Diabetic Foot Ulcers:
Clinical Evidence;
Conflicting Data Reconcilation

Dick Clarke, CHT

Diabetic Foot Ulcers

Review of published clinical research & reconciliation of conflicting data

Primary Training in Hyperbaric Medicine

Columbia, South Carolina

ANNALS OF THE NEW YORK ACADEMY OF SCIENCES

Update on management of diabetic foot ulcers

Everett E, Mathioudakis N. Ann NY Acad Sci 2018

Epidemiology/Consequences

- 9.1-26.1 million DM pts ulcerate annually
- 19-34% DM pts develop ulcers in lifetime
- DFU mortality > 40% at 5 yrs.
- DFUs account for 1/3 of DM costs (US$176b)
- 20% remain unhealed at 1 yr.

"Standard of care practices"

- Vascular assessment…*evaluated for arterial insufficiency* * #
- Infection control… *Dx by inflammation & purulence* * + *cultures obtained before ABN* * #
- Glycemic control…*optimize blood glucose control* * +
- Debridement…*sharp debridement preferred* * #
- Dressing choice…*to allow moist environment & exudate control* * ^
- Wound off-loading…*pressures should be distributed off wound* * ^

*Strength of recommendation…Strong **

Level of evidence …High ^
…Moderate #
…Low +

Everett E, Mathioudakis N
Ann NY Academy Sci 2018

DFU DATA APPRAISAL

Prospective non-formally randomized; 18 HBO 10 no HBO

Diabetic gangrene all inpt. HBO "drastically reduced leg amputations"

2.8 ATA O2 "antibacterial effect" then 2.5 ATA O2 "reparative effect""

Baroni G, *et al.* 1987
Diabetes Care 10;(1):81-86

Retrospective; 168 HBO most with soft tissue & bone infections

Mix of in-outpt. > 50 went to major amputation

Most with angiographic evidence of PVD & absent pedal pulses

Led to study of TCOMS in selection process

Davis JC, 1987
Clinics Pod Med Surg 4(2):429-437

DFU DATA APPRAISAL

Retrospective non-formally randomized pts; 62 HBO 18 no HBO

Diabetic gangrene all inpt; "significant reduction in amputation rate"

Oriani G, *et al.* 1990
J Hyper Med:5(3):171-175

10 yr retrospective 151 pts

Diabetic gangrene all inpt; "significant reduction in amputation rate"

Oriani G, *et al.* 1992
J Hyper Med:7(4):213-221

Adjunctive Systemic Hyperbaric Oxygen Therapy in Treatment of Severe Prevalently Ischemic Diabetic Foot Ulcer

A randomized study

Faglia E, *et al.* Diabetes Care 1996,19(12)

Prospective randomized trial

70 consecutive admitted pts.
35 SC + HBO 33 SC

	SC + HBO	SC	
Major amps.	3 (8.6%)	11 (33.3%)	
Per Wagner Grade			
II	0/4	0/5	
III	1/5 (25%)	0/8	*p* 0.33
IV	2/22 (9.1%)	11/20 (55%)	*p* 0.002

Table 4—*$TcPO_2$ values of s-HBOT and non–s-HBOT groups at admission and at discharge; comparison of increase between the two groups*

	s-HBOT group	non–s-HBOT group	*P* value
n	35	33	
At admission	23.2 ± 10.7	21.3 ± 10.7	0.46
At discharge	37.3 ± 16.1	26.3 ± 13.5	—
Variation	14.0 ± 11.8	5.0 ± 5.4	0.0002

Data are means ± SD and are given as $TcPO_2$ (mmHg). P values were determined by an unpaired Student's *t* test [Satterthwaite (13) degrees of freedom: 48.25].

DFU DATA APPRAISAL

070-165

The Role of Hyperbaric Oxygen Therapy in Ischaemic Diabetic Lower Extremity Ulcers: a Double-blind Randomised-controlled Trial

A. Abidia*, S. Laden*, G. Kuhan*, D. F. Johnson*, A. R. Wilkinson*, P. W. Renwick†, E. A. Masson* and P. T. McCollum*

Abidia A, *et al.* Eur J Vasc Endovasc Surg 2003(25)

Ischemic LE DFU's

Non-healing to SC > 6 weeks

All underwent dx angiography

Flow augmentation pts excluded

25 screened, 18 enrolled, 16 studied

Ulcers healed:	HBO	Sham	
At 6 weeks	5/8	1/8	NS
At 6 months	5/8	2/8	NS
At 1-year	5/8	0/8	0.026

DFU DATA APPRAISAL

Prospective, formally randomized, long-term f/u; 17 HBO 21 no HBO

All outpt. DFU's; effective healing in setting of reversible local hypoxia

Kalani M, *et al.* 2002
J Diabetes Compls;16:153-158

RCT, although unblinded/no sham; 50 HBO 50 no HBO

Infected DFU's, all inpt; effective healing & reduced amputation rate

Duzgun AP, *et al.* 2008
J Foot Ankle Surg;47(6)

DFU DATA APPRAISAL

Hyperbaric Oxygen Therapy Facilitates Healing of Chronic Foot Ulcers in Patients With Diabetes

070-238

Londahl, M *et al.* Diabetes Care 2010;33

DFU > 3 months (mean 10 months)
Wagner grade 2-4

164 assessed; 94 enrolled
57%

SC non-responders > 2 months

Randomized to SC + HBO vs. SC + sham

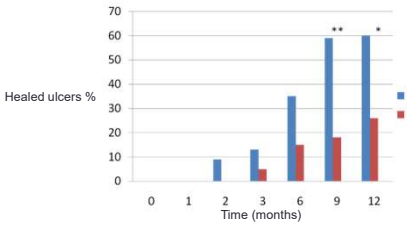
Placebo/sham controls

2.5 ATA (mask) O2 vs. air x 40 sessions

Primary outcome complete healing 1 yr.

Wagner Grade	Lesion
0	Intact skin
1	Superficial ulcer of skin/subcu tissue
2	Ulcer extends into tendon, bone, capsule
3	Deep ulcer with osteomyelitis or abscess
4	Gangrene of toes or forefoot
5	Midfoot or hindfoot gangrene

DFU DATA APPRAISAL



Complete healing at one year:

Intention to treat analysis: ***25/48 (52%) in HBO 12/42 (29%) Sham/SC P < 0.03 NNT 4***

Per protocol analysis: ***23/38 (61%) in HBO 10/37 (27%) Sham/SC P < 0.009 NNT 3***

Londahl M, *et al.* 2010
Diabetes Care;33:998-1003

Specialized Wound Care

We know that having a wound that won't close can be worrisome and affect your quality of life. We can help.
Here's what you can expect when you come to one of our wound centers:

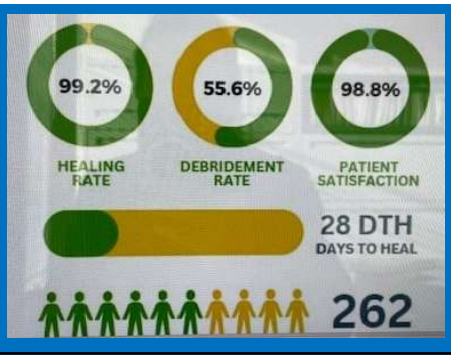
Expertise

Our wound care teams have specialized training in managing and assessing wounds of all types. With access to an ongoing national database that tracks wound treatments and outcomes, we have access to the latest and best therapies.

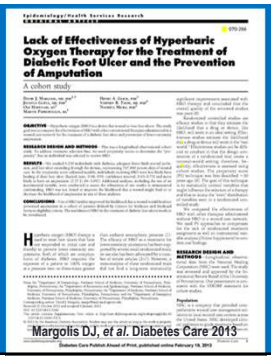
Quality Outcomes

We have consistently excellent outcomes for wound healing.

We successfully close 94 percent of the wounds we treat, higher than the national healing rate of 91 percent
We're skilled at treating even the most complex cases
We prevent limb loss on a daily basis
We heal wounds faster than the national average – often in fewer than 30 days



DFU DATA APPRAISAL



Lack of Effectiveness of Hyperbaric Oxygen Therapy for the Treatment of Diabetic Foot Ulcer and the Prevention of Amputation

A cohort study

Margolis DJ, *et al.* Diabetes Care 2013

Longitudinal observational cohort study

Single wound management company
83 centers in 31 states

11,301 DFU subjects; study limited to 6,259

	HBO not used	HBO used	P
Wound duration (months)	0.96	1.0	NS
Wagner grade ≥ 3 (%)	18.4	45.7 *	<0.0001
Wound size first visit cm2	1.6	1.9	<0.0001
Wounds healed week 16 (%)	49.6	43.2	<0.0001
Major amputation week 16 (%)	1.28	3.28	<0.0001

* *Majority < Grade 3*

DFU DATA APPRAISAL

Hyperbaric Oxygen Therapy Does Not Reduce Indications for Amputation in Patients With Diabetes With Nonhealing Ulcers of the Lower Limb: A Prospective, Double-Blind, Randomized Controlled Clinical Trial

Fedorko L, *et al.* Diabetes Care 2016;39

Trial Design

157 assessed; 107 enrolled; data on 103
68%

SC non-responders > 2 months

DFU > 4 months non-responding SC
Wagner grade 2-4

Randomized to SC + HBO or SC + sham
2.4 ATA O2 vs. 1.2 ATA air

DFU DATA APPRAISAL

Primary outcome measure

Freedom from or meeting criteria for amputation at 12 weeks

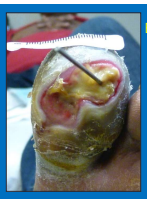
Lack of significant healing; defined as open wound/sepsis risk

Persistent deep infection; hospitalization required

Inability to bear weight on affected limb

Pain causing significant disability

DFU DATA APPRAISAL



Baseline Wagner Grade 3

Post-Study Protocol; 12 Week F/U
Adjudicated for Amputation

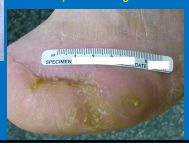
17 Week F/U
Complete Healing

DFU DATA APPRAISAL

Baseline Wagner Grade 3

Post-Study Protocol; 12 Week F/U
Adjudicated for Amputation

16 Week F/U
Complete Healing



DFU DATA APPRAISAL

'Long-term follow-up…will occur at weeks 30 and 52…'

*Both data points missing but 52-week outcomes reported elsewhere **

* Linden R, UHMS ASM 2013

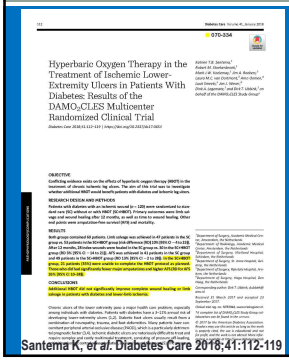
17/37 (46%) adjudicated for AMPUTATION

14/17 not amputated (83% error)

20/37 (54%) adjudicated for NO AMPUTATION

18/37 not amputated (10% error)

DFU DATA APPRAISAL



Hyperbaric Oxygen Therapy in the Treatment of Ischemic Lower-Extremity Ulcers in Patients With Diabetes: Results of the DAMO$_2$CLES Multicenter Randomized Clinical Trial

120 pts randomized; recalculated from 226 required
12% limb salvage difference increased to 25%

SC vs SC + HBO
no sham or blinding

Wagner II-IV present 4 weeks (52% II)

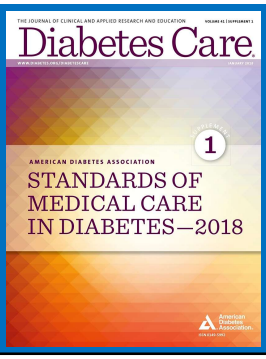
Incomplete tcpO2 testing
local hypoxia (<40 mmHg) no O2 challenge

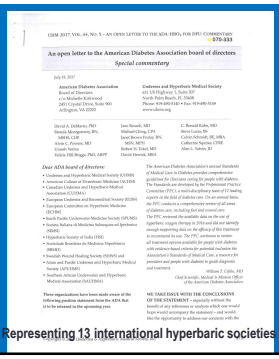
ITT: Amp rates: 12% SC + HBO vs. 22% SC (10% difference)

PP: Amp rates: 5% SC + HBO vs. 22% SC (17% difference)

Santema K, *et al.* Diabetes Care 2018;41:112-119

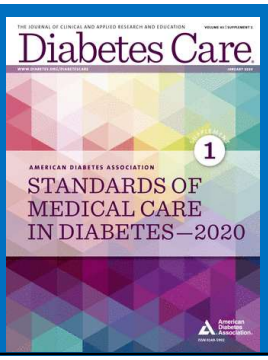
DFU DATA APPRAISAL





Representing 13 international hyperbaric societies

DFU DATA APPRAISAL



Did the ADA get it Wrong with Hyperbaric Medicine?

DFU DATA APPRAISAL

12. Retinopathy, Neuropathy, and Foot Care: Standards of Care in Diabetes—2025

Now takes more nuanced view of HBO therapy

Recognized one positive RCT

Identified two recent RCTs failed to corroborate

While noting trial design deficiencies participant dropouts not evident in the positive RCT

Made point HBO may lower amputation in chronic ischemic ulcers

No benefit from non-ischemic ulcers

ADA Standards of Care in Diabetes 2025;48(Sup. 1

DFU DATA APPRAISAL

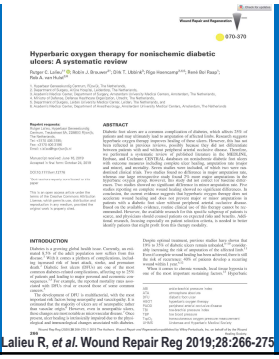
Global vascular guidelines on the management of chronic limb-threatening ischemia

Recognizes HBO-DFU controversy
takes more pragmatic view vs. ADA

"May be a role for HBO to accelerate healing of chronic neuropathic ulcers with low grade ischemia"

"HBO should not be used in setting of significant inflow dz."

Conte MS, *et al.* Eur J Vasc Endovasc Surg 2019



Hyperbaric oxygen therapy for nonischemic diabetic ulcers: A systematic review

"From currently available evidence, it seems pts treated with HBO do not achieve faster healing or benefit in terms of amputation prevention"

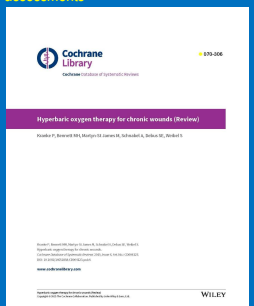
"The RCTs that demonstrate this are of good quality"

Recuring theme; pt. section critical to appropriate HBO use

Lalieu R, *et al.* Wound Repair Reg 2019;28:266-275

DFU DATA APPRAISAL

Evidence assessments


Cochrane Library

Hyperbaric oxygen therapy for chronic wounds (Review)

WILEY

Kranke P, *et al.* Cochrane Database 2015;6

HBO significantly improved short but not long-term healing

Unable to support routine use of HBO for DFU's

May be HBO indication in ischemic ulcers not responding to SC
– *"when revascularization not possible/not entirely successful"*

DFU DATA APPRAISAL

Evidence assessments


Health Quality Ontario

ONTARIO HEALTH TECHNOLOGY ASSESSMENT SERIES

Hyperbaric Oxygen Therapy for the Treatment of Diabetic Foot Ulcers: A Health Technology Assessment

KEY MESSAGES

Ontario Quality Health 2017;17(5):134-143

SC + HBO results in improved ulcer healing vs SC alone

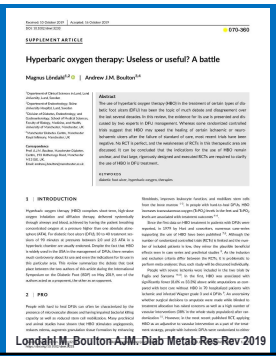
SC + HBO is safe as SC alone

Evidence shortcomings make it difficult to draw definitive

Large degree of uncertainty if SC + HBO cost-effective vs SC alone

Better pt selection methods required

DFU DATA APPRAISAL


Hyperbaric oxygen therapy: Useless or useful? A battle

Magnus Löndahl[1,2] | Andrew J.M. Boulton[3,4]

Londahl M, Boulton AJM. Diab Metab Res Rev 2019

PRO

Presence of microvasc dz; impaired bacterial killing, poor stem cell mobilization = HBO mechanisms

HBO increases tcpO2 levels, such increases associated with improved tx outcomes

Large number of supportive case series, low EBM level but mirror pre-clinical findings

CON

Recent reports of HBO usage lead one to believe many remain in the era of the anecdote

Cochrane review critical of HBO studies
- *lack of blinding*
- *lack of sham*
- *lack of allocation of subjects to groups*
- *lack of ITT*

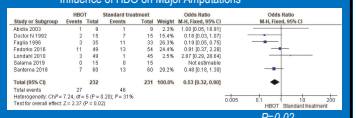
Potential benefits come at high cost & presently difficult to justify

High quality RCT's imperative


The role of hyperbaric oxygen therapy in the treatment of diabetic foot ulcers: a systematic review with meta-analysis of randomized controlled trials on limb amputation and ulcer healing

Moreira Da Cruz DL, *et al.* Int. Angiology 2022;41(1)

Influence of HBO on Major Amputations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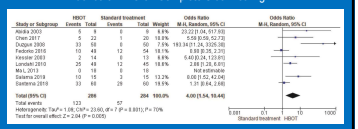
Influence of HBO on Complete Ulcer healing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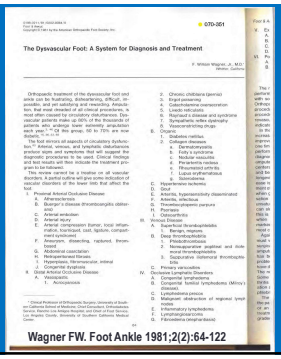

The Dysvascular Foot: A System for Diagnosis and Treatment

Wagner FW. Foot Ankle 1981;2(2):64-122

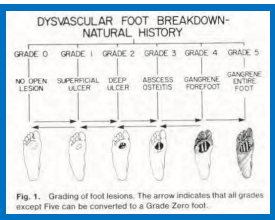


Fig. 1. Grading of foot lesions. The arrow indicates that all grades except Five can be converted to a Grade Zero foot.

Grade 0	Intact skin
Grade 1	Superficial ulcer
Grade 2	Deep ulcer
Grade 3	Ulcer with bone involvement
Grade 4	Forefoot gangrene
Grade 5	Full-foot gangrene

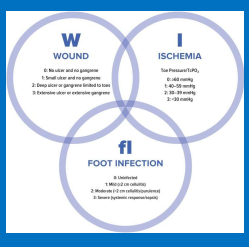
U Texas

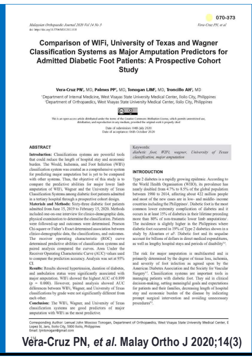
The University of Texas Staging System for Diabetic Foot Ulcers

Stage	Grade 0	Grade I	Grade II	Grade III
A	Pre- or post-ulcerative lesion completely epithelialized	Superficial ulcer, not involving tendon capsule or bone	Ulcer penetrating to tendon or capsule	Ulcer penetrating to bone or joint
B	Infection	Infection	Infection	Infection
C	Ischemia	Ischemia	Ischemia	Ischemia
D	Infection & Ischemia	Infection & Ischemia	Infection & Ischemia	Infection & Ischemia

Score: Grade_____ Stage_____

WIFi





070-373

Malaysian Orthopaedic Journal 2020 Vol 14 No 3 — *Vera-Cruz PN, et al*

Comparison of WIFi, University of Texas and Wagner Classification Systems as Major Amputation Predictors for Admitted Diabetic Foot Patients: A Prospective Cohort Study

Vera-Cruz PN[1], MD, **Palmes PP**[1], MD, **Tonogan LJM**[2], MD, **Troncillo AH**[2], MD

[1]Department of Internal Medicine, West Visayas State University Medical Center, Iloilo City, Philippines
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Date of submission: 04th July 2020
Date of acceptance: 06th October 2020

ABSTRACT

Introduction: Classifications systems are powerful tools that could reduce the length of hospital stay and economic burden. The Would, Ischemia, and Foot Infection (WIFi) classification system was created as a comprehensive system for predicting major amputation but is yet to be compared with other systems. Thus, the objective of this study is to compare the predictive abilities for major lower limb amputation of WIFi, Wagner and the University of Texas Classification Systems among diabetic foot patients admitted in a tertiary hospital through a prospective cohort design.

Keywords: *diabetic foot, WIFi, wagner, University of Texas classification, major amputation*

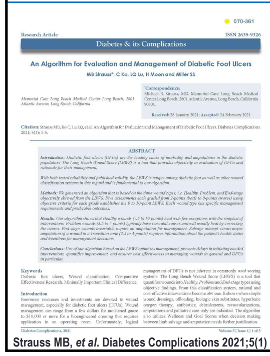
INTRODUCTION

Type 2 diabetes is a rapidly growing epidemic. According to the World Health Organisation (WHO), its prevalence has nearly doubled from 4.7% to 8.5% of the global population between 1980 to 2014, affecting about 422 million people and most of the new cases are in low- and middle- income countries including the Philippines[1].

Vera-Cruz PN, *et al.* Malay Ortho J 2020;14(3)

Small (63 pt) prospective comparison study of admitted DFUs.

All three classification systems good predicters of major amputations with Wifi most predictive although not statistically significant



070-361

Research Article — ISSN 2639-9326

Diabetes & its Complications

An Algorithm for Evaluation and Management of Diabetic Foot Ulcers

MB Strauss*, C Ko, LQ Lu, H Moon and Miller SS

Memorial Care Long Beach Medical Center Long Beach, 2801 Atlantic Avenue, Long Beach, California

*Correspondence: Michael B. Strauss, MD. Memorial Care Long Beach Medical Center Long Beach, 2801 Atlantic Avenue, Long Beach, California 90801.

Received: 28 January 2021; Accepted: 24 February 2021

Citation: Strauss MB, Ko C, Lu LQ, et al. An Algorithm for Evaluation and Management of Diabetic Foot Ulcers. Diabetes Complications. 2021; 5(1); 1-5.

ABSTRACT

Introduction: Diabetic foot ulcers (DFUs) are the leading cause of morbidity and amputations in the diabetic population. The Long Beach Wound Score (LBWS) is a tool that provides objectivity to evaluation of DFUs and rationale for their management.

With both tested reliability and published validity, the LBWS is unique among diabetic foot as well as other wound classification systems in this regard and is fundamental to our algorithm.

Methods: We generated an algorithm that is based on the three wound types, i.e. Healthy, Problem, and End-stage objectively derived from the LBWS. Five assessments each graded from 2-points (best) to 0-points (worse) using objective criteria for each grade establishes the 0 to 10-point LBWS. Each wound type has specific management requirements and predicable outcomes.

Results: Our algorithm shows that Healthy wounds (7.5 to 10-points) heal with few exceptions with the simplest of interventions. Problem wounds (3.5 to 7-points) typically have remedial causes and will usually heal by correcting the causes. End-stage wounds invariable require an amputation for management. Salvage attempt versus major amputation of a wound in a Transition zone (2.5 to 4-points) requires information about the patient's health status and intentions for management decisions.

Strauss MB, *et al.* Diabetes Complications 2021;5(1)

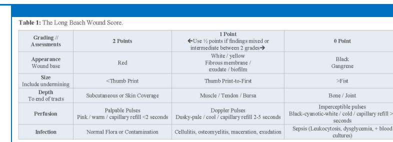
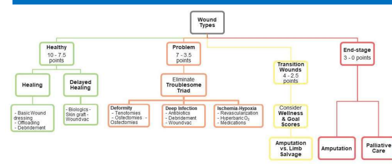


Table 1: The Long Beach Wound Score.

Grading // Assessments	2 Points	1 Point ←Use ½ points if findings mixed or intermediate between 2 grades→	0 Point
Appearance Wound base	Red	White / yellow Fibrous membrane / exudate / biofilm	Black Gangrene
Size Include undermining	<Thumb Print	Thumb Print-to-First	>Fist
Depth To end of tracts	Subcutaneous or Skin Coverage	Muscle / Tendon / Bursa	Bone / Joint
Perfusion	Palpable Pulses Pink / warm / capillary refill <2 seconds	Doppler Pulses Dusky-pale / cool / capillary refill 2-5 seconds	Imperceptible pulses Black-cyanotic-white / cold / capillary refill >5 seconds
Infection	Normal Flora or Contamination	Cellulitis, osteomyelitis, maceration, exudation	Sepsis (Leukocytosis, dysglycemia, + blood cultures)



DFU DATA APPRAISAL

Onus on providers to select appropriately, practice diligently

Resist commercial pressure to *"get patients in the tank"*

Comprehensive work-up - all etiologies identified

Institute standard of care practices
consistent with initial review paper

Failure to respond…*reversible local hypoxia key to HBO use*

HBO to normalize wound repair process vs. heal wound, *per se*