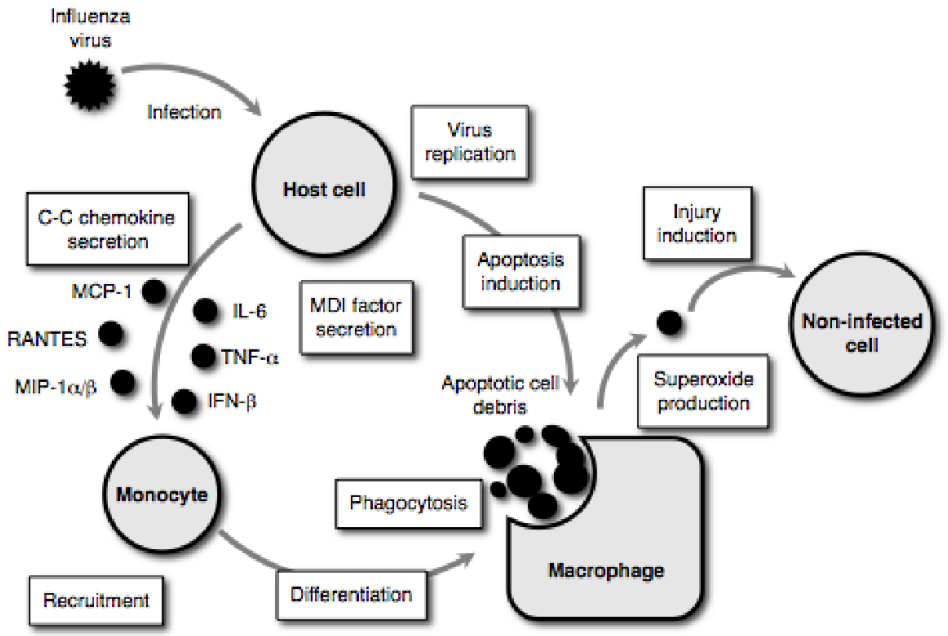
IV Vitamin C Protocols for Infection

- Antioxidant
  - 5-10 g vitamin c along with other anti-oxidant therapeutics (e.g. selenium, glutathione) (see formulations section)
  - Given up to daily in patients
- Antimicrobial
  - 10-50 g vitamin C alongside minerals for repletion (see formulations section)
  - Give to patients up to daily

Glutathione

Oxidation and Infection

Figure 2. Tissue injury model during influenza virus infection.



Glutathione and Influenza

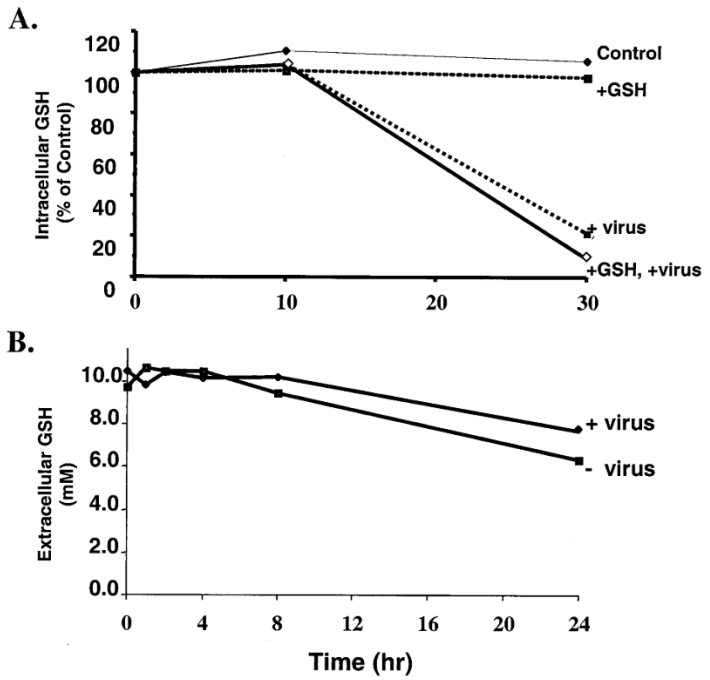


Fig. 4. Effect of influenza infection on cellular GSH. GSH was measured in MDCK cells after infection either with or without the addition of 10 mM GSH. Values are means of two separate experiments with triplicate for each condition.

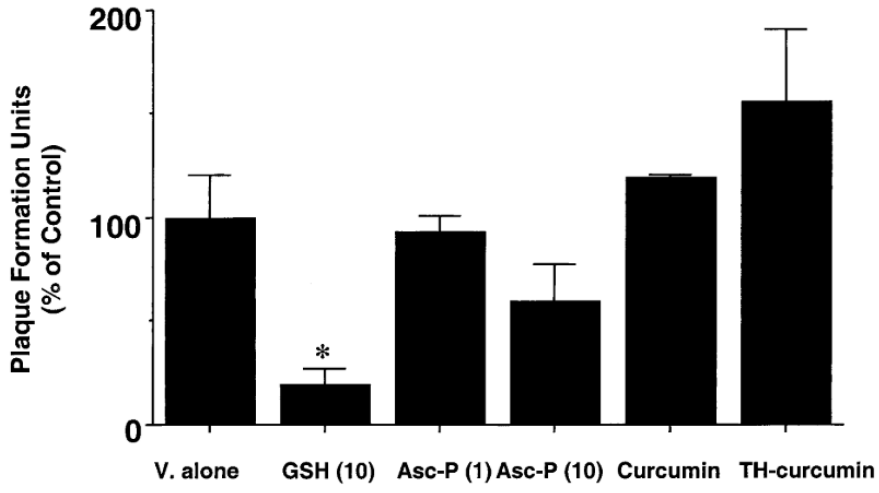
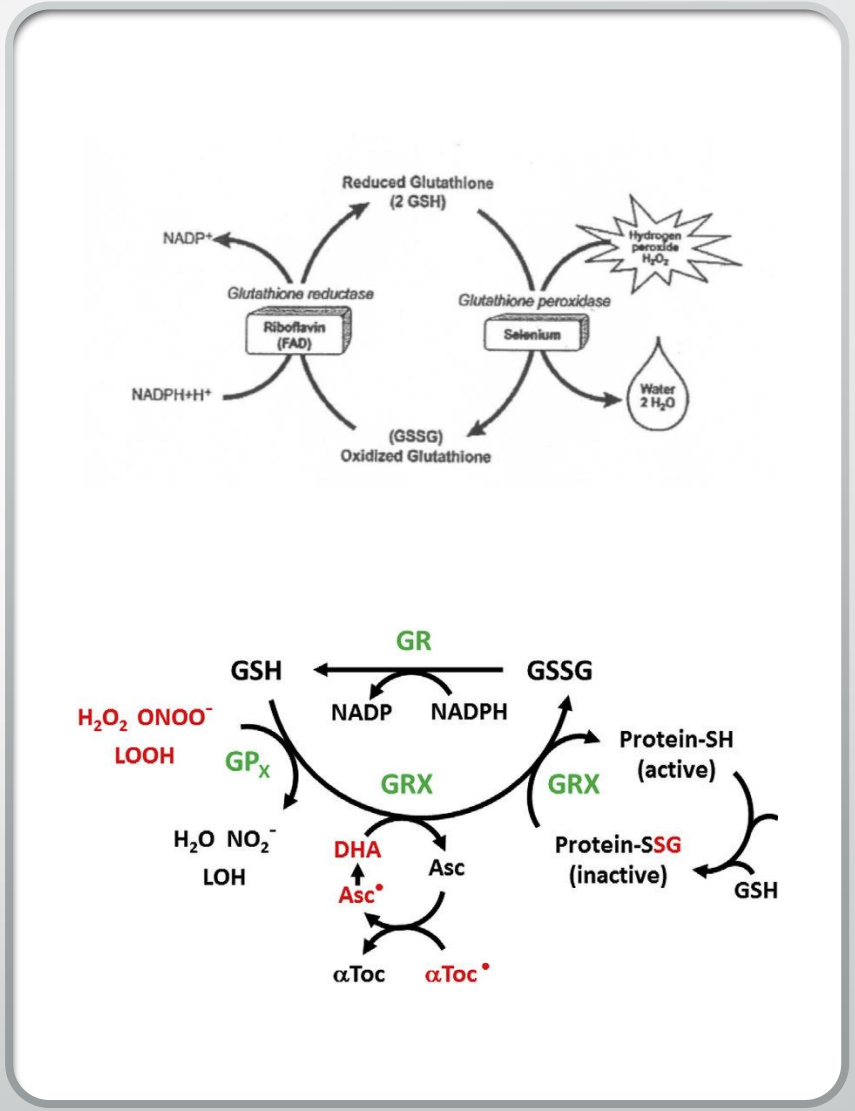


Fig. 10. Effect of other antioxidant compounds on influenza viral production in vitro. After viral inoculation, MDCK cells were cultured for 2 d in the presence of different compounds. Active virus in the medium was measured with plaque assay and normalized to virus alone. GSH (10) = 10 mM GSH; Asc-P (1) and (10) = ascorbate phosphate at 1 mM and 10 mM; TH-curcumin = tetrahydrocurcumin. Data presented are representative of two separate experiments. *Significant at $p < .05$, one-way ANOVA.

Glutathione support (including imaging)

- Approach popularized by Dr. Paul Anderson to improve tolerance and efficacy of glutathione infusions
- Administered a preload of nutrients aimed to support glutathione recycling through:
  - GPx
  - GRx
- Effective to minimize intolerance to glutathione we see in certain patients



Glutathione Effects Relevant to Infectious Disease

- Direct viral inhibition (studies on Influenza strains and HIV)
- Stabilization of leukocytes and improved phagocytosis
- Reduction in overactive inflammatory responses

- Dosing
  - 1,000 – 4,000 mg up to daily with pre-load formulation

Glutathione support

PRELOAD TO ADMINISTER PRE-GLUTATHIONE (30-45 MINUTES)

Formula: Radiation Recovery Formula				
Nutrient	mg/mL	CC	mOsmol/mL	mOsm*vol
Ascorbic Acid	500	20	5.8	116.00
Calcium Chloride	100	10	2.04	20.40
Magnesium Chloride	200	10	2.95	29.50
Zinc	5	5	0.55	2.75
Selenium	40 mcg			
B-Complex 100	n/a			
Dexapanthenol	250			
Pyridoxine	100	1	0.66	0.66
Sodium Bicarbonate	8.40%	25	2	50.00
Sterile Water	0	500		0.00
Total		584		224.12
	Final Osmolality:			383.77

Not on the same day as HDIVC

GLUTATHIONE RAPID DRIP/PUSH ADMINISTERED POST PRELOAD

Formula: Glutathione Push				
Nutrient	mg/mL	CC	mOsmol/mL	mOsm*vol
Glutathione	200	5-10		0.00
0.9% normal saline	0.90%	5-10	0.32	n/a
Total				
	Final Osmolality:			

Administer combination 1-2 times per week for 2-4 weeks post radiation based on patient response starting 1 week after radiotherapy or day before and/or after imaging

Hydrochloric Acid

Historic Application of Hydrochloric Acid

- The use of HCl for infection began during the first world war
- It was first applied in a systematic manner by Dr. Ferguson and Dr. Guy
- Their work was not widely published in higher profile journals at the time
- With the advent of antibiotics no further research has been done on this immune agent

Hydrochloric Acid Usage

- HCl is normally strictly buffered in the blood
- When given IV as a bolus, the net effect is release of cytokines, leading to WBC stimulation, increased phagocytosis, release of inflammatory mediators and an up-regulated immune response
- IV HCL can cause transient flu-like malaise, achiness and fever due to cytokine release

Hydrochloric acid Indications

- Used in all infections where there is a route of drainage for the infection byproducts: eg PID, pneumonia
- Influenza, viral infections, staph and strep
- Chronic fatigue syndrome, fibromyalgia
- Any chronic smoldering infection

Hydrochloric Acid Contraindications

- All CI's are due to its strong cytokine releasing/immunostimulatory properties:
  - Autoimmune conditions
  - Patients on immunosuppressive mediations
  - Avoid in dental abcesses, appendicitis (no route of drainage)
  - avoid in leukemias and lymphomas (undesirable to boost WBC)

HCL Side effects

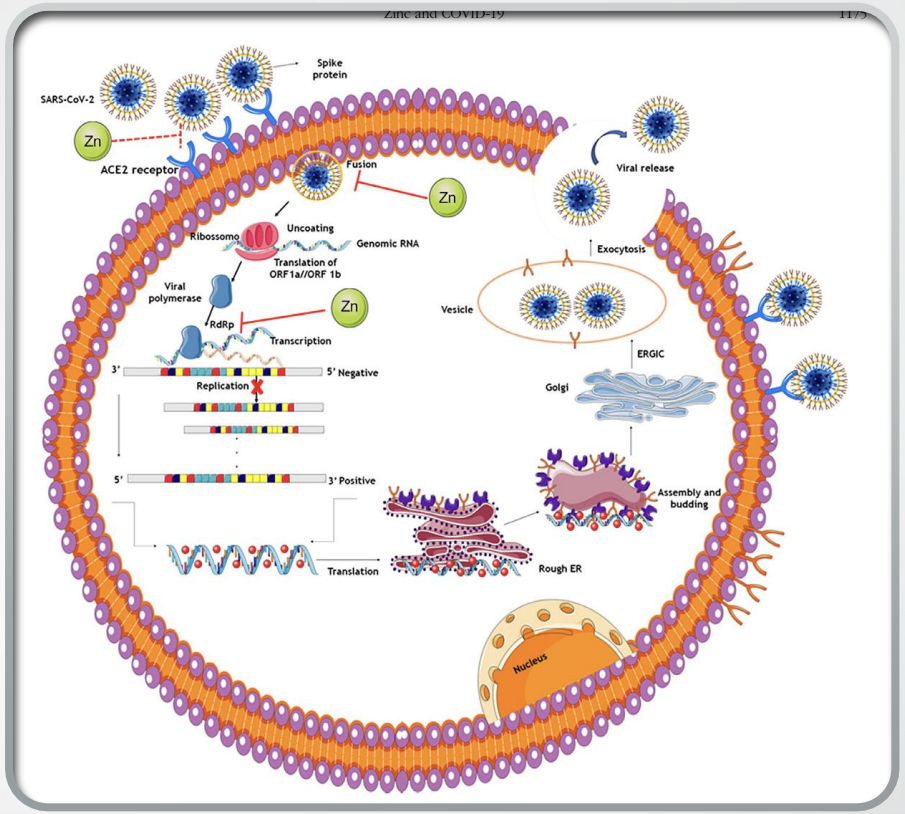
- Most side effects of HCl are related to over stimulation of cytokine release:
  - Fever
  - Malaise
  - Nausea
  - Arthralgia
  - Transient worsening of symptoms associated with infection

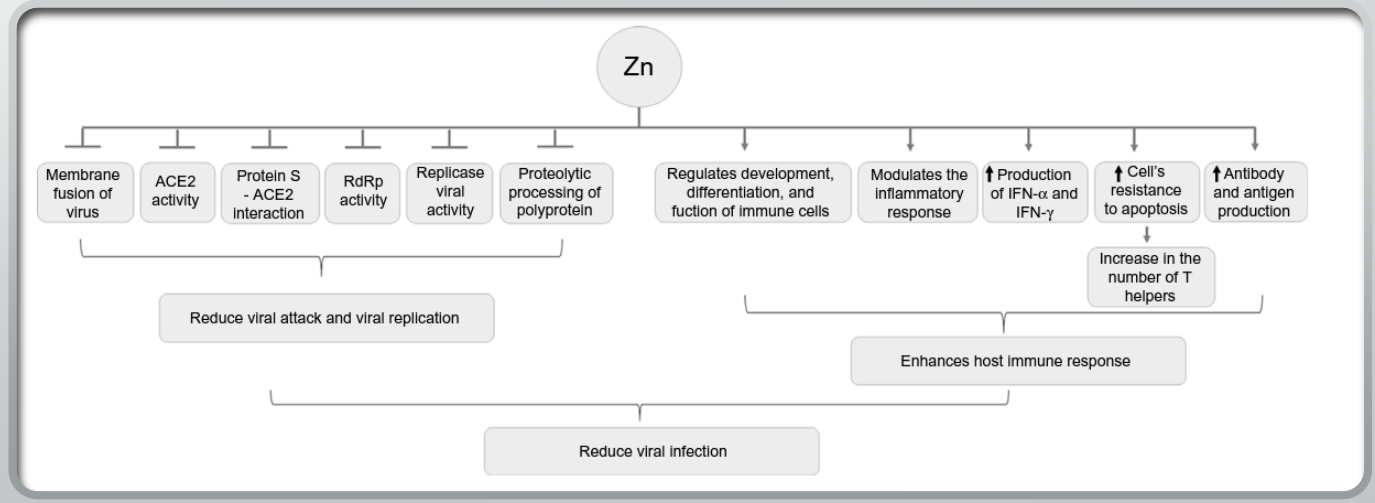
Hydrochloric acid

- Available as 2% solution, 2 mg/ml, 1:500, in a 30 or 50 ml vial, preservative-free
- Can be given as IV push, 2-3 ml, diluted 1:1 in sterile water, at a rate of approx 1 ml per minute
- Also administered as drip, 2-10 ml in IV bag, added near end of treatment into the last 30-50 ml
- Can be added to Myer's cocktail, 5 cc per treatment
- Never administer IM, SC
- May cause discomfort at IV site, phlebitis, and severe pain and tissue damage if infiltrated

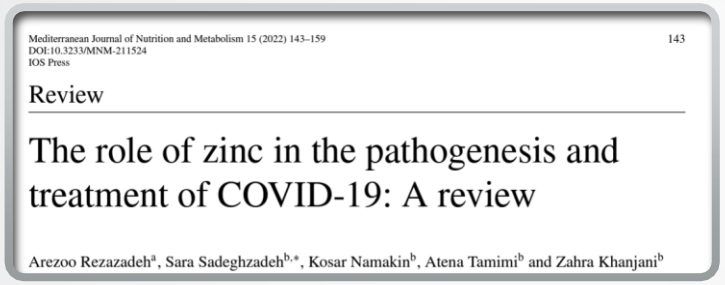
Zinc

Zinc Action on Viral/Immunity





Clinical Trial Data IV Zinc



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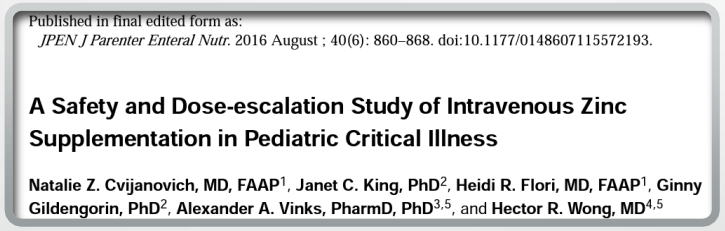
IOS Press

Review

The role of zinc in the pathogenesis and treatment of COVID-19: A review

Arezoo Rezazadeh[a], Sara Sadeghzadeh[b,*], Kosar Namakin[b], Atena Tamimi[b] and Zahra Khanjani[b]



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A Safety and Dose-escalation Study of Intravenous Zinc Supplementation in Pediatric Critical Illness

Natalie Z. Cvijanovich, MD, FAAP[1], **Janet C. King, PhD**[2], **Heidi R. Flori, MD, FAAP**[1], **Ginny Gildengorin, PhD**[2], **Alexander A. Vinks, PharmD, PhD**[3,5], and **Hector R. Wong, MD**[4,5]

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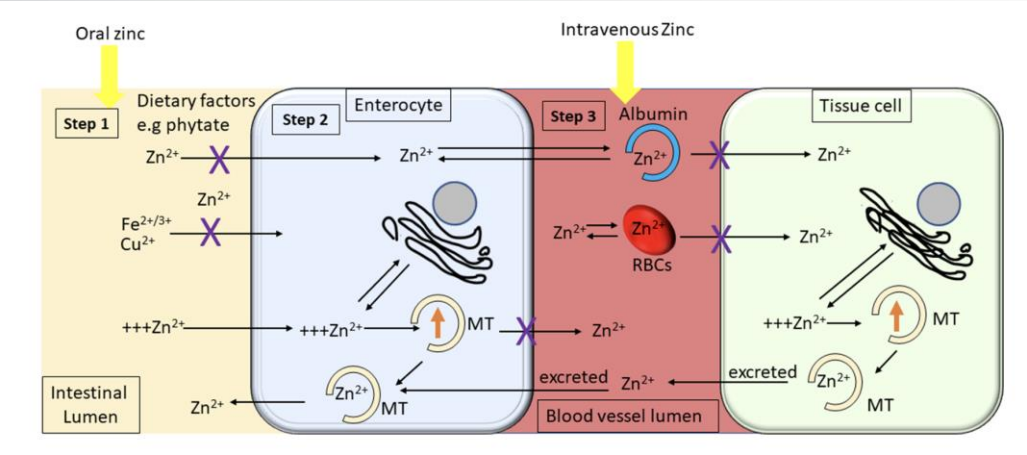
REVIEW ARTICLE

Zinc supplementation as an adjunct therapy for COVID-19: Challenges and opportunities

Vidyasagar Chinni[1,2] | **John El-Khoury**[1,2] | **Marlon Perera**[1,2] | **Rinaldo Bellomo**[3,4] | **Daryl Jones**[1] | **Damien Bolton**[1,2] | **Joseph Ischia**[1,2] | **Oneel Patel**[1]

Why IV Zinc?



- IV administration bypasses steps 1 and 2 which can limit tissue cell absorption and utilization

IV Zinc dosing

- Research in pediatric dosing has shown that 500mcg/kg/day as a safe dose in acute infections
- Doses up to 100 mg have been safely administered in IVs for adults
- We generally administer 20-50 mg/treatment
- Dosing will depend on what you determine is the deficit

IV Infection Foundational Formula (non-febrile)

Formula: Immune Push

Nutrient	mg/mL	CC	mOsmol/mL	mOsm*vol
Calcium Chloride	100	3	2.04	6.12
Magnesium Chloride	200	7	2.95	20.65
Selenium	40 mcg	5	0.005	0.03
Pyridoxine	100	1	0.66	0.66
Dexapanthenol	250	1	1.66	1.66
Hydroxycobalamin	1	1	0.45	0.45
B Complex 100		1	1.44	1.44
Ascorbic Acid	500	4	5.8	23.20
Hydrochloric Acid 1:500		3	0.11	0.33
Sterile Water	0	100	0	0.00
Total		126		54.54
	Final Osmolality:			432.82

IV Infection Foundational Formula (febrile)

Glutathione push post infusion for immune modulation and anti-inflammatory response

Formula: Immune (for viral infection can follow with GZA and/or glutathione)

Nutrient	mg/mL	CC	mOsmol/mL	mOsm*vol
Magnesium sulfate	500 mg	4	4.06	16.24
Selenium	200mcg	1	0.0025	0.00
Zinc	5 mg	1	0.55	0.55
Dexpanthenol	250 mg	2	1.66	3.32
Pyridoxine	100 mg	2	1.11	2.22
Hydroxocobalamin	1 mg	2	0.31	0.62
B-Complex 100		2	1.44	2.88
Ascorbic acid/Sodium ascorbate	500 mg	30	5.8	174.00
0.45% Saline		400	0.145	58.00
Total		444		257.83
	Final Osmolality:			580.70

Immune Support IV Formula Admin Notes

- Commonly used for:
  - Acute, non-urgent/emergent care infections, e.g. viral URTI
  - Chronic infections (EBV, CMV, etc.)
- Frequency:
  - Daily is possible in aggressive settings but caution with the HCl
  - 1-2 times weekly for chronic infections
  - Often more used as needed for patients opting to speed recovery or reduce intensity of illness
- Duration of Treatment:
  - 30 minutes
- Cautions:
  - HCl can exacerbate acute febrile episodes and abscesses use GSH instead (see HCl section)
- Additions
  - GZA can be given in the case of viral illness consecutively after this formula with Glutathione

Tissue and Wound Healing

Formula: Tissue and Wound Healing				
Nutrient	mg/mL	CC	mOsmol/mL	mOsm*vol
Selenium	40 mcg/mL	10	0.0005	0.01
Zinc	5	2	0.55	1.10
B Complex 100		2	1.44	2.88
Dexapanthenol	250	2	1.66	3.32
Pyridoxine	100	2	0.66	1.32
Ascorbic Acid	500	10	5.8	58.00
Glutathione	100	1	0.655	0.66
Taurine	50	4	0	0.00
1/2 Normal Saline	0.45%	250	0.145	36.25
Total		283		103.53
	Final Osmolality:			365.83

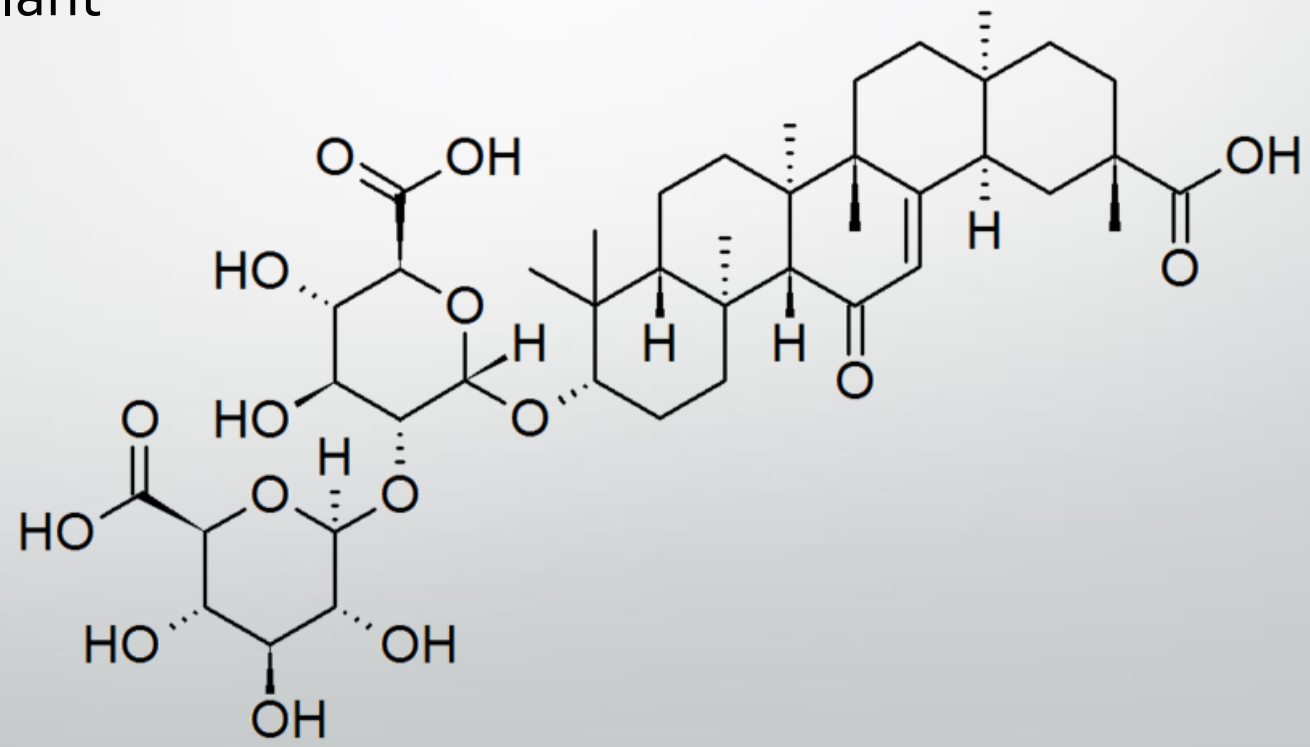
Malnutrition

Formula: Malnutrition Formula				
Nutrient	mg/mL	CC	mOsmol/mL	mOsm*vol
Calcium Chloride	100	5	2.04	10.20
Magnesium Chloride	200	10	2.95	29.50
Selenium	40mcg	5	0.00125	0.01
Potassium Chloride	20 mEq	10	4	40.00
Zinc Sulfate	5	1	1.75	1.75
Manganese	0.1	5	0.87	4.35
Molybdenum	25 mcg	4	0.8	3.20
Dexapanthenol	250	2	1.66	3.32
Pyridoxine	100	3	1.11	3.33
Hydroxycobalamin	1	3	0.31	0.93
B Complex 100		3	1.44	4.32
Compounded Aminos		100	0.742	74.20
Sterile Water	0.00%	400	0	0.00
Total		551		175.11
	Final Osmolality:			317.80

Glycyrrhizic Acid

Glycyrrhizinic Acid (GZA)

- Triterpenoid saponin glycoside which is mainly responsible for the sweet taste of the licorice plant



Metabolism of GZA

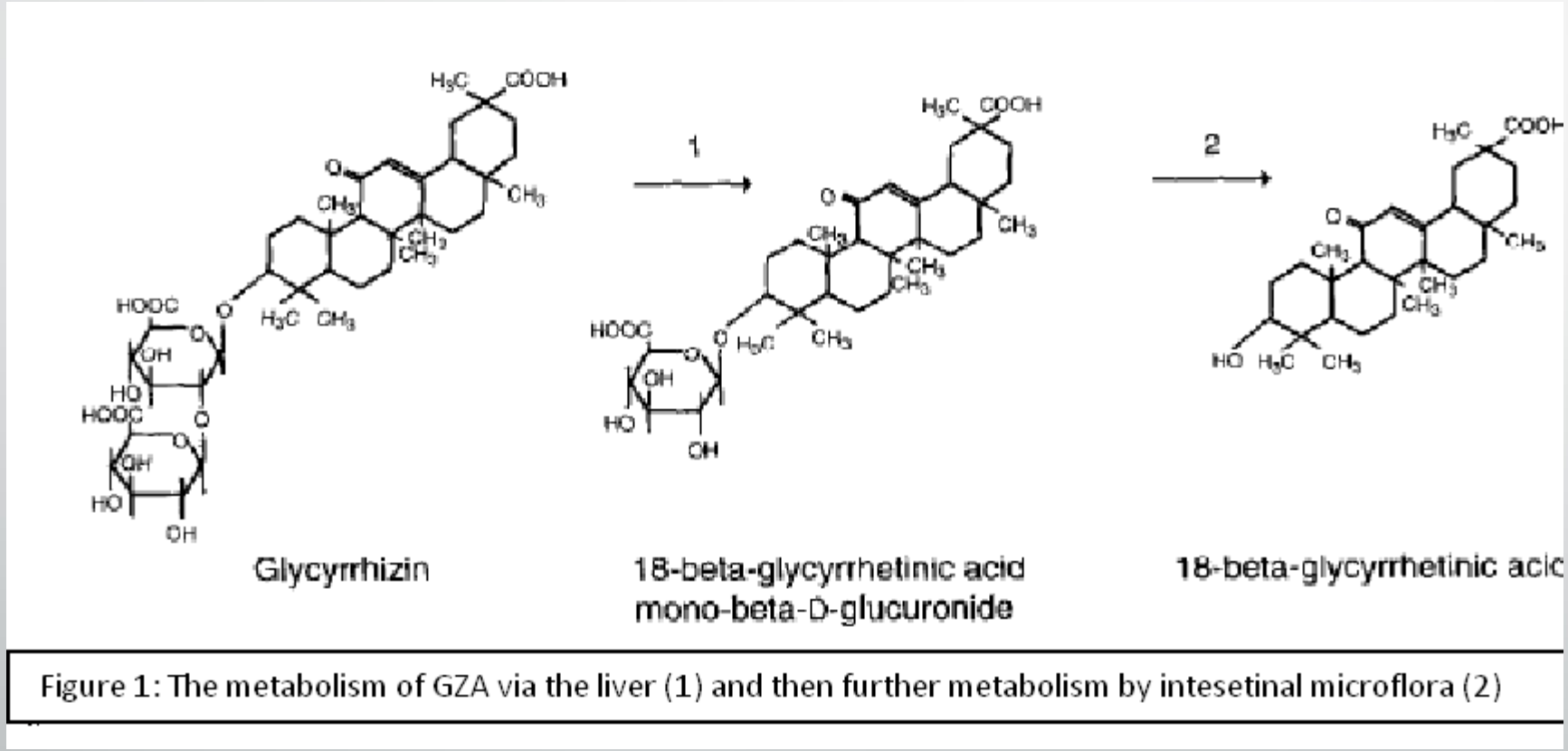


Figure 1: The metabolism of GZA via the liver (1) and then further metabolism by intesetinal microflora (2)

Glycyrrhiznic Acid (GZA) Pharmacokinetics

- Oral administration of GZA is almost entirely cleaved in the bowel by bacteria to glycyrrhetinic acid (GRA)
- Intravenous administration results in part to biphasic process whereby there is a distribution phase then excretion
- GZA is can be excreted unmetabolized (however some metabolism does occur) whereas GRA is metabolized to GRA glucuronide/sulfate
- Both are primarily excreted in the bile

Pharmacokinetics

- General method of admin is rapid drip or bolus push
- ½ life in healthy adults is 4 hours
- ½ life in adults with liver disease averages at 9 hours
- given this it is possible for accumulation
- Clinical trials where GZA treatment of adults was administered daily showed accumulation in 2-4 weeks in some adults
- Chronic oral dosing is the main method of accumulation

Glycyrrhizinic Acid Anti-Viral Effects

- Various in vitro studies have shown GZA has inhibitory effects on the following viruses:
  - Hepatitis A, B, C
  - HSV 1/2
  - HIV
  - Influenza A virus
  - Coronavirus,
  - respiratory syncytial virus
  - arboviruses
  - vaccinia virus
  - vesicular stomatitis virus
- The observed inhibitory effect is though to be due to an inhibition of viral binding and entry into cells

Hepatoprotective Effects

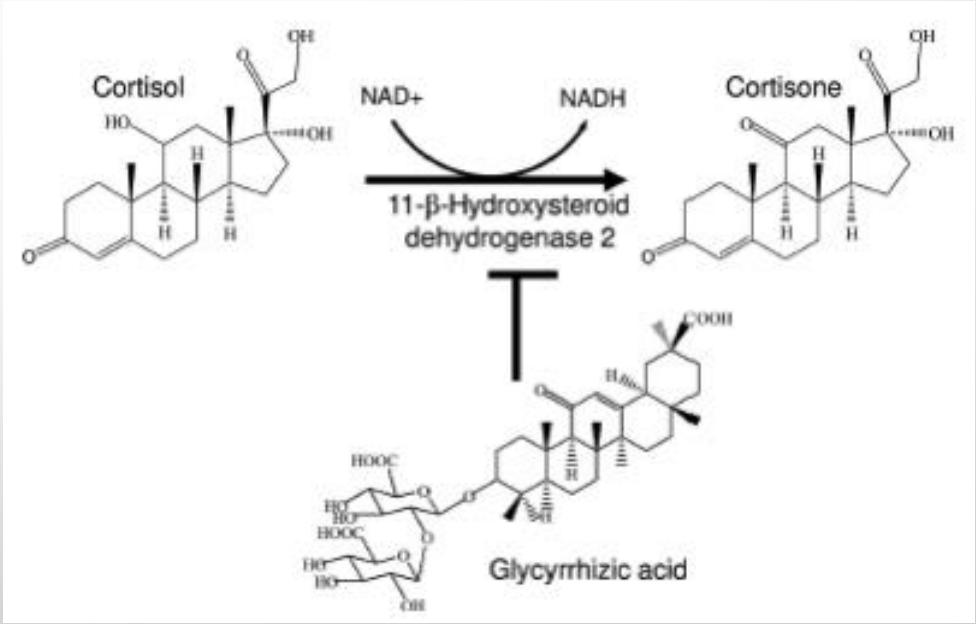
- Animal research showed GZA
  - inhibited the production of phospholipase 2 thereby reducing inflammatory processes in hepatocytes
  - Inhibition TNF alpha
  - Reduced myeloperoxidase activity
  - Up regulation of CYT P enzymes in liver (caution with meds metabolized with this system)
  - Cox-2 inhibition
- Both human and animal studies have shown a strong reduction in transaminase levels after treatment

Glycyrrhizinic Acid And Immunomodulatory Effects

- GZA induces interferon gamma in human and animals
- GZA also shows selective extra thymic activation of T lymphocytes

Pseudoaldosterone Effects

- It is partially metabolised in the body via hydrolytic cleavage to glycyrrhetinic acid and glucoronic acid
- Glycyrrhetinic Acid (GRA) inhibits the conversion of cortisol to cortisone in the kidney



Risks with Pseudoaldosterone Effects

- Hypokalemia
- Hypertension
- Reduced aldosterone/renin
- Resulting Rhabdomyolysis
- Potential death

Clinical Effects of Glycyrrhizinic Acid in Hepatitis C cont'd

- RCT Double Blind trial
- 4 weeks in 57 patients
- No patients in either group had seroconversion
- No difference in ADRs for either group and no patient showed pseudoaldosteronism

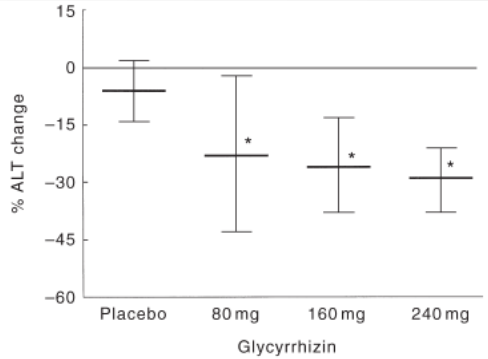


Figure 4 Mean percentage change in alanine aminotransferase (ALT) at the end of treatment with respect to baseline ±95% confidence interval per dosage group. * Significantly greater than placebo group, $P < 0.03$ by the rank-sum test.

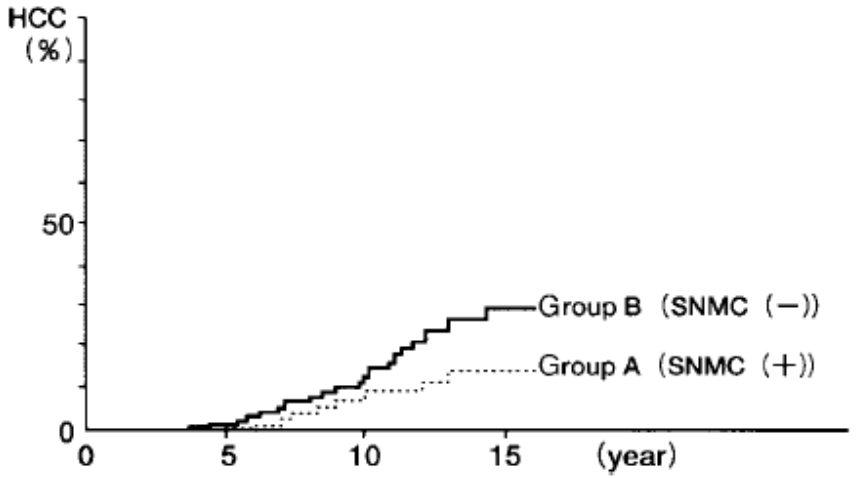
Clinical Effects of Glycyrrhyzinic Acid

- Multiple trials involving the use of GZA alone or in combination with other therapeutics have shown
- SNMC trials using 200 mg GZA, 2 g glycine and 500 mg cysteine showed safe 7 year use in Hep C patients

TABLE 2
Average ALT Levels during Follow-Up Periods between Group A and Group B

Average ALT	Normal (≤50 IU)	Abnormal (>50 IU)
Group A (SNMC (+))	30 (35.7%)	54 (64.3%)
Group B (SNMC (−))	7 (6.4%)	102 (93.6%)

ALT: alanine aminotransferase; SNMC: Stronger Neo-Minophagen C.



Indications For Use

- Established:
  - Active chronic viral hepatitis
  - Prevention of HCC in HBV/HCV patients
  - HIV
- Potential
  - Cancer
  - Adrenal fatigue (intermittent short term)
- Hepatoprotection in EBV/CMV infections

Protocols for Use

- GZA comes in 8 mg/mL
- Begin with 80 mg in slow push or slow drip 20 minutes
- Increase by 80 mg each treatment to between 200-300 mg
- Can be layered on as an additional bag to other treatments
- Can be given daily for 2-4 weeks then either weekly or biweekly thereafter
- Or can start with semi weekly treatments for 2-4 months
- Use with inline filter as compatibility is poor

Cautions

- Patients with severe liver disease (understand increased risk of pseudoaldosterone effects)
- Hypertensive patients
- Congestive heart failure
- Patients on non potassium sparing diuretics
- Patients consuming oral licorice products
- Allergy to licorice

Patient Assessment with GZA

- Proper patient assessment and monitoring can reduce or eliminate the likelihood of significant adverse reactions with GZA. Assessment and monitoring of the following are key for prevention:
  - Blood pressure
  - Serum sodium and potassium
  - Serum transaminases
  - Serum creatinine and eGFR

If Pseudoaldosteronism is Suspected

- Serum aldosterone and renin
- 24 hour urine collection and analysis for potassium and total osmolarity

Treatment of Pseudoaldosteronism

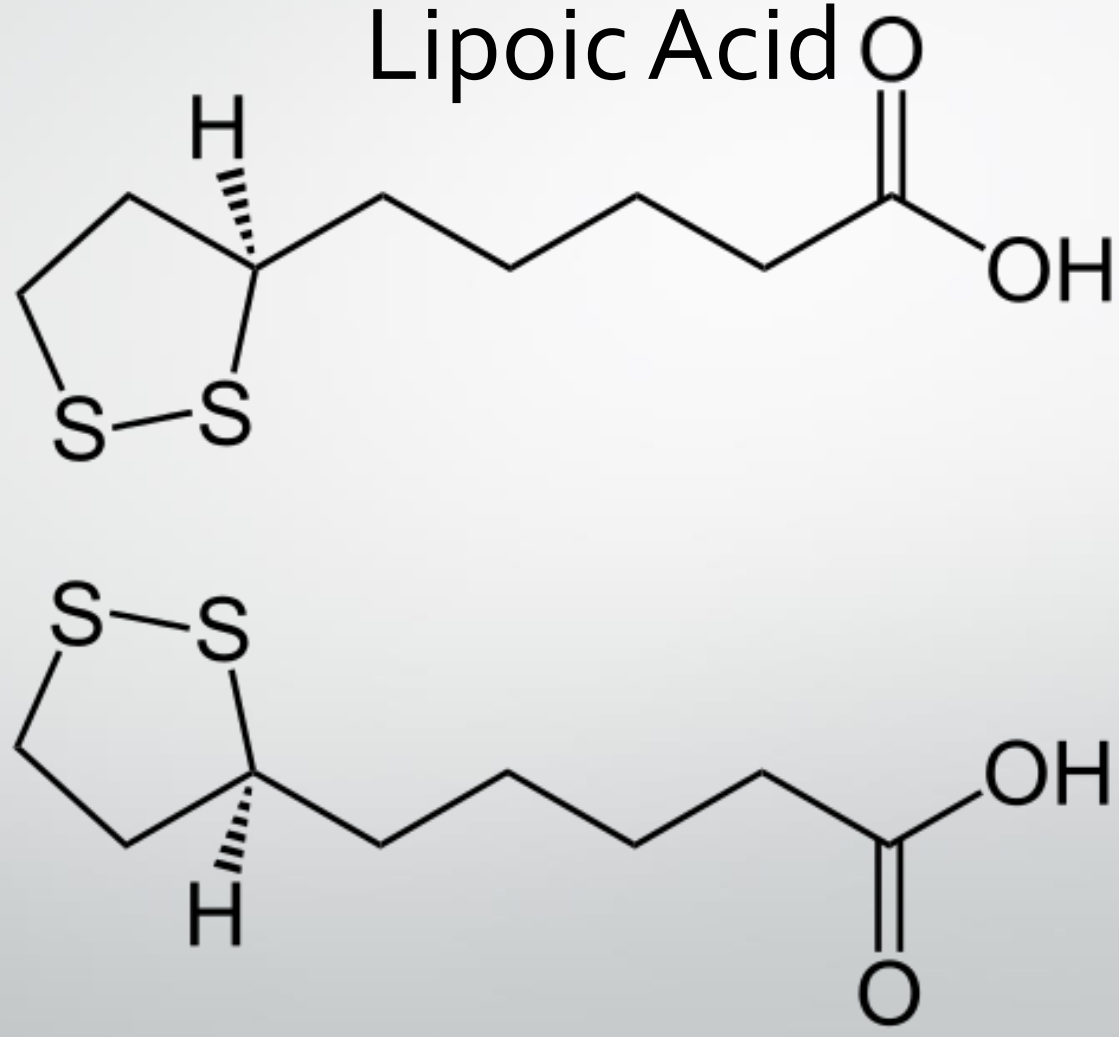
- Treatment of a patient with minor pseudoaldosterone effects
  - Discontinuation of treatment and avoidance of licorice products
  - Potassium supplementation 100-300 mg/day
  - Monitoring blood pressure and blood work for next 4 weeks

Treatment of Pseudoaldosteronism

- Treatment of a patient with severe pseudoaldosterone effects
  - Discontinuation of treatment and avoidance of licorice products
  - Aldosterone or endothelial receptor antagonist treatment to reduce hypertensive trend
  - Potassium supplementation 100-300 mg/day
  - Monitoring blood pressure and blood work for next 4 weeks
- In all case reports of GZA induced pseudoaldosteronism patients returned to normal aldosterone and blood pressure levels within 2-4 weeks.

Alpha Lipoic Acid

Lipoic Acid



Rationale for PT use

- While the majority of its use has been by oral administration ALA's effectiveness is often limited by insufficient absorption and rapid excretion.
- This limits the serum concentration below levels necessary to achieve responses in certain clinical situations like chemotherapeutic induced polyneuropathies and progressive diabetic neuropathies.
- Intravenous administration of alpha lipoic acid has been most prevalent in Germany where it has been used for over 30 years. Its primary clinical indication was as a treatment for diabetic neuropathy and other peripheral neuropathies.

Anti-Oxidant Effects

- ALA has two distinct ways to act as a free radical scavenger.
- What makes ALA a unique anti-oxidant is its amphophyllic nature - It can act as an antioxidant both within the cell cytosol and lipid membrane
- The second ROS quenching mechanism ALA exhibits is the ability to recycle other anti-oxidants. DHLA is the key form responsible for this effect. Vitamin C and glutathione are two key cellular anti-oxidants that can be recycled by DHLA

Insulin Potentiation

- Binding of insulin to receptors leads to enzymatic phosphorylation of tyrosine residues.
- This leads to several downstream processes resulting in eventual translocation of glucose receptors (GLUT 4) to the cell membrane leading to increased uptake of sugar into the cell.
- ALA has been shown to increase translocation of GLUT4 to membrane complex thereby acting as an insulin mimetic.

Heavy Metal Detoxification

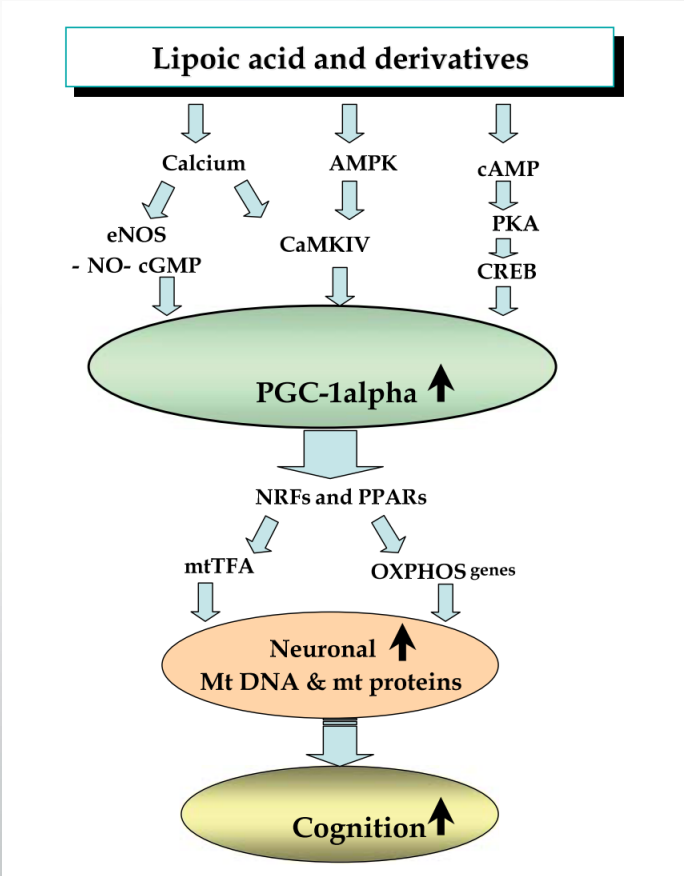
- Many toxic metals present in the body are naturally removed through hepatobiliary excretion complexed with non-protein thiols like glutathione.
- ALA has a known enhancement of glutathione and other thiol compounds.
- Preclinical studies in rats showed that ALA not only stimulated increases in non-protein thiols in the blood, but also stimulated the excretion of glutathione in bile.
- This led to a substantially increased excretion in a dose dependent manner of Mercury and Cadmium
- In-vitro data also suggest that ALA/DHLA can limit ROS generation by Iron and Copper and lead to reduced accumulation of these metals in animals

Neuroprotection

- ALA has been well studied in diabetic neuropathic syndromes and has also hade limited trials in chemotherapy-induced neuropathies.
- In both of these conditions nerve dysfunction is caused by ROS generation leading to alterations in endoneural blood flow and nerve conduction
- ALA has been show improve both of these factors in animal trials

ALA Impact in NDDs

- Fig. 2 Signal pathways of mitochondrial biogenesis that are possibly regulated by a-lipoic acid and its derivatives. AMPK AMP-activated protein kinase, NRF Nuclear respiratory factor, NO Nitric oxide, NOS nitric oxide synthase, CaMKIV Calcium/calmodulin-dependent pro- tein kinase IV, mtTFA mitochondrial transcription factor A, PKA protein kinase A, CREB cAMP-responsive element binding protein, PPARs Peroxisome proliferator-activated receptors, PGC-1a Peroxi- some proliferator-activated receptor-c coactivator-1a (adapted



Proven Clinical Indications of IV Use

- Diabetic Poly-Neuropathy
- Chemotherapy Induced Neuropathy

Dosage

- ALA is administered in doses ranging from 300 - 600 mg infused slowly over 60-90 minutes
- ALA is light sensitive and must be run without exposure to light
  - Compound in low light room
  - Cover IV bag
  - Foil over administration set or use opaque line

Lipoic Acid Therapy

- Racemic Alpha Lipoic Acid 150 – 600 mg
  - escalating to 600 mg in 150 increments
  - If R+ ALA, 75-300 mg, escalating in 75 mg increments
- 0.9% sodium Chloride 100 mL
- Run over 60-90 minutes in a light protected bag and line
- Can be done 1-3 times per week
- Can be done concurrently after glutathione

Contraindications/Interactions

- ALA has no effects on cytochrome series enzymes in the liver and on renal clearance and therefore has no known effect on drug metabolism.
- As a result of ALA's blood sugar lowering effects caution should be used when administering to medicated diabetic patients as it may potentiate hypoglycemic episodes.

Side Effects

- Gastrointestinal symptoms
  - nausea, vomiting and diarrhoea
- Skin reactions (urticaria, generalized pruritis)
- Headaches
- Hot flashes/Chills
- Rare cases of slowly progressing anaphylactoid reactions
- 1 case of serious allergic reaction with laryngospasm
- Most reactions occurred when administered doses exceeded 600 mg

Treatment of ADRs

- Ultimately there are no persistent toxic effects that have been observed at clinically relevant dosing of ALA.
- As mentioned in prior slide most ADRs are dose related and can be prevented by careful dose escalation or reduction of dosage in cases of intolerance.
- For allergic type reactions the obvious approach would be careful patient screening to evaluate potential patients with allergic tendencies where caution should be exercised.
- If allergic reactions occur the appropriate anti-allergic therapy should be prescribed depending on the severity of the reaction and further treatment with ALA should be avoided.

Got Questions?