

# **Diabetic Foot Ulcers: Clinical Evidence; Conflicting Data Reconciliation**

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**Dick Clarke, CHT**



DFU DATA APPRAISAL

070-145

**The Role of Hyperbaric Oxygen Therapy in Ischemic Diabetic Lower Extremity Ulcers: A Double-Blind, Randomized-Controlled Trial**  
 A. Abidia, G. Lauer, G. Lauer, B. J. Johnson, A. S. Williams, P. M. Rowan, L. A. Walker and T. R. DeFronzo

**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	0.025

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

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Prospective, formally randomized, long-term (1y), 17 HBO 21 no HBO

All outpt. DFUs; effective healing in setting of reversible local hypoxia

Kalani 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

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

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070-218

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

DFU > 3 months (mean 10 months)  
 Wagner grade 2-4  
 164 assessed; 94 enrolled  
 37% w/ with tissue hypoxia per tcpO2  
 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/subcutis 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

\* HBO does not induce angiogenesis in normally oxygenated tissue

Londahl M et al. Diabetes Care 2010;33

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Healed ulcers %

Time (months)

Legend: HBO (blue), Placebo (red)

\*\* p<0.01  
 \* p<0.05

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.

99.2% HEALING RATE

55.6% DEBRIDEMENT RATE

98.8% PATIENT SATISFACTION

28 DTH DAYS TO HEAL

262

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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 <sup>2</sup>	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 O<sub>2</sub> 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



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)

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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 HBO  
no sham or blinding  
Wagner II-IV present 4 weeks (52% H)  
Incomplete tcpO<sub>2</sub> testing  
local hypoxia (<40 mmHg) no O<sub>2</sub> 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

1

Representing 13 international hyperbaric societies

DFU DATA APPRAISAL

Diabetes Care

AMERICAN DIABETES ASSOCIATION

STANDARDS OF MEDICAL CARE IN DIABETES—2020

1

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 Standards of Medical Care in Diabetes 2018 got it wrong.

The standard practice guideline about amputation of one or both feet in patients with a foot ulcer, as of 2018, is to use amputation. The single most important evidence of one published hyperbaric study research. The ADA thought amputation was not the best option. The ADA thought amputation was not the best option. The ADA thought amputation was not the best option.

Now makes more measured view

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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Diabetes Care

AMERICAN DIABETES ASSOCIATION

STANDARDS OF MEDICAL CARE IN DIABETES—2025 (Sup. 1)

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

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

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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

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Wound Repair and Regeneration

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"

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

**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

**PRO**

Presence of microvascular impaired bacterial killing, poor stem cell mobilization = HBO medications

HBO increases logO2 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

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

- 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

**Supplemental Article**

**Hyperbaric oxygen therapy: Useless or useful? A battle**

Megaw Lardner MD | Andrew JAJ Boulton MD

**1 INTRODUCTION**

Hyperbaric oxygen therapy (HBO) has been used for a wide range of conditions for over a century. It involves breathing 100% oxygen at pressures greater than 1 atmosphere (101.3 kPa). The most common use is for decompression sickness and arterial gas embolism. Other uses include wound healing, carbon monoxide poisoning, and radiation injury. HBO is also used for the treatment of diabetic foot ulcers (DFUs). The use of HBO for DFUs is controversial, with some studies showing improved healing and others showing no benefit. This article discusses the evidence for and against the use of HBO for DFUs and provides a practical approach to its use.

**2 HBO**

People with DFUs often have a combination of arterial and venous disease. HBO may improve arterial blood flow and oxygenation of the wound bed. It may also have antibacterial effects and stimulate wound healing. However, HBO is expensive and may have side effects. The use of HBO for DFUs should be based on individual patient factors and the availability of resources.

**Londahi M, Boulton AJM. Diab Metab Res Rev 2019**

**Influence of HBO on Major Amputations**

Study or Subgroup	HBO†	Standard treatment	Odds Ratio	Odds Ratio, 95% CI
Albera 2002	1	1	0.2	0.03, 1.8
Chakrabarti 2002	1	7	15.4	0.9, 251.0
Jain 1999	1	11	20.3	0.9, 450.0
Chakrabarti 2016	1	46	1.6	0.9, 2.7
Chakrabarti 2018	1	4	2.8	0.7, 10.8
Chakrabarti 2019	1	15	1.6	0.8, 2.8
Chakrabarti 2020	1	13	0.2	0.01, 1.5
<b>Total (95% CI)</b>	<b>232</b>	<b>231</b>	<b>100%</b>	<b>0.53 [0.33, 0.86]</b>

**Influence of HBO on Complete Ulcer healing**

Study or Subgroup	HBO†	Standard treatment	Odds Ratio	Odds Ratio, 95% CI
Albera 2002	0	0	0	0.0, 0.0
Chakrabarti 2002	0	1	0	0.0, 0.0
Chakrabarti 2016	0	22	0	0.0, 0.0
Chakrabarti 2018	2	14	1.8	0.4, 8.0
Chakrabarti 2019	4	12	1.6	0.6, 4.0
Chakrabarti 2020	0	16	0	0.0, 0.0
Chakrabarti 2021	0	3	1.2	0.2, 5.8
Chakrabarti 2022	1	12	0	0.0, 0.0
<b>Total (95% CI)</b>	<b>208</b>	<b>208</b>	<b>100%</b>	<b>4.05 [1.54, 10.40]</b>

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

**The Dysvascular Foot: A System for Diagnosis and Treatment**

**DYSVASCULAR FOOT BREAKDOWN-NATURAL HISTORY**

GRADE 0: NO OPEN LESION  
GRADE 1: SUPERFICIAL ULCER  
GRADE 2: DEEP ULCER  
GRADE 3: ABSCESS/OSTEITIS  
GRADE 4: GANGRENE FOREFOOT  
GRADE 5: GANGRENE EXTRE 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**

**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**

**WOUND**  
1. No open ulcer  
2. Small ulcer or gangrene  
3. Extensive ulcer or gangrene

**I ISCHEMIA**  
1. No ulcers  
2. No ulcers  
3. No ulcers

**fi FOOT INFECTION**  
1. No infection  
2. Mild infection  
3. Severe infection

**Comparison of WIFI, 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 Wifi 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  
 Strauss MB, et al. Diabetes Complications 2021;5(1)

**Table 1: The Long Beach Wound Score**

Grading / Appearance	2 Pain	3 Edge	4 Plant
Grading / Appearance	Red	White / yellow / black / crust / fibrinous / necrotic / slough / eschar	Black / crust / fibrinous / necrotic / slough / eschar
Pain	Throat Pain	Throat Pain or Foot	Foot
Edge	Substance or Skin Coverage	Moist / Tender / Pain	None / Pain
Plant	Diabetic Ulcer	Diabetic Ulcer	Ischemic Ulcer
Foot	Pain / warm / capillary refill < 2 seconds	Diabetic Ulcer	Diabetic Ulcer
Intervene	Normal Flaps or Contamination	Culture, osteomyelitis, necrosis, eschar	Septic Embolism, thrombosis, + blood cultures

**Wound Type Flowchart:**

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    graph TD
        WT[Wound Type] --> H[Healthy  
0-1 points]
        WT --> P[Problem  
2-3 points]
        WT --> T[Transition Wound  
4-5 points]
        WT --> E[End-stage  
6-9 points]
        
        H --> H1[Healing  
Best Wound Healing Practices]
        H --> H2[Delayed Healing  
Delayed Wound Healing Practices]
        
        P --> P1[Chronic Traumatic Ulcer  
Debridement / Dressings / Compression / Offloading]
        P --> P2[Diabetic Ulcer  
Debridement / Dressings / Compression / Offloading]
        P --> P3[Ischemic Ulcer  
Debridement / Dressings / Compression / Offloading]
        
        T --> T1[Amputation & Limb Salvage  
Amputation / Palliative Care]
        T --> T2[Amputation & Limb Salvage  
Amputation / Palliative Care]
        
        E --> E1[Amputation & Limb Salvage  
Amputation / Palliative Care]
        E --> E2[Amputation & Limb Salvage  
Amputation / Palliative Care]
    
```

**DFU DATA APPRAISAL**

**Onus on providers to select appropriately, practice diligently**

Resist commercial/financial 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 effective HBO use

HBO to normalize wound repair process vs. heal wound\_per se