Therapeutic Synergy with Hyperbaric Medicine:
Clinical experiences in enhancing HBOT effects.

Dr. Paul Anderson

HBOT 2018 - 12th Annual International Symposium

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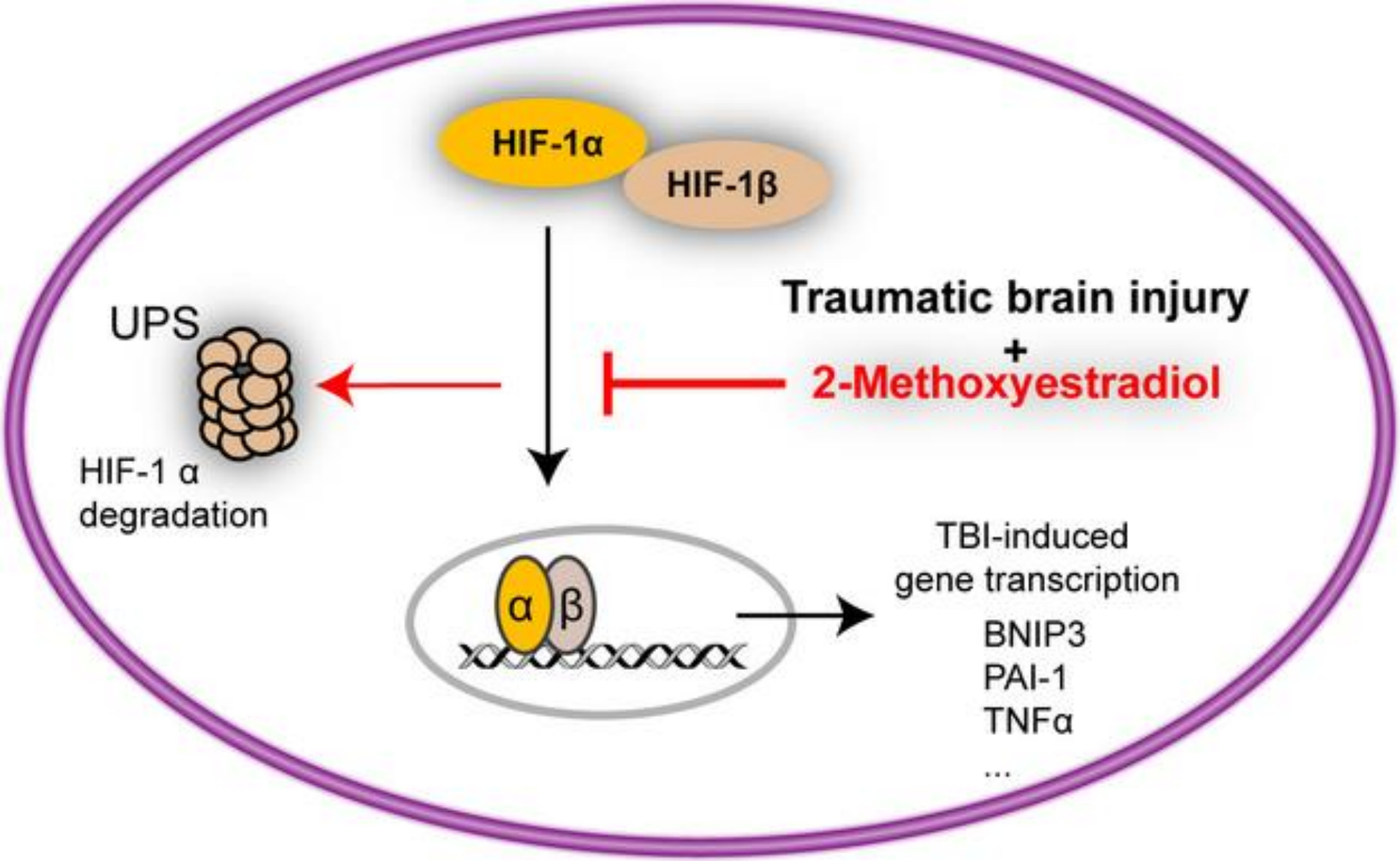
Abstract

Although very little is currently published regarding the use of synergists with HBOT it is an area of great clinical curiosity. For example some animal data using oxidative IV therapies in conjunction with HBOT which showed benefit have had to be modified when transferred to human protocols. Other therapies which have shown theoretical promise have exhibited synergy with HBOT and are emerging as future directions to clinically augment the benefits of HBOT.

Dr. Anderson has many years in clinical research and clinical correlation with many of these potentially synergistic therapies and will share from both published data as well as direct patient care experience.

Targets?

Hypoxia


HIF-1α
HIF-1β
UPS
HIF-1 α
degradation
Traumatic brain injury
+
2-Methoxyestradiol
α
β
TBI-induced
gene transcription
BNIP3
PAI-1
TNFα
...

LAMC Lowers HIF-1

- https://www.scribd.com/document/153860000/Antonawich-Metabolically-Targeted-Therapy
- LAMC Attenuates Hypoxia Inducible Factor (HIF-1) expression in Glioblastoma Multiforme In Vitro. (2007) Townsend Letter, August/September: 107-111.

DCA and HIF-1
Pulmonary Hypertension; J&P Voelkel ISBN-10: 1607950375

Metabolic Modulators

Normalizing the disrupted mitochondria-ROS-HIF-1α-Kv1.5O_2-sensing pathway may be a novel therapeutic option for PAH. Dichloroacetate restores oxidative metabolism in PASMC by inhibiting pyruvate dehydrogenase kinase. Currently dichloroacetate is safely used in children with inherited mitochondrial disorders and lactic acidosis.[165,166] Oral dichloroacetate, when administered to PASMC from FHR and human PAH patients, corrected the mitochondrial-HIF-Kv pathway,[8] reversed the hypoxic phenotype of FHR, restored the relatively depolarized $\Delta\Psi m$ of PASMCs and increased ROS production to normoxic levels. This in turn reversed HIF-1α activation and restored Kv1.5 gene expression. Dichloroacetate therapy also reversed experimental PAH induced by hypoxia (Figure 3.12), monocrotaline, and by transgenic overexpression of the serotonin receptor.[6,127,130] Thus, dichloroacetate may be a promising therapeutic agent for PAH.

Genomic Therapies

Genome

- O2
- Nutrigenomics
  - Assess SNP + Epigenetic patterns
  - Modulate and balance weak genomics
- Genomic Regulators
  - Ascorbate
  - Curcumin
  - Boswellia
  - etc.

Published in final edited form as:

Annu Rev Nutr. 2015 July 17; 35: 545–564. doi:10.1146/annurev-nutr-071714-034228.

Regulation of the Epigenome by Vitamin C

Juan I. Young[1], **Stephan Züchner**[1], and **Gaofeng Wang**[1,2,*]

52 *Current Genomics*, 2010, *11*, 52-57

Ascorbic Acid and Gene Expression: Another Example of Regulation of Gene Expression by Small Molecules?

Sophie Belin[1], Ferdinand Kaya[1,2], Stéphane Burtey[1] and Michel Fontes*,[1]

Journal of Translational Science

open access text

Research Article ISSN: 2059-268X

Gene expression response to ascorbic acid in mice implanted with sarcoma S180 cells

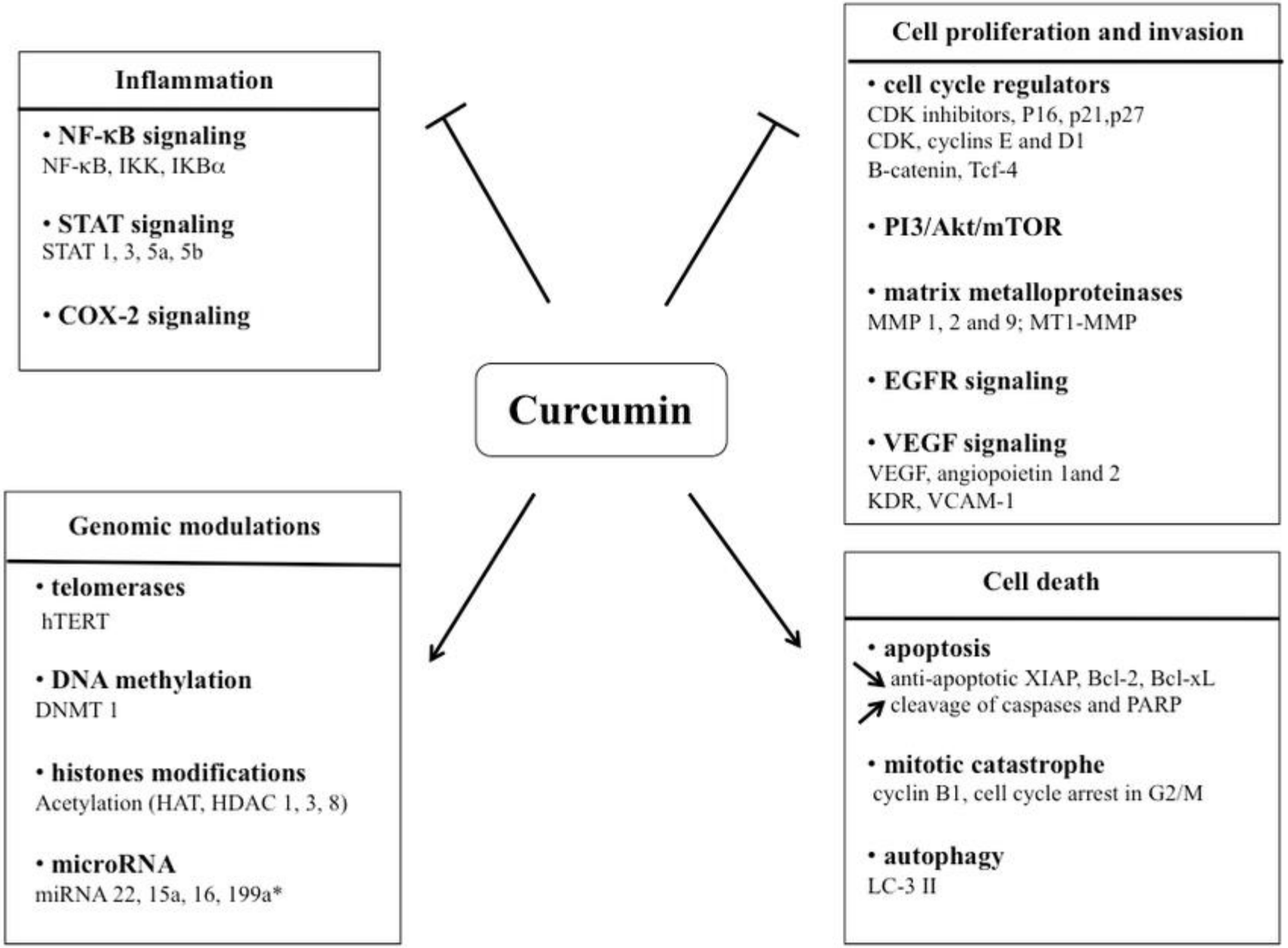
Nina Mikirova[§*] and Ruth C. Scimeca[§]

OPEN ACCESS Freely available online

PLoS NEGLECTED TROPICAL DISEASES

Ascorbic Acid Has Superior Ex Vivo Antiproliferative, Cell Death-Inducing and Immunomodulatory Effects over IFN-α in HTLV-1-Associated Myelopathy

Britta Moens[1*], Daniele Decanine[2¤a], Soraya Maria Menezes[1], Ricardo Khouri[1,2], Gilvanéia Silva-Santos[2¤b], Giovanni Lopez[3], Carolina Alvarez[1,3], Michael Talledo[3], Eduardo Gotuzzo[3,4], Ramon de Almeida Kruschewsky[5], Bernardo Galvão-Castro[2,5], Anne-Mieke Vandamme[1,6], Johan Van Weyenbergh[1,2]



DOI: 10.3390/toxins2010128

Intravenous Ascorbate

and

HBOT

Janine M. DeBlasi, Nathan P. Ward, Angela M. Poff, Andrew P. Koutnik, Christopher Q. Rogers and Dominic P. D'Agostino. **Anti-Cancer Effects of Ascorbic Acid and Hyperbaric Oxygen Therapy in vitro.** The FASEB Journal April 2017 vol. 31 no. 1 Supplement 879.4

[Truncated] - This study's aims are as follows:

(1) to examine the anticancer effect of AA in vitro

(2) to evaluate the mechanism of AA-induced OxS

(3) to investigate the potential synergy between AA and HBOT. We anticipate that this approach will yield significant insight into and further investigate the hypothesis that AA and HBOT can supplement the current standard of care.

Janine M. DeBlasi, Nathan P. Ward, Angela M. Poff, Andrew P. Koutnik, Christopher Q. Rogers and Dominic P. D'Agostino. **Anti-Cancer Effects of Ascorbic Acid and Hyperbaric Oxygen Therapy in vitro.** The FASEB Journal April 2017 vol. 31 no. 1 Supplement 879.4

This data indicates that:

AA exhibits anti-cancer effect in vitro through an OxS mechanism and that HBOT can enhance this therapeutic effect.

These non-toxic, pro-oxidant metabolic therapies should be **further investigated** as adjuvants to the current standard of care.

Clinical Experience with HDIVC and HBOT?

- For three years at the hospital and outpatient center we have run High Dose IV Vitamin-C (HDIVC) with HBOT on the same day.
- The typical protocol is HBOT dive then HDIVC administration.
- In all those administrations we have had few to no complaints of adverse effects.

Clinical Experience with HDIVC and HBOT?

I fielded this question from a clinic in California:

"I have a breast cancer patient receiving HDIVC 50g, also going for hyperbaric therapy. On the days she gets IV prior to hyperbarics, she has an intense peripheral neuropathy as well as pain near her IV port. It doesn't occur when she doesn't get an IV that day."

Clinical Experience with HDIVC and HBOT?

The difference?

- Our protocols (either hard or soft side chambers) start at 1.3 – 1.5 ATA and 45 min dive. We increase dose and time as tolerated.

- This center went directly to 2.0 ATA at 75 minutes.

Data for consideration:

COMPREHENSIVE PHYSIOLOGY

Hyperbaric Environment: Oxygen and Cellular Damage versus Protection

Angela M. Poff,[1] Dawn Kernagis,[2] and Dominic P. D'Agostino[*1,2]

ABSTRACT

The elevation of tissue pO_2 induced by hyperbaric oxygen (HBO) is a physiological stimulus that elicits a variety of cellular responses. These effects are largely mediated by, or in response to, an increase in the production of reactive oxygen and nitrogen species (RONS). The major consequences of elevated RONS include increased oxidative stress and enhanced antioxidant capacity, and modulation of redox-sensitive cell signaling pathways. Interestingly, these phenomena underlie both the therapeutic and potentially toxic effects of HBO. Emerging evidence indicates that supporting mitochondrial health is a potential method of enhancing the therapeutic efficacy of, and preventing oxygen toxicity during, HBO. This review will focus on the cellular consequences of HBO, and explore how these processes mediate a delicate balance of cellular protection versus damage. © 2017 American Physiological Society. *Compr Physiol* 7:213-234, 2017.

Intravenous Ascorbate & HBOT Experiences

- Background dosing of oral ascorbate is advised. “Bowel tolerance” (which changes daily) is the upper limit BUT 1-2 grams 2-3X a day is a good target.
- GSH and LAMC can be sequenced SAME day as Lower dose and Alternate day from Higher dose IVC.

Ascorbate – HBOT Experiences

- IV Ascorbate + HBOT:
  - **Low dose strategies** (under 25 grams with other nutrients followed by GSH, LAMC etc.) pair with **HBOT ATA from 1.3 to 2.5** in our experience. Similar to the IV mentioned in the above case.
  - **High dose strategies** (over 25 grams normally just with minerals and no GSH or LAMC on the same day) should be paired with **1.3 to 1.5 ATA** protocols.

Our Standard HBOT + IV Head Trauma Protocol

- IV three-part formula:
  - Vitamin-Mineral Amino Acid Formula
  - 1 to 3 grams Glutathione
  - Lipoic Acid Mineral Complex IV
  - (in those with chronic injuries / psychiatric overlay we may add IV Phospholipids)
- HBOT Dive:
  - 1.5 ATA on dive-1 then 2.0 on the following dives
  - All at 90 minutes
  - Air breaks PRN

At home oral supplements:

- Vitamin-C: 1 gram 2-3X a day
- Phosphatidylcholine: 500-1000 mg 2-3X a day
- Multi Vit-Min: 1-6 QD per instructions on label
- Tocopherol/Tocotrienol: 40IU/100mg QD
- Alpha Lipoic Acid: 150 – 300 mg 2X a day

At home oral supplements:

- CoQ-10: 200 mg 1-2X a day
- Pregnenolone or Porgesterone as neurosteroid (repair) support:
  - Either (in a MICRONIZED FORM – IDEALLY IN OR WITH OIL)
  - 100 – 400 MG ACUTELY **qhs** THEN DECREASE OR D/C AFTER 30-60 DAYS
- Lipoic-Mineral Complex [LAMC]: 10 to 15 mL 1-2X a day
- Cover-3 gel: 1 pack per day for 14 days then 3 per week for 6 weeks

*Others per case / comorbidity.

Case Study

Combination HBOT – IV Nutrient Therapy

Post MVA - mTBI

Case: “SM” with mTBI - Recent MVA

- 33 year old physician with a recent mTBI presented asking if we thought we could help.
- He consented to having his case assessed and used for presentation.
- Initially was quite concerned due to Sn/Sx post MVA (see below)
- Neurology evaluation post MVA “you had a concussion there is nothing to do for them except symptom management.”

Timeline Notes:

- Mechanism of injury:
  - “I was stopped on E. Pine street and was driving to my clinic when a **1981 El Camino rear ended me probably going 20-30 mph**... he said he was reading the news on his cell phone.”
  - “It's hard to do any work and I still have a clinic to run.”
- MVA to initial therapy with us:
  - **14 Days:** May 30th DOI to June 13 Initial treatment with us.
- Combined HBOT and IV Nutrient Therapies:
  - Protocol used noted in next slide.

Timeline Notes:

- MVA to initial therapy with us:
  - **14 Days:** May 30th DOI to June 13 Initial treatment with us.
- Combined HBOT and IV Nutrient Therapies:
  - Protocol used noted in slides below.

SM Protocol

- HBOT:
  - 1.5 ATA X 90 min #1 then 2.0 ATA X 90 min.
- IV:
  - IV Nutrient base (next slide)
  - Glutathione [2000 mg] in 100 ml 0.9% NS & 200 mcg Molybdenum
  - LAMC 15 mL in 250 mL NS
- At Home:
  - Oral supplements (MVM, ALA, CoQ10, PTC)

SM Nutrient IV

mL	Rx Item
250	Sterile Water
2	CaCl [100 mg/mL (1.36mEq)]
3	MgSO4 [500 mG/mL (4.06 mEq)]
1	KCl [2 mEq/mL]
1	B-100 Complex
1	Methyl B12 [5 mg/mL]
2	l-Carnitine [500 mg/mL]
6	Taurine [50 mg/mL]
5	Ascorbate - C-500 [500 mg/mL]
10	Bicarb 8.4% (as pH buffer)
*Rate	Admin over 60-90 minutes
273	Total Volume [mL]
259	Calc. Osmo mOsm/L

Initial Complaints Reported by SM:

- Brain fog - brain fatigue
- Fatigued easily
- Music even in the background is overstimulating
- Easily angry (good thing I'm home alone this week)
- Have very little perception of time or less than I did before (this is a problem)
- Hard to grab words and do math
- Weepy to things that are sad, but normally wouldn't make me tear up
- I feel like my brain is swimming.

List of Sx he made the day following the MVA:

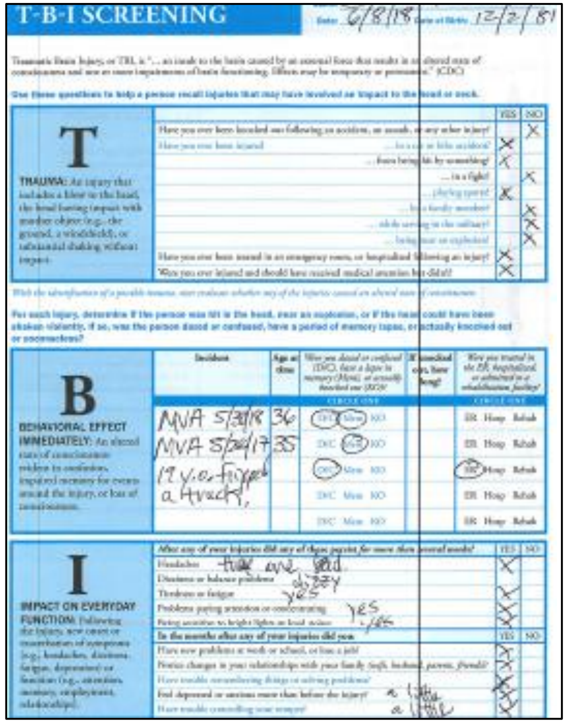
- Tired
- Headaches
- Ocular headaches
- Photosensitivity
- Brain fog - spacey
- Neck pain
- Thoracic pain
- Throbbing neck pain
- Cannot flex neck without pain
- Extreme fatigue
- Mentally Spacey
- Forgetful
- Lacking focus
- Focus problems
- Want to sleep a lot
- Low motivation
- Forgetful
- Grabbing for words.

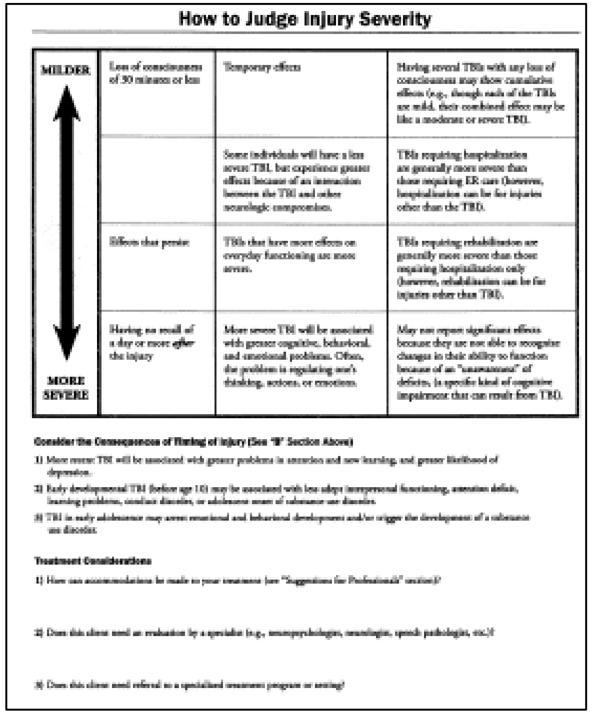
Outcome Assessment

- Standard clinical markers
- TBI assessment tool (below)
- Periodic subjective “overall assessment” by patient

T-B-I Screening Assessment

Ohio State University: James College of Medicine (Wexner Medical Center)





How to Judge Injury Severity

MILDER	Loss of consciousness of 30 minutes or less	Temporary effects	Having several TBIs with any loss of consciousness may show cumulative effects (e.g., though each of the TBIs are mild, their combined effect may be like a moderate or severe TBI).
		Some individuals will have a less severe TBI, but experience greater effects because of an interaction between the TBI and other neurologic compromises.	TBIs requiring hospitalization are generally more severe than those requiring ER care (however, hospitalization can be for injuries other than the TBI).
	Effects that persist	TBIs that have more effects on everyday functioning are more severe.	TBIs requiring rehabilitation are generally more severe than those requiring hospitalization only (however, rehabilitation can be for injuries other than TBI).
MORE SEVERE	Having no recall of a day or more *after* the injury	More severe TBI will be associated with greater cognitive, behavioral, and emotional problems. Often, the problem is regulating one's thinking, actions, or emotions.	May not report significant effects because they are not able to recognize changes in their ability to function because of an "unawareness" of deficits, (a specific kind of cognitive impairment that can result from TBI).

Consider the Consequences of Timing of Injury (See "B" Section Above)

1) More severe TBI will be associated with greater problems in attention and new learning, and greater likelihood of depression.

Treatment Considerations

Intervention schedule:

- DOI + 14 NO Rx.
- HBOT + IV:
  - Week 1 = 2X
  - Week 2 = 2X
  - Week 3 = 2X
  - Week 4 = 1X (Holiday week)
  - Week 5 = 4X
  - Week 6 = 4X

TOTAL COMBINATION THERAPIES TO DATE OF WRITING = 16

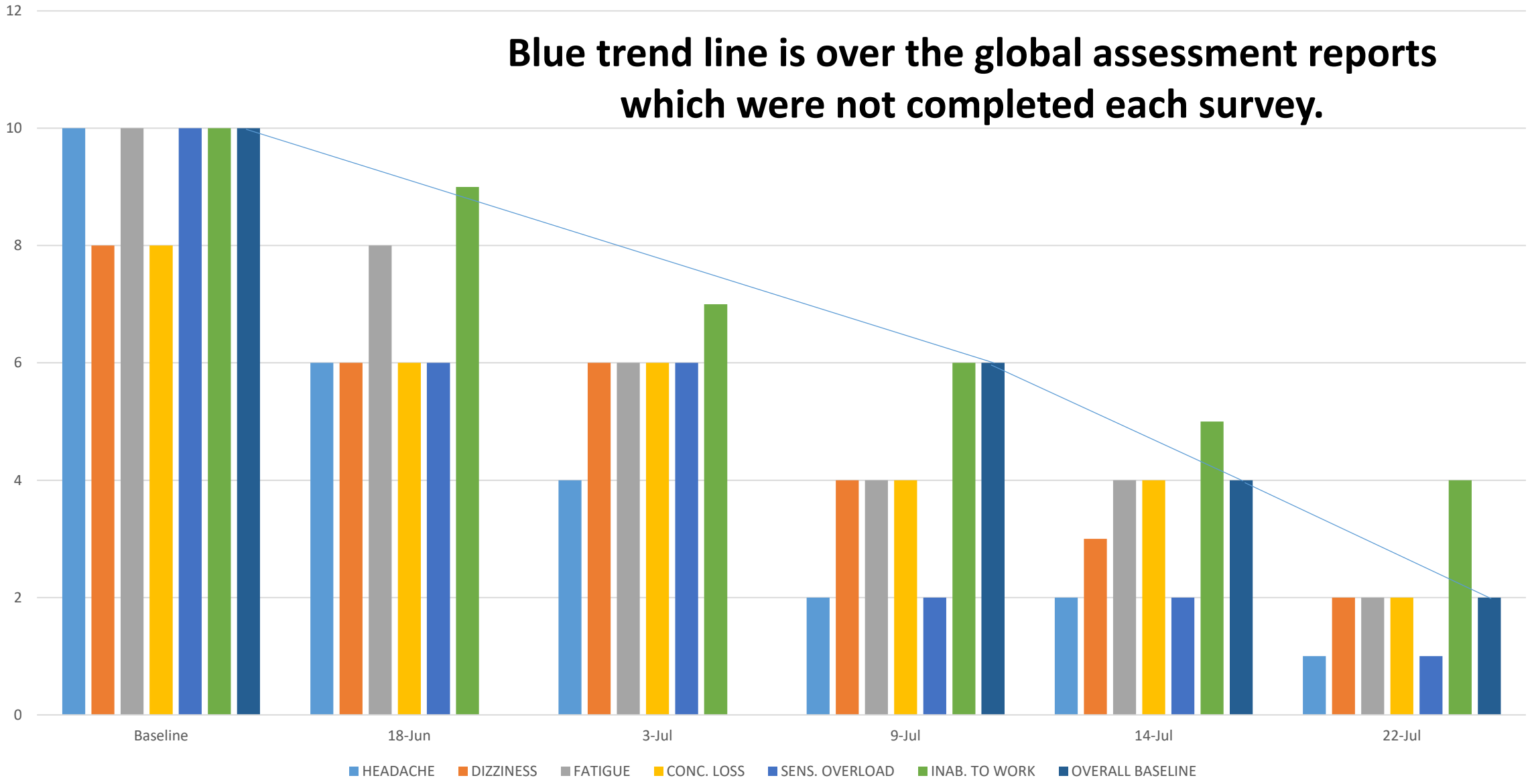
SM Updates after treatment # 16

- ENDURANCE:
  - I was also able to walk 4 miles in the arboretum Friday evening in Seattle.
  - Today I walked 7 miles.
- MEMORY:
  - I find the memory and forgetfulness are still not 100% and the inability to work more than 4 hours 3 times per week.
- But so much has improved!
  - (Physical stamina, endurance at clinic and memory were almost non-existant post MVA).

SM Updates after treatment # 16

- OTHER MEDICAL:
  - With PT my eye movements and balance is not great.
  - The neurological exam last Tuesday was “normal”.
- SUBJECTIVE:
  - (Globally) I think I’m 82% recovered from the accident.
- RESIDUAL:
  - But I still struggle with **memory and working longer than 4 hours 3 times per week. When I push past 4.5 hours at a time then I crash.**
  - 40% recovery with this mental fatigue issue.

SM Sn-Sx



Clinical Impressions

Questions?
&
Thank you!