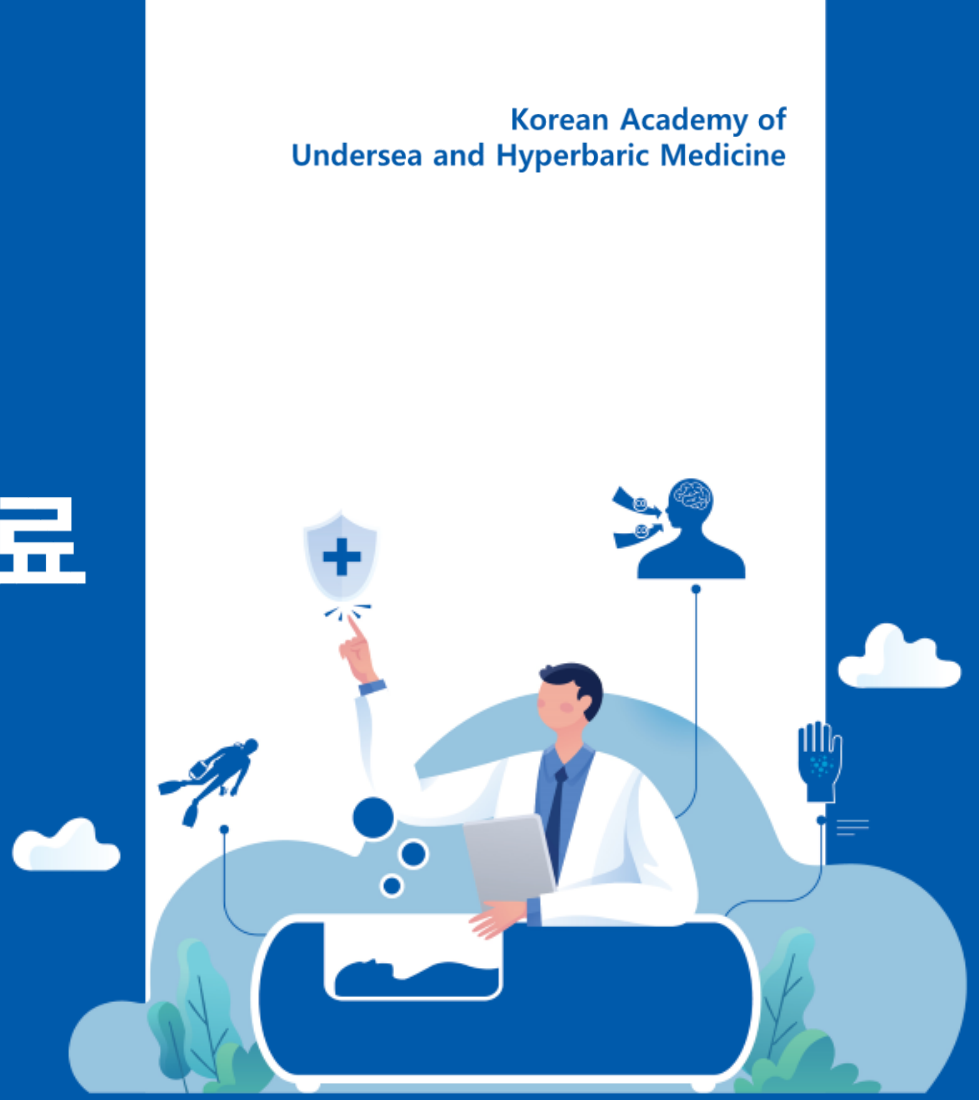
# 연조직 괴사 감염 및 당뇨발에서의 고압산소치료




2021.09.09~10

소 속 : 전남대학교병원 응급의학과
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# 고압산소치료 Mechanisms

**Primary**

- Direct effect of increased oxygen partial pressure
- Direct effects of pressure

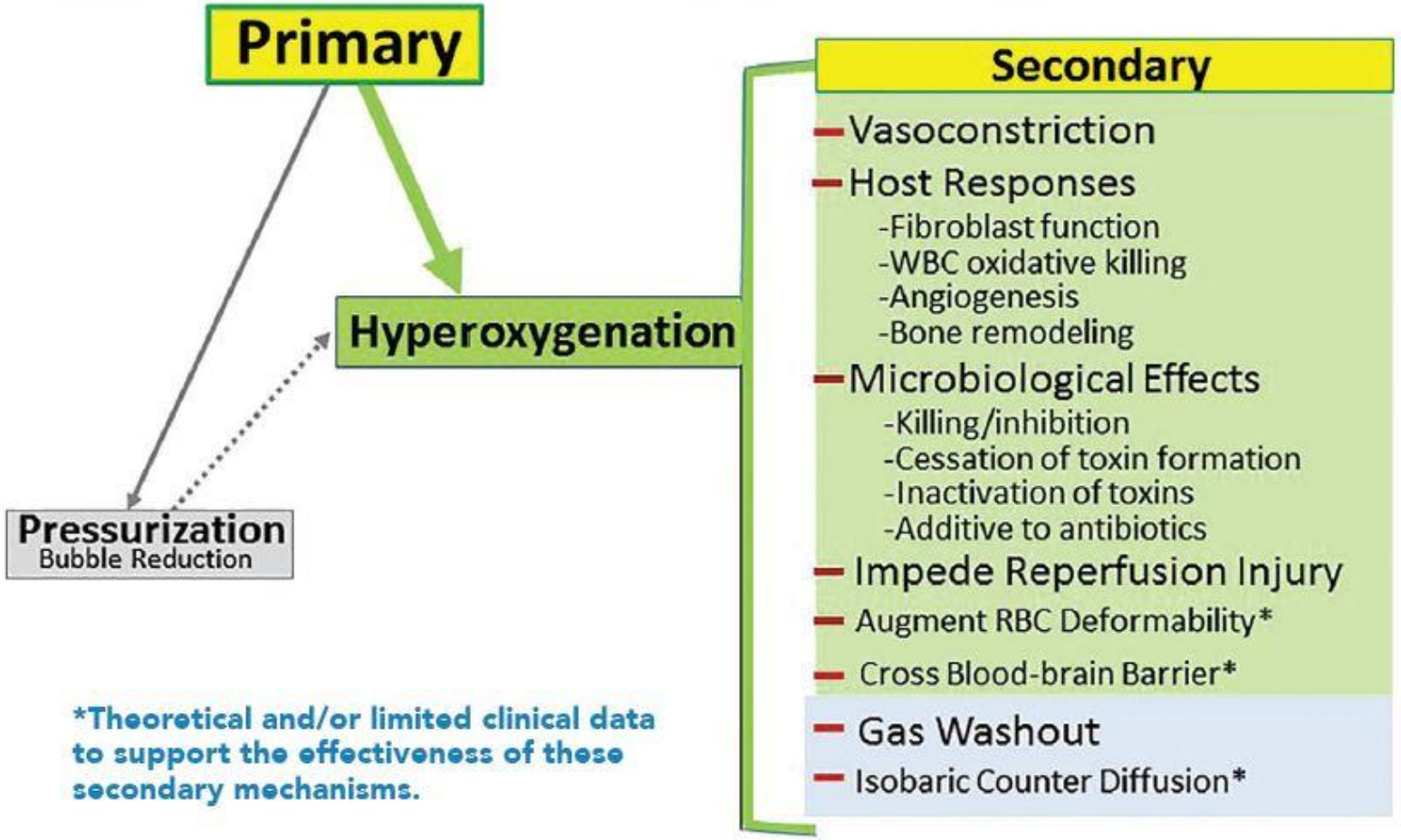
Dose, frequency, duration, effects

**Secondary**

- Effects of enriched oxygen environment have on cellular functions.
- The effects increased ambient pressures have in producing gradients between gases in body tissues.

Accumulative effects

## TABLE 7. MECHANISMS OF HYPERBARIC OXYGEN




*Theoretical and/or limited clinical data to support the effectiveness of these secondary mechanisms.

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# I 연조직 괴사 감염(Necrotizing soft tissue infection) 에 대한 임상적 특징

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# Terminology

## Confusing and illogical

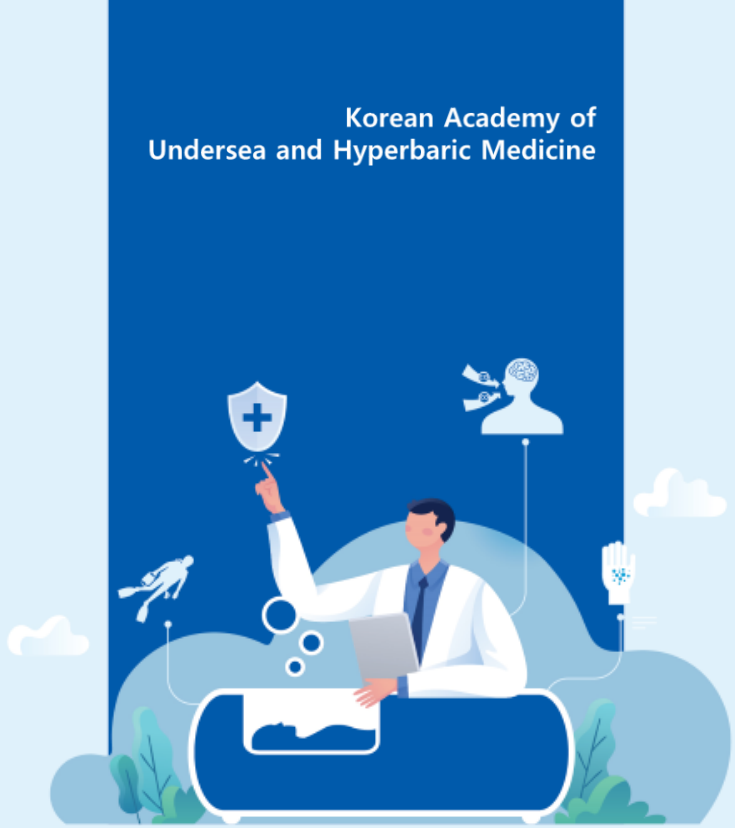
- Necrotizing soft tissue infection
- Gas gangrene/Clostridial myonecrosis
- Necrotizing fasciitis
- Fourniere's gangrene
- Mixed aerobic and anaerobic infection
- Ischemic gangrene with tissue infection

# 개 요

- Aerobic / Anaerobic / Mixed bacterial floras

- Immune-compromised
  - Underlying systemic disease
    - DM, malignancy, vascular insufficiency, alcoholism
  - Transplantation : immunosuppressive drug
  - Neutropenia

- After trauma
- Surgical wound : around foreign body
- Spontaneously : *i.e.* Fournier's gangrene
- Post op. : C-sec (without risk factors), even after "sterile" op.




**suspicion**

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# Epidemiology

- 미국의 경우 한해 약 500-1,500건의 괴사성 연조직염이 발생(10만명 당 4건) , 8-65%(평균 21.9%)의 높은 사망률

- 국내의 경우 2000-2010년 입원한 환자들을 대상으로 한 다기관 연구에서 21.2%(21/99)의 환자가 입원 치료 중 사망, 최근(2012-2015년) 시행된 연구에서도23.2%(39/168)의 환자가 사망

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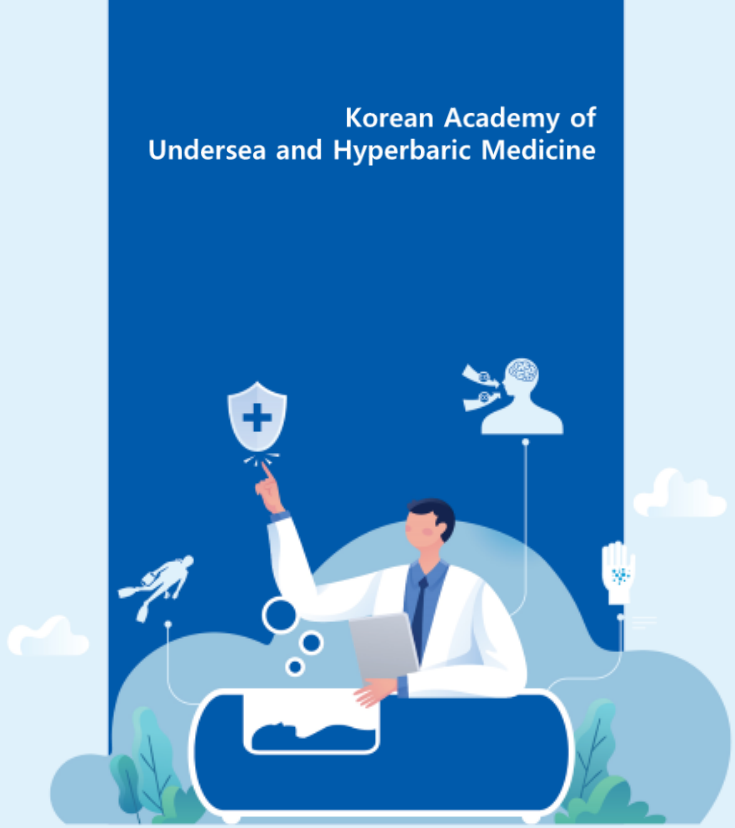
# Pathophysiology

- Deep fascial layer에 infective process (anaerobe)
  - Phlegmon(abscess) with edema and necrosis
- Blood supply to skin is affected
  - Skin: Perfusion pressure ↓, ischemia ↑
    → Rapid progression of Infection
    (hypoxia induced PML dysfunction)
- Local hypoxia with Up-regulation of endothelial adherence molecule
  : leukocyte adhesion, endothelial cytotoxicity
- Tissue necrosis, purulent discharge, gas production

- Early recognition
- Etiology
- Bacteriology
- Clinical course

- Morbidity
- Mortality
  - From 20%
  - Up to 70-80%
    - older, debilitated, diabetic

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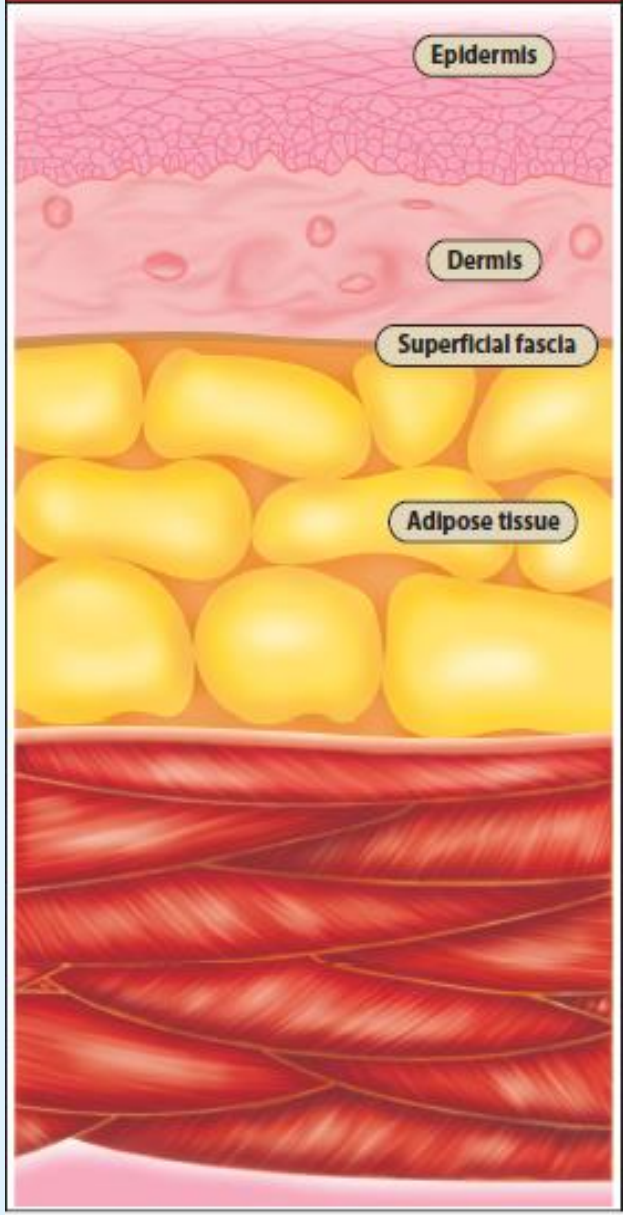


| Anatomy | Syndrome | Etiology |
|---|---|---|
| Skin | Erysipelas | Group A *Streptococcus* |
| | Impetigo | Group A *Streptococcus*<br>*Staphylococcus aureus* |
| | Ecthyma | Group A *Streptococcus*<br>*Pseudomonas aeruginosa* |
| | Folliculitis | *S aureus; P aeruginosa* (whirlpools); rarely *Candida* |
| | Furunculosis | *S aureus*; group A *Streptococcus*<br>*P aeruginosa* |
| Subcutaneous tissue | Cellulitis | Group A *Streptococcus*<br>*S aureus* (MSSA or MRSA)<br>Occasionally gram-negative enteric bacilli<br>*Aeromonas hydrophila; Vibrio vulnificus* |
| | Anaerobic cellulitis | *Clostridium perfringens*<br>*Bacteroides, Peptostreptococcus, Peptococcus, Prevotella* +<br>gram-negative enteric bacilli<br>*(E coli, Klebsiella, Proteus)* |
| Deep fascia | Meleney gangrene | *S aureus* or *Proteus* and microaerophilic streptococci |
| Muscle | Necrotizing fasciitis | Mixed gram-positive and negative organisms (*S aureus, E coli, Klebsiella, Proteus*) and anaerobes (*Bacteroides, Peptostreptococcus, Peptococcus, Prevotella*)<br>Group A *Streptococcus*<br>*S aureus* (MRSA) |
| | Clostridial myonecrosis | *C perfringens* (sometimes non-*perfringens* species) |
| | Nonclostridial synergistic myonecrosis | As for necrotizing fasciitis |
| | Pyomyositis | *S aureus*; rarely group A *Streptococcus*; *P aeruginosa* |

Source: Jesse B. Hall, Gregory A. Schmidt, John P. Kress: *Principles of Critical Care*, 4th Edition: www.accessmedicine.com
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# CLASSIFICATION

*It is difficult to classify...*

- Assumed causative microorganism
- Involved tissue
- Required therapy
- Rate of progression
- Initial clinical findings

**Amsterdam classification**

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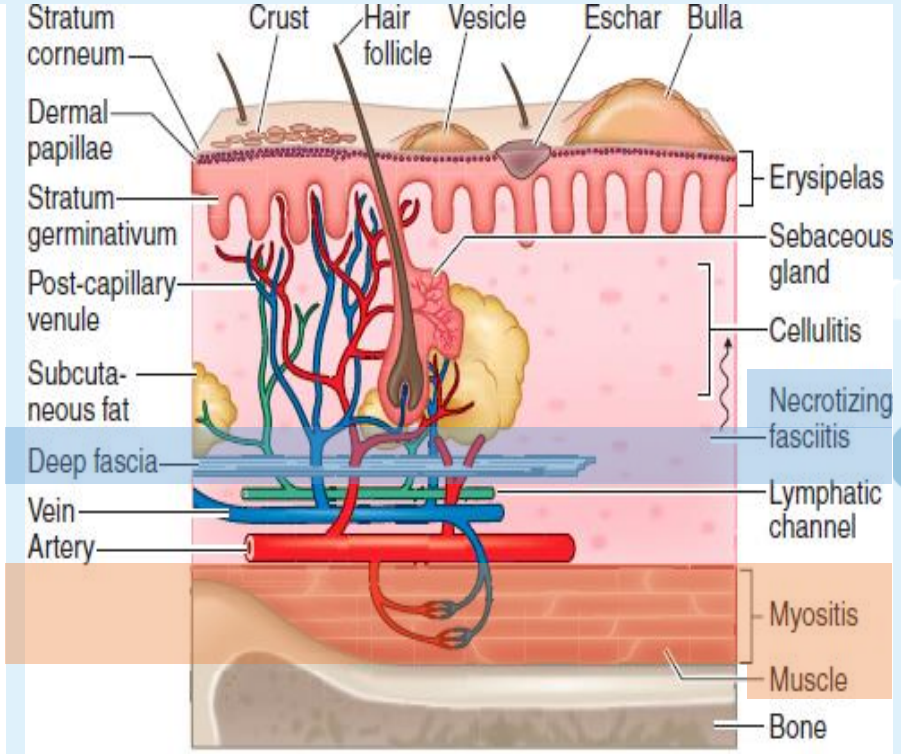
# Amsterdam classification

- Progressive bacterial gangrene
  - Anaerobic
    - Clostridial
    - Nonclostridial
  - Aerobic
  - Mixed
- Necrotizing fasciitis
  - Anaerobic
  - Aerobic
  - Mixed
- Myositis and myonecrosis
  - Anaerobic
    - Clostridial
    - Nonclostridial (streptococcal)
  - Others
    - Aerobes
    - Viruses
    - Parasites




Source: J.L. Jameson, A.S. Fauci, D.L. Kasper, S.L. Hauser, D.L. Longo, J. Loscalzo: Harrison's Principles of Internal Medicine, 20th Edition
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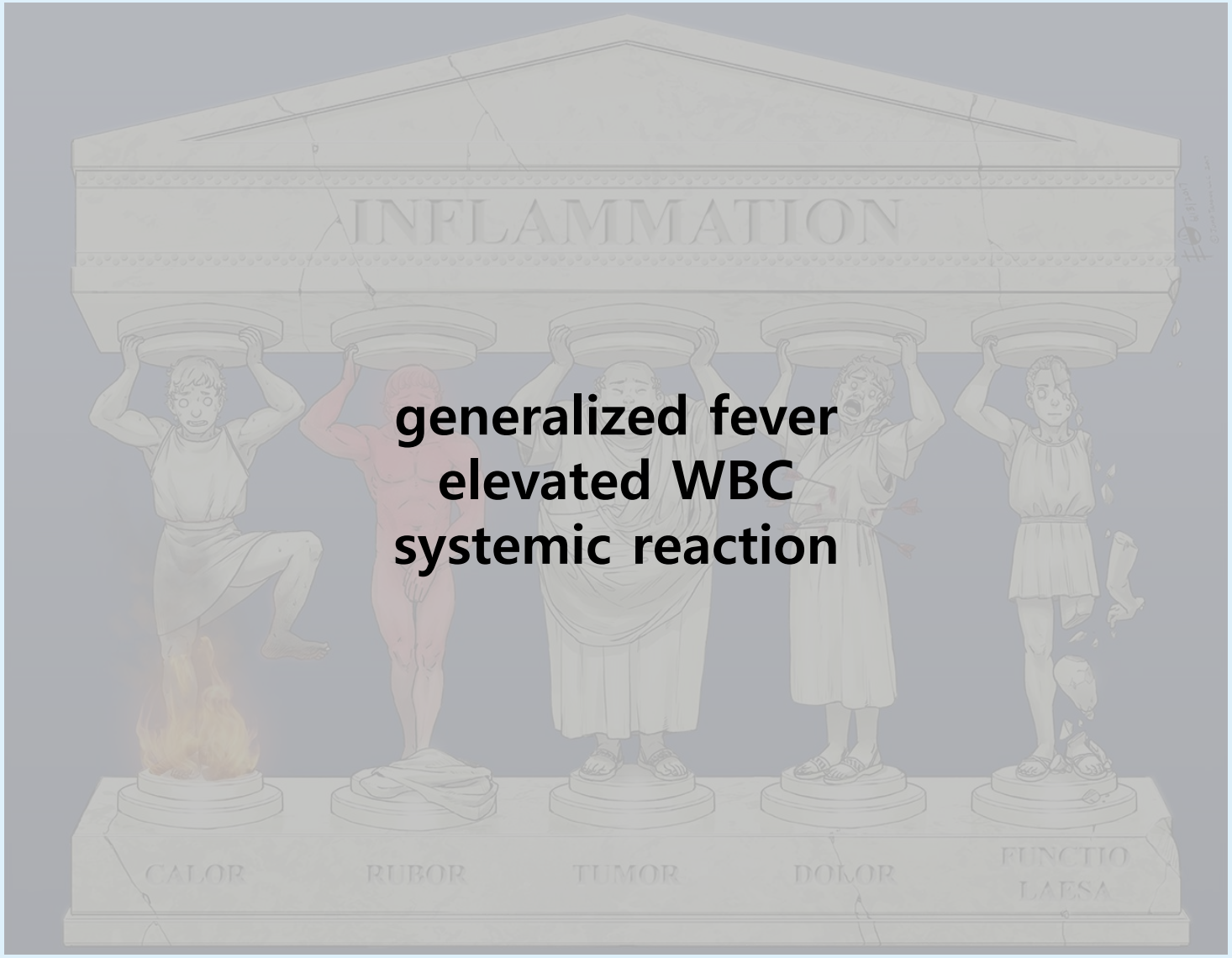
# DIAGNOSIS




generalized fever
elevated WBC
systemic reaction

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- Simple model – necrotizing fasciitis vs. nonnecrotizing ST infection At admission
  - ✓ WBC > 15,400
  - ✓ $Na^+$ < 135 mmol/L

**Laboratory Risk Indicator for Necrotizing Fasciitis (LRINEC) score.**

| Variable, Units | Points |
|---|---|
| C-Reactive Protein, mg/L | |
| < 150 | 0 |
| ≥ 150 | 4 |
| Total white cell count, x $10^3/\mu L$ | |
| < 15 | 0 |
| 15–25 | 1 |
| > 25 | 2 |
| Hemoglobin, g/dL | |
| > 13.5 | 0 |
| 11–13.5 | 1 |
| < 11 | 2 |
| Sodium, mEq/L | |
| ≥ 135 | 0 |
| < 135 | 2 |
| Creatinine, mg/dL | |
| ≤ 1.6 | 0 |
| > 1.6 | 2 |
| Glucose, mg/dL | |
| ≤ 180 | 0 |
| > 180 | 1 |

Modified from Wong et al [8]

The maximum score is 13; a score of ≥ 6 should raise the suspicion of necrotizing fasciitis and a score of ≥ 8 is strongly predictive of this disease.

- A total score of 8 or more is strongly predictive of an NSTI.

# Surgical therapy

- Gram
  "closed infection" needle aspiration → more reliable
- Sonography / CT / MRI : to clarify involved anatomic site

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# Progressive Bacterial Gangrene

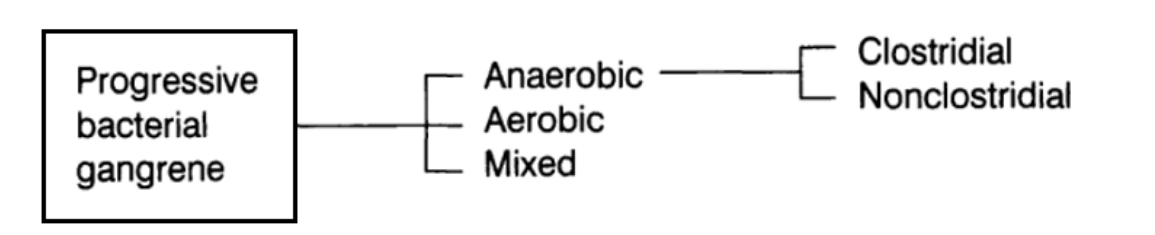
Postoperative progressive bacterial synergistic gangrene
Cullen's ulcer
chronic infectious skin gangrene

- anaerobic crepitant / clostridial cellulitis
- pyoderma gangrenosum
- erysipelas
- gangrenous / necrotizing erysipelas
- symbiotic gangrene
- phagedena geometrica

- directly related to skin infection
- epidermis, dermis, SQ tissue, lymphatics, hair follicle, ~~deep fascia~~

~~muscle compartment~~

- group A streptococci, *S. aureus*
- anaerobic microorganism : *Bacteroides* spp., *Clostridium* spp., Enterobacteriaceae, *Proteus*, *Pseudomonas*...

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# Progressive Bacterial Gangrene

- **Always, Very painful!**

- Infection → marginal cellulitis → centrifugal necrosis skin SQ
  patchy, purplish discoloration

- Extensive ST damage, vascular insufficiency
  → true <u>clostridial</u> <u>myositis / myonecrosis</u>

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# Necrotizing Fasciitis

hemolytic streptococcal gangrene
Meleney's ulcer
acute dermal gangrene

- Hospital gangrene
- Suppurative fasciitis
- Fournier's gangrene
- Synergistic necrotizing cellulitis
- Hemolytic streptococcal gangrene

- **Deep fascia → SQ tissue, skin**
- **rapidly spreading along deep fascial plane**
  **More extended than visible change**

- **Fade-out margin : pathognomonic feature**
- **Surgical wound, injured site, spontaneously**

Necrotizing fasciitis
- Anaerobic
- Aerobic
- Mixed

✓ *Streptococcus pyogenes*

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# Nonclostridial Myonecrosis

- vs. Gas gangrene?
  - Greenish necrotic muscle
    cf. gas gangrene(clostridial myonecrosis): black necrotic muscle
  - More inflamed appearance than gas gangrene
  - Less gas amount

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# THERAPY

- Surgical debridement
- Appropriate antibiotics
- Nutritional support
- Optimal oxygenation – $HBO_2$

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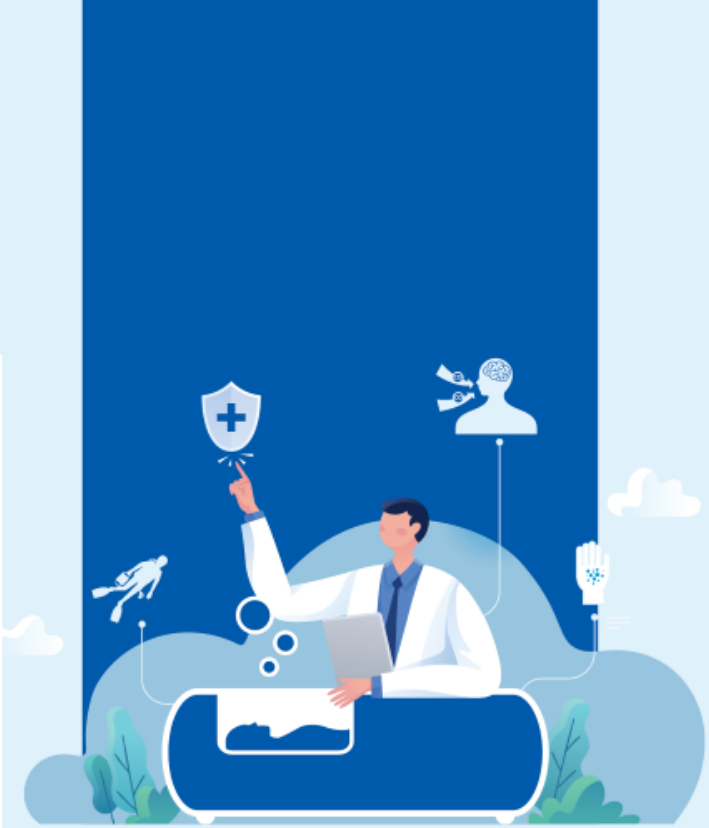
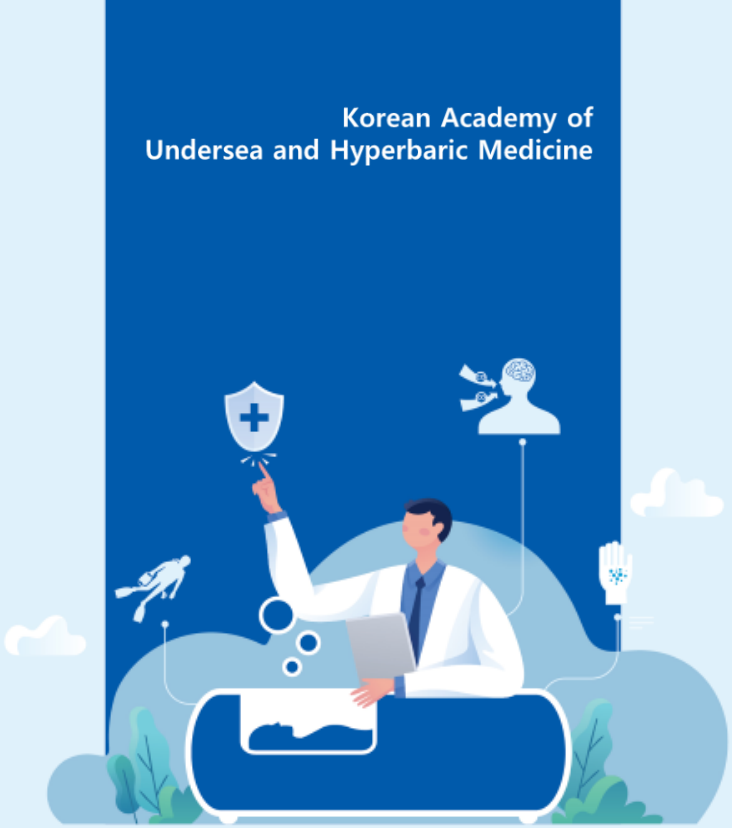
# SURGICAL THERAPY

| | |
|---|---|
| Progressive bacterial gangrene | necrotomy & skin grafting<br>I&D |
| Necrotizing fasciitis | “fillet” procedure (excision of necrotized fascia) |
| Myositis and myonecrosis | muscle removal |



Ⅱ

# 연조직 괴사 감염(Necrotizing soft tissue infection)에서 고압산소치료의 작용 기전과 임상적 적용에 대한 이해

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# Rationale & Mechanism of adjunctiveHBO$_2$

- **MAIN GOALS ➔ host defense & repair mechanisms**

  **↑ tissue PO$_2$**
  **↑ phagocytic function**
  **↓ edema**
  **↑ circulation**
  **↑ fibroblast growth**
  **↑ collagen formation**

- Hypoxic leukocyte dysfunction을 개선
- Enhance oxygen diffusion
  - -Provide oxygen to ischemic area
  - -Limiting spread of infection
- Enhance antibiotic penetration into target bacteria (eg, Aminoglycoside)
- Bacteriostatic/Bactericidal effect
- Hyperoxygenation – preservation of flaps

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# Necrotizing fasciitis $HBO_2$ positive report

- Necrotizing fasciitis
  - Wilkinson and Doolette *(2004 Arch surg)*
    - Retrospective cohort study, 44 patients
    - $HBO_2$ increased survival (odd ratio 8.9)
  - Devaney *(2015 Anaesth Intensive Care)*
    - 341 pts, retrospective case controlled study, 275명 $HBO_2$시행
    - Mortality: HBOT group 12 % Vs. non-HBOT group 24.3%
- Fourniere's gangrene
  - Hollabaugh, retrospective 26 cases *(1998 Plast Reconstr Surg)*
  - Mortality: HBOT group 7% Vs. non-HBOT group 42 %(p=0.04)

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# Necrotizing fasciitis $HBO_2$ positive report

Surg Infect (Larchmt). 2014 Jun 1; 15(3): 328–335. PMCID: PMC4696431
doi: 10.1089/sur.2012.135

## Not Just Full of Hot Air: Hyperbaric Oxygen Therapy Increases Survival in Cases of Necrotizing Soft Tissue Infections

Joshua J. Shaw,[1,2] Charles Psoinos,[1] Timothy A. Emhoff,[1] Shimul A. Shah,[3] and Heena P. Santry[1,2]

Author information ▶ Copyright and License information ▶

This article has been cited by other articles in PMC.

### Abstract

Go to:

***Background:*** The utility of hyperbaric oxygen therapy (HBOT) in the treatment of necrotizing soft tissue infections (NSTIs) has not been proved. Previous studies have been subject to substantial selection bias because HBOT is not available universally at all medical centers, and there is often considerable delay associated with its initiation. We examined the utility of HBOT for the treatment of NSTI in the modern era by isolating centers that have their own HBOT facilities.

***Methods:*** We queried all centers in the University Health Consortium (UHC) database from 2008 to 2010 that have their own HBOT facilities (n=14). Cases of NSTI were identified by *International Classification of Diseases, Ninth Revision* (ICD-9) diagnosis codes, which included Fournier gangrene (608.83), necrotizing fasciitis (728.86), and gas gangrene (040.0). Status of HBOT was identified by the presence (HBOT) or absence (control) of ICD-9 procedure code 93.95. Our cohort was risk-stratified and matched by UHC's validated severity of illness (SOI) score. Comparisons were then made using univariate tests of association and multivariable logistic regression.

***Results:*** There were 1,583 NSTI cases at the 14 HBOT-capable centers. 117 (7%) cases were treated with HBOT. Univariate analysis showed that there was no difference between HBOT and control groups in hospital length of stay, direct cost, complications, and mortality across the three less severe SOI classes (minor, moderate, and major). However, for extreme SOI the HBOT group had fewer complications (45% vs. 66%; $p<0.01$) and fewer deaths (4% vs. 23%; $p<0.01$). Multivariable analysis showed that patients who did not receive HBOT were less likely to survive their index hospitalization (odds ratio, 10.6; 95% CI 5.2–25.1).

***Conclusion:*** At HBOT-capable centers, receiving HBOT was associated with a significant survival benefit. Use of HBOT in conjunction with current practices for the treatment of NSTI can be both a cost-effective and life-saving therapy, in particular for the sickest patients.

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# Necrotizing fasciitis $HBO_2$ negative report

- George ME *(Surg Infect; 2009)*
  - Retrospecitve 78 case
  - HBO does not improve outcome in NSTI
- Massey PR *(J surg Res; 2012)*
  - Retrospective, 80 case
  - HBO does not appear to decrease in-hospital mortality
- Hassan Z *(Undersea Hyperb Med; 2010)*
  - Retrospective, 67 case
  - No difference in mortality

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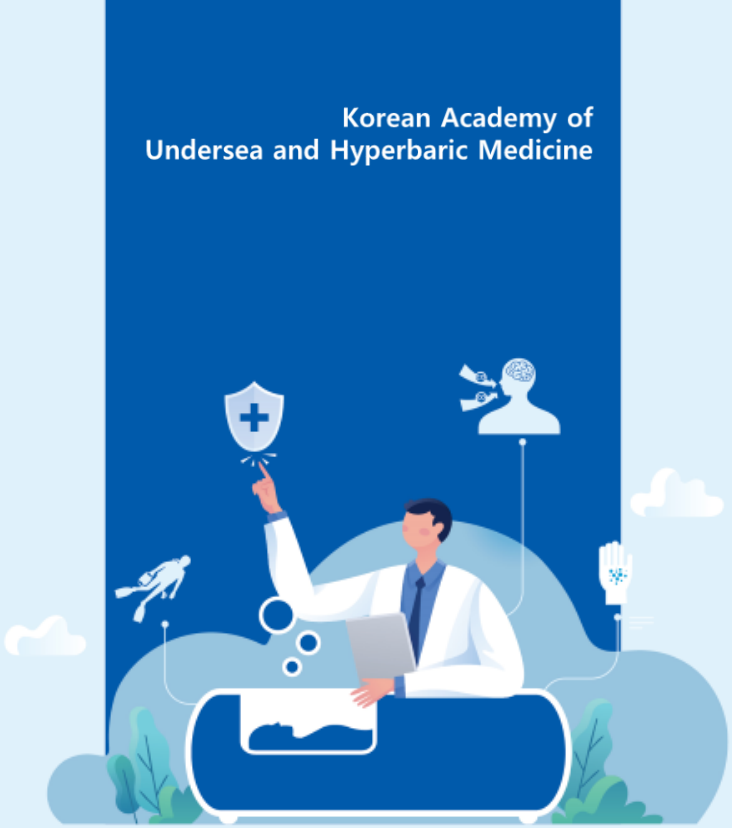
# Ⅲ 연조직 괴사 감염(Necrotizing soft tissue infection)에서 기존 치료와 고압산소치료 통합 알고리즘 소개

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# 치료 과정 알고리즘-1

**괴사성 연조직염**
의심 소견
피부병변(홍반, 부종, 열감)+전신 증상(발열, 저혈압)

전형적 소견
-피부병변(수포, 점상 출혈, 피부 괴사)
-촉진 시 염발음
-감각저하
-임상 소견에 비해 심한 통증

예

혈액 배양 검사
경험적 광범위 항생제

**응급 시험적 수술**
**조직 표본 확보(그람 염색 및 배양 검사, 병리검사)**
**적극적 죽은조직제거술**
**고압산소치료 병행 요법***

**재평가(수술 후 24시간 내)에 따라**
**추가적 죽은조직제거술**

아니오

혈액 배양 검사
경험적 광범위 항생제

영상 검사(CT, MRI, US) 양성
LRINEC score ≥ 6
임상 진찰 소견 악화
-촉진 시 염발음
-임상 증상의 급성 악화
-피부 병변에 비해 심한 통증
-지속적인 염증, 발열, 백혈구 증가

예

아니오

**배양 검사 결과에 따른 항생제 치료 유지**
**보존적 치료**

**고압산소치료 병행요법***
1-3일차: 2.0-2.5기압으로 90분간 2회/24시간
4일차부터: 2.0-2.5기압으로 90분간 1회/24시간
(단, 곰팡이 감염 2.4-3.0기압/클로스트리듐 감염 2.8-3.0 기압)

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# 치료 과정 알고리즘-2

**가스 괴저**
배양 결과 양성 또는
임상 양상에 따라 진단

↓

고용량 항생제
죽은조직제거술

↓

고압산소 치료의
이득과 위험 고려

**이득 요인**
- 포함된 조직의 범위가 넓을 때
- 항생제나 수술의 효과가 미흡할 때
- 수술 하기 어려운 환자 상황
- 면역 저하 환자

**위험 요인**
- 고농도의 승압제/강심제/인공호흡기 적용 시
- 다 장기 부전시
- 고압 챔버의 사용의 환경적 문제

위험에 비해
이득이 크다면

**고압산소 치료 시행**
1일차- 2.8-3.0기압으로 90분간 2-4회
2-3일차: 2.8-3.0기압으로 90분간 2회
4-7일차: 2.8-3.0기압으로 90분간 1회

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# 요 약

- Although RCT's do not exist, the mechanism of HBO make sense in mitigating(완화) the pathophysiology of these conditions

□ $HBO_2$ is always an adjunct to antibiotics and surgery

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# Ⅳ 당뇨발 (Diabetic foot ulcer)의 임상적 특징

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# 당뇨 임상 양상

- Diabetes has a constellation of pathologies

  - Autonomic neuropathy = Mechanical Deformities (*e.g.,* clawfoot)

  - Sensory neuropathy = Loss of protective sensation

  - Hyperglycemia
    = Osmotic diuresis
    = Limits neutrophil functioning
    = Increased catabolism

  - Microvascular disease
    = Lack of hyperemic response to injury
    = Decrease oxygen diffusion across basement membrane

  - Macrovascular disease
    = Increased atherosclerosis of lower extremity vessels

# DFUs (Diabetic foot ulcer) Epidemiology

- DM ⇒ Approximately 25.8 million people, or roughly 8.3% of the U.S. population

National diabetes fact sheet. national estimates and general information on diabetes and prediabetes in the United States. 2011, U.S. Department of Health and Human Services, Centers for Disease Control and Prevention: Atlanta, GA.

- More than 60% of non-traumatic amputations in the US occur in people with DM
  - DM foot ulcer (DFU) precedes 85% of lower-limb amputations in patients with DM.

Cowie Catherine C. Diabetes: 1996 vital statistics. 1996, University of Michigan: American Diabetes Association.

- Contralateral leg amputation ⇒ 56% of patients within three to five years

NIH Cancer Fact Sheet. 2010, National Institutes of Health.

- The five-year mortality rate for DM who have had a single-leg amputation ⇒ 60% ↑ the overall five-year mortality rate of all cancers combined (32%)

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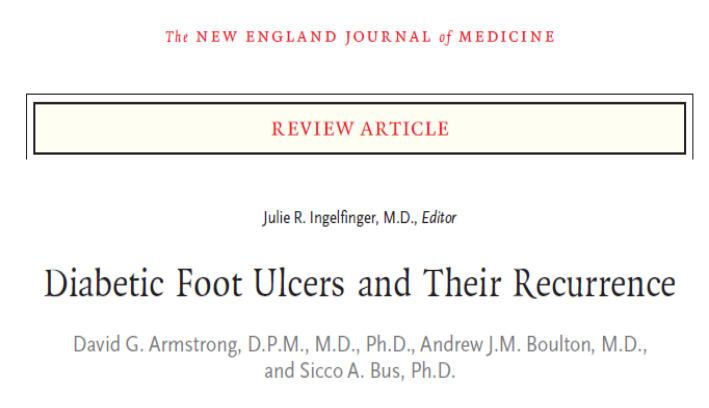
# DFUs 발생 및 재발 과정


The NEW ENGLAND JOURNAL of MEDICINE

REVIEW ARTICLE

Julie R. Ingelfinger, M.D., *Editor*

Diabetic Foot Ulcers and Their Recurrence

David G. Armstrong, D.P.M., M.D., Ph.D., Andrew J.M. Boulton, M.D., and Sicco A. Bus, Ph.D.

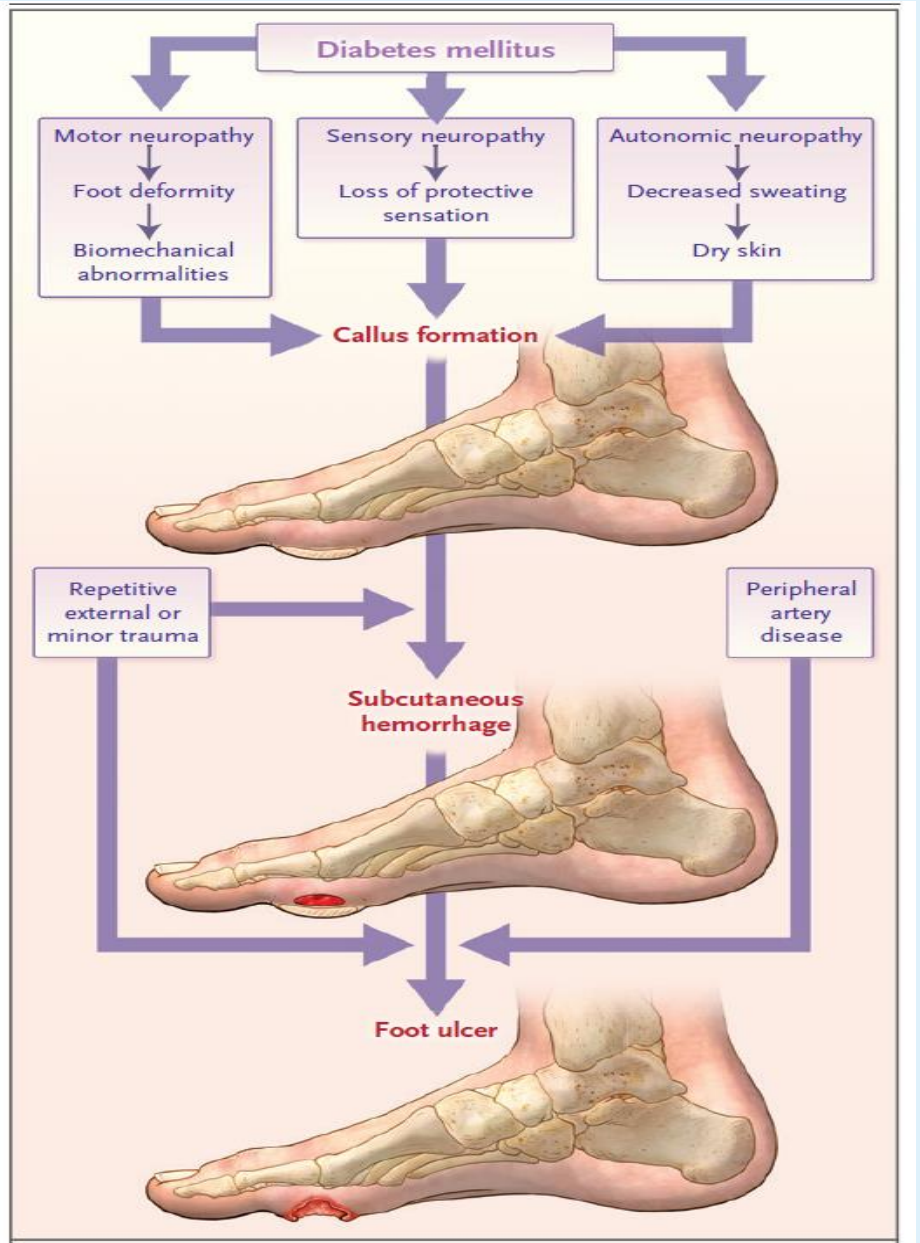



**Figure 1. Common Pathway of Diabetic Foot Ulcer Occurrence and Recurrence.** Diabetic foot ulcers and their recurrences are caused by a number of factors that ultimately lead to skin breakdown. These factors include sequelae related to sensory, autonomic, and motor neuropathies.

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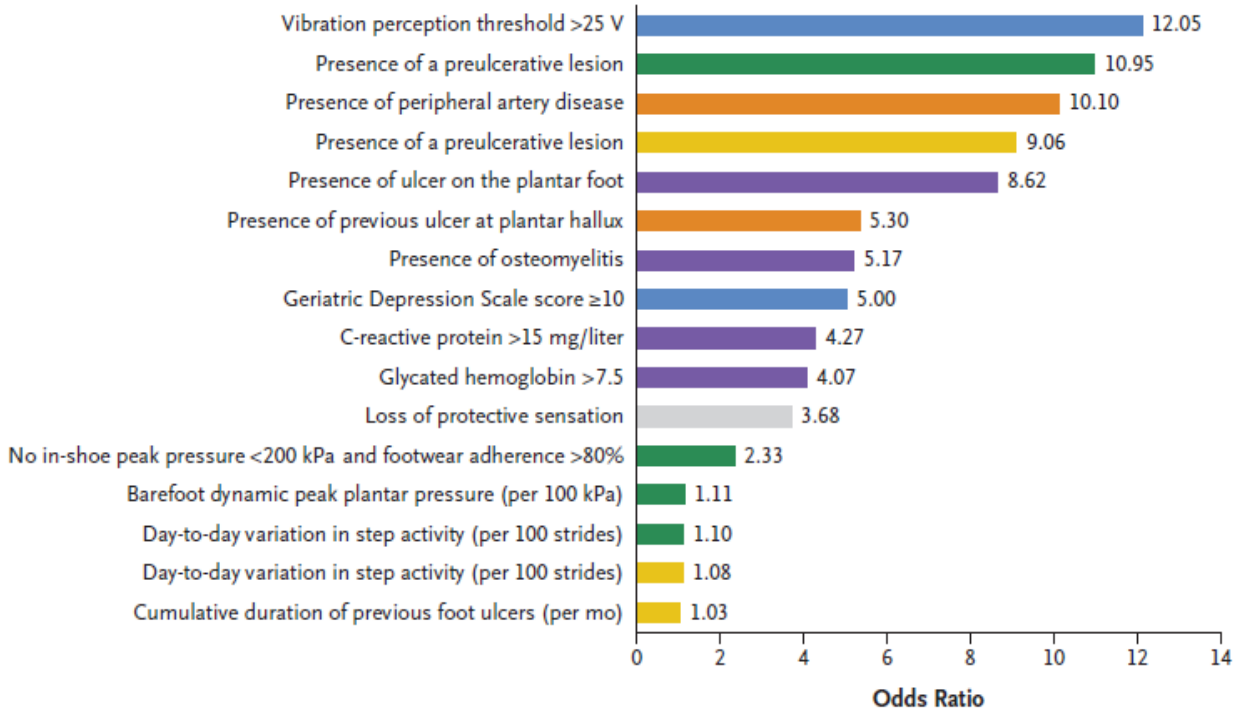
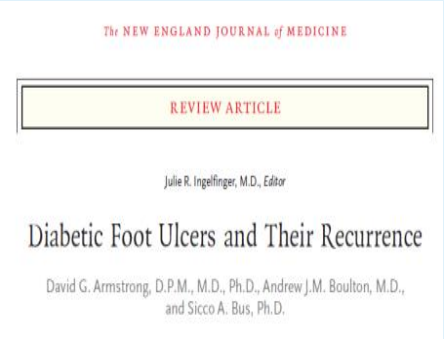



**Figure 3. Risk Factors Independently Associated with Ulcer Recurrence.**

Data are from five studies that reported an odds or risk ratio.[28,33,42,52,56] According to Monami et al.[42] (blue), risk factors for ulcer recurrence are a vibration perception threshold greater than 25 V and a Geriatric Depression Scale score of 10 or higher (scores range from 0 to 15, with higher scores indicating more severe depression). According to Peters et al.[56] (orange), risk factors for ulcer recurrence are the presence of peripheral artery disease and location of the previous ulcer at the plantar hallux. According to Dubský et al.[28] (purple), a plantar location of the ulcer, the presence of osteomyelitis, and elevated blood levels of C-reactive protein and glycated hemoglobin (all of which were determined at the time of study enrollment for patients with an active foot ulcer) are independent predictors of recurrence of foot ulcers. According to Reiber et al.[33] (gray), loss of protective sensation is a risk factor for recurrence of an ulcer on the plantar surface of the foot. According to Waaijman et al.,[52] risk factors for recurrence of an ulcer on the plantar surface of the foot (yellow) include the presence of a preulcerative lesion, low day-to-day variation in step activity, and a long cumulative duration of previous foot ulcers; risk factors for recurrence of a pressure-related plantar ulcer (green) include the presence of a preulcerative lesion, lack of both in-shoe peak pressure below 200 kPa and therapeutic-footwear adherence higher than 80%, high barefoot dynamic peak plantar pressure, and low day-to-day variation in step activity.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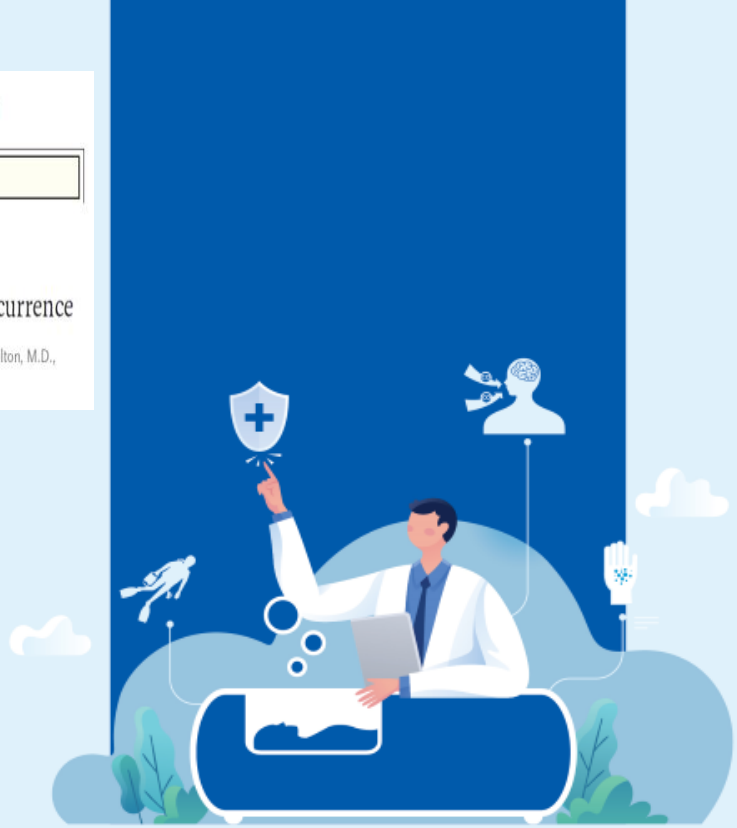

# DFUs 재발 위험인자

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# DFUs 예방 및 치료 과정

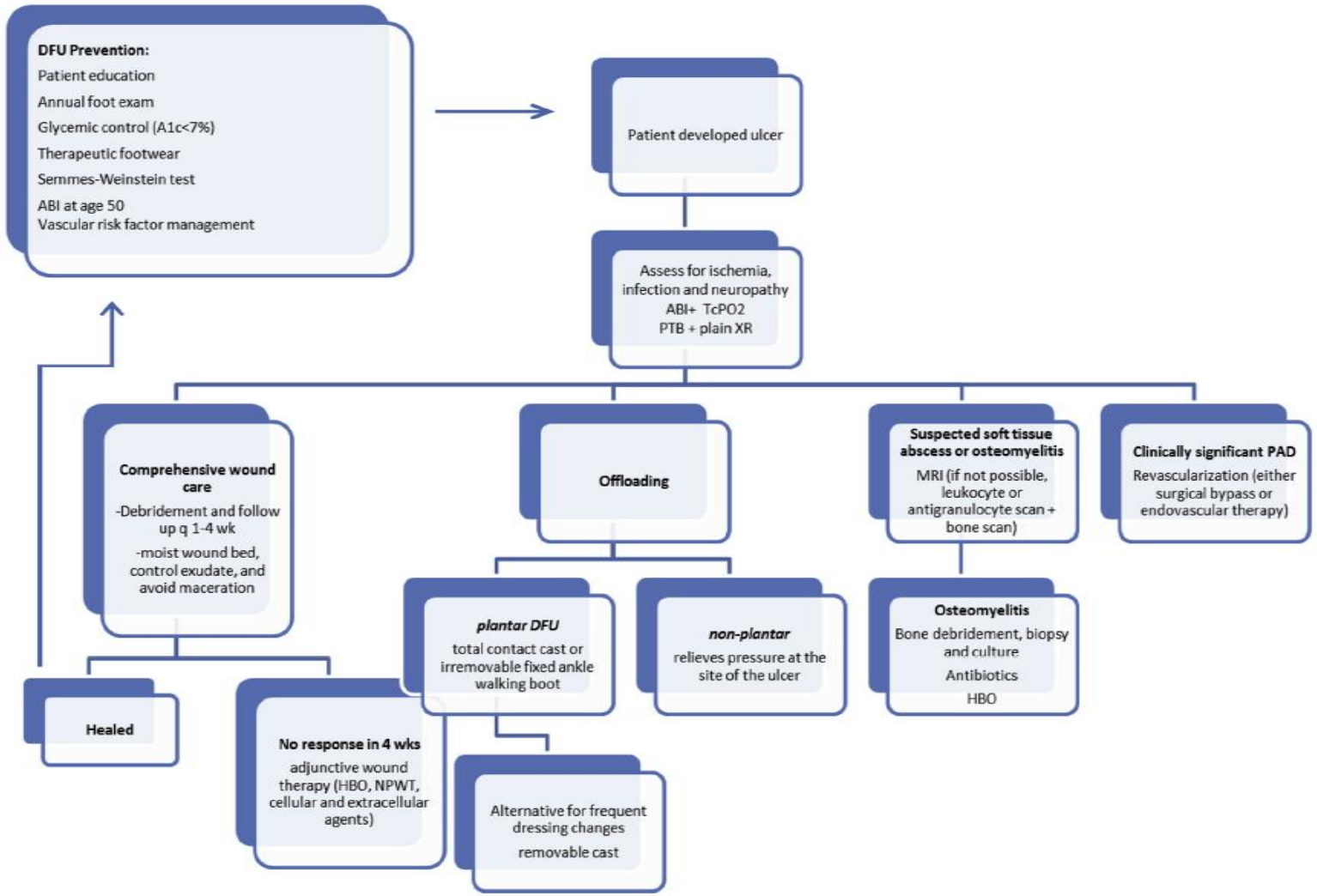


Fig. Algorithm for prevention and care of diabetic foot. *ABI*, Ankle-brachial index; *DFU*, diabetic foot ulcer; *HBO*, hyperbaric oxygen; *MRI*, magnetic resonance imaging; *NPWT*, negative pressure wound therapy; *PAD*, peripheral arterial disease; *PTB*, probe to bone; $TcPo_2$, transcutaneous oxygen pressure; *XR*, radiography.

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- The International Working Group on the Diabetic Foot (IWGDF) guidelines for the best practice treatment of DFUs

- Revascularization if appropriate and feasible (V)
- Off-loading to minimize trauma to the ulcer site (O)
- Treatment of underlying infection (I)
- Management of the wound bed to promote healing (D)

V - Vascular O - Offloading I - Infection D - Diabetes Control

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# Risk evaluation

**Figure 3** Risk categories

| Risk category 0 | Risk category 1 | Risk category 2 | Risk category 3 |
|---|---|---|---|
| Normal Plantar Sensation | Loss of Protective Sensation (LOPS) | LOPS with either High Pressure or Poor Circulation or Structural Foot Deformities or Onychomycosis | History of Ulceration, Amputation or Neuropathic Fracture |
| LOW RISK | MODERATE RISK | HIGH RISK | VERY HIGH RISK |

IDF Clinical Practice Recommendations on the Diabetic Foot – 2017

A guide for healthcare professionals

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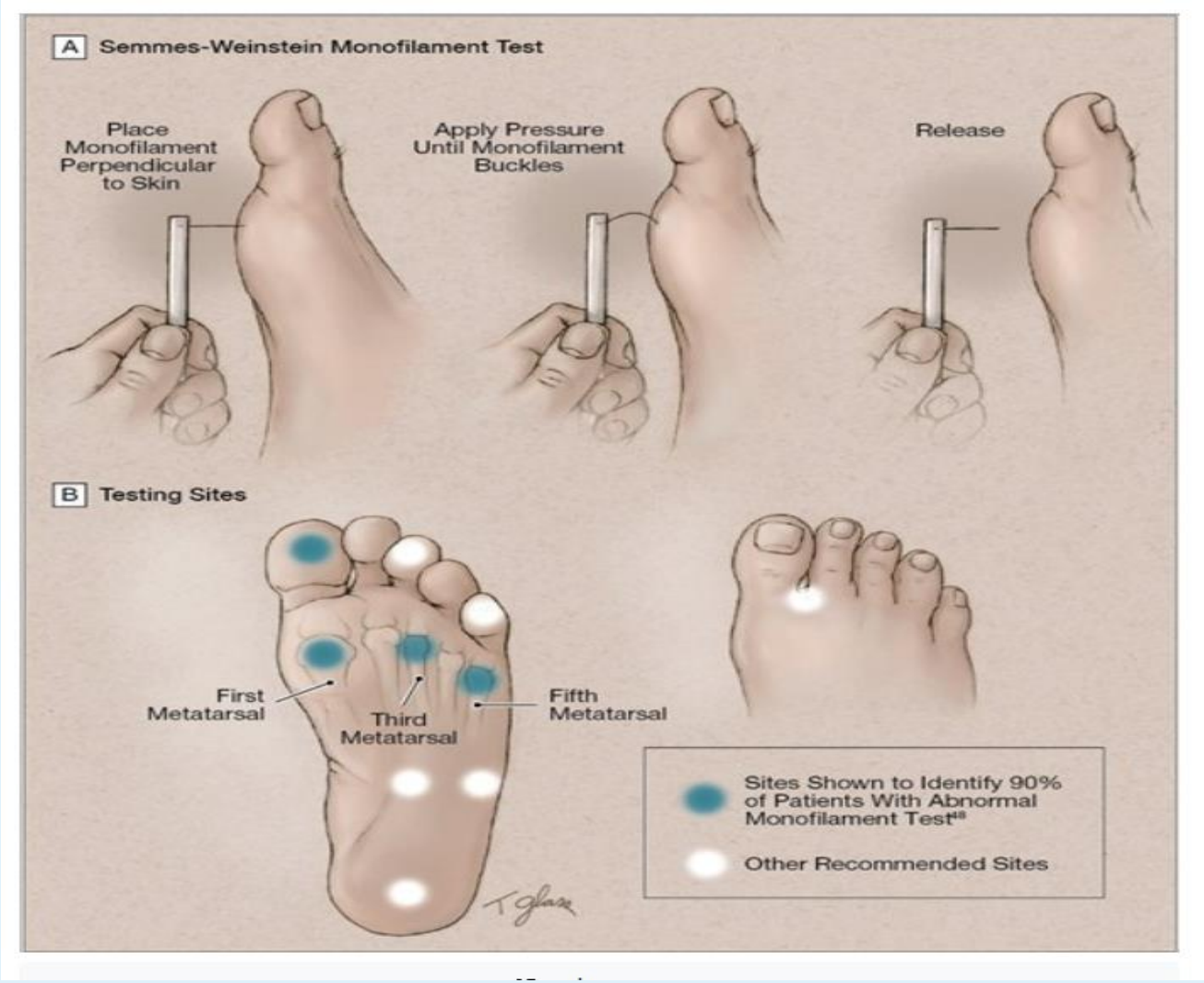
# Prevention

- 

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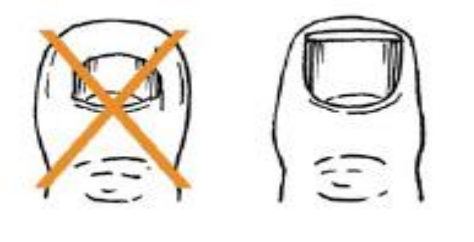
# Prevention

- Educating the patients and their family (1C)
  - Check shoes before putting on
  - Change shoes daily if possible
  - Not check bathwater with their feet
  - Wash feet daily
  - Not use perfumed soaps
  - Keep feet moisturized with creams but not between the toes
  - Never walk barefoot
  - Wear shower shoes

  - Self-inspection criteria
    - Redness
    - Blister
    - Callus
    - Open sore (ulcer)
    - Swelling
    - Dryness
    - Nail thickness, length or tenderness

- Use specialized therapeutic footwear in average risk (2C)
- Use custom therapeutic footwear in high-risk (1B)



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# Prevention

- HbA1C < 7% (2B)
- Against prophylactic arterial revascularization (1C)
  - Indication
    - = Severe claudication
    - = Rest pain
    - = Tissue loss (1B)

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# Off loading DFUs

- Plantar DFU with TCC (1B)
- DFU with frequent dressing remov able cast walker (2C)
  - Against post-op shoes
- With nonplantar wounds anything to relieve pressure (1C)
- For high-risk with healed DFU, we ar therapeutic footwear (1C)

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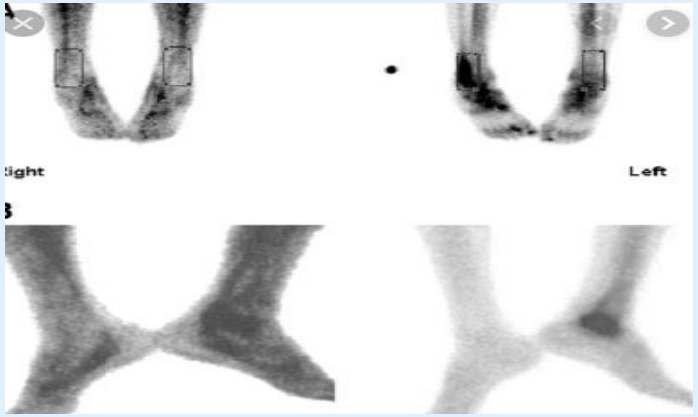
# Diagnosis of diabetic foot osteomyelitis

- Diabetic foot infection (DFI) with an open wound
  - Probe to bone test (2C)
    - Diagnosis of OM
      - 60% sensitivity
      - 91% specificity
  - Plain X-ray (2C)
      - 54% sensitivity
      - 68% specificity
  - MRI (1B)
      - 90% sensitivity
      - 79% specificity
  - Leukocyte or antigranulocyte scan (2B)
    - For MRI contraindicated
      - 81% sensitivity
      - 28% specificity
  - Bone biopsy (1C)
    - When debridement done
      - Limited studies
  - Diagnostic bone biopsy (2C)
    - Bone culture
    - Only when empirical treatment fails



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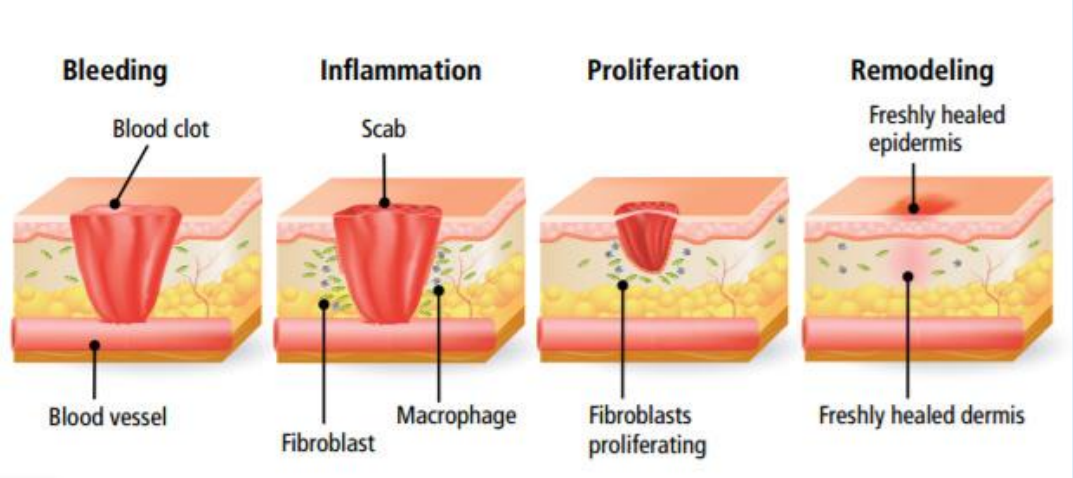
# Wound care

- Requires frequent inspection with irrigation and debride ment, protective dressings, inspection and inflammation control, and plantar off-loading.

- Preserve a moist, non-infected wound environment.

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# Wound care

- Frequent evaluation at 1 to 4 weeks (1C)
  - Wound size reduction
    - Early predictor of treatment outcome
      - 10%-15% per week or more than 50 in 4 weeks
        - » Decreased complication and amputation
  - Initial surgical intervention for abscess, gas or necrotizing fasciitis (1B)
- Use dressing products that maintain a moist wound bed, contr ol exudate, and avoid maceration. (1B)
  - Non-adherent dressings
  - Silmazine, honey, etc

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# Wound care

- Debridement (1B)
  - Drainage of exudate
  - Removal of nonviable tissue
  - Assess the wound
  - Removal of surrounding callus material
- Method of debridement
  - Surgical, Larva, hydrotherapy, ultrasound, hydrogel, enzymatic
  - NO more saline-soaking gauze
- Adjunctive therapy
  - For DFU with no improvement after 4 weeks
    - Negative pressure (2B)
    - PDGF (2B), living cellular (2B), amniotic membrane
    - HBOT (2B) – reduced amputation rate, increased healing rate

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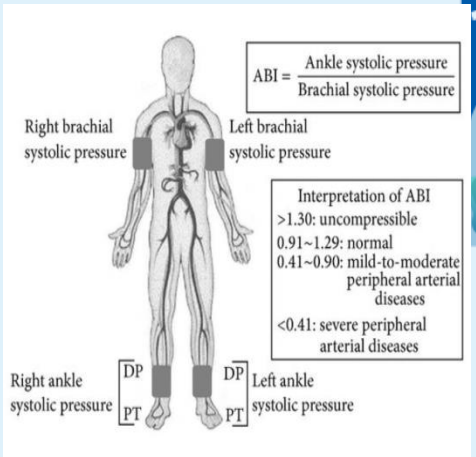
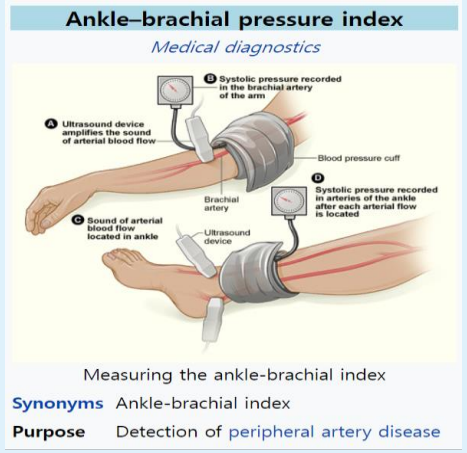
# PAD

- ABI measurement from 50 years of age (2C)
  - <0.8 : increased risk of limb loss
- Pedal perfusion assessed by ABI, pedal doppler arte rial waveforms, toe systolic pressure or TcPO2 (1B)
  - Toe Systolic pressure <30 mmHg : increased risk
- DFU with PAD
  - Surgical or endovascular therapy (1B)



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# V 당뇨발에서의 고압산소치료 기전과 임상적 적용에 대한 이행

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# Hyperbaric oxygen ?

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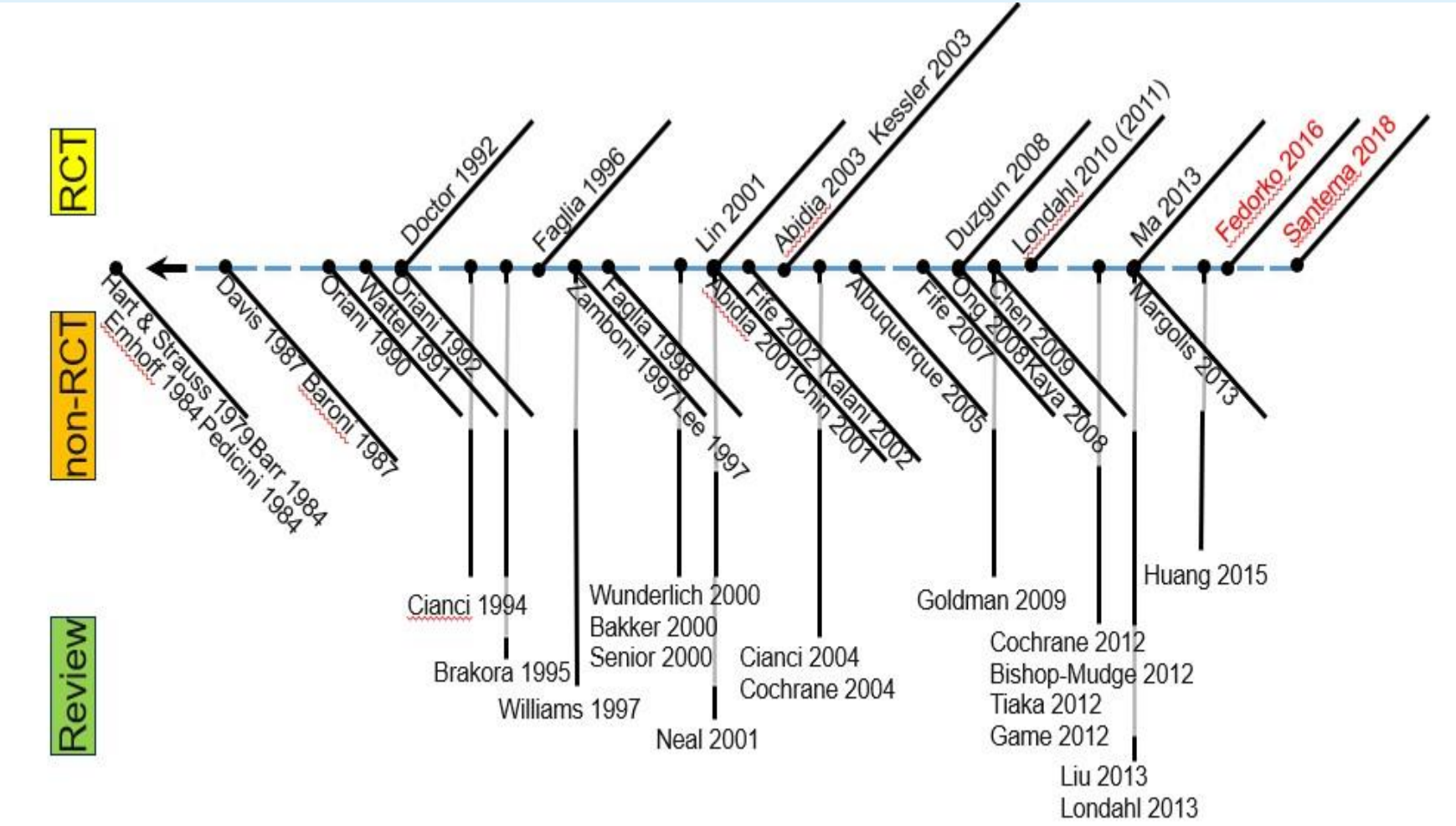
# Timeline of Studies



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# Overview of Studies

| Study | Study Design | N | Study Population (Wagner grade) | Co-Morbidities Addressed | | | | $HBO_2$ Protocol | Strength of Evidence | Generalizable Results |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | V | O | I | D | | | |
| Hart 1979 | RCaS | 11 | NS | ☆ | ☆ | ☆ | ☆ | NS | Low | Low |
| Davis 1987 | RCaS | 168 | NS | ★ | ☆ | ★ | ★ | NS | Low | Moderate |
| Baroni 1987 | PCoT | 18 vs 10 | 1 2 3 4 5 | ★ | ★ | ★ | ★ | 2.5-2.8 Daily | Low | Moderate |
| Oriani 1990 | RCoT | 62 vs 18 | 1 2 3 4 5 | ★ | ★ | ★ | ★ | 2.5-2.8 Daily | Low | Moderate |
| Wattel 1991 | PCaS | 59 | 1 2 3 4 5 | ☆ | ★ | ☆ | ☆ | 2.5 BID | Moderate | High |
| Doctor 1992 | RCT | 15 vs 15 | 1 2 3 4 5 | ★ | ★ | ☆ | ☆ | Atypical | Moderate | Low |
| Faglia 1996 | RCT | 35 vs 33 | 1 2 3 4 5 | ★ | ★ | ★ | ★ | 2.2-2.5 Daily | High | Moderate |
| Zamboni 1997 | PCoS | 5 vs 5 | 1 2 3 4 5 | ☆ | ☆ | ☆ | ★ | 2.0 Daily | Moderate | Moderate |
| Faglia 1998 | RCoT | 51 vs 64 | 1 2 3 4 5 | ☆ | ☆ | ☆ | ☆ | 2.2-2.5 Daily | Moderate | Moderate |
| Lin 2001 | RCT | 17 vs 12 | 1 2 3 4 5 | ☆ | ☆ | ☆ | ☆ | 2.5 Daily | High | Moderate |
| Kalani 2002 | PCoT | 17 vs 21 | 1 2 3 4 5 | ☆ | ☆ | ☆ | ☆ | 2.5 Daily | Moderate | Moderate |
| Fife 2002 | RCaS | 774 | 1 2 3 4 5 | ★ | ☆ | ☆ | ☆ | 2-2.5 Daily | Moderate | Moderate |
| Abidia 2003 | RCT | 9 vs 9 | 1 2 3 4 5 | ☆ | ☆ | ☆ | ☆ | 2.4 Daily | High | Moderate |
| Kessler 2003 | RCT | 14 vs 13 | 1 2 3 4 5 | ☆ | ☆ | ☆ | ☆ | 2.5 BID | Moderate | Low |
| Fife 2007 | RCaS | 971 | 1 2 3 4 5 | ★ | ☆ | ☆ | ☆ | 2-2.5 Daily | Moderate | Moderate |
| Duzgun 2008 | RCT | 100 | 1 2 3 4 5 | ☆ | ☆ | ☆ | ★ | Atypical | Moderate | Moderate |
| Löndahl 2010 | RCT | 38 vs 37 | 1 2 3 4 5 | ★ | ☆ | ☆ | ★ | 2.5 Daily | High | High |
| Ma 2013 | RCT | 18 vs 18 | 1 2 3 4 5 | ★ | ★ | ★ | ★ | 2.5 BID | High | Moderate |
| Margolis 2013 | RCoT | 793 vs 5466 | 1 2 3 4 5 | ☆ | ☆ | ☆ | ☆ | 2-2.5 Daily | Low | Low |

RCT - Randomized Controlled Trial PCoT - Prospective Cohort Trial PCaS - Prospective Case Series RCoT - Retrospective Cohort Trial RCoS - Retrospective Case Series

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# Wagner Grades

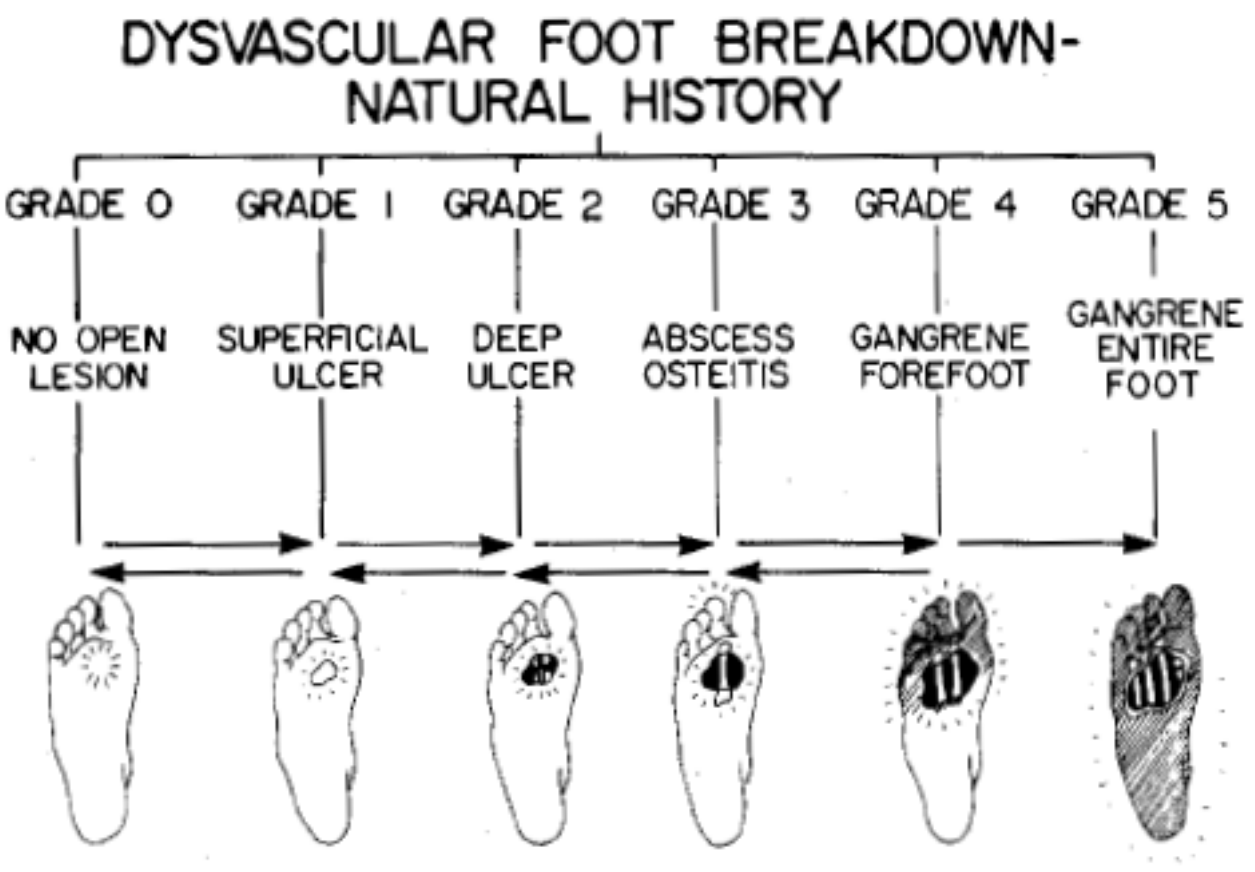


**Fig. 1.** Grading of foot lesions. The arrow indicates that all grades except Five can be converted to a Grade Zero foot.

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Wagner, FW The Dysvascular Foot, Foot & Ankle 2(2) 1981

# Baroni 1987

| | | | | | | |
|---|---|---|---|---|---|---|
| The Question | Does $HBO_2$ improve healing in DFU? | | | | | |
| Study Design | Prospective Cohort Trial (N=28) | | | | Study Population (Wagner grade) | 1 2 3 4 5 |
| | | | | | Comparison | 18 $HBO_2$ vs. 10 Ø$HBO_2$ |
| Co-Morbidities Addressed | V | O | I | D | $HBO_2$ Protocol | 2.5-2.8 ATA x90 min 6/7 days (34±21 Tx) |
| | ★ | ★ | ★ | ★ | | |
| Strength of Evidence | Low | | | | Generalizability | Moderate - all patients hospitalized |
| The Answer | $HBO_2$ significantly improved healing rate (89% vs. 10%,p=.001) and decreased amputation rate (11% vs. 40%, p=.001). It suggests faster healing as decreased hospital LOS (62 days vs 82 days, NS). | | | | | |

★ Well Addressed ★ Moderately Addressed ★ Poorly Addressed ☆ Not Addressed

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# Oriani 1990

| | | | | | |
|---|---|---|---|---|---|
| The Question | Does $HBO_2$ improve healing in DFU? | | | | |
| Study Design | Retrospective Cohort Trial (N=80) | | | Study Population | 1 2 3 4 5 |
| | | | | Comparison | 62 $HBO_2$ vs 18 Ø$HBO_2$ |
| Co-Morbidities Addressed | V | O | I | D | |
| | ★ | ★ | ☆ | ★ | |
| | | | | $HBO_2$ Protocol | 2.5-2.8 ATA x 90 min<br>5-6 days/wk<br>(72±29 Tx) |
| Strength of Evidence | Low | | | Generalizability | Moderate - all patients hospitalized |
| The Answer | $HBO_2$ significantly improved healing rate (96% vs. 67%,p<.001) and decreased amputation rate (5% vs. 33%, p<.001). | | | | |

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# Faglia 1996

ORIGINAL ARTICLE

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

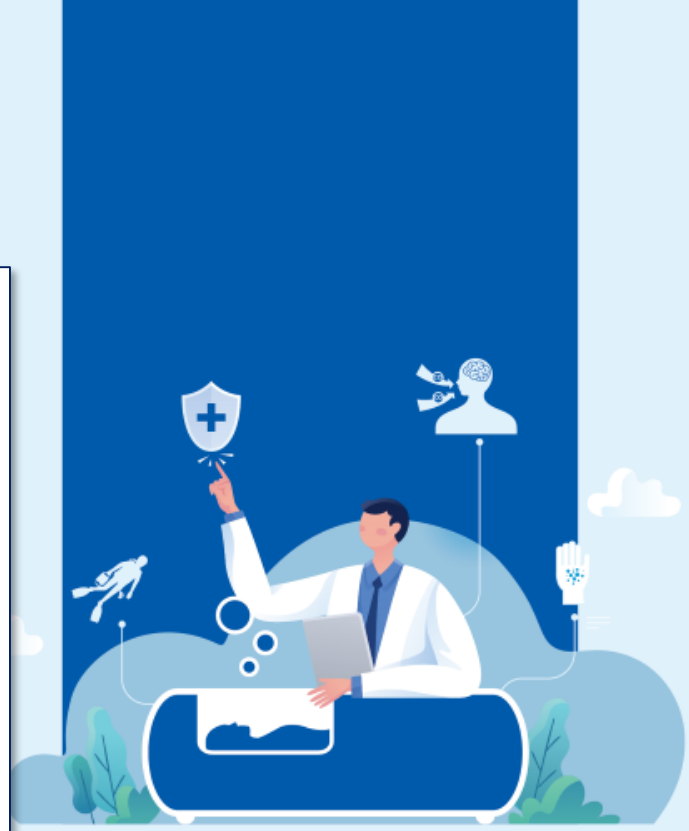
A randomized study

Ezio Faglia, MD
Fabrizio Favales, MD
Antonio Aldeghi, MD
Patrizia Calia, MD
Antonella Quarantiello, MD
Giorgio Oriani, MD
Michael Michael, MD
Pietro Campagnoli, MD
Alberto Morabito, PhD

### RESEARCH DESIGN AND METHODS

**Study Design**

From August 1993 to August 1995, 70 diabetic subjects, consecutively hospitalized in



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# Faglia 1996

| | | | | | | |
|---|---|---|---|---|---|---|
| The Question | Does $HBO_2$ improve healing and decrease amputation rate in DFU? | | | | | |
| Study Design | Randomized Controlled Unblinded Trial (N=68) | | | | Study Population (Wagner grade) | 1 2 3 4 5 |
| | | | | | Comparison | 35 $HBO_2$ vs 35 Ø$HBO_2$ |
| Co-Morbidities Addressed | V | O | I | D | $HBO_2$ Protocol | 2.2-2.5 ATA x 90 min<br>5-7 days/wk<br>(38±8 Tx) |
| | ★ | ☆ | ★ | ★ | | |
| Strength of Evidence | High | | | | Generalizability | Moderate - all patients hospitalized |
| The Answer | $HBO_2$ group had less major amputations (9% vs 33%, p=.002) and greater increase in $P_{tc}O_2$ (14 mm Hg vs. 5 mm Hg, p=.00002) than the control group | | | | | |

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- Limb considered salvaged when plantar support was preserved and the ulcer healed despite minor amputation
  - Reduction in major amputations in Wagner IV DFU (9.1% vs. 55%, p=0.002)
  - No difference in major amputations in Wagner III DFU (25% vs. 0%, p=0.33) or Wagner II DFU (0% vs. 0%)
- Pivotal Study for CMS (Centers for Medicare & Medicaid Services) approval of $HBO_2$ for DFU in the US

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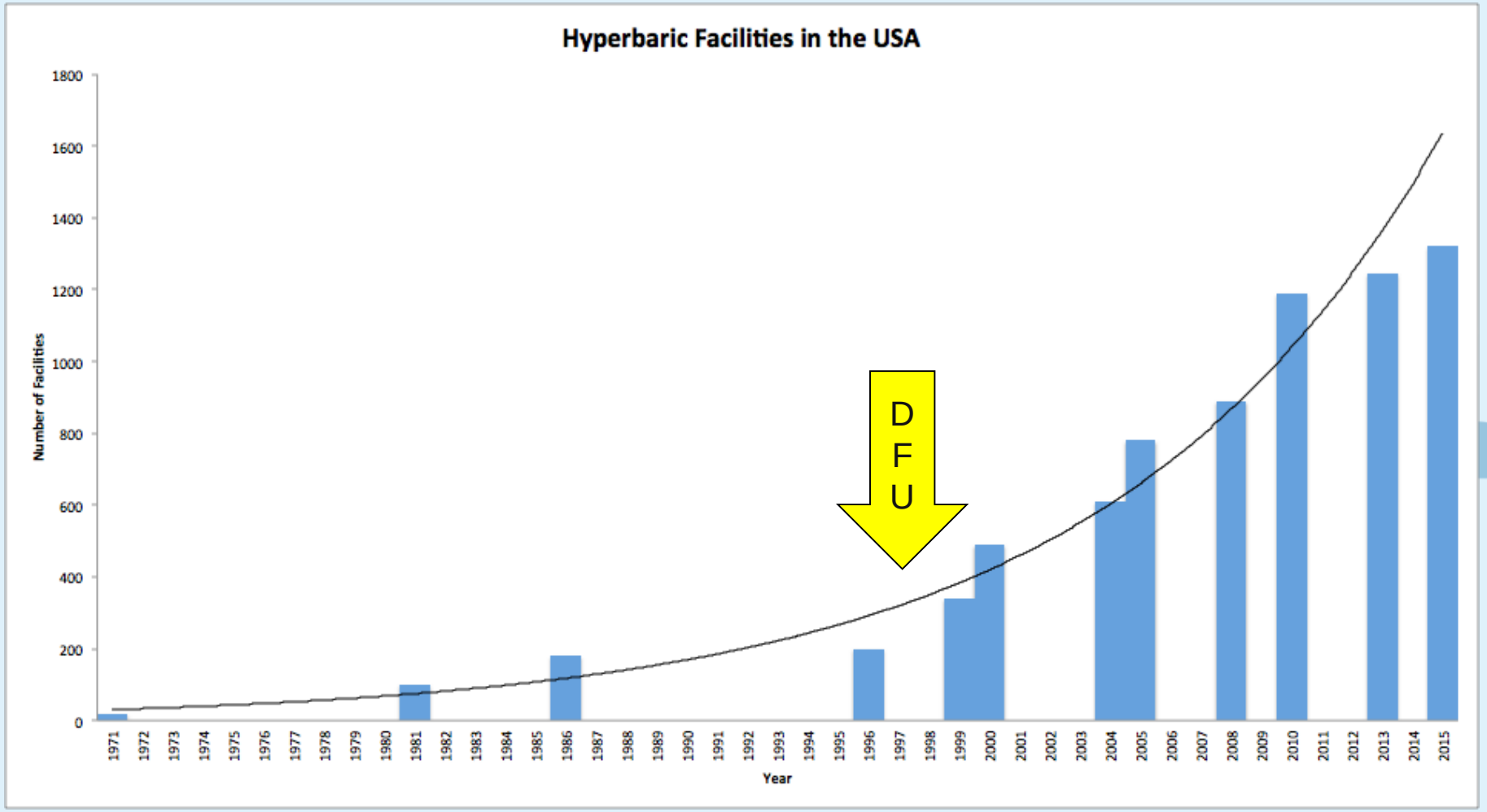

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# Löndahl 2010/2011

Clinical Care/Education/Nutrition/Psychosocial Research

ORIGINAL ARTICLE

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

MAGNUS LÖNDAHL, MD[1]
PER KATZMAN, MD, PHD[1]
ANDERS NILSSON, MD[2]
CHRISTER HAMMARLUND, MD, PHD[3]

grade 1 and 2 ulcers. Therefore, the clinical utility of HBOT in treating diabetic foot ulcers was not established. The final

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# Löndahl 2010/2011

| | | | | | |
|---|---|---|---|---|---|
| The Question | What is the effect of $HBO_2$ on healing of DFU? | | | | |
| Study Design | Randomized, Double-Blinded, Placebo-Controlled Trial (N=75) | | | Study Population | 1 2 3 4 5 |
| | | | | Comparison | 38 $HBO_2$ vs 37 HBAir |
| Co-Morbidities Addressed | V | O | I | D | $HBO_2$ Protocol: 2.5 ATA x 90 min, 5 days/week, up to 40 Tx |
| | ★ | ☆ | ☆ | ★ | |
| Strength of Evidence | High | | | Generalizability | High |
| The Answer | $HBO_2$ group had significantly better healing at 1 year than the control group (52% vs. 29%, p=0.03) using intention-to-treat (ITT) analysis. Per protocol analysis showed even stronger results (61% vs 27%, p=.009). | | | | |

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# Fedorko 2016, Diabetes Care



CrossMark

## 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

*Ludwik Fedorko,[1] James M. Bowen,[2,3] Wilhelmine Jones,[1] George Oreopoulos,[1] Ron Goeree,[2,3] Robert B. Hopkins,[2,3] and Daria J. O'Reilly[2,3]*

DOI: 10.2337/dc15-2001

EPIDEMIOLOGY

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# Fedorko 2016 (negative)

| | | | | | |
|---|---|---|---|---|---|
| The Question | Does $HBO_2$ reduce indication for amputation of DFU? | | | | |
| Study Design | Randomized, Double-Blinded, Placebo-Controlled Trial (N=103) | | | Study Population | 1 2 3 4 5 |
| | | | | Comparison | 49 $HBO_2$ vs 54 Sham |
| Co-Morbidities Addressed | V | O | I | D | $HBO_2$ Protocol: 2.5 ATA x 90 min, 5 days/week, up to 40 Tx |
| | ★ | ☆ | ☆ | ★ | |
| Strength of Evidence | Moderate | | | Generalizability | Low |
| The Answer | Criteria for major amputation were met in 13 of 54 patients in the sham group and 11 of 49 in the HBOT group (odds ratio 0.91 [95% CI 0.37, 2.28], P = 0.846). Twelve (22%) patients in the sham group and 10 (20%) in the HBOT group were healed. | | | | |

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# Primary Outcome

- Meeting criteria of need for amputation or undergoing amputation
  - Lack of significant progress in wound healing
  - Persistent deep infection involving bone/tendon
  - Inability to bear weight on affected limb
  - Pain causing significant disability

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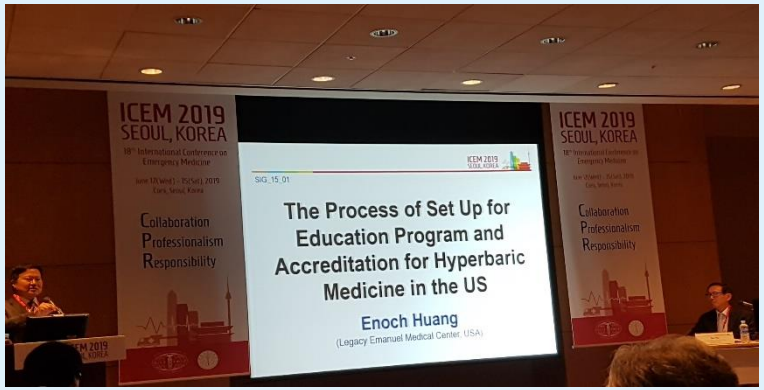
# Letters to the editor

COMMENT ON FEDORKO ET AL.

## 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. Diabetes Care 2016;39:392–399

*Enoch T. Huang*

*Diabetes Care 2016;39:e1–e2 | DOI: 10.2337/dc16-0196*



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# Santema 2018

Diabetes Care 1

Check for updates

## Hyperbaric Oxygen Therapy in the Treatment of Ischemic Lower Extremity Ulcers in Patients With Diabetes: Results of the $DAMO_2CLES$ Multicenter Randomized Clinical Trial

*Katrien T.B. Santema,[1] Robert M. Stoekenbroek,[1] Mark J.W. Koelemay,[1] Jim A. Reekers,[2] Laura M.C. van Dortmont,[3] Arno Oomen,[4] Luuk Smeets,[5] Jan J. Wever,[6] Dink A. Legemate,[1] and Dirk T. Ubbink,[1] on behalf of the $DAMO_2CLES$ Study Group[*]*

*https://doi.org/10.2337/dc17-0654*

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# Santema 2018 (negative)

| | | | | | | |
|---|---|---|---|---|---|---|
| The Question | Does $HBO_2$ improve wound healing and limb salvage of DFU at 12 months? | | | | | |
| Study Design | Randomized Controlled Trial (N=120) | | | | Study Population | 1 2 3 4 5 |
| | | | | | Comparison | 60 SC + $HBO_2$ vs 60 SC |
| Co-Morbidities Addressed | V | O | I | D | $HBO_2$ Protocol | 2.5 ATA x 90 min<br>5 days/week<br>up to 40 Tx |
| | ★ | ☆ | ☆ | ★ | | |
| Strength of Evidence | High | | | | Generalizability | High |
| The Answer | No difference between groups after 12 months (28 index wounds were healed in the SC group vs. 30 in the SC+HBOT group). Limb salvage was achieved in 47 patients in the SC group vs. 53 patients in the SC+HBOT. Amputation-free survival (AFS) was achieved in 41 patients in the SC group and 49 patients in the SC+HBOT group Patients who completed HBOT had significantly less major amputations and higher AFS. In the SC+HBOT group, 21 patients (35%) were unable to complete the HBOT protocol as planned. | | | | | |

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# Letters to the editor

**Diabetes Care** Volume 41, April 2018 e61

COMMENT ON SANTEMA ET AL.

## 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. Diabetes Care 2018;41:112–119

*Enoch Huang*

*Diabetes Care 2018;41:e61 | https://doi.org/10.2337/dc17-2440*

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# A clinical practice guideline for the use of hyperbaric oxygen therapy in the treatment of diabetic foot ulcers

**CPG Authors:** Enoch T. Huang, Jaleh Mansouri, M. Hassan Murad, Warren S. Joseph, Michael B. Strauss, William Tettelbach, Eugene R. Worth

**UHMS CPG Oversight Committee:** Enoch T. Huang, John Feldmeier, Ken LeDez, Phi-Nga Jeannie Le, Jaleh Mansouri, Richard Moon, M. Hassan Murad

CORRESPONDING AUTHOR: Dr. Enoch T. Huang – *enoch.huang@mac.com*

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**Table 2. Steps of the GRADE review methodology**

- **Formulate question (PICO format)**
- **Select outcomes of importance**
- **Rate importance of outcomes (1-9)**
- **Literature review**
  - create evidence profile of outcomes across studies
  - summary of findings and estimate of effect for each outcome
- **Rate quality of evidence for each outcome using criteria in Table 3**
  - rate overall quality of evidence across outcomes based on the lowest quality of critical outcomes
- **Formulate recommendations**
  - for or against
  - strong or conditional
    - taking into account quality of evidence, balance of harms vs. benefits, and the values and preferences of patients and clinicians
    - recommendations may also take into account resource use (cost)

- Outcomes of interest
  - Critical outcomes
    - Major amputation
    - Incomplete healing at one year
  - Importance outcomes
    - Resolution of infection
    - Quality of life (SF36)
    - Minor amputation

E.T. Huang, J. Mansouri, M.H. Murad, et al. UHM 2015, Vol. 42, No. 3

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Table 9. Outcomes reported by study

| type | study | OUTCOME REPORTED: major amputation | incomplete healing (1 yr) | minor amputation | persistent infection | no change in quality of life | COMMENTS |
|---|---|---|---|---|---|---|---|
| RANDOMIZED CONTROLLED TRIALS | Doctor 1992 | | | | | | included |
| | Faglia 1996 | | | | | | included |
| | Lin 2001 | | | | | | excluded: abstract only without any outcomes of interest |
| | Abidia 2003 | | | | | | included: data on quality of life were not able to be included |
| | Kessler 2003 | | | | | | excluded: reported only for short-term outcomes (< 6 weeks) |
| | Duzgun 2008 | | | | | | included |
| | Löndahl 2010 | | | | | | included: data on quality of life were able to be included |
| | Kaur 2012 | | | | | | excluded: did not include populations of interest and did not include outcomes of interest |
| | Ma 2013 | | | | | | excluded: did not include outcomes of interest |
| OBSERVATIONAL TRIALS | Hart 1979 | | | | | | excluded: did not include outcomes of interest |
| | Davis 1987 | | | | | | excluded: did not include outcomes of interest |
| | Baroni 1987<br>Oriani 1990 | | | | | | included: these studies may have had overlapping patients, so the last dataset for 1990 was used for analysis |
| | Oriani 1992 | | | | | | excluded: did not include non-$HBO_2$ comparison grp |
| | Wattel 1991 | | | | | | excluded: did not include non-$HBO_2$ comparison grp |
| | Cianci 1994 | | | | | | excluded: did not include any outcomes of interest |
| | Zamboni 1997 | | | | | | included |
| | Faglia 1998 | | | | | | excluded: did not include non-$HBO_2$ comparison grp |
| | Kalani 2001 | | | | | | included |
| | Grollman 2001 | | | | | | excluded: did not include any outcomes of interest |
| | Fife 2002 | | | | | | excluded: did not include non-$HBO_2$ comparison grp |
| | Strauss 2002 | | | | | | excluded: did not include non-$HBO_2$ comparison grp |
| | Niinikoski 2003 | | | | | | excluded: did not include any outcomes of interest |
| | Fife 2007 | | | | | | excluded: did not include any outcomes of interest |
| | Oubre 2007 | | | | | | excluded: did not include non-$HBO_2$ comparison grp |
| | Ong 2008 | | | | | | excluded: did not include non-$HBO_2$ comparison grp |
| | Lyon 2008 | | | | | | excluded: did not include any outcomes of interest |
| | Kaya 2009 | | | | | | excluded: did not include non-$HBO_2$ comparison grp |
| | Chen 2010 | | | | | | excluded: did not include any outcomes of interest |
| | Margolis 2013 | | | | | | included |
| | Tongson 2013 | | | | | | excluded: did not include any outcomes of interest |
| | Bishop 2013 | | | | | | excluded: did not include non-$HBO_2$ comparison grp |

- Initial review
  - -9 RCTs
  - -21 observational studies
- Subsequent formal review
  - -655 references
  - -Not identify any additional RCTs

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- “standard wound care”

  -The optimal management of surgical debridement

  -Mechanical off-loading

  -Infection control

  -Revascularization

  -Metabolic control

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## Table 7. Levels of evidence

| | |
|---|---|
| **High** | Further research is very unlikely to change our confidence in the estimate of effect. |
| **Moderate** | Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate of effect. |
| **Low** | Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate of effect. |
| **Very low** | Any estimate of effect is very uncertain. |

## Table 8. Strength of recommendations and implications for the general population, healthcare workers and policy-makers

### STRONG

**Population**
Most people in this situation would want the recommended course of action, and only a small proportion would not.

**Healthcare workers**
Most people should receive the recommended course of action.

**Policy-makers**
The recommendation can be adapted as a policy in most situations.

### CONDITIONAL

**Population**
The majority of people in this situation would want the recommended course of action, but many would not.

**Healthcare workers**
Be prepared to help people to make a decision that is consistent with their own values/decision aids and shared decision-making.

**Policy-makers**
There is a need for substantial debate and involvement of stakeholders.

- These four questions

  - For a patient with a diabetic foot ulcer, is $HBO_2$ with standard wound care more effective than standard wound care alone for the outcomes of interest?

  - For a patient with a Wagner Grade 2 or lower DFU that has not shown significant improvement after 30 days of treatment, is $HBO_2$ with standard wound care more effective than standard wound care alone for the outcomes of interest?

  - For a patient with a Wagner Grade 3 or higher DFU that has not shown significant improvement after 30 days of treatment, is $HBO_2$ with standard wound care more effective than standard wound care alone for the outcomes of interest?

  - For a patient with a Wagner Grade 3 or higher DFU who has just had a surgical debridement of the foot (e.g., partial toe or ray amputation; debridement of ulcer with underlying bursa, cicatrix or bone; foot amputation; I&D of deep space abscess; or necrotizing soft tissue infection), is acute postoperative $HBO_2$ with standard wound care more effective than standard wound care alone for the outcomes of interest?

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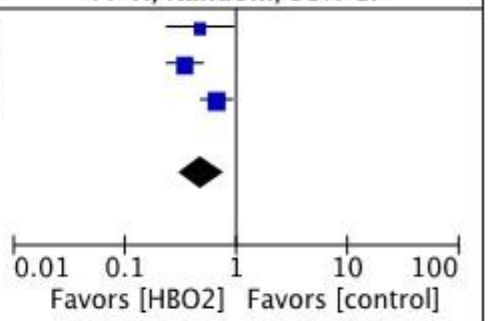
# PICO 1

## Incomplete Healing

| Study or Subgroup | HBO2 Events | HBO2 Total | Control Events | Control Total | Weight | Risk Ratio M-H, Random, 95% CI | Year |
|---|---|---|---|---|---|---|---|
| Abidia 2003 | 4 | 9 | 9 | 9 | 23.4% | 0.47 [0.24, 0.95] | 2003 |
| Duzgun 2008 | 17 | 50 | 50 | 50 | 37.2% | 0.35 [0.24, 0.51] | 2008 |
| Londahl 2010 | 24 | 49 | 33 | 45 | 39.4% | 0.67 [0.48, 0.93] | 2010 |
| **Total (95% CI)** | | **108** | | **104** | **100.0%** | **0.48 [0.30, 0.77]** | |
| Total events | 45 | | 92 | | | | |

Heterogeneity: $Tau^2 = 0.11$; $Chi^2 = 6.58$, df = 2 (P = 0.04); $I^2 = 70\%$

Test for overall effect: Z = 3.07 (P = 0.002)




| Quality assessment | | | | | | | № of patients | | Effect | | Quality | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | HBO+SC | SC | Relative (95% CI) | Absolute (95% CI) | | |
| Incomplete Healing (follow up: 1 years) | | | | | | | | | | | | |
| 3 | randomised trials | serious [1] | serious [2] | not serious | not serious | none | 45/108 (41.7%) | 92/104 (88.5%) | **RR 0.48** (0.30 to 0.77) | 460 fewer per 1000 (from 203 fewer to 619 fewer) | ⊕⊕◯◯ LOW | CRITICAL |

MD – mean difference, RR – relative risk

1. Rated down because of unclear methodology for allocation concealment in 2/3 studies, patients lost to follow-up in 1/3 studies, no blinding in 1/3 studies, and unclear intention to treat analysis in 1/3 studies.
2. The data for Incomplete Healing shows some inconsistency as the I2 was >50%, resulting in rating down 1 point

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# No Recommendation

- Level of Evidence was Low
- Populations too heterogeneous
- Elected to look at more homogenous populations

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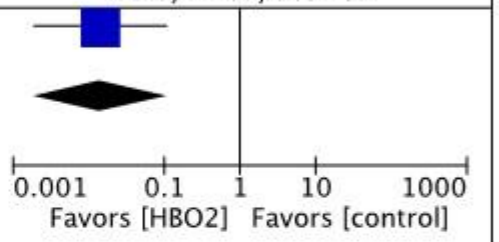
# PICO 2

## Incomplete Healing

| Study or Subgroup | HBO2 Events | HBO2 Total | Control Events | Control Total | Weight | Peto Odds Ratio Peto, Fixed, 95% CI | Year |
|---|---|---|---|---|---|---|---|
| Duzgun 2008 | 0 | 6 | 12 | 12 | 100.0% | 0.01 [0.00, 0.11] | 2008 |
| **Total (95% CI)** | | **6** | | **12** | **100.0%** | **0.01 [0.00, 0.11]** | |
| Total events | 0 | | 12 | | | | |

Heterogeneity: Not applicable

Test for overall effect: Z = 4.12 (P < 0.0001)




| Quality assessment | | | | | | | № of patients | | Effect | | Quality | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | HBO+SC | SC | Relative (95% CI) | Absolute (95% CI) | | |
| Incomplete Healing (follow up: 1 years) | | | | | | | | | | | | |
| 1 | randomised trials | serious [2] | not serious | not serious | very serious [1] | none | 0/6 (0.0%) | 0/12 (0.0%) | **RR 0.48** (0.30 to 0.77) | 0 fewer per 1000 (from 0 fewer to 0 fewer) | ⊕◯◯◯ VERY LOW | CRITICAL |

MD – mean difference, RR – relative risk

1. Wide confidence intervals in a single study with small number of events
2. Study was not blinded

2. Wide confidence intervals in a single study with small number of events

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# Recommendation 1

- In patients with Wagner Grade 2 or lower diabetic foot ulcers, we suggest against using hyperbaric oxygen therapy
  - -Very low-level evidence in support of HBO2, conditional recommendation

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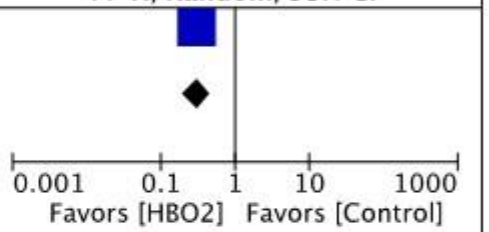
# PICO 3

## Incomplete Healing

| Study or Subgroup | HBO2 Events | HBO2 Total | Control Events | Control Total | Weight | Risk Ratio M-H, Random, 95% CI | Year |
|---|---|---|---|---|---|---|---|
| Duzgun 2008 | 13 | 44 | 38 | 38 | 100.0% | 0.30 [0.19, 0.48] | 2008 |
| **Total (95% CI)** | | **44** | | **38** | **100.0%** | **0.30 [0.19, 0.48]** | |
| Total events | 13 | | 38 | | | | |

Heterogeneity: Not applicable

Test for overall effect: Z = 5.21 (P < 0.00001)




| Quality assessment | | | | | | | № of patients | | Effect | | Quality | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | HBO+SC | SC | Relative (95% CI) | Absolute (95% CI) | | |
| Incomplete Healing (follow up: 1 years) | | | | | | | | | | | | |
| 1 | randomised trials | serious [1] | not serious | not serious | not serious | none | 13/44 (29.5%) | 38/38 (100.0%) | **RR 0.30** (0.19 to 0.48) | 700 fewer per 1000 (from 520 fewer to 810 fewer) | ⊕⊕⊕◯ MODERATE | CRITICAL |

MD – mean difference, RR – relative risk

1. Study was not blinded

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# Recommendation 2

- In patients with Wagner Grade 3 or higher diabetic foot ulcers that have not shown significant improvement after 30 days of treatment, we suggest adding hyperbaric oxygen therapy to the standard of care to reduce the risk of major amputation and incomplete healing
  - Moderate-level evidence, conditional recommendation

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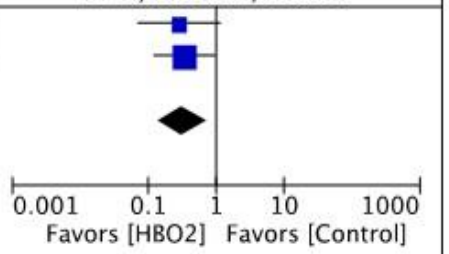
# PICO 4

## Major Amputation

| Study or Subgroup | HBO2 Events | HBO2 Total | Control Events | Control Total | Weight | Risk Ratio M-H, Random, 95% CI | Year |
|---|---|---|---|---|---|---|---|
| Doctor 1992 | 2 | 15 | 7 | 15 | 35.8% | 0.29 [0.07, 1.16] | 1992 |
| Faglia 1996 | 4 | 36 | 11 | 34 | 64.2% | 0.34 [0.12, 0.98] | 1996 |
| **Total (95% CI)** | | **51** | | **49** | **100.0%** | **0.32 [0.14, 0.74]** | |
| Total events | 6 | | 18 | | | | |

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.04$, df = 1 (P = 0.84); $I^2 = 0\%$

Test for overall effect: Z = 2.66 (P = 0.008)




| Quality assessment | | | | | | | № of patients | | Effect | | Quality | Importance |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Acute HBO | SC | Relative (95% CI) | Absolute (95% CI) | | |
| Major Amputation | | | | | | | | | | | | |
| 2 | randomised trials | serious 1 | not serious | not serious | not serious | none | 6/51 (11.8%) | 18/49 (36.7%) | **RR 0.32** (0.14 to 0.74) | 250 fewer per 1000 (from 96 fewer to 316 fewer) | ⊕⊕⊕◯ MODERATE | CRITICAL |

MD - mean difference, RR - relative risk

1. 1/2 studies unblinded and 1/2 had single blinding, 2/2 had unclear allocation concealment, 1/2 had unclear patients lost to follow-up, 1/2 had unclear intention-to-treat analysis and 1/2 had no intention-to-treat analysis

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# Recommendation 3

- In patients with Wagner Grade 3 or higher diabetic foot ulcers who have just had a surgical debridement of an infected foot (e.g., partial toe or ray amputation; debridement of ulcer with underlying bursa, cicatrix or bone; foot amputation; I&D of deep space abscess; or necrotizing soft tissue infection), we suggest adding acute post-operative hyperbaric oxygen therapy to the standard of care to reduce the risk of major amputation

  -Moderate level evidence, conditional recommendation

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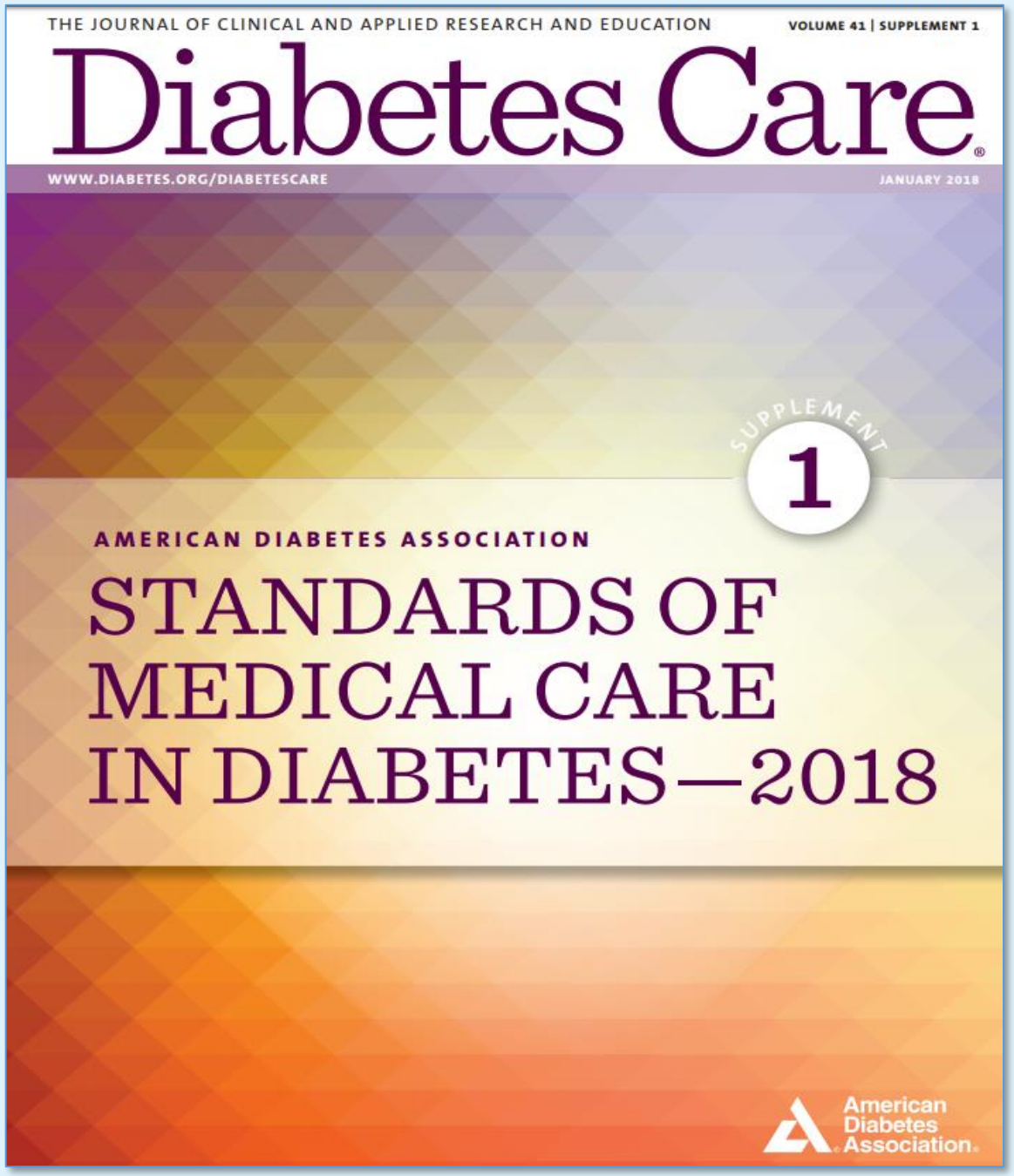

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- Hyperbaric oxygen therapy (HBOT) in patients with diabetic foot ulcers has mixed evidence supporting its use as an adjunctive treatment to enhance wound healing and prevent amputation.

- The Centers for Medicare & Medicaid Services currently covers HBOT for diabetic foot ulcers that have failed a standard course of wound therapy when there are no measurable signs of healing for at least 30 consecutive days.

- HBOT should be a topic of shared decision making before treatment is considered for selected patients with diabetic foot ulcers.

Huang ET, et al. Undersea Hyperb Med 2015;42:205–247

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# UHMS Indications Manual (14th edition)

- Available evidence supports $HBO_2$ for DFU
- 2 – 2.5 ATA for 90 – 120 minutes once or twice daily

  -Serious infection may require IV abx, surgical intervention and glycemic control
- Utilization review after 30 days of treatment

  -At least every 30 days subsequently
- Use of TCOM to risk stratify patients

  -Warrants at least 1 tx to measure $PtcO_2$ in chamber

  -If values low, appropriate to treat 10-15 sessions (2-3 weeks) to see if values increase (neovascularization)

  -If no change in 2-3 weeks, further $HBO_2$ not warranted

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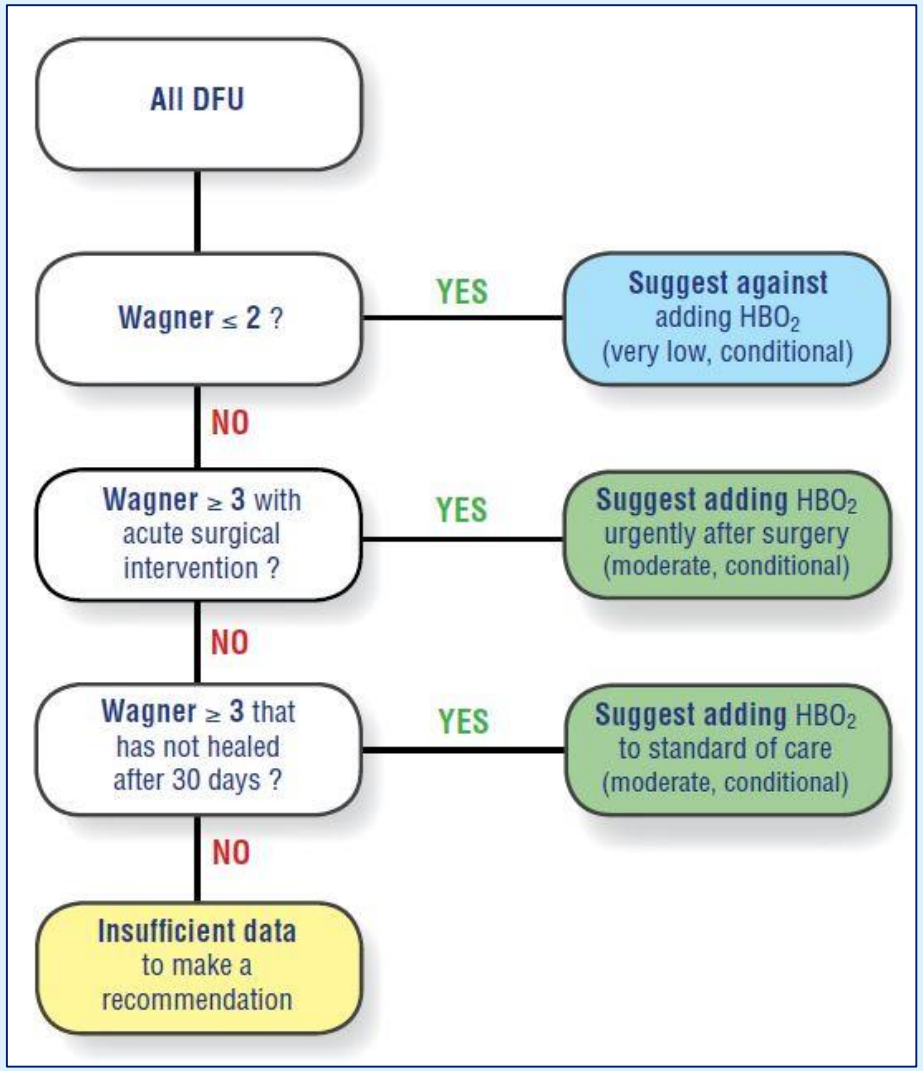
# Algorithm for the use of $HBO_2$



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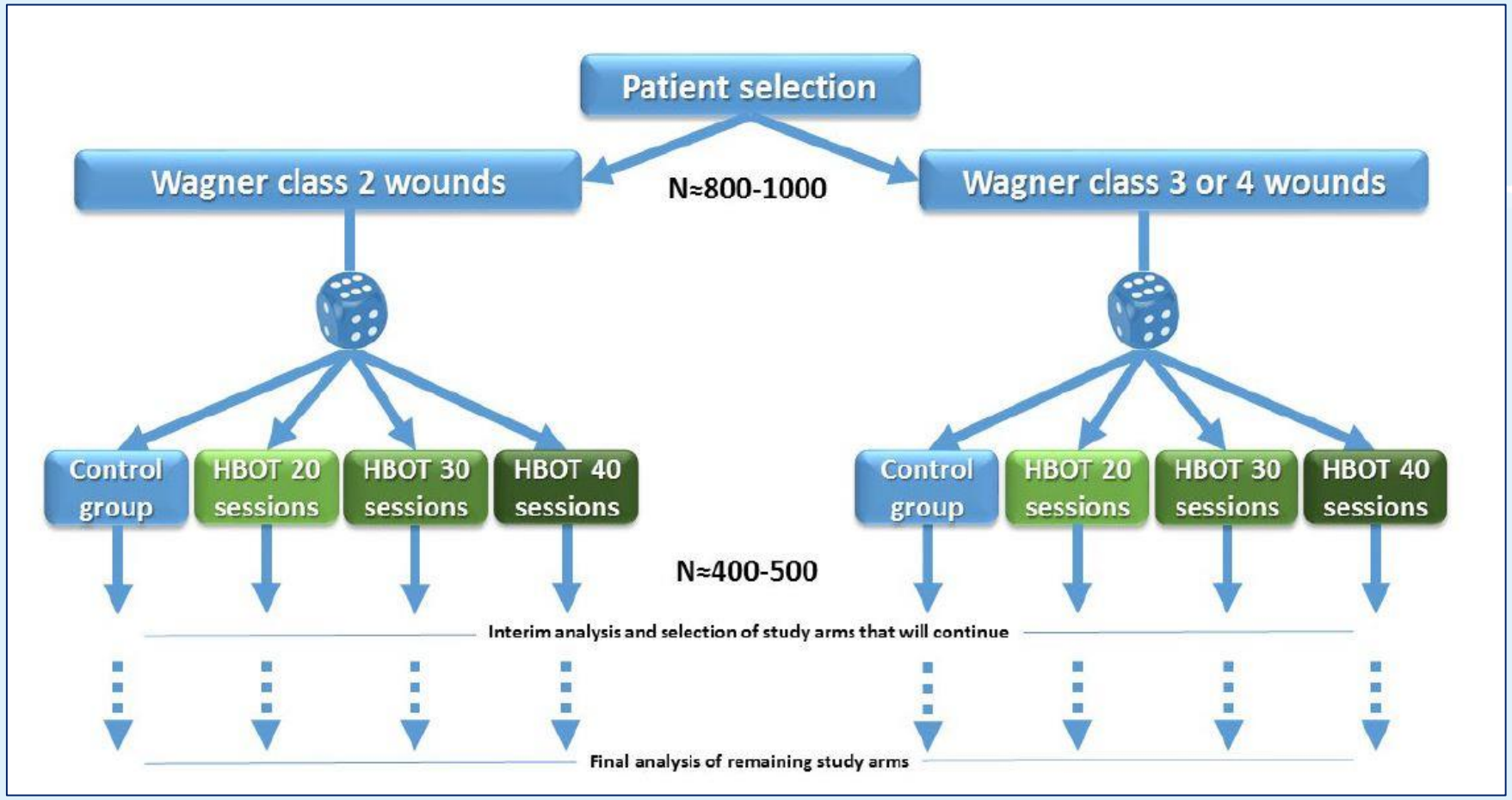
# DIONYSIUS trial

(Does Increasing Oxygen Nurture Your Symptomatic Ischemic Ulcer Sufficiently?/ 2020년부터 시작)



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# 요 약

- Mechanisms of HBO to DFUs
- The major trials on the use of $HBO_2$ for DFU
- The strengths/weaknesses of the two newest randomized controlled studies on the use of $HBO_2$ for DFU
- Know the Undersea and Hyperbaric Medical Society Clinical Practice Guideline on the use of $HBO_2$ for DFU

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# Thank you

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