

# Topical Oxygen: Where Does It fit in Your Practice?

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**Naz Wahab, MD, FAPWCA**

FRIDAY, NOVEMBER 11  
11:30am - 12:15pm



# Disclosures:

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## Gregory Bohn, MD FACS UHM/ABPM

- Aroa Biosurgery : Consultant
- Urgo North America : Consultant
- ULURU : Consultant

## Naz Wahab, MD, FAPWCA

- Refer to her slides



# Objectives

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- Compare and contrast Hyperbaric Oxygen Therapy and Topically Applied Oxygen Therapy
- Review mechanism by which HBOT impacts healing
- Review indications for HBOT in treatment of DFU
- Position Topical Oxygen in treatment pathway



# Comprehensive Wound Care

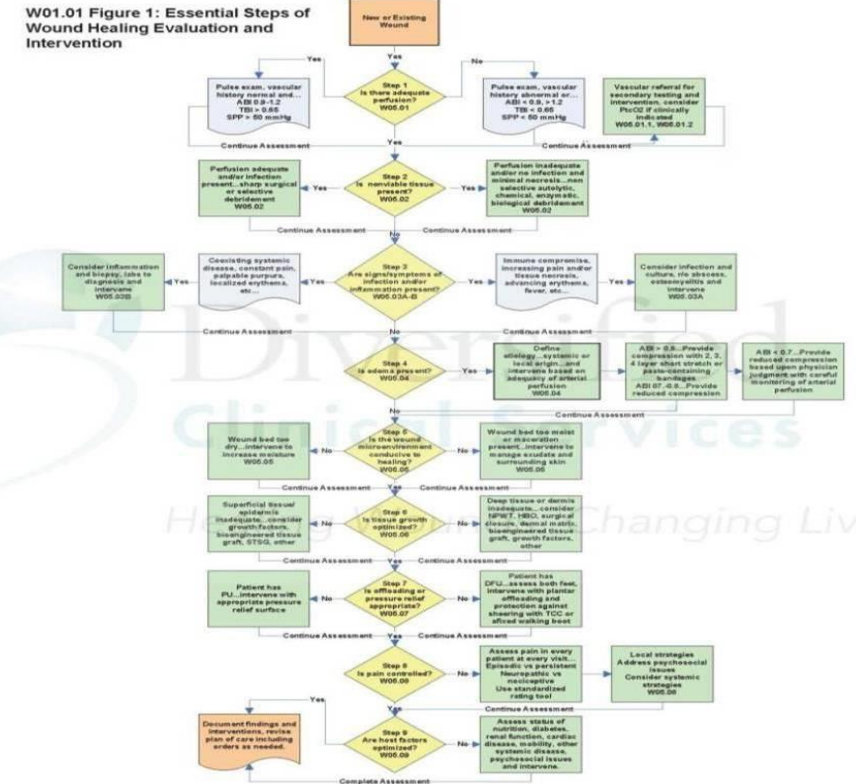
- A multi-disciplinary multi-modality approach to Diabetic Foot Ulcers
    - using all appropriate available modalities
    - to achieve healing in the shortest possible time
    - at the lowest possible cost.
  - Providing treatment in a caring and healing environment
- Evidence-based best practice approach



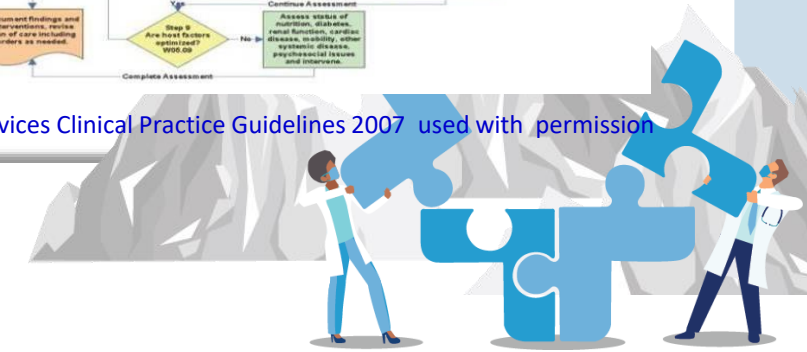
# Organized Approach to Wound Healing

- Adequate perfusion
- Non-viable tissue present
- Signs of infection
- Edema
- Microenvironment conducive to healing
- Tissue growth optimized
- Offloading pressure
- Host factors optimized (diabetes)

DCS CPG: W01.01 **Essentials of Wound Healing**



Diversified Clinical Services Clinical Practice Guidelines 2007 used with permission



# Wagner Classification

- Grade 0 Callus without Ulcer
- Grade 1 Superficial Ulcer without apparent infection
- Grade 2 Deep Ulcer without Abscess or Osteomyelitis
- Grade 3 Deep Ulcer with Abscess, Cellulitis, and/or Osteomyelitis
- Grade 4 Partial Gangrene
- Grade 5 Gangrene of the entire Foot

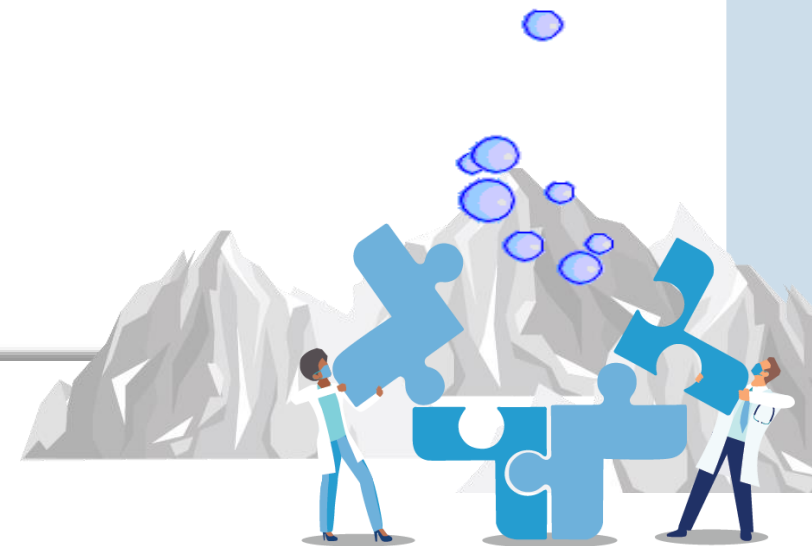


Contemporary Diagnosis and Management of Diabetic Foot Infections 2006 pp. 128



# Benefits of Hyperbaric Oxygen

- **Physiologic Effects: These are systemic effects**
  - Improved leukocyte function and bacterial killing
  - Antibiotic potentiation
  - Enhanced collagen synthesis and cross-linking
- **Pharmacological Effects: These are systemic effects**
  - Direct antimicrobial effects, toxin synthesis suppression
  - Blunting of systemic inflammatory responses
  - Prevention of leukocyte activation and adhesion
  - PDGF-BB receptor stimulation (multiple effects)
  - VEGF release and angiogenesis
  - Detoxification (CO, CN, H<sub>2</sub>S)

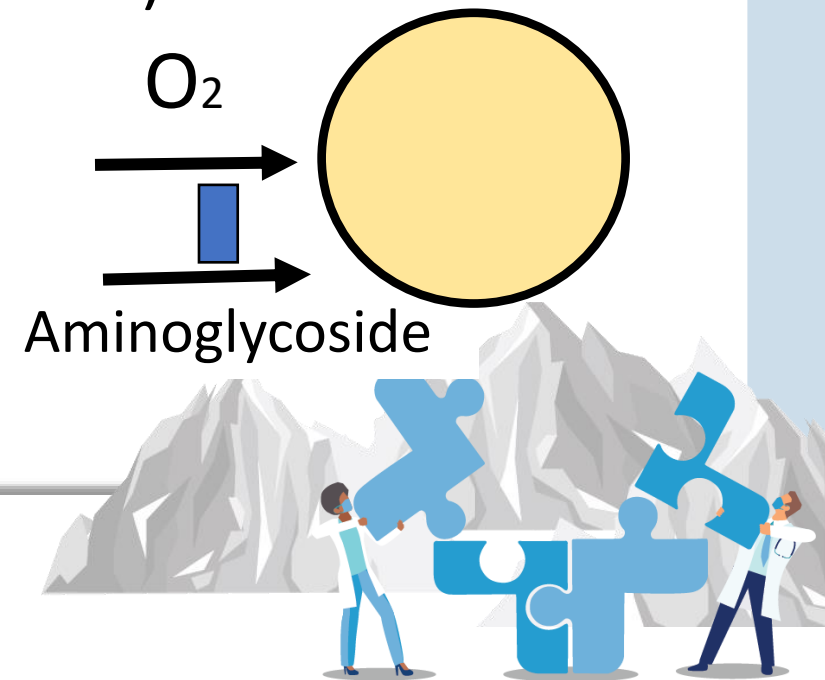


# Beneficial Effects of Hyperbaric Oxygen Therapy in Treating Infection

## Antibacterial Effects

Occurring while patient receiving HBO

- Improved leukocyte-bacterial-killing (adequate leukocyte count critical for benefit)
- Suppression of exotoxin production (may persist hours)
- Increased effectiveness of antibiotics





# HBOT and Antibiotics

- Antibiotic Synergy with HBOT
  - Aminoglycosides
  - Clindamycin
  - Penicillin
  - Cephlosporins
  - Sulfonamides
  - Quinolones
  - Rifampin

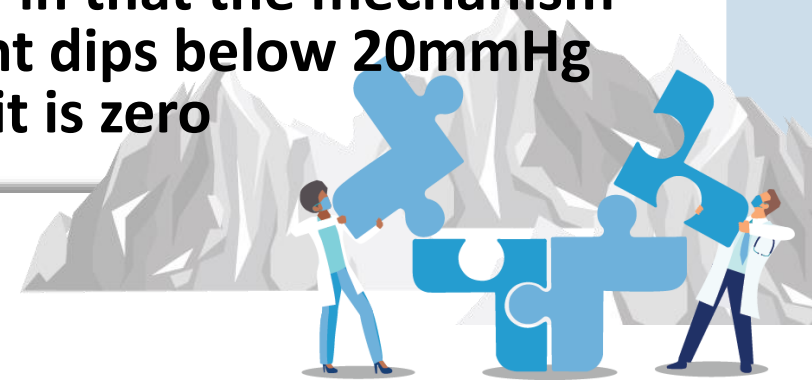
Verklin 1977, Harrell 1977, Keck 1980, Tack 1985, Adams 1987



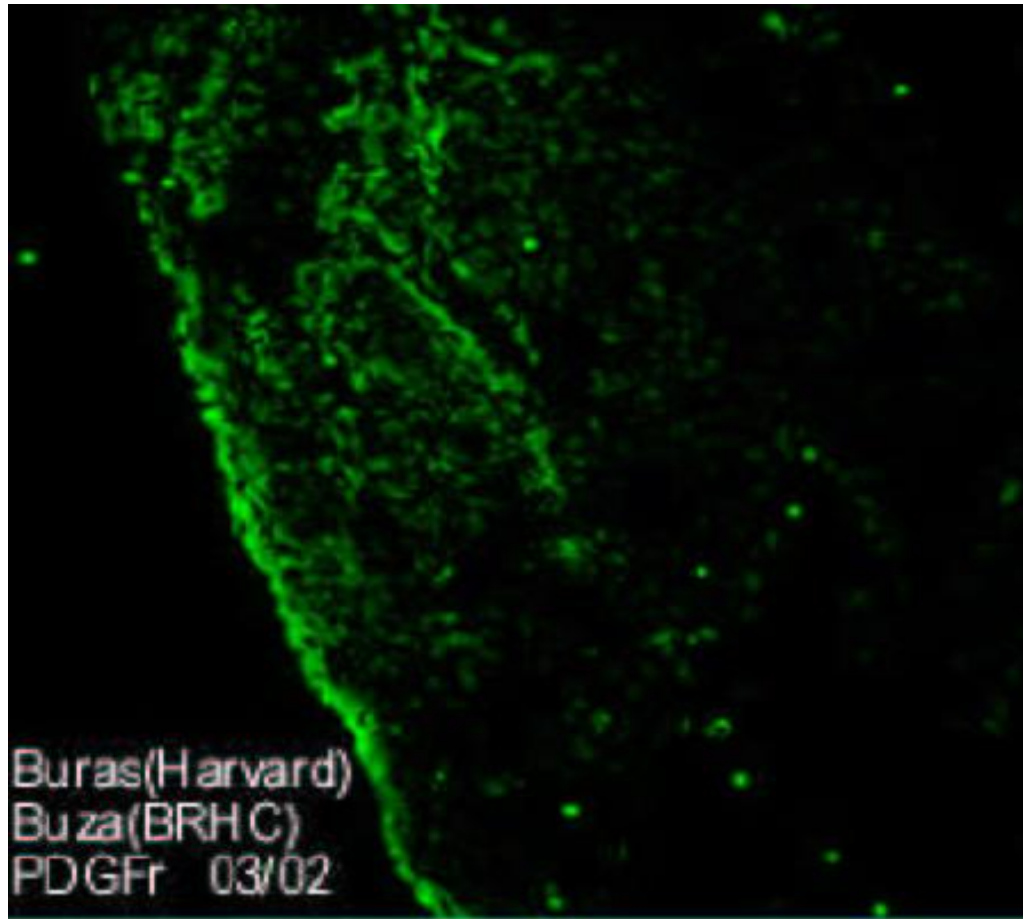
# HBOT and Ischemic Tissues



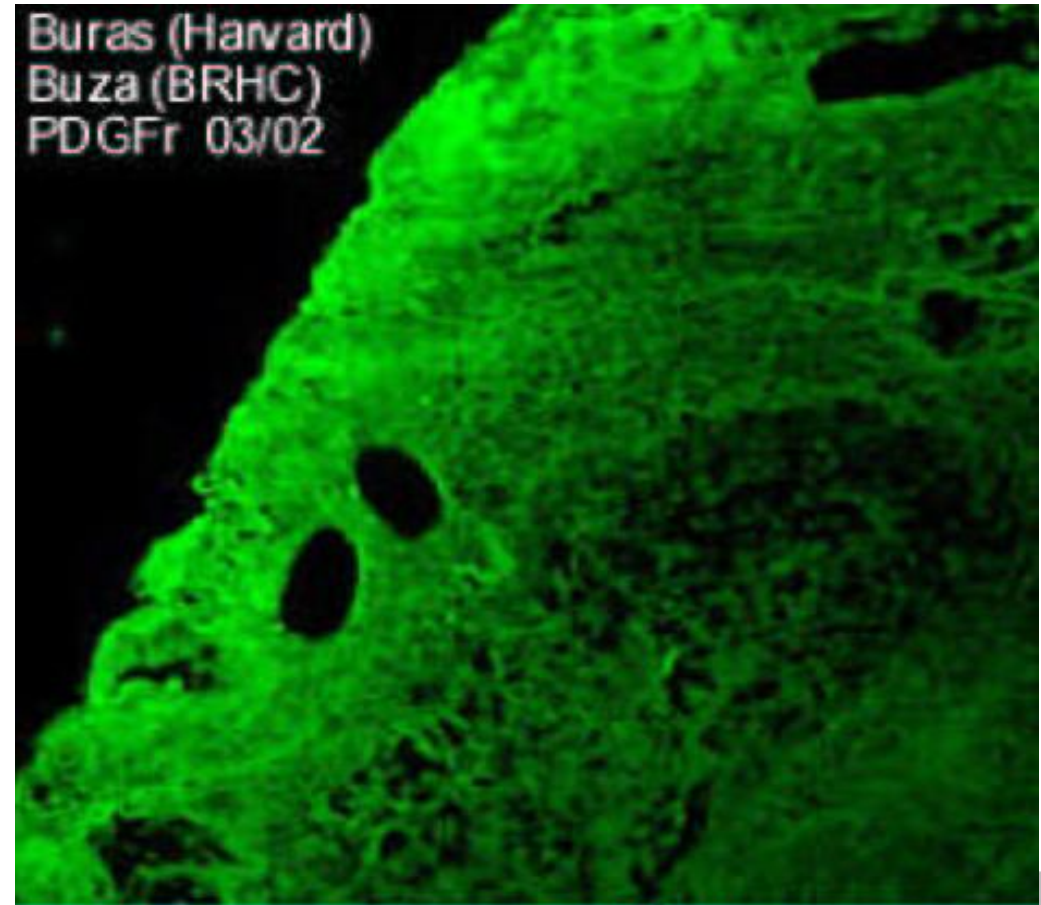
- **Oxygen Gradient (thought to be 20mmHg) is the signal to initiate biochemical steps to angiogenesis**
- **Remains under the same regulatory control as in normal wound healing**
- **When perfusion develops to eliminate oxygen gradients, biochemical messenger response sequence shuts off**
- **Vascular architecture achieves 75-80% of normal tissue and persists for years**
- **This is consistent in theory in that the mechanism shuts off when the gradient dips below 20mmHg and not necessarily when it is zero**



# HBOT and Effects on PDGF



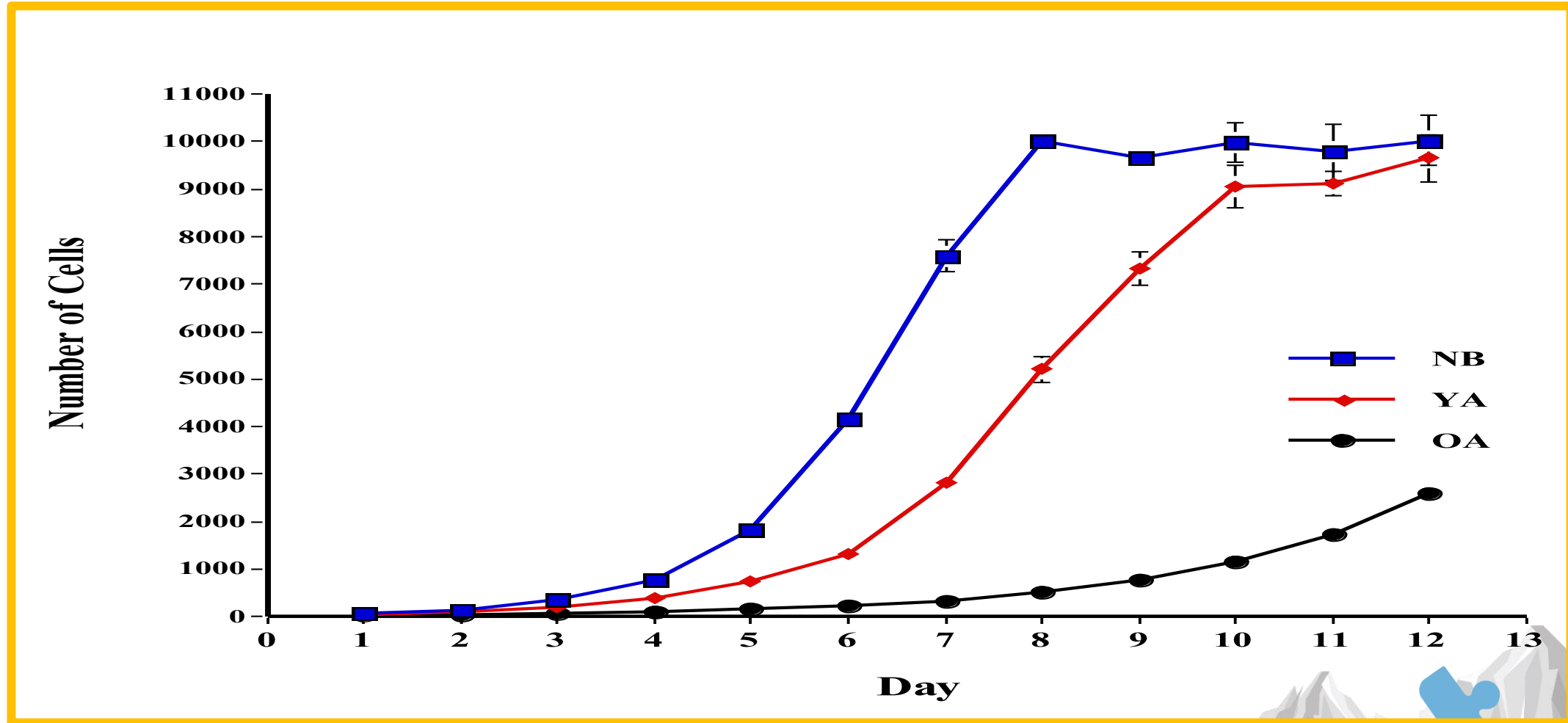
*PDGFr prior to 1st HBOT Treatment*



*PDGFr 24 hrs later prior to 2<sup>nd</sup> HBOT treatment*



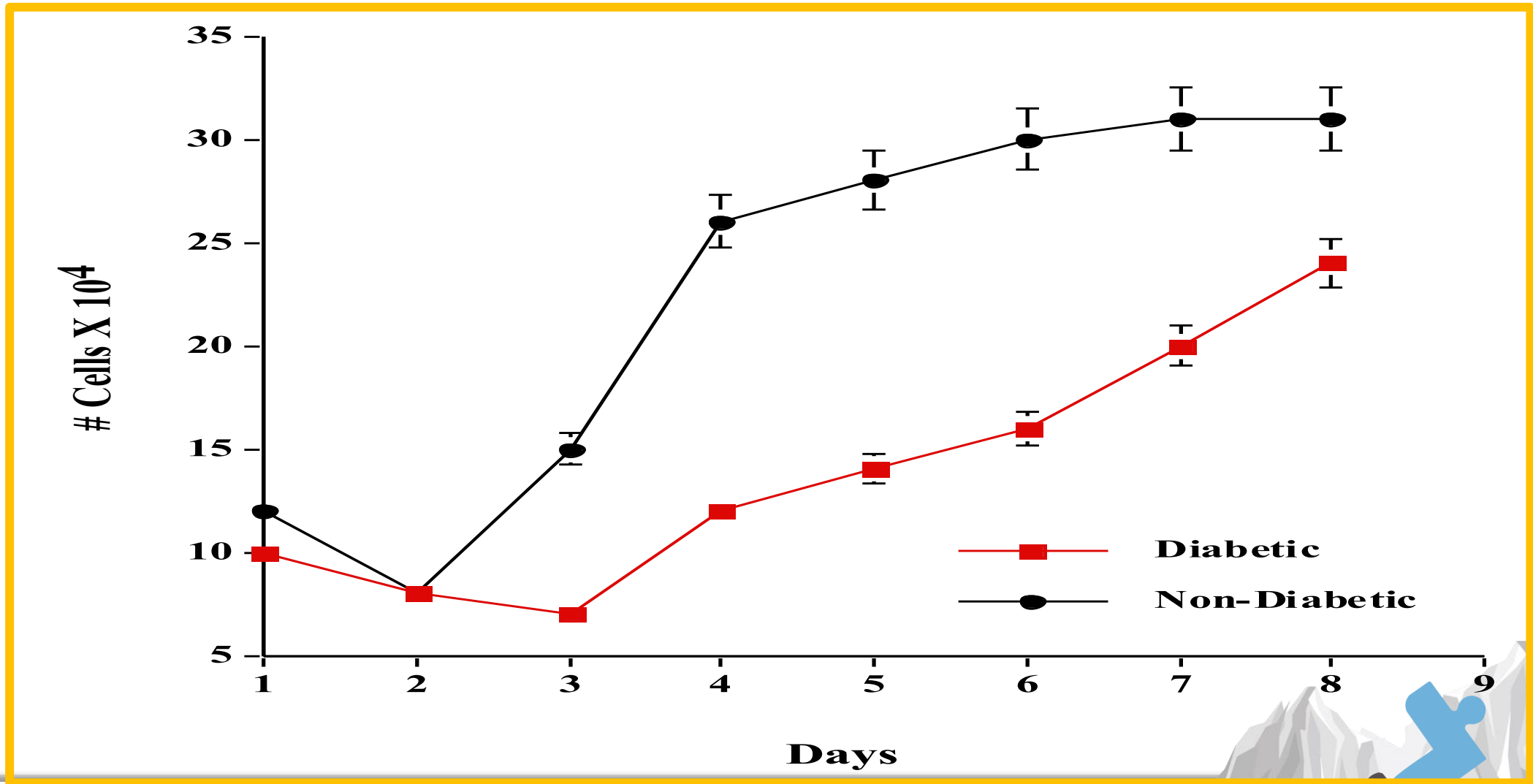
# Age associated differences in cellular Proliferation (*in vitro*)...



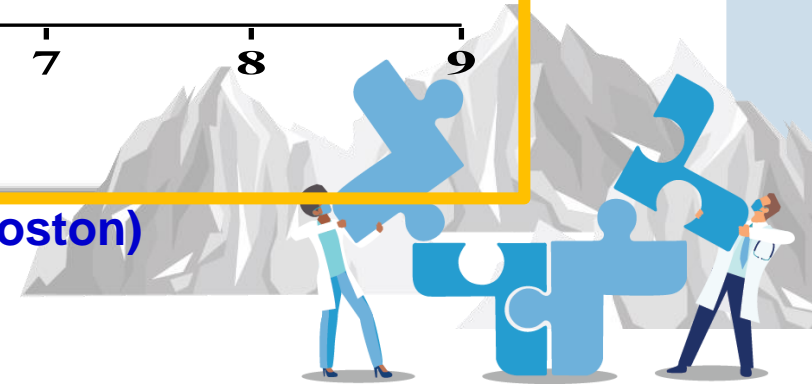
(Buras and Buras, Harvard Medical School, MGH, Boston)



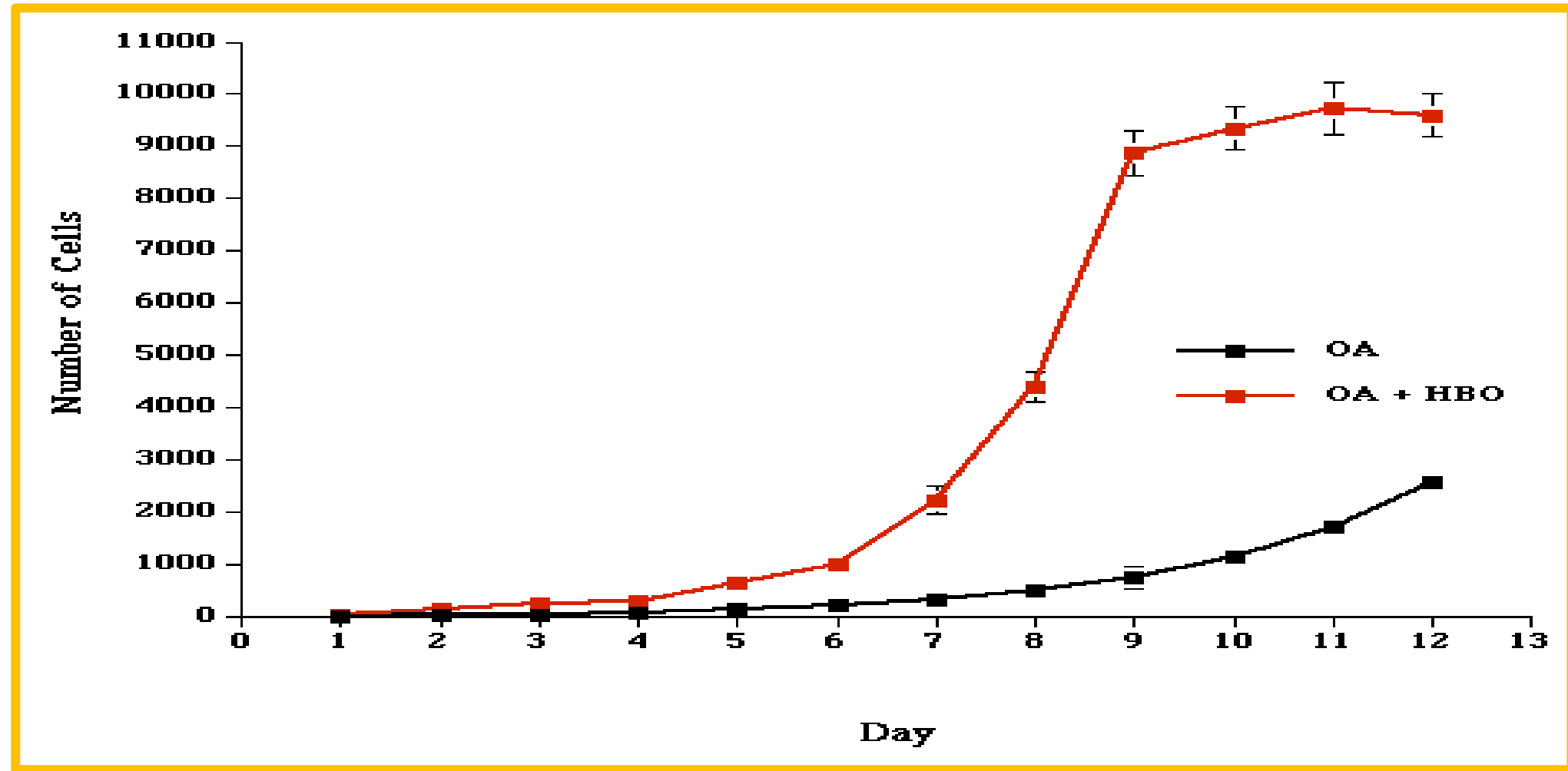
# Decreased cellular proliferation with diabetes...



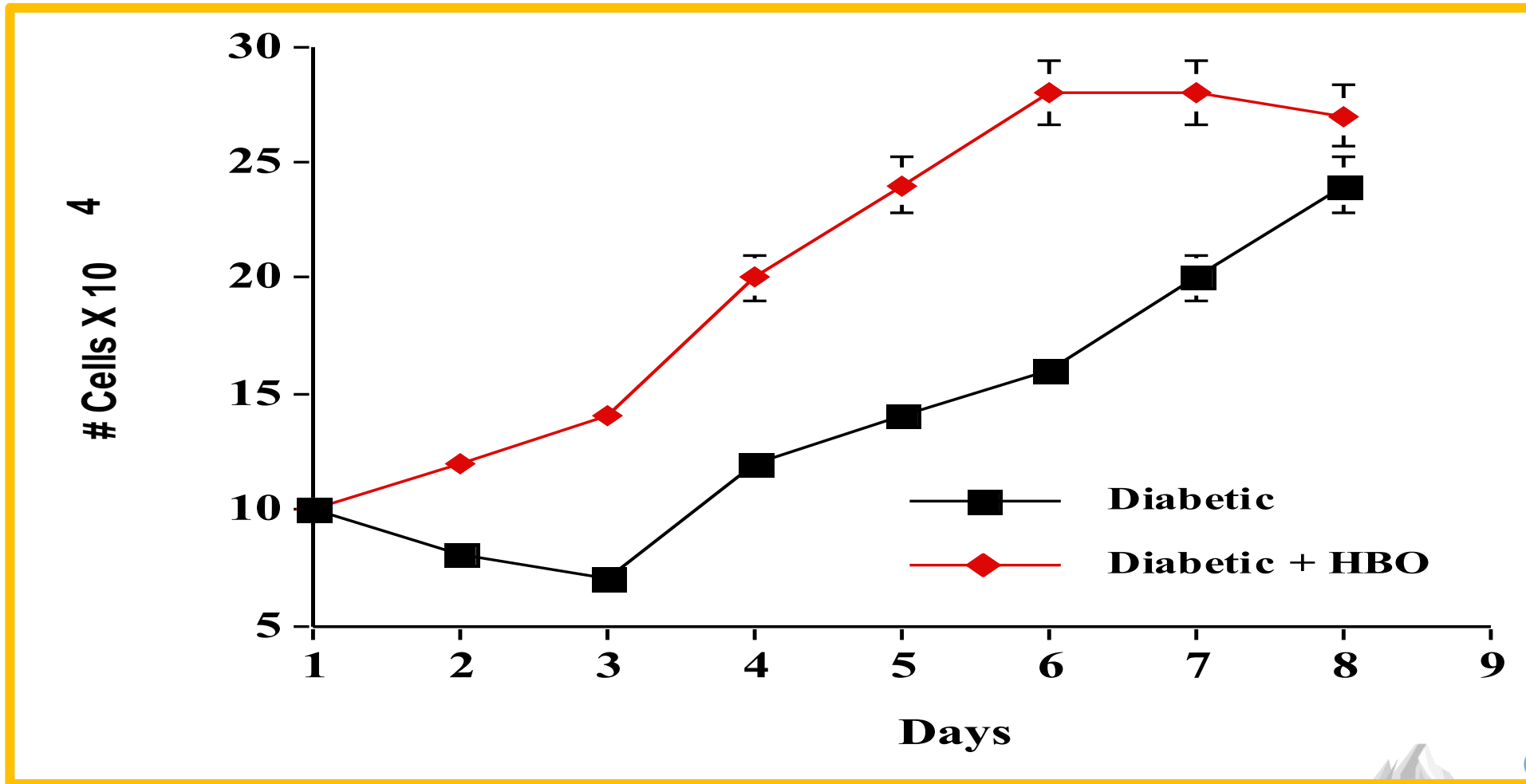
(Buras and Buras, Harvard Medical School, MGH, Boston)



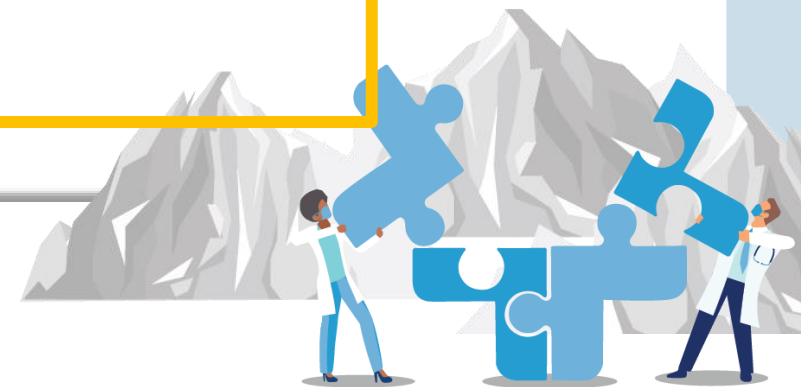
# HBO Dramatically Increases Old Adult Fibroblast Proliferation...



# HBO Dramatically Increases Diabetic Fibroblast Proliferation...



(Buras and Buras, Harvard Medical School, MGH, Boston)



# Stem Cell Mobilization by HBO

- HBO mobilizes stem/progenitor cell release from bone marrow through a nitric oxide dependent mechanism
- Population of CD34 cells in peripheral circulation doubled in response to single HBO treatment (2 ATA, 120 mins)
- Over course of 20 treatments circulating CD34 cells increased 8 fold, total WBC count unchanged

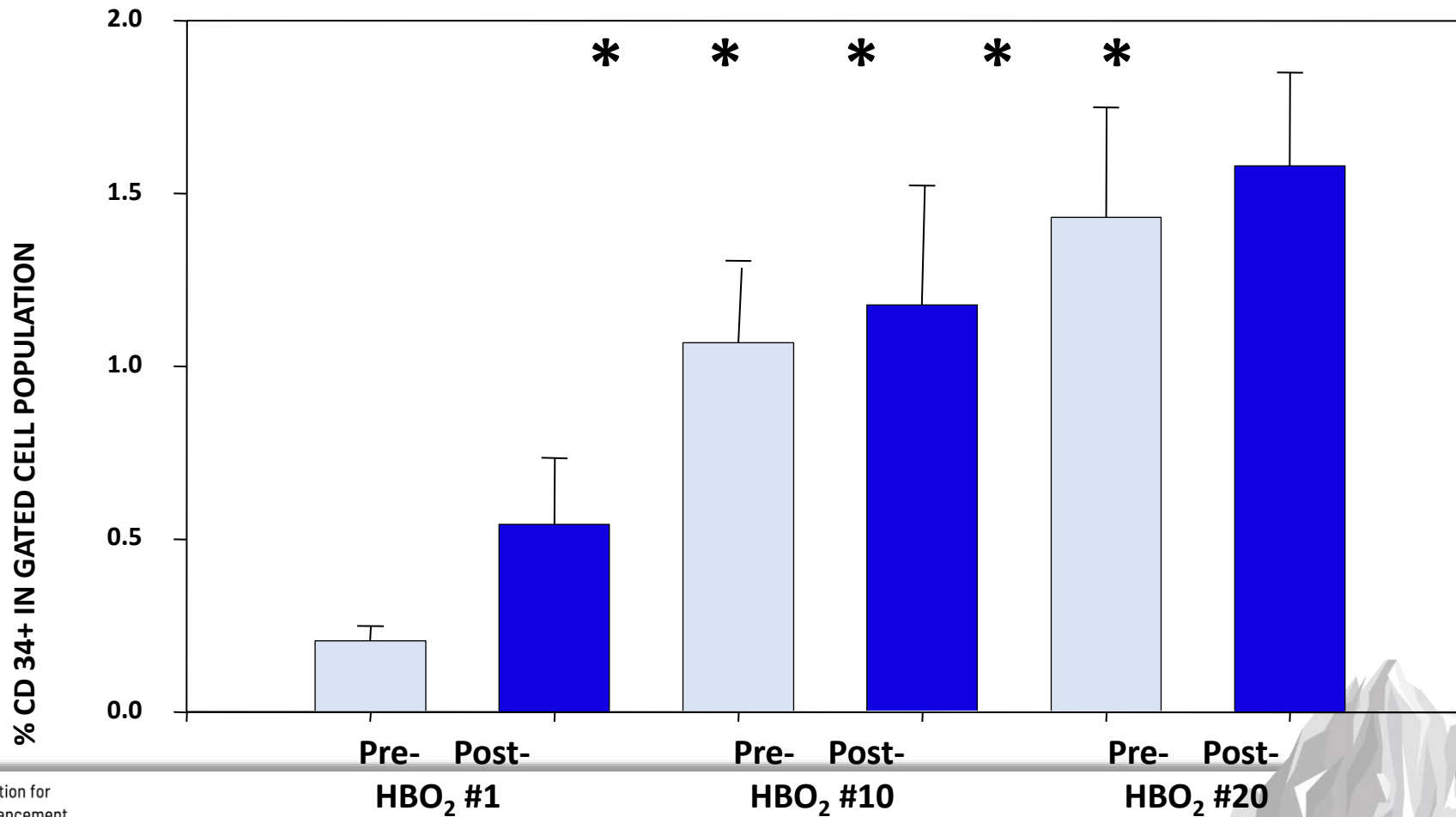
Thom SR, et al. Stem cell mobilization by hyperbaric oxygen. Am J Physiol Heart Circ Physiol 2006; 290:H1378-H1386.



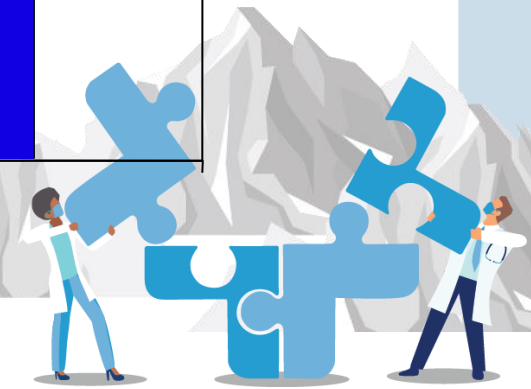
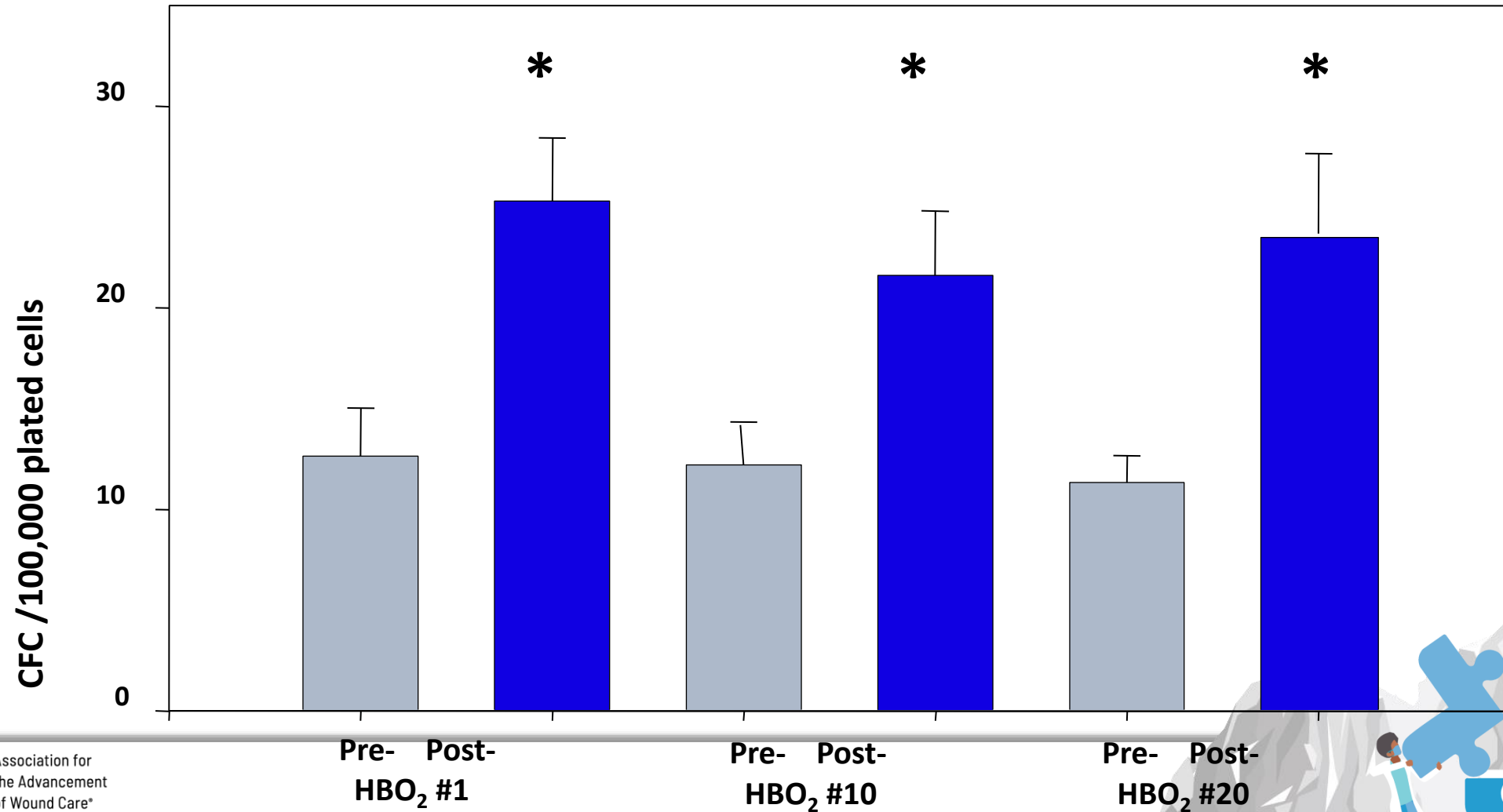


# Stem Cell Mobilization by HBO in Patients

Over course of 20 treatments circulating activated CD34 cells increased 8 fold, total WBC count unchanged

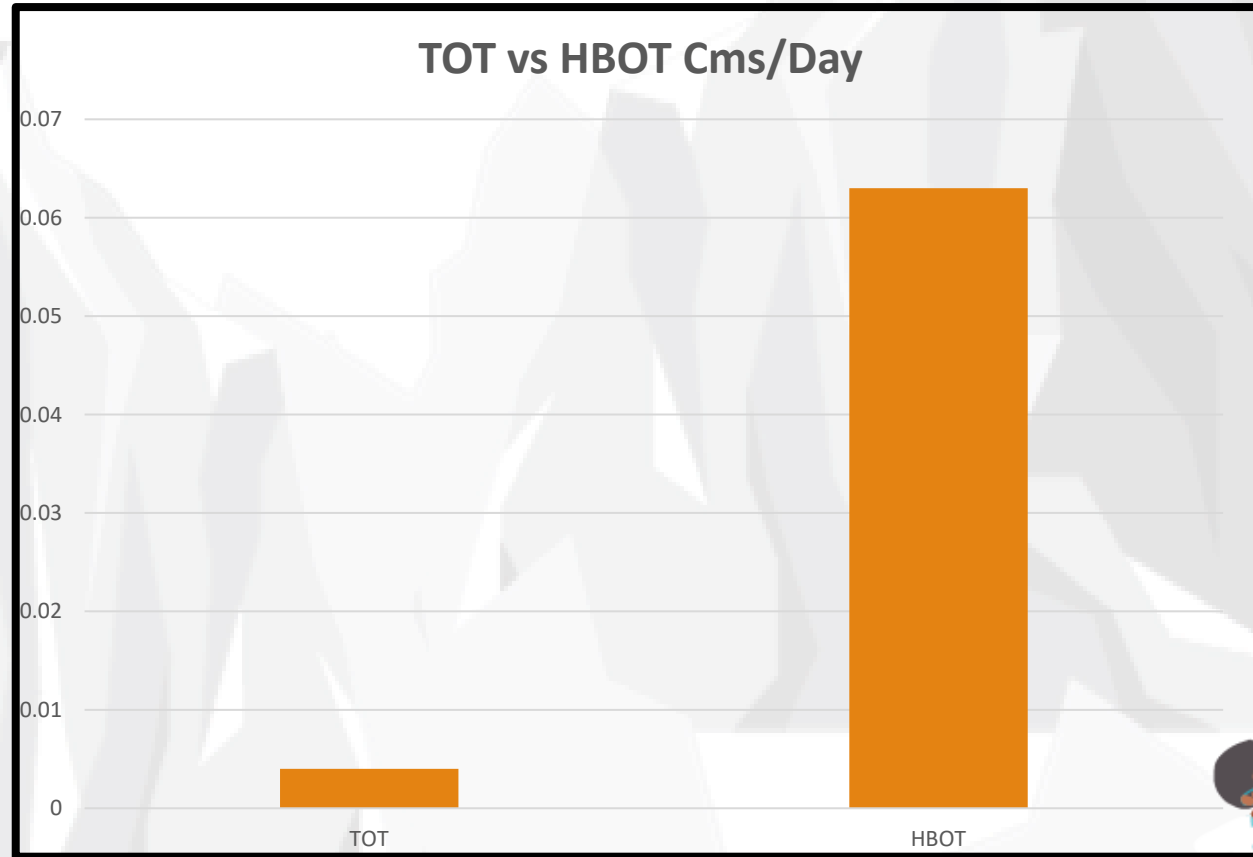


# Growth Potential of Stem Cells Mobilized by HBO in DFU Patients



# Cohort Study Compared TOT to HBOT Treated Wounds

Retrospective Cohort Study compared DFUs treated during the same period with either TOT or HBOT n=22



TOT. 0.004 cms/day  
HBOT 0.063 cms/day

Winfeld B, Topical Oxygen and Hyperbaric Oxygen Therapy Use and Healing Rates in Diabetic Foot Ulcers WOUNDS 2014;26(5):E39-E47



# Wounds in the Topical Oxygen Group were superficial

**Table 1. Topical oxygen therapy.**

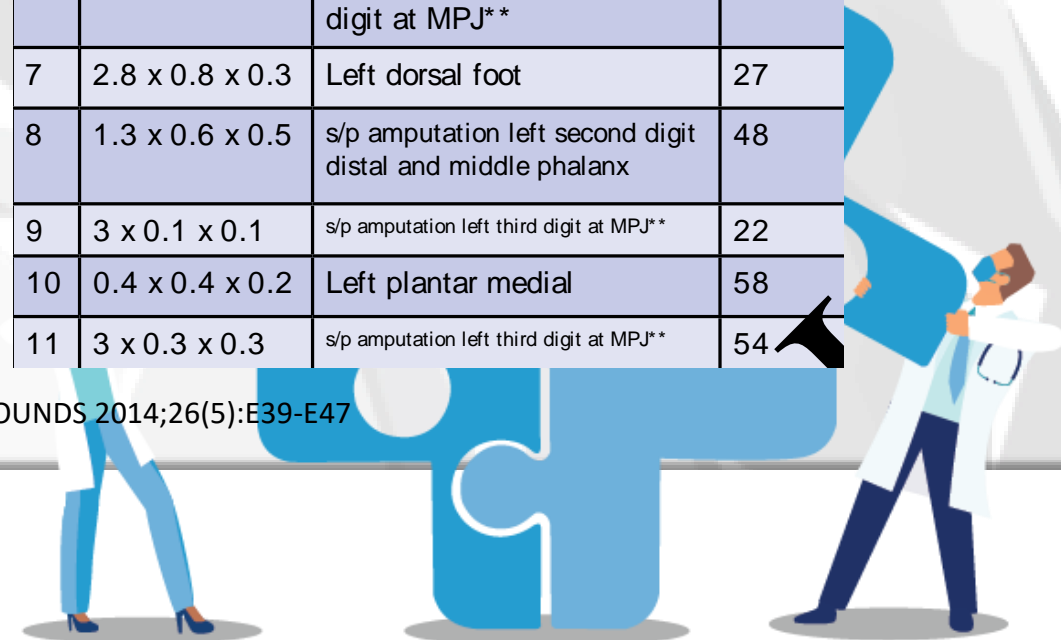
	Size of wound (cm)	Location	Days to closure
1	1.3 x 0.6 x 0.1	Left plantar submetatarsal 5	37
2	2.3 x 2.2 x 0.1	Left hallux	25
3	0.7 x 0.3 x 0.1	Left hallux	52
4	2 x 1.5 x 0.2	Right heel	154
5	0.4 x 0.5 x 0.2	Right fourth toe	132
6	3.5 x 0.7 x 0.2	Left heel	40
7	0.8 x 0.5 x 0.1	Left plantar submetatarsal 2	23
8	0.9 x 0.7 x 0.1	Left plantar foot	40
9	1.5 x 3 x 0.2	Left medial foot	47
10	2.6 x 0.6 x 0.1	s/p Left TMA*	70
11	0.5 x 0.5 x 0.2	Left Plantar ulcer s/p TMA*	60

\*TMA = transmetatarsal amputation

**Table 2. Hyperbaric oxygen therapy.**

	Size of wound (cm)	Location	Days to closure
1	1 x 0.9 x 0.5	s/p amp right second digit at the PIPJ*	102
2	0.2 x 0.2 x 0.3	Right hallux	15
3	3 x 0.5 x 1.5	Left plantar foot	23
4	0.5 x 0.3 x 0.8	s/p amputation left third digit at MPJ**	23
5	5 x 1.8 x 2.5	s/p amputation right fourth digit at MPJ**	65
6	4.5 x 1.7 x 0.8	s/p amputation right third digit at MPJ**	81
7	2.8 x 0.8 x 0.3	Left dorsal foot	27
8	1.3 x 0.6 x 0.5	s/p amputation left second digit distal and middle phalanx	48
9	3 x 0.1 x 0.1	s/p amputation left third digit at MPJ**	22
10	0.4 x 0.4 x 0.2	Left plantar medial	58
11	3 x 0.3 x 0.3	s/p amputation left third digit at MPJ**	54

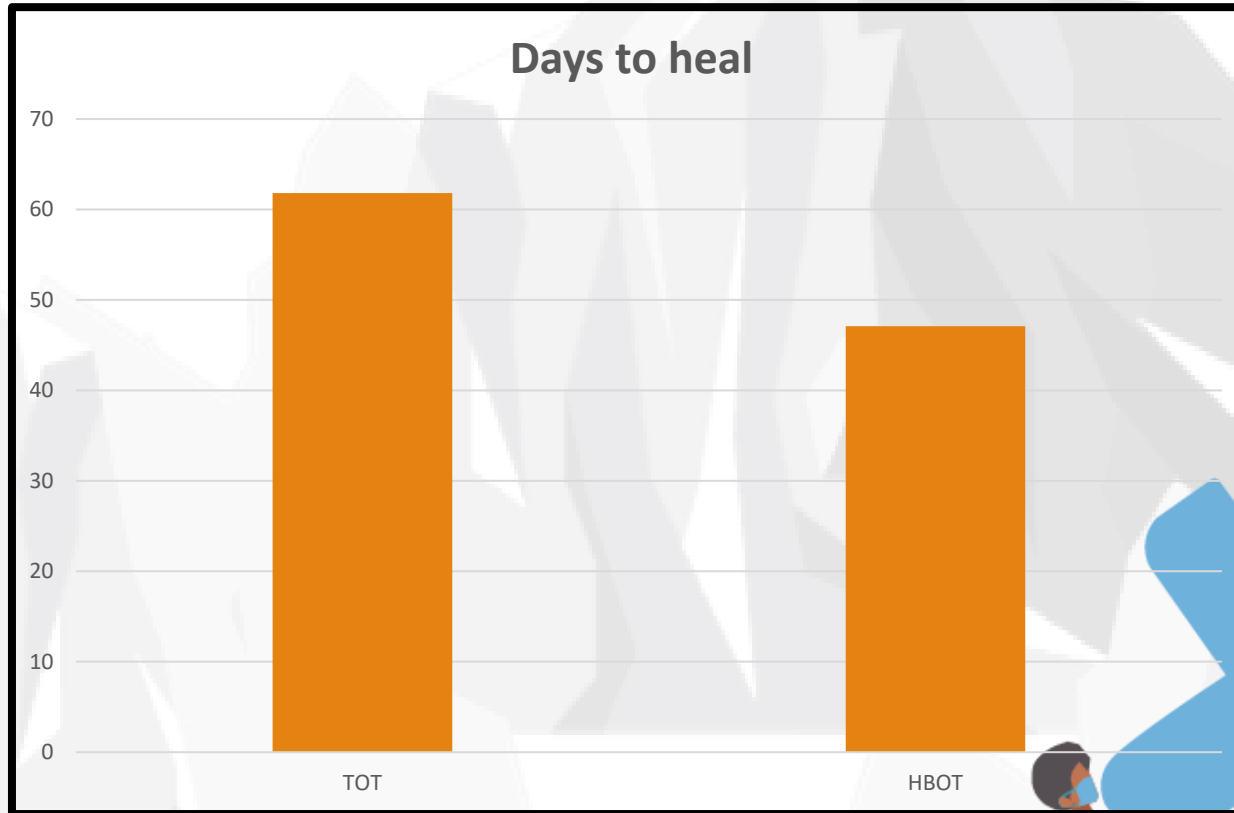
Winfeld B, Topical Oxygen and Hyperbaric Oxygen Therapy Use and Healing Rates in Diabetic Foot Ulcers WOUNDS 2014;26(5):E39-E47



# Cohort Study Compared TOT to HBOT Treated Wounds

Retrospective Cohort Study compared DFUs treated during the same period with either TOT or HBOT n=22

Winfield Study  
Not Randomized,  
Only Retrospective  
Chart Review



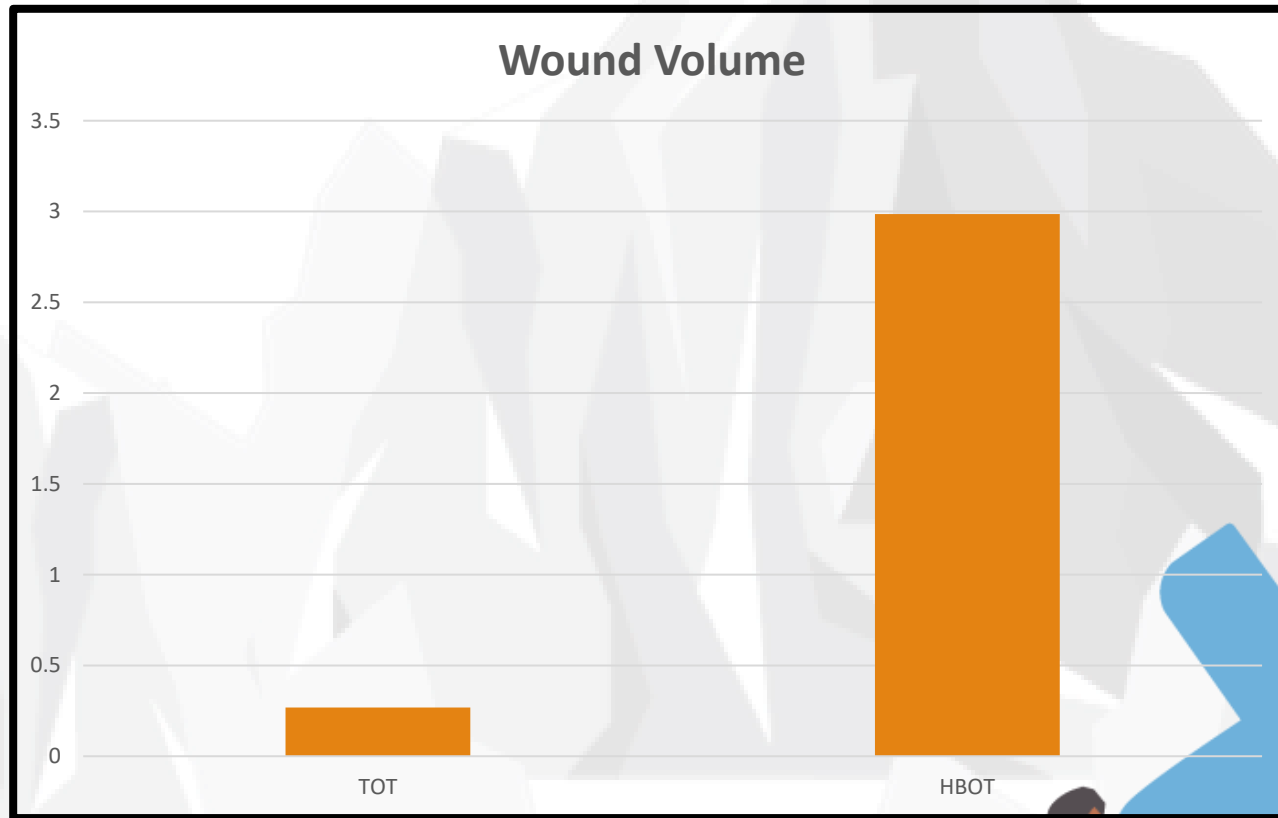
TOT. 61.82 days  
HBOT 47.9 days

Winfield B, Topical Oxygen and Hyperbaric Oxygen Therapy Use and Healing Rates in Diabetic Foot Ulcers WOUNDS 2014;26(5):E39-E47



# Cohort Study Compared TOT to HBOT Treated Wounds

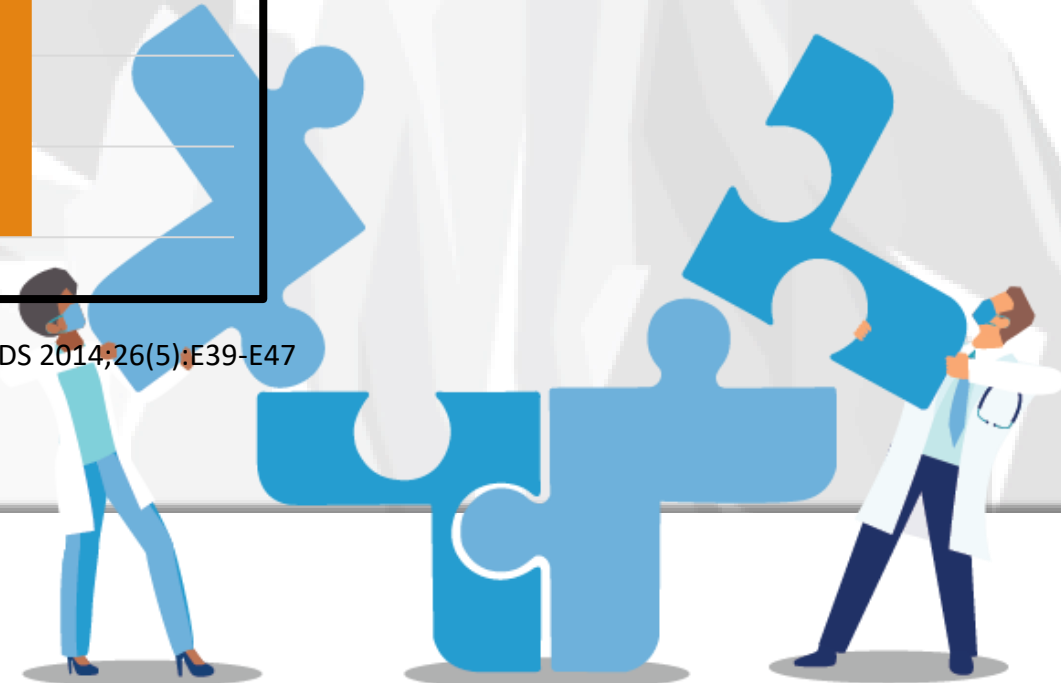
Retrospective Cohort Study compared DFUs treated during the same period with either TOT or HBOT n=22



TOT. 0.268 cms<sup>2</sup>  
HBOT 2.986 cms<sup>2</sup>

Winfield Study  
Not Randomized,  
Only Retrospective  
Chart Review

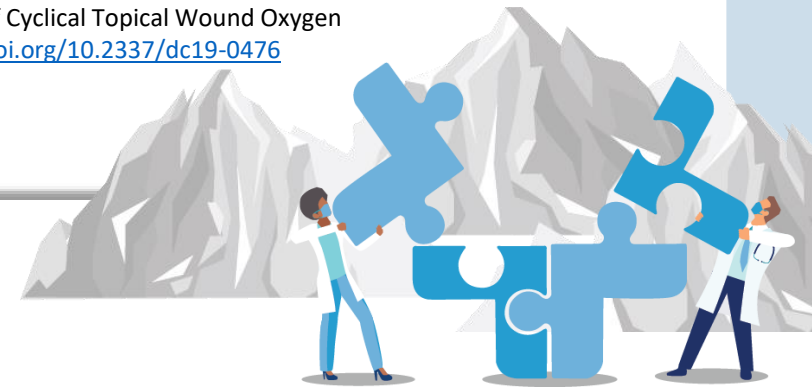
Winfield B, Topical Oxygen and Hyperbaric Oxygen Therapy Use and Healing Rates in Diabetic Foot Ulcers WOUNDS 2014;26(5):E39-E47



# Fryberg, et al: 2020

- 73 patients randomized
- 53 patients UTC Grade 1, 20 patients UTC Grade 2
- Healed ulcers: Treatment 15 patients (41%).  $P = 0.010$   
Sham 5 patients (13.5%)
- Wound Reduction: Treatment 1.97 (2.75) cm<sup>2</sup>  $P = 0.041$   
Sham 0.40 (1.75) cm<sup>2</sup>

Frykberg RG, Franks, PR, et al; A Multinational, Multicenter, Randomized, Double-Blinded, Placebo-Controlled Trial to Evaluate the Efficacy of Cyclical Topical Wound Oxygen (TWO2) Therapy in the Treatment of Chronic Diabetic Foot Ulcers: The TWO2 Study. *Diabetes Care* 1 March 2020; 43 (3): 616–624. <https://doi.org/10.2337/dc19-0476>



# Serena; et al; May 2021

- 145 Wagner Grade 1 or Grade 2 ulcers randomized to SOC or SOC plus TOT
- Healing Rate: SOC. 28% healing at 12 weeks. TOT 44.4%. (p=0.044)
- Wound Area reduction: SOC 40% SOC plus TOT 70% (p=0.005)

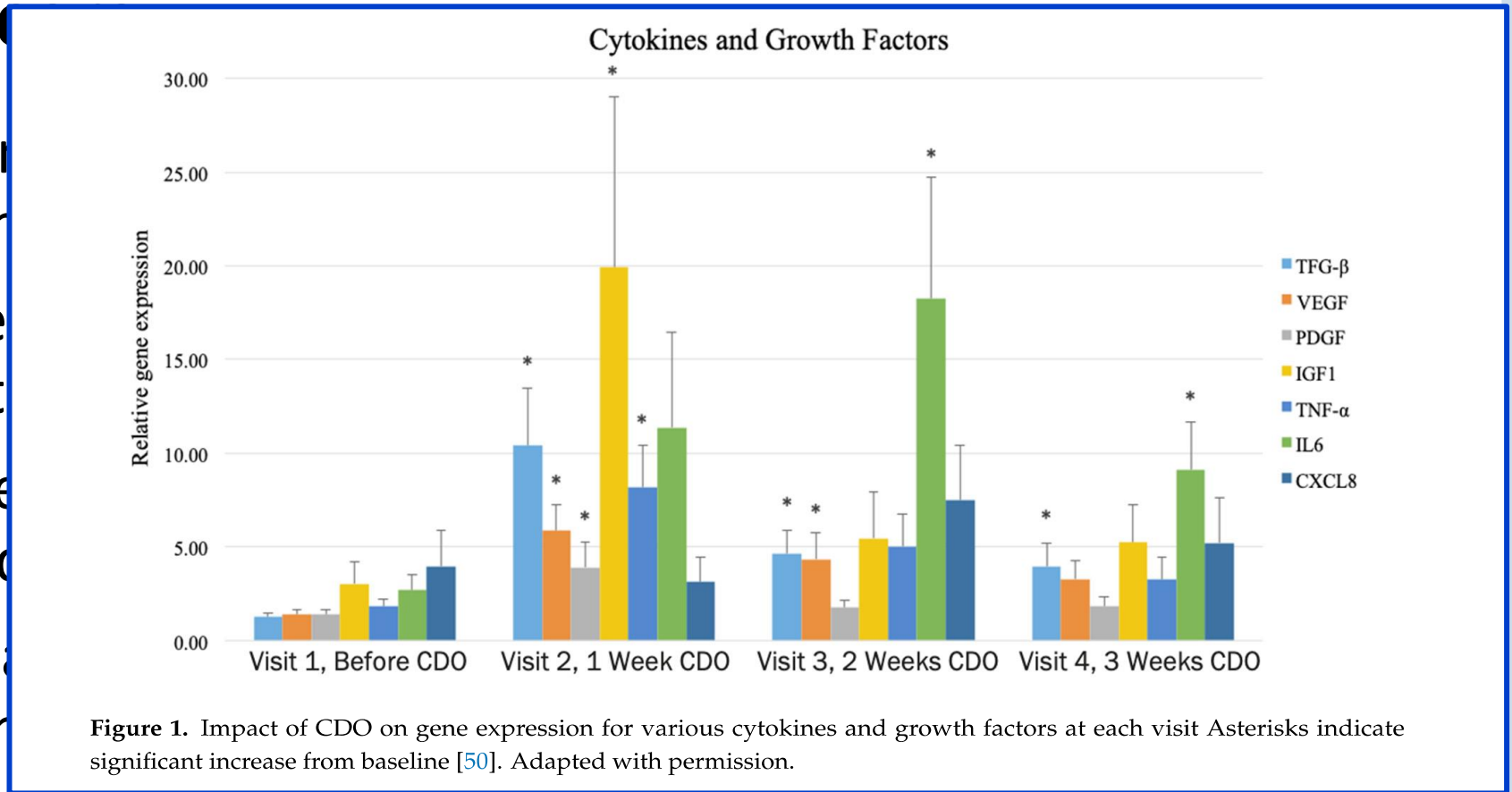
Serena TE, Bullock NM, Cole W, Lantis J, Li L, Moore S, Patel K, Sabo M, Wahab N, Price P. Topical oxygen therapy in the treatment of diabetic foot ulcers: a multicentre, open, randomised controlled clinical trial. *J Wound Care*. 2021 May 1;30(Sup5):S7-S14. doi: 10.12968/jowc.2021.30.Sup5.S7. PMID: 33979229.





# Molecular Biomarkers of Oxygen Therapy in Patients with Diabetic Foot Ulcers

- Growth factors significantly increased (1.5-4 fold) in the first week and remained elevated
- Cytokines (increased levels) in the first two weeks
- Significant increase in CXCL8 (indicated increased bacterial load)
- This is evidence that oxygen diffused to surrounding tissue



Oropallo, A.R.; Serena, T.E.; Armstrong, D.G.; Niederauer, M.Q. Molecular Biomarkers of Oxygen Therapy in Patients with Diabetic Foot Ulcers. *Biomolecules* **2021**, *11*, 925. <https://doi.org/10.3390/>

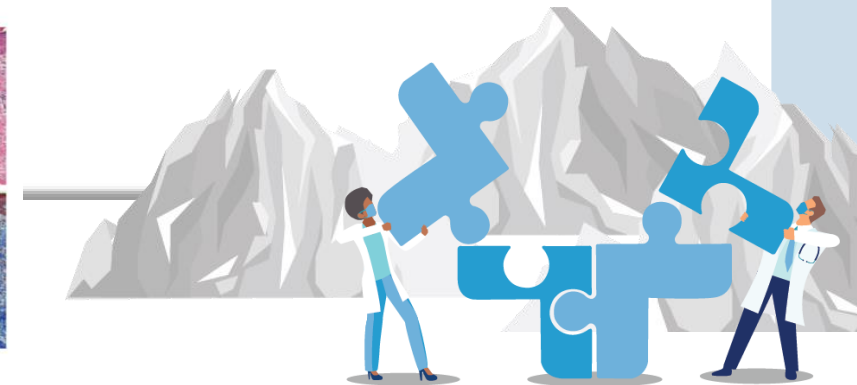
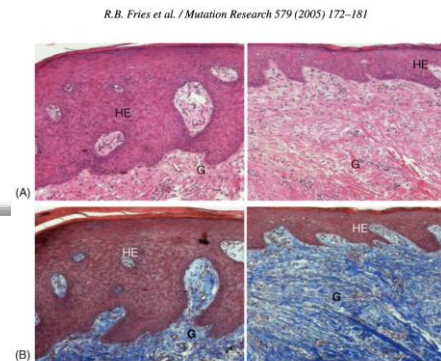
Lavery, L.A.; Killeen, A.L.; Farrar, D.; Akgul, Y.; Crisologo, P.A.; Malone, M.; Davis, K.E. The effect of continuous diffusion of oxygen treatment on cytokines, perfusion, bacterial load, and healing in patients with diabetic foot ulcers. *Int. Wound J.* **2020**, *17*, 1986–1995.



*R.B. Fries et al.* Dermal excisional wound healing in pigs following treatment with topically applied pure oxygen  
*2005*

- Healing is a synchrony of multiple critical factors in the process.
- O<sub>2</sub> and its reactive species stimulate VEGF Expression
- Chronic hypoxia impairs VEGF and impairs wound healing and tissue dysfunction
- Supplemental Topical O<sub>2</sub> sustains VEGF and angiogenesis and fibroblast differentiation
- Topical Oxygen has the potential of benefiting some wound types.

*R.B. Fries et al. / Mutation Research 579 (2005) 172–181*



# Wagner 2 vs Wagner 3



# HBOT

- Effects have been studied as systemic circulating effects
- Therapy Delivered in a Clinic with Hyperbaric Chambers
- Intermittent Therapy for specified number of times
- Restricted indications and types of wounds.
  - Diabetic foot wounds and radiation injury most common

# TWO2

- Local Effects
- Delivered at home or other outpatient setting
- Continuous therapy for number of days or weeks
- Wider indications as per type of wound and severity

