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

Issue: The Year in Diabetes and Obesity

REVIEW

Update on management of diabetic foot ulcers

Estelle Everett and Nastoula Mathioudakis

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

DFU DATA APPRAISAL

070-092

Hyperbaric Oxygen Therapy in Diabetic Foot

NILESH DOCTOR, SANJAY PANDYA, AYMANN SORK

Abstract

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

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

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

A randomized study

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).

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

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

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 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)

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

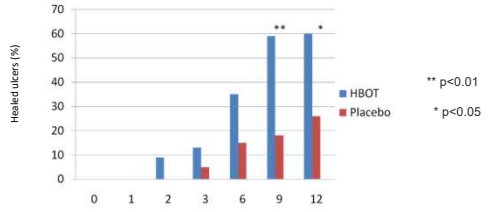
Randomized to SC + HBO vs. SC + sham

Placebo/sham controls

2.5 ATA (mask) O_2 vs. air x 40 sessions

Primary outcome complete healing 1 yr.

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



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:

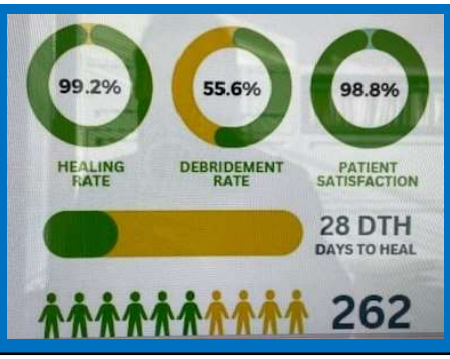
Expertise

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.

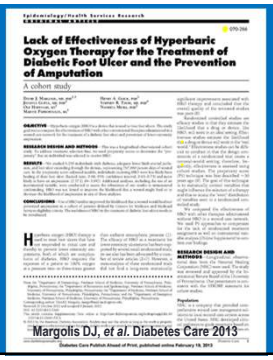
Quality Outcomes

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

Longitudinal observational cohort study

Single wound management company
83 centers in 31 states

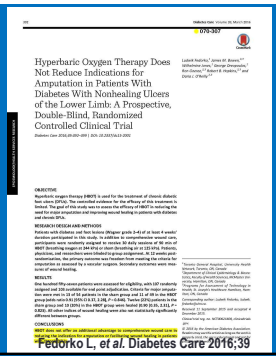
11,301 DFU subjects; study limited to 6,259

	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*

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

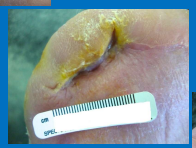
Baseline Wagner Grade 3

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

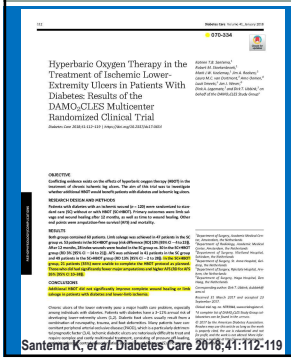
14/17 not amputated (83% error)

20/37 (54%) adjudicated for NO AMPUTATION

18/37 not amputated (10% error)

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 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)

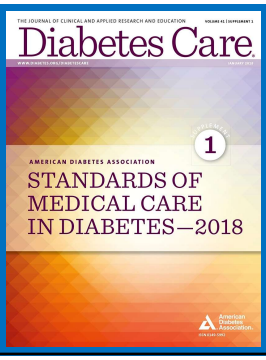
Incomplete tcpO2 testing
local hypoxia (<40 mmHg) no O2 challenge

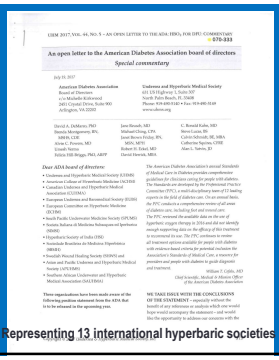
ITT: Amp rates: 12% SC + HBO vs. 22% SC (10% difference)

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

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

DFU DATA APPRAISAL

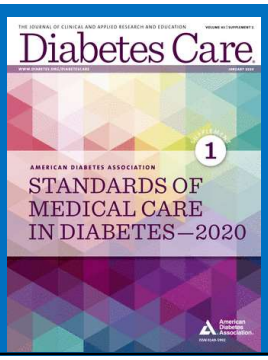




An open letter to the American Diabetes Association board of directors
Special commentary

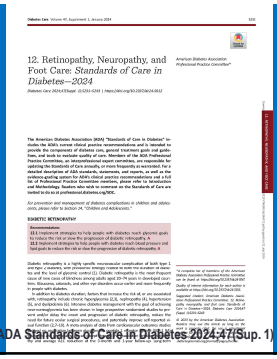
Representing 13 international hyperbaric societies

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—2024*

Now takes more nuanced view of HBO therapy

Recognized one positive RCT

Identified two recent RCTs failed to corroborate

While noting trail 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;47(Sup. 1)

DFU DATA APPRAISAL

CLINICAL PRACTICE GUIDELINE DOCUMENT

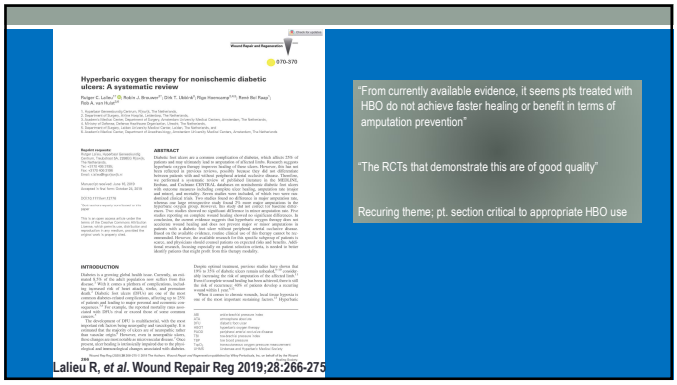
Global vascular guidelines on the management of chronic limb-threatening ischemia

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

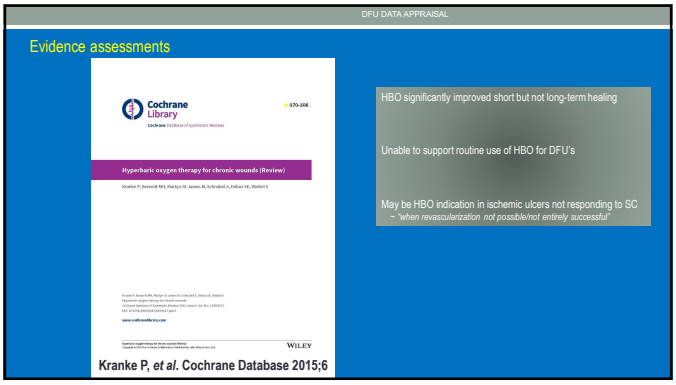
"May be a role for HBO to accelerate healing of chronic neuropathic ulcers with low grade ischemia"

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

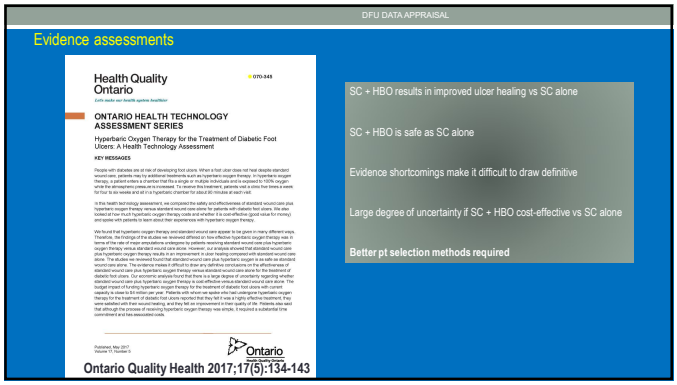
Conte MS, *et al.* Eur J Vasc Endovasc Surg 2019



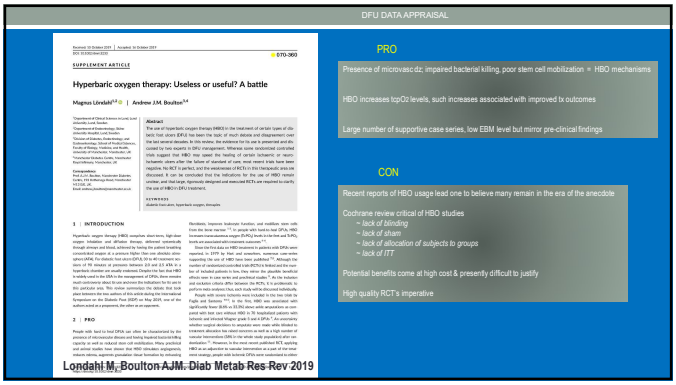
Lalieu R, *et al.* Wound Repair Reg 2019;28:266-275



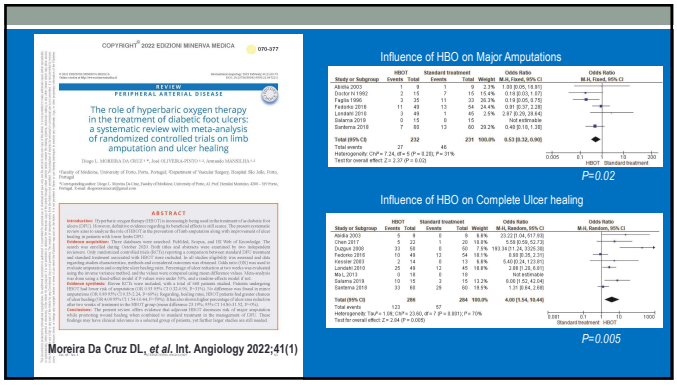
Kranke P, *et al.* Cochrane Database 2015;6



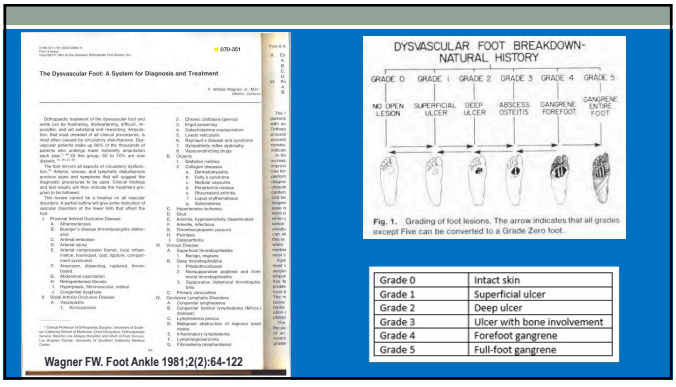
Ontario Quality Health 2017;17(5):134-143



Londahl M, Boulton AJM. Diab Metab Res Rev 2019



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



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

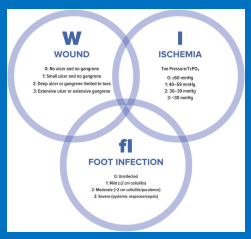
U Texas

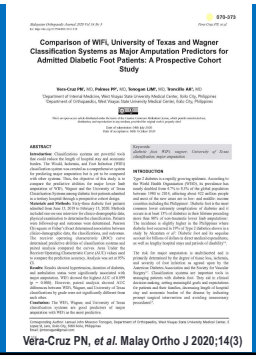
The University of Texas Staging System for Diabetic Foot Ulcers

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





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, MD, Palileo PP, MD, Sonajon LMF, MD, Trancilllo AR², MD

ABSTRACT

Introduction: Classification systems are powerful tools that could reduce the length of hospital stay and economic burden. The WIFI, Wagner and University of Texas classification system was created to be a comprehensive system for predicting major amputation but is yet to be compared. This study is the first prospective cohort study to compare the predictive abilities for major lower limb amputation of WIFI, Wagner and the University of Texas classification systems in admitted diabetic foot patients in a tertiary hospital through a prospective cohort design.

Materials and Methods: Sixty-three diabetic foot patients admitted at the Philippine General Hospital (PGH) were included in our study. Interview, clinico-demographic data, physical examination to determine the classification. Patients were followed-up and outcomes were determined. Pearson Chi-square or Fisher's Exact determined association between the classification systems and major amputation. The receiver operating characteristic (ROC) curve determined predictive abilities of classification systems and Area Under the Curve (AUC) values were used. The Net Reclassification Improvement Curve (AUC) values were used to compare the prediction accuracy. Analysis was set at 95% CI.

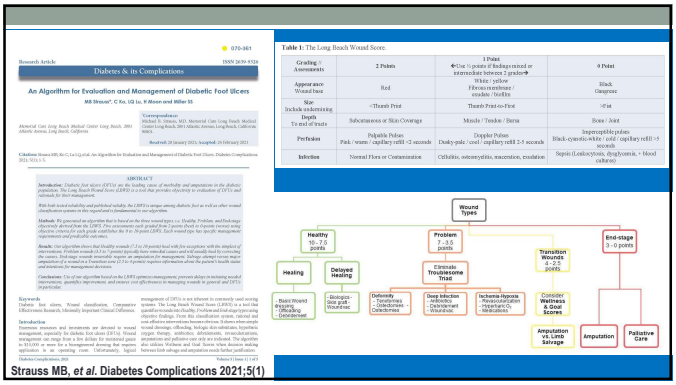
Results: Results showed hypertension, duration of diabetes, and ambulatory status were significantly associated with major amputation ($p = 0.001$, $p = 0.001$, and $p = 0.006$). However, paired analysis showed AUC differences between WIFI, Wagner, and University of Texas classification by grade were not significantly different from each other.

Conclusions: The WIFI, Wagner, and University of Texas classification systems are good predictors of major amputation with WIFI as the most predictive.

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



Diabetes & its Complications

An Algorithm for Evaluation and Management of Diabetic Foot Ulcers

MB Strauss*, C Ko, LG Lo, K Hoon and Hillar SS

ABSTRACT

Introduction: Diabetic foot ulcers (DFUs) are the leading cause of morbidity and amputation 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.

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. Pre-assessments each graded from 3 points (best) to 0 points (worst) using objective criteria for each grade established for the 9 to 30 point LBWS. Each wound type has specific management requirements and predictable outcomes.

Results: Our algorithm shows that Healthy wounds (7.5 to 30 points) heal with few exceptions with the simplest of the routine wound care. Problem wounds (4 to 7 points) typically have vascular issues and will usually heal by correcting the issues. End-stage wounds (0 to 3 points) require an amputation for management. Salvage attempts versus major amputation of a wound or a Transition score (3.5 to 4 points) requires reevaluation when the patient's health status and resources for management decisions.

Conclusions: Use of our algorithm based on the LBWS optimizes management, prevents delays in initiating needed interventions, quantifies improvements, and ensures cost effectiveness in managing wounds in general and DFUs in particular.

Keywords

Diabetic foot ulcers; Wound classification; Comparative Effectiveness Research; Minimally Important Clinical Difference

Introduction

Enormous resources and investments are devoted to wound management in the United States. Costs for DFUs alone in 2012 for management can range from a few dollars for uncomplicated cases to $15,000 or more for a bioengineered dressing that requires application in an operating room. Unfortunately, logical management of DFUs is not inherent in commonly used scoring systems. The Long Beach Wound Score (LBWS) is a tool that quantifies macroscopic Healthy, Problem and End-stage typifying objective findings. From this classification system, rational and cost-effective interventions become robust. It shows when simple wound dressings, offloading, biologic skin substitutes, hyperbaric oxygen therapy, vascular reconstruction, revascularization, amputations and palliative care only are indicated. The algorithm also utilizes Wellness and Goal Scores when decisions making between limb salvage and amputation needs further justification.

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 Fibrosis membrane / exudate / biofilm	Black Gangrene
Size Include undermining	<Thumb Print	Thumb Print-to-Fist	>Fist
Depth To end of bases	Subcutaneous or Skin Coverage	Muscle / Tendon / Bursa	Bone / Joint
Perfusion	Palpable Pulses Pink / warm / capillary refill <2 seconds	Doppler Pulses Dusky-pink / cool / capillary refill 2-5 seconds	Imperceptible pulses Black- cyanotic-white / cold / capillary refill >5 seconds
Infection	Normal Flora or Contamination	Cellulitis, osteomyelitis, nacrotizing, exudation	Sepsis (Leukocytosis, dysglycemia, + blood culture)

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*