

Topical Oxygen Therapy (TOT) Devices

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Introduction

Topical oxygen therapy (TOT) devices are addressed by this guideline.

Health Equity Consideration

Health equity is the highest level of health for all individuals; health inequity is the avoidable difference in health status or distribution of health resources due to the social conditions in which individuals are born, grow, live, work, and age. Social determinants of health are the conditions in the environment that affect a wide range of health, functioning, and quality of life outcomes and risks. Examples include the following: safe housing, transportation, and neighborhoods; racism, discrimination, and violence; education, job opportunities, and income; access to nutritious foods and physical activity opportunities; access to clean air and water; and language and literacy skills.

Criteria

- Topical oxygen therapy (TOT) (HCPCS A4575, E0446) is indicated as an adjunct therapy to standard of care when **all** of the following apply:
 - The individual has a non-healing, Wagner Grade 1 or 2 diabetic ulcer.
 - A wound therapy program has been tried, including **all** of the following, and there are no measurable signs of improved healing:
 - The wound has been assessed, measured, and described.
 - Topical dressings appropriate for wound type have been applied.
 - Debridement has been performed to remove necrotic tissue (if present).
 - Treatment or intervention to correct any infection and/or underlying condition that may hinder the healing process has been performed (if needed).
 - The individual has ongoing care for diabetes.
 - Use of an off-loading, pressure-reducing strategy has been tried, which may include **any** of the following:
 - Total contact cast (TCC), irremovable fixed ankle walking boot, removable cast walker, heel relief shoe, or therapeutic footwear with pressure relieving insoles.
 - The individual had radiographs of the treated area.
 - TOT is not indicated when **any** of the following are present:

- Untreated osteomyelitis near the wound.
- Necrotic tissue with slough or eschar present.
- Wounds with fistulae or deep sinus tracts.
- Cancer present in the wound.
- Exposed nerves or vascular structures.

Additional Information

- Initial rental period of one month (30 days).
- HCPCS E0446 includes all supplies used with this item, such as tape, dressings, tubing, etc.

Continued Rental

- Continued use of TOT (one month) is indicated when **all** of the following apply:
 - There is documentation that wound healing is progressing.
 - There is monthly documentation of wound length, width, and depth.
 - There is monthly documentation of proper use of the device and continued benefit.

Rental Period Exceeding Three (3) months

- Use of a TOT exceeding three months in total duration is indicated when **all** of the following apply:
 - There is monthly documentation that wound healing is progressing.
 - There is monthly documentation of wound length, width, and depth.
 - There is monthly documentation of proper use of the device and continued benefit.
 - There is monthly documentation of specific and detailed information to explain the continuing problems with the wound and what additional measures are being undertaken to address those problems and promote healing.
 - There is monthly documentation of why a switch to alternative treatments alone is not possible.

Definitions

- **Topical Oxygen Therapy (TOT)** is the direct application of oxygen to a wound site. TOT has been proposed as a potential method to oxygenate tissue in a hypoxic wound and can be applied intermittently or continuously through a sealed plastic bag or a cannula secured under a wound dressing covered by film.
- **Hyperbaric oxygen therapy (HBOT)** is defined as systemic treatment in which the individual is placed inside a pressurized chamber and breathes 100% medical grade oxygen (at least 95%) under a pressure greater than sea level pressure (one atmosphere absolute [ATA]).

- **Chronic venous insufficiency (CVI)** occurs when there is persistent ambulatory venous hypertension. Causes include insufficient muscular pumping, reflux in the venous valves, and venous obstruction. Chronic venous insufficiency can lead to edema, telangiectasia, and varicose veins. In the United States, approximately 20% of individuals with chronic venous disease develop venous ulcers. Venous ulcers can be difficult to treat, and impeded healing presents an increased risk for comorbidities such as cellulitis and superficial thrombophlebitis.
- A **chronic ulcer**, or non-healing wound, either does not progress through an orderly and timely sequence of repair, or the repair process is impaired and does not reach resolution.
- **Pressure ulcers** occur most commonly near the sacrum or ischial tuberosities and may occur in other areas including, but not limited to, the knees, heels, or other bony prominences. Risk factors for skin breakdown and pressure ulcers may include spinal cord injury, increased pressure over bony prominences, asymmetric posture, and extended duration of sitting.
- **Diabetic ulcers** are a common complication of advanced diabetes mellitus, and most often occur in the feet. The chronic hyperglycemia of diabetes mellitus can lead to microvascular complications, including diabetic neuropathy and peripheral vascular disease. In diabetic neuropathy, an individual may experience numbness in the distal extremities and a lack of protective sensation, which can lead to injuries that may go unnoticed by the individual, leading to infection.
- The **Wagner system** assesses ulcer depth and the presence of osteomyelitis or gangrene by using the following grades:
 - **Grade 0:** pre- or post-ulcerative lesion
 - **Grade 1:** partial or full thickness ulcer
 - **Grade 2:** probing to tendon or capsule
 - **Grade 3:** deep with osteitis
 - **Grade 4:** partial foot gangrene
 - **Grade 5:** whole foot gangrene

Evidence Discussion

Medical Background

The United States Food and Drug Administration (FDA) reclassified topical oxygen chambers for extremities (TOCE) from Class III devices to Class II devices in 2011 (FDA, 2011). As such, manufacturers of these devices are required to follow the 510(k) process, establishing safety and efficacy, prior to marketing their devices. Examples of topical oxygen therapy devices available in the United States include: Natrox® O2 by Inotec AMD Ltd., and O2BOOT and O2SACRAL from GWR Medical, Inc.

Literature Review

- A 2024 systematic review (Sýkorová, et al.) examined the efficacy of topical oxygen therapies (TOT). Forty-nine studies, including eight systematic reviews and 18 randomized trials, were included in the analysis. Of the eight systematic reviews, six studies focused on diabetic foot ulcers, one study examined chronic and acute wounds, and one study looked at non-healing wounds. Seven out of eight systematic reviews concluded that TOT improved various aspects of wound healing such as reduction in ulcer size and depth, improved wound oxygenation, and increased wound closure. The included study that did not report a favorable outcome with TOT was a systematic review conducted by Vas and colleagues in 2020. The authors of this study determined that TOT does not appear to be as effective as standard of care in the treatment of diabetic foot ulcers, noting that the quality of evidence is low. Despite the findings of the Vas and colleagues study, Sýkorová and colleagues found growing evidence supporting the effectiveness of TOT as an adjunctive method in the treatment of wounds. However, the authors noted that heterogeneity among the included studies made it difficult to make meaningful comparisons. Thus, the authors noted that additional research is needed to better understand the impact of TOT on wounds of various etiologies.
- Carter et al. (2023) performed a systematic review including four randomized controlled trials to evaluate the efficacy of topical oxygen therapy (TOT) as an adjunctive therapy in the treatment of Wagner grade 1 and 2 diabetic foot ulcers. Studies were analyzed for patient and wound characteristics, outcomes, risk of bias, and quality of the evidence. The authors reported moderate evidence that TOT is a viable therapy for the treatment of chronic Wagner grade 1 or 2 diabetic foot ulcers in the absence of infection and ischemia. However, the authors cited several limitations to the analysis, including lack of assessment of patient-centered outcomes, such as quality of life; heterogeneity in the application of standard of care for diabetic foot ulcers between trials; low number of studies included in the analysis; and inability to extend conclusions to a population of individuals with more severe ulcers. Thus, the authors noted that more trials are needed to strengthen the conclusions drawn from this study.
- Sun et al. (2022) performed a systematic review to evaluate the efficacy and safety of topical oxygen therapy (TOT) in the treatment of diabetic foot ulcers (DFUs). A total of seven randomized trials involving 614 participants were included. Compared with the control group, the TOT group had a higher healing rate. Moreover, TOT reduced the ulcer area and improved healing durability and quality of life. Furthermore, it had no effect on the occurrence of adverse events. However, it was unclear whether it would be able to reduce the healing time. The authors concluded that the evidence suggests that TOT is effective and safe for chronic DFUs. The authors reported several limitations to the study including, heterogeneity between the included study designs. The authors noted that additional randomized controlled trials are warranted to validate the findings of this study.

- Thanigaimani et al. (2021) performed a systematic review to examine the benefit of topical oxygen therapy (TOT) in the healing of diabetic foot ulcers (DFUs). Six randomized trials involving 530 participants who had a DFU and trialed TOT were included in the analysis. The primary outcome was ulcer healing, defined as full epithelialization. The analysis suggested that TOT significantly increased the likelihood of ulcer healing compared to controls. However, risk of bias was reported across the included studies. Analysis of the three trials judged to be at low risk of bias suggested that TOT increased the likelihood of ulcer healing compared to controls. Thus, in conclusion, the authors noted that TOT improves the likelihood of DFU healing; however, it was determined that the effect on amputation and cost-effectiveness are unclear.
- Serena et al. (2021) reported on a randomized controlled trial (NOW.T-001) which investigated the effect of topical oxygen on healing rates in individuals with diabetic foot ulcers (DFUs) that were resistant to healing (i.e., unresponsive over four weeks). This trial included 145 individuals with ulcers graded as Infectious Diseases Society of America (IDSA) grade 1 or 2, or Wagner grade 1 or 2. Participants were randomized to standard of care (SOC) with or without continuous topical oxygen therapy (TOT) for 12 weeks. SOC included debridement, offloading with total contact casting, and appropriate moisture balance. Primary endpoints were the number of individuals to achieve complete wound closure and percentage change in ulcer size. Secondary endpoints were pain levels and adverse events. At 12 weeks, 36 out of 81 participants (44.4%) in the SOC plus TOT group healed compared with 18 out of 64 participants (28.1%) in the SOC group. There was a statistically significant reduction in wound area between the groups: the SOC plus TOT group saw a mean reduction of 70%, and the SOC group had a mean reduction of 40%. There were no significant changes in pain levels or adverse events. The authors concluded that the addition of TOT to SOC facilitates wound closure in individuals with difficult-to-heal DFUs.
- As a follow-up to the NOW.T-001 study, Al-Jalodi et al., (2022) conducted a durability study to evaluate the efficacy of topical oxygen therapy (TOT) in the healing of diabetic ulcers at one-year follow-up. Twenty-nine individuals were randomized to TOT plus standard of care (SOC), or standard of care only groups. Of note, seven participants were lost to follow-up. Participants completed four questionnaires through text messages or phone calls within one-year following completion of the trial. At one year follow-up, 85% of the participants in the TOT group and 60% of the participants in the SOC group remained healed. There was one major amputation, which occurred in an SOC-treated patient. The numbers in the long-term follow-up were too small to reach statistical significance; however, the authors cited a trend toward more durable closure in ulcers treated with TOT. The authors noted several limitations of the study including the loss of 19 healed participants from the NOW.T-001 trial who did not consent for the follow-up trial, the small sample size, and the number of participants lost to follow-up (24%). Thus, the authors stated that larger, long-term studies are warranted to further examine these findings.

- Connaghan et al. (2021) conducted a systematic review including eight studies to determine the impact of topical oxygen therapy (TOT) on diabetic foot ulcer (DFU) healing. A meta-analysis of four studies concluded that DFUs are greater than two times more likely to heal with TOT than with standard care alone. In addition, the other four studies also showed that using TOT increased healing rates. The investigators concluded that TOT enhances healing for individuals with hard-to-heal DFUs when used with standard care or over standard care alone. However, the authors noted that the sample sizes in the included studies were generally small, thus, additional randomized controlled trials are warranted to further validate these findings.
- A randomized controlled trial performed by Jonker et al. (2021) evaluated the clinical effectiveness of a topical oxygen therapy (TOT) on the healing of foot ulcers. Thirty-eight individuals with foot ulcers were randomized to standard of care (SOC) versus SOC plus adjunct TOT (Granulox) therapy twice weekly. Outcome measures were collected during the trial phase at six and 12 weeks. After 12 weeks, the median percentage wound size reduction was 100% for the SOC group and 48% for the SOC plus TOT group. In the former, eight of 14 foot ulcers had healed; in the latter, four of 15 ulcers had healed. In the SOC group, two amputations and one withdrawal occurred, whereas in the TOT plus SOC group, one unrelated death and five withdrawals were recorded. In conclusion, the authors reported that they did not achieve favorable healing parameters with TOT. The authors noted that differences in wound chronicity and frequency of TOT application may have affected the study results.
- A multinational randomized controlled trial that included 220 participants assessed the efficacy of multimodality cyclical pressure Topical Wound Oxygen (TWO2) home care therapy in healing refractory diabetic foot ulcers (DFUs) that had failed to heal with standard of care (SOC) alone. The primary outcome was the percentage of ulcers in each group achieving 100% healing at 12 weeks. The results of the study reported a 4.5-fold greater rate of healing in those receiving active topical oxygen therapy at home compared with placebo. The authors concluded that at both 12 weeks and 12 months, adjunctive cyclical pressurized TWO2 therapy was superior in healing chronic DFUs compared with optimal SOC alone. However, the authors noted limitations to the study including a small sample size.

Professional organizations/societies:

- A 2023 update of the 2019 International Working Group on the Diabetic Foot (IWGDF) Guideline provided recommendations regarding interventions to enhance healing of foot ulcers in people with diabetes (Chen et al., 2024). The authors reported low certainty evidence with moderate benefit for the use of topical oxygen in achieving absolute wound healing and reduction in ulcer area for diabetes-related foot ulcers, but no evidence for reduction in amputation up to 12 weeks. The authors cited three randomized controlled trials for the use of topical oxygen. In this review,

the authors noted a lack of cost effectiveness data, but expert opinion agreed upon moderate costs, with therapy requiring multiple units of single-use topical oxygen delivery devices. Thus, the authors cited a conditional recommendation for the use of topical oxygen as an adjunct therapy to standard of care for wound healing in people with diabetes-related foot ulcers where standard of care alone has failed and resources exist to support this intervention.

- In 2021, Serena and colleagues published guidelines for the use of topical oxygen therapy in the treatment of hard-to-heal wounds. The Delphi survey questions focused on the indications for topical oxygen therapy (TOT), when to prescribe therapy, pre-treatment work-up, visit frequency, and length of therapy. The authors recommended the following work-up and procedures prior to ordering TOT: assessment of limb perfusion (e.g., ABI/TBI), clinical assessment of bacterial load, nutritional assessment, debridement, edema management, and offloading. The authors identified diabetic foot ulcers (DFUs) as a wound type likely to benefit from TOT (94% consensus). Specifically, TOT was recommended for hard-to-heal DFUs that have healed by less than 40% in four weeks or is refractory to other therapies. Moreover, the authors recommended that the wound should be reassessed every four weeks and should be continued as long as the wound is improving.
- The American Diabetes Association (ADA) "Standards of Care in Diabetes" Foot Care Recommendation 12.30 (ElSayed et al.) provided Level A evidence for: "chronic diabetic foot ulcers (DFUs) that have failed to heal with optimal standard care alone, adjunctive treatments should be considered, including topical oxygen therapy (TOT)". The authors noted that several high-quality randomized controlled trials, and at least five systematic reviews and meta-analyses support the efficacy of TOT use in healing chronic DFUs at 12 weeks that are refractory to healing. Moreover, the authors reported the benefit of TOT devices to enable home-based therapy rather than the need for daily visits to specialized centers.
- The 2023 Wound Healing Society Chronic Wound Care Guidelines (Lavery et al.) reported Level 1 Evidence that topical oxygen has been shown to increase the incidence of healing and decreases the time to heal in the treatment of diabetic foot ulcers. The authors noted that oxygen is essential to promote wound healing. Topical oxygen diffuses oxygen into the ulcer wound bed. The rationale for topical oxygen is to eliminate hypoxia and stimulate growth factors that contribute to angiogenesis.

Codes addressed in this guideline

HCPCS	Description
A4575	Topical hyperbaric oxygen chamber, disposable
E0446	Topical oxygen delivery system, not otherwise specified, includes all supplies and accessories

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