

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.

ANNALS OF THE NEW YORK ACADEMY OF SCIENCES

DOI 10.1111/anys.12178

Update on management of diabetic foot ulcers

Evellett E. Everett and Mathioudakis N. Ann NY Acad Sci 2018

"Standard of care practices"

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

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

Hyperbaric Oxygen Therapy in Diabetic Foot

HUBER DOCTOR, ANASTAS PAVLOS, KRISTINA GONG

Study Design

30 DM inpatients randomly allocated - "well matched"

SC (I & D; Antibiotics; DM control)

SC + HBO 4 hr 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;36(3)

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

A randomized study

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
IV	2/22 (9.1%)	11/20 (55%)

Table 4—TPO₂ 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
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

This data means a SD and are given as TPO₂ (mmHg). P values were determined by an unpaired Student's t-test. Statview (5.3) degree of freedom: 48, 25.

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

The Role of Hyperbaric Oxygen Therapy in Ischemic Diabetic Lower Extremity Ulcers: A Double-Blind Randomized-controlled Trial

A. Abidia, G. Lohr, G. Kasper, J. P. Gagnier, J. S. Whitson, P. W. Rowan, S. A. Stewart and P. J. Reid

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

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

Prospective, formally randomized, long-term flw; 17 HBO 21 no HBO
All outpt. DFUs; effective healing in setting of reversible local hypoxia

Kellars M, et al. 2002
J Diabetes Compl:16:153-158

RCT, although unblinded/no sham; 50 HBO 50 no HBO
Infected DFUs, all inpt; effective healing & reduced amputation rate

Table 4. Outcomes by Intervention and Last Grade (N = 102)

Outcome	HBO (n = 50)		No HBO (n = 52)	
	n	%	n	%
Healed	35	70	25	48
Amputated	15	30	27	52
Wagner grade at last visit				
0	10	20	5	10
1	10	20	10	19
2	10	20	10	19
3	5	10	10	19
4	0	0	5	10

Duggan AP, et al. 2008
J Foot Ankle Surg 47(6)

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

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.

Londahl, M et al. Diabetes Care 2010;33

Healed ulcers (%)

Week	HBO (%)	Placebo (%)
0	0	0
1	0	0
2	10	0
3	15	5
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

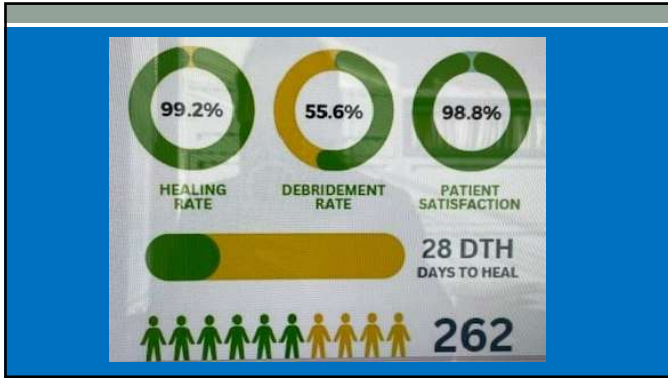
Londahl M, et al. 2010
Diabetes Care;33:998-1003

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



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

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 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 ATA O₂ vs. 1:2 ATA air

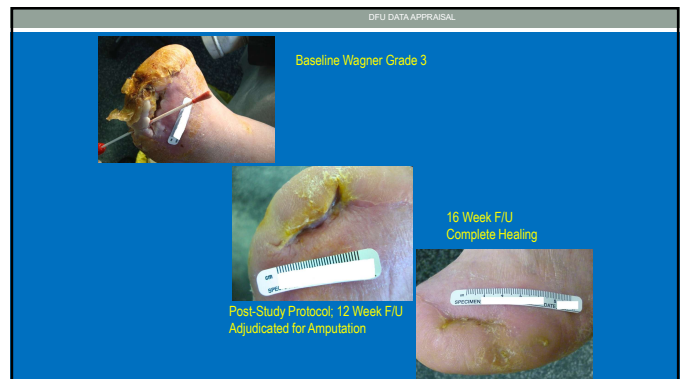
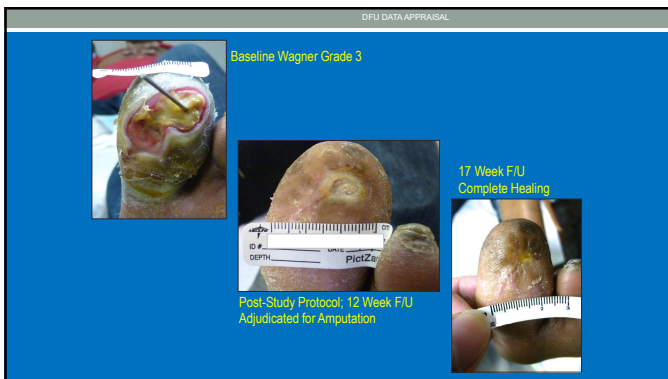
Fedorko L, et al. Diabetes Care 2016;39

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

'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 DIAMOCLES Multicenter Randomized Clinical Trial

120 pts randomized, recalculated from 225 required
12% limb salvage difference increased to 25%

SC vs SC + HBO
no sham or blinding

Wagner I-II-V present 4 weeks (52% #)

Incomplete topO2 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

STANDARDS OF MEDICAL CARE IN DIABETES—2018

Representing 13 international hyperbaric societies

DFU DATA APPRAISAL

Diabetes Care

AMERICAN DIABETES ASSOCIATION

STANDARDS OF MEDICAL CARE IN DIABETES—2020

Did the ADA get it Wrong with Hyperbaric Medicine?

The American Diabetes Association has long promoted the use of HBO therapy for diabetic foot ulcers and their treatment in Diabetes Care in December 2017 in an editorial.

The editorial presents evidence about standards of care for diabetic foot ulcers, or at least that, in my view, the single most identifiable weakness of our guidelines, hyperbaric oxygen therapy. The ADA, though otherwise, is well-served and respected standard of care, particularly in the guidelines for diabetic foot ulcers and their treatment in Diabetes Care in December 2017 in an editorial.

Major diabetes foot ulcers

DFU DATA APPRAISAL

12. Retinopathy, Neuropathy, and Foot Care: Standards of Care in Diabetes—2024

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 2024.7(Sup. 1)

DFU DATA APPRAISAL

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

Evidence assessments

Hyperbaric oxygen therapy for nonischemic diabetic ulcers: A systematic review

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

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. selection critical to appropriate HBO use

Evidence assessments

Hyperbaric oxygen therapy for chronic wounds (Review)

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 DFUs

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

Evidence assessments

Health Quality Ontario

ONTARIO HEALTH TECHNOLOGY ASSESSMENT SERIES

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

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

Evidence assessments

Hyperbaric oxygen therapy: Useless or useful? A battle

Londahi M, Boulton AJM. Diab Metab Res Rev 2019

PRO

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

HBO increases topO2 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

Influence of HBO on Major Amputations

Study or Subgroup	HBO	Standard Treatment	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	Overall Events	M-H, Fixed, 95% CI
Chen 2012	5	7	0	12	0	12	0.18	0.02, 0.01, 0.01	5	0.02, 0.01, 0.01
Fisher 1998	2	35	11	37	32	37	0.18	0.18, 0.18, 0.18	2	0.18, 0.18, 0.18
Fisher 2014	11	48	13	61	54	61	0.28	0.28, 0.28, 0.28	11	0.28, 0.28, 0.28
Livshits 2010	7	48	1	49	45	49	0.28	0.28, 0.28, 0.28	7	0.28, 0.28, 0.28
Schone 2010	5	15	0	15	15	15	0.28	0.28, 0.28, 0.28	5	0.28, 0.28, 0.28
Total (95% CI)	30	133	39	163	156	163	0.93	0.93, 0.93, 0.93	39	0.93, 0.93, 0.93

Influence of HBO on Complete Ulcer healing

Study or Subgroup	HBO	Standard Treatment	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	Overall Events	M-H, Fixed, 95% CI
Chen 2012	5	7	0	12	0	12	0.18	0.02, 0.01, 0.01	5	0.02, 0.01, 0.01
Chen 2017	5	22	1	27	20	27	0.18	0.18, 0.18, 0.18	5	0.18, 0.18, 0.18
Dzau 2006	31	64	10	95	82	95	0.28	0.28, 0.28, 0.28	31	0.28, 0.28, 0.28
Fisher 2010	12	48	1	60	54	60	0.28	0.28, 0.28, 0.28	12	0.28, 0.28, 0.28
Fisher 2014	22	14	0	36	36	36	0.28	0.28, 0.28, 0.28	22	0.28, 0.28, 0.28
Li 2012	0	18	1	18	17	18	0.28	0.28, 0.28, 0.28	0	0.28, 0.28, 0.28
Schone 2010	10	12	2	22	20	22	0.28	0.28, 0.28, 0.28	10	0.28, 0.28, 0.28
Schone 2010	33	49	29	82	53	82	0.28	0.28, 0.28, 0.28	33	0.28, 0.28, 0.28
Total (95% CI)	123	204	50	327	305	327	0.93	0.93, 0.93, 0.93	50	0.93, 0.93, 0.93

The Dysvascular Foot: A System for Diagnosis and Treatment

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

DYSVASCULAR FOOT BREAKDOWN-NATURAL HISTORY

GRADE 0 GRADE 1 GRADE 2 GRADE 3 GRADE 4 GRADE 5

NO OPEN LESION SUPERFICIAL ULCER DEEP ULCER ABSCESS/OSTEITIS GANGRENE FOREFOOT GANGRENE ENTIRE 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

WIFI

The University of Texas System for Diabetic Foot Ulcers

Stage	Grade 0	Grade I	Grade II	Grade III
A	Pre- or post-operative lesion completely epithelialized	Superficial ulcer, not breaking tender capsule of skin	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 ____

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

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

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

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

Diabetes & its Complications

An Algorithm for Evaluation and Management of Diabetic Foot Ulcers

Table 1. The Long Beach Wound Score

Grading Assessment	2 Points	1 Point	0 Points
Appearance	Red	White (pale) or Black (necrotic) or necrotic tissue > 3 pixels*	Black
Wound base	Red	White (pale) or Black (necrotic) or necrotic tissue > 3 pixels*	Black
Wound bed	Red	White (pale) or Black (necrotic) or necrotic tissue > 3 pixels*	Black
Depth	> 10mm	> 5mm	> 2mm
Transfers	Substance of Skin Coverage	Moist / Tender / Bony	None / Dead
Perforation	Palpable Probe	Diagonal Probe	Impassible Probe
Infection	Pink / warm / capillary refill < 2 seconds	Dark / cool / capillary refill > 2 seconds	Black / cyanotic / cool / capillary refill > 2 seconds
Ischemia	Normal Flies or Capillarization	Cyanosis, anisocytosis, leukocytosis, exudate	Sepsis/Leukocytosis, oligocytosis, + blood clotting

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