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ADVANCED IV THERAPIES

52nd Annual Meeting
October 5, 2017
The Chateaux Deer Valley
Park City, Utah

Wm. Alan Ingram, M.D. CME Chairman
Gregg Govett, M.D., FAAEM, DABEM, CME Assistant Chair
Jessica Tran, N.D., Session Chair

The Vision of AAEM:

"Achieving Optimal Health in a Complex Environment"

The Mission of AAEM:

- To educate physicians (MD/DO) regarding the interaction between humans and their environment, and to train them how to incorporate information into their medical practice to improve patient outcomes.
- To promote and support research in the area of Environmental Medicine
- To share information and build relationships with individuals and organizations in order to foster a safe and healthy environment
- To establish and promote high standards for practitioners of environmental medicine

The American Academy of Environmental Medicine is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians.

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SCHEDULE

Advanced IV Therapies

Thursday, October 5, 2017 ❍ Renoir Ballroom

8:00 am	**IV Nutrient Therapy Review and Ascorbic Acid** Jessica Tran, N.D. ***Sponsored by Master Supplements***
9:00 am	**Glutathione: Beyond Redux and Detox** Kelly McCann, M.D. ***Sponsored by Wellness Pharmacy***
10:00 am	Networking Break with Exhibitors
10:30 am	**Artesunate, Lipoic Acid Mineral Complex** Brenden Cochran, N.D. ***Sponsored by ImprimixRX***
11:30 am	Luncheon
1:00 pm	**Phosphatidylcholine** Brenden Cochran, N.D. ***Sponsored by ImprimixRX***
1:30 pm	**Alpha Lipoic Acid** Jessica Tran, N.D. ***Sponsored by Master Supplements***
2:00 pm	**Introduction to Ultraviolet Blood Irradiation (UBI)** Bridghid McMonagle, N.D. ***Sponsored by Merit Pharmaceuticals***
3:00 pm	Networking Break with Exhibitors
3:30 pm	**Introduction to Medical Ozone** Bridghid McMonagle, N.D. ***Sponsored by Merit Pharmaceuticals***
4:30 pm	**Amino Acids, Homeopathics & Mesenchylmal Cells** Brenden Cochran, N.D. ***Sponsored by ImprimixRX***
5:30 pm	***Adjourn***
6:00 pm	Ozone Live Demonstration & Practicum (MUST REGISTER TO ATTEND) Bridghid McMonable, N.D. ***Sponsored by Merit Pharmaceuticals***

Advanced IV Therapies

October 5, 2017

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Advanced Topics in Environmental Medicine

Genetics and the Environment

Molds and Mycotoxins

Sublingual Immunotherapy

March 2—4, 2018
Hilton Park City/Dallas
Dallas, Texas

Call for Papers Open

The Mitochondria in Health and Disease
October 4—7, 2018
The Westin Westminster
Westminster, Colorado

Call for Papers Open

Jessica Tran, N.D.

16251 Laguana Canyon Rd, Ste 175
Irvine, CA 92618
jtran@wellnessintegrative.com

Disclosure Statement:

Dr. Tran has indicated that she is has no relevant financial relationships with any commercial supporters.

IV Nutrient Therapy Review and Ascorbic Acid

Learning Objectives:

At the conclusion of this activity you should be able to...

About Dr. Tran

Jessica Tran is a licensed naturopathic doctor. She received her naturopathic medical degree from Bastyr University. She completed a one-year Family Practice residency, three-year Environmental Medicine fellowship, and served as Clinical Faculty in both the Department of Environmental Medicine and General Medicine at Southwest College of Naturopathic Medicine & Health Sciences. Dr. Tran serves on the Board of Directors and CME Planning Committee of the American Academy of Environmental Medicine. She is in private practice in Irvine, California.

NOTES

Intravenous Nutrient Therapy and Ascorbic Acid

Jessica Tran, ND

October 5, 2017

AAEM

Under Accreditation Council for Continuing Medical Education guideline disclosure must be made regarding relevant financial relationships with commercial interests within the last 12 months.

Jessica Tran, N.D.

Received an educational grant from Master Supplements

Unless otherwise stated, the level of evidence is C and based on clinical experience.

Review of IV Nutrient Therapy

Table II – Dr. Shrader's Office IV Protocols (selected) – 2011

Protocols ⇨ / Nutrients ⇩	mOsm per mL	⇩ IV Push Protocols: Meyer (rev.)	Acute Asthma	Headache Migraine, muscle spasm	Glutathione Protocol	⇐ All IV Infusion protocols: Chronic Asthma	Chronic Illness CFIDS, etc.	Acute Viral Illness	Super - Immuno	Chelation	Chelation Nutritional ⇒
Amino Acids (FreAmine III 8.5%) *	0.81						50				
Ascorbic Acid 500 mg/mL	5.80	4	3			12	20	200	50	15	5
B-6 (Pyridoxine) 100 mg/mL	1.11	1	3	4		5	2	1	2	1	1
B-12 (hydroxocobalamine) 1000 mcg. **	0.31	2	5		1	5 **	5 **	1	15 **	1	1
B-Complex 100 mg/mL	2.14	1	2		1	2	2	1	2	2	2
Bicarbonate Sodium 8.4%	2.00					17	15	60	20	20	10
EDTA (magnesium disodium) 150 mg./mL	1.34									20◢	
Calcium Gluconate 10% 100 mg./mL	0.72	2	2			2	2	40	20		5
Folic Acid 10 mg./mL †^	0.20					1^	1^	1^	1^	1^	1^
Germanium 50 mg./mL †	0.25								10		
Glutathione 100 mg./mL **†	0.38				6 to 25						
Heparin 5,000 U/mL	0.46	Optional								0.5	
Magnesium Chloride 200 mg./mL	2.95	5	10-15	15	5	10	5	5	5	5	10
Magnesium Chloride 500 mg./mL	7.13										
Mineral Mix ***†	0.57					1	2		2		1
Molybdenum 500 mcg./mL †	0.80					1					
N-acetyl cysteine 100 mg./mL	1.91				2						
Pantothenic acid 250 mg./mL	0.85	1	2			2	3	3	3	1	
Potassium chloride 2 mEq/mL	4.00	NO	NO	NO	NO	1	1	1	1	1	1
Selenium 200 mcg./mL	0.09										2
Taurine 50 mg./mL †	0.50						6		10		5
Zinc sulfate (5 mg./mL)	0.11								1		1
Additives		16	26-32	19	15 to 34	54	103	313	125	67.5	45
mOsm Additives		*44.1*	*59.2-73.9*	*48.7*	*23.3 to 30.5*	*151.6*	*217.1*	*1334*	*377*	*179.5*	*95.4*
Sterile Water	0	17	27	16	15	250	500	800 Ÿ	450 *		250
Normal Saline, 9%	.31										
Syringe or IV bottle, in mL		35	60	35	35-60	250	500.0	1000	500	500	250
Osmolarity (mOsm/L)		**1336**	**1095-1253**	**1391**	**776 to 623**	**499**	**360**	**1198**	**655**	**316**	**323**

* Caution: contains preservative (may be compounded preservative-free)
** Given IV push at end of infusion (not counted in volume or osmolarity calculations).
† Not FDA-approved nutrients/mixtures
*** "Shrader's Mineral Mix": the formulation is *boron* 1 mg./mL., *zinc* 5 mg./mL., *copper* 1 mg./mL, *molybdenum* 250 mcg./mL., *selenium* 200 mcg./mL., *chromium* 100 mcg./mL., *manganese* 100 mcg./mL., *vanadium* 100 mcg./mL., *lithium* 5 mg./mL. and *strontium* 1 mg./mL. (College has this formula, and other pharmacies may have this and different formulations available also)
Ÿ Remove 200 mL of water from the IV bottle before adding additives
° Remove 50 mL of water from IV bottle before adding additives
◢ EDTA dose must be calculated before this solution is given! (see text)
^ Add folic acid *last* to all protocols – use a separate syringe

Protocols developed by W.A. Shrader, Jr., MD, except "Meyer" protocol. All have received extensive therapeutic use.

Table II – Dr. Shrader's Office IV Protocols (selected) – 2011

Protocols ⇨ / Nutrients ⇩	mOsm per mL	⇩ IV Push Protocols: Meyer (rev.)	Acute Asthma	Headache Migraine, muscle spasm	Glutathione Protocol	⇐ All IV Infusion protocols: Chronic Asthma	Chronic Illness CFIDS, etc.	Acute Viral Illness	Super - Immuno	Chelation	Chelation Nutritional ⇒
Amino Acids (FreAmine III 8.5%) *	0.81						50				
Ascorbic Acid 500 mg/mL	5.80	4	3			12	20	200	50	15	5
B-6 (Pyridoxine) 100 mg/mL	1.11	1	3	4		5	2	1	2	1	1
B-12 (hydroxocobalamine) 1000 mcg. **	0.31	2	5		1	5 **	5 **	1	15 **	1	1
B-Complex 100 mg/mL	2.14	1	2		1	2	2	1	2	2	2
Bicarbonate Sodium 8.4%	2.00					17	15	60	20	20	10
EDTA (magnesium disodium) 150 mg./mL	1.34									20◢	
Calcium Gluconate 10% 100 mg./mL	0.72	2	2			2	2	40	20		5
Folic Acid 10 mg./mL †^	0.20					1^	1^	1^	1^	1^	1^
Germanium 50 mg./mL †	0.25								10		
Glutathione 100 mg./mL **†	0.38				6 to 25						
Heparin 5,000 U/mL	0.46	Optional								0.5	
Magnesium Chloride 200 mg./mL	2.95	5	10-15	15	5	10	5	5	5	5	10
Magnesium Chloride 500 mg./mL	7.13										
Mineral Mix ***†	0.57					1	2		2		1
Molybdenum 500 mcg./mL †	0.80					1					
N-acetyl cysteine 100 mg./mL	1.91				2						
Pantothenic acid 250 mg./mL	0.85	1	2			2	3	3	3	1	
Potassium chloride 2 mEq/mL	4.00	NO	NO	NO	NO	1	1	1	1	1	1
Selenium 200 mcg./mL	0.09										2
Taurine 50 mg./mL †	0.50						6		10		5
Zinc sulfate (5 mg./mL)	0.11								1		1
Additives		16	26-32	19	15 to 34	54	103	313	125	67.5	45
mOsm Additives		*44.1*	*59.2-73.9*	*48.7*	*23.3 to 30.5*	*151.6*	*217.1*	*1334*	*377*	*179.5*	*95.4*
Sterile Water	0	17	27	16	15	250	500	800 Ÿ	450 *		250
Normal Saline, 9%	.31										
Syringe or IV bottle, in mL		35	60	35	35-60	250	500.0	1000	500	500	250
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*** "Shrader's Mineral Mix": the formulation is *boron* 1 mg./mL., *zinc* 5 mg./mL., *copper* 1 mg./mL, *molybdenum* 250 mcg./mL., *selenium* 200 mcg./mL., *chromium* 100 mcg./mL., *manganese* 100 mcg./mL., *vanadium* 100 mcg./mL., *lithium* 5 mg./mL. and *strontium* 1 mg./mL. (College has this formula, and other pharmacies may have this and different formulations available also)
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° Remove 50 mL of water from IV bottle before adding additives
◢ EDTA dose must be calculated before this solution is given! (see text)
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Protocols developed by W.A. Shrader, Jr., MD, except "Meyer" protocol. All have received extensive therapeutic use.

Laboratory Assessment

- Baseline Complete Blood Count, fasting Chemistry Screen (to include glucose, BUN, creatinine, electrolytes, calcium, liver enzymes), Urinalysis, and lipid levels within last 6 months
- Periodic lab studies should be obtained if the patient is undergoing a series of IV therapies over a prolonged period of time. A minimum complete urinalysis, glucose, BUN, creatinine and electrolyte studies should be obtained.
- Evaluation of the effectiveness of IV mineral therapy may be obtained by a variety of testing. As with all laboratory testing, the information obtained represents a picture of an instant in time and does not provide a complete picture.
- Clinical correlation must be taken into account when assessing the therapy.

Laboratory Assessment

- **CBC, CMP, UA**
- Glucose-6-Phosphate Dehydrogenase, Quantitative
  (if including Vitamin C and **must have** if exceeding 5 grams)
- Vitamins and minerals (Ferritin/Fe, Cu, Zn, Mg, B12/folate, vitamin A, B1, B2, B3, B5, B6, B7 (biotin), C, D-25-oH, E, K, Carotene) whole blood/red blood cell/serum
- Specialty testing for nutritional assessment:
  - Whole Blood Elements/Red Blood Cell Elements/White Blood Cell Elements
  - Amino acids (plasma/urine)
  - Essential fatty acids/Comprehensive fatty acids
  - Glutathione (RBC, whole blood)
  - Iodine
- Other specialty testing:
  - Oxidative Stress (urinary 8-hydroxy-2'-deoxygaunosine, 8-OHdG)
  - MTHFR/Methylation profile

Advantages

- Easy access to rapid administration of solutions
- Continuous or intermittent administration of nutrients
- Rapid changes in circulatory system
- Easy to monitor delivery of fluids, electrolytes and nutrients (for those with impaired GI tracts)

Disadvantages

- Invasive procedure—can cause infection, bleeding, adverse side effects
- More costly than oral or injectable (IM, SC) substances
- One IV site has a limited use/time: usually no more than 72 hours.

Indications

- Asthma
- Migraine
- Fibromyalgia
- Depression
- Cardiovascular Disease
- URTI
- Sinusitis
- Seasonal Allergic Rhinitis
- Narcotic Withdrawal
- Chronic Urticaria
- Athletic Performance
- Thyroid problems
- Component of a cleansing treatment plan for environmental medicine/detoxification

Contraindications

- Sensitivity or allergies to ingredients (know source of ingredients and patient's allergies)
  - Corn vs beet-derived ascorbic acid
- *CHF*
- *G6PD deficiency*
- *Renal insufficiency / renal disease*

Procedure for IV Patients

- Patient must read and sign an informed consent form for IV therapy ~ consider having a separate consent form for various therapies (nutrients, chelation, ALA, PC)
- Laboratory and physical exam
- Pre and post-IV vitals
- Other considerations:
  - G6PD deficiency-if the patient has a diagnosis or history, avoid vitamin C in the IV solution. Do not exceed 5 grams without testing. Hemolytic episode and death can occur with high dose vitamin C
  - Iodine-avoid if patient is sensitive and do not cleanse the venipuncture site with iodine containing antiseptics
  - Latex allergy-apply tourniquet over the patient's shirt sleeve, or use a BP cuff. Use non-latex examination gloves.

IV Nutritional Therapy Summary

- IV Nutritional Therapy can be beneficial for many conditions
- Comply with OSHA regulations
- Patients must understand risks, benefits, and alternative to therapy. Sign consent form before starting therapy
- Ensure accurate osmolarity calculation for each IV therapy
- Accurately document IV nutritional therapy
- Scope of practice

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Nutrients in Myers' Cocktail

Original Myers' Cocktail

- Magnesium chloride hexahydrate 2%
- Calcium gluconate
- Thiamine
- Vitamin B6
- Vitamin B12
- Calcium pantothenate
- Vitamin B complex
- Vitamin C
- Dilute hydrochloric acid
- Sterile water

10 mL syringe, slow push

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Nutrients in Myers' Cocktail

Table 1. Nutrients in Myers' Cocktail **Alan R. Gaby, MD**

Magnesium chloride hexahydrate 20% (magnesium)	2-5 mL
Calcium gluconate 10% (calcium)	1-3 mL
Hydroxocobalamin 1,000 mcg/mL (B12)	1 mL
Pyridoxine hydrochloride 100 mg/mL (B6)	1 mL
Dexpanthenol 250 mg/mL (B5)	1 mL
B complex 100 (B complex)	1 mL
Vitamin C 222 mg/mL (C)	4-20 mL

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Nutrients in Myers' Cocktail

(commonly used)

• Magnesium chloride hexahydrate 20%	4 mL
• Calcium gluconate 10%	2 mL
• Hydroxocobalamin 1,000 mcg/mL (B12)	1 mL
• Pyridoxine hydrochloride 100 mg/mL (B6)	1 mL
• Dexpanthenol 250 mg/mL (B5)	1 mL
• B complex 100	1 mL
• Vitamin C 222 mg/mL	6 mL
• Sterile water	8 mL
	24 mL

Time: 5-15 minutes, 25 G butterfly needle

1 mL B-complex 100 = 100 mg each of thiamine and niacinamide, and
2 mg each of riboflavin, dexpanthenol, and pyridoxine

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Nutrients in Myers' Cocktail

Asthma v1

• Vitamin C 222 mg/mL	6 mL
• Magnesium chloride hexahydrate 20%	1.4 mL
• Calcium gluconate 10%	0.5 mL
• Hydroxocobalamin 1,000 mcg/mL (B12)	1 mL
• Pyridoxine hydrochloride 100 mg/mL (B6)	1 mL
• Dexpanthenol 250 mg/mL (B5)	1 mL
• B complex 100	1 mL

Mixed with sterile water or normal saline to the ideal osmolarity

Time: 5-15 minutes, 25 G butterfly needle

1 mL B-complex 100 = 100 mg each of thiamine and niacinamide, and
2 mg each of riboflavin, dexpanthenol, and pyridoxine

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Nutrients in Myers' Cocktail

Asthma v2

- Vitamin C 222 mg/mL — 10 mL
- Magnesium chloride hexahydrate 20% — 3 mL
- Calcium gluconate 10% — 1.5 mL
- Hydroxocobalamin 1,000 mcg/mL (B12) — 1 mL
- Pyridoxine hydrochloride 100 mg/mL (B6) — 1 mL
- Dexpanthenol 250 mg/mL (B5) — 1 mL
- B complex 100 — 1 mL

Mixed with sterile water or normal saline to the ideal osmolarity

Time: 5-15 minutes, 25 G butterfly needle

1 mL B-complex 100 = 100 mg each of thiamine and niacinamide, and
2 mg each of riboflavin, dexpanthenol, and pyridoxine

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Nutrients in Myers' Cocktail

Migraine

- Vitamin C 222 mg/mL — 16 mL
- Magnesium chloride hexahydrate 20% — 5 mL
- Calcium gluconate 10% — 4 mL
- Hydroxocobalamin 1,000 mcg/mL (B12) — 1 mL
- Pyridoxine hydrochloride 100 mg/mL (B6) — 2 mL
- Dexpanthenol 250 mg/mL (B5) — 1 mL
- B complex 100 — 1 mL

Mixed with sterile water or normal saline to the ideal osmolarity

Time: 5-15 minutes, 25 G butterfly needle

Intramuscular injection: B12 + folic acid

1 mL B-complex 100 = 100 mg each of thiamine and niacinamide, and
2 mg each of riboflavin, dexpanthenol, and pyridoxine

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Nutrients in Myers' Cocktail
Fibromyalgia

- Vitamin C 222 mg/mL 6 mL
- Magnesium chloride hexahydrate 20% 4 mL
- Calcium gluconate 10% 2.5 mL
- Hydroxocobalamin 1,000 mcg/mL (B12) 1 mL
- Pyridoxine hydrochloride 100 mg/mL (B6) 1 mL
- Dexpanthenol 250 mg/mL (B5) 1 mL
- B complex 100 1 mL

Mixed with sterile water or normal saline to the ideal osmolarity

Time: 5-15 minutes, 25 G butterfly needle

1 mL B-complex 100 = 100 mg each of thiamine and niacinamide, and
2 mg each of riboflavin, dexpanthenol, and pyridoxine

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Nutrients in Myers' Cocktail
Depression-consumption of alcohol v1

- Magnesium chloride hexahydrate 20% 1 mL
- Hydroxocobalamin 1,000 mcg/mL (B12) 1 mL
- Pyridoxine hydrochloride 100 mg/mL (B6) 1 mL
- Dexpanthenol 250 mg/mL (B5) 1 mL
- B complex 100 1 mL

Mixed with normal saline to the ideal osmolarity

Time: 5-15 minutes, 25 G butterfly needle

1 mL B-complex 100 = 100 mg each of thiamine and niacinamide, and
2 mg each of riboflavin, dexpanthenol, and pyridoxine

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Nutrients in Myers' Cocktail
Depression-consumption of alcohol v2

- Magnesium chloride hexahydrate 20% 5 mL
- Hydroxocobalamin 1,000 mcg/mL (B12) 1 mL
- Pyridoxine hydrochloride 100 mg/mL (B6) 1 mL
- Dexpanthenol 250 mg/mL (B5) 1 mL
- B complex 100 3 mL

Mixed with normal saline to the ideal osmolarity

Time: 5-15 minutes, 25 G butterfly needle

1 mL B-complex 100 = 100 mg each of thiamine and niacinamide, and
2 mg each of riboflavin, dexpanthenol, and pyridoxine

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Nutrients in Myers' Cocktail
Cardiovascular Disease

Leave calcium out for CVD

- Magnesium chloride hexahydrate 20% 5 mL
- Hydroxocobalamin 1,000 mcg/mL (B12) 1 mL
- Pyridoxine hydrochloride 100 mg/mL (B6) 1 mL
- Dexpanthenol 250 mg/mL (B5) 1 mL
- B complex 100 1 mL

Time: 5-15 minutes, 25 G butterfly needle

- Mix Trace Elements-5 (MTE-5) 0.2 mL
  - Administered over a period of 1-2 minutes in a separate syringe at the end of the Myers' push.

1 mL MTE-5 = 1 mg Zinc, 0.4 mg Copper, 0.1 mg Manganese, 4 mcg Chromium; 20 mcg Selenium

1 mL B-complex 100 = 100 mg each of thiamine and niacinamide, and
2 mg each of riboflavin, dexpanthenol, and pyridoxine

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Nutrients in Myers' Cocktail

URTI-1 day hx of fatigue nasal congestion & rhinorrhea

- Vitamin C 222 mg/mL 16 mL
- Magnesium chloride hexahydrate 20% 3 mL
- Calcium gluconate 10% 1.5 mL
- Hydroxocobalamin 1,000 mcg/mL (B12) 1 mL
- Pyridoxine hydrochloride 100 mg/mL (B6) 1 mL
- Dexpanthenol 250 mg/mL (B5) 1 mL
- B complex 100 1 mL

Mixed with Sterile water or Normal Saline to the ideal osmolarity

Time: 5-15 minutes, 25 G butterfly needle

Intramuscular injection: B12 + folic acid

1 mL B-complex 100 = 100 mg each of thiamine and niacinamide, and
2 mg each of riboflavin, dexpanthenol, and pyridoxine

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Nutrients in Myers' Cocktail

Sinusitis

- Vitamin C 222 mg/mL 20 mL
- Magnesium chloride hexahydrate 20% 4 mL
- Calcium gluconate 10% 2 mL
- Hydroxocobalamin 1,000 mcg/mL (B12) 1 mL
- Pyridoxine hydrochloride 100 mg/mL (B6) 1 mL
- Dexpanthenol 250 mg/mL (B5) 1 mL
- B complex 100 1 mL

Mixed with Sterile water or Normal Saline to the ideal osmolarity

Time: 5-15 minutes, 25 G butterfly needle

1 mL B-complex 100 = 100 mg each of thiamine and niacinamide, and
2 mg each of riboflavin, dexpanthenol, and pyridoxine

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Nutrients in Myers' Cocktail
Seasonal Allergic Rhinitis

• Vitamin C 222 mg/mL	12 mL
• Magnesium chloride hexahydrate 20%	3 mL
• Calcium gluconate 10%	2 mL
• Hydroxocobalamin 1,000 mcg/mL (B12)	1 mL
• Pyridoxine hydrochloride 100 mg/mL (B6)	1 mL
• Dexpanthenol 250 mg/mL (B5)	1 mL
• B complex 100	1 mL

Mixed with Sterile water or Normal Saline to the ideal osmolarity

Time: 5-15 minutes, 25 G butterfly needle

1 mL B-complex 100 = 100 mg each of thiamine and niacinamide, and
2 mg each of riboflavin, dexpanthenol, and pyridoxine

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Nutrients in Myers' Cocktail
Narcotic Withdrawal

• Vitamin C 222 mg/mL	16 mL
• Magnesium chloride hexahydrate 20%	5 mL
• Calcium gluconate 10%	2.5 mL
• Hydroxocobalamin 1,000 mcg/mL (B12)	1 mL
• Pyridoxine hydrochloride 100 mg/mL (B6)	1 mL
• Dexpanthenol 250 mg/mL (B5)	1 mL
• B complex 100	1 mL

Mixed with Sterile water or Normal Saline to the ideal osmolarity

Time: 5-15 minutes, 25 G butterfly needle

1 mL B-complex 100 = 100 mg each of thiamine and niacinamide, and
2 mg each of riboflavin, dexpanthenol, and pyridoxine

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Nutrients in Myers' Cocktail
Chronic Urticaria

- Vitamin C 222 mg/mL 12 mL
- Magnesium chloride hexahydrate 20% 3 mL
- Calcium gluconate 10% 1.5 mL
- Hydroxocobalamin 1,000 mcg/mL (B12) 1 mL
- Pyridoxine hydrochloride 100 mg/mL (B6) 1 mL
- Dexpanthenol 250 mg/mL (B5) 1 mL
- B complex 100 1 mL

Mixed with Sterile water or Normal Saline to the ideal osmolarity

Time: 5-15 minutes, 25 G butterfly needle

1 mL B-complex 100 = 100 mg each of thiamine and niacinamide, and
2 mg each of riboflavin, dexpanthenol, and pyridoxine

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Nutrients in Myers' Cocktail
Athletic Performance

- Vitamin C 222 mg/mL 16 mL
- Magnesium chloride hexahydrate 20% 5 mL
- Calcium gluconate 10% 2.5 mL
- Hydroxocobalamin 1,000 mcg/mL (B12) 1 mL
- Pyridoxine hydrochloride 100 mg/mL (B6) 1 mL
- Dexpanthenol 250 mg/mL (B5) 1 mL
- B complex 100 1 mL

Mixed with Sterile water or Normal Saline to the ideal osmolarity

Time: 5-15 minutes, 25 G butterfly needle

1 mL B-complex 100 = 100 mg each of thiamine and niacinamide, and
2 mg each of riboflavin, dexpanthenol, and pyridoxine

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Nutrients in Myers' Cocktail
Hyperthyroidism

- IV Myers' once or twice weekly for several weeks
- Daily IM injections of magnesium chloride (20 ML of a 14 percent solution) for 3-7 weeks
- IV vitamin B6 (50 mg per day) reported to relieve muscle weakness in 3 patients (Rosenbaum, et al, *J lab Clin Med* 1941; 27:763-770)

Time: 5-15 minutes, 25 G butterfly needle

1 mL B-complex 100 = 100 mg each of thiamine and niacinamide, and
2 mg each of riboflavin, dexpanthenol, and pyridoxine

Alternative Medicine Review ◆ Volume 7, Number 5 ◆ 2002

Nutrients in Myers' Cocktail
Selection of Ingredients

Alan R. Gaby, MD

- Cyanocobalamin (widely available) vs hydroxocobalamin (compounded & available commercially)
  - Hydroxocobalamin is preferred because it produces more prolonged increases in serum vitamin B12 levels (Glass GB, Skeggs HR, Lee DH, et al. Applicability of hydroxocobalamin as a long-acting vitamin B12. *Nature* 1961; 189:138-140)
  - Hydroxoycobalamin:
    - Has 2x circulatory half-life compared to cyanocobalamin (36 hours vs 18 hours)
    - Has increased protein receptor binding sites, so less excretion, thus longer half-life
    - No concern for possible cyanide poisoning with daily parenteral doses of 5 ml or more daily
    - Has been used for treatment of cyanide poisoning using high doses

Alternative Medicine Review ◆ Volume 7, Number 5 ◆ 2002

Nutrients in Myers' Cocktail
Selection of Ingredients

Alan R. Gaby, MD

- Magnesium chloride hexahydrate (20% solution) vs Magnesium sulfate heptahydrate (50% solution)
  - Most clinical research has been done with magnesium sulfate, some experts prefer magnesium chloride for IV use because of its greater retention in the body.

    (Durlach J, Bara M, Theophanides T. A hint on pharmacological and toxicological differences between magnesium chloride and magnesium sulphate, or of scallops of men. *Magnes Res* 1996; 9:217-219.)
  - IM magnesium sulfate

Alternative Medicine Review ◆ Volume 7, Number 5 ◆ 2002

Nutrients in Myers' Cocktail
Selection of Ingredients

Alan R. Gaby, MD

- Vitamin C available in concentrations of 222 and 500 mg per mL
  - Gaby typically uses the lower concentration for IV therapy

Alternative Medicine Review ◆ Volume 7, Number 5 ◆ 2002

Nutrients in Myers' Cocktail

Selection of Ingredients

Alan R. Gaby, MD

- MTE-5
  - Usual dose: 0.2-0.5 mL
  - 1 mL MTE-5 = 1 mg Zinc, 0.4 mg Copper, 0.1 mg Manganese, 4 mcg Chromium; 20 mcg Selenium
  - Administered over a period of 1-2 minutes in a separate syringe at the end of the Myers' push

Alternative Medicine Review ◆ Volume 7, Number 5 ◆ 2002

Nutrients in Myers' Cocktail

Side Effects and Precautions

Alan R. Gaby, MD

- Sensation of heat, with large doses or rapid administration, due to magnesium. Similar effect has been noted with calcium
- Too rapid administration of magnesium can cause hypotension→ lightheadedness or syncope
- Some patients experience more pronounced benefits from rapid infusions than from slower ones, presumably because of higher peak serum concentrations of nutrients

Alternative Medicine Review ◆ Volume 7, Number 5 ◆ 2002

Nutrients in Myers' Cocktail

Side Effects and Precautions

Alan R. Gaby, MD

- When administering the Myers' to a patient for the first time, it is best to give 0.5 – 1.0 mL and then wait 30 seconds before proceeding to distinguish between a vasovagal reaction and a hypotensive response to the injected compounds
- For elderly or frail individuals, start with lower doses or consider IM administration of Mg and B vitamins

Alternative Medicine Review ◆ Volume 7, Number 5 ◆ 2002

Nutrients in Myers' Cocktail

Side Effects and Precautions

Alan R. Gaby, MD

- Patients who are deficient in both magnesium and potassium may have an influx of potassium into the cells after receiving IV magnesium.
- This occurs because magnesium activates the membrane pump that promotes the intracellular uptake of potassium. The shift of potassium from the serum to the intracellular space can trigger hypokalemia.
- Possible to have severe muscle cramps several hours after receiving a Myers'
- Caution with patients taking medications known to deplete potassium

Alternative Medicine Review ◆ Volume 7, Number 5 ◆ 2002

Nutrients in Myers' Cocktail

Side Effects and Precautions

Alan R. Gaby, MD

- Patients considered to be at risk of potassium deficiency include those taking potassium depleting diuretics, beta-agonists, or glucocorticoids; those with diarrhea or vomiting; and those who are generally malnourished.
- If a patient is hypokalemic, the hypokalemia should be corrected before IV magnesium therapy is considered.
- A normal serum potassium concentration is not a guarantee against intracellular potassium depletion.
- For patients considered to be at risk of potassium deficiency, administration of 10-20 mEq of potassium orally just prior to the infusion, and again 4-6 hours later is recommended to avoid magnesium-induced muscle cramps

Alternative Medicine Review ◆ Volume 7, Number 5 ◆ 2002

Nutrients in Myers' Cocktail

Side Effects and Precautions

Alan R. Gaby, MD

- Intravenous calcium is contraindicated in patients taking digoxin
- Hypercalcemia can cause cardiac arrhythmias
- Anaphylactic reactions to IV thiamine have been reported on rare occasions
- Reactions have occurred after oral, IV, IM, or subcutaneous administration, and are believed to be due in part to a nonspecific release of histamine
- Many patients who receive parenteral thiamine are alcoholics, and alcoholism frequently causes magnesium deficiency.

Alternative Medicine Review ◆ Volume 7, Number 5 ◆ 2002

Nutrients in Myers' Cocktail

Side Effects and Precautions

Alan R. Gaby, MD

- A deficiency of magnesium can lead to spontaneous release of histamine
- A small number of patients (approximately one percent) felt "out of sorts" for up to a day after receiving an injection and, in two cases, this reaction lasted one and two weeks, respectively. It is not clear whether these reactions were due to the preservatives in some of the injectable preparations (e.g., benzyl alcohol, methylparabens, or others) or to the nutrients themselves.

Alternative Medicine Review ◆ Volume 7, Number 5 ◆ 2002

Nutrients in Myers' Cocktail

Side Effects and Precautions

Alan R. Gaby, MD

- Some patients experienced a burning sensation at the injection site during the infusion; this was often corrected by re-positioning the needle or by further diluting the nutrients

Alternative Medicine Review ◆ Volume 7, Number 5 ◆ 2002

Cost Considerations

Alan R. Gaby, MD

- Cost of the materials for a Myers' ~ $5.00 (1995)
- Fee of Myers' was $38.00 (Gaby). Other doctors have charged as little as $15.00 or as much as $100.00 or more.
- Cost of most of the injectable preparations has increased by 50-100 percent, since 1995

Alternative Medicine Review ◆ Volume 7, Number 5 ◆ 2002

Safety & Effectiveness

Alan R. Gaby, MD

- The Myers' has been found by Gaby and hundreds of other practitioners to be a safe and effective treatment for a wide range of clinical conditions.
- Evidence is anecdotal, some published research has demonstrated the efficacy of the Myers' or some of its components.

(Altern Med Rev 1999;4(1):37-44)

Derrick Lonsdale, M.D., Raymond J Shamberger, Ph.D., John P. Stahl, Ph.D., Ronald Evans, M.A.

Table 1. Myer's Cocktail.

Dextrose 5% in sterile water			50 - 100 cc
Magnesium Chloride 20%			2 - 5 cc
Calcium Gluconate 10%			10 cc
Pyridoxine Hydrochloride (100 mg/cc)			1 cc
Dexpanthenol (250 mg/cc)			1 cc
Vitamin C (222 mg/cc)			30 cc
Hydroxocobalamin (1000 mcg/cc)			1 cc
Thiamine Hydrochloride (100 mg/cc)			0.5 cc
Trace Mineral Mixture			1 - 2 cc
Each ml contains:	Zinc	5 mg	
	Copper	1 mg	
	Manganese	0.5 mg	
	Chromium	10 mcg	
	Selenium	60 mcg	

(Altern Med Rev 1999;4(1):37-44)

Table 2. Nutritional I.V.

Sterile Water		500 cc
Magnesium Chloride		2 gm (10 cc)
Potassium Chloride		5 meq (2.5 cc)
Dexpanthenol		500 mg (2 cc)
Folic Acid		10 mg (1 cc)
Manganese Chloride		1 mg (0.5 cc)
Zinc Chloride		10 mg (1 cc)
Selenium		200 mcg (5 cc)
Chromium		40 mcg (10 cc)
Ascorbic Acid		20 gm (40 cc)
Adenosine 5' Monophosphate		125 mg (0.5 cc)
Procaine 2% (pm)		100 mg (5 cc)
Pyridoxine Hydrochloride		100 mg (1 cc)
Hydroxocobalamin		1000 mcg (1 cc)
Vitamin B Complex 100		2 cc
Each ml contains:	Thiamine HCl	100 mg
	Riboflavin 5' Phosphate Sodium	2 mg
	Pyridoxine HCl	2 mg
	Dexpanthenol	2 mg
	Niacinamide	100 mg

ALTERNATIVE THERAPIES, MAY/JUNE 2007, VOL. 13, NO. 3

Patrick B. Massey, MD, PhD

TABLE Modified Myers' Intravenous Nutrient Formula

Vitamin/Mineral	Dose
Magnesium chloride hexahydrate	400 mg
Calcium gluconate	40 mg
Vitamin C	3000 mg
Hydroxocobalamin (B_{12})	1,000 µg
Pyridoxine hydrochloride (B_6)	100 mg
Dexpanthenol (B_5)	250 mg
Riboflavin (B_2)	2 mg
Thiamine (B_1)	100 mg
Niacinamide	100 mg

Participants received IVNT once per week for 8 weeks, using the modified Myers' formula (see Table) diluted in 100 mL of normal saline. The infusion was given in a peripheral vein over 20-30 minutes. There were no complications or reported side effects. Pain levels (initial and final) and fatigue levels (initial and final) were analyzed using the Student's *t* test (n=7, $P<.005$).

THE JOURNAL OF ALTERNATIVE AND COMPLEMENTARY MEDICINE
Volume 15, Number 3, 2009, pp. 247–257

Intravenous Micronutrient Therapy (Myers' Cocktail) for Fibromyalgia: A Placebo-Controlled Pilot Study

Ather Ali, N.D., M.P.H.,[1] Valentine Yanchou Njike, M.D., M.P.H.,[1] Veronika Northrup, M.P.H.,[1] Alyse B. Sabina, M.P.H.,[1] Anna-Leila Williams, P.A.-C., M.P.H.,[1] Lauren S. Liberti, M.S.,[1] Adam I. Perlman, M.D., M.P.H.,[2] Harry Adelson, N.D.,[1] and David L. Katz, M.D., M.P.H.[1]

The intervention is based on the current Myers' cocktail[33] containing:

- 5 mL of magnesium chloride hexahydrate (20%)
- 3 mL of calcium gluconate (10%)
- 1 mL of hydroxocobalamin (1,000 µg/mL)
- 1 mL of pyridoxine hydrochloride (100 mg/mL)
- 1 mL of dexpanthenol (250 mg/mL)
- 1 mL of B-complex 100 containing:
  - 100 mg of thiamine HCl, 2 mg of riboflavin, 2 mg of pyridoxine HCl, and 2 mg of panthenol
  - 100 mg of niacinamide, 2% benxyl alcohol
  - 5 mL of vitamin C (500 mg/mL)
  - 20 mL of sterile water.

Weekly x 8 weeks

Immune Drip

- 500 cc Bag Sterile Water
- 1 bottle of Vitamin C 500 mg/ml-50 ml
- 2 cc of B12 1000 mcg/ml
- 2 cc of B-complex 100 mg/ml
- 1 bottle of Calcium gluconate 10%- 10 cc
- 2 cc of Chromium 40 mcg/ml
- 2 cc of B6 100 mg/ml
- 1 cc of B5 250 mg/ml
- 5 cc of Potassium chloride 40 mEq
- 2 cc of Zinc 1 mg/ml
- 1 cc of Selenium 40 mcg/ml
- ½ cc of Folic acid 5 mg/ml
- 6 cc of Magnesium chloride 500 mg/ml

- 2.5 cc of Glutathione 200 mg/ml plus 10 ml normal saline PUSH
- Infused over 1-1.5 hour
- Indications: cold/influenza, chronic fatigue
- *Check G6PD*
- 24 G catheter

Cancer Cachexia-Malnutrition

• Sterile Water	500 cc
• FreAmine III 8.5%	100 cc
• B-complex 100	3 cc
• Calcium gluconate 100 mg/ml	5 cc
• Dexpanthenol 250 mg/ml	2 cc
• Hydroxocobalamin 1 mg/ml	1 cc
• Magnesium sulfate 500 mg/ml	5 cc
• Manganese 0.1 mg/ml	5 cc
• Molybdenum 25 mcg/ml	4 cc
• Potassium chloride 20 mEq	10 cc
• Pyridoxine 100 mg/ml	3 cc
• Selenium 100 mcg/ml	2 cc
• Zinc sulfate 5 mg/ml	1 cc

- Osmolarity: 286 mOsm/L
- 1.5% amino acid solution
- Est tx time: 3-4 hrs
- Desired drip rate: 3-4 ml/min

Mineral IV

- Calcium gluconate (10%) 4 g
- Magnesium sulfate (50%) 2 g
- Chromium 50 mcg
- Copper 1 mg
- Manganese 0.1 mg
- Molybdenum 100 mcg
- Selenium 200 mcg
- Zinc 10 mg
- Rubidium 50 mcg
- Boron 500 mcg
- Lithium 2 mg
- Strontium 200 mcg
- Vanadium 25 mcg
- 0.45% Saline 250 ml

- Osmolarity:
  ~280 mOsm/L
- Est tx time: 2-3 hrs
- Desired drip rate:
  12 gtt per 15 sec when using 20 gtt per ml filter tubing set.

Measurement of all minerals, except Calcium or Magnesium, is elemental.

Blood Osmolarity

- Normal blood plasma is 290 mOsm/L.

Osmolarity

$$\text{Osmolarity} = \frac{\text{Osmoles}}{\text{Volume}}$$

We refer to osmolarity in *milli*osmoles

$$\text{mOsm/L} = \frac{\text{Milliosmoles}}{\text{Liter}}$$

$$\text{mOsm/mL} = \frac{\text{Milliosmoles}}{\text{Milliliter}}$$

Isotonic Fluids

- Osmolarity between 240-375 mOm/L and are used to expand the extracellular fluid compartment.
- **Normal saline** (0.9% sodium chloride), **D5W** (5% dextrose solution) and **Lactated Ringers** (an electrolyte solution) are all isotonic.

Hypertonic Fluids

- Osmolarity of 375 mOsm/L or higher.
- Used to replace electrolytes.
- Most nutritional IV solutions are hypertonic.
- They shift extracellular fluid from the interstitial space to the plasma.-*sucks fluid into the vasculature*
- Hypertonic fluids can result in circulatory overload as fluids drawn out of the cells.

Hypotonic Fluids

- Osmolarity below 250 mOsm/L

  45% NaCl:
- 0.45% sodium chloride (NaCl) has an osmolarity of 145 mOsm/L. It can be used to hydrate cells and for low serum sodium levels *(Hyponatremia can begin at about 280mOsm/L)*.
- Do not use alone in a clinical setting. It is useful to dilute hypertonic nutrient prescriptions.
- Hypotonic solutions can deplete the circulatory system and incur hypotension and shock.

Osmolarity Calculation

$$\left(\frac{\text{Sum (mOsm per solute * ml of solute)}}{\text{Total volume of solution (ml)}} \right) \text{X } 1000 = \underline{\text{mOsm/L}}$$

mOsm/L

- Various between different compounding pharmacies

Solution	Compounding Pharmacy	
	A	B
Ascorbic Acid,500mg/ml	5.80 mOsm/L	5.05 mOsm/L
Pyridoxine 100 mg/ml	1.11 mOsm/L	0.97 mOsm/L

Nutrient IV Solution Osmolarity

Component	Volume (**ml**-*same as cc)*	mOsm/ml *(constant per solute)*	Total mOsmo Volume (ml) X mOsm
Ascorbic Acid,500mg/ml	100	5.80	580.0
Calcium gluconate 10%	50	0.72	36.0
Magnesium sulfate 500 mg/ml	4	4.06	16.16
B-Complex 100	5	2.14	10.7
Pyridoxine 100 mg/ml	3.33	1.11	3.33
Hydroxycobalamin, 1000 mcg/ml	3	0.31	.93
Selenium, 40 mcg/ml	10	0.0005	0.005
Sodium bicarbonate, 8.4%	10	2.0	20.0
Sterile water	450	0	0
Totals	***Sum = 635***		***Sum = 667***

Nutrient IV Solution Osmolarity

$$\left(\frac{\text{Sum (mOsm per solute * ml of solute)}}{\text{Total volume of solution (ml)}} \right) \text{X } 1000 = \underline{\text{mOsm/L}}$$

- 667/635 X 1000 = solution osmolarity = **<u>1050 mOsm/L</u>**

CALCULATING OSMOLARITY FOR ALL IVS

Plasma Osmolarity averages from about
0.280 to .310 mOsm/ml, or
280 – 310 mOsm/L

Most IVs are slightly to moderately hypertonic

*Hypo*tonic IVs can be dangerous

SAFE OSMOLARITY LIMITS

IV Push (mOsm/ml)	
Large vein	1.40
Medium vein	0.950
Any vein	0.400
IV Infusion (mOsm/ml)	
Large vein	1.20
Medium vein	0.700
Any vein	0.400

The longer the infusion and the smaller the vein, the more conservative you should be with the osmolarity

Shrader IV Nutrient Osmolarity

Nutrients	mOsm per mL	Shrader IV
Ascorbic Acid 500 mg/mL	5.8	4
B-6 (Pyridoxine) 100 mg/mL	1.11	1
B-12 (hydroxocobalamine) 1000 mcg	0.31	2
B-complex 100 mg/mL	2.14	1
Calcium Gluconate 10% 100 mg/mL	0.72	2
Magnesium chloride 200 mg/mL	2.95	5
Pantothenic acid 250 mg/mL	0.85	1
Total Additives		16
mOsm Additives		44.1
Sterile water	0	17
Syringe, in mL		35
Osmolarity (mOsm/L)		**1336**

Shrader IV Nutrient Osmolarity

Volume	Osmolarity
19 cc Sterile Water	1336 mOsm/L
44 cc Sterile Water	800 mOsm/L
50 cc Normal Saline	963 mOsm/L
100 cc Normal Saline	699 mOsm/L
250 cc Normal Saline	503 mOsm/L

Calculating Drip Rates

$$\left(\frac{\text{Total Volume of IV solution ml}}{\text{Recommended drip rate in minutes}}\right) \text{X (Drip Rate of IV tubing)= drops/min.}$$

- **Divide this # of drops/min by 4, this is # of drops per 15 seconds thru drip chamber**

Calculating Drip Rates

$$\left(\frac{\text{Total Volume of IV solution ml}}{\text{Recommended drip rate in minutes}}\right) \text{X (Drip Rate of IV tubing)= drops/min.}$$

- **Using CaEDTA as Example Solution:**

  [120 ml/(30 min)](20 $^{drops}/_{ml}$)

  = drip rate=80 $^{drops}/_{min}$

  (20 drops/15 sec)

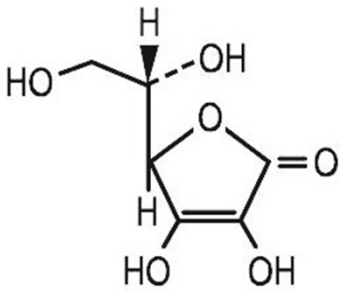
- **Using NaEDTA as Example Solution:**

  [310.5 ml/(180 min)](20 $^{drops}/_{ml}$)

  = drip rate=35 $^{drops}/_{min}$

  (8-9 drops/15 sec)

Ascorbic Acid



Ascorbic Acid

Benefits

- Preoperative and postoperative maintenance of optimal health
- Increased vitamin requirements or replacement therapy in severe burns, extensive injury and infections
- Hemovascular disorders
- Promotes healthy capillaries, gums and teeth
- Delayed fracture and wound healing
- Aids iron absorption
- Treats urinary tract infections
- Forms collagen in connective tissues, prevents wrinkling
- Reduces allergic reactions
- Prevents scurvy

Ascorbic Acid

Symptoms of deficiency

- Scurvy - muscle weakness, swollen and bleeding gums, loss of teeth, tiredness, depression, irritability, bleeding under skin
- Shortness of breath
- Digestive difficulties
- Easy bruising
- Swollen painful joints
- Nosebleeds
- Anemia: weakness, tiredness, paleness
- Frequent infections
- Slow wound healing
- Behavioral symptoms - lassitude, hypochondrias, depression, hysteria

Ascorbic Acid

- Precautions
  - Bowel flush is diagnosis for vitamin C saturation (oral)
  - Antagonizes anticoagulants.
  - Controversy and debate over whether large doses of vitamin C cause renal calculi. Use caution in renal calculi/colic patients.
  - Use caution in cardiac and renal patients. Sodium content may contribute to fluid retention and congestive heart failure.
  - Side effects: temporary dizziness and faintness occur with too rapid injection.
  - Test for allergy in sensitive patients.

Ascorbic Acid

- Research

Chem.-Biol. Interactions, 9 (1974) 285–315

THE ORTHOMOLECULAR TREATMENT OF CANCER*
II. CLINICAL TRIAL OF HIGH-DOSE ASCORBIC ACID SUPPLEMENTS IN ADVANCED HUMAN CANCER

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(Accepted July 15th, 1974)

Ascorbic Acid

[Original Research **Critical Care**]

CHEST

Hydrocortisone, Vitamin C, and Thiamine for the Treatment of Severe Sepsis and Septic Shock

A Retrospective Before-After Study

Paul E. Marik, MD, FCCP; Vikramjit Khangoora, MD; Racquel Rivera, PharmD; Michael H. Hooper, MD; and John Catravas, PhD, FCCP

BACKGROUND: The global burden of sepsis is estimated as 15 to 19 million cases annually, with a mortality rate approaching 60% in low-income countries.

METHODS: In this retrospective before-after clinical study, we compared the outcome and clinical course of consecutive septic patients treated with intravenous vitamin C, hydrocortisone, and thiamine during a 7-month period (treatment group) with a control group treated in our ICU during the preceding 7 months. The primary outcome was hospital survival. A propensity score was generated to adjust the primary outcome.

RESULTS: There were 47 patients in both treatment and control groups, with no significant differences in baseline characteristics between the two groups. The hospital mortality was 8.5% (4 of 47) in the treatment group compared with 40.4% (19 of 47) in the control group ($P < .001$). The propensity adjusted odds of mortality in the patients treated with the vitamin

Ascorbic Acid

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CLINICAL RESEARCH

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

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F

ACDE Nina A. Mikirova
A Ronald Hunninghake

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

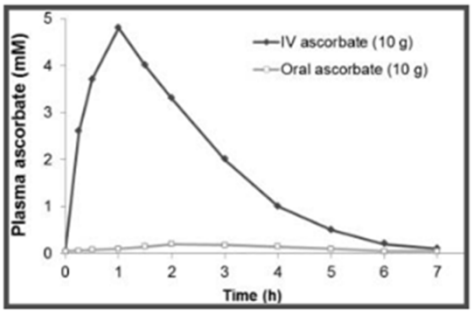
Conclusions:

The clinical study of ascorbic acid and EBV infection showed the reduction in EBV EA IgG and EBV VCA IgM antibody levels over time during IVC therapy that is consistent with observations from the literature that millimolar levels of ascorbate hinder viral infection and replication *in vitro*.

Ascorbic Acid

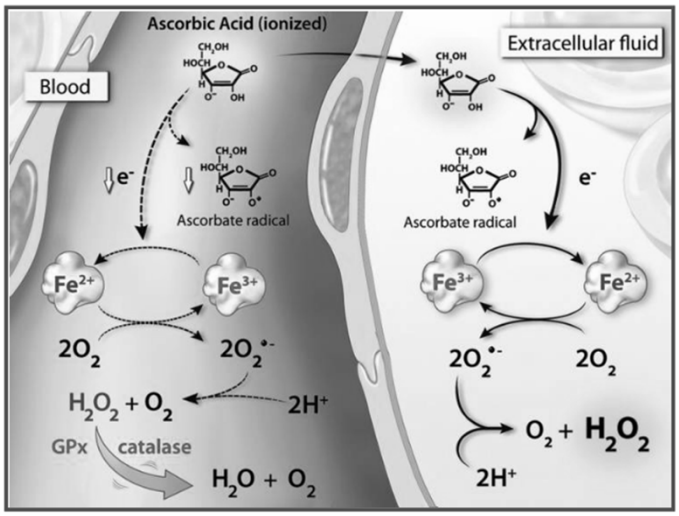
Can. J. Physiol. Pharmacol. Vol. 93, 2015

Fig. 2. Intravenous and oral administration of high-dose ascorbate has totally different pharmacokinetics. While Pauling and Cameron used both intravenous and oral administration in their cancer trials, Moertel's trials used only oral ascorbate. The different administration routes could explain the conflicting outcomes between the 2 kinds of clinical studies. (Figure is based on data derived from Levine et al. 1996; Padayatty et al. 2004; Chen et al. 2008; and Hoffer et al. 2008).



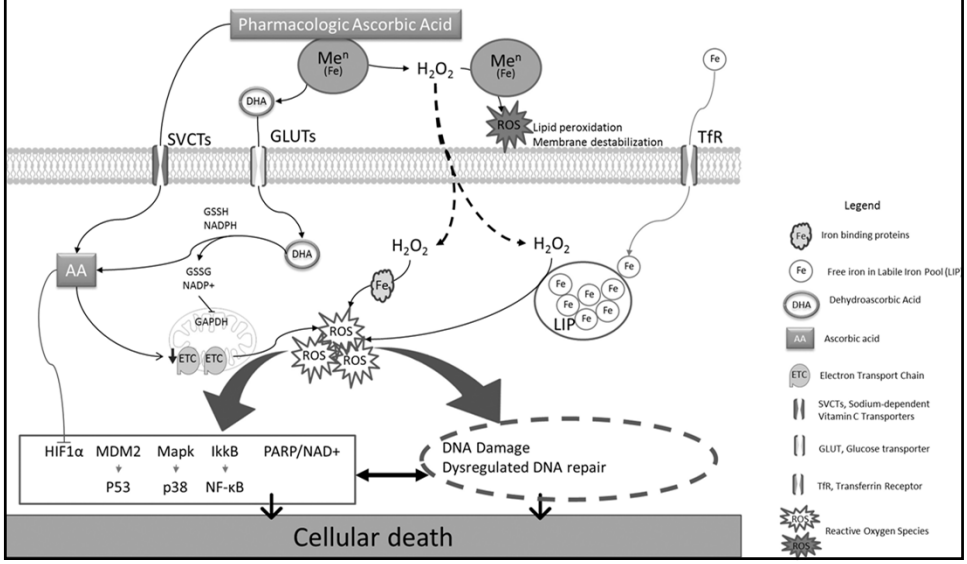
Ascorbic Acid

Can. J. Physiol. Pharmacol. 93: 1055–1063 (2015) dx.doi.org/10.1139/cjpp-2014-0509



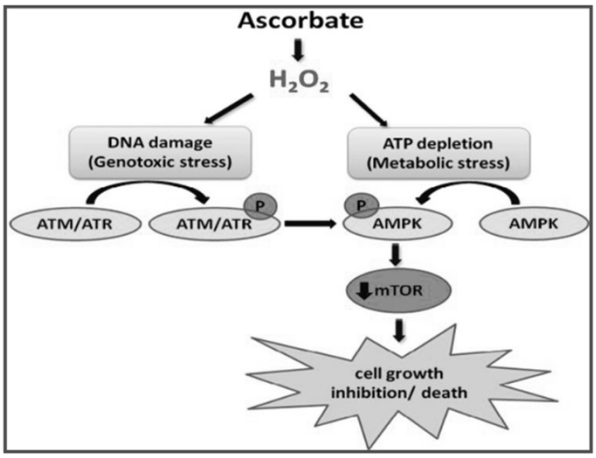
Ascorbic Acid

http://dx.doi.org/10.1016/j.ccell.2017.03.008



Ascorbic Acid

Fig. 4. A simplified diagram for the mechanism of ascorbate-induced cancer-cell death. (From Ma et al. 2014; reprinted with permission from American Association for the Advancement of Science).



Ascorbic Acid

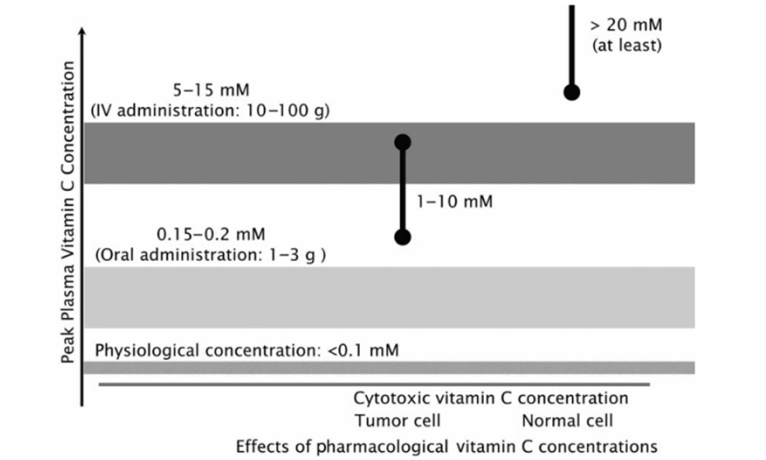


Figure 1. *Peak plasma vitamin C concentrations after oral or intravenous (IV) administration of vitamin C and cytotoxic effect of pharmacological vitamin C concentrations on tumor and normal cells. Plasma vitamin C concentrations that cause toxicity to cancer cells in vitro can be achieved clinically by intravenous, but not oral, administration of ascorbate.*

Ascorbic Acid

ANTICANCER RESEARCH 29: 809-816 (2009)

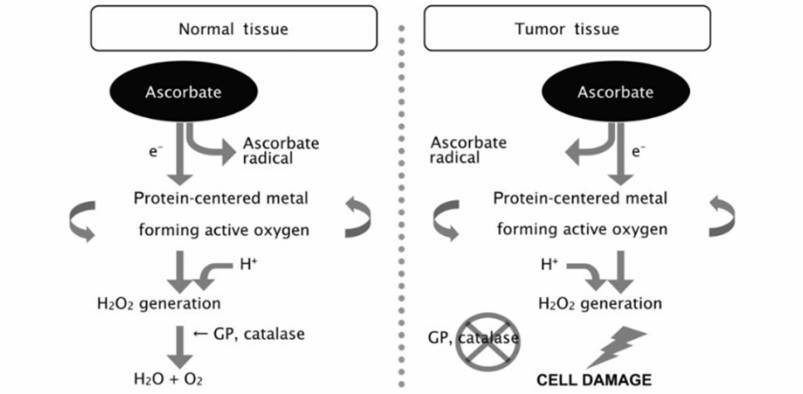


Figure 2. *Proposed mechanism of antitumor effects of vitamin C. The administration of more than 10 g of ascorbate is proposed to achieve plasma concentrations of 1 to 5 mM. At this time, vitamin C at high plasma concentration may function as a pro-oxidant. This occurs in the presence of free transition metals, such as copper and iron, which are reduced by ascorbate and, in turn, react with hydrogen peroxide (H_2O_2), leading to the formation of highly reactive and damaging hydroxyl radicals. As normal tissue receives adequate blood flow and is rich in antioxidant enzymes (e.g. catalase, glutathione peroxidase; GP) in the blood, any H_2O_2 formed will be immediately destroyed. Meanwhile, tumor tissue is often associated with reduced blood flow and antioxidant enzymes, and consequently formed H_2O_2 remains active leading to cell damage and death.*

Ascorbic Acid

CLINICAL SCIENCES

Intravenous Ascorbic Acid: Protocol for its Application and Use

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High dose intravenous (IV) ascorbic acid (AA) has been used as therapy for infectious disease from bacterial and viral origin and adjuvant therapy for cancer. In this publication we describe a clinical protocol that has been developed over the past twenty years utilizing high dose IV AA as therapy for cancer. This includes principles of treatment, rationale, baseline workup, infusion protocol, precautions and side effects.

Key words: Intravenous ascorbic acid, Intravenous vitamin C, Cancer

High dose intravenous ascorbic acid (IAA) has been used as a therapy for bacterial infection, viral infection, and as adjuvant therapy for Cancer (1-7). The treatment rationale for the use or IAA in treatment

pain and in many cases improved survival times beyond predictions of experienced oncologists. Later using 30 grams of IAA, twice per week, it was found that metastatic lesions in lung and liver of a man with primary renal cell

Ascorbic Acid

Infusion. As indicated in the precautions, a small starting dose of 15gm AA in 250ml RL over 1hr is recommended and the patient is observed closely for any adverse event.

The dose can be gradually increased over time but the infusion rate should not exceed 1gm AA per min., 0.5 gm/min is well tolerated by most patients. Although there is variability due to scheduling and tolerance, a typical protocol may consist of the following infusions:

week 1: 1 x 15gm.	infusion per day	2-3 per week
week 2: 1 x 30gm.	infusion per day	2-3 per week
week 3: 1 x 65gm.	infusion per day	2-3 per week
week 4: 1 x 100gm.	infusion per day	2-3 per week

- Infusion rate: 0.5 gram/minute

Ascorbic Acid

Riordan Clinic Research Institute

February 2013

The Riordan IVC Protocol for Adjunctive Cancer Care

Intravenous Ascorbate as a Chemotherapeutic and Biological Response Modifying Agent

solution, MEGA-C-PLUS®, 500 mg/mL, pH range 5.5-7.0 from Merit Pharmaceuticals, Los Angeles, CA, 90065.

Treatment volume of Ascorbic acid	Solution Volume		Withdraw from solution and discard	remaining solution	Inject volume of AA into solution	inject volume of $MgCl_2$ into solution	final volume	Infusion rate	total infusion time
	Ringer Lactate	Sterile water							
15 grams (30cc)	250 cc		31cc	219 cc	30 cc	1 cc	250 cc	0.5-1.0 g/min	~ 0.5 h
25grams (50cc)	500cc		51cc	449cc	50cc	1cc	500cc	0.5-1.0 g/min	~ 1 h
50 grams (100cc)		500cc	102cc	398 cc	100 cc	2cc	500cc	0.5-1.0 g/min	~ 1.5 h
75 grams (150cc)		750cc	152cc	598cc	150cc	2cc	750cc	0.5-1.0 g/min	~ 2.5 h
100grams		1000cc	202cc	798cc	200cc	2cc	1000cc	0.5-1.0 g/min	~ 3.5 h

https://riordanclinic.org/research-study/vitamin-c-research-ivc-protocol/

Ascorbic Acid

Administration of IVC

Having taken all precautions listed above and having obtained informed consent from the patient, the administering physician begins with a series of three consecutive IVC infusions at the 15, 25, and 50 gram dosages followed by post IVC plasma vitamin C levels in order to determine the oxidative burden for that patient so that subsequent IVCs can be optimally dosed.

The initial three infusions are monitored with post IVC infusion plasma vitamin C levels. As noted above (Scientific Rational), research and experience has shown that a therapeutic goal of reaching a peak-plasma concentration of ~20 mM (350- 400 mg/dL) is most efficacious. (No increased toxicity for post IVC plasma vitamin C levels up to 780 mg/dL has been observed.) The first post IVC plasma level following the 15 gram IVC has been shown to be clinically instructive: levels below 100 mg/dL correlate with higher levels of existent oxidative stress, presumably from higher tumor burden, chemo/radiation damage, hidden infection, or other oxidative insult, such as smoking.

https://riordanclinic.org/research-study/vitamin-c-research-ivc-protocol/

Ascorbic Acid

Shrader's Protocols

Vitamin C Protocols for the Adjunctive Treatment of Cancer

	Vitamin C						
	15 grams	**30 grams**	**45 grams**	**50 grams**	**60 grams***	**60 grams**	**100 grams**
			500 cc bottle			1000 cc bottle	
				Amounts to add (cc)			
Ascorbic Acid 500 mg/ml	30	60	90	100	120	120	200
B-6 (Pyridoxine) 100 mg/ml	1	1	1	1	1	1	1
B-12 (hydroxocobalamine) 1000 mcg.	1	1	1	1	1	1	1
B-Complex 100 mg/ml	1	1	1	1	1	1	1
Sodium Bicarbonate 8.4%	18	18	28	45	50	50	60
Calcium Gluconate 10% 100 mg./ml	10	10	15	25	40	40	40
Folic Acid 10 mg./ml †	1	1	1	1	1	1	1
Magnesium Chloride 200 mg./ml	5	5	5	5	5	5	2
Pantothenic acid 250 mg./ml	1	1	1	1	1	1	1
Additives	68	98	143	180	220	220	307
Milliosmoles of additives	213	411	608	707	844	844	1308.9
Sterile Water (bottle size)	500	500	500	500	*500*	*1000*	1000
Remove:			**40**	**80**	**100**	**300**	**200**
Total Volume	568	598	603	600	620	920	1020
Osmolarity (mOsm/L)	**385**	**687**	**1009**	**1179**	**1362***	**918**	**1182**
Infusion rate (drops/min.):	*120*	*130*	*130*	*130*	*130*	*180*	*185*

Note: this solution is quite hypertonic and some patients will tolerate it only in a large vein, if then. It may easily and very safely be given via an implanted central venous IV port.

Ascorbic Acid

- Anderson P., Naydis E., Standish L. (2011, November). *High Dose IV Ascorbic Acid Therapy: the Bastyr Experience*. Poster session presented at the Society for Integrative Oncology, Cleveland, OH.
- Interventional Study: HDIVC and Electrolyte Shifts

Ascorbic Acid

- Questions regarding electrolyte shifts and HDIVC administration.
  - Hypocalcemia
  - Hypokalemia
  - Hypernatremia
  - Hypochloremia

Anderson P., Naydis E., Standish L. (2011, November)

Ascorbic Acid

Base IVC Formula

- For research purposes Anderson et al. attempted to emulate the 'modified Drisko protocol' which had minimal additives:
  - Carrier Solution: Sterile Water
  - Vitamin C: C-500 (commercial 500 mg / mL)
  - Magnesium Sulfate: 50% $MgSO_4$

Anderson P., Naydis E., Standish L. (2011, November), image used with permission
http://www.naturalmedicinejournal.com/journal/2014-02/intravenous-vitamin-c-cancer

Ascorbic Acid

High Dose IVC and Electrolyte changes data:

- Baseline:
  - Na (N=135-145)
    - Mean = 140
  - Cl (N=98-111)
    - Mean = 102
  - Ca (N=8.5-10.5)
    - Mean = 9.1
  - K (N=3.5-5.4)
    - Mean = 4.1
- Directly post IVC:
  - Na
    - Mean = 147.3 **(HIGH)**
  - Cl
    - Mean = 90.25 **(LOW)**
  - Ca
    - Mean = 8.4 **(LOW)**
  - K
    - Mean = 4.58 **(Normal)**

Anderson P., Naydis E., Standish L. (2011, November), image used with permission

Ascorbic Acid

High Dose IVC and Electrolyte changes data - New Formula

- Baseline:
  - Na (N=135-145)
    - Mean = 140
  - Cl (N=98-111)
    - Mean = 102
  - Ca (N=8.5-10.5)
    - Mean = 9.1
  - K (N=3.5-5.4)
    - Mean = 4.1
- Directly post IVC:
  - Na
    - Mean = 144.93 **(Normal)**
  - Cl
    - Mean = 94.59 **(LOW)**
  - Ca
    - Mean = 8.64 **(Normal)**
  - K
    - Mean = 4.70 **(Normal)**

Anderson P., Naydis E., Standish L. (2011, November), image used with permission

Ascorbic Acid

Table 1. BIORC Formula for an Infusion of 25 g of Intravenous Vitamin C

Nutrient	Concentration	Amount Added
Vitamin C	500 mg/mL	50 mL
Calcium chloride	100 mg/mL	1 mL
Magnesium chloride	200 mg/mL	2 mL
Potassium chloride	2 mEq	1 mL
Sterile water		500 mL

For a total volume of 554 mL and an osmolarity of 558 mOsm/L.

Anderson P., Naydis E., Standish L. (2011, November)
http://www.naturalmedicinejournal.com/journal/2014-02/intravenous-vitamin-c-cancer

Ascorbic Acid

Table 2. BIORC Formula for an Infusion of 50 g of Intravenous Vitamin C

Nutrient	Concentration	Amount Added
C-500	500 mg/mL	100 mL
Calcium chloride	100 mg/mL	3 mL
Potassium chloride	2 mEq	4 mL
Magnesium chloride	200 mg/mL	5 mL
Sterile water		500 mL

For a total volume of 612 mL and an osmolarity of 1001 mOsm/L.

Anderson P., Naydis E., Standish L. (2011, November)
http://www.naturalmedicinejournal.com/journal/2014-02/intravenous-vitamin-c-cancer

Ascorbic Acid

Rx: 75 Gram IVC

750 mL	**SWI**
150 mL	**C-500 (75 grams)**
4	**Calcium Chloride (5.44 mEq)**
7	**Magnesium Chloride (13.79 mEq)**
6	**Potassium Chloride (12 mEq)**

Total Volume: 917 mL Osmolarity: 1006 mOsm/L

Anderson P., Naydis E., Standish L. (2011, November), image used with permission
http://www.naturalmedicinejournal.com/journal/2014-02/intravenous-vitamin-c-cancer

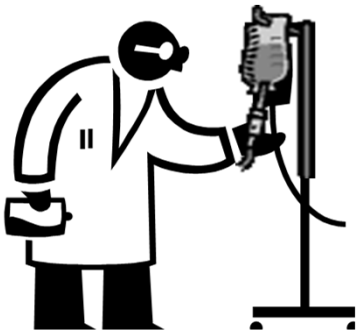
Ascorbic Acid

Rx: 100 Gram IVC

1000 mL	**SWI**
200 mL	**C-500 (100 Grams)**
5	**Calcium Chloride (6.8 mEq)**
10	**Magnesium Chloride (19.7 mEq)**
8	**Potassium Chloride (16 mEq)**

Total Volume: 1223 mL Osmolarity: 1007 mOsm/L

Anderson P., Naydis E., Standish L. (2011, November), image used with permission
http://www.naturalmedicinejournal.com/journal/2014-02/intravenous-vitamin-c-cancer



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Disclosure Statement:

Dr. McCann has indicated that she has no relevant financial relationships with any commercial supporters.

Glutathione: Beyond Redux and Detox

Glutathione is the master antioxidant in addition to many cellular functions in the body. This lecture reviews the functions of glutathione and its relationship to oxidative stress in the body. We will covers the myriad of conditions associated with low glutathione looking at the medical literature and explore options for testing to assist the clinician in determining who might benefit from glutathione administration, with an emphasis on intravenous administration. Glutathione genetic variants, relationship with GGT, Fenton reactions and the cell danger response will also be discussed.

Learning Objectives:

At the conclusion of this activity you should be able to...

1) Explain the functions of glutathione, its synthesis and regeneration and its relationship to oxidative stress
2) Compare direct and indirect testing options to help inform clinical decision making.
3) Delineate the numerous conditions associated with low glutathione levels and who might benefit from supplemental administration
4) Administer IV glutathione safely and effectively

About Dr. McCann

Dr. McCann received a B.A. in Music from Brown University and a Master's in Library Science from University at Albany. She went on to receive her Doctor of Medicine degree (MD) and simultaneously earned a Master's in Public Health (MPH) in Tropical Medicine (TM) at Tulane University in New Orleans. She completed both an Internal Medicine residency at Banner Samaritan Medical Center and a Pediatrics residency at Phoenix Children's Hospital in Phoenix, AZ.

Dr. McCann practiced medicine at the Arizona Center for Integrative Medicine where she worked and trained with renowned Andrew Weil, M.D., as one of 35 distinguished fellows in residence throughout the world. The residential fellowship provided the curriculum for Dr. Weil's current online fellowship, which now trains hundreds of practitioners, and this unique group of residential fellows lead the field of integrative medicine today.

After completion of the Fellowship, she continued her pursuit of knowledge. Dr. McCann became certified in medical acupuncture through the American Academy of Medical Acupuncture, studied environmental medicine and chelation with Dr. Walter Crinnion and biotoxins with Dr. Ritchie Shoemaker. She also attends numerous conferences annually including ILADS – International Lyme and Associated Diseases Society meetings, Membrane Medicine meetings regarding the PK protocol and other nutritional and integrative medicine trainings. Dr. McCann recently became certified by the Institute of Functional Medicine completing a rigorous program in functional medicine. Notable physicians in the functional medicine arena include Dr. Mark Hyman, Jeffrey Bland, PhD and David Perlmutter, MD. Functional medicine addresses the root causes of chronic illness through a whole-system approach to medicine.

Dr. McCann is on staff at Hoag Memorial Hospital in Newport Beach, California and has been in private practice in Costa Mesa since 2008. She founded Partners in Health at the Spring Center in August 2009.

NOTES

Glutathione: beyond redox and detox

KELLY K. MCCANN, MD, MPH
AMERICAN ACADEMY OF ENVIRONMENTAL MEDICINE
PARK CITY, UTAH
OCTOBER 5, 2017

Under Accreditation Council for Continuing Medical Education guideline disclosure must be made regarding relevant financial relationships with commercial interests within the last 12 months.

Kelly McCann, M.D.

Received an educational grant from Wellness Pharmacy

Unless otherwise stated, the level of evidence is C and based on clinical experience.

Glutathione....the unsung hero

- Other antioxidants that the body produces or consumes are like noble Jedi knights-- but glutathione, is Yoda. And Yoda, as we movie lovers know, can do wondrous things.

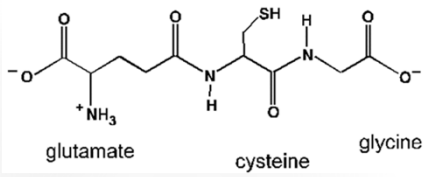
  - Julie Buckley, MD

Objectives: Glutathione

- What is it?
- Why is it important?
- What governs levels? Synthesis and regeneration
- How do we test it?
- Who needs it?
- What conditions is it beneficial in?
- How do we deliver it?

Glutathione – the master antioxidant

glutathione (GSH)



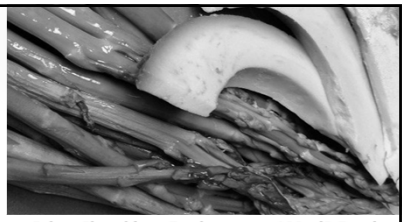
- Glutathione (GSH) is composed of three amino acids -cysteine, glycine, and glutamic acid –and can be found in every cell of the human body.
- Acts as an antioxidant due to the presence of the sulfur group on cysteine
- Supports detoxification
- Regulates cellular activity as a secondary messenger, including gene expression, DNA and protein synthesis, apoptosis and cell proliferation.
- Is involved with immune regulation
- Highest concentration in the liver and in the spleen, kidney, lens, erythrocytes, and leukocytes.

PMID: 14988435
PMID: 11804544

Dietary sources of Glutathione

- Daily glutathione intake from glutathione foods averages 100-150 mg. A healthy adult has about 10g of glutathione circulating in the body tissues. Thus, dietary intake comprises only 1-1.5% of circulating GSH.
- The rest of glutathione is produced by cells using glutathione precursors - amino-acids glutamate, glycine and cysteine.
  - Foods are highest in glutathione when they are uncooked, unprocessed and unpasteurized.
- Certain chemicals (cyanohydroxybutene, diindolylmethane, glucoraphanin, sulphraphane, indole-3-carbinol, betalains and chrolophyll) found in foods and spices are known to contribute to glutathione production in the body, assist in recycling, ad boost the synthesis and the activity of important glutathione enzymes – glutathione peroxidase (GPx) and glutathione S-transferase (GST).

Sources: Glutathione in foods listed in the National Cancer Institute's Health Habits and History Food Frequency Questionnaire. Jones DP Nutr Cancer. 1992;17(1):57-75.; Alan Pressman "Glutathione. The Ultimate Antioxidant"; Leo Nollet "Handbook of Analysis of Active Compounds in Functional Foods", pp.73-74; Lester Packer "Handbook of Antioxidants", pp. 551-552



Select Glutathione Foods, mg per 100g (3.5 oz.)

Food	GSH Content
Asparagus	28.3
Avocado	27.7
Spinach	11.4
Okra	11.3
Broccoli	9.1
Cantaloupe	9.0
Tomato	9.0
Carrot	7.9
Grapefruit	7.9
Orange	7.3
Zucchini	7.0
Strawberry	6.9
Watermelon	6.6
Papaya	5.8
Red bell pepper	5.5
Peach	5.0
Lemon	4.8
Mango	4.3
Banana	4.1
Cauliflower	4.0
Walnuts	3.7
Cucumber	3.5

Roles of glutathione in animals

Antioxidant defense
- Scavenging free radicals and other reactive species
- Removing hydrogen and lipid peroxides
- Preventing oxidation of biomolecules

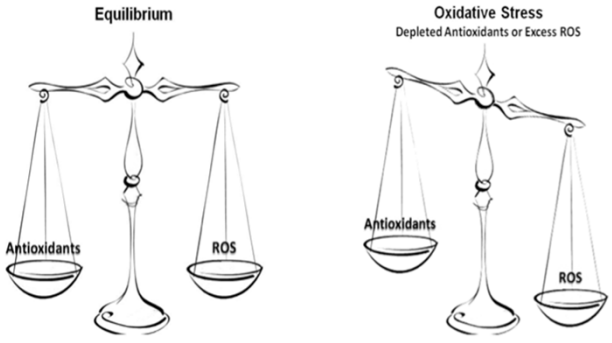
Metabolism
- Synthesis of leukotrienes and prostaglandins
- Conversion of formaldehyde to formate
- Production of D-lactate from methylglyoxal
- Formation of mercapturates from electrophiles
- Formation of glutathione-NO adduct
- Storage and transport of cysteine

Regulation
- Intracellular redox status
- Signal transduction and gene expression
- DNA and protein synthesis, and proteolysis
- Cell proliferation and apoptosis
- Cytokine production and immune response
- Protein glutathionylation
- Mitochondrial function and integrity

Wu, et al. Glutathione metabolism and its implications for heatlh. J Nutr 2004 mar 134(3): 489-92. PMID: 14988435

Oxidative stress depletes glutathione/ Glutathione deficiency contributes to oxidative stress.

- Alternations in its concentration are a common feature in many pathological conditions.
- Oxidative stressors can deplete GSH including radiation, infections, environmental toxins, household chemicals, and heavy metals, surgery, inflammation, burns, septic shock, and dietary deficiencies of GSH precursors and enzyme cofactors.
- Its intracellular depletion ultimately results in apoptosis.



Defining terms

- **Oxidative stress** – an imbalance in pro-oxidants and anti-oxidants, which results in macromolecular damage and disruption fo the redox signaling and control. (Sies and Jones, 2007.)
- **Free radicals** – small diffusible molecules that have an unpaired electron which makes them highly reactive, causing chain reactions in which a single free radical initiation event can be propagated to damage multiple molecules.
- **Redox cycling** – refers to the ability to cycle back and forth between oxidation/reduction forms of oxidants.
- **ROS** (reactive oxygen species)
- **RNS** (reactive nitrogen species)
- Antioxidant defenses against free radicals include:
  - Scavenging enzyme systems (SOD, Catalase, Glutathione peroxidase)
  - Radical scavenging chemicals (Vit C, Vit E, etc)
  - Thiols, like Glutathione

Sies H, Jones DP, Oxidative stress. In: Fink G (eds) Encyclopedia of stress. 2nd ed, vol 3, Elsevier, Amsterdam, pp 45–48, 2007.

Conditions related to low glutathione

- Acetaminophen toxicity
- Acne
- Addictions (including tobacco)
- AIDS and HIV
- Aging
- Allergies
- ALS (amyotrophic lateral sclerosis or Lou Gehrig's disease)
- Alzheimer's disease
- Anemia (hemolytic, sickle cell)
- Anxiety
- Arthritis

Antioxidant defense in centenarians

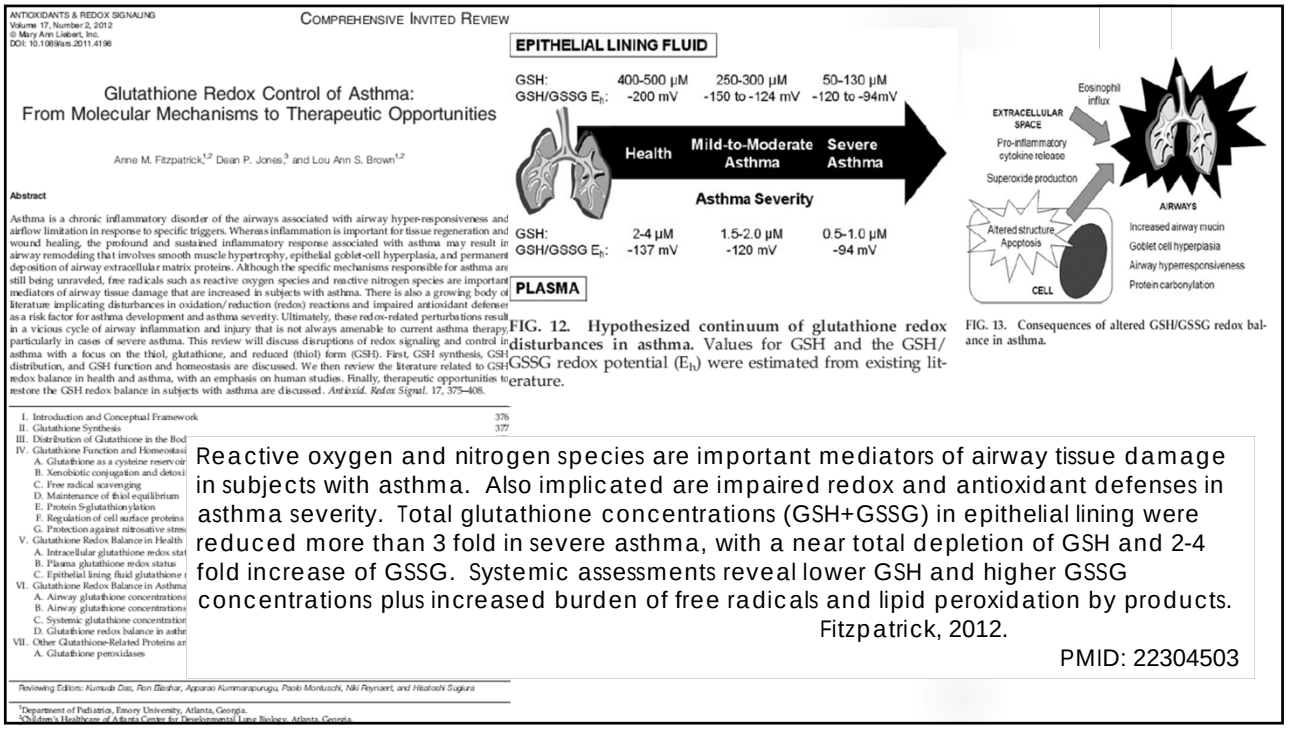
- Study of 16 centenarians (1 male and 15 females age 101-105 years)
- Living in upper Silesia district in Poland

➢ Results find human longevity results in part from increased capacity for antioxidant defense mainly due to high activity of enzymes glutathione reductase and catalase.
➢Levels were higher than 20-22 year old female controls.

PMID: 11051193

Conditions related to low glutathione

- Asthma
- Attention deficit disorder
- Autism
- Bipolar disorder
- Bronchitis
- Burns
- Cancer (all cancers, including breast, brain, head and neck, cervical, colon, thyroid, lung, esophagus, stomach, intestine, liver, pancreas, kidney, uterine, ovarian, prostrate, leukemia, lymphoma, multiple myeloma and others) (over 20,000 scientific papers)



ANTIOXIDANTS & REDOX SIGNALING
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DOI: 10.1089/ars.2011.4198

COMPREHENSIVE INVITED REVIEW

Glutathione Redox Control of Asthma:
From Molecular Mechanisms to Therapeutic Opportunities

Anne M. Fitzpatrick,[1,2] Dean P. Jones,[3] and Lou Ann S. Brown[1,2]

Abstract

Asthma is a chronic inflammatory disorder of the airways associated with airway hyper-responsiveness and airflow limitation in response to specific triggers. Whereas inflammation is important for tissue regeneration and wound healing, the profound and sustained inflammatory response associated with asthma may result in airway remodeling that involves smooth muscle hypertrophy, epithelial goblet-cell hyperplasia, and permanent deposition of airway extracellular matrix proteins. Although the specific mechanisms responsible for asthma are still being unraveled, free radicals such as reactive oxygen species and reactive nitrogen species are important mediators of airway tissue damage that are increased in subjects with asthma. There is also a growing body of literature implicating disturbances in oxidation/reduction (redox) reactions and impaired antioxidant defenses as a risk factor for asthma development and asthma severity. Ultimately, these redox-related perturbations result in a vicious cycle of airway inflammation and injury that is not always amenable to current asthma therapy, particularly in cases of severe asthma. This review will discuss disruptions of redox signaling and control in asthma with a focus on the thiol, glutathione, and reduced (thiol) form (GSH). First, GSH synthesis, GSH distribution, and GSH function and homeostasis are discussed. We then review the literature related to GSH redox balance in health and asthma, with an emphasis on human studies. Finally, therapeutic opportunities to restore the GSH redox balance in subjects with asthma are discussed. *Antioxid. Redox Signal.* 17, 375–408.

Reviewing Editors: Kumuda Das, Ron Eliashar, Apparao Kummarapurugu, Paolo Montuschi, Niki Reynaert, and Hisatoshi Sugiura

[1]Department of Pediatrics, Emory University, Atlanta, Georgia.
[2]Children's Healthcare of Atlanta Center for Developmental Lung Biology, Atlanta, Georgia.

FIG. 12. **Hypothesized continuum of glutathione redox disturbances in asthma.** Values for GSH and the GSH/GSSG redox potential (E_h) were estimated from existing literature.

FIG. 13. Consequences of altered GSH/GSSG redox balance in asthma.

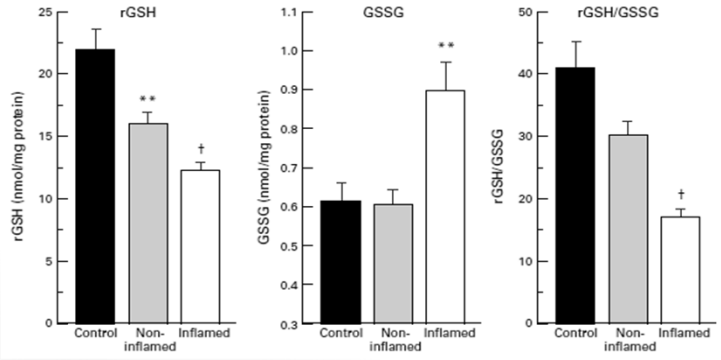
Reactive oxygen and nitrogen species are important mediators of airway tissue damage in subjects with asthma. Also implicated are impaired redox and antioxidant defenses in asthma severity. Total glutathione concentrations (GSH+GSSG) in epithelial lining were reduced more than 3 fold in severe asthma, with a near total depletion of GSH and 2-4 fold increase of GSSG. Systemic assessments reveal lower GSH and higher GSSG concentrations plus increased burden of free radicals and lipid peroxidation by products.

Fitzpatrick, 2012.

PMID: 22304503

Conditions related to low glutathione

- Cataracts
- Cholesterol/ coronary artery disease
- Chronic fatigue syndrome
- Colitis
- Crohn's disease
- Cystic fibrosis
- Dementia
- Depression
- Diabetes
- Eczema
- Emphysema
- Erectile dysfunction
- Fetal alcohol syndrome



Gut 1998;42:485–492

Impairment of intestinal glutathione synthesis in patients with inflammatory bowel disease

B Sido, V Hack, A Hochlehnert, H Lipps, C Herfarth, W Dröge

Abstract

***Background*—Reactive oxygen species contribute to tissue injury in inflammatory bowel disease (IBD). The tripeptide glutathione (GSH) is the most important intracellular antioxidant.**

***Aims*—To investigate constituent amino acid plasma levels and the GSH redox status in different compartments in IBD with emphasis on intestinal GSH synthesis in Crohn's disease.**

***Methods*—Precursor amino acid levels were analysed in plasma and intestinal mucosa. Reduced (rGSH) and oxidised glutathione (GSSG) were determined enzymatically in peripheral blood mononuclear cells (PBMC), red blood cells (RBC), muscle, and in non-inflamed and inflamed ileum mucosa. Mucosal enzyme activity of γ-glutamylcysteine synthetase (γGCS) and γ-glutamyl transferase (γGT) was analysed. Blood of healthy subjects and normal mucosa from a bowel segment resected for tumour growth were used as controls.**

***Results*—Abnormally low plasma cysteine and cystine levels were associated with inflammation in IBD ($p<10^{-6}$). Decreased rGSH levels were demonstrated in non-inflamed mucosa ($p<0.01$) and inflamed mucosa ($p\leq10^{-6}$) in patients with IBD,**

oxygen species (ROS).[1-4] Excessive production of ROS could be also demonstrated for circulating phagocytic cells in patients with IBD[5] and was shown to be involved in several models of experimental colitis.[6-8] The mucosa is endowed with various endogenous antioxidant defence systems to remove ROS resulting from normal metabolism. However, enzyme activities of catalase, superoxide dismutase, and glutathione peroxidase were reported to be low at only 4%, 8%, and 45 %, respectively, in healthy colonic mucosa compared with the liver.[9] ROS are highly toxic to cells and oxygen radical formation in excess of physiological amounts may overtax the limited intestinal antioxidant defence system initiating oxidative injury to the gut.[10-13] Deterioration of antioxidative glutathione metabolism[12] and increased colonic oxidative damage to proteins and DNA in association with impaired enzyme activity of CuZn superoxide dismutase has been reported previously in patients with Crohn's disease (CD).[13] Efficacy of current standard therapy in IBD was suggested to be related to antioxidant actions: 5-aminosalicylic acid is a highly potent scavenger of ROS[14] and was shown to reduce lipid peroxidation in CD and ulcerative colitis (UC).[15] Preliminary uncontrolled clinical trials showed that CuZn superoxide dismutase may be of benefit in CD[16] and UC.[17] Several classical antioxidants were reportedly effective in

Correspondence to: Dr B Sido, Department of Surgery, University of Heidelberg, Im Neuenheimer Feld 110, 69120 Heidelberg, Germany.

Infiltrating macrophages and neutrophils are abundantly present in inflamed gut in patients with inflammatory bowel disease (IBD). There is a growing body of evidence that these cells

enzyme in GSH synthesis (labelled 2 in fig 1), is controlled via a feedback mechanism by the end product GSH.[24] High intracellular glutamate levels support GSH synthesis as glutamate competes with GSH at the regulatory site

- Abnormally low plasma cysteine and cystine were associated with inflammation in IBD. Both non-inflamed and inflamed mucosa, revealed decreased GSH with increase GSSG with inflammation. The activity of enzymes involved in GSH synthesis were also impacted. GSH levels were found to be normal or even increased in the extra-intestinal compartment, so the availability of cysteine is a consequence, not a primary mechanism. Sido, 1998.

Conditions related to low glutathione

- Fibromyalgia
- Gaucher's disease
- Gastritis
- Gastroenteritis
- Gingivitis
- Gout
- Headaches
- Hearing loss
- Heavy metal toxicity
- Hepatitis
- Herpes
- Huntington's disease
- Hypertension
- Hyper and hypothyroidism

Glutathione and hearing loss

- Age-related hearing loss is associated with loss of sensory hair cells, spiral ganglion neurons and stria vascularis degeneration in the cochlea.
- Inducing activation of Slrt3, a member of the sirtuin family, mediates the anti-aging effects of calorie restriction.
- Activation of glutathione reductase or anything that will increase mitochondrial glutathione levels will likely have similar anti-aging effect of calorie restriction on human inner ear cells.

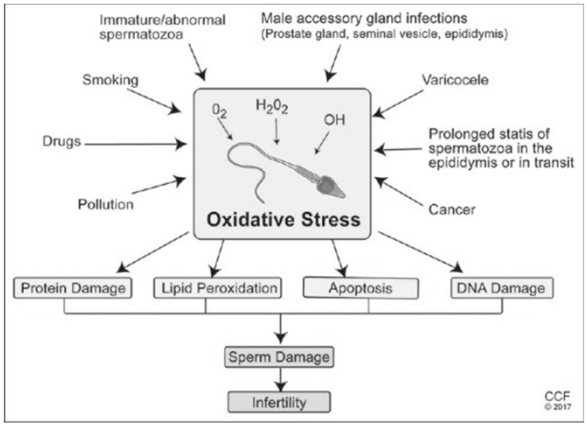
PMID: 23454634

Conditions related to low glutathione

- Hypoxia (stroke, tissue ischemia, inflammation, solid-tumor formation)
- Infertility
- Insomnia
- Liver disease
- Lou Gehrig's disease (ALS)
- Lung disorders and COPD (chronic obstructive pulmonary disease)
- Lupus
- Lyme disease
- Macular degeneration
- Migraines
- Multiple sclerosis (MS)

Infertility and oxidative stress (OS)

- Infertility is a common medical condition prevalent in about 15% of couples worldwide.
- "male factor infertility" - occurs in 50% of couples, but 30% of these, it is considered idiopathic.
- Reactive oxygen species (ROS) are beneficial for optimal sperm functions for regulation of sperm maturation and enhancement of cellular signaling pathways.
- However higher levels of ROS , induce lipid peroxidation, sperm DNA damage, and apoptosis.
- Spermatozoa are vulnerable, lacking antioxidant repair systems. Also, the polyunsaturated fatty membrane renders them at risk of lipid peroxidation.
- 20%–40% of infertile men have significantly higher levels of ROS in their semen when compared with fertile men.
- In a placebo-controlled, double-blind, cross-over trial, 600 mg of GSH administered intramuscularly every other day for 2 months led to an improvement in sperm motility and morphology in 20 men with varicocele genital tract inflammation.



Majzoub and Agarwal. Antioxidant therapy in idiopathic oligoasthenoteratozoospermia. Indian J Urol. 2017 Jul-Sep; 33(3): 207–214. PMID: 28717270

Multiple Sclerosis and glutathione

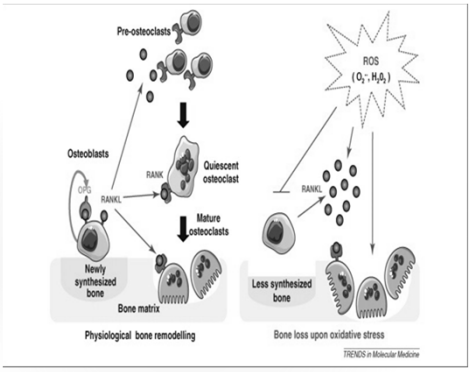
- Study compared 13 multiple sclerosis (with secondary progressive MS) patients and 12 controls over 3-5 years.
- GSH mapping in frontal and parietal regions of brain using multiple quantum chemical imaging.
- Brain GSH concentrations in MS patients were lower at baseline and follow ups.
- Clinical assessments included disability, gait, motor strength, ataxia, tremor, vision changes and brainstem function.
- Blinded assessments by neurologists found greater clinical progression associated with larger frontal GSH concentration declines.

Choi, et al. Longitudinal changes of cerebral glutathione (GSH) levels associated with the clinical course of disease progression in patients with secondary progressive multiple sclerosis. Mult Scler. 2017 Jun;23(7):956-962. PMID: 27620894

Conditions related to low glutathione

- Myocardia ischemia
- Neurodegenerative disease
- Obesity
- Osteoarthritis
- Osteoporosis
- Pain
- Pancreatitis
- Parkinson's disease
- Pre-eclampsia
- Psoriasis

Oxidative stress and postmenopausal osteoporosis



- Meta-analysis supports the relationship between OS-related biomarkers osteoporosis patients.
- Results showed an increase in homocysteine and nitric oxide in osteoporosis patients.
- Decreased levels of total antioxidants and folate and lower activity of Superoxide dismustase (SOD) and glutathione peroxidase (GPx)

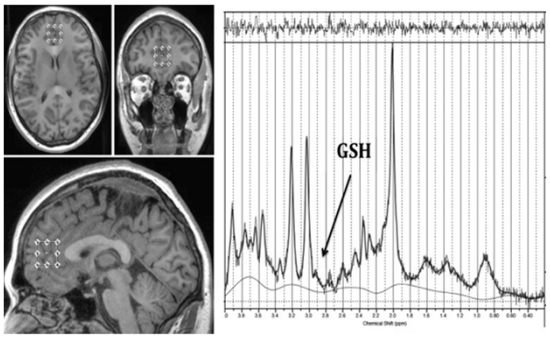
Zhou, et al. Oxidative Stress-Related Biomarkers in Postmenopausal Osteoporosis: A Systematic Review and Meta-Analyses. Dis Markers. 2016. Article ID 7067984. PMID: 27594735.

Conditions related to low glutathione

- Pulmonary fibrosis
- Schizophrenia
- Seizures
- Sepsis
- Sinusitis
- Sleeping disorders
- Spontaneous abortions
- Stroke
- Viral infections

Sleep disorders and oxidative stress

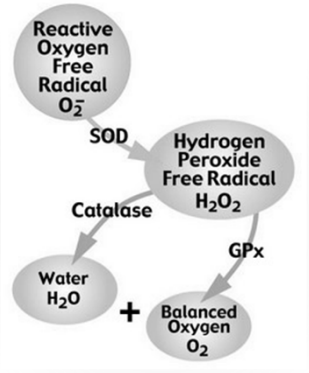
- 30 patients with primary insomnia and 30 healthy controls.
- Oxidative stress biomarkers were evaluated. Patients with insomnia had lower glutathione peroxidase (GSH-Px), lower levels of reduced glutathione (GSH) and higher levels of malondialdehyde (MDA) compared with the controls.
- 24 older adults at risk for dementia and sleep disordered breathing were assessed.
- Increased levels of GSH/Cr as measured in MRS in the anterior cingulate was associated lower oxygen levels and more severe apnea.
- This study demonstrates for the first time that SDB and associated nocturnal hypoxemia are linked to cerebral oxidative stress in the ACC in older adults at-risk for dementia



•Duff, et al. Association of Anterior Cingulate Glutathione with Sleep Apnea in Older Adults At-Risk for Dementia. Sleep. 2016 Apr 1; 39(4): 899–906. PMID:26856906
•Gulec, et al. Oxidative stress in patients with primary insomnia. Prog Neuropsychopharmacol Biol Psychiatry. 2012 Jun 1;37(2):247-51. PMID: 22401887

Oxidative stress leads to disease

Oxidative stress free radicals are neutralized by antioxidants and enzymes

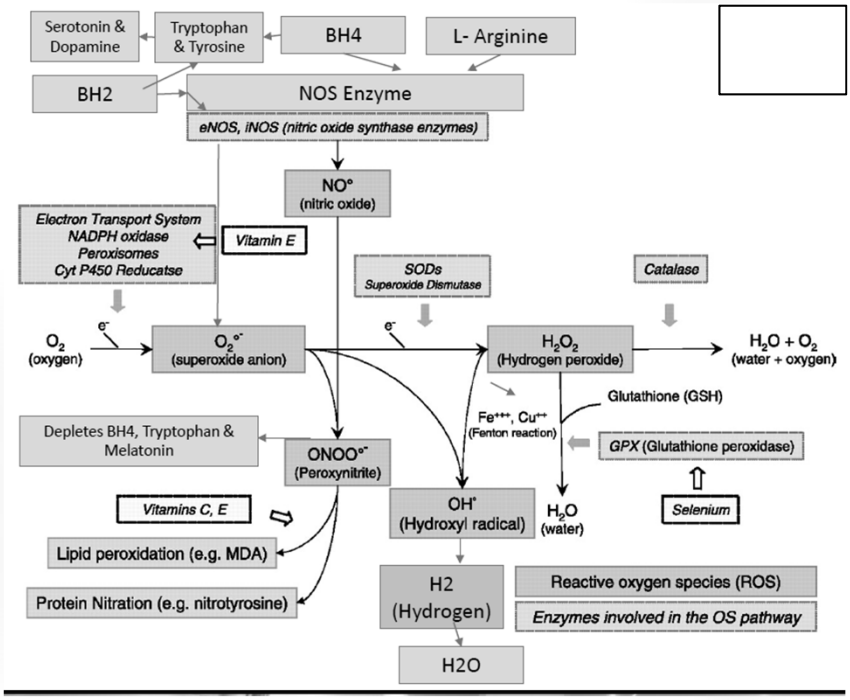


Enzyme systems

- Superoxide dismutase (SOD)
- Catalase (CAT)
- Glutathione peroxidase (GPx)

Antioxidants

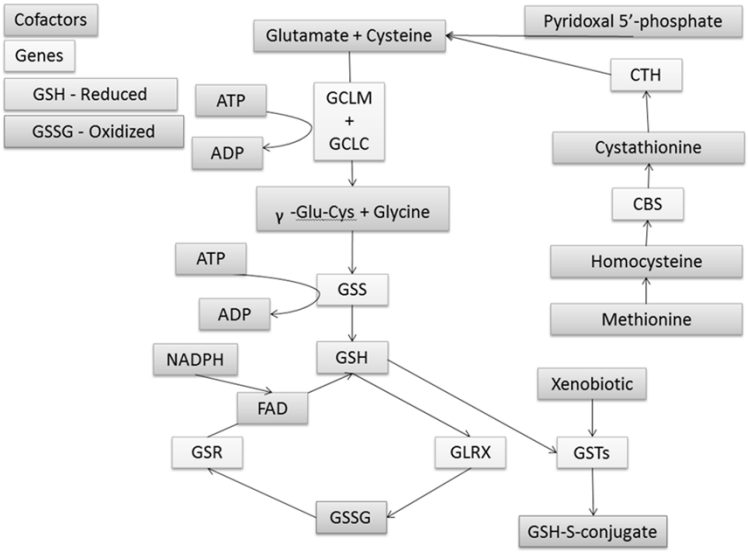
- Glutathione (GSH)
- Vitamin C, vitamin E, selenium, N-acetyl cysteine, melatonin, etc.



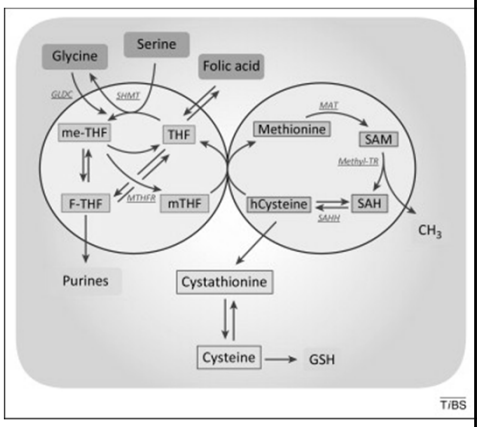
Glutathione production and usage

- **Biosynthesis** - Cells make glutathione in two ATP-dependent steps:
  - First, gamma-glutamylcysteine is synthesized from L-glutamate and cysteine via the enzyme glutamate cysteine ligase (GCL). This is the rate-limiting step.
  - Second, glycine is added to the C-terminal of gamma-glutamylcysteine via the enzyme glutathione synthetase.
- **Regeneration**
  - Glutathione exists in both reduced (GSH) and oxidized (GSSG) states. Reduced glutathione donates an electron, quenching the free radical, becoming reactive (pro-oxidative) and readily reacts with another reactive glutathione to form glutathione disulfide (GSSG).
  - GSH can be regenerated from GSSG by the enzyme glutathione reductase (GSR)
- **Glutathione s-transferases** - Cytosolic GSTs of mammals are classified into Alpha, Mu, Pi and Theta classes. (GSTM1, GSTT1, GSTP1, etc) They are major phase II detoxification enzymes which conjugate electrophilic substrates (especially toxins) to glutathione (GSH).

Glutathione synthesis



Trans-sulfuration pathway



Methionine to cysteine to glutathione

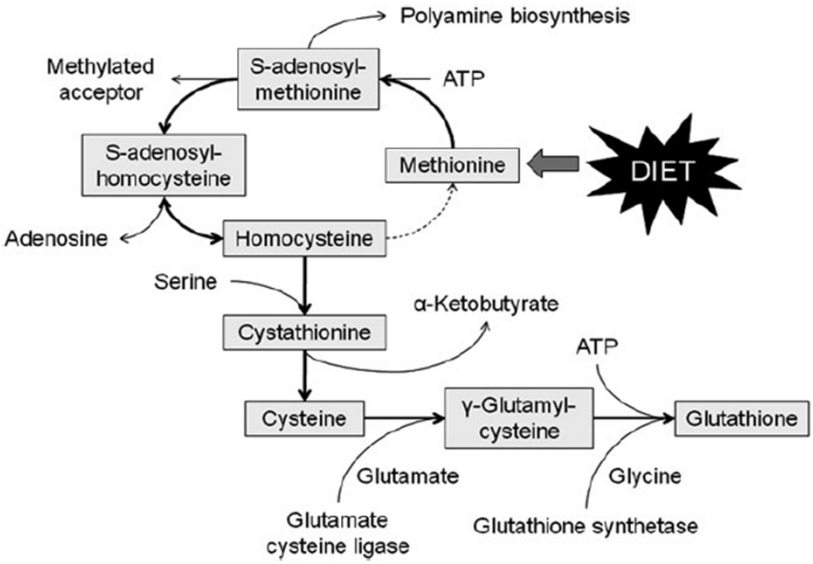
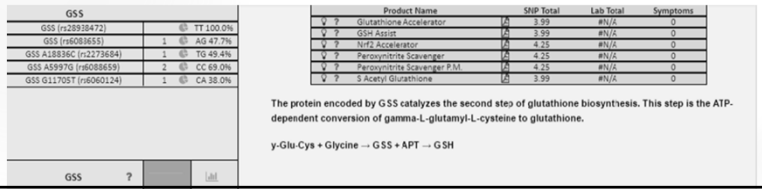


FIG. 3. **Methionine metabolism.** Methionine is metabolized to homocysteine, which is either (i) methylated back to methionine through the remethylation pathway or (ii) converted to cysteine through the trans-sulfuration pathway. The cysteine that is formed may be used for protein synthesis or formation of glutathione.

PMID: 22304503

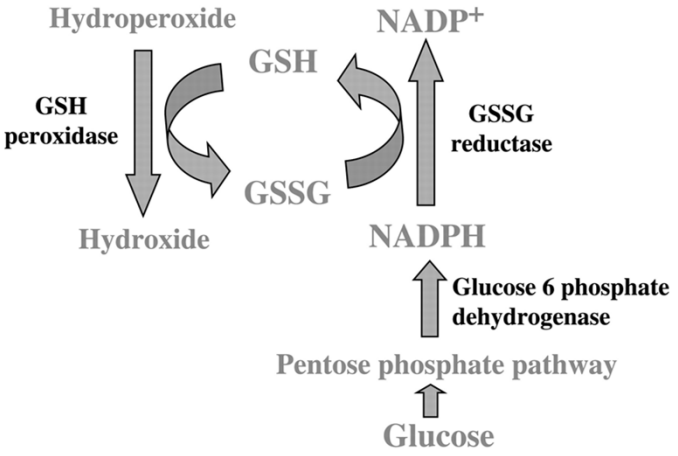
Making glutathione – relevant SNPs

- **CTH** – catalizes the last step in the trans-sulfuration pathway from methionine to cysteine. Cysteine is needed for glutathione and its availability is rate limiting.
- **SHMT** – is the gene responsible for making glycine which is another glutathione building block.
- **GCL/GCLC/GCLM** – glutamate cysteine ligase or gamma-glutamylcystine synthetase is composed of 2 subunits, the catalycic GCLC and modifier GCLM.
- **GSS** – catalyzes the 2nd step of ATP-dependent conversion of gamma-L-glutamyl-L-cysteine to glutathione.

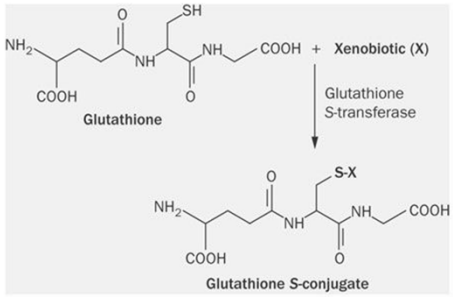


Glutathione –redox or regeneration reactions

- **Glutathione peroxidase GPx (or GLRX – in Methylgenetic Nutrition software**)- encodes for a member of the glutaredoxin family which catalyzes the redox reaction of GSH to GSSG.
- **Glutathione reductase – GSR** - encodes for a enzyme member of the pyridine nucleotide-disulfides oxidoreducatase family which reduces the oxidized glutathione disulfide (GSSG) back to GSH.



Glutathione S-Transferases



- Family of genes that code for enzymes that function to add glutathione to detoxify compounds including drugs, environmental toxins and other products of oxidative stress. This action is an important step in detoxification of these compounds.
- GSTs include the following classes:
- A- (alpha-), P- (pi-), M- (mu-), O- (omega), T- (theta), and Z - (Zeta)
- Genes have variable tissue distribution
- The enzymes GSTA1, GSTA2, GSTA3, GSTA4, GSTA5, GSTK1, GSTM1, GSTM2, GSTM3, GSTM4, GSTM5, GSTO1, GSTO2, GSTP1, GSTT1, and GSTZ1 can all be found in 23andme.com raw data.

Null mutations of GSTM1/GSTT1 has potential effects

- Loss of GSTM1 in Tin study
  - Caucasians 51.2% null and 39.8% missing one copy; African Americans 25.6% null and 48.5% missing one copy
  - Higher risk of kidney failure (hazard ratio 1.66) and heart failure (HR 1.16)
  - Risk was not statistically significant if one or both genes were absent.
- GSTM1/GSTT1 null mutations in Mercury toxicity
  - Reduce excretion/increased retention of mercury in hair, blood, RBC and urine seen.
  - Most problematic for babies of mothers with higher blood levels and null genotypes.
- Double null mutations in GSTM1/GSTT1 increase risk of treatment resistant schizophrenia.
  - Frequencies of GSTT1-null and GSTM1-null genotypes were 24.1 and 51.9%. Control group, 12.8 and 46.2% . The double-null genotype confers a 4.6-fold increased risk.
- GSTM1 null associated with increase risk of systemic lupus erythematosus in Asians.

Andreoli, et al. Genetics Aspects of Susceptibility to Mercury Toxicity. Int. J. Environ.Res. Public.Health 2017, 14, 93. PMID: 28106810.
Parajuli et al. Genetic polymorphisms area assoicated with merucry levels in ADA study participants. Environ Res 2016 Aug; 149:247-258. PMID: 26673400.
Tin, et al. The Loss of GSTM1 Associates with Kidney Failure and Heart Failure. J Am Soc Nephrol 2017 July 18. PMID 28720685
Pinheiro, et al. GSTM1/GSTT1 double-null genotype increases risk of treatment-resistant schizophrenia: A genetic association study in Brazilian patients. PLoS One. 2017 Aug 24;12(8) PMID: 28837637
Lee. Association between GSTM1, GSTP1 and lupus susceptibiltiy. Cell. Mol. Bio. 2016 Sept 30; 62(11):21-26. PMID: 27755947.

How do you know your patient needs glutathione?

- Chronic diseases
- High oxidative stress burden
- For detoxification from environmental exposures
- Lifestyle factors
- Genetics
- Based on test results

Testing for glutathione - options

- Glutathione – whole blood (available at Lab Corp and Quest)
- Glutathione – Erythrocyte levels
- Oxidative Stress tests – blood and urine
  - Lipid peroxidation
  - 8-Hydroxy-2-deoxyguanosine (8-OHdG)
  - Ox LDL
  - F2-Isoprostanes
- Organic acid tests – indirect measures of glutathione, precursors and oxidative stress
  - Pyroglutamate
  - Beta-hydroxybutrate
- Methylation panels – with and without including glutathione
- Hepatic detoxification markers

Total glutathione levels

Tests	Result	Flag	Units	Reference Interval	Lab
Glutathione, Total					
Glutathione	729		uM	544-1228	E=

The performance characteristics of the listed assay was validated by Cambridge Biomedical Inc. The US FDA has not approved or cleared this test. The results of these assay can be used for clinical diagnosis without FDA approval. Cambridge Biomedical Inc. is a CLIA certified, CAP accredited laboratory for performing high complexity assays such as this one.

RBC Glutathione levels

Glutathione; Erythrocytes

	Within	Outside	Reference Range
Glutathione*	1368		1000 - 2000 µmoles/L

Glutathione (GSH) is a tripeptide (λ-glutamyl-cysteinylglycine) synthesized in most cells. The level of GSH in erythrocytes is a sensitive indicator of intracellular GSH status, the overall health of cells, and of the ability to endure toxic challenges. GSH is the most abundant non-protein thiol in mammalian cells. It is involved in many biological processes including detoxification of xenobiotics, removal of oxygen-reactive species, regulation of the redox state of cells and the oxidative state of important protein sulfhydryl groups, and regulation of immune function. GSH levels are thousands of times higher in cells than in plasma. Plasma GSH represents primarily that synthesized and exported from the liver. Reduced GSH (rGSH) is the active form of the tripeptide and the ratio of rGSH: oxidized GSH (GSSH) is normally about 9:1. Once a blood sample is obtained, Erythrocyte rGSH is very susceptible to oxidation and the rGSH:GSSH ratio drops rapidly. Specimen handling to prevent the *ex vivo* oxidation of rGSH is impractical and direct measurement of rGSH *in vivo* is not feasible outside of a research setting. However, research clearly indicates that undesirable ratios of rGSH:GSSH are equally associated with abnormally low levels of total cellular GSH. Therefore, it is clinically meaningful to assess the level of total erythrocyte GSH as an indicator of GSH status and metabolism.

Oxidative stress markers – blood/ urine

Oxidative Stress

BLOOD

Protection		Reference Range
Glutathione (GSH)	526	>= 669 micromol/L
Total Antioxidant Capacity (TAC)	0.52	>=0.54 mmol/L
Cysteine (Cys-SH)	0.81	0.61-1.16 mg/dL
Sulfate	3.5	3.0-5.9 mg/dL
Cysteine/Sulfate Ratio	0.23	0.12-0.32
Cystine (Cys-S-S-Cys)	1.99	1.60-3.22 mg/dL
Cysteine/Cystine Ratio	0.35	0.23-0.53
Enzymes		**Reference Range**
Glutathione Peroxidase (GPX)	24.2	20.0-38.0 U/g Hb
Superoxide Dismutase (SOD)	14,967	5,275-16,662 U/g Hb
Damage		**Reference Range**
Lipid Peroxides	16.7	<= 10.0 micromol/L

Oxidative Stress

URINE

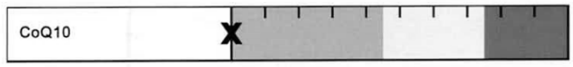
Damage		Reference Range
Lipid Peroxides	16.7	<= 10.0 micromol/g Creatinine
8-OHdG	11.0	<= 16.0 mcg/g Creat.

Oxidative stress – DNA/RNA Damage

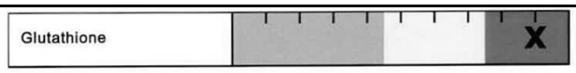
DNA/RNA Oxidative Damage Assay; Urine

	RESULT / UNIT	REFERENCE INTERVAL	LOW MODERATE HIGH
8-hydroxy-2'-deoxyguanosine* (8-OHdG)	**10.4ng/mg creat**	< 8.2	
			PERCENTILE 2.5th 16th 50th 84th 97.5th
Creatinine	**226 mg/dL**	35- 240	

Oxidation of DNA and RNA occurs most readily at the guanine residues and measurement of these biomarkers in urine provides a quantitative assessment of oxidative stress. Although about 20 oxidative lesions in DNA have been identified to date, RNA is more sensitive to reactive oxygen species in part due to their compartmentalization in the cytosol as well as the nucleus. The most abundant lesion in DNA and RNA is 8-hydroxyguanosine (8-OHG); 8-OHG is the only measurable oxidized RNA lesion. With respect to oxidized DNA lesions, 8-hydroxy-2'-deoxyguanosine (8-OHdG) and it's analog 8-hydroxyguanine are the most commonly studied and detected by-products of DNA damage that are excreted in the urine upon DNA repair. Urinary 8-OHdG and its analogs, 8-OHG and 8-hydroxyguanine, are sensitive biomarkers of oxidative stress and have been associated with many diseases, including bladder and prostate cancer, cystic fibrosis, atopic dermatitis and rheumatoid arthritis, Park[illegible]ington's disease. Elevated levels of DNA and RNA damage have been meas[illegible].



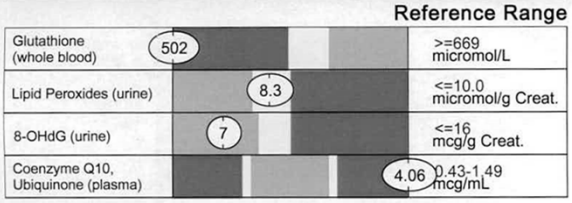
- CoQ10 is a powerful antioxidant that is synthesized in the body and contained in cell membranes. CoQ10 is also essential for energy production & pH regulation.
- CoQ10 deficiency may occur with HMG-CoA reductase inhibitors (statins), several anti-diabetic medication classes (biguanides, sulfonylureas) or beta-blockers.
- Low levels may aggravate oxidative stress, diabetes, cancer, congestive heart failure, cardiac arrhythmias, gingivitis and neurologic diseases.
- Main food sources include meat, poultry, fish, soybean, canola oil, nuts and whole grains. Moderate sources include fruits, vegetables, eggs and dairy.



- Glutathione (GSH) is composed of cysteine, glutamine & glycine. GSH is a source of sulfate and plays a key role in antioxidant activity and detoxification of toxins.
- GSH requirement is increased with high-fat diets, cigarette smoke, cystinuria, chronic alcoholism, chronic acetaminophen use, infection, inflammation and toxic exposure.
- Deficiency may result in oxidative stress & damage, impaired detoxification, altered immunity, macular degeneration and increased risk of chronic illness.
- Food sources of GSH precursors include meats, poultry, fish, soy, corn, nuts, seeds, wheat germ, milk and cheese.

- Oxidative stress is the imbalance between the production of free radicals and the body's ability to readily detoxify these reactive species and/or repair the resulting damage with anti-oxidants.
- Oxidative stress can be endogenous (energy production and inflammation) or exogenous (exercise, exposure to environmental toxins).
- Oxidative stress has been implicated clinically in the development of neurodegenerative diseases, cardiovascular diseases and chronic fatigue syndrome.
- Antioxidants may be found in whole food sources (e.g., brightly colored fruits & vegetables, green tea, turmeric) as well as nutraceuticals (e.g., resveratrol, EGCG, lutein, lycopene, ginkgo, milk thistle, etc.).

Oxidative Stress Markers



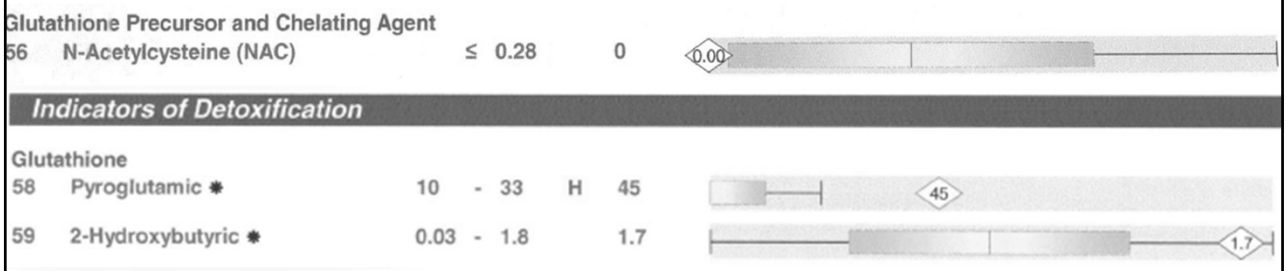
The Oxidative Stress reference ranges are based on an adult population.

Oxidized LDL and F2-Isoprostane

OxLDL	51			LOW	<60	U/L
Based on a recent study of an 'apparently healthy' and non-metabolic syndrome population-1, the following cut-offs have been defined for OxLDL: A cut-off of <60 U/L defines a population with a low relative risk of developing metabolic syndrome, a range of 60 to 69 U/L defines a population with a moderate relative risk (2.8 fold) and >=70 U/L defines a population with a high relative risk (3.5-fold). (Reference: 1-Holvoet et al. JAMA. 2008; 299: 2287-2293.)						
F_2-Isoprostane/Creatinine[3]	0.33				<0.86	ng/mg
Elevated urinary F2-Isoprostanes are associated with an increased risk of coronary heart disease (CHD) (1). (Reference: 1-Schwedhelm et al. Circulation. 2004; 109: 843-848).						
F_2-Isoprostane	0.55					ng/mL
Creatinine, Urine, Random	164.6				20.0-300.0	mg/dL

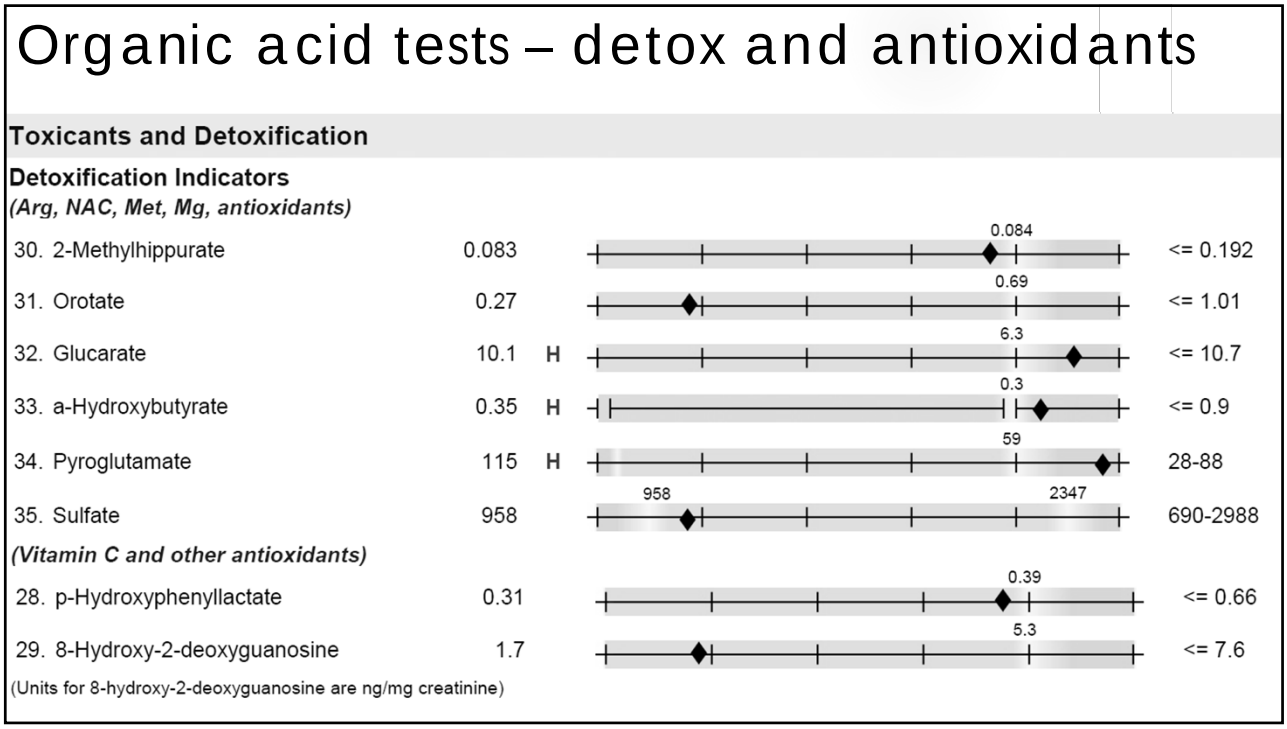
- F_2-IsoPs are prostaglandin-like compounds formed from the free radical-mediated oxidation of arachidonic acid, and are the 'gold standard' for measuring oxidative stress in the body. F_2-IsoPs also have potent biological effects associated with inflammation and therefore may mediate chronic disease initiation and progression. Additionally, F_2-IsoPs may also act as potent vasoconstrictors via thromboxane formation in the endothelium, and promote platelet activation resulting in thrombus formation.
- OxLDL measures protein damage due to the oxidative modification of the ApoB subunit on LDL cholesterol. The oxidation of LDL cholesterol is one of the first steps in the development of atherosclerosis. Briefly, LDL-C enters the artery wall where it becomes oxidized. OxLDL is then recognized by scavenger receptors on macrophages which engulf OxLDL, resulting in foam cell formation, vascular inflammation and the initiation of atherosclerosis.

Organic acid tests – indirect measures of glutathione and NAC



Glutathione Precursor and Chelating Agent					
56	N-Acetylcysteine (NAC)	≤ 0.28		0	
Indicators of Detoxification					
Glutathione					
58	Pyroglutamic ✱	10 - 33	H	45	
59	2-Hydroxybutyric ✱	0.03 - 1.8		1.7	

Organic acid tests – detox and antioxidants

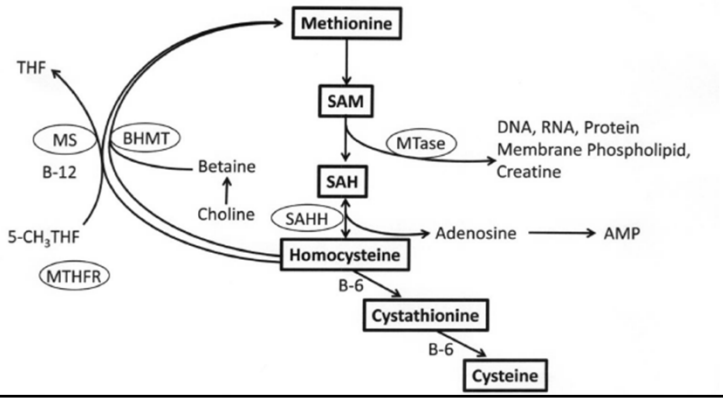


Toxicants and Detoxification				
Detoxification Indicators				
(Arg, NAC, Met, Mg, antioxidants)				
30. 2-Methylhippurate	0.083		0.084	<= 0.192
31. Orotate	0.27		0.69	<= 1.01
32. Glucarate	10.1	H	6.3	<= 10.7
33. a-Hydroxybutyrate	0.35	H	0.3	<= 0.9
34. Pyroglutamate	115	H	59	28-88
35. Sulfate	958		958 2347	690-2988
(Vitamin C and other antioxidants)				
28. p-Hydroxyphenyllactate	0.31		0.39	<= 0.66
29. 8-Hydroxy-2-deoxyguanosine	1.7		5.3	<= 7.6
(Units for 8-hydroxy-2-deoxyguanosine are ng/mg creatinine)				

Methylation Profile; plasma

PRIMARY & INTERMEDIATE METABOLITES	RESULT/UNIT		REFERENCE INTERVAL	PERCENTILE 2.5th 16th 50th 84th 97.5th
Methionine	1.9	µmol/dL	1.6 - 3.6	
Cysteine	27	µmol/dL	20 - 38	
S-adnosylmethionine (SAM)	106	nmol/L	86 - 145	
S-adenosylhomocysteine (SAH)	10.3	nmol/L	10 - 22	
Homocysteine	5.9	µmol/L	< 11	68th 95th
Cystathionine	0.01	µmol/dL	< 0.05	

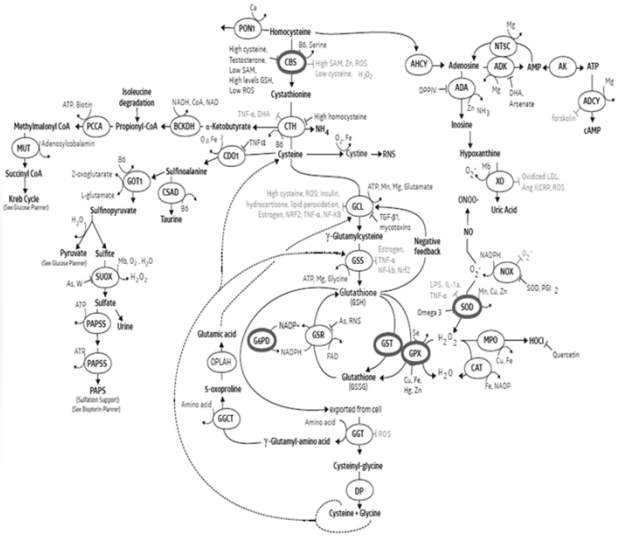
METHYLATION INDEX	RESULT	REFERENCE INTERVAL	PERCENTILE 68th 95th
SAM : SAH	11.3	> 4	



Methylation Panel

- Glutathione is not measured in this panel

Methylation panel



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Page 1
Analysis report
Date of print: 7/5/2016 08:43 AM

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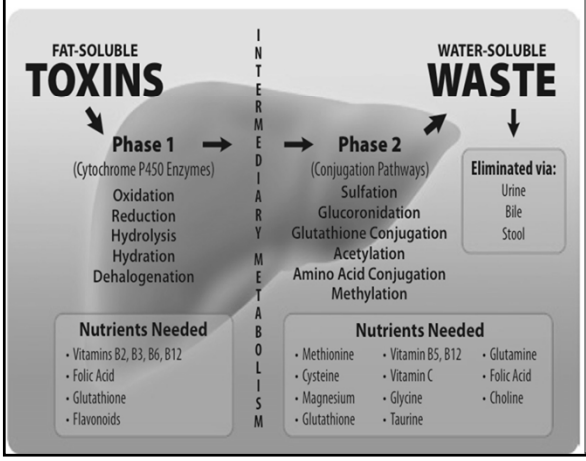
Applicant	McCann
Appoint. date	5/25/16
Appoint. time	01:22 PM
Appoint. No.	210550

		Unit	Ref. Range
DERIVATES			
S-Adenosylmethionine (RBC)	214	µmol/dl	221 - 256
S-Adenosylhomocysteine (RBC)	36.8	µmol/dl	38.0 - 49.0
FOLIC ACID DERIVATES			
5-CH3-THF	7.4	nmol/l	8.4 - 72.6
10-Formyl-THF	1.2	nmol/l	1.5 - 8.2
5-Formyl-THF	1.00	nmol/l	1.20 - 11.70
THF	0.48	nmol/l	0.60 - 6.80
Folic Acid	8.0	nmol/l	8.9 - 24.6
Folinic Acid (WB)	6.9	nmol/l	9.0 - 35.5
Active folate (RBC)	318	nmol/l	400 - 1500
NUCLEOSIDE			
Adenosine	16.0	10^-8 M	16.8 - 21.4
AMINOACIDS IN PLASMA			
Cystathionine	0.22	µmol/L	0.00 - 2.00
Homocysteine	0.82	µmol/L	0.00 - 2.00
Cysteine	11.15	µmol/L	15.00 - 60.00
Taurine	59	µmol/l	60 - 240
Methionine	7.94	µmol/L	14.30 - 28.70
Glutathione (oxidised)	0.37	µmol/L	0.16 - 0.50
Glutathione (reduced)	3.0	µmol/L	3.8 - 5.5

Hepatic Detox Profile



Hepatic Detox Profile; Urine

TOXIC EXPOSURE MARKERS

	RESULT per creatinine	REFERENCE INTERVAL	PERCENTILE (2.5th 16th 50th 84th 97.5th)
D-Glucaric Acid (Phase I)	430 nM/mg	25 - 300	
Mercapturic Acids (Phase II)	67 µM/mM	36 - 90	

URINE CREATININE

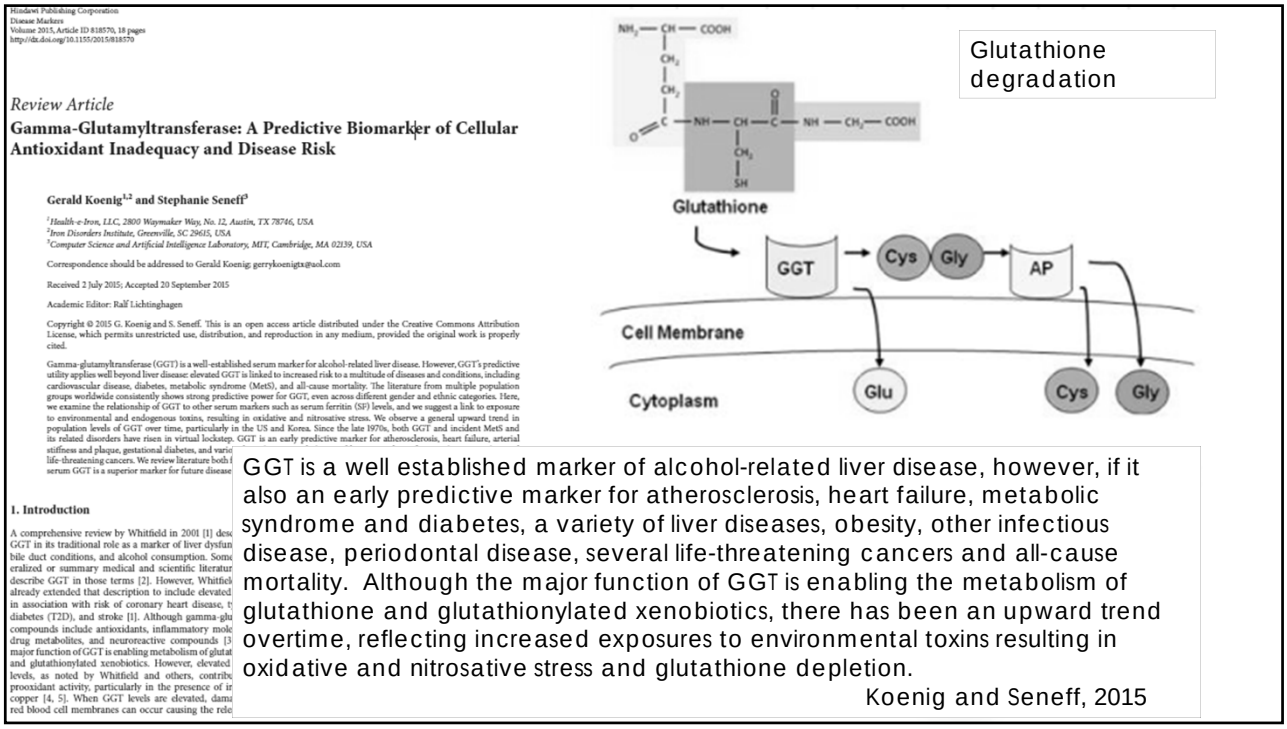
	RESULT mg/dL	REFERENCE INTERVAL	-2SD -1SD MEAN +1SD +2SD
Creatinine	113	45 - 225	

INFORMATION

The human body attempts to eliminate xenobiotics (foreign organic chemicals) through a concerted effort of enzymatic "functionalization" (phase I) and conjugation (phase II). Functionalization involves chemical modification of the xenobiotic by the cytochrome P-450 or the "mixed function oxidase" enzyme systems. Once functionalized, the altered xenobiotic can then be conjugated and excreted. Urinary D-glucaric acid, a hepatic byproduct of enzymatic response to chemical toxins (phase I), is a reliable indicator of exposure to xenobiotics. Mercapturic acids are direct, excretory end products of the functionalized xenobiotics that have been conjugated with glutathione prior to excretion. Together, the urinary levels of these metabolites provide valuable information about exposure to xenobiotics, liver disease, and quantitative assessment of the status of hepatic phase II detoxification.

D-GLUCARIC ACID ELEVATED: The level of D-glucaric acid, a marker of exposure to hepatotoxic substances, is abnormally high for age and gender in this sample. The results are consistent with clinically significant exposure to xenobiotics and enhanced phase I detoxification. Check mercapturic acid levels to evaluate the status of phase II detoxification that is required for the final elimination of the toxin(s). Severe xenobiotic exposure with markedly elevated D-glucaric acid levels (>3X normal) may be associated with impaired chemical functionalization or limited phase II activity. Elevated urinary excretion of D-glucaric acid is an indication of induction of cytochrome P-450 enzymes (phase I) in the liver that may be the result of exposure to any of over 200 different xenobiotics (e.g. pesticides, herbicides, fungicides, petrochemicals, drugs, alcohol, toluene, xylene, formaldehyde, styrenes, ibuprofen etc.). Occupational and environmental exposure to toxic compounds causes induction of the glucuronic acid enzyme pathway and production of D-glucaric acid, thus D-glucaric acid excretion is considered an indirect by-product of detoxification reactions. Elevated levels of urinary D-glucaric acid have been correlated with viral hepatitis and jaundice, and have also been found in patients receiving antirheumatic drugs, independent of disease activity. With elevated levels of D-glucaric acid, there is an increased need for antioxidant protection because toxins that are processed through phase I generate free radicals that require quenching or neutralization. It is important to consider that phase I detoxification tends to become less active with aging.

MERCAPTURIC ACIDS MARGINALLY ELEVATED: The levels of mercapturic acids (MA) in this patient's urine sample are marginally elevated for age and gender, and may be consistent with mild exposure to xenobiotics and enhanced detoxification via glutathione conjugation (phase II). Check for elevated levels of D-glucaric acid as an indicator of xenobiotic exposure. MA are final excretory products of detoxification and include a variety of functionalized xenobiotics that have been conjugated with cysteine, or glutathione. Ideally, urinary levels of MA should be increased with exposure to xenobiotics and enhanced phase I detoxification; MA levels will gradually return to basal levels commensurate with successful hepatic detoxification and removal of the patient from the source of exposure. If warranted, detoxification should be supported with supplemental vitamins C, E, and lipoic acid, selenium, Mg, K, rGSH, and sulfur containing amino acids. It should be noted that falsely elevated levels of MA can occur in patients with cystinuria, or with the use of thiol chelators (D-penicillamine, DMSA and DMPS), and some 'thio-capto' type medications (e.g. thioridazine, captodiamine).



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Review Article

Gamma-Glutamyltransferase: A Predictive Biomarker of Cellular Antioxidant Inadequacy and Disease Risk

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Gamma-glutamyltransferase (GGT) is a well-established serum marker for alcohol-related liver disease. However, GGT's predictive utility applies well beyond liver disease: elevated GGT is linked to increased risk to a multitude of diseases and conditions, including cardiovascular disease, diabetes, metabolic syndrome (MetS), and all-cause mortality. The literature from multiple population groups worldwide consistently shows strong predictive power for GGT, even across different gender and ethnic categories. Here, we examine the relationship of GGT to other serum markers such as serum ferritin (SF) levels, and we suggest a link to exposure to environmental and endogenous toxins, resulting in oxidative and nitrosative stress. We observe a general upward trend in population levels of GGT over time, particularly in the US and Korea. Since the late 1970s, both GGT and incident MetS and its related disorders have risen in virtual lockstep. GGT is an early predictive marker for atherosclerosis, heart failure, arterial stiffness and plaque, gestational diabetes, and vario... life-threatening cancers. We review literature both f... serum GGT is a superior marker for future disease...

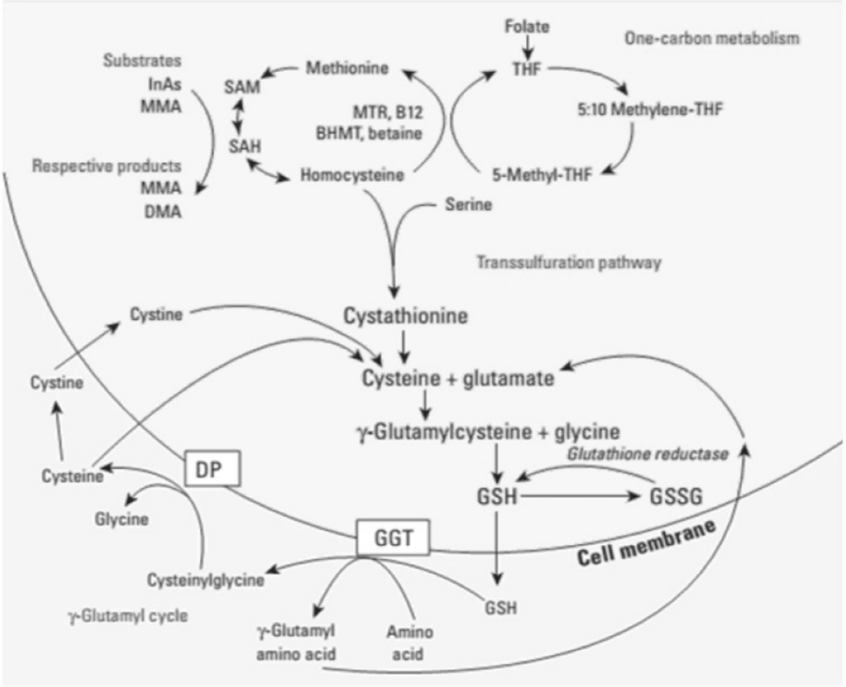
1. Introduction

A comprehensive review by Whitfield in 2001 [1] desc... GGT in its traditional role as a marker of liver dysfun... bile duct conditions, and alcohol consumption. Some... eralized or summary medical and scientific literatur... describe GGT in those terms [2]. However, Whitfiel... already extended that description to include elevated... in association with risk of coronary heart disease, t... diabetes (T2D), and stroke [1]. Although gamma-glu... compounds include antioxidants, inflammatory mole... drug metabolites, and neuroreactive compounds [3... major function of GGT is enabling metabolism of glutat... and glutathionylated xenobiotics. However, elevated... levels, as noted by Whitfield and others, contribu... prooxidant activity, particularly in the presence of ir... copper [4, 5]. When GGT levels are elevated, dama... red blood cell membranes can occur causing the rele...

Glutathione degradation

GGT is a well established marker of alcohol-related liver disease, however, if it also an early predictive marker for atherosclerosis, heart failure, metabolic syndrome and diabetes, a variety of liver diseases, obesity, other infectious disease, periodontal disease, several life-threatening cancers and all-cause mortality. Although the major function of GGT is enabling the metabolism of glutathione and glutathionylated xenobiotics, there has been an upward trend overtime, reflecting increased exposures to environmental toxins resulting in oxidative and nitrosative stress and glutathione depletion.

Koenig and Seneff, 2015



GGT and risk of disease

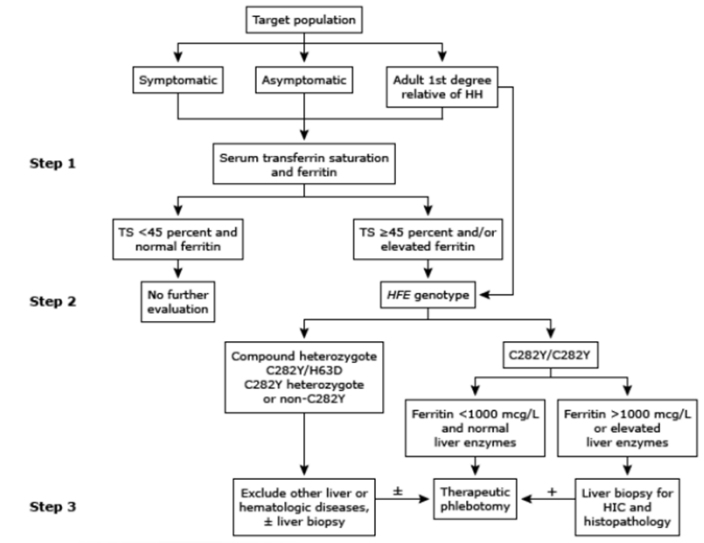
- Epidemiological studies in USA, Europe and Korea show baseline median GGT for men 16 U/L and for women 9 U/L starting with Framingham Offspring Study (1978-1983) with similar levels in other studies.
- NHANES III data normal baseline GGT is up to 51 U/L in men and 33 U/L in women. GGT considered to be elevated >83.7U/L. Individuals with elevated GGT had liver disease mortality risk between 13-19 fold.
- In a Vienna hospital study from 2007, GGT >56U/L for men and GGT>36 U/L for women experienced a 100% increased mortality risk. 130% increased risk of cancer mortality, 60% for vascular or ischemic disease and 40% for stroke.
- There is a dose-response relationship for GGT with greatest mortality in highest GGT levels
- A 2005 Austrian study on GGT and CVD mortalities revealed:

Men –	GGT 14-27 U/L	17% increased risk	Women -	GGT >18/L	35% increased risk
	GGT 18-24 U/L	28% increased risk		GGT 18-26 U/L	46% increased risk
	GGT 42-55 U/L	39% increased risk		GGT >36 U/L	51% increased risk
	GGT >56 U/L	56% increased risk			

Points of concern: GGT and Iron

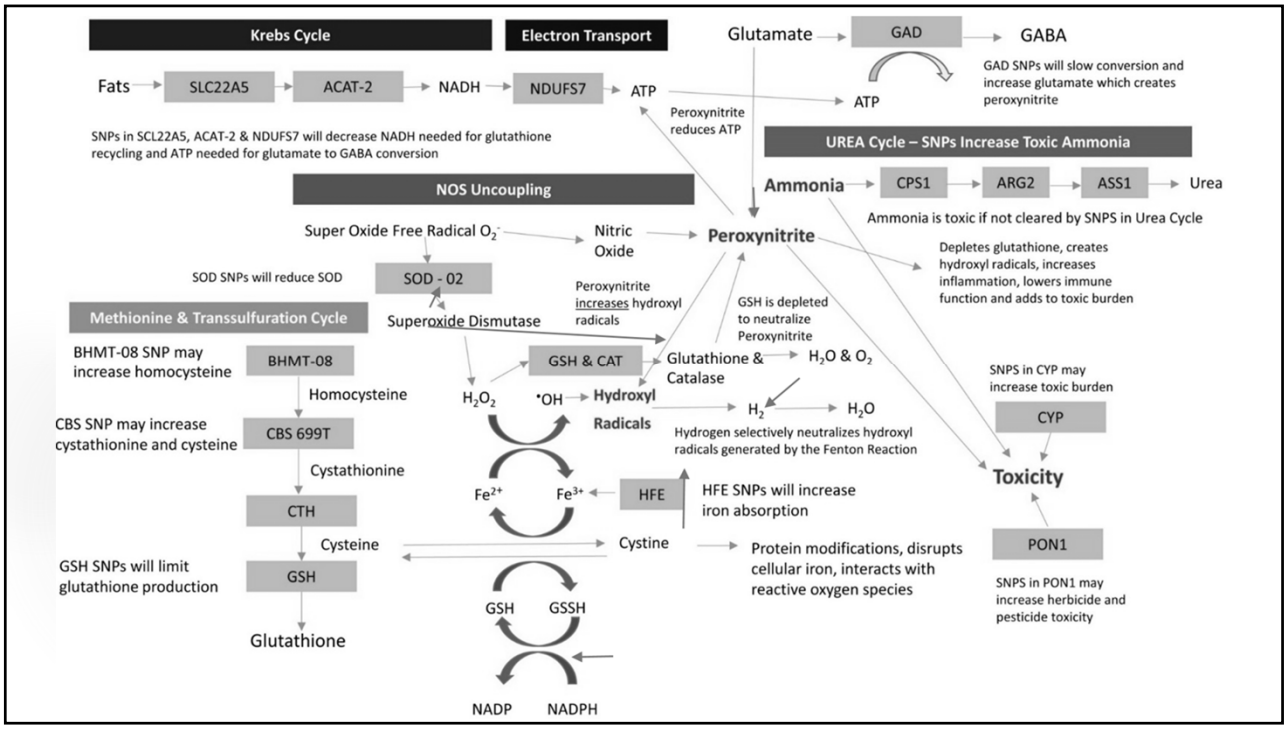
- When GGT breaks down glutathione into cysteinyl glycine, this dipeptide reacts with free iron to induce the Fenton reaction and create more oxidative stress.
- From study in 2009, serum ferritin levels in African American men and women are 1.78-2.05 fold higher than their African counterparts, despite 20% of Africans with Hepatitis B or C.
- The NHANES III (1988-1994) data compared to the HEIRS (Hemachromatosis and Iron Overload screening Study – 2000-2006) data showed ferritin level increases of at least 60 mcg/L in African American men and 50mcg/L increase in Caucasian men.
- Serum ferritin mean levels for AA men – 231 mcg/L; AA women with DM type 2 113 mcg/L and 85 mcg/L without.
- WHO published statement that a serum ferritin above 300mcg/L in men and 200mcg/L in women could be considered at risk for severe iron overload.

Algorithm for the testing for iron overload and hereditary hemochromatosis



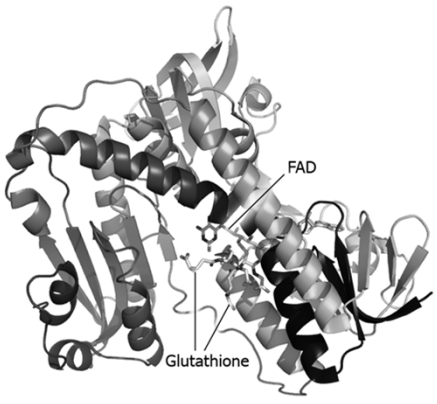
Fenton reactions

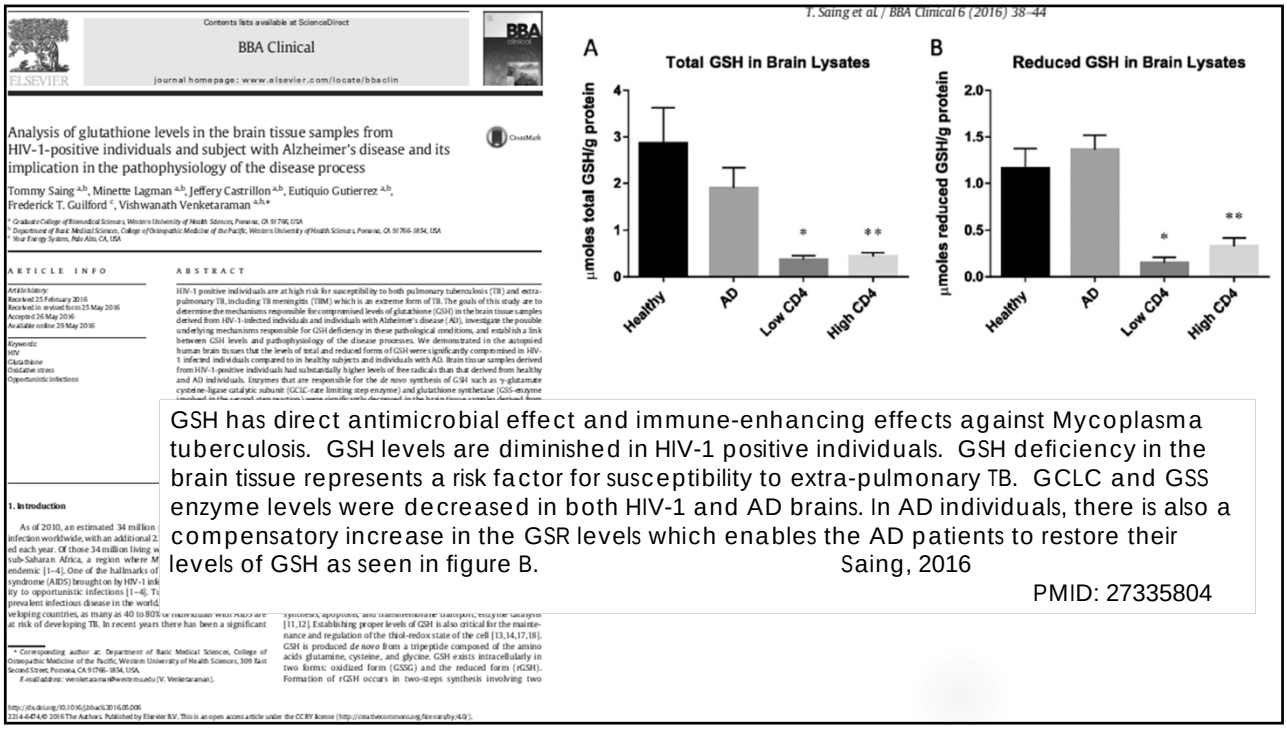
- The 2011 guidelines from the AASLD regarding the appropriate cutoff levels for transferrin saturation (greater than 45 percent) and serum ferritin (greater than 200 ng/mL in men and greater than 150 ng/mL in women) for screening patients with iron overload are in general agreement with the above-noted values.
- Fenton reactions can happen at lower levels of iron leading to oxidative damage.
- Mild elevations of ferritin and GGT may have a synergistic, deleterious effect.



Specific disease states low in glutathione

- Alzheimer's disease
- Autism
- Cardiovascular disease
- Diabetes type 2
- HIV/Infection
- Liver disease and transplantation
- Mercury exposure
- Mold exposure
- Parkinson's





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Analysis of glutathione levels in the brain tissue samples from HIV-1-positive individuals and subject with Alzheimer's disease and its implication in the pathophysiology of the disease process

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ABSTRACT

HIV-1 positive individuals are at high risk for susceptibility to both pulmonary tuberculosis (TB) and extra-pulmonary TB, including TB meningitis (TBM) which is an extreme form of TB. The goals of this study are to determine the mechanisms responsible for compromised levels of glutathione (GSH) in the brain tissue samples derived from HIV-1-infected individuals and individuals with Alzheimer's disease (AD), investigate the possible underlying mechanisms responsible for GSH deficiency in these pathological conditions, and establish a link between GSH levels and pathophysiology of the disease processes. We demonstrated in the autopsied human brain tissues that the levels of total and reduced forms of GSH were significantly compromised in HIV-1 infected individuals compared to in healthy subjects and individuals with AD. Brain tissue samples derived from HIV-1-positive individuals had substantially higher levels of free radicals than that derived from healthy and AD individuals. Enzymes that are responsible for the *de novo* synthesis of GSH such as γ-glutamate cysteine-ligase catalytic subunit (GCLC-rate limiting step enzyme) and glutathione synthetase (GSS-enzyme

1. Introduction

As of 2010, an estimated 34 million
infection worldwide, with an additional 2.
ed each year. Of those 34 million living w
sub-Saharan Africa, a region where M
endemic [1–4]. One of the hallmarks of
syndrome (AIDS) brought on by HIV-1 infe
ty to opportunistic infections [1–4]. Tu
prevalent infectious disease in the world,
veloping countries, as many as 40 to 80%
at risk of developing TB. In recent years there has been a significant

[11,12]. Establishing proper levels of GSH is also critical for the maintenance and regulation of the thiol-redox state of the cell [13,14,17,18]. GSH is produced *de novo* from a tripeptide composed of the amino acids glutamine, cysteine, and glycine. GSH exists intracellularly in two forms: oxidized form (GSSG) and the reduced form (rGSH). Formation of rGSH occurs in two-steps synthesis involving two

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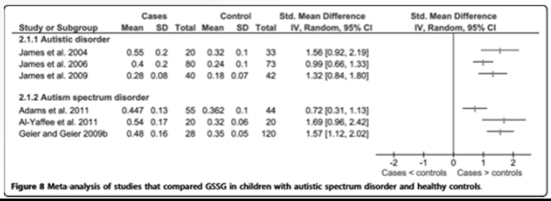
T. Saing et al. / BBA Clinical 6 (2016) 38–44

GSH has direct antimicrobial effect and immune-enhancing effects against Mycoplasma tuberculosis. GSH levels are diminished in HIV-1 positive individuals. GSH deficiency in the brain tissue represents a risk factor for susceptibility to extra-pulmonary TB. GCLC and GSS enzyme levels were decreased in both HIV-1 and AD brains. In AD individuals, there is also a compensatory increase in the GSR levels which enables the AD patients to restore their levels of GSH as seen in figure B. Saing, 2016

PMID: 27335804

Autism and glutathione: meta-analysis

- 42 studies included in the meta-analysis. 29 on metabolites, 6 on interventions, 6 on genetics, 8 regarding enzyme activity, 1 in vitro study.
- Largest study of multiple metabolites of the GSH and trans-sulfuration pathway showed 32% lower levels of GSH and higher levels of GSSG by 66% compared to controls.
- Overall autistic children have lower plasma tGSH:GSSG ratios. Serum cysteine levels are also lower.

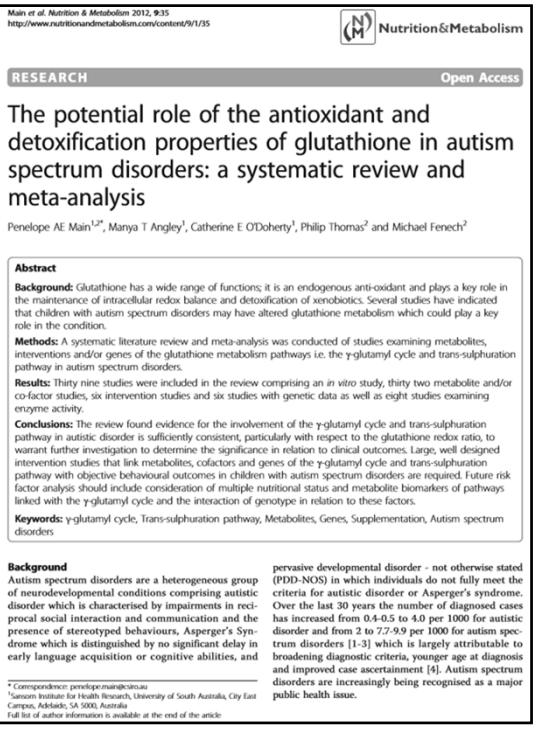


Study or Subgroup	Cases Mean	SD	Total	Control Mean	SD	Total	Std. Mean Difference IV, Random, 95% CI
2.1.1 Autistic disorder							
James et al. 2004	0.55	0.2	20	0.32	0.1	33	1.56 [0.92, 2.19]
James et al. 2006	0.4	0.2	80	0.24	0.1	73	0.99 [0.66, 1.33]
James et al. 2009	0.28	0.08	40	0.18	0.07	42	1.32 [0.84, 1.80]
2.1.2 Autism spectrum disorder							
Adams et al. 2011	0.447	0.13	55	0.362	0.1	44	0.72 [0.31, 1.13]
Al-Yaffee et al. 2011	0.54	0.17	20	0.32	0.06	20	1.69 [0.96, 2.42]
Geier and Geier 2009b	0.48	0.16	28	0.35	0.05	120	1.57 [1.12, 2.02]

Std. Mean Difference IV, Random, 95% CI

-2 -1 0 1 2
Cases < controls Cases > controls

Figure 8 Meta-analysis of studies that compared GSSG in children with autistic spectrum disorder and healthy controls.



Main *et al. Nutrition & Metabolism* 2012, 9:35
http://www.nutritionandmetabolism.com/content/9/1/35

Nutrition&Metabolism

RESEARCH Open Access

The potential role of the antioxidant and detoxification properties of glutathione in autism spectrum disorders: a systematic review and meta-analysis

Penelope AE Main[1,2*], Manya T Angley[1], Catherine E O'Doherty[1], Philip Thomas[2] and Michael Fenech[2]

Abstract

Background: Glutathione has a wide range of functions; it is an endogenous anti-oxidant and plays a key role in the maintenance of intracellular redox balance and detoxification of xenobiotics. Several studies have indicated that children with autism spectrum disorders may have altered glutathione metabolism which could play a key role in the condition.

Methods: A systematic literature review and meta-analysis was conducted of studies examining metabolites, interventions and/or genes of the glutathione metabolism pathways i.e. the γ-glutamyl cycle and trans-sulphuration pathway in autism spectrum disorders.

Results: Thirty nine studies were included in the review comprising an *in vitro* study, thirty two metabolite and/or co-factor studies, six intervention studies and six studies with genetic data as well as eight studies examining enzyme activity.

Conclusions: The review found evidence for the involvement of the γ-glutamyl cycle and trans-sulphuration pathway in autistic disorder is sufficiently consistent, particularly with respect to the glutathione redox ratio, to warrant further investigation to determine the significance in relation to clinical outcomes. Large, well designed intervention studies that link metabolites, cofactors and genes of the γ-glutamyl cycle and trans-sulphuration pathway with objective behavioural outcomes in children with autism spectrum disorders are required. Future risk factor analysis should include consideration of multiple nutritional status and metabolite biomarkers of pathways linked with the γ-glutamyl cycle and the interaction of genotype in relation to these factors.

Keywords: γ-glutamyl cycle, Trans-sulphuration pathway, Metabolites, Genes, Supplementation, Autism spectrum disorders

Background

Autism spectrum disorders are a heterogeneous group of neurodevelopmental conditions comprising autistic disorder which is characterised by impairments in reciprocal social interaction and communication and the presence of stereotyped behaviours, Asperger's Syndrome which is distinguished by no significant delay in early language acquisition or cognitive abilities, and pervasive developmental disorder - not otherwise stated (PDD-NOS) in which individuals do not fully meet the criteria for autistic disorder or Asperger's syndrome. Over the last 30 years the number of diagnosed cases has increased from 0.4-0.5 to 4.0 per 1000 for autistic disorder and from 2 to 7.7-9.9 per 1000 for autism spectrum disorders [1-3] which is largely attributable to broadening diagnostic criteria, younger age at diagnosis and improved case ascertainment [4]. Autism spectrum disorders are increasingly being recognised as a major public health issue.

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Full list of author information is available at the end of the article

Autism and glutathione - Immunity

- Autism is associated with diminished Natural Killer Cell activity
- Adding glutathione to the culture improved the NK activity.

Table 10 Correlation between NK cell activity and reduced glutathione in peripheral blood mononuclear cells obtained from children with autistic disorder

Study	NK Activity (LU)	GSH (ng/3 × 10^6 PBMCs)	Significance	Finding
Vojdani *et al.* 2008	0-10	610 ± 286	ANOVA F = 3.99, $P <$ 0.05	Direct correlation between cellular levels of reduced glutathione and NK lytic activity.
[79]	11-20	947 ± 458		
	21-50	1760 ± 895		
	51-100	2280 ± 1341		

NK Natural killer cells LU Lytic units GSH reduced glutathione ng nanograms PBMCs Peripheral blood mononuclear cells ANOVA One way analysis of variance

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A clinical trial of glutathione supplementation in autism spectrum disorders

Authors' Contribution:
A Study Design
B Data Collection
C Statistical Analysis
D Data Interpretation
E Manuscript Preparation
F Literature Search
G Funds Collection

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Summary

Background: Recent evidence shows that subjects diagnosed with an autism spectrum disorder (ASD) have significantly lower levels of glutathione than typically developing children. The purpose of this study was to examine the use of two commonly used glutathione supplements in subjects diagnosed with an ASD to determine their efficacy in increasing blood glutathione levels in subjects diagnosed with an ASD.

Material/Methods: The study was an eight-week, open-label trial using oral lipoceutical glutathione (n=13) or transdermal glutathione (n=13) in children, 3–13 years of age, with a diagnosis of an ASD. Subjects underwent pre- and post-treatment lab testing to evaluate plasma reduced glutathione, oxidized glutathione, cysteine, taurine, free and total sulfate, and whole-blood glutathione levels.

Results: The oral treatment group showed significant increases in plasma reduced glutathione, but not whole-blood glutathione levels following supplementation. Both the oral and transdermal treatment groups showed significant increases in plasma sulfate, cysteine, and taurine following supplementation.

Conclusions: The results suggest that oral and transdermal glutathione supplementation may have some benefit in improving some of the transsulfuration metabolites. Future studies among subjects diagnosed with an ASD should further explore the pharmacokinetics of glutathione supplementation and evaluate the potential effects of glutathione supplementation upon clinical symptoms.

key words: autism • glutathione • transsulfuration metabolites • oral • transdermal

Full-text PDF: http://www.medscimonit.com/fulltxt.php?ICID=882125

Glutathione as an intervention

- 8 week, open trial using oral lipsoaml glutathione (n=13) or trans-dermal glutathione (n=13)
- Age 3-13 with diagnosis of autism spectrum disorder
- Evaluated plasma reduced glutathione, oxidized glutathione, cysteine, taurine, free and total sulfate and whole blood glutathione levels.
- Dose was 50mg per 30lb Bid for 5 days, and increasing by 50mg/30Lb increments to max 200mg/30lb BID
- Oral treatment increased plasma reduced glutathione by 16%, but not whole blood glutathione.
- Both oral and transdermal increased sulfate, cysteine and taurine.
- Minimal side effects in most. 15% had intolerable side effects of rash and irritability.

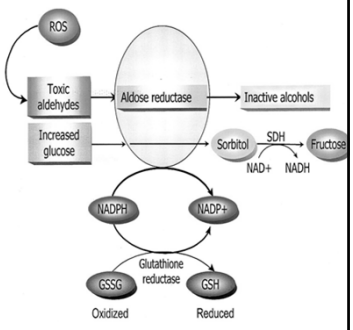
Glutathione and cardiovascular health

- Several early studies by Usal in 1996 and Khab in 2003 report low GSH levels in patients after acute myocardial infarction. (1,2)
- A 2007 study of 97 MI patients. Those with the lowest levels reduced plasma glutathione levels at discharge were associated with increased risk of adverse cardiac events. (7)
- 2013 study shows chronic low GSH exacerbates remodeling and dysfunction in mouse model for congestive heart failure. Administration of GSH reverses the left-ventricular dilation, contractile dysfunction and the increased myocardial fibrosis. (5)
- Prasad in 1999 showed that infusions of glutathione to patients with atherosclerosis enhanced microvascular dilation and increase cGMP in response to acetyl choline, especially in compromised patients. (3)
- Amano showed that infusions of glutathione of 200mg/kg before cardiopulmonary bypass, and for post-op days 1 and 2, resulted in favorable renal and vascular hemodynamics and preserved renal functioning. (4)
- Kugiyama revealed GSH improved coronary endothelial vasomotor function, particularly in subjects with coronary risk factors, and it potentiated the vasodilator effect of nitroglycerin in human coronary arteries. (6)
- Arosio shows in 2002, that in patients with peripheral artery disease, IV glutathione infusions BID prolongs pain free walking distance and improvements of macrocirculatory and microcirculatory parameters. (8)

1PMID: 12944689
2PMID: 8676544
3PMID: 10440166
4PMID: 7952483
5PMID: 23129588
6PMID: 9639372
7PMID: 17301597
8PMID: 12173710

Diabetes and glutathione

- In 1998, De Mattia showed abnormal intracellular GSH redox status plays an important role in reducing insulin sensitivity in NIDDM patients. Intravenous GSH infusion significantly increased both RBC GSH/GSSG ratio and total glucose uptake in the same patients. (1)
- Ciuchi initially showed that RBC sorbitol correlates with fasting blood glucose and lower levels of GSH, and that there is a progressive worsening as glucose and sorbitol increases, GSH worsens. (2)
- The follow-up study, administration of 1200mg of IV GSH lowered the sorbitol levels in type 2 diabetics but not normal controls. GSH allows glucose to proceed to pyruvate through the polyol pathway.(3)
- In 1992, Paolisso revealed that glutathione infusions enhances insulin secretion in elderly people with impaired glucose tolerance. Infusions ran at 10mg/min during baseline testing and with oral and IV glucose tolerance tests. (4)



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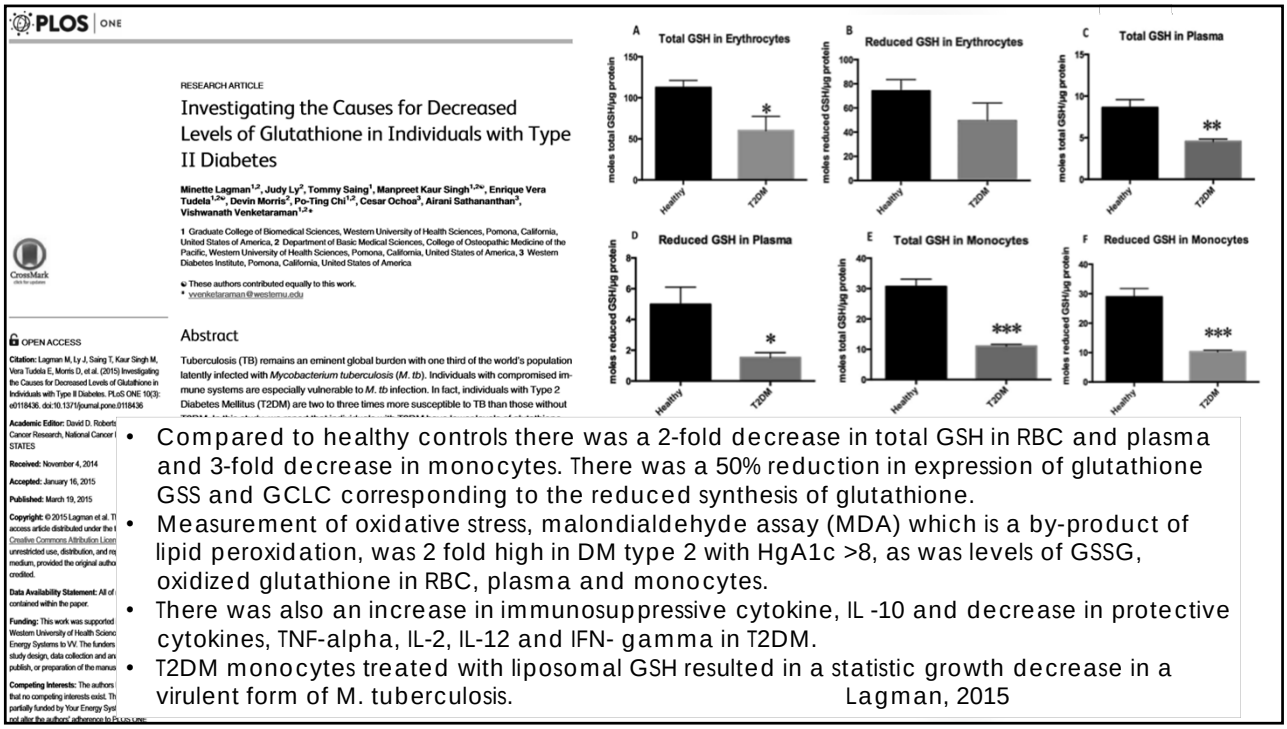
3PMID: 9059767
4PMID: 1737525



PLOS ONE

RESEARCH ARTICLE

Investigating the Causes for Decreased Levels of Glutathione in Individuals with Type II Diabetes

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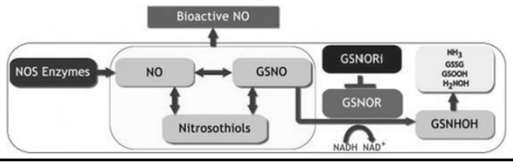
Abstract

Tuberculosis (TB) remains an eminent global burden with one third of the world's population latently infected with *Mycobacterium tuberculosis* (*M. tb*). Individuals with compromised immune systems are especially vulnerable to *M. tb* infection. In fact, individuals with Type 2 Diabetes Mellitus (T2DM) are two to three times more susceptible to TB than those without

- Compared to healthy controls there was a 2-fold decrease in total GSH in RBC and plasma and 3-fold decrease in monocytes. There was a 50% reduction in expression of glutathione GSS and GCLC corresponding to the reduced synthesis of glutathione.
- Measurement of oxidative stress, malondialdehyde assay (MDA) which is a by-product of lipid peroxidation, was 2 fold high in DM type 2 with HgA1c >8, as was levels of GSSG, oxidized glutathione in RBC, plasma and monocytes.
- There was also an increase in immunosuppressive cytokine, IL -10 and decrease in protective cytokines, TNF-alpha, IL-2, IL-12 and IFN- gamma in T2DM.
- T2DM monocytes treated with liposomal GSH resulted in a statistic growth decrease in a virulent form of M. tuberculosis. Lagman, 2015

Glutathione, Immune system and TB

- Innate Immune System and Antimicrobial activity of GSH
  - Mycobacteria don't produce GSH, so exposure to high concentrations creates redox imbalance leading to growth inhibition of TB.
  - GSH is structurally similar to antibiotic precursors from the fungi Penicillium and Cephalasporium. GSH may have a beta-lactam form.
  - GSH is a precursor to S-nitrosoglutathione (GSNO).
  - It alters cytokine responses in macrophages.
  - GSH enhances Natural Killer cell function leading to apoptosis of infected cells, and inhibits growth within neutrophils.
- Adaptive Immune System – TH1/TH2 responses and GSH
  - High intracellular GSH favors TH1 resulting in favorable cytokine production leading to control of Mycobacteria.



PMID: 23089304 Morris, D et al. Glutathione and Infection. Biochimia. Biophys Acta 2012. http://dx.doi.org/10.1016/j.bbagen.2012.10.012

HIV-1/AIDS and glutathione

- GSH levels in plasma, erythrocytes and peripheral blood mononuclear cells (PBMCs), Natural Killer cells and T cells of HIV+ individuals are compromised.
- GSH synthesis and recycling is compromised. GCLC, GSS and GSR levels in RBCs are decreased in HIV+ compared to healthy controls.
- HIV+ individuals have increased levels of free radicals and proinflammatory cytokines, which decreases GSH because the antioxidant is trying to deal with the free radicals.
- HIV+ individuals have elevated levels of TGF-beta, transforming growth factor, which blocks the production of GCLC.
- GSH deficiency in HIV+ impairs both innate and adaptive immune responses.
- Restoring GSH mitigates the production of ROS and improves the ability of the macrophages to kill *M. Tb* intracellularly through several mechanisms:
  - Direct antimicrobial effects
  - Enhanced functioning of NK and T cells
  - Antioxidant effects
  - Carrier molecule for NO
  - Reduces levels of pro-inflammtory cytokines

PMID: 26133750
PMID: 24782776
PMID: 23409922
PMID: 22164280
PMID: 22242038
PMID: 23089304

Liver and glutathione

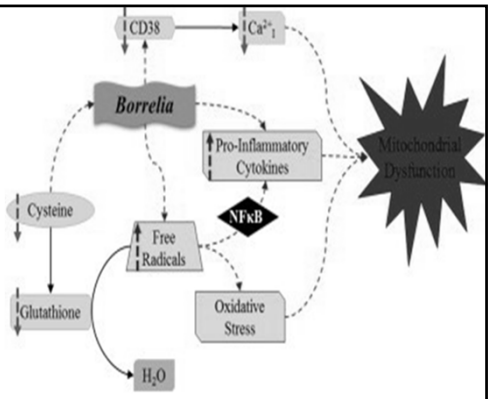
- Glutathione for Non-alcoholic fatty liver.
- Open label, single arm pilot study
- 29/34 participants finished the study
- 300mg/day for 4 months
- ALT levels diminished by >12.9%. Also triglycerides, fatty acids and ferritin.
- Liver fat and fibrosis evaluated by vibration controlled transient elastography and was improved, but not quantifed.
- Younger and non-diabetics responded more favorably.

Honda, et al. BMC Gastroenterology (2017) 17:96

- IV glutathione infusion protects liver parenchymal cells against reperfusion injury following rat liver transplantation. GSH administered at 100Micromol/(h per kg) more protective. PMID: 15040034
- 50 chronic Hep C patients given oral antioxidant mixture plus IV glycyrrhizin, vit C, L-glutathione, B-complex twice weekly for the first 10 weeks. This induced a favorable response in 48%. 25% had decrease in viral load. PMID: 16082287
- IV high dose glutathione in patients with chronic fatty liver disease improves LFTS even several months after treatment interruption. The optimal results obtained in patients receiving **1800 mg/IV**. PMID: 7569285
- **2.4g/day** GSH for 15 days improved GSH in plasma and RBCs and LFTs in alcohol abstaining patients with Alcoholic liver cirrhosis. PMID: 8869667

Lyme disease – inflammation and oxidative stress

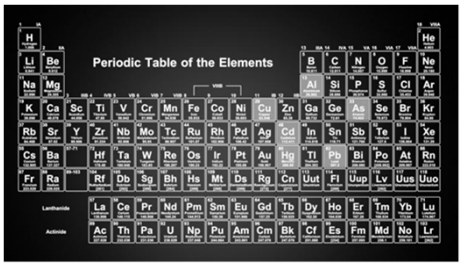
- Significant rise in mitochondrial superoxide and decrease in ionized calcium indicate oxidative stress, mitochondrial membrane instability and release of pro-inflammatory cytokines in Lyme borreliosis patients.
- Activation of Inflammation and host immune responses cause damage leading to hallmarks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



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

Glutathione and heavy metals

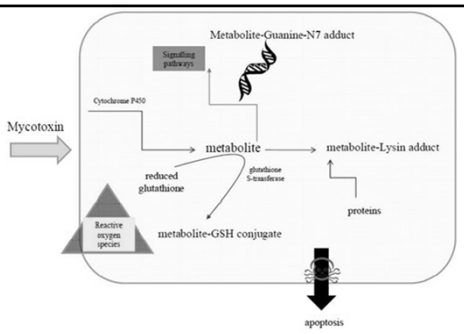
- Thimerosal exposure in dendritic cells modulates a TH2 response through the depletion of GSH. (1)
- Depletion of GSH increases methyl Mercury (MeHg) accumulation and enhances Me-Hg induced oxidative stress. Supplementation of GSH precursors protects in vitro. (2)
- Glutathione plus Ca2+EDTA removes cadmium and protects kidneys in cadmium toxic patient. 500mg of EDTA plus 50mg/kg glutathione in 1 L NS over 24 hours and repeated for 12 days. Blood cadmium and renal excretion of cadmium higher with the GSH without any kidney compromise for subsequent 6 months. (3)
- Mercury elimination with oral DMPS, DMSA, Vit C and IV glutathione resulted in an average 69% reduction of urine by provocation analysis. (4)



1 PMID: 17079650
2 PMID: 16513172
3 PMID: 20413561
4 PMID: 16708769

Mold and mycotoxins induce oxidative stress and inflammation

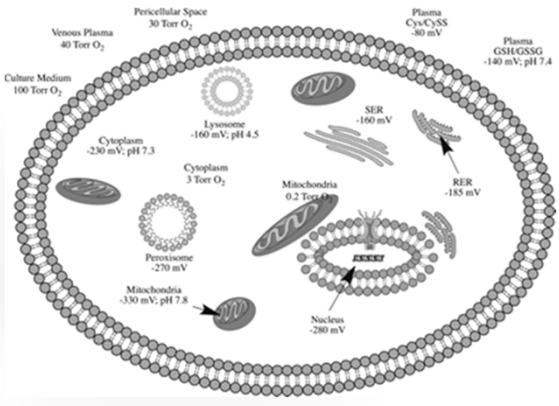
- Chronic mold exposures induce changes in inflammatory and immune responses to specific mold and mycotoxin challenges.
- Mold exposed patients had different cytokine and chemokine profiles when their peripheral blood mononuclear cells (PBMCs) were exposed to mold vs non-exposed controls.
- Mold toxins may suppress the immune system through a balance of cytotoxicity and altered Th1/Th2 balance. 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.



- 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).

Oxidative shielding rather than oxidative stress

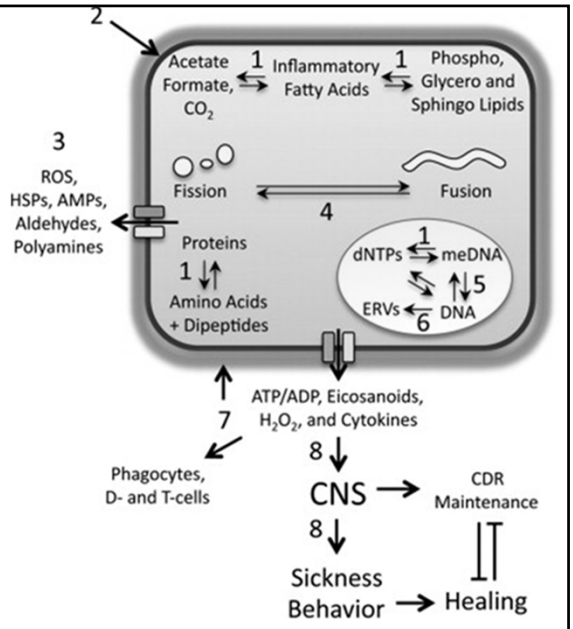


Naviaux. Journal of Pharmacology and Experimental Therapeutics. 2012, 342(3):608-18.

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

Cell Danger Response

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



Naviaux. Mitochondrion. 2014. 16:7–17

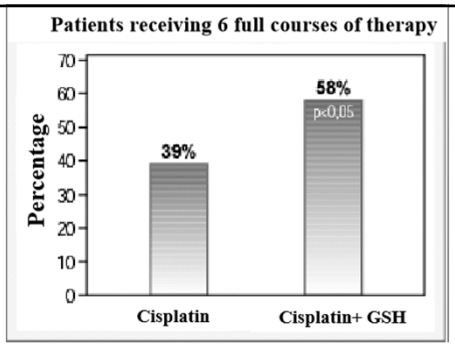
Cell Danger Response

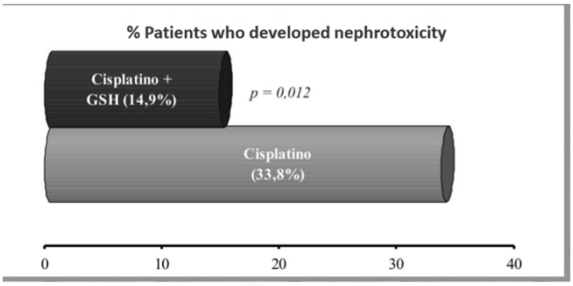
- The acute CDR produces at least 8 functional changes:
- 1) it shifts cellular metabolism to prevent the hijacking and assembly of cellular resources by intracellular pathogens.
- 2) it stiffens the membranes of the cell
- 3) releases antiviral and antimicrobial chemicals into the pericellular environment
- 4) increases autophagy and mitochondrial fission to remove intracellular pathogens
- 5) changes DNA methylation and histone modification to alter gene expression
- 6) mobilizes endogenous retroviruses and other mobile genetic elements like the long interspersed nuclear elements (LINEs) to produce genetic variations
- 7) warns neighboring cells and distant effector cells of the danger
- 8) alters the behavior of the host to prevent the spread of infection to kin and sleep patterns to facilitate healing

Glutathione in Oncology

Ovarian Cancer

- Glutathione reduces the toxicity and improves quality of life of women diagnosed with ovarian cancer treated with cisplatin: results of a double-blind, randomised trial.
- 150 women with ovarian cancer (stages 1-IV) given cisplatin +/- GSH
- GSH enabled the patients to complete the full 6 courses of chemo (58% vs 39%)
- GSH increased the complete vs partial responses to treatment (74 vs 62%)
- Quality of Life scores were statistically improved for depression, emesis, peripheral neurotoxicity, hair loss, shortness of breath and difficulty concentrating.
- They were less likely to develop nephrotoxicity. (14.9% vs 33.8%)
- Not statistically significant, GSH group had better overall outcomes. (73% vs 62%)





Smyth et al. Ann Oncol. 1997 Jun;8(6):569-73.
PMID: 9261526

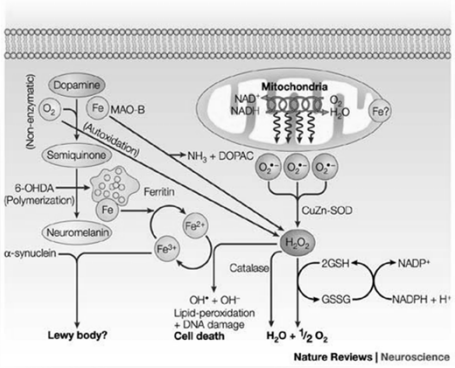
Glutathione in Oncology

Gastric Cancer and reduction in chemo-induced neuropathy with glutathione

- 50 patients with advanced gastric cancer in a randomized, double-blind placebo controlled trial of efficacy of Glutathione in the prevention of cisplatin induced neuropathy.
- GSH given 1.5g/m2 in 100mL normal saline over 15 minutes immediately before cisplatin administration. NS only for controls. And 600mg IM on day 2 to 5.
- At 9 weeks, GSH arm showed no neuropathy vs. 16 of controls and at week 15 only 4/24 vs 16/18 placebo arm had symptoms. 4.2% vs 72.2% p = 0.0001
- GSH reduced need for transfusions and treatment delays.
- The response rate was 76% (20% complete response) in the GSH group and 52% (12% complete response) in the placebo arm, confirming preliminary reports about the lack of reduction in activity of cytotoxic drugs induced by GSH.

Cascinu, et al. J Clin Oncol.
1995 Jan;13(1):26-32.
PMID: 7799029

Glutathione and Parkinson's Disease



- PD is a progressive neurodegenerative disease results in aggregations of mis-folded proteins and significant loss of dopaminergic neurons in the substantia nigra (SN).
- There is 40-50% less glutathione in PD brains, esp in the SN, therefore less capacity to handle oxidative stress.
- There is also higher levels of iron in the SN of PD patients.
- Reduced iron (Fe 2+) readily reacts with H202 to form OH- via the Fenton reaction. Typically Fe2+ and Fe3+ (oxidized) are in a 1:1 ratio, but 1:3 in a PD brain.
- SN also contains neuromelanin which interacts with pesticides and heavy metals, producing more free radicals and overwhelming the oxidative balance.

Morris. The Glutathione System. Mol Neurobiol (2014) 50:1059-1084.
Smeyne. Glutathione Metaoblism and Parkinsons' disease. Free Radic Biol Med 2013 Sept; 62:13-25.

Movement Disorders
Vol. 24, No. 7, 2009, pp. 979-983

Randomized, Double-Blind, Pilot Evaluation of Intravenous Glutathione in Parkinson's Disease

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[2]*Department of Molecular Pharmacology and Physiology, University of South Florida and Tampa General Healthcare, NPF Center of Excellence, Tampa, Florida*
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[4]*Perlmutter Health Center, Naples, Florida*

Abstract: The objective of this study was to evaluate the safety, tolerability, and preliminary efficacy of intravenous glutathione in Parkinson's disease (PD) patients. This was a randomized, placebo-controlled, double-blind, pilot trial in subjects with PD whose motor symptoms were not adequately controlled with their current medication regimen. Subjects were randomly assigned to receive intravenous glutathione 1,400 mg or placebo administered three times a week for 4 weeks. Twenty-one subjects were randomly assigned, 11 to glutathione and 10 to placebo. One subject who was assigned to glutathione withdrew from the study for personal reasons prior to undergoing any postrandomization efficacy assessments. Glutathione was well tolerated and there were no withdrawals because of adverse events in either group. Reported adverse events were similar in the two groups. There were no significant differences in changes in Unified Parkinson's Disease Rating Scale (UPDRS) scores. Over the 4 weeks of study medication administration, UPDRS ADL + motor scores improved by a mean of 2.8 units more in the glutathione group ($P = 0.32$), and over the subsequent 8 weeks worsened by a mean of 3.5 units more in the glutathione group ($P = 0.54$). Glutathione was well tolerated and no safety concerns were identified. Preliminary efficacy data suggest the possibility of a mild symptomatic effect, but this remains to be evaluated in a larger study. © 2009 Movement Disorder Society

Key words: glutathione; Parkinson's disease; treatment; antioxidant; neuroprotection; UPDRS

Glutathione is a tripeptide of glutamate, cysteine, and glycine, that plays multiple roles in the brain.[1] It serves as an important central nervous system antioxidant, clears free radicals including superoxide radicals, hydroxyl radicals, nitric oxide, and carbon radicals,[2,3] and helps clear hydrogen peroxide.[4] In addition, glutathione helps maintain the cellular redox state of protein thiols and low-molecular-weight antioxidants such as vitamin E and ascorbate.[5] Recent evidence suggests that glutathione can also act as a neurotransmitter and neurohormone.[6]

In Parkinson's disease (PD), glutathione is reduced by 40–50%.[7–11] This reduction is specific within the brain to the substantia nigra[9] and correlates with

Additional Supporting Information may be found in the online version of this article.

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Potential conflict of interest: All authors have indicated that they have nothing to disclose regarding Wellness Health and Pharmaceuticals or glutathione. Dr. Robert Hauser has received honoraria or consulting fees from Bayer Schering Pharma AG, Bertek, Boehringer Ingelheim, Centopharm, Eisai, Genzyme, GlaxoSmithKline, Impax, Kyowa Pharmaceutical, Merck KgaA, Ortho McNeil, Novartis, Pfizer, Prestwick, Schwarz Pharma, Schering, Solvay, Synosia, Teva Neuroscience, Valeant, and Vernalis. Dr. Kelly Lyons has received honoraria or consulting fees from Advanced Neuromodulation Systems, GlaxoSmithKline, Novartis, Teva Neuroscience, UCB Pharma, and Valeant Pharmaceuticals. Terry McClain has received honoraria or consulting fees from Eisai, GlaxoSmithKline, Kyowa Pharmaceutical, Solvay, Teva Neuroscience, Serono, and Vernalis. Summer Carter has received honoraria or consulting fees from Solvay and Asubio Pharmaceuticals. Dr. David Perlmutter reports nothing to disclose.

Received 8 July 2008; Revised 20 August 2008; Accepted 24 October 2008

Published online 19 February 2009 in Wiley InterScience (www.interscience.wiley.com). DOI: 10.1002/mds.22401

IV glutathione for Parkinson's

- 21 Parkinson's patients not well controlled (in terms of tremor, bradykinesia or rigidity) on their medications.
- IV glutathione push administered 1,400mg/10mL three times weekly for 4 weeks vs placebo. Total GSH 16,800mg.
- GSH was well tolerated. Minimal adverse effects. Side effects included HA, myalgias, nausea and dizziness/lightheadedness, but there were similar side effects in the placebo group.
- No significant improvement in Parkinson's signs and symptoms was observed.
- Sechi et al. previously reported a 42% decline in PD disability with 600 mg glutathione administered IV BID for 30 days. The therapeutic effect was observed to last for 2 to 4 months. Pts received a total of 36,000mg of glutathione and were in early stages of the disease.

Sechi G, et al. Reduced intravenous glutathione in the treatment of early Parkinson's disease. Prog Neuropsychopharmacol Biol Psychiatry 1996;20:1159–1170.

Intravenous glutathione

- **Kinetics** – 1991 study by Aebi of healthy volunteers determined that IV glutathione infusion of 2 grams/m2 increased total glutathione in plasma from 17.5 ± 13.4 μmol 1^{-1} to 823 ± 326 μmol 1^{-1}.
- Cysteine in plasma also increased. Urinary excretion of glutathione and cysteine increased 300-fold and 10-fold, respectively, 90 mins post infusion. The GSH T1/2 is 15 minutes as it redistributes to the extracellular compartments. (1)
- 50mg/kg IV glutathione administered over 10 min degrades into its constituent amino acids with a T1/2 of 10 minutes. Increased concentration of Cysteine to over 20μM suppressed intracellular ROS by 50% for about 60 minutes in a study looking for solutions to paraquat intoxication. (2)
- Kim's 2010 follow up study confirmed that treatment with 50 mg/kg GSH significantly suppressed serum Reactive Oxygen Metabolites (ROM) levels in Paraquat (PQ)-intoxicated patients. However, this dose was not sufficient to suppress ROM levels when the PQ concentration was extremely high.(3)

1 PMID: 1907548
2 PMID: 16224142
3 PMID: 20830225

IV glutathione – what to do?

Glutathione IV push

- 200mg/mL plus 1mL sterile water in 1:1 or D5W add 2mL
  - i.e. 8mL (1600mg) plus 8mL sterile water or 10mL of D5W in syringe
  - Push slowly over 5-15 minutes. More slowly if sensitive. Or add more sterile water.
  - If develops HA, nausea or dizziness, slow the administration, lower the dose or give Potassium Bicarb.
  - Have Benadryl on hand for histamine reactions.
- For sensitive patients or those with CBS/BHMT snps, start much smaller dose, like 300-400mg and work up as tolerated.

Glutathione Infusion

- 300mg-600mg in 500mL bag of saline and infuse over 1- 1½ hours, up to 3 hours. For extremely chemically sensitive or mold exposed patients run at 1 drop/sec.
- Depending on indication, such as neurodegenerative disease like Parkinson's, can work up to 2-3 grams glutathione per infusion. Sechi used 600mg twice weekly. Hauser /Perlmutter used 1.4g three times weekly.
- Dr Shrader states he will use doses up to 2.5g.
- Quality is important so look around for high quality products.
- Always use preservative free IV nutrients.

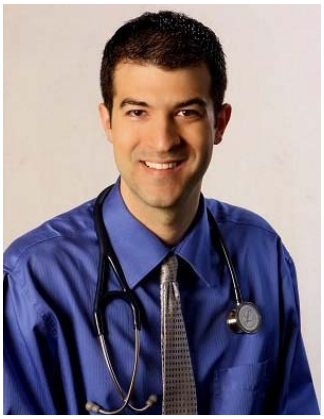
Glutathione plus other nutrients

- Glutathione 600-1000mg
- B12 1000mcg
- N-acetyl cysteine
- B complex
- Magnesium Chloride 500-1000mg
- Possibly used in lieu of higher doses of glutathione

- Glutathione as part of the PK protocol with phenylbutyrate, Essentiale Phosphatidyl choline, leucovorin, B12

- Glutathione as part of heavy metal protocol with IV DMPS ± Ca2+ EDTA.

NOTES



Brenden Cochran, N.D.

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Disclosure Statement:

Dr. Cochran has indicated that he has no relevant financial relationships with any commercial supporters.

Artesunate, Lipoic Acid Mineral Complex & Phosphatidylcholine

This presentation will be on Artesunate and Lipoic Acid complex. Artesunate I will focus on some case studies and examples of usage with chronic infectious need with virus and bacteria. Lipoic Acid complex will focus on cases where it has been useful in mitochondria health, chronic fatigue, fluoroquinolone toxicity, usage with difficult heavy metal courses and understanding of the basic pharmacology.

Learning Objectives:

At the conclusion of this activity you should be able to…

- Discuss safe applications of the substances and utilization in proper patient conditions.
- Apply additional therapies to your current treatment practice.

About Dr. Cochran

Dr. Brenden Cochran received his Doctorate in Naturopathic Medicine from Basytr University. He founded Interactive Health Clinic, a family practice with specialty focuses in pain, integrative oncology, chronic disease management, injection and intravenous therapies. He has additional training in IV therapy, Neural Therapy, Medical Ozone injections/Applications, Master Level Training in Neural Prolotherapy, and Biological Allograph Progenitor cells. He served as faculty at Bastyr University with a focus on Advance IV Therapy. He also served as the medical fellow/director of intravenous therapy at the Bastyr Integrative Oncology Research Center (BIORC), Bastyr University's cancer research center. He currently lectures with International IV Therapy for Professionals and guest lectures at many other venues. He is an instructor of Neural Therapy, Neural Prolotherapy (Perineural Injections), Ozone injections, Biological Allograph Progenitor cells to doctors around the world. As a keynote speaker and content creator, Dr. Cochran is dedicated to empowering doctors to build successful models in outcome-based medicine.

NOTES

Artesunate, Lipoic Acid Mineral Complex & Phosphatidylcholine

Brenden Cochran, ND

2017 – AAEM

Under Accreditation Council for Continuing Medical Education guideline disclosure must be made regarding relevant financial relationships with commercial interests within the last 12 months.

Brenden Cochran, N.D.

Received an educational grant from ImprimixRX

Unless otherwise stated, the level of evidence is C and based on clinical experience.

Intravenous Artesunate

Case 1

46 year old female referred to me for difficult EBV

- Symptoms of fatigue and exercise resistance
- Onset presented 3-4 months after double mastectomy (prevention due to BRACA)
- Tried oral protocols with lysine, monolaurin, vitamin A
- Started oral Artemesinin + once every other week IV Mega C (25-50 grams Vitamin C, nutrients and lysine) + IV Artesunate
- Usually would to once weekly but due to finances

Case 1

46 year old female referred to me for difficult EBV

2/2016: Initial labs EBV Early Antigen 36.7 U/ml
3/2016: 38.4 U/ml
4/2016: 37.3 U/ml
7/2016: 29.3 U/ml

Drastic improvement in energy and able to return to exercise without extreme exhaustion 3 months into treatment. Patient discontinued treatment due to feeling well and another practitioner told her to let her body handle the EBV.

Case 2

41 year old female referred to me for chronic fatigue

- Initial work up suggested past exposure with EBV high VCA and Nuclear Antigen
- Further workup shows Lyme WB borderline positive confirmed positive with Ispot lyme test.

History of not tolerating Artemesinin orally. Feeling unwell.

Case 2

41 year old female referred to me for chronic fatigue

Test dosage of 30 mg Artesunate IV to start and tolerated well without issues. Able to work up to therapeutic dosage 120 mg without issues.

IV Mega C + Artesunate once per week for 4-5 months. Initial month ups and downs. Currenlty seeing improvement in symptoms and lyme titers showing resolution of p23 band.

Case 3

68 year old male initially came in early 2014 with metastatic non small cell lung cancer with metastasis to brain and bone.

- Environmental hx. Mill work, asphalt, smoking history, lumber worker, asbestos exposure and high red meat intake.
- On oral erlotinib
- Only abnormal lab finding was CMV IgG 8.30 U/ml (2014)

Worked up to 100 gram IVC + DMSO + Artesunate given once every other week due to finances and travel distance. Also on oral 1 tsp 5 days per week liposomal Artemesinin.

Case 3

68 year old male

- After 3 months infusions patient PET and MRI showed improvements:

-Lung mass, brain and bone mets.

- 6 months

Lung nodule stable to resolved

Bone mets resolved

Brain still present but stable

Currently August 2017. No lung nodules, no bone mets, stable but present brain lesion.

CMV is now at 6.6 IgG

ART and CMV Virus

From the Abstract:

"This is the first report of treatment of cytomegalovirus infection with artesunate, for a stem cell transplant recipient with a newly identified foscarnet-resistant and ganciclovir resistant DNA polymerase L776M mutation. Artesunate treatment resulted in a 1.7–2.1-log reduction in viral load by treatment day 7, with a viral half-life of 0.9–1.9 days, indicating a highly effective block in viral replication."

Shapira MY, et. Al. Artesunate as a Potent Antiviral Agent in a Patient with Late Drug-Resistant Cytomegalovirus Infection after Hematopoietic Stem Cell Transplantation. Clinical Infectious Diseases 2008; 46:1455–7

ART and CMV Virus

And a cell line study bore out the superiority of Artesunate over other Artemesia compoinds in CMV:

Flobinus A. Stability and antiviral activity against human cytomegalovirus of artemisinin derivatives. J. Antimicrob. Chemother. (2014) 69 (1): 34-40. doi: 10.1093/jac/dkt346

ART and Bacteria

"Artemisinin and nine of its semisynthetic derivatives were tested for antibacterial activity against anaerobic, facultative anaerobic, microaerophilic and aerobic bacteria. Only anaerobic bacteria and gonococci showed sensitivity to artemisinin derivatives."

Shoeb HA, Tawfik AF, Shibl AM, el-Feraly FS. Antimicrobial activity of artemisinin and its derivatives against anaerobic bacteria. Journal of Chemotherapy (Florence, Italy) [1990, 2(6):362-367] (PMID:2128751)

ART Pharmacokinetics

Abstract

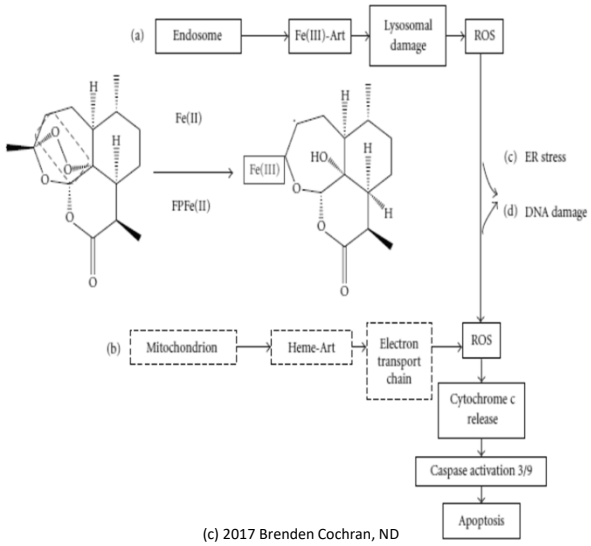
- The pharmacokinetics of good manufacturing process injection of artesunate (AS) were evaluated after single doses at 0.5, 1, 2, 4, and 8 mg/kg with a 2-minute infusion in 40 healthy subjects. Drug concentrations were analyzed by validated liquid chromatography and mass spectrometry system (LC-MS/MS) procedures. The drug was immediately converted to dihydroartemisinin (DHA), with elimination half-lives ranging 0.12-0.24 and 1.15-2.37 hours for AS and DHA, respectively. Pharmacokinetic model-dependent analysis is suitable for AS, whereas DHA fits both model-dependent and -independent methods. Although DHA concentration was superior to that of AS with a 1.12-1.87 ratio of area under the curve (AUC)(DHA/AS), peak concentration of AS was much higher than that of DHA, with a 2.80- to 4.51-fold ratio of peak concentration (C(max AS/DHA)). Therefore, AS effectiveness has been attributed not only to its rapid hydrolysis to DHA, but also to itself high initial C(max).
- Li Q, Cantilena LR, Leary KJ, Saviolakis GA, Miller RS, Melendez V, Weina PJ. Pharmacokinetic profiles of artesunate after single intravenous doses at 0.5, 1, 2, 4, and 8 mg/kg in healthy volunteers: a phase I study.Am J Trop Med Hyg. 2009 Oct;81(4):615-21. PMID: 19815876

Artesunate

- Artesunate (ART), a derivative of artemisinin, can be a potent and selective antitumor agent as well as antimicrobial agent.
- Importantly, ART has produced a dose-dependent tumor regression in an in vivo pancreatic cancer xenografts model.
- **The in vivo antitumor activity of ART was similar to that of gemcitabine.**
- ART is considered to produce a ROS burst which may alter cancer cell activity.
- Additionally ART appears to be a synergist with oxidative therapies such as high dose ascorbic acid.
- Potential COX-2 inhibitor
  - **Artesunate inhibits the growth and induces apoptosis of human gastric cancer cells by downregulating COX-2. (Onco Targets Ther 2015 Apr 16;8:845-54)**

https://www.academia.edu/20316500/Artesunate_Monograph

Maria P. Crespo-Ortiz and Ming Q.Wei. Antitumor Activity of Artemisinin and Its Derivatives: From aWell-Known Antimalarial Agent to a Potential Anticancer Drug .Journal of Biomedicine and Biotechnology. Volume 2012, Article ID 247597, 18 pages. doi:10.1155/2012/247597



J. Biol Chem. Artesunate induces cell death in human cancer in human cancer cells via enhancing lysosomal function and lysosomal degradation of ferritin. 2014 Nov. 28;289(48):33425-41. doi: 10.1074/jbc.M114.564567. Epub 2014 Oct 10
Yang ND, Tan SH, Shi Y, et al

In summary, our study demonstrates that ART treatment activates lysosomal function and **then promotes ferritin degradation, subsequently leading to the increase of lysosomal iron that is utilized by ART for its cytotoxic effect on cancer cells.**

Protocol for Artesunate

- **D5W or NS**
  - **100 mL bag**
- **Infuse directly prior or after HDIVC (High Dose IVC)**
- **Infuse 60mg on the first occasion as a test dose**
- **120mg IV Artesunate on subsequent doses**
- **Frequency: Once to twice weekly as directed;**
  - **Re-evaluate after 10-15 treatments.**
- **Short half life: oxidant within 20 min (not after 2 hours or less)**
- **Oxidative treatment**
  - **Compatible with IVC and other oxidants**

Uses include infections (especially viral) and oncology

Oral Artesunate

Artesunate
- 200 mg per day oral Artesunate

Artemesinin
- 300 mg three times per day x 3-5 days on 9-11 days off. (Pulsed dosage due to GI absorption issues).
  Best to take with food, preferably fat.

Liposomal Artemesinin (more effective than oil)
- 1 tsp once to twice daily. Improved absorption.

Dosage: How high could you go?

Zhou X, Sun WJ, Wang WM, Chen K, Zheng JH, Lu MD, Li PH, Zheng ZQ . Artesunate inhibits the growth of gastric cancer cells through the mechanism of promoting oncosis both in vitro and in vivo. Anticancer Drugs. 2013 Oct;24(9):920-7. doi:10.1097/CAD.0b013e328364a109 Epub 2013.

This study aims to investigate the significance and mechanism of artesunate involved in suppressing the proliferation of gastric cancer in vitro and in vivo. In the in-vitro experiments, artesunate inhibited the growth of gastric cancer cell lines (SGC-7901, BGC-823, and AGS) with concentration-dependent activity, with no significant effect on GES-1 cells. BGC-823 cells treated with artesunate showed the typical morphologic features of oncosis rather than apoptosis. Meanwhile, we observed calcium overload, downregulation of vascular endothelial growth factor expression, and upregulation of calpain-2 expression in the artesunate-treated BGC-823 cells. In addition, the in-vivo study showed that artesunate produced a dose-dependent tumor regression in **nude mice**. **The antitumor activity of 240 mg/kg artesunate was similar to that of 10 mg/kg docetaxel.** Furthermore, compared with the control group, no significant difference was observed in the body weight of artesunate-treated nude mice other than docetaxel-treated nude mice. These observations show that artesunate has concentration-dependent inhibitory activities against gastric cancer in vitro and in vivo by promoting cell oncosis through an impact of calcium, vascular endothelial growth factor, and calpain-2 expression.

Toxicity

- Oral Toxicity

No toxicity in dogs using oral 45 mg/kg q6 hours x 3 weeks. Most common side effect was anorexia. Bioavailability wasn't high enough.

- Minimal AST, ALT elevations
- No neutropenia
- No anemia
- 556 mg/kg Artemether per day no toxicity in beagles
- No toxicity in monkeys which received 292 mg/kg (642 mg/pound) of Artemether over 1-3 months

Artesunate References

Stockwin LH. et. al. Artemisinin dimer anti-cancer activity correlates with hemecatalyzed ROS generation and ER stress induction. Int J Cancer. 2009 September 15; 125(6): 1266–1275. doi:10.1002/ijc.24496.

Efferth T. Molecular pharmacology and pharmacogenomics of artemisinin and its derivatives in cancer cells. Curr Drug Targets. 2006; 7:407–21. [PubMed: 16611029]

Paik IH, Xie S, Shapiro TA, Labonte T, Narducci Sarjeant AA, Baege AC, Posner GH. Second generation, orally active, antimalarial, artemisinin-derived trioxane dimers with high stability, efficacy, and anticancer activity. J Med Chem. 2006; 49:2731–4. [PubMed: 16640333]

Nam W, Tak J, Ryu JK, Jung M, Yook JI, Kim HJ, Cha IH. Effects of artemisinin and its derivatives on growth inhibition and apoptosis of oral cancer cells. Head Neck. 2007; 29:335–40. [PubMed:17163469]

Chen HH. et. al. Antimalarial dihydroartemisinin also inhibits angiogenesis. Cancer Chemother Pharmacol (2004) 53: 423–432. DOI 10.1007/s00280-003-0751-4

Chen HH. et. al. Inhibitory Effects of Artesunate on Angiogenesis and on Expressions of Vascular Endothelial Growth Factor and VEGF Receptor KDR/flk-1 Pharmacology 2004;71:1–9 DOI: 10.1159/000076256

Efferth T, et. al. The anti-malarial artesunate is also effective against cancer. International journal of Oncology. 2001. 18; 767-773

Yang J, et. al. Dihydroartemisinin is an inhibitor of ovarian cancer cell growth. Acta Pharmacol Sin 2007 Jul; 28 (7): 1045–1056. doi: 10.1111/j.1745-7254.2007.00612.x

Yan Yang, Xiaomin Zhang, Xiofen Wang, et. Enhanced delivery of artemisinin and its analogues to cancer cells by their adducts with human serum transferrin. International Journal of Pharmaceutics. 2014, March 2014, 467 (1-2):113-122 doi:10.1016/j.ijpharm.2014.03.044

Lipoic Acid Mineral Complex

Case 1

- 21 year old female presented to me initially in March 2016 with chronic GI problems, POTS and chronic nerve and joint pain.
  - GI problems onset December 2014
  - POTS diagnosed Oct-November 2014
  - Chronic nerve and joint pains onset April 2011
- Chronic pain/Fatigue started after taking 1 pill of levofloxacin for a sinus infection. Next morning woke up very weak, severe joint pain, swelling, cold, burning in leg muscles with weakness. Was put on gabapentin 600 mg daily for managing the pain.
- Patient able to work off gabapentin by November 2016 using intravenous nutrients + Glutathione + LAMC.
  - Initially was only getting Nutrients + Glutathione which showed improvement but after adding LAMC within a month of initial IV's this really allowed her to speed recover.

Case 1

- Was also getting many URI at the time.
- After going off the gabapentin noticed URI reduced frequency, GI issues resolved, POTS became more controlled, nerve and joint pain completely resolved by end of 2016.
- March 2017 IV once a week. May 2017 transitioned to IV once a month and using oral LAMC.
- April-May I diagnosed her with mast cell activation syndrome due to symptoms of unusual swelling, respiratory SOB, high histamines and response with anti-histamines.
- May 2017 on IV's once per month and oral LAMC. Fatigue completely resolved.
- Currently working on the mast cell activation syndrome.

Strauchman, M et al. Fluoroquinolone toxicity symptoms in a patient presenting with low back pain. Case Study. Natural Wellness & Pain Relief Centers, Grand Blanc, MI

Case 2

- 55 year old female inherited from another physician who retired. Symptoms of chronic infections, lead toxicity resistant to chelation, hypothyroid, mitochondrial dysfunction, chronic fatigue at times needing to collapse for a 10 minute nap, hypertension, chemical sensitivity, SNP profile indicates very poor detoxification genetics.
- Initially was treated for lead toxicity but developed stage II uterine cancer. This was treated with conventional oncological treatments and integrative oncology support.
- 30-50 chelation infusions before my care.
- Post chemotherapy neuropathy and worsening chronic fatigue.
- Multiple allergies. Very allergic to corn.

Case 2

- Comes into my care with very high liver enzymes and ferritin, multiple infections, fatigue pattern and metal toxicity. Has been getting nutrient IV's + Glutathione for 2-3 years. Months before seeing me started on Lipoic Acid Mineral Complex.
- 5 ml Lipoic Acid Mineral Complex caused massive reaction and extreme rollercoaster of fatigue. Reduced dosage better.
- After 3-4 months of LAMC patient improves to tolerating 10-15 ml. Reporting increased energy, sulfur dumping every time dosage increased. Neuropathy resolved. Energy has improved 60%
- Increased dosage to 25 ml beginning of this year which has increase energy more.

Case 2

- Other issues managed include hormones
- Heavy metals starting to move
- Energy more stable less rollercoaster
- Currently continuing once weekly nutrient + LAMC+glutathione
- Will be starting IVIgG soon for infections.
  - C. pneumonia
  - M. pneumonia
  - EBV, HHV6 (tx. with valcyte recently)
  - Low IgG (low to mid 500's) and subclass Igg
- Ferritin has reduced from 650 to 222 ng/ml with nutrient support and has had 2-3 therapeutic phlebotomies to get it down to 122 ng/ml

LAMC

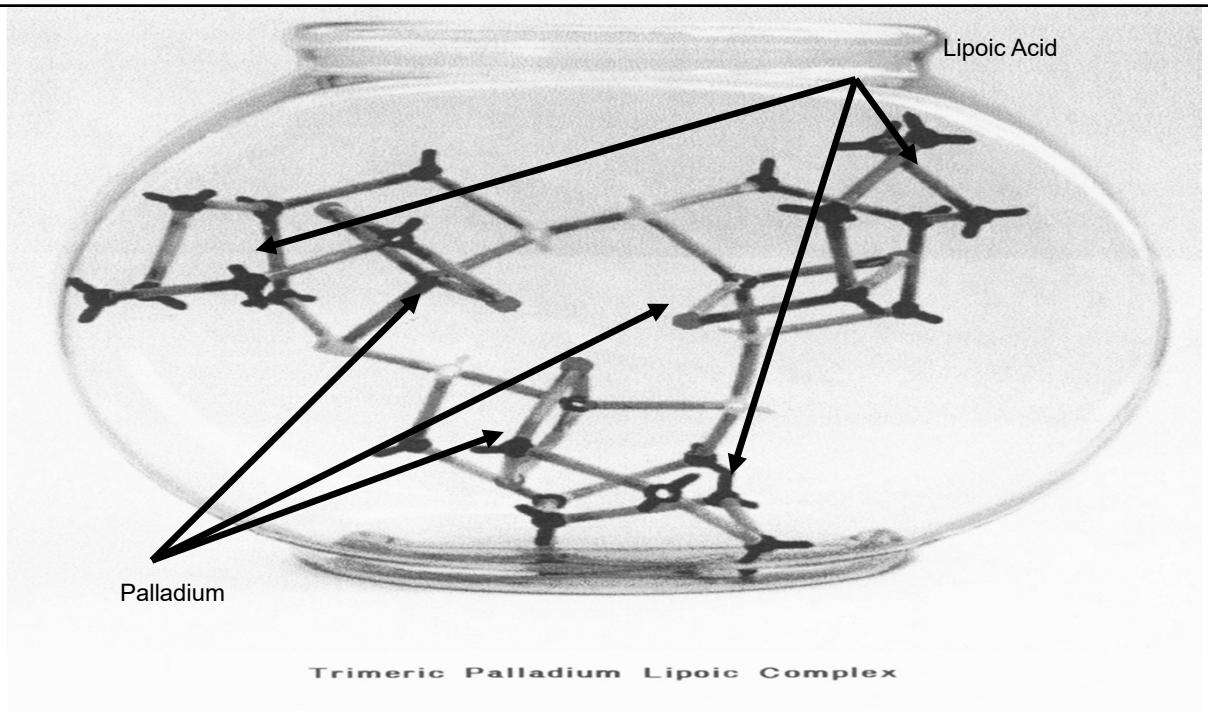
Composition of POLY-MVA*.

Palladium α-lipoic acid complex (1:1)	3.72×10^{-2} mmol/L
Thiamine	2.17×10^{-3} mmol/L
N-acetyl cysteine	1.13×10^{-3} mmol/L
Riboflavin	4.62×10^{-4} mmol/L
N-formyl methionine	1.46×10^{-4} mmol/L
Cyanocobalamin (Vitamin B12)	1.37×10^{-4} mmol/L
Rhodium	1.34×10^{-4} mmol/L
Molybdenum	4.63×10^{-4} mmol/L
Ruthenium	1.42×10^{-5} mmol/L
Sodium chloride	2.64×10^{-1} mmol/L

* Data supplied by manufacturer of POLY-MVA, El-Gen LLC, 7 Shirley Street, Bohemia, NY 11716-1735, USA.

Overview of actions

- Anti-oxidant
- DNA protection and repair
- Red Blood Cell protection
- Increases spleen colony formation
- Attenuation of radiation-induced weight loss
- Enhanced radiotherapy
- Strong mitochondrial supporting agent
- Improves chronic fatigue
- Support mitochondrial detoxification



LAMC

- Notice no free palladium and no free alpha lipoic acid. This enhances solubility in fat and water.
- Palladium bound is non toxic and a novel way of using a transition mineral to serve as a very efficient catalyst in aerobic respiration.
- More efficient redox since it is a polymer, rather than a single molecule.
- LAMC provides cellular energy by facilitating aerobic metabolism

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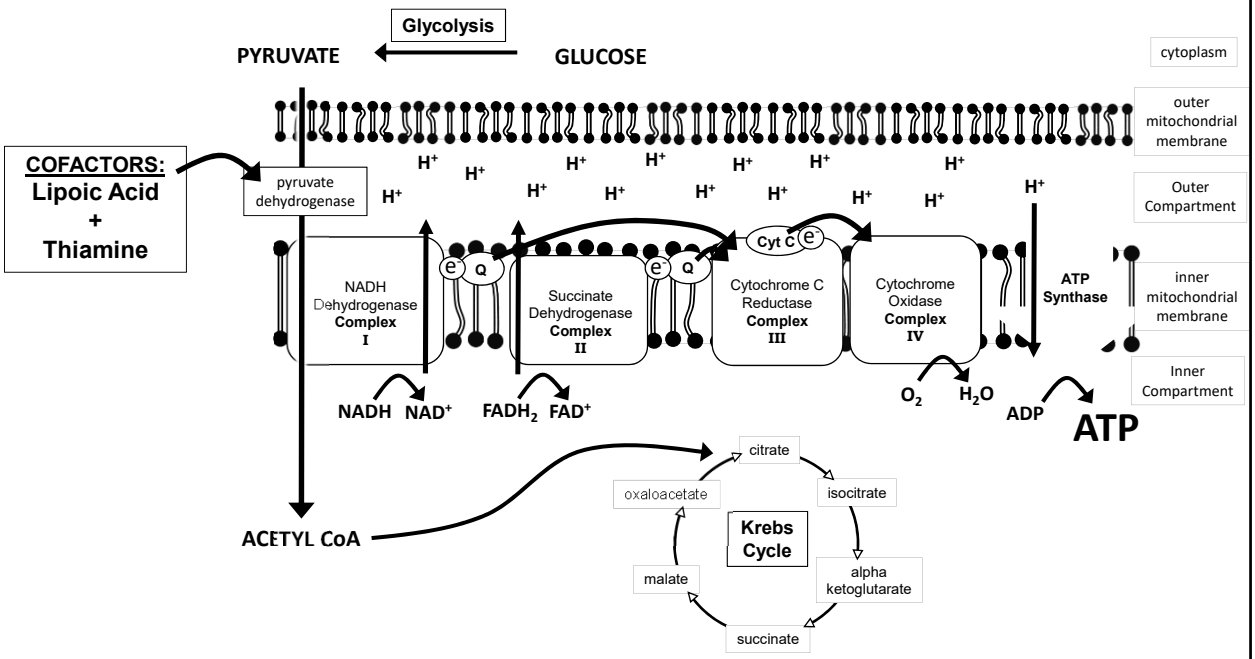
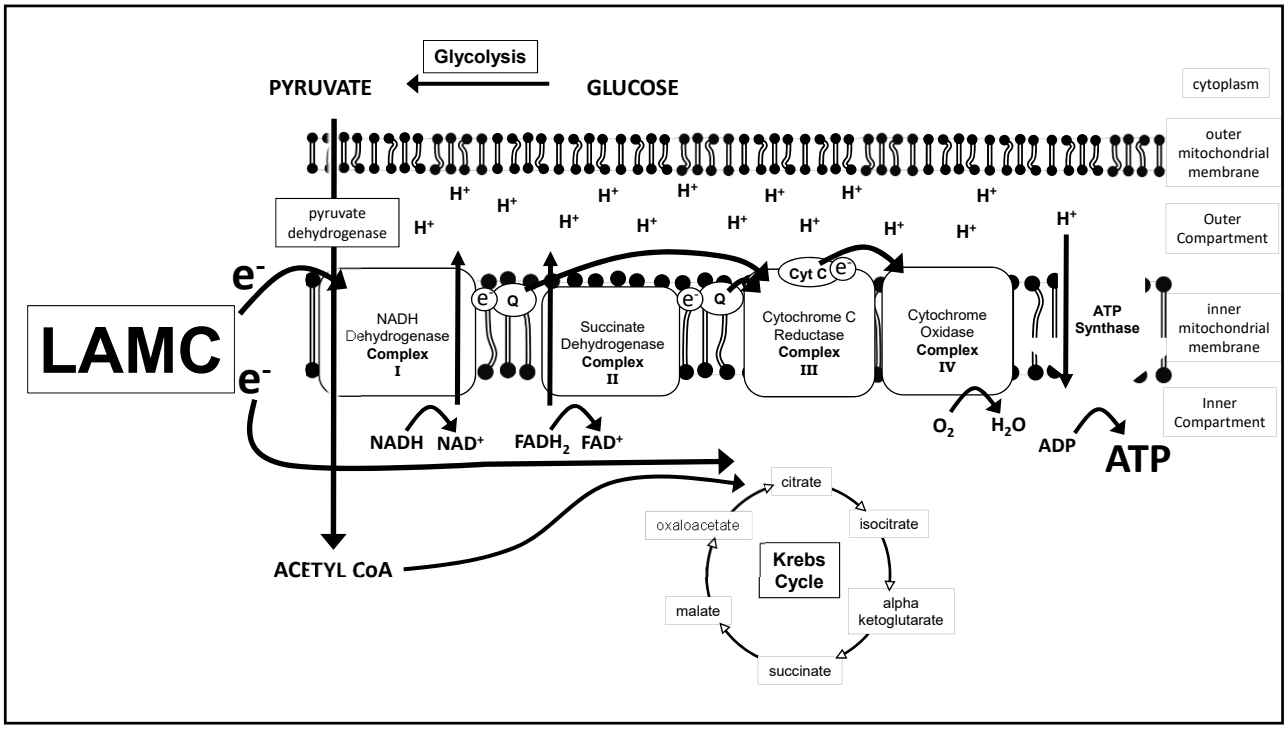
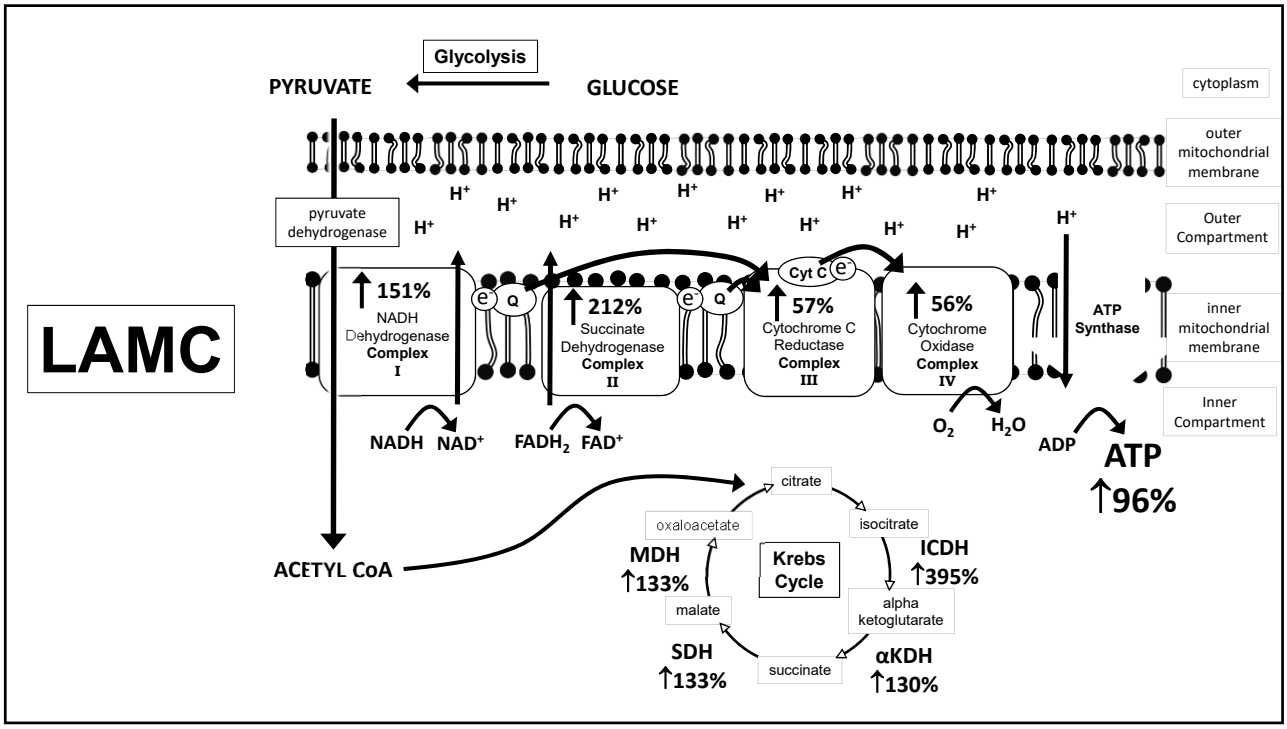



Glycolysis
PYRUVATE
GLUCOSE
cytoplasm
outer mitochondrial membrane
pyruvate dehydrogenase
Outer Compartment
LAMC
e-
e-
NADH Dehydrogenase Complex I
Succinate Dehydrogenase Complex II
Cytochrome C Reductase Complex III
Cytochrome Oxidase Complex IV
Cyt C
ATP Synthase
inner mitochondrial membrane
Inner Compartment
NADH NAD+
FADH2 FAD+
O2
H2O
ADP
ATP
citrate
oxaloacetate
isocitrate
Krebs Cycle
alpha ketoglutarate
malate
succinate
ACETYL CoA


Glycolysis
PYRUVATE
GLUCOSE
cytoplasm
outer mitochondrial membrane
pyruvate dehydrogenase
Outer Compartment
LAMC
151%
NADH Dehydrogenase Complex I
212%
Succinate Dehydrogenase Complex II
57%
Cytochrome C Reductase Complex III
56%
Cytochrome Oxidase Complex IV
Cyt C
ATP Synthase
inner mitochondrial membrane
Inner Compartment
NADH NAD+
FADH2 FAD+
O2
H2O
ADP
ATP
↑96%
citrate
oxaloacetate
isocitrate
MDH ↑133%
Krebs Cycle
ICDH ↑395%
alpha ketoglutarate
malate
SDH ↑133%
succinate
αKDH ↑130%
ACETYL CoA

LAMC: Research Areas

- Chronic Neurological Disease
  - Mitochondrial support
  - Cell support
- Fatigue States
  - Mitochondrial energy / repair support
- Adjunctive Cancer Care
  - Quality of life
  - Potential for antimetabolic supporrt

LAMC / MOA

Is LAMC's proposed mechanism of action directly related to its structural formulation?

LAMC's unique electronic and redox properties appear to be the key to its physiological effectiveness. When glucose enters a cell, it is broken down under anaerobic conditions (absence of oxygen) into pyruvate. Pyruvate subsequently enters the mitochondria, via complex I, and is quickly oxidized, in the presence of alpha-lipoic acid, to acetyl-CoA. In aerobic respiration, acetyl-CoA is then channeled into the Krebs/Citric Acid Cycle to create the reduced forms of nicotinamide adenine dinucleotide (NADH) and flavin adenine dinucleotide (FADH2). NADH and FADH2 donate their electrons to the electron transport chain to make the high energy molecule ATP.

Studies in India (Sudheesh et al., 2009) have demonstrated Palladium Lipoic Acid Complex's ability to facilitate aerobic metabolism, which is responsible for ATP production in healthy cells. The energy needs of the body are supplied by splitting ATP into adenosine diphosphate (ADP) and a free phosphate (Griffin et al. 2006).

LAMC / MOA

Studies have demonstrated that LAMC provides electrons to DNA, via the mitochondria. Electrons are lost in normal cells as a result of oxidative damage from radiation and chemotherapy (Garnett and Garnett 1996).

LAMC electron transfer provides an additional energy source to normal cells. However, cancer cells are metabolically challenged, and function in a hypoxic environment. Since there is less oxygen and more free electrons in the cancer cell, generation of free radicals occurs at the tumor mitochondrial membrane (Antonawich et al. 2004).

This activates apoptosis by facilitating the release of cytochrome C from the inner mitochondrial membrane, allowing the formation of an apoptotic complex in the cytoplasm. This complex, results in the subsequent activation of the caspase cascade of enzymes that destroy the malignant cells.

Food and Chemical Toxicology 48 (2010) 1858–1862

Contents lists available at ScienceDirect

Food and Chemical Toxicology

journal homepage: www.elsevier.com/locate/foodchemtox

Effect of POLY-MVA, a palladium α-lipoic acid complex formulation against declined mitochondrial antioxidant status in the myocardium of aged rats

N.P. Sudheesh [a], T.A. Ajith [b], K.K. Janardhanan [a], C.V. Krishnan [c,d,*]

Results of this study reveal that palladium α-lipoic acid formulation is an effective agent to protect the age-linked decline of myocardial mitochondrial antioxidant status and thus is capable to enhance the energy production of normal cell mitochondria.

LAMC

- Oral form available
  - Orally given 2-4 tsp/day often for fatigue, neurological, mitochondrial issues.
  - Up to 8 tsp per day in oncology support
- Intravenous form available
  - Given without other additives
  - Generally added to a small normal saline (NS) bag

  (See protocol section)

Lipoic-Mineral Complex

Nutrient	mg/ml	mL	mOsm/ml	mOsm*vol
1. LAMC		5 - 40		
2. D5W or 0.9% Saline		100 - 250		

Est. Treatment time: 0.5 – 1.5 hours **Desired drip rate: 3-4 mL/min**
Final osmolarity: Approx. Iso-osmolar

Technical notes:
1.DO NOT add any other nutrients or injectables to this solution.
2.Can be used in series with other nutrients
3.The **first treatment dose** should be 5 – 10 mL
4.LAMC may be increased to 40 mL with successive treatment if the first IV is well tolerated.

LAMC in Regeneration & Mitochondrial Dysfunction

- We have used oral and IV LAMC in the setting of mitochondrial damage and dysfunction – oncology radiation, chemotherapy, fluoroquinolone toxicity, fibromyalgia, etc.
- Doses in the Autoimmune - Fatigue – Mitochondrially injured – Neurodegenerative population need to be lower and ramped up more slowly than in the oncology patient.
  - Oral doses can be 5 to 15 mL BID
  - IV doses are given in 100 to 250 mL D5W or NS
    - 5 mL test dose
    - Ramp up to 20-25 mL
    - Give in series (as a separate bag) with other nutrients

Sequencing in Regenerative Cases:

- Often we will sequence IV's on the same day to increase synergy and speed healing. (see case in the PTC notes).
- Often this is some or all of the following:

1. Vitamin-Mineral IV
2. Glutathione
3. ALA or LAMC
4. Phospholipids (often added once the patient is past an acute phase)

LAMC

LAMC for IV Use:

1 – No oxidative therapies / HDIVC within 12 hours of Poly-MVA IV

2 – Infuse LAMC per protocol over 30-90 minutes

3- Infusion Frequency: Two IV's weekly for six weeks then re-evaluate

LAMC References

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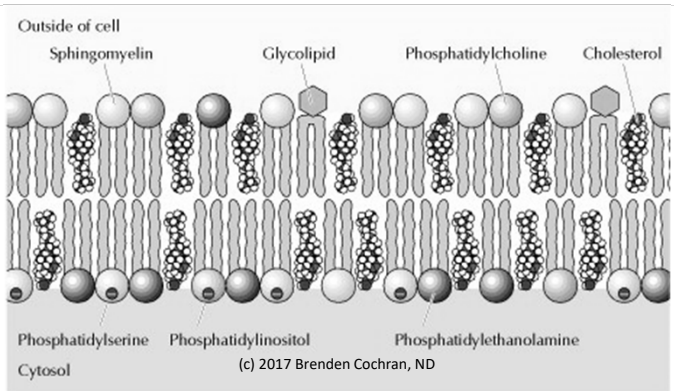
Phosphatidylcholine



Case

- 21 year old male with visual field disturbances, numbness and coordination issues. Diagnosed with multiple sclerosis treated with natalizumab as one of the more recent treatments which showed little to no benefit.
- Part of treatment included PTC + Nutrients which was helpful but more noticeable stabilization in symptoms using Nutrients, Glutathione, Poly-MVA, PTC.

Indications

- Liver
- Cardiovascular
- Post stroke recovery: Glycerophosphocholine
- Encephalopathy
- Memory, cognitive decline

Phosphatidylcholine (PTC)

- Methyl donor
- Cell Membrane structural support and maintenance
- Highly metabolic tissues
  - Brain / Heart / Kidney / GI
  - High concentration in brain CM's
    - May help with concentration
    - Donates Choline for ACh synthesis
      - Used for cognitive support
- Liver damage (Drug / ETOH / Hep - B,C)
  - Also appropriate in NASH

The ***Alt Med Rev*** Monograph is reprinted in your notes.

Phosphatidylcholine (PTC)

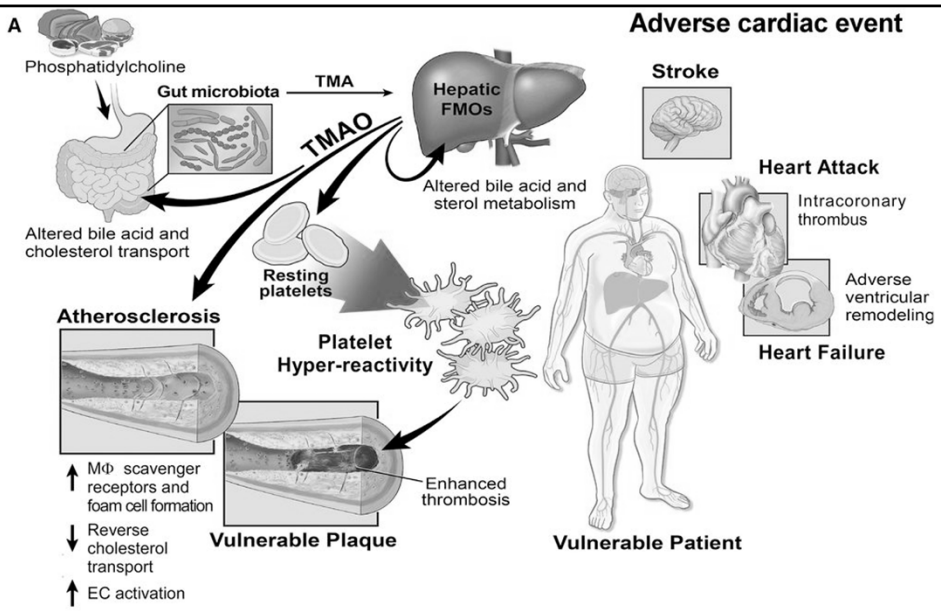
- Multiple IV protocols are published.
  - All appear to have their own merit based on clinical reports from physicians employing them in similar groups of patients.
  - The following is the protocol I feel is best to begin with, and has the least phlebitis and other side effect potential

Phosphatidylcholine (PTC)

- Protocol:
  - Infuse slowly (higher concentrations and faster administration will cause phlebitis) over 1 hour if tolerated.
  - No other additives are mixed with this infusion
  - You can follow or lead with a different nutrient bag.
  - **MUST FLUSH OR CHANGE LINE** between bags
  - Sensitive patients (MCS, Elderly, Multiple co-morbidities) may experience **GI distress** – RAMP Those patients doses up slowly from 10 mL starting dose.

IV PTC benefit to Oral

- **IV is best until you know your patient!**
- Cleveland clinic has found that choline can contact certain bacteria in the intestines which converts choline to TMA. In the liver there is an enzyme that makes TMAO (Trimethylamine-N-oxide)
- TMAO forms vascular inflammation and unstable plaques in the arterial walls.



http://dx.dol.org/10.1016/j.cell.2016.02.01101

PTC (Intravenous Protocol)

- PC 35mg/mL OR 50mg/ml, Sodium Deoxycholate 24mg/mL, Benzyl Alcohol 0.9% and Ethanol 0.2%.
- Basic protocol:
  - Increment dose and infuse over 90 minutes
  - 25 ml PTC (maximum 50 ml) in 250 mL D5W **(MUST BE IN NON-IONIC carrier)**
  - Optional: Follow with glutathione push
- Caution is can cause GI upset and diarrhea. Work up slow and consider fiber.

Rx: Phosphatidylcholine

		PTC (35-50 mg) (3-50 mls)			
		D5W (250-500 ml)			

Additions /Subtractions:

Glutathione + 0.9% Normal Saline

Total Volume: mL Osmolarity: mOsm/L

(The "Push Protocol")

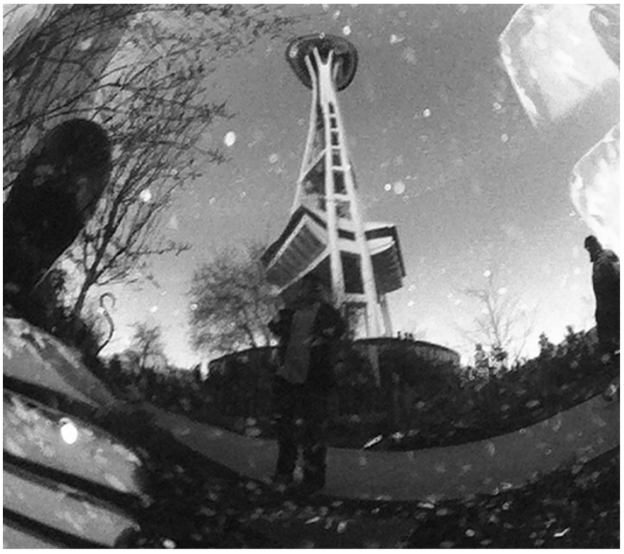
- Draw 5 to 10 ml Essentiale-N into a syringe at least twice the volume, leave 5 ml air in syringe
  - Some add 0.5 mL heparin, 1000 IU/mL
- Establish the IV using a 21 or 23 gauge butterfly set & draw an equal volume blood into syringe
- Mix the blood and Essentiale-N during and after drawing sufficient blood into the syringe
- Immediately inject the mixture over 2-3 minutes, keeping the air bubble uppermost in syringe to avoid injecting air
- Remove empty syringe and attach syringe for glutathione push, 600-2500 mg
- Injections are given 3-5 times weekly until liver tests normalize
- It may be more prudent to add the Essentiale-N to 250 mL D5W and infuse over 90 minutes
- Flush butterfly – administer glutathione IV push

Parenteral PC Caution

- Phosphatidylcholine is compounded by a number of pharmacies in the U.S. for use in Mesotherapy. This is commonly 100 mg/mL concentration. This formulation can not be used for intravenous applications.

drcochran@interactivehealthclinic.com

Thank You!



NOTES

Jessica Tran, N.D.

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Disclosure Statement:

Dr. Tran has indicated that she is has no relevant financial relationships with any commercial supporters.

Alpha Lipoic Acid

Learning Objectives:

At the conclusion of this activity you should be able to...

About Dr. Tran

Jessica Tran is a licensed naturopathic doctor. She received her naturopathic medical degree from Bastyr University. She completed a one-year Family Practice residency, three-year Environmental Medicine fellowship, and served as Clinical Faculty in both the Department of Environmental Medicine and General Medicine at Southwest College of Naturopathic Medicine & Health Sciences. Dr. Tran serves on the Board of Directors and CME Planning Committee of the American Academy of Environmental Medicine. She is in private practice in Irvine, California.

NOTES

Intravenous Alpha-Lipoic Acid

Jessica Tran, ND

October 5, 2017

AAEM

Under Accreditation Council for Continuing Medical Education guideline disclosure must be made regarding relevant financial relationships with commercial interests within the last 12 months.

Jessica Tran, N.D.

Received an educational grant from Master Supplements

Unless otherwise stated, the level of evidence is C and based on clinical experience.

Indications

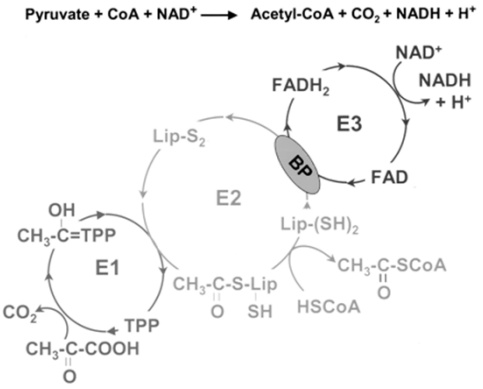
- Some evidence for use in the following conditions
  - Diabetes mellitus
  - Diabetic neuropathy
  - Glaucoma
  - HIV
  - Hepatitis, Liver regeneration
  - Burning mouth syndrome
  - Mushroom poisoning
  - Toxic metal poisoning
  - Slow or stop progression of cancer

Contraindications

- Allergy
- Unable to have IV therapy
- Any previous adverse reactions

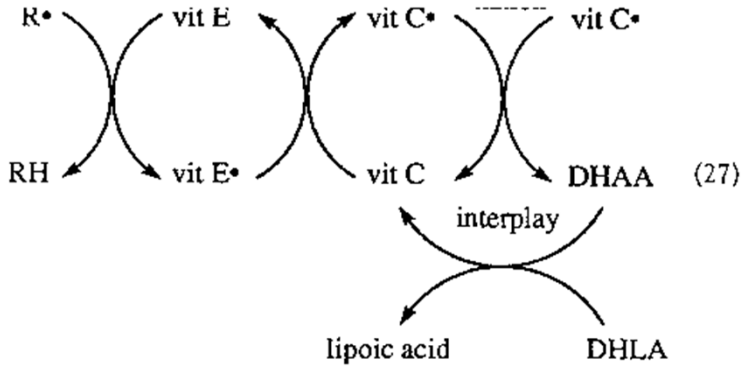
Mechanisms of Action

- Functions as a potent antioxidant and as a cofactor for various enzymes (e.g. pyruvate dehydrogenase and alpha-ketoglutarate dehydrogenase) in energy-producing metabolic reactions of the Krebs cycle.



Mechanisms of Action

- Improves recycling of other antioxidant compounds, including vitamins C and E, coenzyme Q, and glutathione.



Biewenga, 1997

Mechanisms of Action

- Speculated to protect against arsenic, cadmium, lead, and mercury poisoning.

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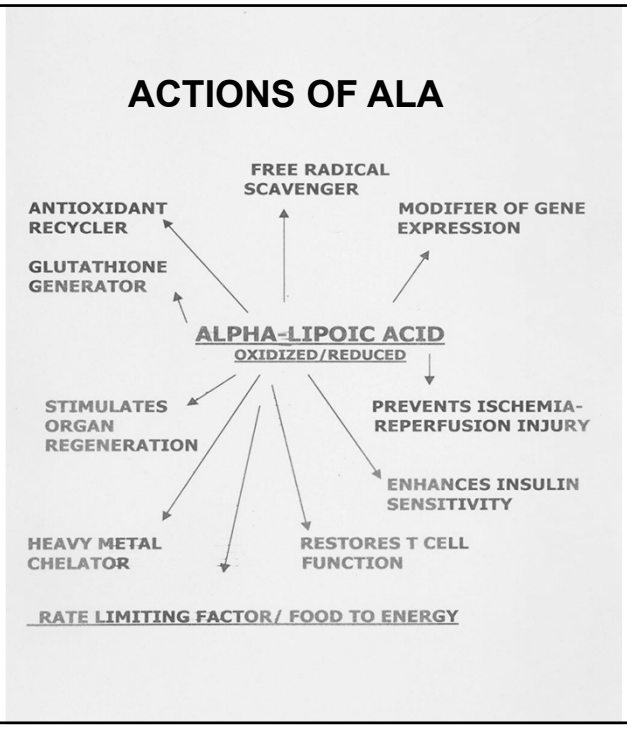


Longtime picker meets match in mushroom patch

By Karen R. Long

Gregg Finohr swears he'll never do it again.

Finohr, an 11-year veteran of mushroom-picking who usually hunts carefully with a field guide, entered Mount Sinai Hospital last Friday with severe mushroom poisoning. He still has muscle cramps but is grateful to be alive.

"God, I'll never eat them again," he said. "This is just crazy. I can't believe this happened."

Finohr, 28, nearly died after eating between 10 and 14 wild mushroom he assumed were related to the edible inky-cap species.

"I stopped at a field out by Avon Lake to kill some time," he said yesterday from his hospital bed. "I noticed a lot of mushrooms around. I usually have a field guide with me, but I didn't this time. I picked a quantity, went home, cleaned and stored them, eating a few while I cleaned. The next morning I ate a few more from the refrigerator and that's when I got sick."

Finohr, of 13988 Clifton Blvd., Lakewood, did not make the common mistake of thinking he had the flu. He called the Union Central Center poisoning specialist, Dr. Burton M. Berkson.

Berkson did not pump Finohr's stomach.

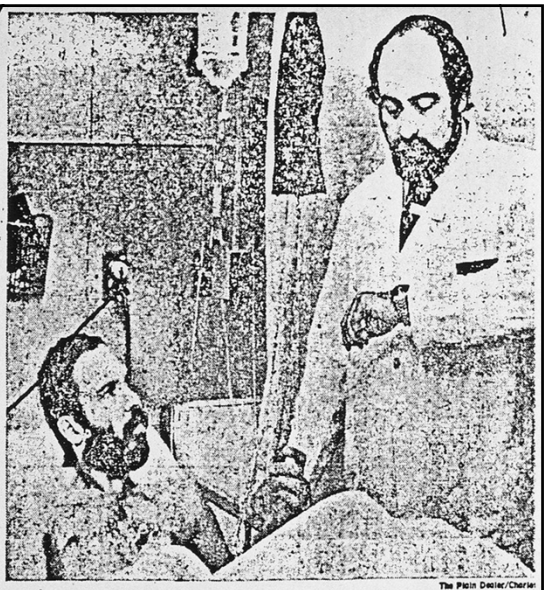
"He didn't get sick until 16 hours after eating them," the doctor said. "By that time all the poison was absorbed. I gave him an antibiotic to bind (deactivate) any unboupd toxins which might still be in his bloodstream."

Berkson, who has a doctorate in mycology, the study of fungi, believes Finohr ate a member of the genus Cortinarius. He ordered a special drug, thioctic acid, to be flown in from Washington, D.C.

The characteristics of mushroom poisoning are divided into four stages. Finohr suffered the first two before his thioctic acid treatments began Saturday.

The first stage is a period of well-being, lasting 12 to 36 hours. The second is similar to stomach flu, with diarrhea and vomiting, and lasts one or two days. The third stage is apparent recovery, when the doctor may think the patient is better. The last phase is hepatic coma and sometimes death.

Cleveland had one death from



The Plain Dealer/Charles

cases last year.

This is the season for mushroom picking — a pastime that Berkson said is especially popular in Greater Cleveland. His advice is to refrain. "But I have the feeling people aren't going to avoid them, so it's best if they know the mushroom character-

species of the genus that poisoned Finohr.

The young construction worker said he hopes others take note of his ordeal. He said he was "very grateful Dr. Berkson knows what he does. I'd read about it (the danger) but I never thought it would happen to me —

Dr. Burton Ber
checks the pul
Gregg Finohr, a
of mushroom po
ing.

February 15, 1979 N Engl J Med 1979; 300:371

THIOCTIC ACID IN TREATMENT OF HEPATOTOXIC MUSHROOM (PHALLOIDES) POISONING

To the Editor: I have used thioctic acid to treat six patients over the past year who suffered the hepatotoxic effects of mushroom poisoning. Some of them had liver enzymes over 4000 μU per milliliter. The patients were admitted to the medical intensive-care unit. Intravenous glucose was supplied, and blood levels were carefully followed. Every patient survived, and each walked out of the hospital, feeling well, within three weeks. Not one patient had signs of hypoglycemia while being treated with thioctic acid.

I believe that physicians should be encouraged to try thioctic acid for any patient who is unfortunate enough to have ingested a hepatotoxic mushroom.[1-4]

B. M. Berkson, M.D., M.S., Ph.D.
Mount Sinai Hospital
Cleveland, OH 44106

1. Alleva F: Thioctic acid and mushroom poisoning. Science 187:216, 1975
2. Bartter FC: Thioctic acid and mushroom poisoning. Science 187:216, 1975
3. Bartter FC, Berkson BM, et al: Thioctic acid in the treatment of poisoning with alph-amanitin, International Symposium on Amanita Toxins and Amanita Poisoning, 1978 (in press)
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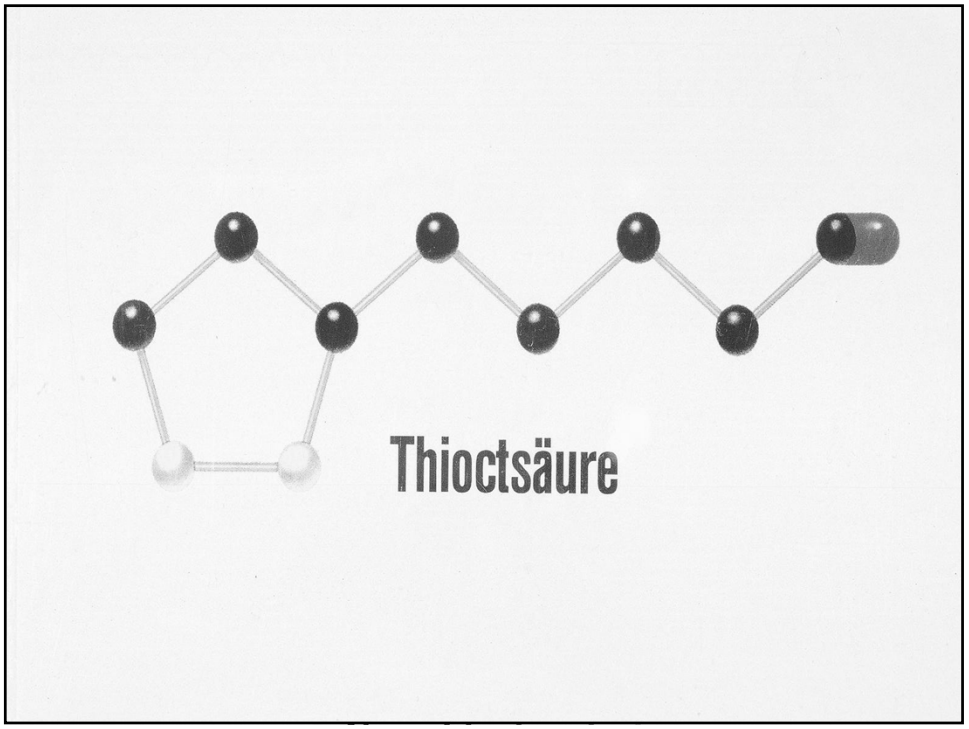
THIOCTIC ACID IN THE TREATMENT OF POISONING WITH ALPHA-AMANITIN

Bartter FC, Berkson B, Gallelli P, Hiranaka P 1980, Amanita Toxins and Poisoning, eds Faulstich et al, Verlag Gerhard Witzstrock, Baden-Baden, New York

Max Planck Institute for Medical Research
Heidelberg 1978



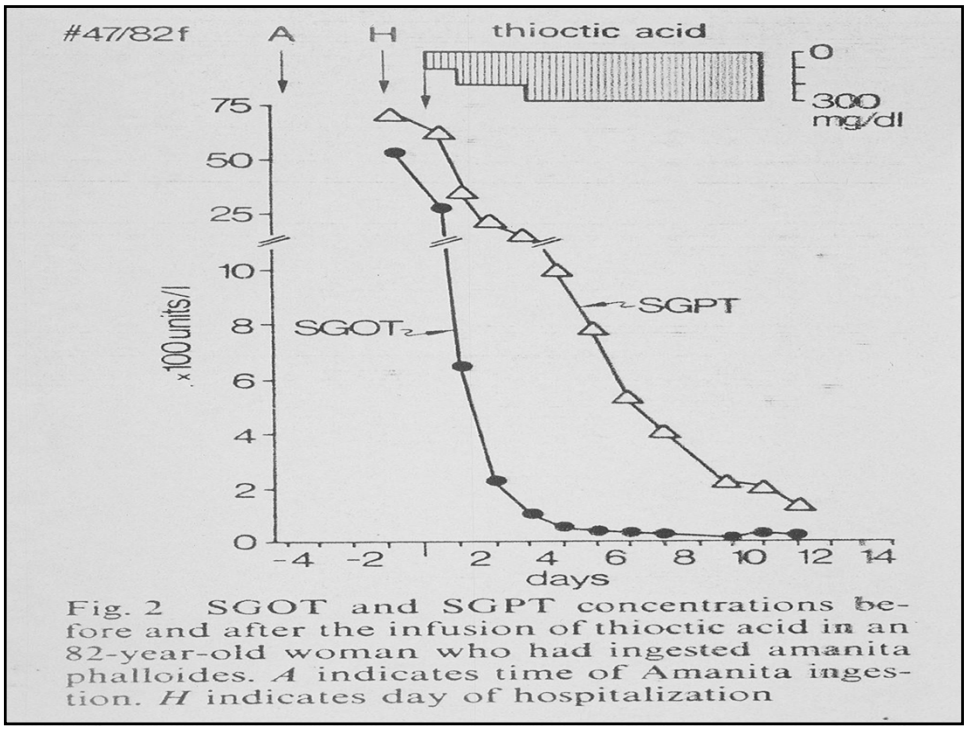


Fig. 2 SGOT and SGPT concentrations before and after the infusion of thioctic acid in an 82-year-old woman who had ingested amanita phalloides. *A* indicates time of Amanita ingestion. *H* indicates day of hospitalization

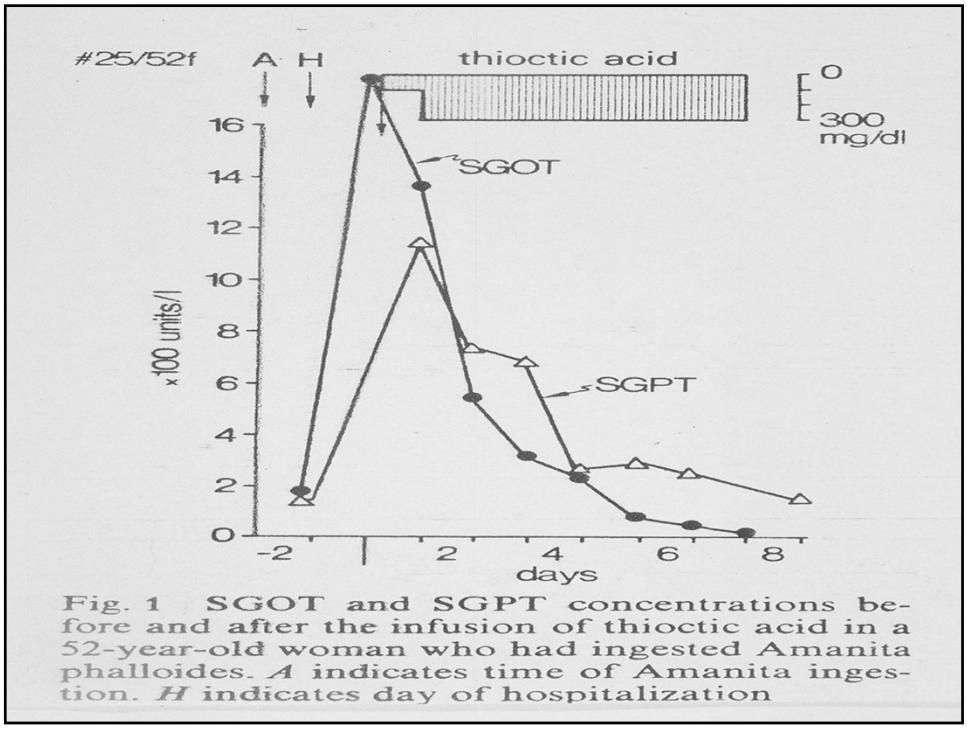


Fig. 1 SGOT and SGPT concentrations before and after the infusion of thioctic acid in a 52-year-old woman who had ingested Amanita phalloides. *A* indicates time of Amanita ingestion. *H* indicates day of hospitalization

Med Klin (Munich). 1999 Oct 15;94 Suppl 3:84-9.

A conservative triple antioxidant approach to the treatment of hepatitis C. Combination of alpha lipoic acid (thioctic acid), silymarin, and selenium: three case histories.

Berkson BM[1].

⊕ **Author information**

Abstract

BACKGROUND: There has been an increase in the number of adults seeking liver transplantation for hepatitis C in the last few years and the count is going up rapidly. There is no reliable and effective therapy for chronic hepatitis C since interferon and antivirals work no more than 30% of the time, and liver transplant surgery is uncertain and tentative over the long run. This is because, ultimately, residual hepatitis C viremia infects the new liver. Furthermore, liver transplantation can be painful, disabling and extremely costly.

TREATMENT PROGRAM: The author describes a low cost and efficacious treatment program in 3 patients with cirrhosis, portal hypertension and esophageal varices secondary to chronic hepatitis C infection. This effective and conservative regimen combines 3 potent antioxidants (alpha-lipoic acid [thioctic acid], silymarin, and selenium) that possess antiviral, free radical quenching and immune boosting qualities.

CONCLUSION: There are no remarkably effective treatments for chronic hepatitis C in general use. Interferon and antivirals have less than a 30% response rate and because of the residual viremia, a newly transplanted liver usually becomes infected again. The triple antioxidant combination of alpha-lipoic acid, silymarin and selenium was chosen for a conservative treatment of hepatitis C because these substances protect the liver from free radical damage, increase the levels of other fundamental antioxidants, and interfere with viral proliferation. The 3 patients presented in this paper followed the triple antioxidant program and recovered quickly and their laboratory values remarkably improved. Furthermore, liver transplantation was avoided and the patients are back at work, carrying out their normal activities, and feeling healthy. The author offers a more conservative approach to the treatment of hepatitis C, that is exceedingly less expensive. One year of the triple antioxidant therapy described in this paper costs less than $2,000, as compared to mor than $300,000 a year for liver transplant surgery. It appears reasonable, that prior to liver transplant surgery evaluation, or during the transplant evaluation process, the conservative triple antioxidant treatment approach should be considered. If these is a significant betterment in the patient's condition, liver transplant surgery may be avoided.

www.gahmj.com • January 2014 • Volume 3, Number 1

ORIGINAL RESEARCH

Adverse Effects of High Doses of Intravenous Alpha Lipoic Acid on Liver Mitochondria

静脉注射高剂量α硫辛酸对肝线粒体的不良影响

Efectos adversos de altas dosis de alfa-ácido lipoico intravenoso en las mitocondrias hepáticas

Michael Vigil, MD, *United States*; Burton M. Berkson, MD, MS, PhD, *United States*; Ana Patricia Garcia, DVM, MS, PhD, *United States*

ABSTRACT

Alpha lipoic acid (ALA, thioctic acid), among other actions, is an essential coenzyme in the conversion of pyruvate to acetyl co-enzyme A. Therefore, it is necessary for the production of energy for aerobic organisms. Scientists have found that it can be used medically to help regenerate liver tissue, reverse the complications of diabetes mellitus, slow or stop the growth of cancer cells, and chelate heavy metals, among other actions. In this article, the authors describe the cellular mitochondrial damage from excessively high doses of this beneficial agent.

摘要

在丙酮酸盐转化成乙酰辅酶 A 这类反应中，α 硫辛酸（ALA，硫辛酸）是一种必需的辅酶。 科学家们已经发现，这种辅酶可以应用在医疗领域，从而帮助肝组织再生，逆转糖尿病并发症，减缓或终止癌细胞生长以及螯合重金属，诸如此类。 在本文中，作者叙述了以过高剂量施用这种有益药剂对细胞线粒体所造成的伤害。

SINOPSIS

El alfa-ácido lipoico (ALA, ácido tióctico), entre otras acciones, es una coenzima esencial en la conversión del piruvato en acetil coenzima A. Por lo tanto, es necesario para la producción de energía para los organismos aerobios. Los científicos han descubierto que puede ser utilizado médicamente para ayudar a regenerar el tejido hepático, invertir las complicaciones de la diabetes mellitus, ralentizar o detener el crecimiento de células cancerígenas y frenar la toxicidad de los metales pesados, entre otras acciones. En este artículo, los autores describen el daño mitocondrial celular causado por dosis excesivamente altas de este agente beneficioso.

Author Affiliations

Department of Biochemistry, New Mexico State University, Las Cruces (Dr Vigil); Integrative Medical Center of New Mexico, Las Cruces, Department of Entomology, Plant Pathology, and Weed Science, New Mexico State University (Dr Berkson); Department of Pathology and Laboratory Medicine, Emory University School of Medicine, Atlanta, Georgia (Dr Garcia).

Citation

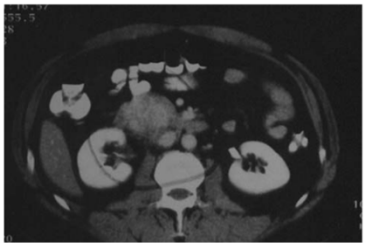
Global Adv Health Med. 2014;3(1):25-27. DOI: 10.7453/gahmj.2013.011

INTEGRATIVE CANCER THERAPIES 5(1); 2006 pp. 83-89

The Long-term Survival of a Patient With Pancreatic Cancer With Metastases to the Liver After Treatment With the Intravenous α-Lipoic Acid/Low-Dose Naltrexone Protocol

Burton M. Berkson, Daniel M. Rubin, and Arthur J. Berkson

The authors describe the long-term survival of a patient with pancreatic cancer without any toxic adverse effects. The treatment regimen includes the intravenous α-lipoic acid and low-dose naltrexone (ALA-N) protocol and a healthy lifestyle program. The patient was told by a reputable university oncology center in October 2002 that there was little hope for his survival. Today, January 2006, however, he is back at work, free from symptoms, and without appreciable progression of his malignancy. The integrative protocol described in this article may have the possibility of extending the life of a patient who would be customarily considered to be terminal. The authors believe that life scientists will one day develop a cure for metastatic pancreatic cancer, perhaps via gene therapy or another biological platform. But until



Integrative Cancer Therapies 8(4)

Revisiting the ALA/N (α-Lipoic Acid/Low-Dose Naltrexone) Protocol for People With Metastatic and Nonmetastatic Pancreatic Cancer: A Report of 3 New Cases

Integrative Cancer Therapies
8(4) 416–422

DOI: 10.1177/1534735409352082
http://ict.sagepub.com
SAGE

Burton M. Berkson, MD, MS, PhD,[1,2] Daniel M. Rubin, ND, FABNO,[3] and Arthur J. Berkson, MD[1]

Abstract

The authors, in a previous article, described the long-term survival of a man with pancreatic cancer and metastases to the liver, treated with intravenous alpha-lipoic acid and oral low-dose naltrexone (ALA/N) without any adverse effects. He is alive and well 78 months after initial presentation. Three additional pancreatic cancer case studies are presented in this article. At the time of this writing, the first patient, GB, is alive and well 39 months after presenting with adenocarcinoma of the pancreas with metastases to the liver. The second patient, JK, who presented to the clinic with the same diagnosis was treated with the ALA/N protocol and after 5 months of therapy, PET scan demonstrated no evidence of disease. The third patient, RC, in addition to his pancreatic cancer with liver and retroperitoneal metastases, has a history of B-cell lymphoma and prostate adenocarcinoma. After 4 months of the ALA/N protocol his PET scan demonstrated no signs of cancer. In this article, the authors discuss the poly activity of ALA: as an agent that reduces oxidative stress, its ability to stabilize $NF_{\kappa}B$, its ability to stimulate pro-oxidant apoptosic activity, and its discriminative ability to discourage the proliferation of malignant cells. In addition, the ability of lowdose naltrexone to modulate an endogenous immune response is discussed. This is the second article published on the ALA/N protocol and the authors believe the protocol warrants clinical trial.

doi:10.4317/medoral.20410
http://dx.doi.org/doi:10.4317/medoral.20410

2015

Med Oral Patol Oral Cir Bucal. 2015 Jul 1;20 (4):e435-40.

Journal section: Oral Medicine and Pathology
Publication Types: Research

doi:10.4317/medoral.20410
http://dx.doi.org/doi:10.4317/medoral.20410

Alpha lipoic acid efficacy in burning mouth syndrome. A controlled clinical trial

Begoña Palacios-Sánchez [1], Luis-Alberto Moreno-López [2], Rocío Cerero-Lapiedra [1], Silvia Llamas-Martínez [1], Germán Esparza-Gómez [1]

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[2] DMD, PhD Unidad de Medicina y Cirugía Oral. GAP Toledo. SESCAM. Toledo. Spain

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Treatment consisted of a dose of 600 mg/day of alpha lipoic acid administered in 3 capsules of 200 mg every 8 hours for 2 months.

Palacios-Sánchez B, Moreno-López LA, Cerero-Lapiedra R, Llamas-Martínez S, Esparza-Gómez G. Alpha lipoic acid efficacy in burning mouth syndrome. A controlled clinical trial. Med Oral Patol Oral Cir Bucal. 2015 Jul 1;20 (4):e435-40.
http://www.medicinaoral.com/medoralfree01/v20i4/medoralv20i4p435.pdf

European Journal of Pain 13 (2009) 492–496

2009

Contents lists available at ScienceDirect

European Journal of Pain

journal homepage: www.EuropeanJournalPain.com

Lack of efficacy of alpha-lipoic acid in burning mouth syndrome: A double-blind, randomized, placebo-controlled study

Mario Carbone [a,1], Monica Pentenero [b,1], Marco Carrozzo [c,1], Alessio Ippolito [a,1], Sergio Gandolfo [b,*,1]

[a] Department of Biomedical Sciences and Human Oncology, Oral Medicine Section, University of Turin, Italy
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Therapy

ABSTRACT

Background: A systematic review from the Cochrane Collaboration stated that alpha-lipoic acid (ALA) may help in the management of burning mouth syndrome (BMS). Because all of the data on ALA came from a single group, it has been stressed that its effectiveness should be reproduced in other populations.

Aim: A double-blind, randomized, placebo-controlled study, including two test groups (Group A and Group B) and one control group (Group C), was carried out to evaluate the efficacy of systemic ALA (400 mg) and ALA (400 mg) plus vitamins in the treatment of BMS.

Methods: Sixty-six patients (54 females and 12 males) were included in an 8-week trial. Symptoms were evaluated by using a visual analogue scale (VAS) and the McGill Pain Questionnaire (MPQ) at 0, 2, 4, 8 and 16 weeks.

Results: Fifty-two patients (43 females and 9 males, aged 67.3 ± 11.9 years) completed the study. All three groups had significant reductions in the VAS score and in the mixed affective/evaluative subscale of the MPQ; the responders' rate (at least 50% improvement in the VAS score) was about 30%. No significant differences were observed among the groups either in the response rate or in the mean latency of the therapeutic effect.

Conclusions: The fairly high placebo effect observed is very similar to data obtained from patients affected by atypical facial pain. This study failed to support a role for ALA in the treatment of BMS, and further investigations are needed to identify the cause of BMS in order to develop efficacious therapies.

Capasso *et al. Trials* 2013, **14**:273
http://www.trialsjournal.com/content/14/1/273

TRIALS

RESEARCH Open Access

Combination of inositol and alpha lipoic acid in metabolic syndrome-affected women: a randomized placebo-controlled trial

Immacolata Capasso[1*], Emanuela Esposito[1], Nicola Maurea[2], Maurizio Montella[3], Anna Crispo[3], Michelino De Laurentiis[1], Massimiliano D'Aiuto[1], Giuseppe Frasci[1], Gerardo Botti[6], Maria Grimaldi[3], Ernesta Cavalcanti[4], Giuseppe Esposito[5], Alfredo Fucito[1], Giuseppe Brillante[1], Giuseppe D'Aiuto[1] and Gennaro Ciliberto[1]

Conclusions: Inositol combined with alpha lipoic acid can be used as a dietary supplement in insulin-resistant patients in order to increase their insulin sensitiveness. Daily consumption of inositol combined with alpha lipoic acid has a significant bearing on metabolic syndrome. As metabolic syndrome is considered a modifiable risk factor of breast tumorigenesis, further studies are required to assess whether inositol combined with alpha lipoic acid can be administered as a dietary supplement in breast cancer primary prevention.

Trial registration: Current Controlled Trial ISRCTN74096908.

were asked to follow a low calorie diet and were assigned randomly to daily consumption of a combination of inositol and alpha lipoic acid (77 pts) or placebo (78 pts) for six months. Primary outcomes we wanted to achieve were both reduction of more than 20% of the HOMA-IR index and of triglycerides serum levels. Secondary outcomes expected were both the improvement of high-density lipoprotein cholesterol levels and the reduction of anthropometric features such as body mass index and waist-hip ratio.

DM

Effects of 3-week oral treatment with the antioxidant thioctic acid (α-lipoic acid) in symptomatic diabetic polyneuropathy

K. -J. Ruhnau†, H. P. Meissner†, J. -R. Finn‡, M. Reljanovic‡‡, M. Lobisch¶, K. Schütte¶, D. Nehrdich**, H. J. Tritschler††, H. Mehnert§ and D. Ziegler*

Conclusions These preliminary findings indicate that oral treatment with 600 mg of TA *t.i.d.* for 3 weeks may improve symptoms and deficits resulting from polyneuropathy in Type 2 diabetic patients, without causing significant adverse reactions.

Diabet. Med. 16, 1040–1043 (1999)

§Stadtkrankenhaus Schwabing, München, Germany

¶Medizinische Forschung and **Biometrie and ††Zentrales Produktmanagement ASTA, Medica AG. Frankfurt am Main, Germany

‡‡University Clinic for Diabetes, Endocrinology and Metabolic Diseases 'Vuk Vrhovac', Medical Faculty, University of Zagreb, Croatia

(pain, burning, paraesthesiae, and numbness) in the feet were scored at weekly intervals and summarized as a Total Symptom Score (TSS). The Hamburg Pain Adjective List (HPAL) and the Neuropathy Disability Score (NDS) were assessed at baseline and day 19.

Results At baseline the TSS, HPAL, and NDS were not significantly different between the groups. The TSS in the foot decreased from baseline to day 19 by -3.75 ± 1.88 points (-47%) in the TA group and by -1.94 ± 1.50 points

IV Alpha-Lipoic Acid

- D5W or Normal Saline
- 100 ml per 300-600 mg of ALA
- 250 ml for patients who report a burning sensation in their veins.
- Infusion rate is 30 to 50 minutes depending on the patient.
- Start with 100 mg to determine tolerance.
- 600 mg can be tolerated for most patients
- Lipoic acid 25 mg/ml or 40 mg/ml

IV Alpha-Lipoic Acid

- Never mix with any other nutrients.
- B.Berkson MD, PhD was advised by Dr. FC Bartter (former Chief, Hypertension and Endocrinology, National Institues of Health, USA) to never mix with any other antioxidants. It could potentially cause a thrombus to form in the patient's blood vessels.

IV Alpha-Lipoic Acid

- Adverse Effects
  - Hypoglycemia.
    - Ensure patient has eaten prior to the infusion.
  - Burning sensation in the blood vessel
    - Rapid administration
    - ALA is not sufficiently diluted in the carrier solution.

IV Alpha-Lipoic Acid

- Always protect the IV from light.

IV Alpha-Lipoic Acid

- Frequency per B.Berkson MD, PhD
  - Every day for the first and second week.
  - Continue for a week or two of therapy every 2 or 3 months.

IV Alpha-Lipoic Acid

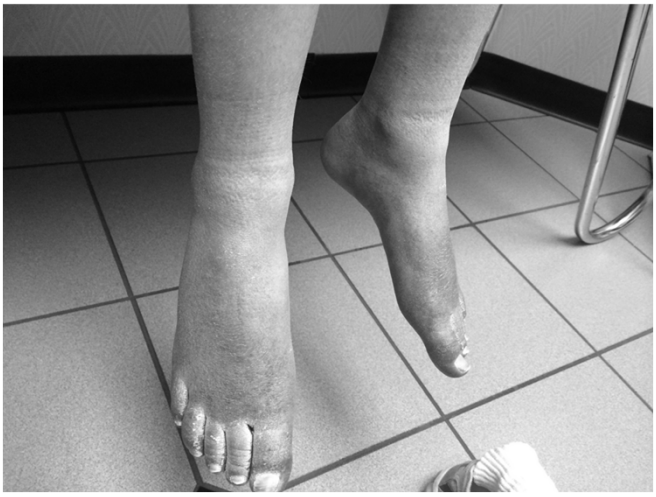
- Combining therapy with IVC for patients with cancer per B. Berkson, MD, PhD
  - Some patients are treated with IVC in the morning and receive IV ALA after lunch.
  - IV ALA recycles the vitamin C from the morning. ALA is a powerful regenerator of glutathione.

IV Alpha-Lipoic Acid

- Not available commercially in the United States.
- Available from compounding pharmacies
  - Lipoic acid 25 mg/ml or 40 mg/ml

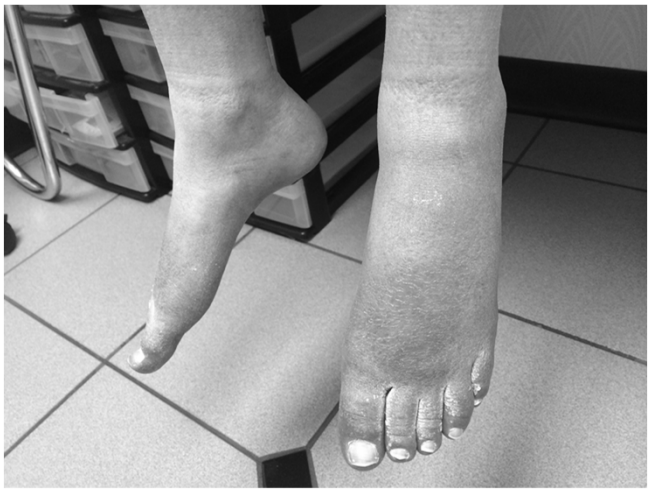
March 8, 2014

Case: Pre-IV ALA



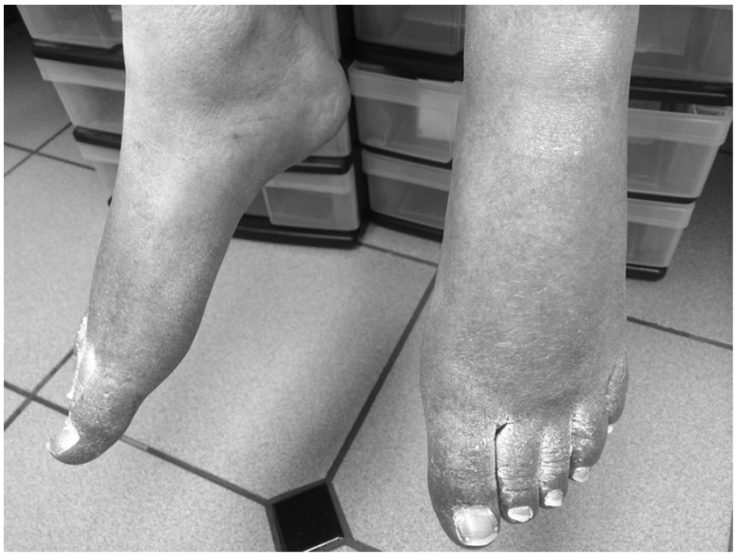
March 8, 2014

Case: Pre-IV ALA



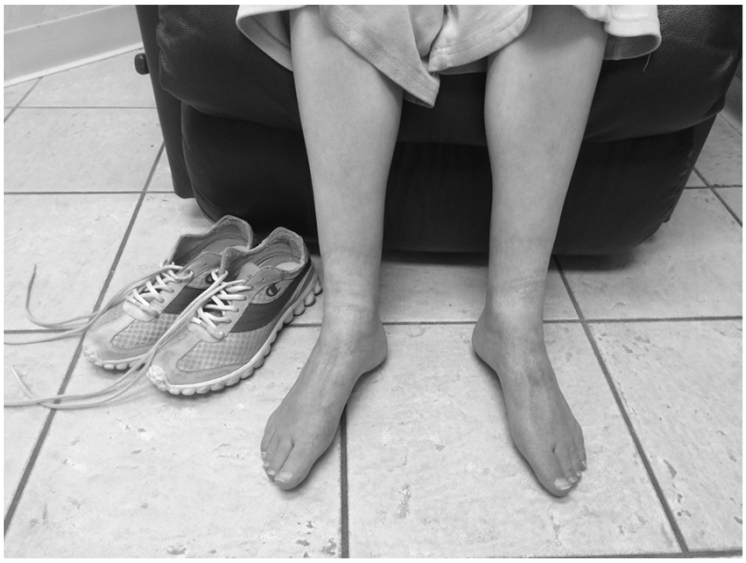
April 5, 2014

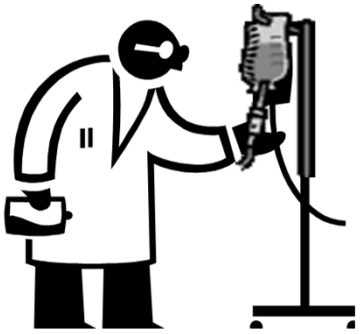
Case: Pre-IV ALA



July 22, 2015

Case: Post-IV ALA





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Reference: HIV

- Filina AA, Davydova NG, Endrikhovskii SN, et al. Lipoic acid as a means of metabolic therapy of openangle glaucoma. Vestn Oftalmol 1995; 111(4): 6– 8.

NOTES

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Bridghid McMonagle, N.D.

470 6th St Ste C
Lake Oswego, OR 97034

Disclosure Statement:

Dr. McMonagle has not indicated whether she has no relevant financial relationships with any commercial supporters.

Introduction to Ultraviolet Blood Irradiation (UBI)

Who knew that in a 1949 Time magazine, UBI therapy was shown to be an effective treatment for children with rheumatic heart disease? What happened to this inexpensive, safe and effective therapy? In this hour long discussion, you will have the opportunity to learn the extensive history of light therapy, it's clinical indications, and review patient testimonials and case studies.

Learning Objectives:

At the conclusion of this activity you should be able to…

1) Recognize the history of UBI
2) List the types of UV therapies available and how to administer them in your office
3) Discuss where to attain training and cost/set-up for your clinic

About Dr. McMonagle

Dr. Bridghid McMonagle graduated from Bastyr University and completed a residency at the National College of Natural Medicine (NCNM) where she performed rotations at the Oregon Health & Science University (OHSU) involving dermatology, gastroenterology, women's health, and emergency care. She is certified in Wilson Temperature Protocol, Prolozone, Major Autohemotherapy, LENS neurofeedback system, IV therapy, and has taken several seminars regarding bioidentical hormones, heavy metal chelation, neurofeedback, and injection techniques.

Dr. McMonagle was the first certified ozone practitioner in Oregon. She has trained extensively in ozone therapies. Dr. McMonagle has trained with Dr. Frank Shallenberger, Dr. Robert Rowen, Dr. Howard Robbins, Dr. Adrianna Schwartz, Dr. Lohadny and many more.

Dr. McMonagle has been practicing family medicine in Lake Oswego since 2006 and sees patients of all ages. She enjoys motivating individuals to improve their health.

Prior to medical school, Dr. McMonagle finished her undergraduate at the University of Washington in Environmental Health with a minor in chemistry. She then completed over 2 years in the Peace Corps in Thailand teaching environmental medicine and writing grants. During her time in the Peace Corps, she became fascinated with herbal medicine and various treatment options which inspired her to pursue naturopathic medicine.

Dr. McMonagle feels very fortunate to practice medicine, and have witnessed tremendous results through blending holistic and standard primary care. She enjoys traveling, soccer, crossfit, rock climbing, gardening, and staying active in the outdoors.

NOTES

Intro to Ultraviolet Blood Irradiation (UBI) ©

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Bridghid McMonagle, N.D.

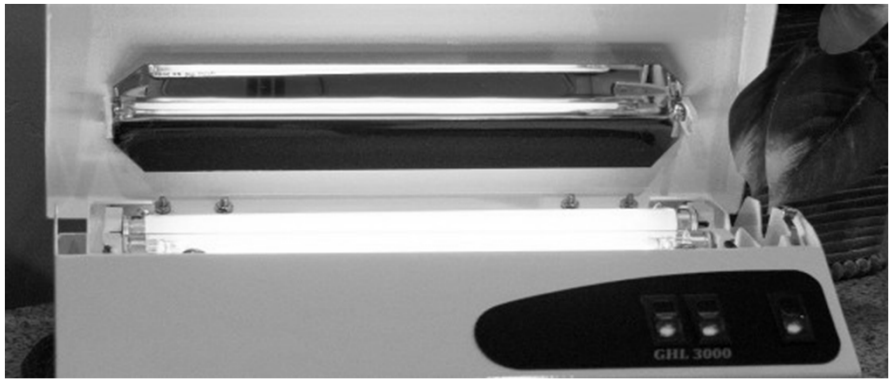
Received an educational grant from Merit Pharmaceuticals

Unless otherwise stated, the level of evidence is C and based on clinical experience.

Dr. McMonagle training & experience

- Dr. McMonagle graduated from University of Washington in 1998 with a bachelors of science in environmental health and a minor in chemistry.
- She spent over 2 years in the US Peace Corps in Thailand
- Dr. McMonagle graduated from Bastyr University in 2005.
- She completed a residency at NCNM in Portland, Oregon with rotations at Outside In, OHSU and with several specialists.
- Dr. McMonagle has using UBI therapy for about a decade.

UBI



Time Magazine June 13, 1949

- Doctors have known for 15 years that irradiating the blood with invisible ultraviolet rays helps in some diseases, notably blood poisoning. Three years ago Drs. Valinta P. Wasson, George P. Miley and Preston M. Dunning of the New York Infirmary decided to use the technique on children with acute rheumatic heart disease.
- **Last week they reported success in 22 consecutive cases.**
- All of the children, aged three to 13, were acutely ill with inflamed heart muscles (one result of the disease), the doctors told the American Blood Irradiation Society in Atlantic City's Chalfonte-Haddon...

- All of the children, aged three to 13, were acutely ill with inflamed heart muscles (one result of the disease). the doctors told the American Blood Irradiation Society in Atlantic City's Chalfonte-Haddon Hall. The process took only 15 to 25 minutes each time it was done. The doctors drew an amount of blood depending on the child's weight (1.5 cubic centimeters for each pound), added citrate to prevent clotting, fed it into the machine called a Knott Hemo-Irradiator that exposes the blood to ultraviolet light. Then the blood was returned to the child's arm through the same needle.
- Treatments were given a week apart at first, then at longer intervals depending on the patient's response; average number given was less than three. **All of the patients left the hospital without sign of rheumatic heart disease except mechanical damage that had already taken place in the heart**; 20 have returned to normal activity; one dies, from another disease, and one "gained immesurably." The three docotors concluded that "UBI" (Ultraviolet blood iradiation) is safe and may prove, after further tests, to be the best treatment available."

A Cure That Time Forgot…

- J Photochem Photobiol B. 2016 Apr;157:89-96. doi: 10.1016/j.jphotobiol.2016.02.007. Epub 2016 Feb 5.
- **Ultraviolet blood irradiation: Is it time to remember "the cure that time forgot"?** Wu X[1], Hu X[2], Hamblin MR[3].

- Ultraviolet blood irradiation (UBI) was extensively used in the **1940s and 1950s** to treat many diseases including **septicemia, pneumonia, tuberculosis, arthritis, asthma, and even poliomyelitis**.
- The early studies were carried out by several physicians in USA and **published in the American Journal of Surgery**.
- However, with the development of antibiotics, the use of UBI declined and it has now been called "the cure that time forgot."
- Later studies were mostly performed by Russian workers, and in other Eastern countries, and the modern view in Western countries is that UBI remains highly controversial. This review discusses the potential of UBI as an alternative approach to current methods used to treat infections, as an **immune-modulating** therapy and as a method for **normalizing blood parameters**. Low and mild doses of UV **kill microorganisms** by damaging the DNA, while any DNA damage in host cells can be rapidly repaired by DNA repair enzymes. However, the use of UBI to treat septicemia cannot be solely due to UV-mediated killing of bacteria in the bloodstream, as **only 5-7% of blood volume needs to be treated with UV to produce the optimum benefit**, and higher doses can be damaging. There may be some similarities to extracorporeal photopheresis (ECP) using psoralens and UVA irradiation. However, there are differences between UBI and ECP in that **UBI tends to stimulate the immune system**, while ECP tends to be immunosuppressive.
- **With the recent emergence of bacteria that are resistant to all known antibiotics, UBI should be more investigated as an alternative approach to infections, and as an immune-modulating therapy.**

- **KEYWORDS:** Blood cells; Bone marrow; Cytokines; DNA repair; Extracorporeal photopheresis; Lymphocytes; Phagocytes; Systemic infections; Ultraviolet irradiation of blood
- PMID: 26894849 PMCID: PMC4783265 DOI: 10.1016/j.jphotobiol.2016.02.007

The Procedure

- Prepare a syringe with Heparin, connect all tubing, drain the line
- Withdraw 30-60 cc blood via butterfly 21g or catheter
- Add to saline (newer technique)
- Via gravity pass through light in sterile tubing
- Monitor for infiltation
- Bell in room…
- Any IV procedures: Remind patients to hydrate and exercise before

Procedure Video courtesy of Tom Lowe

Over 75 years of history

- Photonic Therapy: UBI, LLLT, Red Light, Nasal Light, Blue Light
- Also known as: UBI, UVBI
- Developed by Russian scientists and used since the **early 1920's**, ultraviolet blood irradiation therapy reinforces the concept of light as energy. During therapy, blood soaks up the light and, depending on the combination of UV light used, a number of positive health outcomes can be achieved.

History www.drsubi.com

- **In 1928,** Emmitt K. Knott, a scientist in Seattle, ran some experiments on exposing the blood to UVC rays for women with severe bacterial infections due to abortions
- **In 1939** Dr. George Miley, MD, made a study of the effects of 97 blood irradiation treatments given to people suffering from various diseases. His observations were:
  - 1. A 58% increase in the venous oxygen content in ten minutes.
    2. A 9% decrease in venous oxygen after a half hour.
    3. A 50% increase in venous oxygen one hour to one month after treatment.
- **By the 1940's** UBI had really begun to roll. Dr. Miley reported using UBI on viral pneumonia, this cured the condition rather quickly. Here is what he reported:
- Complete subsidence of toxic symptoms 24-76 hours after a single treatment.
- Disappearance of cough in 3-7 days.
- X-ray evidence of complete clearing of the lungs within 24-96 hours after a single treatment (Miley, American Journal of Bacteriology)

Knott

DEVELOPMENT OF ULTRAVIOLET BLOOD IRRADIATION

E. K. KNOTT, D.Sc.
Seattle, Washington

THE development of ultraviolet blood irradiation therapy was an outgrowth of an attempt to utilize the bactericidal properties of ultraviolet rays in the treatment of blood stream infections. If the greatest advantage was to be derived from the bactericidal properties of the rays, a method of applying them directly to the blood stream of the patient had to

inside of the chamber had a labyrinthian passage connecting the inlet and outlet formed by baffle plates that were ground to fit flush against the quartz window that formed the top of the chamber. Thus the blood must flow through the labyrinth by passing around one end of each baffle plate instead of across them. The labyrinth was approximately 1 cm. deep.

History

- Dr. Henry Barrett reported on 110 cases of UBI in **1940** (Medical Clinics of America, May, 1940). Most patients received one treatment, but some received up to eight. In his research, Dr. Barrett noted several patients suffering from rheumatoid arthritis. After UBI treatment, these patients improved remarkably within a few hours. Another case involved a patient with four years of serious bronchial asthma attacks. Dr. Barrett found this patient in the hospital. Despite medication, she was having several asthma attacks per day. After one UBI treatment her doctor reported the next day that she had only one attack that day. After that she had two to three asthma episodes a week for three weeks. The attacks became fewer and fewer and became absent for months after a single treatment.

- Barrett reported on his 110 cases:

- 1. No detrimental reactions from UBI.
  2. Improvement is frequently immediate.
  3. Increase in peripheral circulation (due to vasodilation).
  4. Increase in oxygen combining power of the blood.
  5. Inactivation of toxins in the blood.

History

- In January,**1942**, Dr. Miley made the following observations, "The detoxification effect of ultraviolet is generally not known by the medical profession and certainly has not been emphasized enough.
- The inactivation of snake venom and bacterial toxins are examples of what may be accomplished by ultraviolet.
- The increased of blood irradiated with ultraviolet to absorb oxygen has been demonstrated.
- As a rule, rather low dosages of externally applied ultraviolet radiations stimulate the general resistance of animals and human beings to infection." (NY State Journal of Medicine).

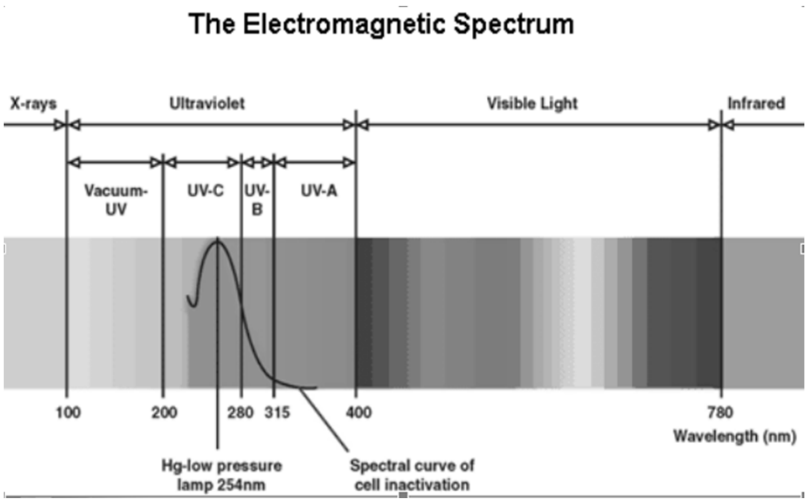
History

- **In the 1950's** enthusiasm over antibiotics and vaccines caused the UBI therapy to be replaced, despite its superiority for certain indications (hepatitis, viral pneumonia, and streptococcal toxemia). Research into this effective therapy came to a virtual halt.
- **From 1955 until the 1990's**, only a few American physicians continued to work with UBI. Russia and Germany took the lead in Light Therapy producing scores of clinical studies.
- **From 1990's to the present** over 250 practitioners in the US and over 3,000 in Europe began to use the therapy. Over one million UBI treatments have been successfully administered with astounding results and minimal side effects.

UBI

- Over 200 medical studies
- Rhelogical effects
- Immune effects
  - Positive results in research with autoimmune diseases
- Germicidal: Anti bacterial and antiviral at 254 nm
- Oxygenation effects

How does it work?



Healing affects of UBI: Russian Study

IE Ganelina & KA Samoilova 1986

- More O2 to organs
- Vasodilation and better Microcirculation
- Decrease viscosity
- Better peripheral Circulation
- Increased Red Blood cell production
- Decreased Platelet
- Improved oxygen supply.

Research

- G Ital Dermatol Venereol. 2017 Jul 28. doi: 10.23736/S0392-0488.17.05737-6. [Epub ahead of print]
- **Phototherapy of mycosis fungoides.** Trautinger F[1,2].
- Mycosis fungoides (MF), the most common variant of among cutaneous T cell lymphomas (CTCL), is characterised in its early stages by clonal proliferation of malignant T-cells in the skin manifesting as erythematous patches and plaques with a chronic course and progression to cutaneous tumors and extracutaneous organs in some patients. Skin directed therapies (SDT) are primarily used for effective palliation in early stage disease. Phototherapy with ultraviolet A radiation combined with 8-methoxypsoralen (PUVA) and with ultraviolet B radiation (UVB) has a longstanding history in the treatment of MF and are highly effective in inducing remissions. Patients with erythroderma and blood involvement benefit from treatment with extracorporeal photochemotherapy (ECP) where peripheral blood is exposed to PUVA. Phototherapy can be safely combined with systemic agents, most notably interferon-alpha and retinoids. Recently updated treatment guidelines have been published to provide evidence based algorithms for the stage-oriented treatment of MF. **PUVA and narrow-band UVB (NB-UVB) are recommended as first line treatment for early stages** with combination modalities reserved for refractory and more advanced cases and ECP is among the standard treatments for MF erythroderma. Areas of uncertainty relate to optimized treatment dose and schedules, the use of phototherapy for maintenance, and the role of newer phototherapeutic modalities (e.g. ultraviolet A1 radiation, excimer sources, photodynamic therapy) in the treatment of MF.
- PMID: 28845954 DOI: 10.23736/S0392-0488.17.05737-6

Research

- Int J Infect Dis. 2015 Aug;37:58-63. doi: 10.1016/j.ijid.2015.06.006. Epub 2015 Jun 17.
- **The treatment of infectious disease with a medical device: results of a clinical trial of ultraviolet blood irradiation (UVBI) in patients with hepatitis C infection.**
- Kuenstner JT[1], Mukherjee S[2], Weg S[3], Landry T[4], Petrie T[5].
- Prior to the advent of therapies with sustained virological response rates of 94%, this study was conducted for the **US Food and Drug Administration (FDA) to assess the safety and efficacy of ultraviolet blood irradiation (UVBI) for the treatment of hepatitis C virus (HCV) infection**.
- Nine patients received **15 UVBI treatments over the course of 22 weeks** with the AVIcure Hemo-modulator, which was modified from the original Knott Hemo-irradiator. The patients' viral loads and liver function tests were obtained periodically during the study and analyzed during the course of the trial.
- At the end of the study, the **overall mean reduction in HCV viral load was 21.5%** (p = 0.023); on day 140, **direct bilirubin declined by 41.1%** (p=0.0059), **aspartate aminotransferase declined by 15.2%** (p=0.0069), and **alanine aminotransferase declined by 19.3%** (p=0.0031). The nadir of the mean and median viral load occurred on day 259, and it corresponded to a mean viral load reduction of 44.9% (p=0.0048). During the course of the study, three patients had a greater than 0.5 log reduction in viral load (patient 1, 0.56 log reduction on day 259; patient 4, 0.69 log reduction at the end of the study; patient 11, 0.91 log reduction on day 259). Two patients showed **marked improvement in their concurrent psoriasis** at the conclusion of the trial.
- In this study, **UVBI was safe and had a beneficial effect in the treatment of HCV**. This device should be studied for use in psoriasis and in infectious diseases that have few treatment options. This article describes a prospective, controlled, phase II clinical trial submitted to the FDA of this device used for the treatment of HCV infection (Investigational Device Exemption (IDE) #G030242).

Research

- Iran J Microbiol. 2017 Feb;9(1):50-54.
- **Inactivation of model viruses and bacteria in human fresh frozen plasma using riboflavin and long wave ultraviolet rays.**
- Elikaei A[1], Hosseini SM[2], Sharifi Z[3].
- Pathogen reduction technologies are among methods to eliminate transfusion transmitted infections. Mirasol method using riboflavin in combination with ultraviolet rays is one of them. The aims of this study were to investigate the effectiveness of Mirasol method to inactivate some model pathogens as well as examination of the sensitivity of plasma proteins after treatment.
- Riboflavin in 50µM concentration and **ultraviolet (365 nm)** in three different energy doses (3.6, 7.2, and 10.8 j/cm^2) were employed to inactivate model pathogens. Four standard viruses were used in this study including *Vesicular Stomatitis Virus* (VSV), *Herpes Simplex Virus1* (HSV-1), *Bovine Viral Diarrhea Virus* (BVDV) and *Polio Virus*. 50% Tissue Culture Infectious Dose ($TCID_{50}$) and Reed-Muench Methods were used to estimate viruses' titers. *E. coli* and *Staphylococcus aureus* were used as bacterial models. Four plasma proteins including factor V, VIII, fibrinogen and antithromin were used to determine their sensitivity to pathogen inactivation treatment.
- The most pathogen reduction titre was determined for 15 minutes irradiation period equal to 10.8 J/cm^2 that is corresponding to Log 6.10 for BVDV, Log 6.09 for HSV-1, Log 6.62 for VSV and Log 3.36 for Polio. Bacterial reduction titer was Log 6.94 for *E. coli* and Log 7.00 for *S. aureus*. Indicator proteins for plasma activity were determined to be 75% for factor V, 88% for factor VIII, 52% for fibrinogen and 94% for antithrombin.
- Results showed that the employed method **can inactivate most of the pathogens in fresh frozen plasma**. The acceptable activities of selected plasma proteins remained after treatment.

Research

- Lupus. 2017 Jan 1:961203317707064. doi: 10.1177/0961203317707064. [Epub ahead of print]
- **Ultraviolet-A1 irradiation therapy for systemic lupus erythematosus.**
- McGrath H Jr[1].
- Systemic lupus erythematosus (lupus, SLE) is a chronic autoimmune disease characterized by the production of autoantibodies, which bind to antigens and are deposited within tissues to fix complement, resulting in widespread systemic inflammation. The studies presented herein are consistent with hyperpolarized, adenosine triphosphate (ATP)-deficient mitochondria being central to the disease process. These hyperpolarized mitochondria resist the depolarization required for activation-induced apoptosis. The mitochondrial ATP deficits add to this resistance to apoptosis and also reduce the macrophage energy that is needed to clear apoptotic bodies. In both cases, necrosis, the alternative pathway of cell death, results. Intracellular constituents spill into the blood and tissues, eliciting inflammatory responses directed at their removal. What results is "autoimmunity."
- Ultraviolet (UV)-A1 photons have the capacity to remediate this aberrancy. Exogenous exposure to low-dose, full-body, UV-A1 radiation generates singlet oxygen. Singlet oxygen has two major palliative actions in patients with lupus and the UV-A1 photons themselves have several more. Singlet oxygen depolarizes the hyperpolarized mitochondrion, triggering non-ATP-dependent apoptosis that deters necrosis. Next, singlet oxygen activates the gene encoding heme oxygenase (HO-1), a major governor of systemic homeostasis. HO-1 catalyzes the degradation of the oxidant heme into biliverdin (converted to bilirubin), Fe, and carbon monoxide (CO), the first three of these exerting powerful antioxidant effects, and in conjunction with a fourth, CO, protecting against injury to the coronary arteries, the central nervous system, and the lungs. **The UV-A1 photons themselves directly attenuate disease in lupus by reducing B cell activity, preventing the suppression of cell-mediated immunity, slowing an epigenetic progression toward SLE, and ameliorating discoid and subacute cutaneous lupus.** Finally, a combination of these mechanisms **reduces levels of anticardiolipin antibodies and protects during lupus pregnancy.**
- **Capping all of this is that UV-A1 irradiationis an essentially innocuous, highly manageable, and comfortable therapeutic agency**.

Patient Testimonial courtesy Tom Lowe

Patient testimonial UBI with Ozone, Lake Oswego Health Center

Types of machines

- Knott Machine
- Longevity
- Champion
- New machines with multiple light options

Benefits

- Low cost
- Limited side effects
  - Discuss autoimmune flares
- Other complaints than CC can improve

Resources

- Pubmed research listed within the slide
- Tom Lowe, drsubi.com
- www.lakeosweghealth.com - website has more research listed

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Introduction to Medical Ozone

Medical ozone has been used for over a 100 years. It is an amazing way to treat of variety of illnesses safely and effectively. In this presentation, you will obtain a thorough understanding regarding the history of medical ozone therapy, it's uses in health care, case studies using ozone, and how to attain enough training to start using it in your practice.

Learning Objectives:

At the conclusion of this activity you should be able to…

1) Discuss the expansive history of medical ozone
2) List the main clinical indications for ozone therapy
3) Recognize the variety of ways ozone therapy can be used in your clinical practice.

About Dr. McMonagle

Dr. Bridghid McMonagle graduated from Bastyr University and completed a residency at the National College of Natural Medicine (NCNM) where she performed rotations at the Oregon Health & Science University (OHSU) involving dermatology, gastroenterology, women's health, and emergency care. She is certified in Wilson Temperature Protocol, Prolozone, Major Autohemotherapy, LENS neurofeedback system, IV therapy, and has taken several seminars regarding bioidentical hormones, heavy metal chelation, neurofeedback, and injection techniques.

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Intro to Medical Ozone ©

Dr. Bridghid McMonagle

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Dr. McMonagle training & experience

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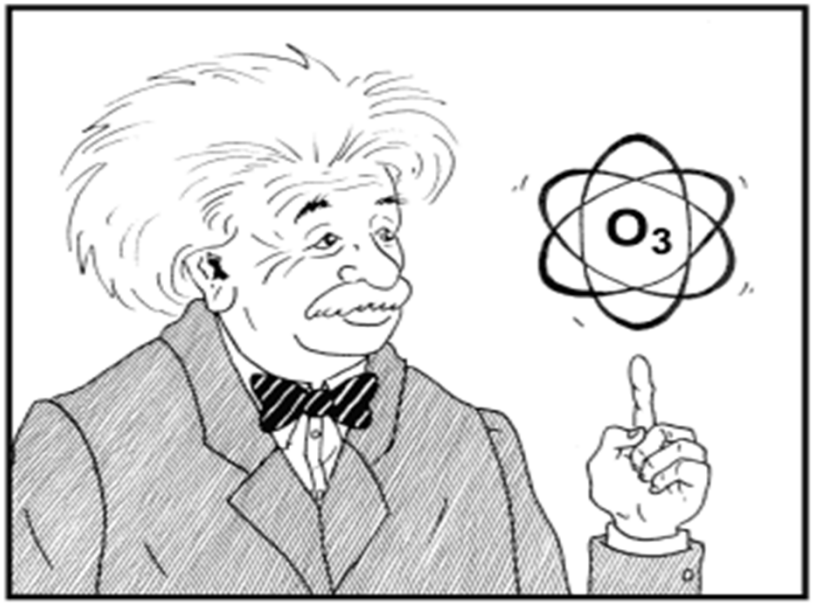
- She spent over 2 years in the US Peace Corps in Thailand
- Dr. McMonagle graduated from Bastyr University in 2005.
- She completed a residency at NCNM in Portland, Oregon with rotations at Outside In, OHSU and with several specialists.
- Dr. McMonagle became fascinated with ozone therapy about a decade ago when she experienced the benefits with her own health.
- Dr. McMonagle has been the longest certified ozone practitioner in Oregon and has a thriving private practice in Lake Oswego.



History of Medical Ozone

- Christian Schönbein was appointed a professor in 1835 of physics and chemistry at the University of Basel.
- Schönbein is known primarily for his work on ozone. While working on water experiments, he noted the odor that is now recognized as ozone. This was first noted by the Dutch chemist van Marum (1785).
- Schönbein recognized that the substance is a gas, produced at the anode and resembles chlorine and bromine in its chemical and electric properties. Schönbein saw a strong analogy between ozone and the halogens chlorine and bromine.
- In 1845 Marignac and Auguste Arthur de la Rive also worked on ozone.

History of Medical Ozone

- A more recognizable name in ozone research is Nicola Tesla.
- In 1896, Nicola Tesla was given a patent for his ozone generator. This machine was in the **1904** Sears catalog.
  - All types of physicians were using and recommending this therapy
  - Back then, patients could breath ozone that had been bubbled through oil

History of Medical Ozone

- **1898: Dr. Benedict Lust practicing in New York, the originator and founder of Naturopathy, wrote books and articles on ozone.**
- 1899: Ozone was first commercially used for disinfection in France.
- 1900: Medical ozone was used in the U.S. by Nikola Tesla
- 1902: J.H. Clarke's "A Dictionary of Practical Materia Medica" described the successful medical use of ozonated water in treating anemia, cough, cancer, diabetes, influenza, morphine poisoning, canker sores, strychnine poisoning, and whooping-cough.
- 1911: Noble M. Eberhart M.D., Phd published "Ozone; Nature; Physiological Action; Methods of Administration; Diseases In Which It Is Indicated."

History of Medical Ozone

- 1929: "Ozone and Its Therapeutic Action" **published in the US listing 114 diseases**, the 40 authors were the heads of the leading American hospitals.
- 1931: Dr. Otto Warburg wins first the Nobel Prize for work proving cancer is caused by a lack of oxygen in the cells. He stated in "The Prime Cause and Prevention of Cancer" that the cause of cancer is no longer a mystery, we know it occurs whenever any cell is denied 60% of its oxygen requirements.
- 1933: The American Medical Association (AMA), headed by Morris Fishbein, set out to eliminate all medical treatments that were competitive with drug therapy. The suppression of ozone therapy in the United States begins.
  - At the behest of the AMA, the **FDA began seizing generators in the 1940s**.
- 1938: Dr. Aubourg French physicians wrote "Medical Ozone: Production, Dosage and Methods of Clinical Application" **8000 applications**

History of Medical Ozone

- 1900's: The Violet Ray: Used during the early 20th century as electrotherapy.
- Made of glass evacuated tubes, they were advertised to cure many common conditions.
- Back pain, brain fog, infections and much more.
- During the 1940s and 1950s, the US government ordered recalls and seizures, destroying most of them.
- 1951: The last manufacturer of violet ray electrotherapy, had their devices seized by the FDA.

History of Medical Ozone

- 1940s: German Dr. Hans Wolff wrote the book "Medical Ozone."
- Mid 1940s: During World War II, Dr. Robert Mayer learned of ozone therapy from German prisoners of war.
- 1957: Dr. J. Hansler patented an ozone generator causing the expansion ozone therapy.
- 1971: The German Medical Society for Ozone Therapy was founded.
- 1980: Dr. Horst Kief reported success with ozone therapy for AIDS patients.
- 1982: German medical textbook "Medical Ozone" is published by Dr. Fischer

History of Medical Ozone

- 1983: The first International Ozone Association medical ozone conference held in Washington, D.C. Abstracts were published in "Medical Applications of Ozone,".
- 1985, Dr. Renate Viebahn "The Biochemical Process Underlying O3 Therapy".
- 1990: The Cubans reported success in treating glaucoma, conjunctivitis and retinitis pigmentosa with ozone."
- AAO founded in 2010: An academy of health professionals dedicated to establishing standards for the art and science of Ozonotherapy, educating the public and other health professionals about the many uses of Ozonotherapy in medicine, & promoting research in Ozonotherapy.
- 2014: Dr. Rowen and Dr. Robbins travel to Sierra Leone to train doctors how to use ozone for Ebola. Their results were published in an African infectious disease journal.

Making ozone & how does it work?

- Generating ozone:
  - Medical grade oxygen.
  - Ozone generators split apart the oxygen (O2) molecule creating singlet oxygen. This is unstable and quickly recombines as O2 and O3 (ozone). There are several types of machines available.
  - This O2/O3 gas mixture can be drawn up into a syringe or in an ozone resistant bag.
  - Ozone is referred to as a free radical & is a highly reactive.
  - Oxidative stress leads to cellular degeneration.
    - Oxidative stressors: smoking cigarettes, alcohol, poor nutrition, stress & prescriptions
    - Healthy cells produce enzymes to help combats these stressors (glutathione peroxidase, super-oxide dismutase, catalase, & reductase).
    - Bacteria & viruses lack anti-oxidant enzymes in their cell membranes & are unable to protect themselves from ozone. At low levels, ozone is both an oxidant and an antioxidant.
    - A recent study showed that our own antibodies create ozone to protect us.

Summary of how medical O3 works

- Ozone acts as an anti-inflammatory affecting cytokines
- Inactivates bacteria, viruses, yeast & protozoa
- Improves mitochondrial function & number
- Our own antibodies produce small levels of ozone to kill bacteria
- Ozone improves blood flow & oxygen uptake in the body
- Ozone has been proposed as an antioxidant enzyme activator, immunomodulator, & cellular metabolic activator.

Oxidative shielding or oxidative stress?

- J Pharmacol Exp Ther. 2012 Sep;342(3):608-18. doi: 10.1124/jpet.112.192120. Epub 2012 Jun 13. Naviaux RK1.
  - http://www.ncbi.nlm.nih.gov/pubmed/22700427
- Reactive oxygen species (ROS) and chronic oxidative changes in membrane lipids and proteins found in many chronic diseases are not the result of accidental damage.
- These changes are the result of a highly evolved, stereotyped, & protein-catalyzed "oxidative shielding" response that all eukaryotes adopt when placed in a chemically or microbially hostile environment.
- The machinery of oxidative shielding evolved from pathways of innate immunity designed to protect the cell from attack & limit spread of infection.
- Both oxidative & reductive stress trigger oxidative shielding. Functional & metabolic defects occur in the cell before the increase in ROS & oxidative changes.
- **ROS are the response to disease, not the cause.**
- This perspective is relevant to diseases that range from **autism, type 1 diabetes, type 2 diabetes, cancer, heart disease, schizophrenia, Parkinson's disease, and Alzheimer disease**.
- Oxidative shielding is protective & is a misguided target for therapy. Identification of the causal chemistry & environmental factors that trigger innate immunity & metabolic memory that initiate & sustain oxidative shielding is paramount for human health.

Oxygen-Ozone therapy in medicine: an update.

- Blood Purif. 2009;28(4):373-6. doi: 10.1159/000236365. Epub 2009 Sep 10. Bocci V1, Di Paolo N.

- O3-O2 therapy, initially started as an empirical approach, has now reached a stage where most of the biological mechanisms of action of ozone have been clarified, showing that they are in the realm of orthodox biochemistry, physiology & pharmacology.
- Ozone therapy is particularly useful in **cardiovascular disorders and tissue ischemia**. In **chronic viral infections**, it is unable to eliminate the viremia but it may display supportive help by **stimulating the immune system**.
- Recently, its use has been successfully extended to the **herniated disk pathology** and therapy of **primary caries in children**.

The case for oxygen-ozonetherapy.

- Br J Biomed Sci. 2007;64(1):44-9. Bocci V1.
- Ozone is a very reactive gas & toxic to the respiratory system.
  - Under controlled conditions, it can be therapeutically useful in several human diseases.
- An unfavorable combination of factors (ozone is one of the worst troposphere pollutants) & past misuse have led to misgivings about ozone therapy.
- Interestingly, judicious doses of ozone dissolved in blood trigger a cascade of well-defined chemical compounds acting on multiple cellular targets according to well-known molecular, biochemical & pharmacological pathways.
- Ozone therapy is proving to be very useful in **age-related macular degeneration**, **ischemic and infectious diseases**, & in **wound healing disorders**, where conventional medicine has failed.
- Critical evaluation of the potential therapeutic utility of this simple, inexpensive medical application by national & international health authorities is warranted & may lead to clinical benefit for a large proportion of the world's population.

Virion disruption by O3-mediated ROS

- J Virol Methods. 2008 Oct;153(1):74-7. doi: 10.1016/j.jviromet.2008.06.004. Epub 2008 Jul 24. Murray BK1, Ohmine S, Tomer DP, Jensen KJ, Johnson FB, Kirsi JJ, Robison RA, O'Neill KL.
- It is well documented in the scientific literature that O3-O2 mixtures inactivate microorganisms including bacteria, fungi and viruses.
- In the current study, delivery & absorption of precisely known concentrations of O3 (in liquid media) were used to inactivate virus infectivity.
- An O3-O2 delivery system capable of monitoring & recording ozone concentrations in real time was used to inactivate a series of enveloped & non-enveloped viruses including **herpes simplex virus type-1**, vesicular stomatitis Indiana virus, vaccinia virus, adenovirus type-2, & the PR8 strain of **influenza A virus.**
- The results of the study showed that O3 exposure reduced viral infectivity by lipid peroxidation & subsequent lipid envelope & protein shell damage.
- These data suggest that a wide range of virus types can be inactivated in an environment of known ozone exposure.

Diane, a hair stylist, describes results from local Prolozone

Nancy with multiple health complaints shows significant improvement with systemic ozone therapy

Case: 20 YO Female w/ Herpes

- 20 yo female PTC with:
  - Recent herpes infection,
  - chronic low back & ankle pain,
  - Eczema & acne
  - Mild fatigue that she attributes to her recent anti-viral medication.
  - Patient was treated with ozone therapy. 24 hours after her first high dose treatment, patients eczema on her hands completely resolved, ow back pain was gone, & her ankle pain was significantly better. Her skin cleared dramatically within the week. She is no longer on acne medication or prescription anti-virals.
- Pt had a very small outbreak in the same location. Pt was treated locally with injections, insufflations & system treatment. Pt labs dramatically improved.
- No outbreaks since.

Case: metastatic breast cancer

- LW xx old female
- Pain pump
- Low back pain
- Prolozone was very helpful
- Less pain and regained leg strength

Case: 59 YO Female w/ Hip & Knee Pain

- 59 yo female PTC with right hip and knee pain. Pt has had Prolozone in the past at another doctor's office. Pt had a back injury 25 yrs ago. Hip pain since a trip to the ER. Pt stands for long periods at work on a hard surface.
- Pt was seen on 10/6/14 for injections, 12/1/14 only slight hip pain remaining. Received injections and sleeping much better. 1/16/15 injections. 2/11/15-3/30/15 worked on weight loss. Pt was last seen on 1/13/16. She has lost 45 pounds and kept that off, she is walking 5-10 miles per day and her energy is good.
- She states, "No knee pain, no hip pain, no SI pain, no pain at all.

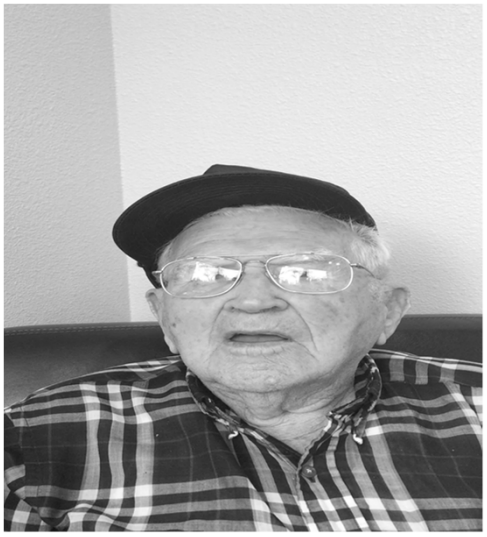
Case: 46 YO Female w/ Multiple Health Complaints

- 46 yo female PTC with multiple health complaints including past diagnosis of brain fog, Bipolar, Depression, HTN, hyperlipidemia, Heartburn, Hypothyroidism, Fatigue, Sciatica, Neck pain (7/10), Back pain (8-10/10, and Hip pain (5/10). Patient was on 6 prescription medications. Office visit 4/8/15. Injections and uv/ozone 4/17/15, 4/22/15 uv/ozone. 4/23/15 patient call – much better energy and less body pain. 5/1/15 less hip pain, had uv/ozone. 5/18 uv/ozone. 6/1/15 right hip injection. 8/14/15 uv/ozone. Rented an ozone generator to clear air in house and breathing better. 8/28/15 hand pain for 1+ years, prolozone right hand.
- Since then overall pain is significantly improved, brain fog is better, depression is better, energy is better, and hand pain is almost resolved.
- Patient was able to be more active and lost 30 pounds.

Case: 99 YO Male w/ History of Fatigue

- 99 yo male PTC with history of fatigue, right shoulder pain, bladder cancer (diagnosed 6-7 yrs ago), macular degeneration (1 yr ago), glaucoma, body pain and hypertension.
- Pt was seen on 4/27/15 and had uv/ozone. 5/11/15 uv/ozone. 5/21/15 pt noted extreme difference in pain levels and had #3 uv/ozone.
- 5/27/15 energy is 25% better, sciatica and overall pain is 80% better.
- Pt is waking every 2-3 hours with right shoulder pain. Treatment: uv/ozone #4. 6/4/15 uv/ozone #5 and right shoulder injection.
- **7/1/15 bladder cancer is gone!**
- uv/ozone #6, BL shoulder injection. 7/20/15 right shoulder 50% better. Not waking every night. 11/18/15 uv/ozone #7.
- Eye doctor noted that his macular degeneration and glaucoma was improving.
- 11/24/15 uv/ozone #8. 12/2/15 uv/ozone #9 right shoulder is still 50% better and left shoulder is 80% better.

Patient testimonial at Lake Oswego Health Center



Potentiality of O2/O3 to improve the health of aging people.

- Curr Aging Sci. 2010 Dec;3(3):177-87. Bocci V1, Zanardi I, Travagli V.
- During the last century the lifespan of human beings has increased from about 49 to almost 80 years owing to the great advances of biomedical sciences.
- This fact has strongly stimulated the idea that it may be possible to prolong productive life for another twenty years but paradoxically the problem of both hyper & hyponutrition severely jeopardizes this objective all over the world.
- So far only a moderate restriction of caloric intake that does not alter essential nutrients has proved capable of keeping animals & humans healthier for a prolonged time. This modality appears to activate critical longevity genes that can prolong survival.
- We propose to evaluate an easy and well accepted treatment based on a weekly quasi-total body exposure to O3-O2.
- The rational exposure to a minimal amount of **ozone acting as a mild stressor induces a striking improvement of crucial metabolic activities capable of preserving a good health for several years.**

Chemistry Behind Ozone Therapy:

Bocci Mechanism of Action

- "Due to the high ozone reactivity, these biochemical reactions occur in a few seconds and in fact, ozone is totally exhausted while about 95% oxygen, dissolved in the plasma water, fully saturates hemoglobin."
- "During the initial fast & multiple reactions of ozone with the plasmatic components, a variable amount of the ozone dose is neutralized by the wealth of the hydrophilic antioxidants.
- It is noteworthy that, with the exception of uric acid oxidized to allantoin, dehydroascorbate and GSH disulfide are **reduced back to their normal value in less than twenty minutes** due to the exceptional efficiency of the recycling system based on a multitude of reducing molecules such as alpha-lipoate, Vitamin E, thioredoxin, & last but not least NADPH acting in a well-coordinated sequence of electron donations"

Chemistry Behind Ozone Therapy:

Bocci Mechanism of Action

- "Owing to the potent antioxidant capacity of blood due to its hydrophilic, lipophilic antioxidants & cellular enzymes, some of the ozone dose dissolved in the water of plasma is instantly quenched by free antioxidants (mainly uric acid, ascorbic acid, reduced glutathione - GSH, cysteine and albumin), while the remaining ozone reacts with polyunsaturated fatty acid (PUFA) mostly present in the three hydrophobic tasks of albumin."
- "The potential energy of ozone is finally transferred into two fundamental messengers such as H2O2 and superoxide as a reactive oxygen species (ROS) and aldehydic molecules of which 4-hydroxynonenal (4-HNE) and trans-4-hydroxyhexenal (4-HHE) are the relevant lipid oxidation products (LOP)"

Chemistry Behind Ozone Therapy:

Bocci Mechanism of Action

- "H2O2, rapidly enters into all blood cells & the chemical gradient between plasma-cells has been measured to be about 10% of the extracellular concentration."
- "The sudden inflow of this small amount of H2O2 inside blood cells is the indispensable stimulus to activate a series of biochemical reactions as follows:"
- "In erythrocytes: **activation of glycolysis with increase of ATP and 2,3-diphosphoglycerate**.
- "**Increasing the release of oxygen at the tissue level**. The erythrocytes mop up most of the H2O2 and promptly reduce it to water by GSH. The sudden formation of GSSG (oxidized glutathione) alters the GSH/GSSG ratio but the cell quickly correct it by either extruding some glutathione-disulphide or by reducing it via GSH reductase at the expense of either ascorbic acid or thioredoxin, which has two-SH groups. Moreover, the activation of glucose-6-phosphate dehydrogenase (G6PDH) provides reducing power and activate glycolysis."

Chemistry Behind Ozone Therapy:

Bocci Mechanism of Action

- "**Leukocytes: neutrophil phagocytic activity is enhanced**.
- Inside monocytes and lymphocytes, H2O2 activates a tyrosin-kinase with consequent phosphorylation of IkB, one of the trimeric components at rest of the NF-kB. The phosphorylated IkB detaches from the trimer and it is broken down in the proteasome. The remaining eterodimer p50-p65 is transferred into the nucleus where it can activate about 100 genes. Of great significance it is the final release of some cytokines (IFNγ and IL-8) and of some acute-phase proteins"
- "Platelets: In relation to the ozone concentration, we have measured release of PDGF-AB, TGFβ-1 and IL-8. **Growth factors have a specific relevance in enhancing ulcer's healing in peripheral arterial disease** (PAD)."

Chemistry Behind Ozone Therapy:

Bocci Mechanism of Action

- "Finally, the majority of patients, undergoing several treatments, report a **feeling of euphoria and a sense of wellness** probably due to an improved hormonal secretion and/or better utilization of neurotransmitters."
- "Most importantly, by using the above reported therapeutic range of ozone concentrations strictly related to the blood volume, it must be noted that **neither acute nor chronic toxicity has been ever observed during or after ozone therapy**."

Chemistry Behind Ozone Therapy:

Bocci Mechanism of Action

- "There is a wide consensus on the relevance of the induction of protective molecules during repeated oxidative stress and it is of interest that these small stresses are of crucial importance for preventing and treating **hypertension, stroke and heart infarction**."
- "Indeed in our clinical trial in peripheral arterial disease (PAD) ozonetherapy has proved to be better than the orthodox infusion of iloprost."
- "Ozone therapy is based upon a real hormetic concept where the optimal ozone dose must never overwhelm the potent antioxidant capacity of blood."
- "At the time of ozonated blood infusion, 4-HNE-Cys adduct can also act on the vast expanse of endothelial cells and, by stimulating the endothelial nitric oxide synthase (eNOS) enhances the biosynthesis of NO via the 5-electron oxidation of L-arginine. NO, S-nitrosothiols and a trace of CO released with bilirubin via the upregulation of HO-1 activity allows vasodilation, thus improving tissue oxygenation in ischemic tissues.
- Moreover, an increased production of NO counteracts the excessive endothelial release of O2- caused by the chronic inflammation typical of atherosclerosis."

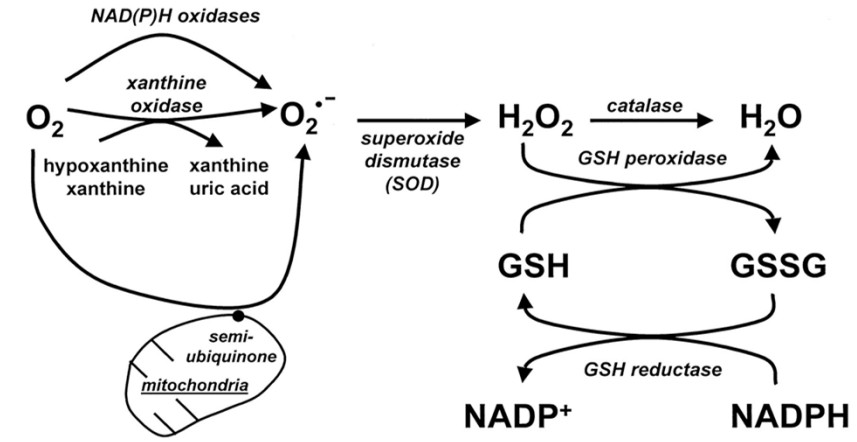
Other Research

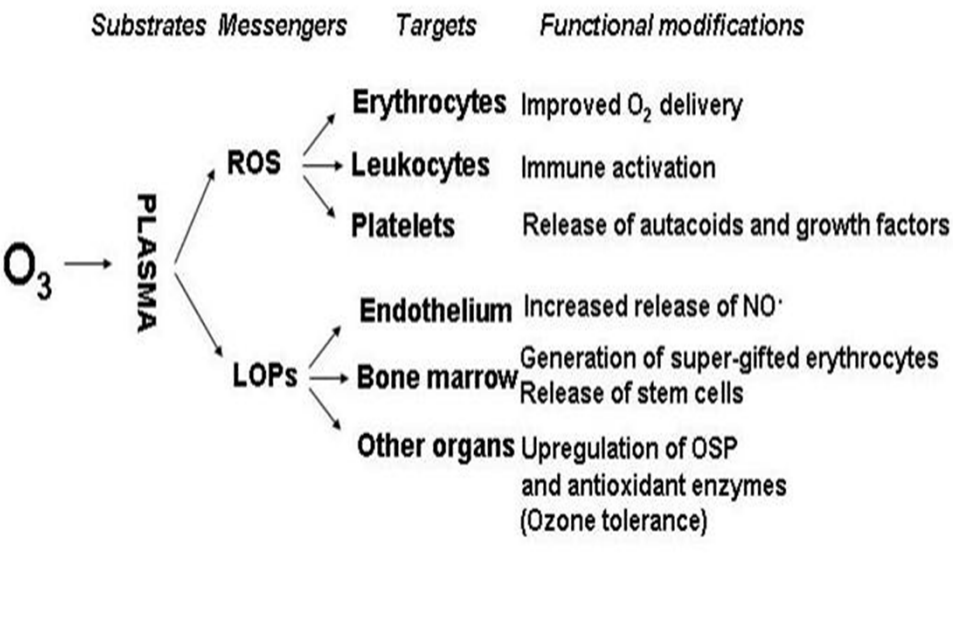
- Surg Neurol. 1997 Jun;47(6):575-81; discussion 581-2.
- Oxidative stress following traumatic brain injury in rats.
- Free radicals may be involved in the pathophysiology of traumatic brain injury (TBI) through oxidative damage of neurovascular structures. Endogenous antioxidants, such as ascorbate and alpha-tocopherol, may play a critical role in combating these oxidative reactions and their oxidized products can serve as an important index of oxidative stress
- Ozone therapy increased the latency for the first seizure and the survival percentage.

Other Research

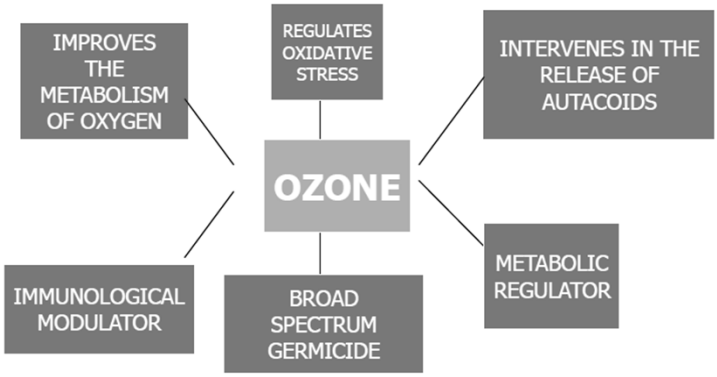
- https://scholar.google.com/scholar?start=10&q=brain+injury+and+major+autohemotherapy&hl=en&as_sdt=0,38&as_vis=1 - Ozone Therapy: Experiences in Critically ill Patients; José Turrent[1], Silvia Menéndez*[2]
- Eur J Pharmacol. 2009 Jan 28;603(1-3):42-9. doi: 10.1016/j.ejphar.2008.11.060. Epub 2008 Dec 6.; A single subcutaneous injection of ozone prevents allodynia and decreases the over-expression of pro-inflammatory caspases in the orbito-frontal cortex of neuropathic mice.; These preliminary data show that peripheral neuropathy induced over-expression of pro-inflammatory/pro-apoptotic caspases in the orbito-frontal cortex and that ozone, by mechanisms that are as yet unknown, can regulate the expression of the genes that play a pivotal role in the onset and maintenance of allodynia.

Pathways of ROS production and clearance





Simplified Clinical Effects of Medical Ozone



How can we use medical ozone ?

- Prolozone: Joint injections (osteoarthritis, torn meniscus, frozen shoulder, rotator cuff strains, bulging discs) and trigger point therapy
- Insufflations: Bladder, Vagina, Rectal, Ear, Sinus
- Systemic: Major autohemotherapy, minor autohemotherapy, DIV, High dose ozone
- Water and ice
- Ozone sauna
- Ozone oil (toenail fungus, wound healing)
- Limb bagging and cupping (speed wound healing)
- Ozone in Vet clinic and Dental clinics
- Direct injections into tumors – beyond the scope. Some doctors in other countries doing this.
- Cosmetics: Fine lines, scars, cellulite, lipolysis

Other Applications of Ozone

- Odor removal
  - Laundry
- Waste water treatment
- Drinking water treatment
- Disinfectant
- Food processing & food storage
- Air treatment
- Swimming pools and spas

Simplified Clinical Effects of Medical Ozone

- 1. Bactericidal, fungicidal and virucidal.
- 2. Therapeutic ozone indirectly activates the non-specific defense system as well as components of cellular and humoral immunity.
- 3. Anti-inflammatory effect oxidizes the compounds containing double bonds which participate in the development & the sustaining of the inflammatory process, regulates metabolic reactions and resolves pH.
- 4. Ozone analgesic effect oxidates the products that act on the nerve endings in the damaged tissue & determine the intensity of pain response.
- 5. Detoxification effect correction & activation of metabolic processes in the hepatic & renal tissues

Simplified Clinical Effects of Medical Ozone

- 6. Activation of oxygen-dependent processes. Increase in the content of free & dissolved blood oxygen plus mitochondrion activation resulting in ATP synthesis.
- 7. Optimization of pro- and anti-oxidant influence on cellular membranes & bringing to balance the levels of lipid peroxidation products
- 8. Ozone hemostatic effect depends on the dose. High concentrations external use cause hyper coagulation effect, while parenteral administration of low concentrations is characterized by the decrease in thrombocytic & coagulative values
- 9. Ozone immune-modulating patients with auto-immune pathology (rheumatoid disease, disseminated sclerosis, sclerodermia, etc.) are helped

Safety of Ozone

- Unlike prescription drugs, ozone therapy has no side effects. According to a 1978 FDA report, 1.5 million people were hospitalized due to pharmaceutical side effects and 140,000 deaths were attributed to prescription drug usage. A 1980 Report on Ozone Therapy by the German Medical Society documented 5.6 million ozone treatments with 40 reported cases of side effects *(less than 1 in 100,000)* and 4 reported deaths *(less than 1 in a million)*.
- In Germany, Eastern Europe, and Russia, it is common to find low dose ozone being used to purify the air in hospitals, factories, airports, slaughterhouses and other places where poor quality air is common. Sensors are placed throughout the facilities to monitor the amount of ozone that is entering the rooms making the ozonated air safe for humans to breath.

Safety: Contraindications

- 1. All cases with Blood Coagulation Failure
- 2. Bleeding Organs
- 3. Thrombocytopenia
- 4. Ozone Allergy (I have not met one doctor who has seen this)
  - Possibly some respiratory sensitivity in some patients at very low levels
- 5. Hemorrhagic or Apoplectic Stroke
- 6. Ozone Intolerance (I have never seen this)
- 7. Recent Myocardial Infarction
- 8. Alcohol Intoxication

World Use of Medicine Ozone

Conference held in D.C. 1982, **Ozone is effective**…

- at removing bacteria and viruses from blood;
- in decontaminating blood products infected with hepatitis, HIV, and syphilis;
- in treating peripheral vascular disease; cardiovascular and cerebrovascular disease, arteriosclerosis, and hypercholesterolemia;
- at restoring circulation and relieving angina pain and **improving brain function**;
- at eliminating cancerous tumors, lymphomas and leukemia;
- for treating all forms of rheumatoid and arthritis collagen disease;
- in treating allergies;

World Use of Medicine Ozone

Conference held in D.C. 1982, **Ozone is effective**…

- at improving neurological diseases including senility, multiple sclerosis and Parkinson's disease;
- externally for treating burns, acne, leg ulcers, open cuts and wounds, eczema, fungal and other skin disorders;
- using rectal insufflation for proctitis, colitis, prostatitis and fissures;
- using vaginal insufflation for yeast infections like candidiasis and for vaginitis;
- using bladder insufflation for cystitis, bladder fistulas and cancer;

World Use of Medicine Ozone

Conference held in D.C. 1982, **Ozone is effective**…

- in treating AIDS, herpes, hepatitis, mononucleosis and cirrhosis of the liver.
- It activates the immune system in infectious diseases.
- It improves the cellular utilization of oxygen that reduces ischemia in cardiovascular diseases, and in many of the infirmities of aging.
- It causes the release of growth factors that stimulate damaged joints and degenerative discs to regenerate.
- It can dramatically reduce or even eliminate many cases of chronic pain through its action on pain receptors.

Other Research

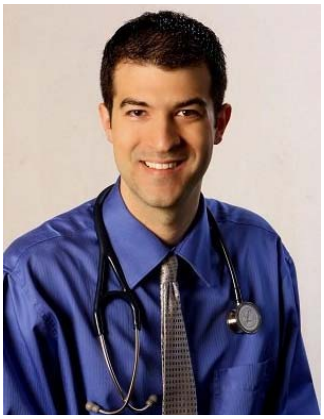
- Lancet. 2008 Jan 19;371(9608):228-36. doi: 10.1016/S0140-6736(08)60134-8. Results of a non-specific immunomodulation therapy in chronic heart failure (ACCLAIM trial): a placebo-controlled randomized trial.
- Neural Regen Res. 2013 Feb 15;8(5):461-8. doi: 10.3969/j.issn.1673-5374.2013.05.010. Major ozonated autohemotherapy promotes the recovery of upper limb motor function in patients with acute cerebral infarction.
- J Altern Complement Med. 2013 May;19(5):453-8. doi: 10.1089/acm.2012.0273. Epub 2012 Dec 7. Long-term improvement in refractory headache following ozone therapy.
- J Altern Complement Med. 2005 Apr;11(2):363-7. Major ozonated autohemotherapy in chronic limb ischemia with ulcerations.
- A protocol for the ischemic stroke in patients to be treated with major ozonated autohemotherapy (MOAHT) - http://neu.sagepub.com/content/26/3/243.short - Ischemic Stroke Penumbra and Extracorporeal Ozone Treatment

- Other ideas to improve results
  - Joint pain – foods
  - Sleep – EMF, wifi, lights, noise
  - Sleep hygiene, spouse, apnea, weight
  - Stress management
  - Caffeine
  - Rx drug evaluation
  - OTC evaluation
  - GMO, organophosphates
  - Heavy metal testing – improving cell membranes. Toxic profile testing, GI testing
  - Other IV therapy, Vit C – collagen, etc
  - MOVE! Exercise, demo in office. Video exercises.
  - Hormone replacement
  - EWOT, DC, Lac.
  - OA xrays actually an infection
  - Dental infections – root canals, wisdom teeth extractions – later cavitations. Biological dentist

Resources

- The Application of Ozone Therapy in Pain Management, Rheumatic and Orthopedic Diseases. Fahmy Z. German Medical
- Guide to the medical use of ozone therapy foundations and indications in Spanish Adriana Schwartz et al.. Asociación Española de Profesionales Médicos en
- Oxygen-Ozone Therapy: A Critical Evaluation. Bocci, Velio 472 pp. 1st Edition. 2010
- Ozone: A new medical drug. Bocci, Velio Netherlands 2010. 295 pages. 2010
- Ozone Oxygen Therapy A Practical Handbook. in German Viebahn-Hänsler,
- Ozone Therapy in Practice: Health Manual. Ministry of Health Service of the Russian
- Aspects of Ozone Therapy - Ozone Center Basic and Clinical Applications Menéndez Cepero, Silvia et al , La Habana, Cuba. (2008)
- Bocci Papers & Book – Ozone the new Medical Drug
- Ozone in Medicine: The Low-Dose Ozone Concept
- Ozone Therapy and Its Scientific Foundations ISC03
- Madrid Declaration
- Russian Ozone Therapy in Practice

NOTES



Brenden Cochran, N.D.

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Disclosure Statement:

Dr. Cochran has indicated that he has no relevant financial relationships with any commercial supporters.

Amino Acids, Homeopathics & Mesenchymal Cells

This presentation will focus on Homeopathic injectable that are currently available and how they can be used. The special topic lecture will talk briefly about amino acids with neurotransmitter support, cachexia and athletic performance. I will also mention briefly about the useage of IV biological allograph progenitor cell infusions and future potentials.

Learning Objectives:

At the conclusion of this activity you should be able to…

- Discuss safe applications of the substances and utilization in proper patient conditions.
- Apply additional therapies to your current treatment practice.

About Dr. Cochran

Dr. Brenden Cochran received his Doctorate in Naturopathic Medicine from Basytr University. He founded Interactive Health Clinic, a family practice with specialty focuses in pain, integrative oncology, chronic disease management, injection and intravenous therapies. He has additional training in IV therapy, Neural Therapy, Medical Ozone injections/Applications, Master Level Training in Neural Prolotherapy, and Biological Allograph Progenitor cells. He served as faculty at Bastyr University with a focus on Advance IV Therapy. He also served as the medical fellow/director of intravenous therapy at the Bastyr Integrative Oncology Research Center (BIORC), Bastyr University's cancer research center. He currently lectures with International IV Therapy for Professionals and guest lectures at many other venues. He is an instructor of Neural Therapy, Neural Prolotherapy (Perineural Injections), Ozone injections, Biological Allograph Progenitor cells to doctors around the world. As a keynote speaker and content creator, Dr. Cochran is dedicated to empowering doctors to build successful models in outcome-based medicine.

NOTES

Amino Acids, Homeopathics & Mesenchymal Cells

Brenden Cochran, ND

2017 – AAEM

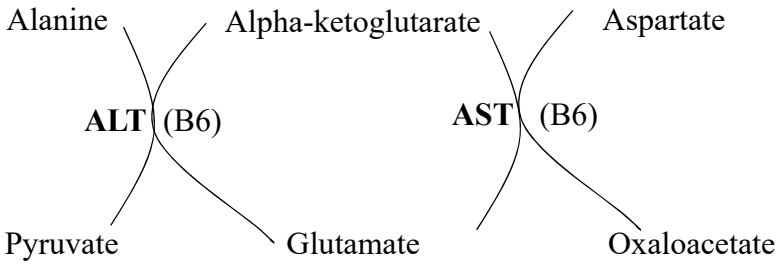
Under Accreditation Council for Continuing Medical Education guideline disclosure must be made regarding relevant financial relationships with commercial interests within the last 12 months.

Brenden Cochran, N.D.

Received an educational grant from ImprimixRX

Unless otherwise stated, the level of evidence is C and based on clinical experience.

Amino Acids



Trace minerals are also important in metabolism

Amino Acid mixtures

- Store in a dark place
- Peripheral dosing not to exceed 2.5% Amino Acid
  - This equals 100 ml of an 8.5% solution in 500 ml Sterile Water
  - In TPN (central line in hospital) may get 1-2 L. 8.5% solution in 24 hours
- Hyperosmolar solution in full strength
- Adverse effects:
  - Hyperglycemia (DM-1 patients may need increased insulin)
  - Increased liver function tests
  - Metabolic Acidosis
  - Flushing
  - Allergic Reactions

Neurotransmitter Precursors

Amino Acid	Neurotransmitter(s)
Cysteine	Cysteic acid
Glutamine	GABA, Glutamate
Histidine	Histamine
Lysine	Pipecolic acid
Phenylalanine	Dopamine, Norepinephrine, Epinephrine, Tyramine
Tyrosine	Dopamine, Norepi, Epi
Tryptophan, 5-HTP	Serotonin, Melatonin

Amino Acids as Neurotransmitters

Amino Acid	Function
Alanine	Inhibitory or calming
Aspartic acid	Excitatory
GABA	Inhibitory or calming
Glutamate	Excitatory
Glycine	Inhibitory or calming
Taurine	Inhibitory or calming

Brain Transmitter Physiology

- Uppers:
  - Serotonin
  - Acetylcholine
  - Norepinephrine
  - Epinephrine
  - Dopamine
  - Histamine**
  - [Glycine]**

- Downers:
  - GABA
  - Nitric Oxide
  - Neurosteroids
  - [Histamine]**
  - Glycine**

Balancing / Leveling: Serotonin – Glycine – Acetylcholine - Histamine

Amino Acid Infusions, Crystalline
Combination Products

Examples

- Aminosyn , Aminosyn II, Aminosyn-PF
- FreAmine III
- Novamine
- Travasol
- Trophamine

Amino Acid Infusions, Crystalline
Combination Products

Examples

- Aminosyn , Aminosyn II, Aminosyn-PF
- FreAmine III
- Novamine
- Travasol
- Trophamine

(c) 2017 Brenden Cochran, ND

Note – Caution with severe liver disease

- Some patients with severely compromised liver function may experience increased blood ammonia levels on receiving amino acids
  - Dose related
- This can result in severe encephalitis and can require treatment with dialysis

Aminosyn II, 8.5%

Essential Amino Acids in mg/100 ml

- Isoleucine 561
- Leucine 850
- Lysine 893
- Methionine 146
- Phenylalanine 253
- Threonine 340
- Tryptophan 170
- Valine 425

Aminosyn II, 8.5%

Non-essential Amino Acids in mg/100 ml

- Alanine 844
- Arginine 865
- L-Aspartic acid 595
- Glycine 425
- Histidine 255
- Proline 614
- Serine 450
- **N-Acetyl-L-Tyrosine** 230
- **L-Glutamic Acid** 627
- (Remember Glutamate and Tyrosine are excitable!)

FreAmine III, 10%

Essential Amino Acids in mg/100 ml

- Isoleucine 690
- Leucine 910
- Lysine 730
- Methionine 530
- Phenylalanine 560
- Threonine 400
- Tryptophan 150
- Valine 660

FreAmine III, 10%

Non-essential Amino Acids in mg/100 ml

Alanine 710	Arginine 950
Cysteine 16	Glycine 1400
Histidine 280	Proline 1120
Serine 590	

FreAmine III, 10%

Non-amino acid constituents per 100 ml

- Phosphoric acid NF 120 mg
- Sodium bisulfite < 100 mg
- SWUSP qs
- pH adjusted with glacial acetic acid USP to pH 6.5 (6.0-7.0)
- Calculated osmolarity 950 mOsm/L

Clinisol, 15% (sulfite free)

Essential Amino Acids in mg/100 ml

- Lysine 1180
- Leucine 1040
- Phenylalanine 1040
- Valine 960
- Isoleucine 749
- Tryptophan 250
- Methionine 749
- Threonine 749

Clinisol, 15% (sulfite free)

Non-essential Amino Acids in mg/100 ml

- Alanine 2170
- Glutamic Acid 749
- Tyrosine 39
- Serine 592
- Histidine 894
- Arginine 1470
- Glycine 1040
- Proline 894
- Aspartic Acid 434

Clinisol, 15% (sulfite free)

Non-amino acid constituents per 100 ml

- Total Nitrogen 2037 mg
- SWUSP qs
- pH adjusted with glacial acetic acid USP to pH 6.0 (5.0-7.0)
- Calculated osmolarity 1357 mOsm/L

Premasol, 6% or 10% (sulfite free)

Essential Amino Acids in mg/100 ml

Lysine 490/820
Leucine 840/1400
Phenylalanine 290/480
Valine 470/780
Isoleucine 490/820
Tryptophan 120/200
Methionine 200/340
Threonine 250/420

Premasol, 6% or 10% (sulfite free)

Non-essential Amino Acids in mg/100 ml

Alanine 320/540	Arginine 730/1200
Glutamic Acid 300/500	Glycine 220/360
Tyrosine 140/240	Proline 410/680
Serine 230/380	Aspartic Acid 190/320
Histidine 290/480	Cysteine 14/16
Taurine 15/25	

Clinisol, 15% (sulfite free)

Non-amino acid constituents per 100 ml

- Total Nitrogen 930/1550 mg
- SWUSP qs
- pH adjusted with glacial acetic acid USP to pH 5.5 (5.0-6.0)
- Calculated osmolarity 520/865 mOsm/L

Amino Acid Infusions, Crystalline
Combination Product Dosing

Nutritional IV Therapy

- Common dosage is 100 ml 10% FreAmine III, Aminosyn II, 8.5% solution, Premasol 6%/10% or adjusted Clinisol 15%
- Provides 8.5-10 grams AA
- Limit peripheral infusions to 2.5% AA (Nurses Drug Handbook 2000, p. 1140)
- 100 ml 10% diluted in 400 ml sterile water, is a 2.0% AA solution

Amino Acid Infusions, Crystalline
Combination Product Adverse Reactions

- CV: thrombophlebitis, thrombosis, edema
- GI: nausea
- GU: glycosuria, osmotic diuresis
- Hepatic: increased liver enzymes
- Skin: flushing
- Other: hypersensitivity reactions, hyperglycemia, metabolic acidosis

Case 1

- 52 yr female with controlled hepatitis C
- Complains of fatigue and lack of endurance during her runs. Usually runs 2-3 miles used to do 8-12 miles.
- Infusions with 50-100 ml Aminosyn 8.5% and nutrients along with added lysine, carnitine, and glycyrrhizic acid. Infusions were given twice per week for 3 weeks and then once a week for additional 6 weeks.
- After the 6-8 infusion patient reports energy improvements and able to now do 8-10 mile run without severe fatigue and exhaustion.

Current Research Delineates many benefits of Oral or IV Arginine

Arginine metabolism and nutrition in growth, health and disease.

Wu G, et.al.

Amino Acids. 2009 May;37(1):153-68

L-Arginine (Arg) is synthesised from glutamine, glutamate, and proline via the intestinal-renal axis in humans and most other mammals (including pigs, sheep and rats). Arg degradation occurs via multiple pathways that are initiated by arginase, nitric-oxide synthase, Arg:glycine amidinotransferase, and Arg decarboxylase. These pathways produce nitric oxide, polyamines, proline, glutamate, creatine, and agmatine with each having enormous biological importance. Arg is also required for the detoxification of ammonia, which is an extremely toxic substance for the central nervous system. There is compelling evidence that Arg regulates interorgan metabolism of energy substrates and the function of multiple organs. The results of both experimental and clinical studies indicate that Arg is a nutritionally essential amino acid (AA) for spermatogenesis, embryonic survival, fetal and neonatal growth, as well as maintenance of vascular tone and hemodynamics. Moreover, a growing body of evidence clearly indicates that dietary supplementation or intravenous administration of Arg is beneficial in improving reproductive, cardiovascular, pulmonary, renal, gastrointestinal, liver and immune functions, as well as facilitating wound healing, enhancing insulin sensitivity, and maintaining tissue integrity. Additionally, Arg or L-citrulline may provide novel and effective therapies for obesity, diabetes, and the metabolic syndrome. The effect of Arg in treating many developmental and health problems is unique among AAs, and offers great promise for improved health and wellbeing of humans and animals.

L-Arginine

A review of 17 sets of data from 11 different randomized controlled trials showed Growth Hormone increases with Intravenous Arginine and NOT oral Arginine.

Dosage:

- One oral group taking 170 mg/kg orally note a 4 fold GH increase.
  - Side effect stomach cramps and diarrhea
- Intravenous dosages were generally 0.5 mg/kg without SE picture. Up to a 13 fold GH increase was noted.
- Finding were 90 minutes after oral dose or infusion dosage.

Chromiak JA, Antonio J. Use of amino acids as growth hormone-releasing agents by athletes. *Nutrition*. 2002;18(7-8):657-661.

L-Carnitine

- Acetyl-L-Carnitine can increase intramuscular carnitine.
- Insulin plays an important role in moving carnitine into the muscle.
- Once in the muscle carnitine regulates acety-CoA/CoAsh and beta-oxidation.
  - These are critical in delaying muscle fatigue.
- Increased intramuscular carnitine causes glucose to be stored as glycogen and inhibited glycolytic flux (reducing lactate levels).
- Most impact is noticed in athletes working above VO2max 70%.
  - Thus delaying fatigue and increasing exercise performance.

L-Carnitine

- Stephens FB, Constantin-Teodosiu D, Laithwaite D, et al. Insulin stimulates L-carnitine accumulation in human skeletal muscle. *FASEB J*. 2006;20(2):377-379.
- Stephens FB, Galloway SD. Carnitine and fat oxidation. *Nestle Nutr Inst Workshop Ser*. 2013;76:13-23.
- Stephens FB, Constantin-Teodosiu D, Laithwaite D, et al. An acute increase in skeletal muscle carnitine content alters fuel metabolism in resting human skeletal muscle. *J Clin Endocrinol Metab*. 2006;91(12):5013-5018.
- Mackay-Timmermans, Drew and Etcheverry, Chase. Nutrition for Athletes: Making a Case for IV Nutrient Supplementation. NDNR. November 2015

L-Glutamine

- 30 mg/ml
- Most common AA in body
- Primary fuel source for immune system, intestines and colon
- Maintain and support GSH levels
- IV dosages up to 0.5 mg/kg

Eur J Appl Physiol Occup Physiol. 1996;73(5):488-90.
Does glutamine have a role in reducing infections in athletes?
Castell LM[1], Poortmans JR, Newsholme EA.

Abstract
There is an increased risk of infections in athletes undertaking prolonged, strenuous exercise. There is also some evidence that cells of the immune system are less able to mount a defense against infections after such exercise. The level of plasma glutamine, an important fuel for cells of the immune system, is decreased in athletes after endurance exercise; this may be partly responsible for the apparent immunosuppression which occurs in these individuals. We monitored levels of infection in more than 200 runners and towers. The levels of infection were lowest in middle-distance runners, and highest in runners after a full or ultramarathon and in elite rowers after intensive training. In the present study, athletes participating in different types of exercise consumed two drinks, containing either glutamine (Group G) or placebo (Group P) immediately after and 2 h after exercise. They subsequently completed questionnaires (n = 151) about the incidence of infections during the 7 days following the exercise. The percentage of athletes reporting no infections was considerably higher in Group G (81%, n = 72) than in Group P (49%, n = 79, p < 0.001).

Dosing and Efficacy of Glutamine Supplementation in Human Exercise and Sport Training[1,2]
Michael Gleeson[*]

Abstract
Some athletes can have high intakes of L-glutamine because of their high energy and protein intakes and also because they consume protein supplements, protein hydrolysates, and free amino acids. Prolonged exercise and periods of heavy training are associated with a decrease in the plasma glutamine concentration and this has been suggested to be a potential cause of the exercise-induced immune impairment and increased susceptibility to infection in athletes. However, several recent glutamine feeding intervention studies indicate that although the plasma glutamine concentration can be kept constant during and after prolonged strenuous exercise, the glutamine supplementation does not prevent the postexercise changes in several aspects of immune function. Although glutamine is essential for lymphocyte proliferation, the plasma glutamine concentration does not fall sufficiently low after exercise to compromise the rate of proliferation. Acute intakes of glutamine of ~20–30 g seem to be without ill effect in healthy adult humans and no harm was reported in 1 study in which athletes consumed 28 g glutamine every day for 14 d. Doses of up to 0.65 g/kg body mass of glutamine (in solution or as a suspension) have been reported to be tolerated by patients and did not result in abnormal plasma ammonia levels. However, the suggested reasons for taking glutamine supplements (support for immune system, increased glycogen synthesis, anticatabolic effect) have received little support from well-controlled scientific studies in healthy, well-nourished humans.

L-Glutamine & The Brain

- Glutamine is a derivative of glutamic acid, chemical name glutamic acid 5-amide
- Glutamine can more easily pass through the blood brain barrier than glutamic acid
  - Glutamine + glutamate synthetase → glutamate
- Glutamate is the most common neurotransmitter in the brain and is always excitatory
- If patients receiving glutamine can't sleep, they may be over expressing the conversion to glutamate
  - This tendency can be decreased by giving organic lithium, e.g. Lithium orotate, 20 mg q.d.

Taurine

- **Helps maintain cellular mineral transport and levels**
  - **Works with Na and Ca channels, as well as multiple mineral transport channels**
- Works as a membrane stabilizer and specifically acts to functionally stabilize Ca++ in cardiocytes.
  - Helps in cardiac protection during excessive and inadequate Ca++
  - Appears to protect against Ca++ dependent cardiac cellular damage
  - Modulates voltage gated Ca++ channels and Na+ channels

Amino Acids. 2004 Mar;26(2):203-7. Epub 2003 May 9.

Role of taurine supplementation to prevent exercise-induced oxidative stress in healthy young men.

Zhang M[1], Izumi I, Kagamimori S, Sokejima S, Yamagami T, Liu Z, Qi B.

⊕ Author information

Abstract

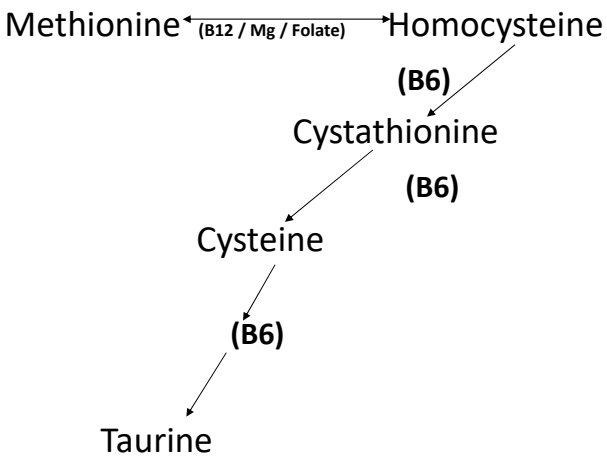
To evaluate the protective effects of taurine supplementation on exercise-induced oxidative stress and exercise performance, eleven men aged 18-20 years were selected to participate in two identical bicycle ergometer exercises until exhaustion. Single cell gel assay (SCG assay) was used to study DNA damage in white blood cells (WBC). Pre-supplementation of taurine, a significant negative correlation was found between plasma taurine concentration before exercise and plasma thiobaribituric-acid reactive substance (TBARS) 6 hr after exercise ($r = -0.642$, $p<0.05$). WBC showed a significant increase in DNA strand breakage 6 hr and 24 hr after exercise. Seven-day taurine supplementation reduced serum TBARS before exercise ($p<0.05$) and resulted in a significantly reduced DNA migration 24 hr after exercise ($p<0.01$). Significant increases were also found in VO(2)max, exercise time to exhaustion and maximal workload in test with taurine supplementation ($p<0.05$). After supplementation, the change in taurine concentration showed positive correlations with the changes in exercise time to exhaustion and maximal workload. The results suggest that taurine may attenuate exercise-induced DNA damage and enhance the capacity of exercise due to its cellular protective properties.

Taurine

- Prevents Na/K ATPase Suppression
- Tissues specifically targeted:
  - Skeletal, Cardiac and smooth muscle
  - Liver
  - Eye
  - Brain
- Dose is 200 to 2000 mg
  - up to 20 Grams IV dosed without toxicity

See the excellent review by Birdsall, AltMedRev, Vol3 No2, 1998

Taurine Synthesis



Taurine: Research Overview

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Chazov, et. al., Taurine and Electrical Activity of the Heart, Supplement III to Circulation Research, Vols. 34 and 35. September 1974.

Eby , Halcomb; Elimination of cardiac arrhythmias using oral taurine with L-arginine with case histories: Hypothesis for nitric oxide stabilization of the sinus node; Medical Hypotheses (2006) http://intl.elsevierhealth.com/journals/mehy

El-Sherbeny, et. al., Osmoregulation of Taurine Transporter Function and Expression in Retinal Pigment Epithelial, Ganglion, and Mu¨ller Cells, Investigative Ophthalmology & Visual Science, February 2004, Vol. 45, No. 2

J.D. Militante et al.; The role of taurine in the pathogenesis of the cardiomyopathy of insulin-dependent diabetes mellitus; Cardiovascular Research 46 (2000) 393 –402

Nobuhisa, et. al.; Acute haemodynamic effect of taurine on hearts in vivo with normal and depressed myocardial function; Cardiovasc Res (1987) 21 (4): 241-247. doi: 10.1093/cvr/21.4.241

Rahimi AR, et. al.; Taurine: effect on myocardial relaxation; Clin Exp Pharmacol Physiol. 1989 Jan;16(1):41-7.

Satoh H, Nakatani T, Tanaka T, Haga S.; Cardiac functions and taurine's actions at different extracellular calcium concentrations in forced swimming stress-loaded rats; Biol Trace Elem Res. 2002 Summer;87(1-3):171-82.

Taurine: Research Overview

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Alvarellos, O et al., A series of case reports: clinical evaluation of a complex homeopathic injection therapy in the management of pain in patients after breast cancer treatment. Altern Ther Health Med. 2010 Jan-Feb; 16(1):54-9

Steinmannn, D et al. Effect of Traumeel S on pain and discomfort in radiation-induced oral mucositis: a preliminary observational study. Altern Ther Health Med. 2012 Jul-Aug; 18(4): 12-8.

Bossche, L, Vanderstraeten G. A multi-center, double-blind, randomized, placebo-controlled trial protocol to assess Traumeel injection vs dexamethasone injection in rotator cuff syndrome: the Traumeel in Rotator cuff syndrome study protocol. BMC Musculoskelet Disord. 2015 Feb 4;16:8.

Amino Acids (Collagen Support)

- **Lysine**
  - Dose 100 – 800 mg
- **Proline**
  - Dose 100 – 800 mg
- **Glycine**
  - Dose 100 – 1000 mg

Athlete Mini

Volume: 303 ml Osmolarity: 579 mOsm/L

	250 mL	Sterile Water		2 ml	L-Carnitine (1000 mg)
	10 mL	C-500 (5 grams)		3 mL	B-100 Complex
	2 mL	Magnesium Chloride (2.63 mEq)		5 ml	8.4% Na Bicarbonate
	1 ml	Calcium Chloride (1.36 mEq)		1 ml	Methyl-B12 (10 mg)
	1 ml	Potassium Chloride (2 mEq)			
	2 ml	Taurine (100 mg)		1 ml	Pyridoxine (100 mg)
	3 ml	Proline (150 mg)		1 ml	Dexpanthenol (250 mg)
	2 ml	Lysine (200 mg)		10	Arginine (1000 mg)
	4 ml	Glycine (100 mg)			
	3 ml	Prolo or Connective Tissue Homeopathic		2 ml	Zinc chloride or sulfate (20 mg)

Infusion Time: 45-60 minutes

Rx: Rehydration 500 mL plus Amino Acids

Total Volume: 598 mL Osmolarity: 285 mOsm/L

	500 mL	Sterile Water		1 mL	Pyridoxine / B-6 (100mg)
	5 mL	C-500 (2.5 grams)		3 mL	B-100 Complex
	6 mL	Calcium Chloride (8.16 mEq)		2 mL	Dexpanthenol / B-5 (500mg)
	10 mL	Magnesium Chloride (19.7 mEq)		0.5 mL	5MTHF (2.5 mg)
	4 mL	Potassium Chloride (8 mEq)		2 mL	Methyl-B12 (10 mg)
	15 mL	8.4% Sodium Bicarbonate		50 mL	Aminosyn 8.5% Solution
	*	10 – 30 mg Zinc			
	*	100 – 200 mcg Molybdenum			

Infusion Time: 45-60 minutes

Homeopathics

Homeopathics

- In my clinical experience they compliment your nutrient therapies and are best to give along side.
- They can be given as intramuscular, subcutaneous (segmental) or intravenous.
- Remember since they are glass ampoules:

1) Clean the outside with alcohol
2) Use a filter needle (one way filter)

Homeopathics

- **Engystol:** Echinacea. Immune stimulant specifically best viral.
- **Traumeel:** Bruising, injury or pain, inflammation
- **Lymphomyosot:** Edema, lymphatic movement
- **Zeel:** Relief of arthritic pain
- **Neuralgo Rheum:** Chronic arthritis, neuralgia
- **Spascupreel:** Muscle spasms, trigger point

Homeopathics

- **Arnica:** Muscle pain, bruising, stiffness
- **Hepar comp:** Liver and biliary support
- **Gelsemium:** Nerve pain
- **Calmvalera:** Anxiety, Depression, mental exhaustion, insomnia, restlessness
- **Lymphaden:** Edema or swollen lymph nodes

Homeopathics (Compounded)

Systemic Detox: All organ support
Mesenchyme: Connective tissue, matrix, lymphatics
Lymph: Lymph specific drainage
Liver: Liver drainage
Ki-UB: Kidney drainage
GI: Small and large intestine drainage
Infla: Calms inflammation
Intra-Cell: Improves metabolism and energy
Female+: Endocrine support
Male+: Endocrine support
Relief+: Calm emotional reactions
Thyro: Thyroid support
Collagen, Articula, Connectissue, MuSkel, Prolo: Connective tissue specific
Prolo Neural: Nerve inflammation

Mesenchymal Stem Cells

Biologic Allograft

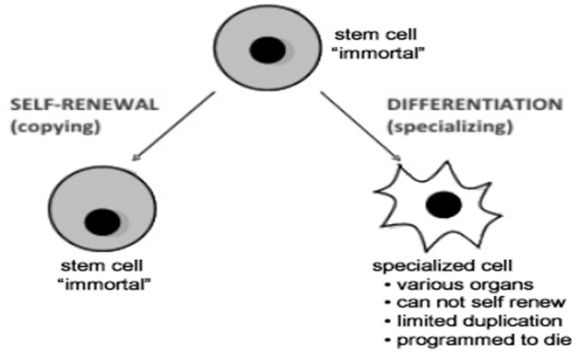
- -Understand Tissue Viability and why more cells per CC may not be better
- -Use the best delivery system for IV or Injections
- -Do Fat and Bone stem cells produce the same results when you age?
- -At birth 1 stem cell will produce 1 billion healthy cells a month (Neil Riordan, PhD)
- -By age 60 one stem cell produces 200 Healthy cells a month (Neil Riordan, PhD)
- -Activate the bodies own stem cells for regeneration
- -300 million cells die every minute in the body
- -The body rebuilds all the cells in 5 to 7 years

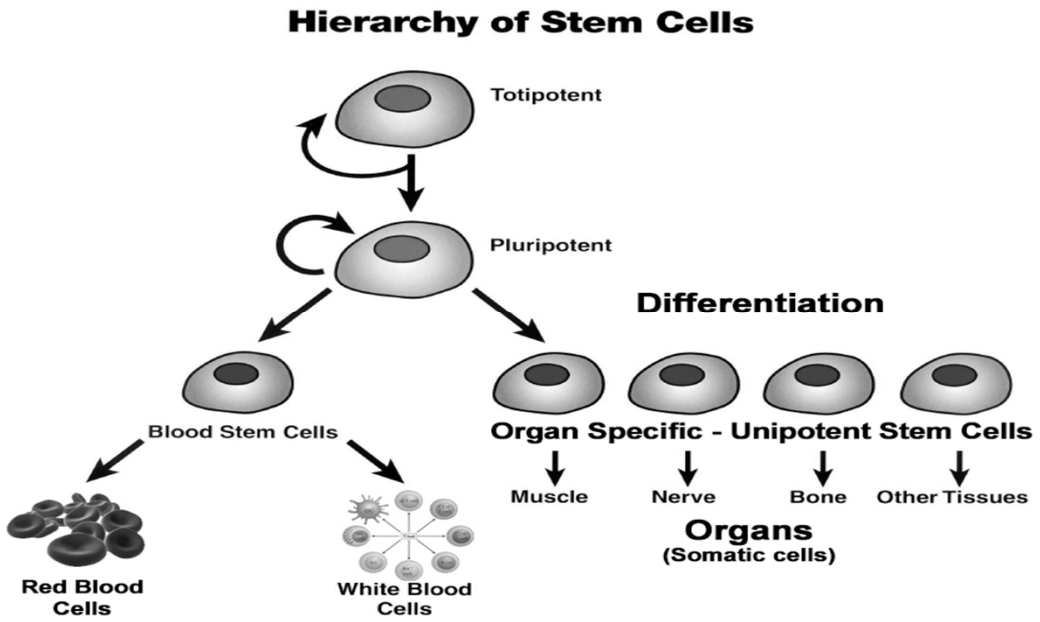
Case 2

- 81 yr old male developed severe dementia and malnourishment. History of radical prostatectomy and testosterone deprivation therapy for prostate cancer in 60's. Difficulty walking, mostly wheel chair and when he was trying to walk or sit would freeze.
- Interventions:
  - Corrected very low testosterone
  - Added pregnenolone
  - Provided push of experimental mesenchymal stem cells following with IV nutrients (amino acids included).
  - Continued weekly hydration and nutrients with amino acids.
  - 6 weeks patient begins to walk without wheelchair. Appetite has returned and no longer needing nutrient infusions. Dementia has improved, still present. The home health nurses commenting that his function has improved which in their careers they don't usually see in stage he initially presented.
  - Future: Patient needs repeat MSC infusion every 2-3 weeks.

Tissue Turnover

- Cells are programmed to die and be replaced.
- Stem Cells are the engine of regeneration.





Sources of Stem Cells

- Embryonic Stem Cell
- Placental / Cord Stem Cell
- Adult Stem Cell (organ)
    - A. Bone marrow
    - B. Blood
    - C. Fat

Adult Stem Cells

1. Harvested from the patient
2. Cleansed
3. Administered / injection

Concerns

1. Pain
2. Infection
3. Contamination
4. Tired / limited potential

Adult Stem Cell	Cord Stem Cell
30 days =	30 days =
200 cells	1 billion cells
	
14 inches	1,100 miles

Umbilical cord
Mesenchymal Stem Cells
Function

1. Homing to damaged tissue
2. Attach to micro-capillaries
3. Do not engraft
4. Release messaging molecules

Medicinal signaling cells - magic soup

Umbilical cord
Mesenchymal Stem Cells
Key Properties

1. Reduce inflammation
2. Modulate autoimmune dysfunction
3. Stimulate regeneration
4. Immune privileged
5. Tumor-ocidal

Programmed cell death

coordinated with

Ongoing cellular turnover

creates

Organ regeneration

A very good thing!

Mesenchymal Stem Cells

- **Mesenchymal stem cells (MSCs) are self-renewing, multipotent progenitor cells with multilineage potential to differentiate into cell types of mesodermal origin, such as adipocytes, osteocytes, and chondrocytes.**
- MSCs can migrate to sites of inflammation and exert potent immunosuppressive and anti-inflammatory effects through interactions between lymphocytes associated with both the innate and adaptive immune system
- In the clinical setting, MSCs are being explored in trials of various conditions, including orthopedic injuries, graft versus host disease following bone marrow transplantation, cardiovascular diseases, autoimmune diseases, neurological and liver diseases.
- The Korean Journal of Internal Medicine 2013; 28(4): 387-402.
- Published online: July 01, 2013
- PubMed ID: 23864795

Therapeutic potential of mesenchymal stem cell based therapy for osteoarthritis

- Conclusions: Current treatment strategies for OA are inadequate and costly. Due to the increasing incidence and prevalence of OA, more innovative and effective therapeutic modalities need to be investigated, including MSCs.
- More randomized clinical trials need to be completed in order to demonstrate the efficacy, safety, and benefits of MSCs in treating patients with OA. Most of MSC research on humans only involves knee OA, and additional analysis should include clinical trials for ankle OA, shoulder OA, hip OA, and elbow OA.
- MSC-based cellular therapy has the potential and opportunity to effectively combat OA, but more extensive clinical trial and animal studies are required to understand the basic molecular mechanisms of MSC dependent cartilage regeneration. Further research is also necessary to better understand the potential of MSC-derived exosomes in the treatment of OA
- Burke et al. Clin Trans Med (2016) 5:27

Mesenchymal stem cell therapy for osteoarthritis: current perspectives

- Arthritis is the most common source of disability among adults in the United States; in 2003, the disease afflicted 50 million Americans and this number is expected to increase to 67 million by 2030.5,6 The cost attributable to arthritis in the United States in 2003 was $128 billion, a figure that will certainly increase in conjunction with health care cost inflation and the number of patients projected to be afflicted with degenerative joint disease.6 Complicating this reality are the limited treatment options for OA. 2016--????
- Mesenchymal stem cells (MSCs) have been proposed as an optimal regenerative cellular therapeutic for degenerative musculoskeletal conditions like OA.16 These cells are found in a variety of tissues and have the ability to rapidly proliferate and differentiate to musculoskeletal lineages including bone and cartilage.17 A significant body of research has also demonstrated that these cells orchestrate important immunologic functions through modulation of the local inflammatory response. Taken together, these factors support the theoretical ability of MSCs to deter degenerative joint disease
- Mayo Medical School, 2Department of Orthopedic Surgery, 3Division of Cardiovascular Diseases, Mayo Clinic, Rochester, MN, USA

MSCs are among the most promising candidates for future regenerative medicine regimens. They can be obtained from many different adult tissue sources, are easy to isolate readily adapt to culture conditions, and undergo to rapid in vitro expansion. Besides their multipotency,

MSCs possess strong paracrine activity; they release a broad spectrum of molecules that affect angiogenesis, inflammation and immunity. Thus they appear to play a central role in controlling tissue homeostasis and in participating in tissue regeneration.

For these reasons MSCs offer a large number of possible applications for the treatment of many diseases. Since they have been included among AMT products, they are subjected to the same conditions that govern the production and use of drugs.

Freitag et al. BMC Musculoskeletal Disorders (2016) 17:230 DOI 10.1186/s12891-016-1085-9

FDA Insert Requirements

- Cryopreserved Human Amniotic Allograft
- **Product Instructions and Information**
- In accordance with FDA Article 21 CFR Part 1271, this package contains human cells, tissues, and cellular and tissue-based products (HCT/P).
- **Contraindications**
- Product should NOT be injected into the spinal canal, vital organs (including the heart and other areas of the central nervous system), nor the circulatory system. This product is not intended to be used as a bone substitute. Product should NOT be injected in the area of, or patients with, active infections nor patients that have conditions that would cause substantial risk to the health of patients using this product. Product has not been tested in combination with other products.

FDA and "Stem Cells"

- Biological Allograft cells engage the patient's own Dormant Stem Cells to cause a Dedifferentiation of their own cells.

-MSC's are not really stem cells

-Progenitor cells help activate your host stem cells

-Cord blood may have protein markers

-Many labs are approved by the FDA for transplant level purity

-No procedures are FDA approved

interactive
HEALTH CLINIC

Proactive Medicine that Rejuvenates You

16108 Ash Way, Suite 107 Lynnwood, WA 98087 425.361.7945

Thank you

Questions?

NOTES

NOTES