

Diabetic Foot Ulcers: Clinical Evidence; Conflicting Data Reconciliation

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Diabetic Foot Ulcers

Review of published clinical research & reconciliation of conflicting data

Primary Training in Hyperbaric Medicine

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Update on management of diabetic foot ulcers

Diabetic foot ulcers (DFUs) are a leading cause of morbidity and mortality in patients with diabetes mellitus. The management of DFUs is complex and often challenging, requiring a multidisciplinary approach. This review discusses the latest evidence on the management of DFUs, focusing on the use of hyperbaric oxygen (HBO) therapy.

Key findings:

- 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"

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. 1997
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

Prospective formally randomized: 35 HBO 33 no HBO

Diabetic gangrene all inpt. "significant reduction in major amputation rate"

Faglia E, et al 1996
Diabetes Care 19(10):1261-64

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

Parameter	Results		p
	Study Group	Control Group	
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: A randomized study

First prospective & randomized trial

70 consecutive admitted pts.
35 SC + HBO 33 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—Tiffi 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 \pm SD and are given as Tiffi (cmHg). P values were determined by an unpaired Student's t-test. Data between (33) degrees 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, R. Lohar, S. Kishor, A. P. Kishor, A. S. Kishor, J. R. Kishor, S. S. Kishor, and P. Kishor

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

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

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

Infected DFUs, all inpt: effective healing & reduced amputation rate

Table 4. Outcome by intervention and ulcer grade (N = 102)

Intervention	Grade 1 (N = 10)	Grade 2 (N = 10)	Grade 3 (N = 10)	Grade 4 (N = 10)	Grade 5 (N = 10)	Grade 6 (N = 10)	Grade 7 (N = 10)	Grade 8 (N = 10)	Grade 9 (N = 10)	Grade 10 (N = 10)	Grade 11 (N = 10)	Grade 12 (N = 10)	P value
HBO	10	10	10	10	10	10	10	10	10	10	10	10	0.002
No HBO	10	10	10	10	10	10	10	10	10	10	10	10	0.002

Katani M, et al 2002
J Diabetes Comp 16:153-158

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

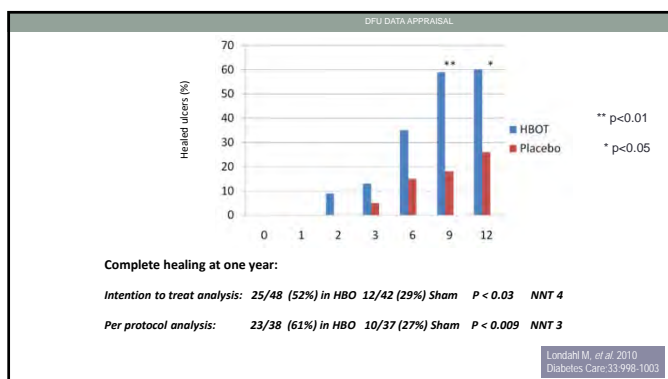
Randomized to SC + HBO vs. SC + sham

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



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

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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 ≥ 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 Or vs. 1:2 ATA air

Fedorko L, et al Diabetes Care 2016:39

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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

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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



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'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

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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 IgD2 testing
local hypoxia (<40 mmHg) no O2 challenge

ITT: No significant difference (10% difference)

PP: Amp decrease (5% SC + HBO vs 22% SC)
39/60 completed HBO

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

DFU DATA APPRAISAL

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Representing 13 International hyperbaric societies

DFU DATA APPRAISAL

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Did the ADA get it Wrong with Hyperbaric Medicine?

Diabetes Care

STANDARDS OF MEDICAL CARE IN DIABETES—2020

Diabetes Care

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Diabetes Care

STANDARDS OF MEDICAL CARE IN DIABETES—2020

DFU DATA APPRAISAL

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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

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

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

Abstract

Background: The purpose of this study was to compare the predictive accuracy of three classification systems (Wifit, University of Texas, and Wagner) for major amputation in diabetic foot patients. The study was a prospective cohort study conducted over 12 months. The study included 63 patients who were admitted to the hospital with a diabetic foot ulcer. The patients were classified into three groups based on the classification system used. The Wifit classification system was used for the first group, the University of Texas classification system for the second group, and the Wagner classification system for the third group. The primary outcome was the rate of major amputation. The secondary outcome was the rate of minor amputation. The results showed that the Wifit classification system was the most accurate predictor of major amputation. The University of Texas classification system was the second most accurate predictor, and the Wagner classification system was the least accurate predictor. The study concluded that the Wifit classification system is the most accurate predictor of major amputation in diabetic foot patients.

Conclusion: The Wifit classification system is the most accurate predictor of major amputation in diabetic foot patients. The University of Texas classification system is the second most accurate predictor, and the Wagner classification system is the least accurate predictor. The study concluded that the Wifit classification system is the most accurate predictor of major amputation in diabetic foot patients.

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 predictors of major amputations with Wifit most predictive although not statistically significant

Diabetes & its Complications

An Algorithm for Evaluation and Management of Diabetic Foot Ulcers

Abstract

Background: The purpose of this study was to develop an algorithm for the evaluation and management of diabetic foot ulcers. The study was a retrospective cohort study conducted over 12 months. The study included 100 patients who were admitted to the hospital with a diabetic foot ulcer. The patients were classified into three groups based on the severity of the ulcer. The first group included patients with a mild ulcer, the second group included patients with a moderate ulcer, and the third group included patients with a severe ulcer. The primary outcome was the rate of major amputation. The secondary outcome was the rate of minor amputation. The results showed that the algorithm was effective in predicting the rate of major amputation. The algorithm was also effective in predicting the rate of minor amputation. The study concluded that the algorithm is an effective tool for the evaluation and management of diabetic foot ulcers.

Conclusion: The algorithm is an effective tool for the evaluation and management of diabetic foot ulcers. The algorithm is also effective in predicting the rate of major amputation and the rate of minor amputation. The study concluded that the algorithm is an effective tool for the evaluation and management of diabetic foot ulcers.

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

A Multinational, Multicenter, Randomized, Double-Blinded, Placebo-Controlled Trial to Evaluate the Efficacy of Cyclical Topical Wound Oxygen Therapy (TWOG) in the Treatment of Chronic Diabetic Foot Ulcers: The TWOG Study

Abstract

Background: The purpose of this study was to evaluate the efficacy of cyclical topical wound oxygen therapy (TWOG) in the treatment of chronic diabetic foot ulcers. The study was a multinational, multicenter, randomized, double-blinded, placebo-controlled trial conducted over 12 months. The study included 100 patients who were admitted to the hospital with a chronic diabetic foot ulcer. The patients were classified into two groups based on the treatment they received. The first group included patients who received TWOG, and the second group included patients who received a placebo. The primary outcome was the rate of major amputation. The secondary outcome was the rate of minor amputation. The results showed that TWOG was effective in reducing the rate of major amputation. TWOG was also effective in reducing the rate of minor amputation. The study concluded that TWOG is an effective treatment for chronic diabetic foot ulcers.

Conclusion: TWOG is an effective treatment for chronic diabetic foot ulcers. TWOG is also effective in reducing the rate of major amputation and the rate of minor amputation. The study concluded that TWOG is an effective treatment for chronic diabetic foot ulcers.

Frykberg RG, et al. *Diabetes Care* 2019

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*