

WELCOME

A NEW RESOURCE FOR THE FULL WOUND CARE TEAM

Wound care sits at a complex clinical crossroads, where physicians, advanced practice providers, nurses, case managers, and home health partners all bring different lenses to the same patient. This complexity becomes a strength when the team aligns around shared evidence and patient outcomes.

Clinical Perspectives is a quarterly newsletter for the full wound care team. Each issue distills recent evidence, guideline updates, and practical insights you can apply in practice. We will cover why wounds fail to heal, the therapies used to address those challenges, and the data that should guide treatment decisions.

We are committed to presenting the data honestly. Where studies have methodological limitations, we will say so. Our goal is to help you evaluate the evidence, not to evaluate it for you.

We hope this newsletter becomes a valuable addition to your clinical reading, and we welcome your feedback on topics and formats that would be most useful to your practice and care setting.

FROM THE CHIEF MEDICAL OFFICER

A MESSAGE FROM OUR CHIEF MEDICAL OFFICER

In this inaugural edition of *Clinical Perspectives*, we focus on the growing evidence base supporting Intermittent Topical Oxygen Therapy, (TWO2 therapy from AOTI). Recent studies reinforce its mechanisms of action, demonstrate improved healing outcomes across larger patient populations, and show meaningful long-term outcomes that together benefit patients, providers, and payers.

Chronic wounds remain common, costly, and difficult to treat, with millions of patients experiencing prolonged care journeys without durable healing. Historically, wound care has lacked the rigorous evidence base seen in other specialties, relying more on tradition than consistently replicated data.

We now have a stronger body of research to clarify what works, for whom, and why. This issue introduces that evolving evidence, with future editions exploring different wound types, patient selection, and remaining gaps.

I am glad you are here. The patients in your care are the reason this work matters.



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Chief Medical Officer
Past President, American Podiatric Medical Association
Immediate Past Chair, Alliance of Wound Care Stakeholders

CLINICAL FOCUS

FROM CONTROLLED TRIAL TO CLINICAL PRACTICE:
WHAT THE TWO2 THERAPY EVIDENCE BASE NOW TELLS US

Lohr JM et al., *JVS-Vascular Insights*, 2026 · Frykberg RG et al., *Diabetes Care*, 2020 · Yellin A et al., *Advances in Wound Care*, 2022

A persistent challenge in wound care is the mismatch between clinical trial populations and the patients seen in everyday practice. Trial participants are often younger, have fewer comorbidities, and adhere more closely to treatment than real-world patients. As a result, outcomes observed in controlled settings may not translate directly to broader use. Bridging this gap requires both high quality randomized controlled trials (RCT) for rigor and real-world evidence (RWE) data for generalizability. For intermittent topical oxygen therapy (ITOT), both are now available, and they point in the same direction.

The evidence base begins with randomized controlled trial data

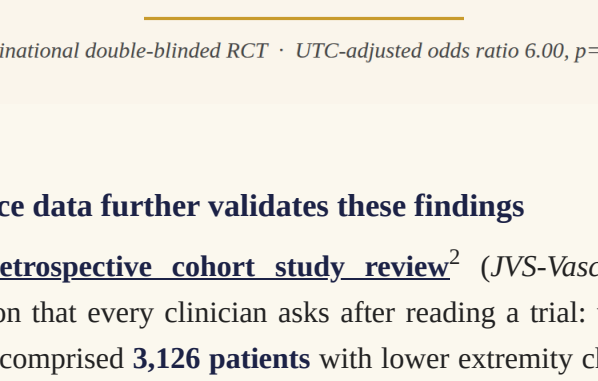
The [Frykberg et al. multinational double-blinded placebo-controlled RCT¹](#) (*Diabetes Care*, 2020) remains the foundation of the ITOT evidence base. Across 17 centers in five countries, patients with diabetic foot ulcers (DFUs) of University of Texas (UT) Classification grade 1-2 A-D that were proven failures of optimal standard care were randomized (double-blind) to either ITOT or a sham device, both in addition to optimal standard care. Utilizing only the most stringent intention-to-treat analysis, complete healing at 12 weeks was **41.7%** in the ITOT group versus **13.5%** in the sham group, translating to a **6-fold greater likelihood of healing** in multivariate analysis after adjustment for ulcer grade (odds ratio 6.00, p=0.004). Sustained healing at 12 months was also shown, 56% versus 27%, and wound recurrence was just 6.7% versus 40% in the sham arm. The trial was stopped at the first predetermined interim analysis point, as the clear superiority of ITOT was confirmed.

Notably, this was a hard-to-heal population, where more than half of patients had at least moderate ischemia. Quality of life improved significantly in the ITOT group, and no device-related adverse events were reported. The RCT therefore supports two conclusions with high confidence: ITOT markedly increases the likelihood of wound closure, and the healed tissue is more durable, with 12-month recurrence rates of **6.7%**, being far lower than the well established **40%** recurrence rate typically seen in this population.

RANDOMIZED CONTROLLED TRIAL · DIABETES CARE, 2020

Complete Healing of Chronic DFUs at 12 Weeks

6× more likely to heal



Multinational double-blinded RCT · UTC-adjusted odds ratio 6.00, p=0.004

Real-world-evidence data further validates these findings

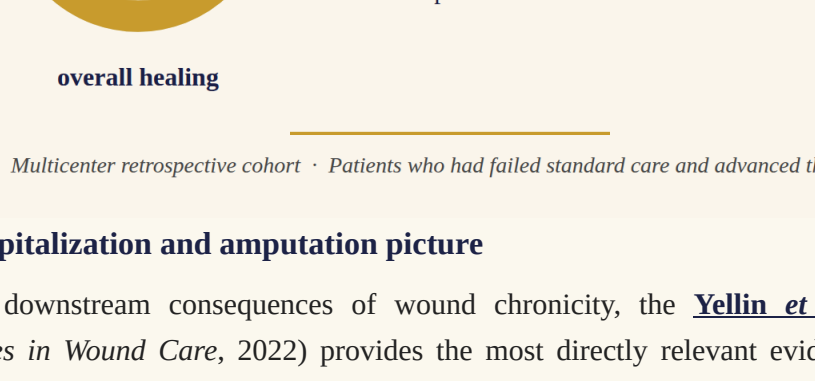
The [Lohr et al. retrospective cohort study review²](#) (*JVS-Vascular Insights*, 2026) addressed the question that every clinician asks after reading a trial: will this work for my patients? The cohort comprised **3,126 patients** with lower extremity chronic wounds treated between January 2023 and December 2024, the majority through Veterans Administration centers. Wound types included DFUs (72%), venous leg ulcers (20%), arterial ulcers (7%), and atypical wounds (1%), reflecting the mixed caseload of a real wound care practice. Mean patient age was nearly 70 years, and mean pretreatment wound age was **7 months**. These were patients who had already failed standard care and other advanced therapies before ITOT was initiated.

Complete healing was achieved in **64.8% of patients in a mean of 4.2 months**. For context, the US Wound Registry reports healing rates of 45% for DFUs and 57% for VLU across all patients receiving standard and advanced therapies within 20 and 16 weeks respectively. The Lohr cohort greatly exceeded those benchmarks in patients who had already failed other treatment options. Outcomes were consistent across wound types, age groups, and both sexes, with the Cox proportional hazards model confirming that wound age, wound type, and number of wounds were the primary independent predictors of healing probability. Also, wound recurrence was shown to be only **2.7%** over an astounding **13.9 months**.

The real-world cohort is particularly well-suited to answering questions about healing rates and treatment adherence in a more complex, comorbid population. On those questions, the data are compelling and consistent with the RCT findings.

REAL-WORLD COHORT STUDY · JVS-VASCULAR INSIGHTS, 2026

ITOT in 3,126 Chronic Lower-Extremity Wound Patients



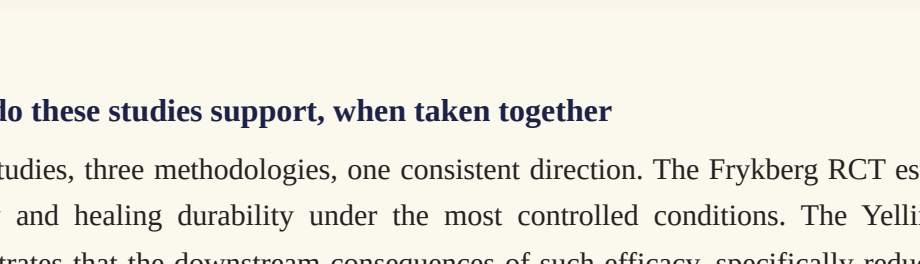
Multicenter retrospective cohort · Patients who had failed standard care and advanced therapies

The hospitalization and amputation picture

For the downstream consequences of wound chronicity, the [Yellin et al. VA study³](#) (*Advances in Wound Care*, 2022) provides the most directly relevant evidence. Designed specifically to evaluate hospitalizations and amputations as primary endpoints, the study reported outcomes for both a propensity score-matched cohort of **140 DFU patients (70 ITOT vs 70 no ITOT)** with comparable baseline risk and the full unmatched cohort of **202 patients**. In the matched cohort, ITOT-treated patients showed an **82% reduction in hospitalizations** (7.1% vs 40.0%) and a **73% reduction in amputations** (8.6% vs 31.4%) at 12 months. Logistic regression demonstrated that patients who did not receive ITOT had a **9-fold greater risk of hospitalization** and a **5-fold greater risk of amputation**. These findings speak directly to the downstream clinical and economic benefits of achieving more durable wound healing.

REAL-WORLD COHORT STUDY · ADVANCES IN WOUND CARE, 2022

Hospitalization and Amputation at 12 Months in DFU Patients



Propensity score matched cohort for comparison · n=140

What do these studies support, when taken together

Three studies, three methodologies, one consistent direction. The Frykberg RCT establishes efficacy and healing durability under the most controlled conditions. The Yellin cohort demonstrates that the downstream consequences of such efficacy, specifically reduced rates of hospitalizations and amputations, are deliverable in real-world practice. The retrospective study by Lohr and colleagues confirms that ITOT's healing outcomes hold at scale, across various wound types and comorbid patient profiles that reflect the full complexity of clinical practice.

Together they address the questions that matter most: Does ITOT work? Yes, demonstrated under controlled conditions. Does it work in my patients? Yes, demonstrated at scale in a real-world population. Does it change what happens to my patients beyond just healing the wound? Yes, demonstrated in a study designed specifically to examine differences in hospitalization and amputation rates. This convergence across study designs is the strongest form of clinical evidence available, which has also been validated in multiple systematic reviews, and it is the reason ITOT now carries formal treatment recommendations across multiple leading societies' clinical practice guidelines: the American Diabetes Association,⁴ the International Working Group on the Diabetic Foot,⁵ the Wound Healing Society,⁶ NICE (United Kingdom),⁷ and the Journal of Wound Care international expert consensus.⁸

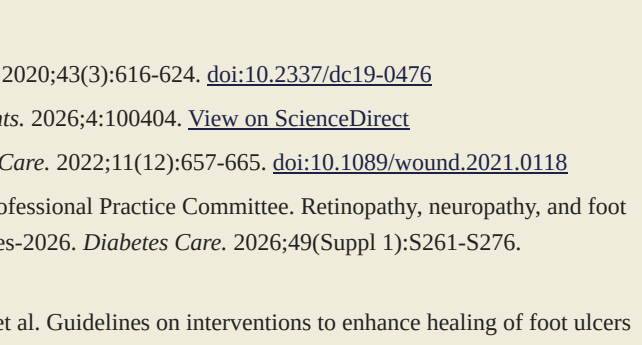
FEATURED DISCUSSION

A MULTIDISCIPLINARY APPROACH TO LIMB SALVAGE:
CASE-BASED DISCUSSION

PRESENT Podcast, Inaugural Episode

A case-based conversation with Anahita Dua, MD, MBA (MGH / Harvard) and Sara Rose-Sauld, DPM (MGH / Harvard), moderated by Dr. Mike Griffiths (AOTI), exploring multidisciplinary limb salvage and the real-world evidence behind the 3,126-patient study featured in this issue.

Watch Podcast >



AOTI-sponsored educational content

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ABOUT THIS NEWSLETTER

WHAT WE COVER

Clinical Perspectives is a quarterly resource for the wound care team, covering the evidence and clinical practice of treating hard-to-heal wounds. Issues feature evidence reviews, case studies, guideline updates, and practical considerations across the wound types and patient populations clinicians encounter most often.

Clinical Perspectives

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