

Diabetic Foot Ulcers: Clinical Evidence; Conflicting Data Reconciliation

Dick Clarke, CHT

Diabetic Foot Ulcers

Review of published clinical research & reconciliation of conflicting data

Primary Training in Hyperbaric Medicine
Columbia, South Carolina

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.

Everett E, Mathioudakis N: Ann NY Acad Sci 2018

"Standard of care practices"

<p>Vascular assessment... <i>evaluated for arterial insufficiency</i> * #</p> <p>Infection control... <i>Dx by inflammation & purulence cultures obtained before ABN</i> * #</p> <p>Glycemic control... <i>optimize blood glucose control</i> * #</p> <p>Debridement... <i>sharp debridement preferred</i> * #</p> <p>Dressing choice... <i>to allow moist environment & exudate control</i> * #</p> <p>Wound off-loading... <i>pressures should be distributed off wound</i> * #</p>	<p><i>Strength of recommendation... Strong *</i></p> <p><i>Level of evidence... High *</i></p> <p><i>...Moderate #</i></p> <p><i>...Low +</i></p>
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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 'repairative 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'

Orlani 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'

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

DFU DATA APPRAISAL

Study Design

30 DM inpatients randomly allocated - 'well matched'

SC (I & D) Antibiotics; DM control)

SC + HBO 4 tx over 2 weeks 3.0 ATA x 45 mins

Assessed wound cultures pre-post HBO, LOS, wound response, amputation & its level

Results				
Parameter	Study Group	Control Group	p	
LOS (days)	40.6 (23-65)	47 (20-68)	NS	
Major amps.	2	7	<0.05	
Minor amps.	4	2	NS	
+ Cultures				
Pre- Post	19/3	16/12	<0.05	

Doctor N, et al. J Postgrad Med 1992;38(3)

Adjunctive Systemic Hyperbaric Oxygen Therapy in Treatment of Severe Prevalently Ischemic Diabetic Foot Ulcer
Faglia E, et al. Diabetes Care 1996,19(12)

First 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—TcPO₂ 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

These are means ± SD and are given as TcPO₂ (mmHg). P values were determined by an unpaired Student's t test. Data shown (33 degrees of freedom): 48.32.

The Role of Hyperbaric Oxygen Therapy in Ischemic Diabetic Lower Extremity Ulcers: A Double-Blind Randomized-Controlled Trial
Abidia A, et al. Eur J Vasc Endovasc Surg 2003(25)

Ischemic LE DFUs
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

Prospective, formally randomized, long-term flw: 17 HBO 21 no HBO
All outpt. DFUs: effective healing in setting of reversible local hypoxia
Kallani M, et al 2002
J Diabetes Comp 16:153-158

RCT, although unblinded/no sham: 50 HBO 50 no HBO
Infected DFUs, all inpt: effective healing & reduced amputation rate
Duggan AP, et al 2008
J Foot Ankle Surg 47 (6)

Intervention	Grade 1 (n = 31)		Grade 2 (n = 31)		Grade 3 (n = 31)		Grade 4 (n = 9)	
	SC	HBO	SC	HBO	SC	HBO	SC	HBO
Healed (%)	100	100	100	100	100	100	100	100
Healed at 1 yr (%)	100	100	100	100	100	100	100	100
Healed at 2 yr (%)	100	100	100	100	100	100	100	100
Healed at 3 yr (%)	100	100	100	100	100	100	100	100
Healed at 4 yr (%)	100	100	100	100	100	100	100	100
Healed at 5 yr (%)	100	100	100	100	100	100	100	100
Healed at 6 yr (%)	100	100	100	100	100	100	100	100
Healed at 7 yr (%)	100	100	100	100	100	100	100	100
Healed at 8 yr (%)	100	100	100	100	100	100	100	100
Healed at 9 yr (%)	100	100	100	100	100	100	100	100
Healed at 10 yr (%)	100	100	100	100	100	100	100	100
Healed at 11 yr (%)	100	100	100	100	100	100	100	100
Healed at 12 yr (%)	100	100	100	100	100	100	100	100

Hyperbaric Oxygen Therapy Facilitates Healing of Chronic Foot Ulcers in Patients With Diabetes
Londahl, M et al. Diabetes Care 2010;33

Trial Design/Primary Outcome
164 assessed: 94 enrolled
57%
SC non-responders > 2 months
DFU > 3 months (mean 10 months)
Wagner grade 2-4
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.

Healed ulcers (%)

Week	HBO (%)	Placebo (%)
0	0	0
1	0	0
2	~10	~5
3	~15	~10
6	~35	~15
9	~60	~20
12	~65	~25

Complete healing at one year:
Intention to treat analysis: 25/48 (52%) in HBO 12/42 (29%) Sham P < 0.03 NNT 4
Per protocol analysis: 23/38 (61%) in HBO 10/37 (27%) Sham 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

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

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

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 \geq 3 (%)	18.4	45.7 *	<0.0001
Wound size first visit cm ²	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

Margolis DJ, et al Diabetes Care 2013

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

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

2:4:1:1:0:2 vs. 1:2:1:1:0:2

Fedorko L, et al Diabetes Care 2016;39

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




17 Week F/U Complete Healing




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

DFU DATA APPRAISAL

Baseline Wagner Grade 3



16 Week F/U Complete Healing



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

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)

TCOM screening per protocol but not employed

DFU DATA APPRAISAL

Hyperbaric Oxygen Therapy in the Treatment of Ischemic Lower Extremity Ulcers in Patients With Diabetes: Results of the DAMOCLES 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 IspO₂ 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

Diabetes Care

AMERICAN DIABETES ASSOCIATION

1

STANDARDS OF MEDICAL CARE IN DIABETES—2018

Representing 13 international hyperbaric societies

DFU DATA APPRAISAL

Diabetes Care

AMERICAN DIABETES ASSOCIATION

1

STANDARDS OF MEDICAL CARE IN DIABETES—2020

Did the ADA get it wrong with Hyperbaric Medicine?

The American Diabetes Association has long advocated the use of HBO for diabetic foot ulcers, and the Standards of Medical Care in Diabetes 2020 is no exception.

This standard states that patients with diabetic foot ulcers should be treated with HBO if and only if they have Wagner II or III ulcers, and the standard also states that HBO should not be used for Wagner I or IV ulcers.

One might be inclined to believe the ADA's decision for allowing that these patients, particularly those who have Wagner II or III ulcers, should be treated with HBO. However, a review of the literature and other sources (1) for evidence that HBO is an effective treatment for diabetic foot ulcers is presented in this article.

Hyperbaric Medicine, Inc.

DFU DATA APPRAISAL

Diabetes Care

AMERICAN DIABETES ASSOCIATION

Supplement 1

Standards of Care in Diabetes—2023

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

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CLINICAL PRACTICE GUIDELINE DOCUMENT

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

DFU DATA APPRAISAL

Hyperbaric oxygen therapy for nonischemic diabetic ulcers: A systematic review

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

"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"

Recurring theme: pt. section critical to appropriate HBO use

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

DFU DATA APPRAISAL

Evidence assessments



HBO significantly improved short but not long-term healing


Unable to support routine use of HBO for DFUs

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

Kranke P, et al. Cochrane Database 2015:6

DFU DATA APPRAISAL

Evidence assessments



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

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

DFU DATA APPRAISAL

Evidence assessments



PRO

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

HBO increases IgG levels, such increases associated with improved outcomes

Large number of supportive case series, low EBM level but minor 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 allocation of subjects to groups
- lack of ITT


Potential benefits come at high cost & presently difficult to justify

High quality RCT's imperative

Londahl M, Boulton AJM. Diab Metab Res Rev 2019

DFU DATA APPRAISAL

Evidence assessments



Influence of HBO on Major Amputations

Study or Subgroup	Events	Number	Events	Number	Weight	M-H, Random, 95% CI
Wagner 2002	1	48	2	48	11.2%	1.00 [0.05, 19.95]
Wagner 2005	1	105	7	105	24.2%	1.00 [0.05, 19.95]
Wagner 2008	1	45	1	45	11.2%	1.00 [0.05, 19.95]
Wagner 2010	1	93	3	93	22.8%	1.00 [0.05, 19.95]
Wagner 2012	1	45	1	45	11.2%	1.00 [0.05, 19.95]
Total events		236	14	236	100%	0.02 [0.00, 0.04]

P=0.02

Influence of HBO on Complete Ulcer healing

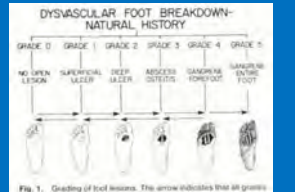
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Wagner 2010	2	93	2	93	22.8%	1.00 [0.05, 19.95]
Wagner 2012	1	45	1	45	11.2%	1.00 [0.05, 19.95]
Total events		236	8	236	100%	0.03 [0.01, 0.05]

P=0.005

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

DFU DATA APPRAISAL

Evidence assessments



DYSVASCULAR FOOT BREAKDOWN-NATURAL HISTORY

GRADE 0: NO OPEN LESION
 GRADE 1: SUPERFICIAL LESION
 GRADE 2: DEEP ULCER
 GRADE 3: ABSCESS, OSTEOITIS
 GRADE 4: GANGRENE FOREFOOT
 GRADE 5: GANGRENE FORE & MIDDLE FOOT

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

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

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Evidence assessments

U Texas

Step	Grade 0	Grade 1	Grade 2	Grade 3
A	Pre or post observation Non-infectious No wound bed or exposed tissue	Superficial ulcer, not requiring medical attention or surgery	Ulcer penetrating to bone or joint	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 ____ Step ____

WIFI



W WOUND

- 1. No wound or ulcers
- 2. Small ulcer or ulcers
- 3. Large ulcer or ulcers
- 4. Ulcer with exposed bone or tendon
- 5. Ulcer with exposed bone or tendon and infection

I ISCHEMIA

- 1. No ischemia
- 2. Mild ischemia
- 3. Moderate ischemia
- 4. Severe ischemia

fi FOOT INFECTION

- 1. No infection
- 2. Mild infection
- 3. Moderate infection
- 4. Severe infection

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

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

All three classification systems good predictors of major amputations with Waii most predictive although not statistically significant.

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

Diabetes & Its Complications

An Algorithm for Evaluation and Management of Diabetic Foot Ulcers

Wagner's Classification

Wagner's	1 Phase	2 Phase	3 Phase
Classification	Ulcer	Ulcer + Ischemia	Ulcer + Ischemia + Infection
Appearance	Red	White/gray	Black
Depth	Epithelium	Epithelium + dermis	Epithelium + dermis + bone
Ischemia	None	Minimal	Severe
Infection	None	None	Present

Table 3: The Long Beach Wound Study

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

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*