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## Retrospective review of 3126 patients with chronic lower extremity wounds treated with intermittent topical oxygen therapy

Joann M. Lohr, MD,<sup>a</sup> Andrew J. M. Boulton, MD,<sup>b</sup> Anil Hingorani, MD,<sup>c</sup> Palma M. Shaw, MD,<sup>d</sup> Vincent L. Rowe, MD,<sup>e</sup> Lee C. Rogers, DPM,<sup>f</sup> and Anahita Dua, MD,<sup>g</sup> *Columbia, SC; Manchester, United Kingdom; Brooklyn and Syracuse, NY; Los Angeles, CA; San Antonio, TX; and Boston, MA*

### ABSTRACT

**Objective:** This study evaluated the effectiveness of a unique multi-modality combination therapy that delivers noncontact cyclical compression with pressurized topical oxygen (intermittent topical oxygen therapy [ITOT]), in the treatment of chronic lower extremity wounds.

**Methods:** Data from 5318 patients treated between January 2023 and December 2024 for lower extremity wounds were retrospectively analyzed. Patients who were still receiving therapy and did not have outcome data ( $n = 1408$ ), had incomplete data ( $n = 423$ ), or who discontinued therapy for non-medical reasons ( $n = 361$ ), were excluded, resulting in a final cohort of 3126 patients, 89.4% ( $n = 2794$ ) male and 10.6% ( $n = 332$ ) female. Chronic wounds treated included diabetic foot ulcers (72.2%;  $n = 2257$ ), venous leg ulcers (20.1%;  $n = 628$ ), arterial ulcers (6.7%;  $n = 209$ ), and atypical wounds (1%;  $n = 32$ ). The outcomes assessed included healing rates, retreatment rates, and complications. The mean patient age was  $69.6 \pm 12.3$  years. The mean pretreatment wound age was  $7 \pm 15.9$  months, and the mean number of wounds per patient was  $1.1 \pm 0.4$ .

**Results:** Of the wounds, 64.8% ( $n = 2027$ ) achieved complete healing in  $4.2 \pm 2.5$  months, despite a mean pretreatment wound age of  $7 \pm 15.9$  months. The need for retreatment due to wound recurrence was low, 2.7% ( $n = 54$ ), with a mean follow-up time of  $13.9 \pm 4.9$  months. The rates of hospitalization and amputation were 3.7% ( $n = 115$ ) and 6.1% ( $n = 191$ ), respectively, with subgroup analyses showing consistent healing rates. ITOT therapy significantly reduced amputation and hospitalization rates compared with historical standards.

**Conclusions:** Multi-modality ITOT is an effective, noninvasive, patient-applied therapy that synergistically addresses the root causes of chronicity seen in nonhealing wounds: inflammation, edema, and tissue hypoxia. In this large cohort study, ITOT demonstrated superior wound healing outcomes in complex, comorbid populations, compared with those reported in population-based real-world studies. The results of this study support the durable healing outcomes demonstrated in previously published ITOT randomized controlled trial and real-world evidence studies. (JVS-Vascular Insights 2026;4:100404.)

**Keywords:** Advanced wound care; Chronic wound; Edema management; Inflammation resolution; Intermittent topical oxygen therapy (ITOT)

Chronic lower extremity wounds represent a significant clinical and economic challenge. Despite advancements in wound management, a considerable number of wounds fail to heal, leading to serious

medical complications and significant health care and socioeconomic costs.<sup>1,2</sup> In these wounds, the tightly coordinated sequence of events necessary for healing is often disrupted by persistent inflammation,

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tissue hypoxia, lymphatic dysfunction, and edema.<sup>3</sup> Therapeutic interventions that holistically address these issues are urgently needed.

### MECHANISMS UNDERLYING WOUND CHRONICITY

Evidence from multiple disciplines has clarified the complex and interconnected mechanisms underlying wound chronicity. Prolonged inflammation perpetuates local tissue damage, disrupts lymphatic function, and inhibits wound healing progression.<sup>4</sup> Inflammation-related edema further compromises tissue perfusion, impairing oxygenation and lymphatic function.<sup>5</sup> Insufficient removal of inflammatory mediators by the lymphatics results in amplified inflammatory signaling, increased edema and lymphatic overload, elevated metabolic demand, and tissue hypoxia.<sup>6</sup> Hypoxic, inflammatory wound environments encourage microbial growth and biofilm formation, further increasing inflammation and tissue hypoxia.<sup>7</sup> Chronic lower extremity wounds are predisposed to cycles of ischemia-reperfusion injury with shifts in upright and resting hemodynamic and hydrostatic pressures, compounding local oxidative stress, microvascular damage, and fibrosis.<sup>8</sup> Comorbidities frequently complicate wound healing by further impairing vascular, lymphatic, or immune function. Collectively, these mechanisms create a self-amplifying feedback loop of inflammation, edema, and tissue hypoxia that delays healing and prolongs the chronic wound state.<sup>7,8</sup>

### THERAPEUTIC INTERVENTIONS

Given the high percentage of patients who are refractory to best practice standard wound care, there is significant potential benefit to therapeutic interventions that concurrently address the underlying causes of wound chronicity. Until recently, there have been very few well-designed randomized controlled trials (RCTs) of new therapies for the treatment of chronic wounds that fail to respond to current standard of care.<sup>9</sup> One example is the Explorer study that, for the first time, showed that a dressing containing sucrose octasulfate, significantly reduced the healing time of chronic neuroischemic diabetic foot ulcers (DFUs).<sup>10</sup> In contrast, hyperbaric oxygen therapy (HBOT), which is widely used in the United States for chronic wounds, has minimal evidence to support the use of this expensive intervention.

### INTERMITTENT TOPICAL OXYGEN THERAPY

One promising therapy, intermittent topical oxygen therapy (ITOT), combines non-contact cyclical compression with pressurized topical oxygen delivery in a single integrated device that can be applied, without removing gas permeable dressings, by the patient or other non-clinical individuals. This multi-modality approach has robust RCT and real-world clinical evidence and is

### ARTICLE HIGHLIGHTS

- **Type of Research:** Multicenter retrospective cohort study
- **Key Findings:** Treatment of recalcitrant chronic lower extremity wounds of varied etiologies in a complex, comorbid population with a combined therapy consisting of topical oxygen and cyclical compression (intermittent topical oxygen therapy [ITOT]), in 3126 patients resulted in superior wound healing outcomes, compared with those reported in population-based real-world studies. The overall healing rate was 64.8% in a mean time of 4.2 months, despite a mean pretreatment wound age of 7 months. The need for retreatment due to wound recurrence was 2.7%, with a mean follow-up time of 13.9 months. The rates of hospitalization and amputation were 3.7% and 6.1%, respectively, with subgroup analyses showing consistent healing rates.
- **Take Home Message:** Multi-modality ITOT is a noninvasive, patient-applied therapy that synergistically addresses the root causes of wound chronicity. ITOT represents a compelling adjunct to standard care that may significantly improve patient outcomes, even in complex, comorbid populations.

designed to address the key drivers of wound chronicity through complementary synergistic mechanisms.<sup>9</sup>

### MECHANISTIC INTEGRATION: THE WHOLE IS GREATER THAN THE SUM OF THE PARTS

Topical oxygen therapy enhances host defense, immune regulation, angiogenesis, fibroblast activity, collagen crosslinking, and epithelialization through oxygen-dependent pathways such as nicotinamide adenine dinucleotide phosphate (NADPH) oxidase activation, redox signaling, endothelial cell modulation, and specialized pro-resolving mediator (SPM) biosynthesis.<sup>11–17</sup>

Cyclical compression complements these effects by reducing edema, normalizing capillary pressure gradients, improving perfusion, and activating mechano-transductive pathways in endothelial cells, macrophages, fibroblasts, and keratinocytes. These effects collectively promote inflammation resolution, angiogenesis, extracellular matrix remodeling, and lymphatic clearance of inflammatory mediators.<sup>5,7,18–23</sup>

When combined, topical oxygen therapy and cyclical compression synergistically increase tissue oxygen tension, amplify the efficacy of oxygen delivery, and potentiate anti-inflammatory, tissue perfusion, and reparative signaling pathways.<sup>17,24–30</sup> By simultaneously addressing edema, inflammation, and hypoxia, ITOT has been shown to enhance wound healing outcomes, reduce recurrence, and improve overall quality of care.<sup>26–28,31–33</sup>

However, until now, there has been no published study of ITOT in a large patient cohort with chronic wounds of diverse etiologies.

### STUDY DESCRIPTION

This study evaluates the efficacy of ITOT in a large real-world cohort of patients with chronic lower extremity wounds, focusing on treatment outcomes and timeframes. The study protocol was reviewed by the Western Institutional Review Board-Copernicus Group and granted exemption from Institutional Review Board oversight under 45 CFR 46.104(d) (4), tracking number 20,251,216.

### METHODS

**Study design.** A retrospective review of deidentified source patient records was conducted. Patient data had been submitted by prescribing physicians to establish medical necessity for therapy utilization and to satisfy payor coverage requirements.

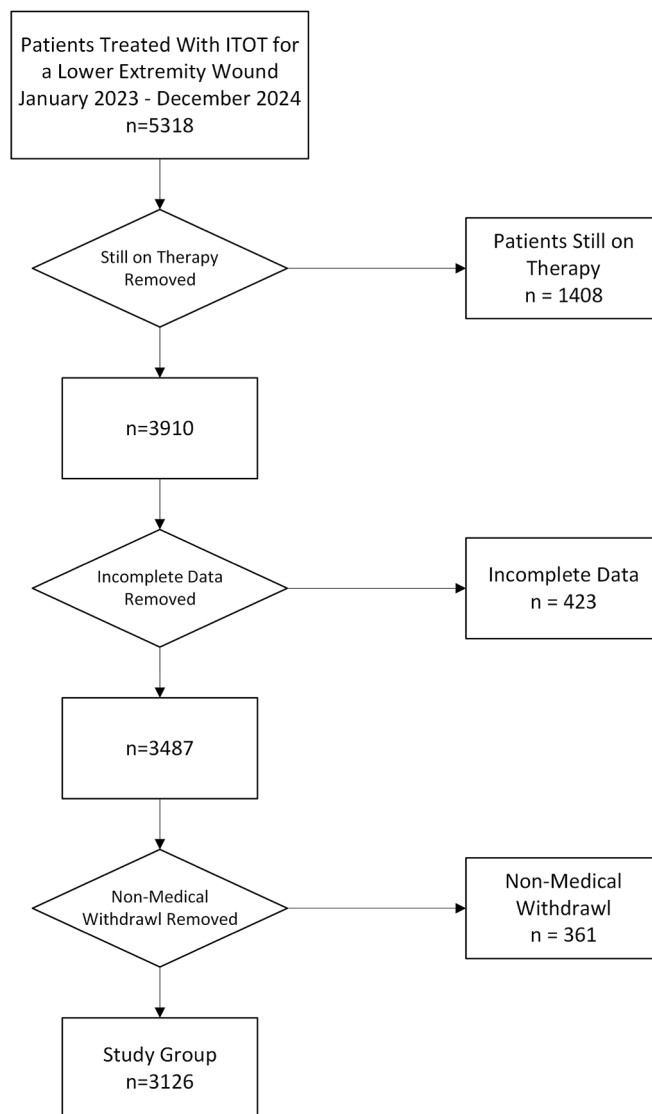
**Population.** Health Insurance Portability and Accountability Act (HIPAA)-compliant source registry data were collected for all patients with chronic lower extremity wounds treated with multi-modality ITOT between January 2023 and December 2024 ( $n = 5318$ ). Patients who were still actively receiving therapy ( $n = 1408$ ), had incomplete data ( $n = 423$ ), or who discontinued therapy for non-medical reasons (such as a change in living situation or caregiver support that did not allow for completion of therapy) ( $n = 361$ ) were excluded, resulting in a final cohort of 3126 patients (Fig 1).

**Therapeutic intervention.** Therapy was provided utilizing the commercially available ITOT device (TWO2 therapy; AOTI Ltd), which delivers oxygen at 10 L/min, within a disposable extremity chamber under pressures that cycle between 7.5 and 37.5 mmHg, providing an oxygen partial pressure around the limb of  $\sim 800$  mmHg (Fig 2). ITOT was administered over gas permeable dressings by the patient at home, or by facility staff in skilled nursing settings, as an adjunct to standard wound care. The recommended treatment protocol is 90 minutes per session, five times per week (Fig 2).

**Outcome measures.** The primary outcome was complete wound healing (complete epithelialization). Secondary outcomes included time to wound closure, retreatment rates, amputation incidence, hospitalization rates, and therapy-related complications.

**Subgroup analyses.** Subgroup analyses included DFUs, venous leg ulcers (VLUs), arterial ulcers, and atypical wounds.

**Statistical analyses.** Kaplan-Meier (KM) curves were used to estimate the cumulative likelihood of wound closure across strata of key covariates, including etiology,



**Fig 1.** Study cohort selection flow diagram. Consolidated Standards of Reporting Trials (CONSORT) diagram of study group selection for patients treated with intermittent topical oxygen therapy (ITOT) for lower extremity wounds between January 2023 and December 2024. Of 5318 patients initially treated, 1408 still on therapy were excluded, leaving 3910 patients. After further exclusion of 784 patients with incomplete data or non-medical withdrawal, the final study group comprised 3126 patients.

wound age, number of wounds, gender, and patient age. Group comparisons were performed using the log-rank test.

A multivariable Cox proportional hazards model was used to assess the independent association between covariates and time to closure. Variables were selected based on clinical relevance and univariable results. Multicollinearity was assessed using a Pearson correlation matrix. No variable pairs exceeded a correlation coefficient of 0.3, indicating low risk of multicollinearity.



**Fig 2.** Multi-modality intermittent topical oxygen therapy (ITOT) therapy device. The multi-modality ITOT device combines intermittent topical oxygen therapy with noncontact cyclical compression. The system consists of an inflatable limb chamber for localized delivery of pressurized oxygen and compression, a control unit that regulates therapy parameters, and a 10-L/min oxygen concentrator (not pictured).

All analyses were conducted using Python (Lifelines package). A two-tailed  $P$ -value  $< .05$  was considered statistically significant.

## RESULTS

**Cohort overview.** Patient demographics are detailed in Table I. Due to a large Veterans Administration (VA) contingent; the group was predominantly (89.4%;  $n = 2794$ ) male and 10.6% ( $n = 332$ ) female. The mean patient age was  $69.6 \pm 12.3$  years. The mean pretreatment wound age was  $7 \pm 15.9$  months, and the mean number of wounds per patient was  $1.1 \pm 0.4$ . The majority (72.2%;  $n = 2257$ ) of wounds were of diabetic etiology, 20.1% ( $n = 628$ ) were venous, 6.7% ( $n = 209$ ) were arterial, and 1% ( $n = 32$ ) were atypical.

**Primary outcomes.** Wound outcomes categorized by wound type are shown in Table II. The primary outcome of complete wound healing was achieved in 64.8% ( $n = 2027$ ) of patients, in a mean time of  $4.2 \pm 2.5$  months. Surgical closure was performed in only 0.1% ( $n = 3$ ) of patients.

**Table I.** Patient demographics

Demographics	Data
Female	10.6 (332)
Male	89.4 (2794)
Patient age, years	$69.6 \pm 12.3$
Pretreatment wound age, months	$7 \pm 15.9$
Wounds per patient	$1.1 \pm 0.4$
DFU	72.2 (2257)
VLU	20.1 (628)
Arterial ulcer	6.7 (209)
Atypical wound	1 (32)

DFU, Diabetic foot ulcer; VLU, venous leg ulcer.  
Data are presented as percentage (number) or mean  $\pm$  standard deviation.

**Secondary outcomes.** Of those that did not heal, 1.2% ( $n = 36$ ) were discharged from therapy due to sufficient wound improvement, 4.9% ( $n = 154$ ) stopped therapy due to insurance discontinuation, and 1.1% ( $n = 33$ ) were withdrawn due to medical complications. Within this last group, 0.38% ( $n = 12$ ) were withdrawn due to non-wound-related medical complications, 0.22% ( $n = 7$ ) due to need for vascular intervention, 0.19% ( $n = 6$ ) due to difficulty tolerating therapy, 0.16% ( $n = 5$ ) due to a surgical procedure, 0.06% ( $n = 2$ ) due to wound decline, and 0.03% ( $n = 1$ ) due to a malignancy in the wound area.

Retreatment due to healed wound recurrence occurred in only 2.7% of patients ( $n = 54$ ), over a mean follow-up time of  $13.9 \pm 4.9$  months. The rate of withdrawal due to hospitalization and amputation was 3.7% ( $n = 115$ ) and 6.1% ( $n = 191$ ), respectively. A small group of patients (0.5%;  $n = 15$ ) were placed on hospice/palliative care, and 5.5% of patients ( $n = 171$ ) died from non-treatment-related causes.

**Correlation assessment.** The correlation matrix showed minimal relationships between predictors. All Pearson coefficients were  $< 0.3$ . For example, number of wounds and gender had the highest observed correlation ( $r = 0.25$ ), supporting inclusion of all covariates in the multivariable model.

**Cox proportional hazard analysis.** Pretreatment wound age, wound type, and the number of wounds each patient had were significant indicators of wound healing probability (Fig 3).

**Sub-group analysis.** All wound types were associated with an increased likelihood of complete healing with ITOT treatment.

DFUs comprised 72.2% of the study group ( $n = 2257$ ), had a mean pretreatment wound age of  $6 \pm 10.3$  months, a healing rate of 63.3% ( $n = 1429$ ) in a mean time of  $4.2 \pm 2.5$  months, and a retreatment rate of 3% ( $n = 43$ ) over a mean follow-up time of  $14.3 \pm 4.4$  months.

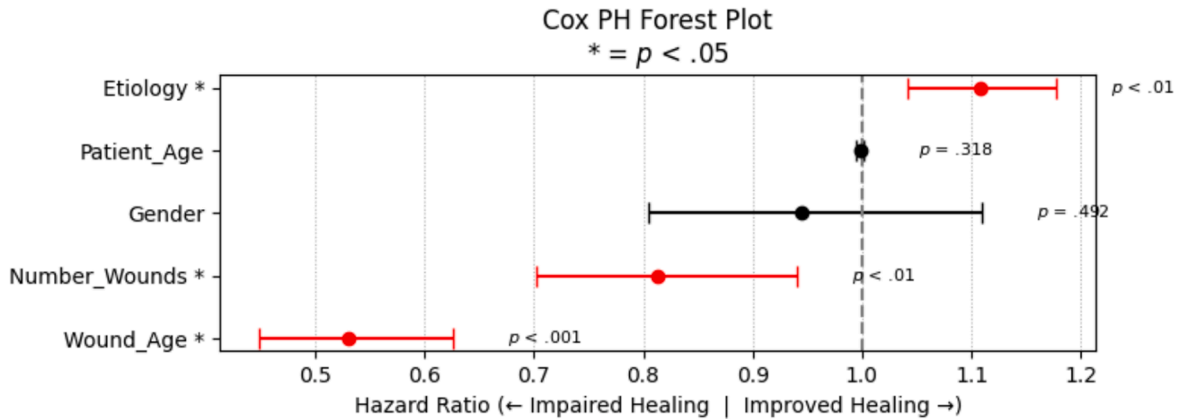
**Table II.** Results

	Healed	Surgical closure	Sufficient wound progress	Change in treatment plan	Medical hold	Hospitalized	Amputation	Hospice/palliative care	Deceased	Insurance D/C	Grand total
<b>DFUs</b>											
Therapy outcome	63.3 (1429)	0.1 (3)	1.1 (25)	11.4 (258)	0.8 (19)	4.3 (96)	7.4 (166)	0.6 (14)	6.9 (155)	4.1 (92)	72.2 (2257)
Wound age, months	5.5 (9.6)	8.7 (13.3)	7 (14)	7.8 (12)	12.6 (19.2)	5.7 (10.2)	5.7 (11.7)	2.6 (4)	5.7 (7.7)	10.4 (12.6)	6 (10.3)
Time to healing, months	4.2 (2.5)										4.2 (2.5)
Retreatment	3 (43)										3 (43)
Time to retreatment, months	14.3 (4.4)										14.3 (4.4)
<b>VLUs</b>											
Therapy outcome	72.1 (453)		1.4 (9)	14.8 (93)	0.6 (4)	1.6 (10)			0.3 (2)	9.1 (57)	20.1 (628)
Wound age, months	8.8 (31.3)		6.7 (8)	14.3 (19.9)	24.3 (25.6)	20.5 (32)			4.5 (4.9)	15.3 (17.6)	10.4 (28.7)
Time to healing, months	4 (2.6)										4 (2.6)
Retreatment	1.1 (5)										1.1 (5)
Time to retreatment, months	13.6 (6.9)										13.6 (6.9)
<b>Arterial ulcers</b>											
Therapy outcome	59.3 (124)		1 (2)	11 (23)	4.3 (9)	3.8 (8)	12 (25)		6.2 (13)	2.4 (5)	6.7 (209)
Wound age, months	6.1 (9.8)		6.5	6.6	4.7	3.1	6.3		9.2	6.4	6.2 (9.6)
Time to healing, months	3.9 (2.5)										3.9 (2.5)
Retreatment	4.8 (6)										4.8 (6)
Time to retreatment, months	11.3 (6.4)										11.3 (6.4)
<b>Atypical wounds</b>											
Therapy outcome	65.6 (21)			21.9 (7)	3.1 (1)	3.1 (1)		3.1 (1)	3.1 (1)		1 (32)
Wound age, months	9 (9)			8.3	60.0	12.0		1.0	8.0		10.3 (13)
Time to healing, months	4 (2.3)										4 (2.3)
Retreatment											
Time to retreatment, months											
<b>Totals</b>											
Therapy outcome	64.8 (2027)	0.1 (3)	1.2 (36)	12.2 (381)	1.1 (33)	3.7 (115)	6.1 (191)	0.5 (15)	5.5 (171)	4.9 (154)	100 (3126)
Wound age, months	6.3 (17.1)	8.7 (13.3)	6.9 (12.3)	9.3 (14.5)	13.3 (19.5)	6.8 (13.7)	5.8 (11.7)	2.5 (3.9)	6 (7.9)	12.1 (14.7)	7 (15.9)
Time to healing, months	4.2 (2.5)										4.2 (2.5)
Retreatment	2.7 (54)										2.7 (54)
Time to retreatment, months	13.9 (4.9)										13.9 (4.9)

D/C, Discontinuation; DFU, diabetic foot ulcer; VLU, venous leg ulcer.  
Data are presented as percentage (number) or mean (standard deviation).

VLUs comprised 20.1% of the group (n = 628), had a mean wound age of 10.4 ± 28.7 months, a healing rate of 72.1% (n = 453) in a mean time of 4 ± 2.6 months, and a retreatment rate of 1.1% (n = 5) over a mean follow-up time of 13.6 ± 6.9 months.

Arterial ulcers comprised 6.7% of the group (n = 209), had a mean wound age of 6.2 ± 9.6 months, a healing rate of 59.3% (n = 124) in a mean time of 3.9 ± 2.5 months, and a retreatment rate of 4.8% (n = 6) over a follow-up of 11.3 ± 6.4 months. Information regarding



**Fig 3.** Cox proportional hazard (PH) forest plot displaying the hazard ratios and 95% confidence intervals for variables included in the Cox proportional hazards regression model for wound healing. Significant predictors ( $P < .05$ , indicated by \*) include etiology, number of wounds, and wound age. Hazard ratios less than 1 indicate impaired healing, whereas hazard ratios greater than 1 indicate improved healing. Nonsignificant variables include patient age and gender.  $P$ -values are shown for each variable.

revascularization procedures or interventions was not available within the registry data.

Atypical wounds comprised 1% of the group ( $n = 32$ ), included wounds related to autoimmune disorders, cancer, chemotherapy, frostbite, necrotizing soft tissue infection, pyoderma gangrenosum, calciphylaxis, soft tissue radio necrosis, spider bite dermonecrosis, vasculitis, and late-effect agent orange exposure, and had a mean wound age of  $10.3 \pm 13$  months, a healing rate of 65.6% ( $n = 21$ ) in a mean time of  $4 \pm 2.3$  months, and a retreatment rate of 0%.

Kaplan-Meier analysis of likelihood and trajectories of healing between wound types is shown in Fig 4 (log-rank  $P = .0004$ ).

**Pre-ITOT treatment wound age.** Overall, healing rates were lower and time to healing was longer in wounds that had been present for more than 1 year prior to treatment. Among wounds  $\leq 1$  year old, 66.6% ( $n = 1871$ ) healed in a mean time of  $4.1 \pm 2.4$  months. In contrast, only 49.5% of wounds  $>1$  year old ( $n = 156$ ) healed, with a mean time to healing of  $5.2 \pm 2.9$  months.

Although pretreatment wound age was a significant independent predictor of healing in the Cox regression model ( $P < .001$ ), the unadjusted comparison between wound age groups did not reach statistical significance (log-rank  $P = .2693$ ).

**Number of wounds.** Likelihood of wound healing, stratified by the number of wounds each patient had, is shown in Fig 5. Patients with only one wound were more likely to heal than those with multiple wounds, with healing rates of 66.1% ( $n = 1918$ ) and 48.2% ( $n = 109$ ), respectively. The average time to healing was not significantly different between groups:  $4.2 \pm 2.5$  months for patients with a single wound, and  $4.1 \pm 2.9$  months for those with more than

one. This difference in healing probability was statistically significant (log-rank  $P = .04$ ).

**Gender.** Most patients in this study were male (89.4%) (Table III), largely because 77% ( $n = 2418$ ) were veterans, and nationwide coverage for ITOT therapy is available through the VA. Among female patients, only 15.4% ( $n = 51/332$ ) were veterans, compared with 87.3% ( $n = 2438/2794$ ) of males.

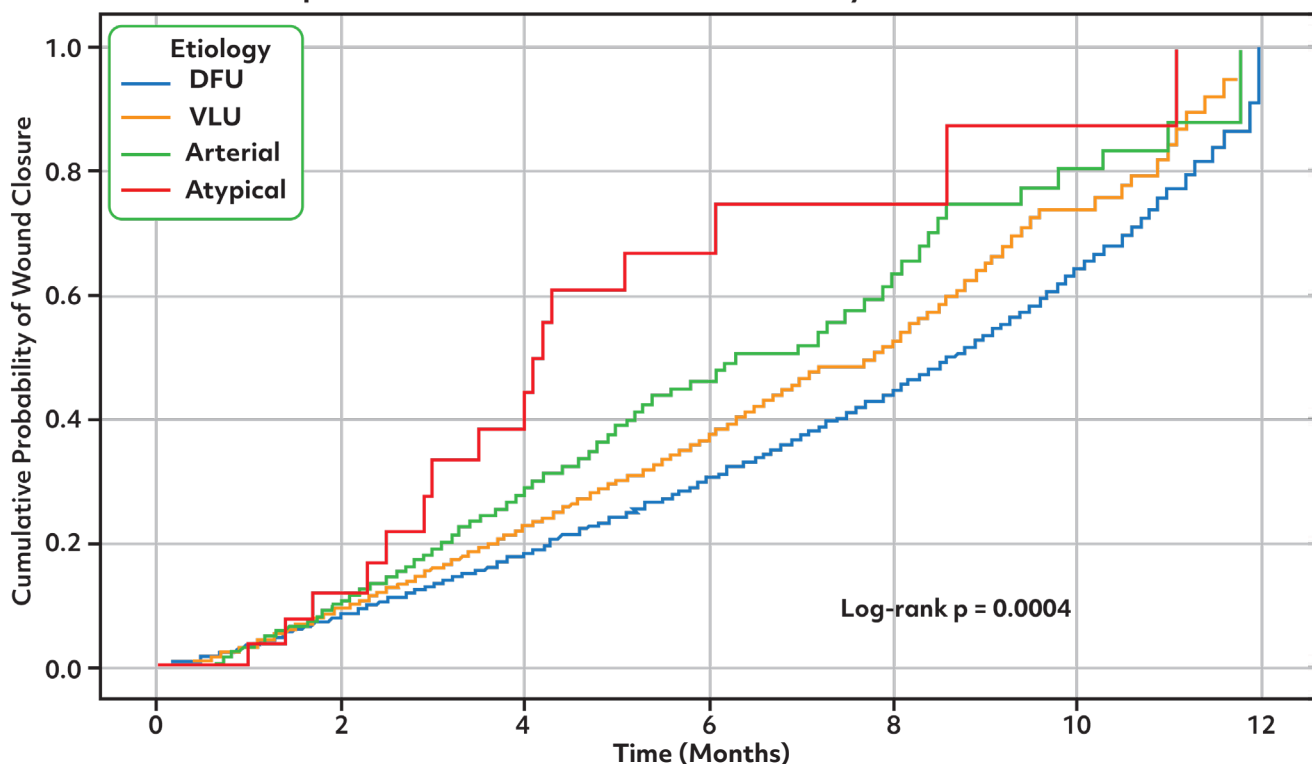
Although gender was not a significant predictor of wound healing in the multivariable Cox regression, KM analysis showed a significant difference in healing probability between genders (log-rank  $P = .01$ ) (Fig 6). This suggests that unadjusted survival outcomes differed by gender, potentially influenced by baseline differences in access to care or wound characteristics. This may also be an artifact created by the low number of females in the study group.

## DISCUSSION

These findings indicate that the number of wounds, wound type, and wound age significantly affect the likelihood of healing. These results are consistent with published literature identifying these factors as key predictors of delayed wound healing.<sup>34–36</sup> KM analyses further highlighted significant intergroup differences in healing likelihood.

Interestingly, the types of wounds that are typically more difficult to heal had steeper trajectories of wound healing over time, suggesting that these wounds had a proportionally greater benefit from therapy. Arterial wounds had the lowest incidence of healing but had a steeper rate of healing starting around treatment month two, although data pertaining to revascularization procedures or interventions was not available within the data set. Atypical wounds had both a high rate of healing and a faster trajectory of healing over time. Similarly,

### Kaplan-Meier (Cumulative Probability of Wound Closure)



**Fig 4.** Likelihood of wound closure by etiology. Kaplan-Meier (KM) plot displaying the cumulative likelihood of wound closure over 12 months, stratified by wound etiology: diabetic foot ulcer (DFU), venous leg ulcer (VLU), arterial ulcer, and atypical wound. The log-rank test ( $P = .0004$ ) indicates a significant difference in wound closure rates between etiologic groups.

patients with more than one wound, and females (who had more wounds per patient and older wounds) had faster rates of wound healing.

Atypical, arterial, and highly comorbid wounds are particularly resistant to healing, due to the chronicity and severity of inflammation, hypoxia, microbial burden, and fibrotic tissue changes associated with them. However, ITOT addresses each of these barriers to healing through multiple pathways. It may provide proportionally greater benefit to more complex and comorbid wound populations.

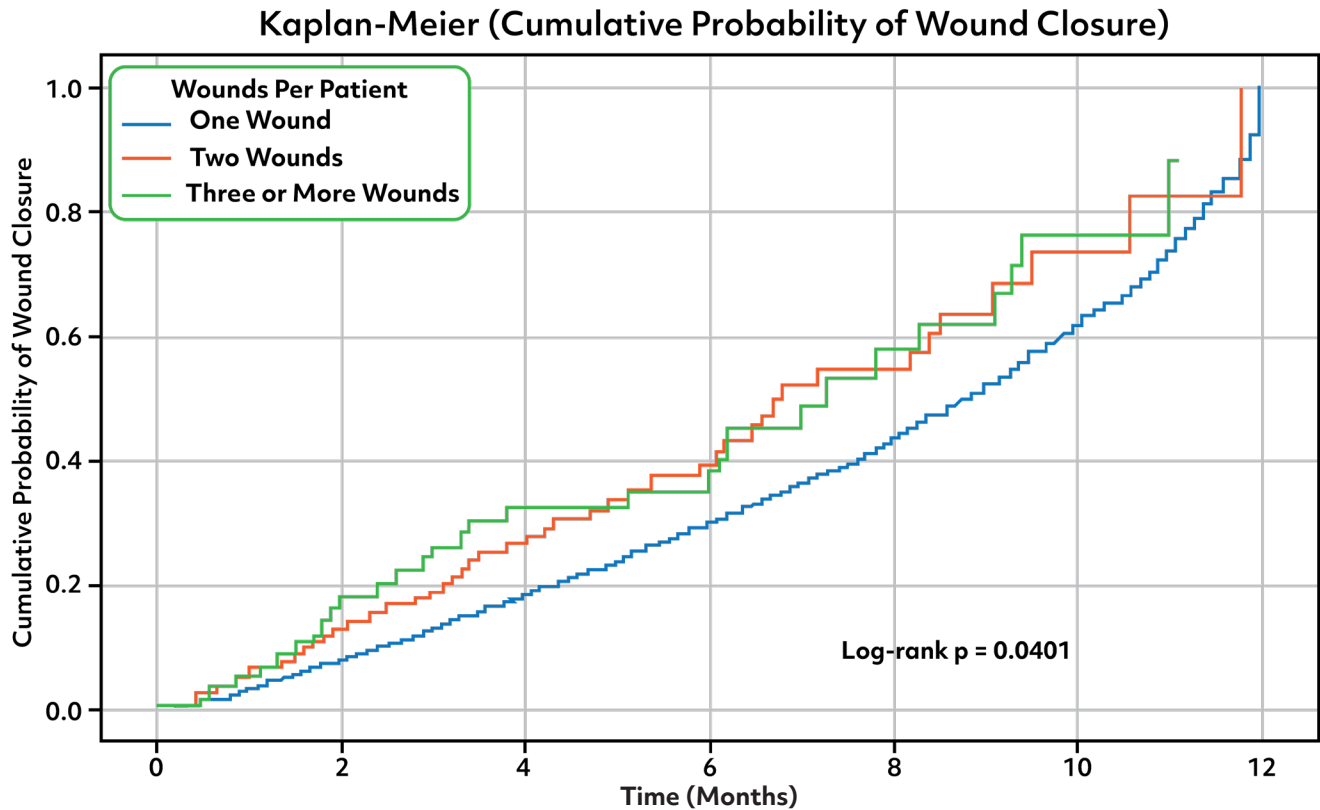
These results are consistent with a prospective RCT of TOT in diabetic foot ulcers by Niederauer et al. They found that, overall, the TOT group had a 2× greater healing rate compared with the sham group (46% vs 22%), but in a subset of more chronic wounds, the TOT healing rate was 3× greater (42.5% vs 13.5%).<sup>37</sup>

Notably, the TOT device used in this study was both unpressurized and not multi-modal; it is likely that the additional and synergistic effects of higher-pressure cyclical compression, as provided with ITOT, further increases the relative effects of TOT in very chronic wounds.

**Pain reduction and adherence to therapy.** Although not specifically addressed in this study, there have

been numerous anecdotal reports from practitioners, clinicians, and patients of rapid pain reduction and, in diabetic patients, improvement in sensation with the use of ITOT. These observations align with findings by Tawfick et al, who reported significant pain relief in patients with recalcitrant VLUs, demonstrating a mean pain score reduction from 8 of 10 to 3 of 10 after 2 weeks of ITOT treatment.<sup>27</sup> This reported and observed pain reduction is likely due to the complementary mechanisms through which ITOT reduces inflammation and improves perfusion.

Effective clearance of inflammatory mediators via lymphatic drainage, optimization of microbial defense via oxidative burst and improved perfusion, normalization of tissue hemodynamics, upregulation of anti-inflammatory and pro-resolution mediators, and stimulation of angiogenesis/lymphatic angiogenesis all contribute to pain reduction. Redox signaling and endothelial cell activation are central to these processes. Notably, SPMs play a particularly important role in pain modulation by suppressing inflammatory signaling, enhancing efferocytosis, and upregulating pro-resolution and tissue protective mediators. Moreover, SPMs modulate the perception of pain by directly influencing signal transduction systems that control



**Fig 5.** Likelihood of wound closure by number of wounds per patient. Kaplan-Meier (KM) plot displaying the cumulative likelihood of wound closure over 12 months, stratified by the number of wounds per patient (one wound, two wounds, or three or more wounds). Patients with multiple wounds exhibited a higher likelihood of wound closure compared with those with only one wound. The log-rank test ( $P = .0401$ ) indicates a statistically significant difference in wound closure rates among the groups.

nociception, such as those driven by opioid receptors and transient receptor potential channels.<sup>38</sup>

Additionally, the noncontact nature of ITOT's cyclical compression may improve patient tolerance compared with conventional compression methods. The clinical significance of pain reduction, particularly regarding patient adherence to therapy protocols and resultant patient outcomes, warrants further exploration.

**Real-world wound registry data.** Fife, et al, in a review of United States Wound Registry (USWR) data that included 62,964 DFUs and 97,420 VLU, treated with both standard and advanced therapies, found that only 45% of DFUs and 57% of VLUs healed within a 20- and 16-week follow-up period, respectively.<sup>2</sup> In this study, the healing rates were 63% in a mean time of 18 weeks for DFUs and 72% in a mean time of 17 weeks

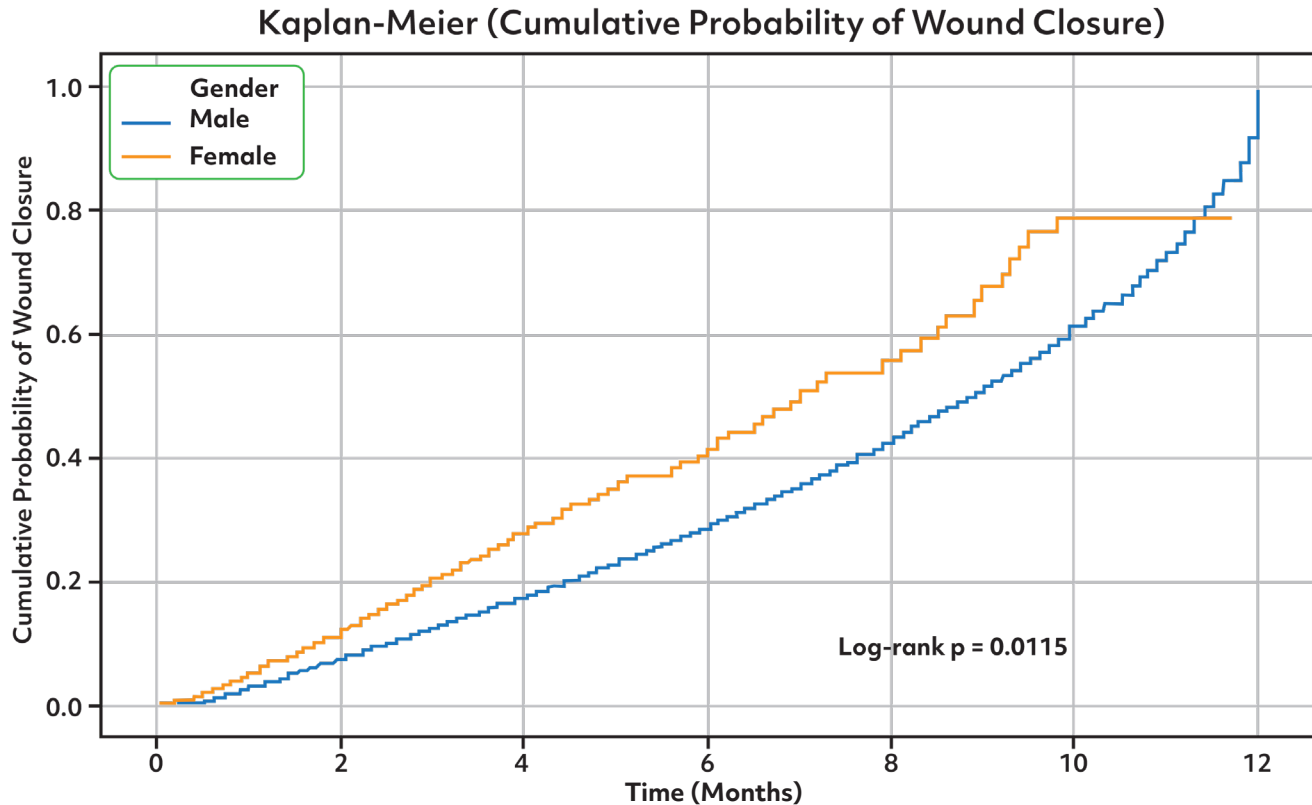
for VLUs. Furthermore, the USWR data represents a less medically complex population than the patients in this study because it includes patients who healed without the need for advanced wound therapies. In a previous USWR study that included 5024 patients, 65.8% healed but ~50% did so with only the use of moist wound care.<sup>39</sup> Remarkably, even though patients in this present study had failed standard care and advanced therapies for an average of 7 months prior to ITOT treatment, they demonstrated healing rates exceeding those reported in the broader population-based registries.

**ITOT RCT in DFU.** Although the results of retrospective studies cannot be directly compared with RCTs, the outcomes of this study are consistent with Frykberg et al, who, in a rigorous double-blinded, placebo-controlled RCT of ITOT in DFUs, demonstrated a 42% closure rate at

**Table III.** Wound characteristics and outcomes by gender

	Cohort, % (n)	Healed, % (n)	Time to healing, months	Pretreatment wound age, months	Wounds per patient
Male	89.4 (2794)	66.2 (177)	4.2 ± 2.5	6.7 ± 16.3	1.1 (0.3)
Female	10.6 (332)	53.3 (1850)	3.4 ± 2.4	9.1 ± 11.2	1.4 (0.7)

Data are presented as percentage (number) or mean ± standard deviation.



**Fig 6.** Likelihood of wound closure by gender. Kaplan-Meier (KM) plot displaying the cumulative likelihood of wound closure over 12 months, stratified by gender. Females exhibited a higher likelihood of wound closure compared with males. The log-rank test ( $P = .0115$ ) indicates a statistically significant difference in wound closure rates between genders.

12 weeks (vs 13.5% in the control group), and a 56% closure rate at 12 months post enrollment (vs 27% for the control group).<sup>31</sup> Approximately 40% of all patients with DFUs experience a recurrence within 1 year after the ulcer has healed.<sup>40</sup> In the Frykberg study, there was only a 6.7% vs 40% recurrence rate at 12 months in the treatment and control groups, respectively. In this current study, involving a more complex and comorbid, real-world patient population, there was a closure rate of 63.3% in a mean time of 4.2 months, and a retreatment rate due to wound recurrence of 3% at 14 months.

Mechanistic evidence provides ample explanation for reduced wound recurrence in ITOT-treated wounds. The efficiency and quality of collagen synthesis and crosslinking, necessary for tissue strength, is directly proportional to the availability of oxygen up to a  $pO_2$  of ~250 mmHg. Consequently, improvements in tissue oxygenation enhance the quality and strength of healed tissue.<sup>41</sup> Fries et al demonstrated this histologically, showing advanced tissue remodeling and healing, with better developed dermal-epidermal junctions in TOT-treated wounds. Additionally, they showed an increased expression of vascular endothelial growth factor, leading to more and better distributed capillary formation in the TOT-treated wounds, resulting in 10-fold higher tissue

$pO_2$  values post healing. The benefits of cyclical compression—improved perfusion, timely inflammation resolution, minimized tissue fibrosis, and enhanced extracellular matrix synthesis and remodeling—have been well-described and undoubtedly contribute to the durability and function of healed tissue in ITOT-treated wounds.

**Real-world evidence for ITOT in DFUs.** Approximately 20% of people who develop DFUs will require lower-extremity amputation.<sup>42</sup> Similar to the heterogeneous real-world patient population studied here, a well-designed 202-patient retrospective study of ITOT in the treatment of DFUs in veterans by Yellin et al showed a hospitalization rate of just 7.1% in the treatment group, compared with 40% in a matched cohort, and an amputation rate of 8.6% in the treatment group vs 31.4% in the matched cohort, both at 12 months.<sup>26</sup> In this study, 4.3% of patients with DFUs were withdrawn from therapy due to being hospitalized and 7.4% due to amputations, with a mean follow-up time of 14 months.

**VLU healing and recurrence with ITOT.** The recurrence rate for VLUs is reported to be between 24% and 57% at 12 months.<sup>43,44</sup> Tawfik et al, in a prospective controlled

study, compared ITOT with conventional compression dressings (CCDs) in the management of nonhealing VLU, present for greater than 2 years.<sup>28</sup> They demonstrated a healed wound recurrence rate of only 6% (3 of 51) for patients healed with ITOT vs a 47% (14 of 30) recurrence rate in the CCD group at 36 months. In this study, 1.1% of patients with healed VLUs (5 of 453) underwent retreatment due to wound recurrence in a mean follow-up period of 14 months.

**Therapy dose and frequency.** An interesting component of the Tawfick study was the length and frequency of treatment: two 3-hour sessions per day, 7 days per week. With this more aggressive protocol, they observed wound size reduction after only 5 days of treatment and demonstrated a 76% closure rate at 12 weeks, with a mean time to closure of 57 days (vs. 46% for the CCD group, in a mean time of 107 days). Additionally, 11 of 24 wounds in the treatment group that were methicillin-resistant staphylococcus aureus (MRSA)-positive at baseline became MRSA-negative after 5 weeks, whereas none of the 19 MRSA-positive wounds in the control group became MRSA-negative.

In a separate prospective randomized study, Heng et al followed a protocol of one 4-hour session per day, 4 days per week, over a 4-week period. They reported a 90% closure rate in the TOT group, compared with 22% in the control group, along with a significantly higher capillary density in TOT-treated wounds.<sup>45</sup>

These findings align with other published evidence indicating that the immediate and downstream effects of topical oxygen are cumulative as well as dose- and frequency-dependent.<sup>41,46,47</sup> It also suggests that current treatment protocols could be expanded to achieve optimal therapeutic outcomes.

**Cost effectiveness of ITOT.** The potential cost savings of using ITOT as an adjunctive, patient-applied, at-home treatment for lower extremity wounds have been evaluated in multiple peer-reviewed studies. In a real-world analysis of highly comorbid patients, Yellin et al concluded that ITOT offers meaningful health economic benefits, attributed to more durable healing and corresponding reductions in wound recurrence, hospitalizations, and amputations.<sup>26</sup>

More recently, Kerr et al conducted a formal cost-benefit analysis of ITOT for DFUs using National Health Service costing norms in England. Their findings showed that ITOT both increased quality-adjusted life years and reduced overall treatment costs by an estimated 16% over 2 years. The study concluded that ITOT met the cost-effectiveness threshold defined by the National Institute for Health and Care Excellence, indicating that ITOT is cost-effective and appropriate for public health care funding.<sup>26</sup>

Given that the cost of managing lower extremity wounds is significantly higher in the United States than in the United Kingdom, these economic benefits could be even more substantial if ITOT were adopted more broadly in the United States health care system.

**Patient access.** Despite robust clinical evidence, including six independent systematic reviews and meta-analyses supporting TOT for the treatment of chronic wounds,<sup>48–53</sup> a Local Coverage Determination remains under review with the Centers for Medicare and Medicaid Services (CMS) Medicare Administrative Contractors. As a result, ITOT, which has been designated a distinct Healthcare Common Procedure Coding System code: A4575, by CMS, is not yet covered by Medicare or many third-party payers. Although ITOT is covered nationwide through the VA and by Medicaid in select states, many patients with chronic, nonhealing wounds and limited treatment options remain without access to this proven, noninvasive, limb-saving therapy.

Further support for TOT is reflected in recent Standard of Care Guidelines from the American Diabetes Association, the Wound Healing Society, and the International Working Group on the Diabetic Foot, all of which now recommend TOT for the treatment of DFUs that have not healed with standard care alone.<sup>54–56</sup> Moreover, although the American Diabetes Association recommends the use of TOT in hard-to-heal DFUs, they do not recommend HBO for such ulcers.<sup>57</sup> Aligning coverage policies with these evidence-based guidelines could substantially improve outcomes and reduce the clinical and economic burden of chronic wounds, particularly among low-income, minority, underserved, and high-risk populations, who are disproportionately afflicted by these conditions.

**Study limitations.** This was a retrospective patient medical records review, subject to normal reporting variability and some gaps in available clinical information. As summarized in the study flow diagram, patients with ongoing treatment at the time of data cut, insufficient data, or non-medical discontinuation (eg, change in living situation or caregiver support) were not included in the analytic cohort. This could introduce potential bias, which could affect healing and complication rates if these patients were more or less likely to heal or experienced complications that were not captured because of incomplete follow-up.

DFUs were disproportionately represented. In addition, several clinically important wound-level and patient-level covariates (such as wound size, depth, infection status, offloading strategies, and details of arterial revascularization) were unavailable, limiting risk adjustment and potentially confounding subgroup analyses, particularly among patients with arterial disease and diabetes.

Patients were predominantly male and largely derived from the VA system, which may reflect distinct care access patterns, comorbidity profiles, and follow-up practices compared with non-VA settings. Although this constrains generalizability, the VA population is often characterized by substantial comorbidity burden and complex care needs, providing a clinically relevant context for evaluating therapy performance in medically complex patients. These findings are consistent with prior ITOT studies across diverse lower-extremity wound etiologies.

## CONCLUSIONS

Multi-modality ITOT is a well-tolerated, highly effective, noninvasive, patient-applied therapy that synergistically addresses the root causes of chronicity seen in nonhealing wounds: inflammation, edema, and tissue hypoxia. Supported by robust RCTs and real-world evidence, ITOT has demonstrated significantly improved healing rates and lower wound recurrence, including in complex, comorbid populations. ITOT represents a compelling adjunct to standard care that may significantly improve both patient outcomes and total cost of care. Future research should expand on current evidence and further explore the health economic benefits of integrating ITOT into standard care protocols.

## AUTHOR CONTRIBUTIONS

Conception and design: JL  
Analysis and interpretation: JL, AB  
Data collection: JL, AB, AH, PS, VR, LR, AD  
Writing the article: JL, AB  
Critical revision of the article: JL, AB, AH, PS, VR, LR, AD  
Final approval of the article: JL, AB, AH, PS, VR, LR, AD  
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J.L. and J.R. are employed by the Veterans Administration; however, the views expressed in this article are those of the authors and do not represent the views of the Department of Veterans Affairs or the United States government. A.B., A.H., and L.R. are members of the Advanced Oxygen Therapy Inc Scientific Clinical Advisory Board.

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