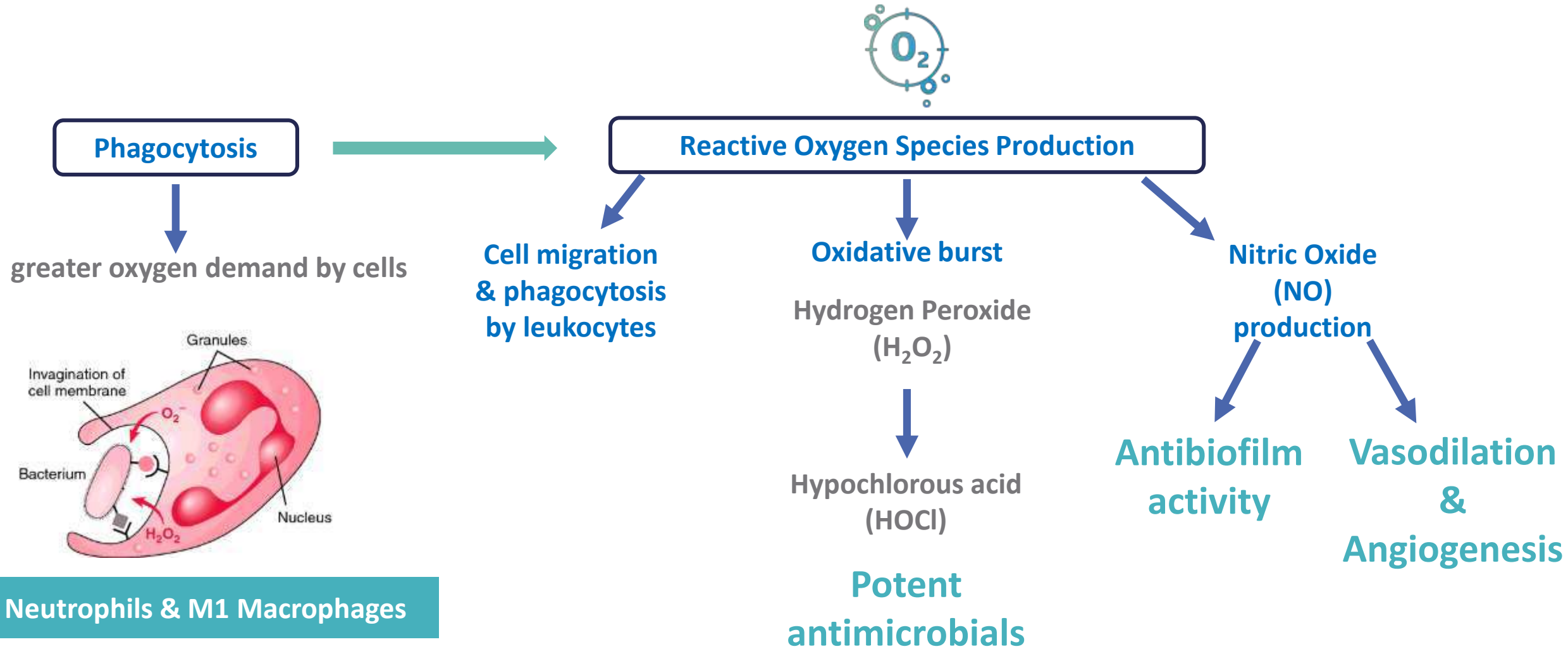


Role of Oxygen in Wound Healing

The science, evidence and guidelines supporting
continuous Topical Oxygen Therapy (cTOT)

Emma Woodmansey PhD
Global Clinical Director, NATROX® Wound Care

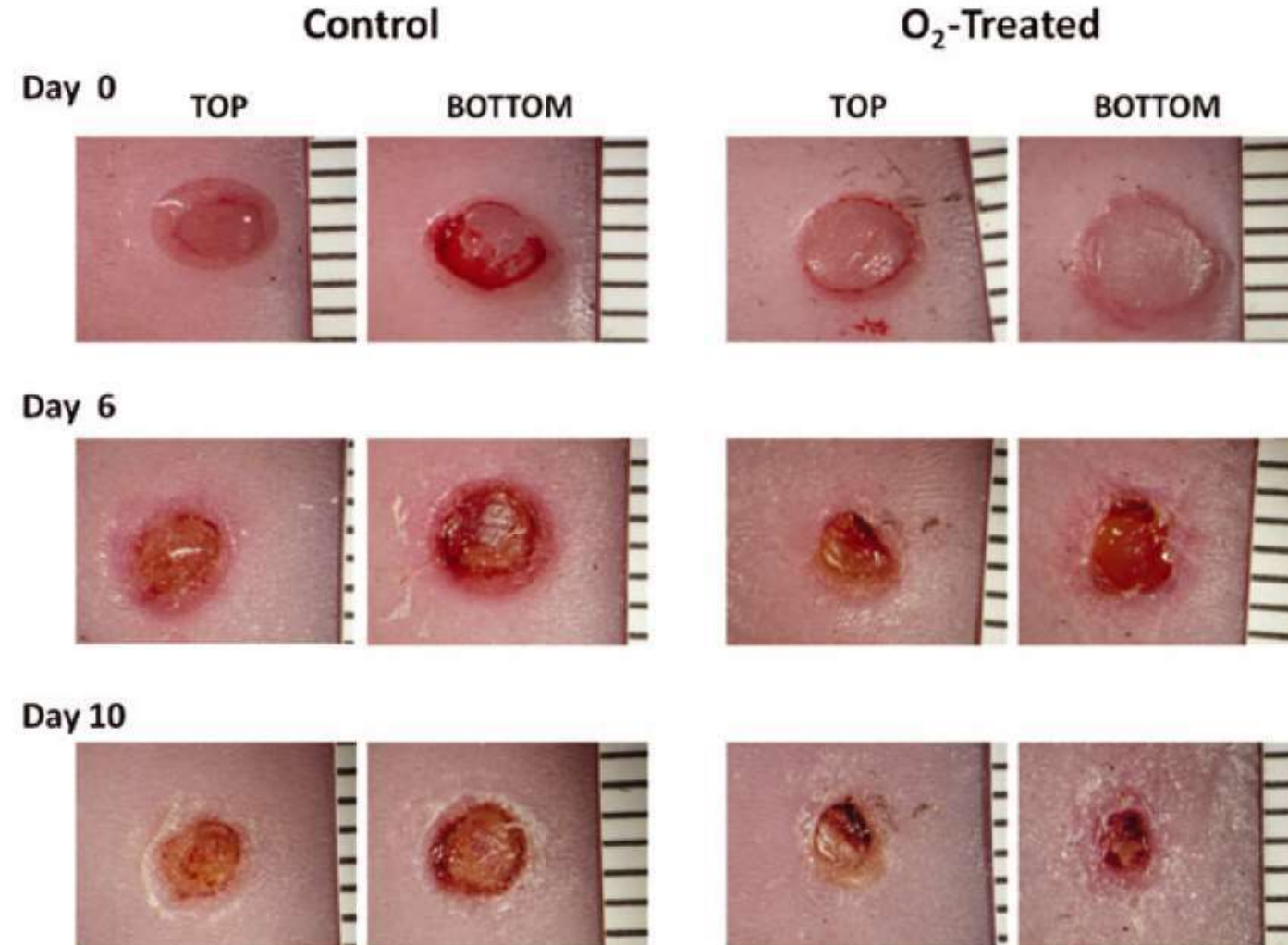
Critical Role of Oxygen Against Infection



Frykberg, R. et al. Use of Topical Oxygen Therapy in hard to heal wounds. *J Wound Care* 32, S1–S32 (2023).

TOT Increases Epithelialization in Diabetic Skin Wound Model

Mouse model of diabetic skin wounds: TOT vs Control



EPITHELIALIZATION

Mean reduction of wound size

- Day 6: **60%** (TOT) vs. 45% (Control)
- Day 10: **83%** (TOT) vs. 71% (Control)

Complete re-epithelialization at Day 10 in **57%** TOT wounds vs. **25 %** control

COLLAGEN RE-MODELLING

- Increased collagen deposit at wound base after TOT.
- Collagen fibres appear **more organised, fibrous appearance** with TOT
- Suggests **remodelling significantly more advanced** than in control.

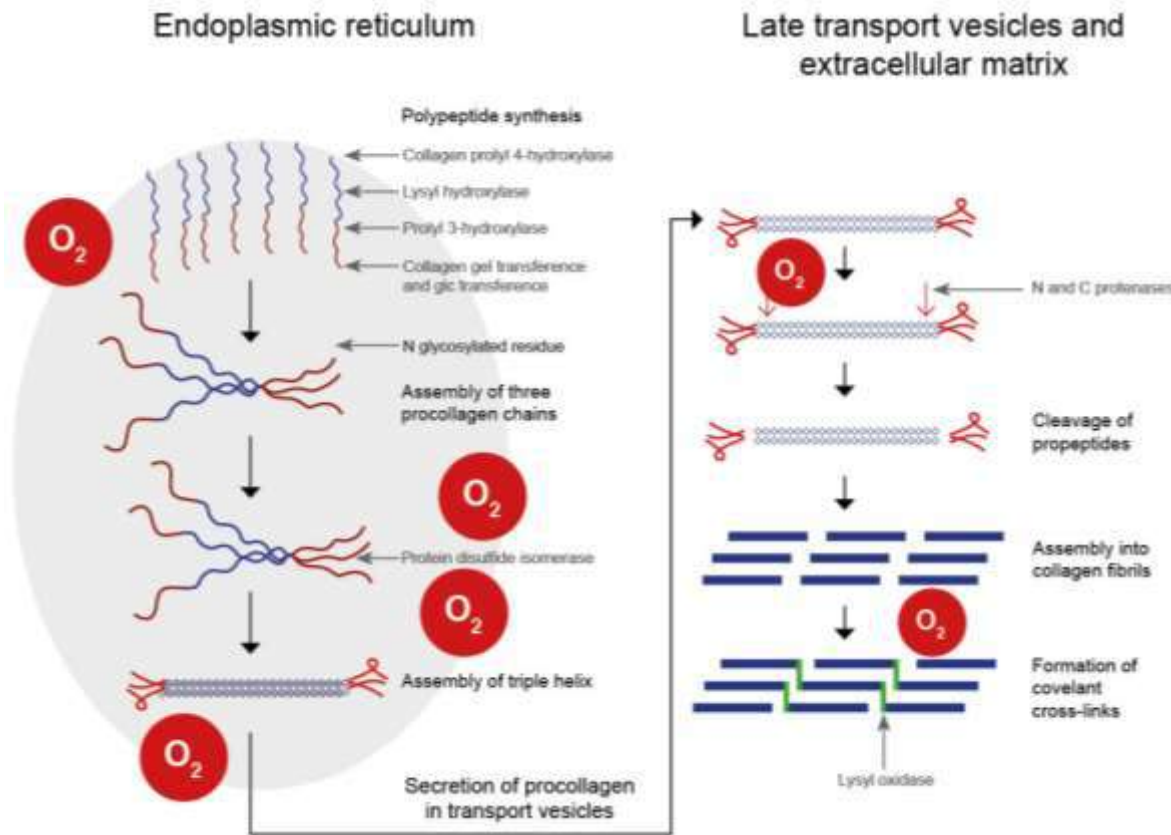
Remodelling: Collagen Synthesis & Stability O₂ Dependent

Collagen deposition, polymerization (enzymes prolyl hydroxylase & lysyl hydroxylase) and covalent cross-linking require optimal levels of molecular oxygen

Low O₂ - collagen hydroxylation and maturation *reduced* and *collagen remains fragile*; new vessels fail to mature and break.

Collagen deposition proceeds in direct proportion to pO_2

- new vessels cannot even approach their greatest possible rate of growth unless the wound tissue pO_2 is high



Sen, C. K. Wound healing essentials: Let there be oxygen. *Wound Repair and Regeneration* **17**, 1–18 (2009).

Collagen formed in hypoxic environments only 30% as strong as collagen formed in normal oxygen concentrations.

Reasons for Wound Hypoxia

HYPOXIA = Reduction in oxygen delivery below tissue demand



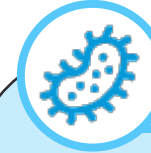
Patient

- Peripheral Vascular Disease (PVD)
- Oedema
- Damage to blood vessels due to comorbidities (e.g. diabetes)
- Co-incident conditions (e.g. infection, pain, anxiety and hyperthermia)
- Compromised pulmonary health (e.g. COPD)



Wound

- Micro-vasculature/ capillary damage due to trauma
- Contraction of vessels in traumatized tissue
- Oedema
- Necrotic tissue
- Infection / Biofilm – further tissue damage



Cellular activity

- Infection: Bacterial & fungal proliferation consume energy
- Host cells need energy (ATP) to function
- Immune cells (migration, phagocytosis, de-granulation, differentiation)
- Immune response – Production of Reactive Oxygen Species
- Migration & repair (epithelial cells)

Sen, C. K. Wound healing essentials: Let there be oxygen. *Wound Repair and Regeneration* **17**, 1–18 (2009).

NATROX® O₂ - Simple Technology in Action



1. Oxygen Generator (OG)



2. Batteries (rechargeable)

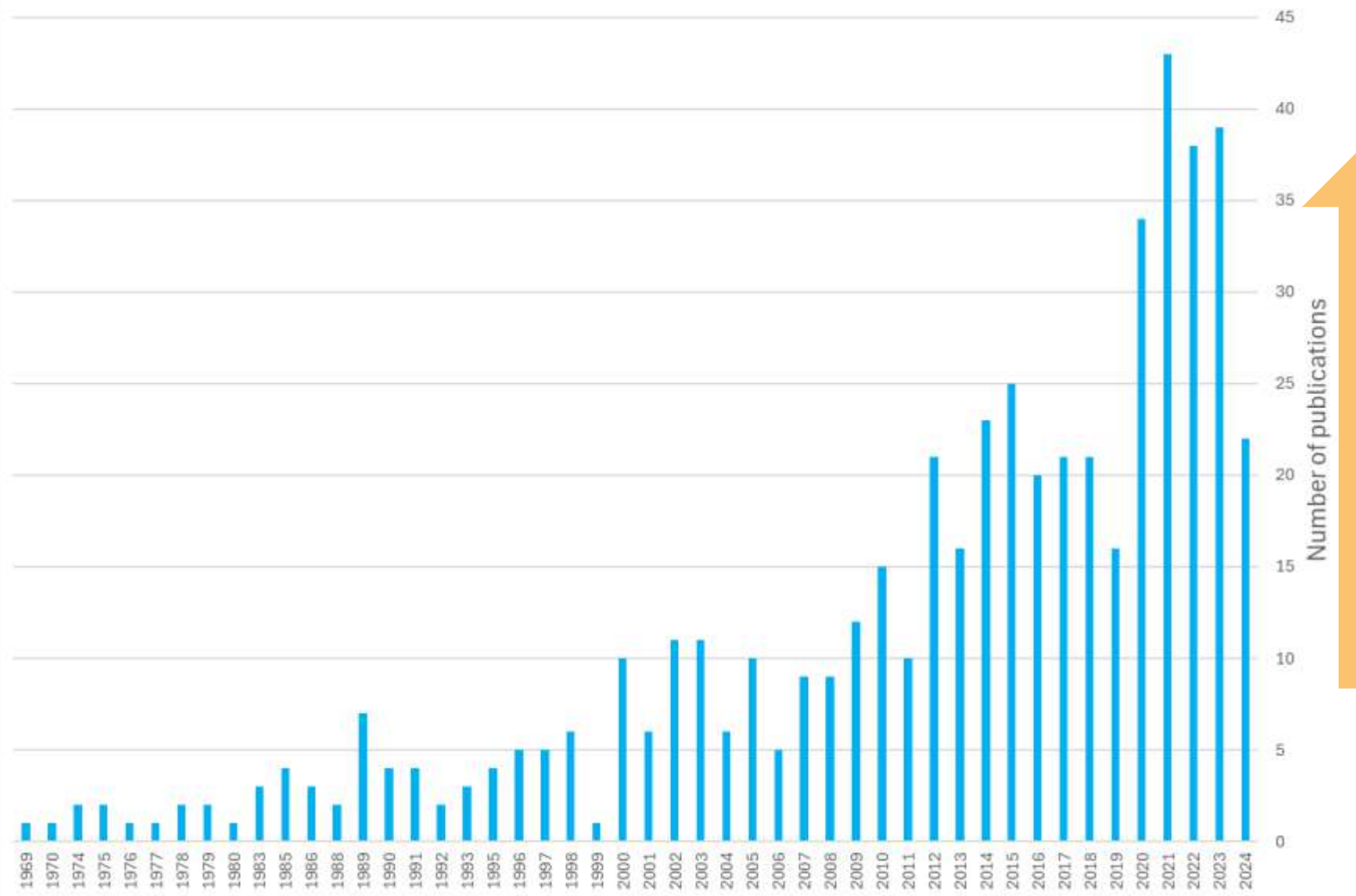


3. Oxygen Delivery System (ODS)

Practical for carer and patient

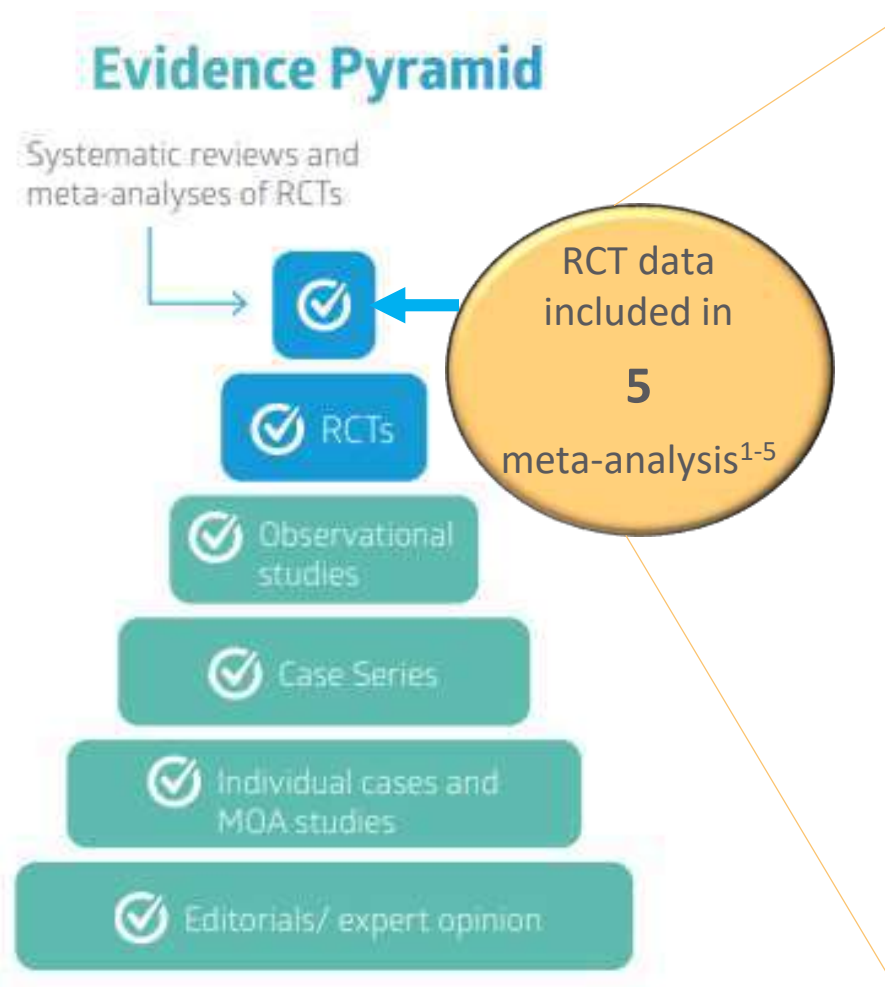


Number of publications per year
Pubmed Search (Topical Oxygen Therapy) AND (Wounds) June 2024



Evidence is
GROWING
for
**TOPICAL
OXYGEN
THERAPY**

cTOT High Evidence Levels



	Author	Study	Wound	Intervention	Key Outcomes
SLR & Meta-analysis	Carter 2023 ¹	Systematic review (SLR) and Meta-analysis	DFU	cTOT vs SHAM or SoC	A random-effects meta-analysis of four RCTs showed that TOT improved wound healing at 12 weeks over SOC alone - supporting the use of TOT for the treatment of chronic Wagner 1 or 2 DFU in the absence of infection and ischemia The overall GRADE level of evidence for TOT was moderate RR: 1.59; 95% CI: 1.07–2.37; p = 0.021
	Sethi 2022 ²	Systematic review (SLR) and Meta-analysis	DFU	cTOT vs SHAM or SoC	Meta-analysis of four RCT's demonstrated that use of adjuvant TOT showed higher rate of complete by approximately 60% at 12 weeks wound healing in DFU compared to SoC alone RR: 1.59; 95% CI: 1.07–2.37;p = 0.021. RR 1.59 95% confidence interval 1.07, 2.37 p = 0.02; NNT 6.3
	Sun 2022 ³	Systematic review (SLR) and Meta-analysis	DFU	cTOT vs SHAM or SoC	Meta-analysis of seven trials demonstrated that TOT group had higher healing rate with no effect on adverse events RR = 1.63, 95% CI [1.33, 2.00] p=0.096
	Thanigaimani 2021 ⁴	Systematic review (SLR) and Meta-analysis	DFU	cTOT vs SHAM or SoC	Meta-analysis of six RCT's showed TOT significantly increased the likelihood of ulcer healing compared to controls RR 1.94; 95% CI 1.19, 3.17; I2 = 57%; NNT = 5.33 p=0.04
	Connaghan 2021 ⁵	Systematic review (SLR) and Meta-analysis	DFU	cTOT vs SHAM or SoC	Meta-analysis of five RCT's demonstrated that DFUs are >2 times more likely to heal with TOT than with SoC alone. OR healing 2.49 (95% CI: 1.59– 3.90; p=0.00001 Z=4.00 (p<0.0001)

1. Carter, M. J. *et al. Adv Wound Care (New Rochelle)* **12**, 177–186 (2023), 2. Sethi, A., *et al. Health Sciences Review* **3**, 100028 (2022), 3. Sun, X. *et al. Int Wound J* **19**, 2200–2209 (2022), 4. Thanigaimani, S.,*et al. Diabetic Medicine* **38**, (2021), 5. Connaghan, F., Avsar, P., Patton, D., O’Connor, T. & Moore, ZJ *Wound Care* 30, 823–829 (2021)

research

Background: The patient and blood-sugar levels are frequently unaffected in patients with heart-to-heart sounds due to poor circulation, vascular dysfunction and neuroendocrine, reducing the lungs capacity to store. This study aimed to investigate the effect of topical oxygen on healing rates in patients with heart-to-heart diastolic foot ulcers (DFU) (i.e., non-exposed over four weeks).

Methods: This multicenter, open-label, community-based randomized controlled-comparative study (NCT01301000) with or without continuous topical oxygen therapy (T2) for 16 weeks in patients with DFUs or venous ulcers (VUs) was conducted in 10 hospitals, utilizing a split-ventral randomization (T2C) and appropriate randomization. Primary endpoints were the number of patients in active treatment (total ulcers and percentage change in ulcer size). Secondary endpoints were pain levels and adverse events.

Results: For this study, 100 patients were randomized with index

study group included Chinese citizens of American descent ($n = 1$, or Vagstad¹ or E_2). In the intention-to-treat analysis, 1054 (80.7%) patients had the T3C group and 17 women compared with 9679 (84.0%) in the SOC plus T3T group (quadrant). There was a statistically significant reduction in wound area between the groups. SOC group mean reduction: 40% [intention-to-treat] (SD 12.1); SOC plus T3T group mean reduction: 65% (SD 16.2; p -value post hoc $p < 0.008$). These results suggest differences in changes to post-healed or adverse events.

Conclusion: This study suggests that the addition of T3C to SOC significantly worsened clinical endpoints with hard-to-heal wounds.

Declaration of interest: Inpage, AMT Ltd., UK funded RASER Group; is design, conduct and member the study. Inpage RASER Ltd. acted as the study sponsor. The authors have no other conflicts of interest to declare.

chronic wound + critical limb + diabetes + diabetic foot ulcer + dressing + hard-to-heal wound + infection + topical oxygen therapy + total contact casting + ulcer + wound

Researchers recognize the increased numbers of patients presenting with complications associated with diabetes, such as the *Robertson Report* is now considered the very leading cause of global disease burden and disability. Many of these patients are complex individuals, with both medical and psychosocial issues, but they represent points of time to build stronger provider care in endocrinology settings, and the management of such women presents clinicians with a challenge from both the clinical and cost-effectiveness perspectives. In this context, it is undoubtedly that clinicians are looking for innovations in women's health to support their patients, particularly those with hard-to-control women.

In Yao and Farnum's highlighted in their abstract, the scope of this review included some other relevant studies. Driver et al.²⁴ in a study of 136 patients, found no difference in the feeding rates for patients receiving enteral or oral feeds. In contrast, 1997, with 10 patients, while variables have shown consistently in favour of NGT. Most recent is a review of 146 patients, demonstrated a two-fold increase in the rate of feeding in 52 weeks when using continuously infused TPN. Trillinger et al.²⁵ concluded that subcutaneous TPN applied with passive, manual cyclical, can lead to even higher feeding rates.

[illegible]

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Matthew Dwyer, MD, Professor, **West Virginia**, MD, Professor of Medical Care Services,
Publicis Policy, PhD, Associate Professor

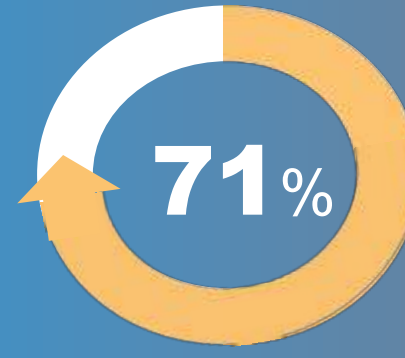
Corresponding author email: tom.lawrence@neanet.com

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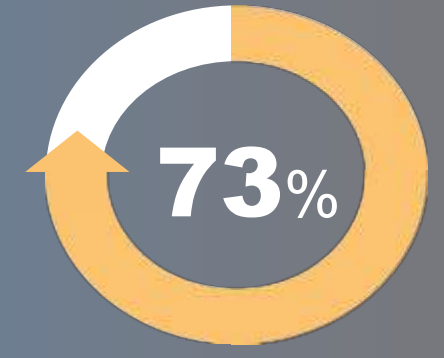
SYNOPSIS: *Journal of Interpersonal Violence* 26(12) 3091–3107, 2011. © 2011 Sage Publications. 10.1177/0886260511419111

A donut chart with a blue background. The chart is divided into two segments: a white segment representing 52% and an orange segment representing the remaining 48%. The text '52%' is written in white in the center of the white segment.

Healed
completely



Greater healing rate**



Greater average %
reduction in wound size**

** Compared to control

Serena, T. E. *et al.* Topical oxygen therapy in the treatment of diabetic foot ulcers: a multicentre, open, randomised controlled clinical trial. *J Wound Care* **30**, S7–S14 (2021).

cTOT and Durability – RCT follow up

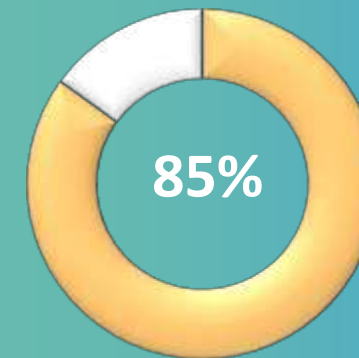
- Follow up study to the RCT
- 22 patients participated



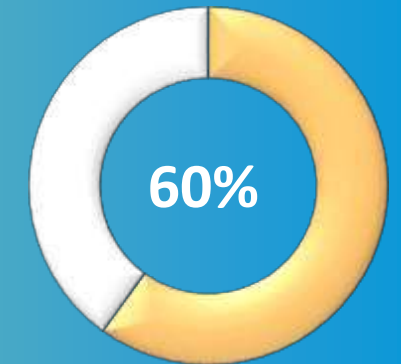
RESULTS:

Patients that remained healed at one year

NATROX® O₂



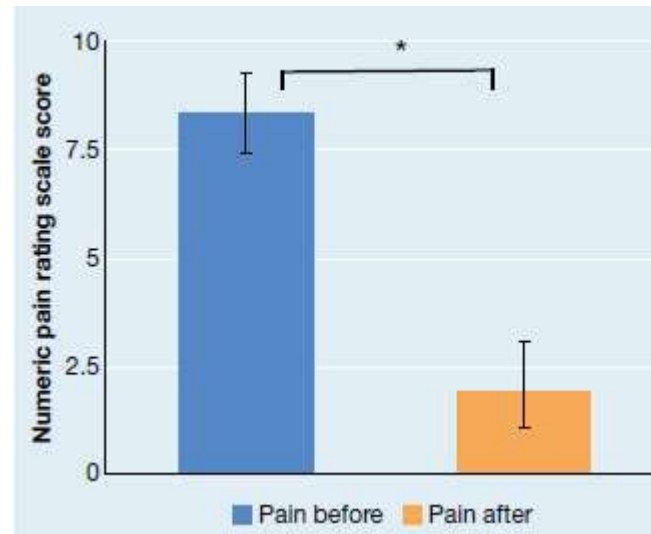
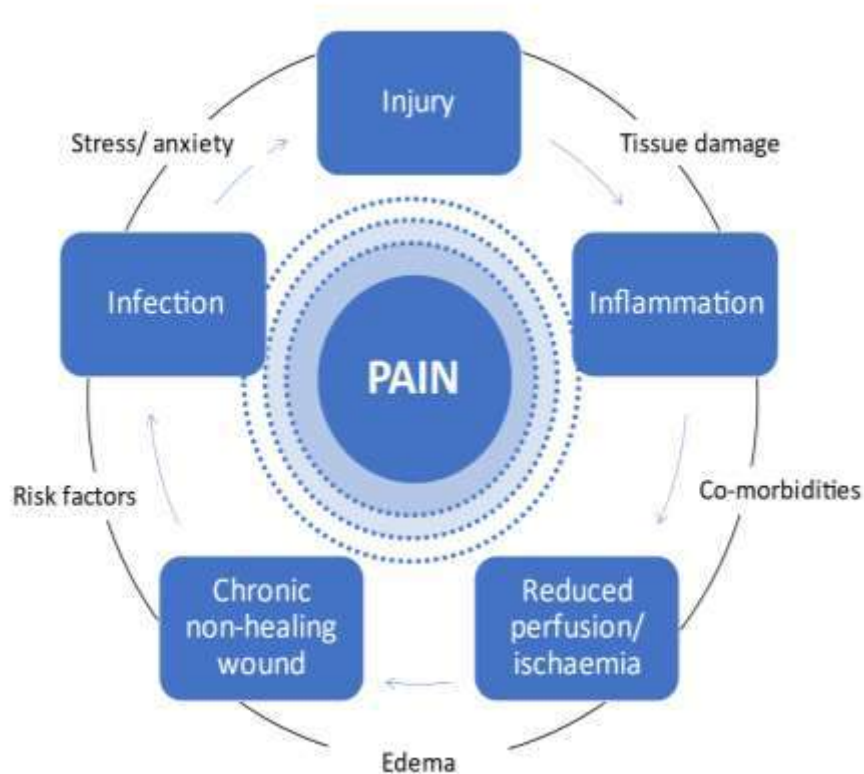
SoC



Only 1 major amputation occurred, which was in a SoC-treated patient.

Al-Jalodi, O., Kupcella, M., Breisinger, K., et al. (2022) A multicenter clinical trial evaluating the durability of diabetic foot ulcer healing in ulcers treated with topical oxygen and standard of care versus standard of care alone 1 year post healing. *International Wound Journal*, 19(7) pp. 1-5.

Pain reduction and improved healing VLU

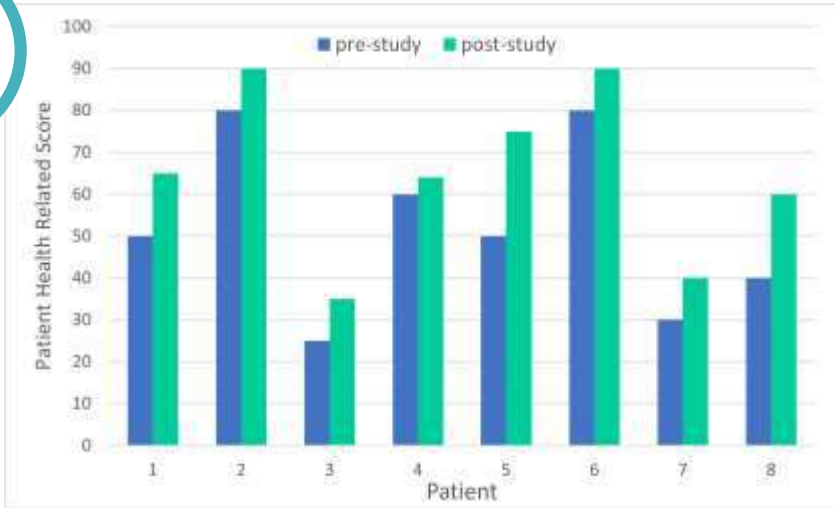
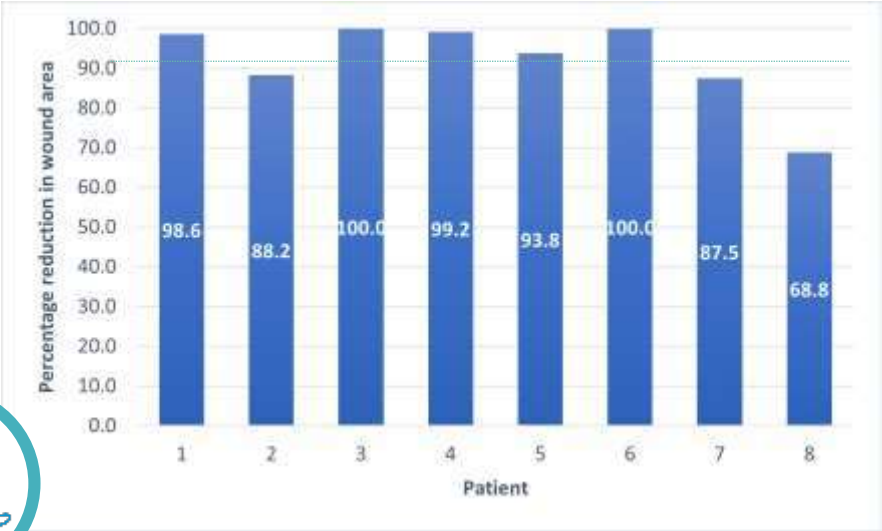


Leg ulcer pain before (mean 8.2) and after (mean 1.9) topical continuous oxygen treatment using the numeric pain rating scale: average patient data
* $p < 0.00001$. Error bars indicate standard error

- 40% of hard to heal wounds healed with cTOT
- Significant reduction in wound pain after cTOT ($p < 0.00001$)
- 69% patients stopped taking opioids

Jebril, W. *et al.* Topical oxygen treatment relieves pain from hard-to-heal leg ulcers and improves healing: a case series. *J Wound Care* **31**, 4–11 (2022).

Shared care - outcomes



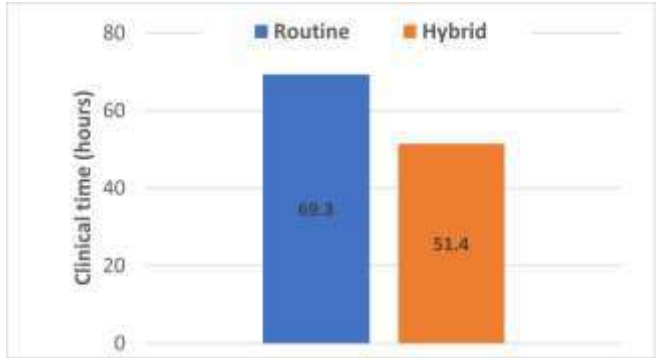
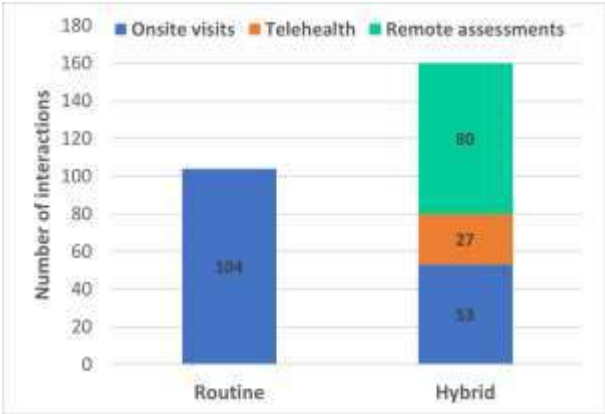
Improved PRHS QoL in all 8 patients



54 % increase clinical interactions

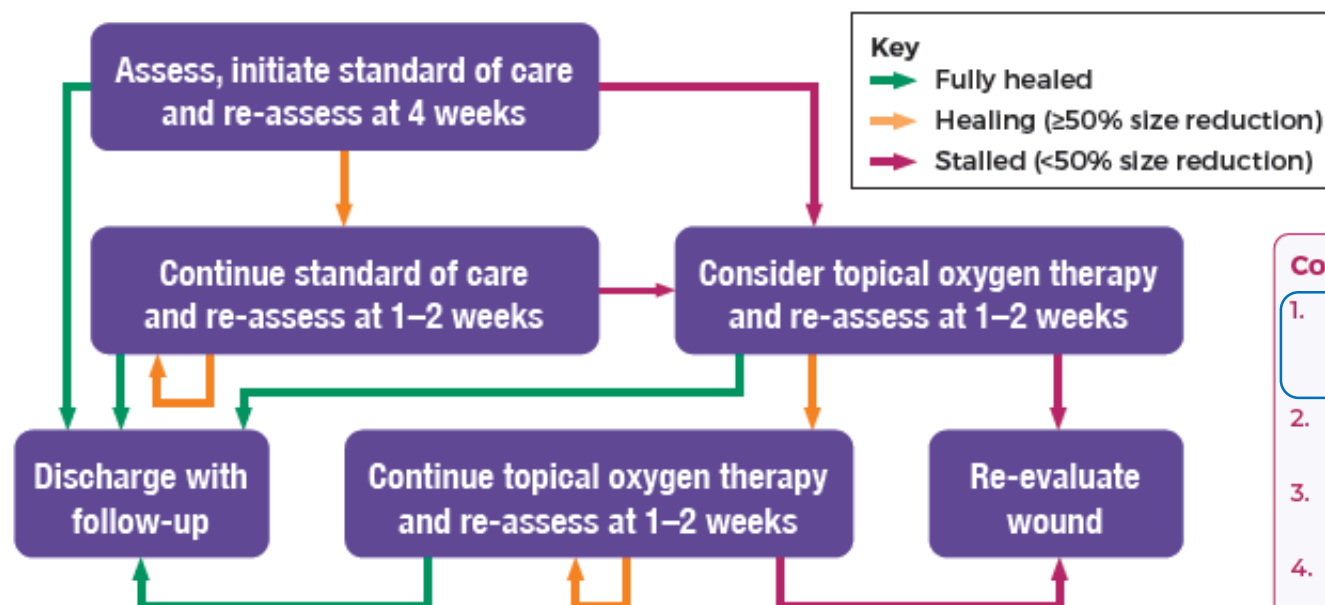


25.8 % reduction in clinical time



Lee, A., Woodmansey, E., Klopfenstein, B., O’Leary, J. L. & Cole, W. Remote assessment and monitoring with advanced wound therapy to optimise clinical outcomes, access and resources. *J Wound Care* 33, 90–101 (2024).

International Consensus on TOT



Consensus panel recommendations

1. Consideration in hard-to-heal wounds (those that have failed to achieve a 50% size reduction after 4 weeks of standard of care)
2. Applicability to most kinds of non-neoplastic hard-to-heal wounds
3. Contraindication in untreated infection, malignancy or necrosis
4. Avoidance in critical limb ischaemia while there is insufficient evidence
5. Earlier rather than later consideration
6. Initial vascular assessment and possible vascular intervention
7. Frequent and adequate debridement
8. Adjunctive use alongside standard of care
9. Treatment of underlying aetiology, such as offloading, compression or glucose control
10. Management of any pain, infection or comorbidities
11. Avoidance of wound dressings that might impede oxygen diffusion
12. Multidisciplinary approach to treatment
13. Appropriate training to facilitate self-administration by patients or caregivers
14. Broad access, with appropriate reimbursement by payers and healthcare systems
15. Education of providers, insurers and payers on cost-efficacy of treatment
16. Collection of health-economic data on cost-effectiveness in different wound types
17. Creation of a European or global wound register to further evaluate benefits
18. Development of assessment tools to identify regional ischaemia
19. Research into potential as a first-line therapy

Frykberg, R. *et al.* Use of Topical Oxygen Therapy in Wound Healing. *J Wound Care* 32, S1–S32 (2023).

International Working Group for the Diabetic Foot 2023



- The evidence on topical oxygen has substantially expanded in the last four years with several new RCTs
- **“Consider 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”**

1. Chen, P. *et al.* www.iwgdfguidelines.org (2023)



TOT Recommendations – International Guidelines

ADA Standards of Care in Diabetes 2023 & 2024^{1,2}

TOT receives an “A grade” recommendation as an adjunctive treatment for chronic DFUs based its strength of evidence

International Working Group on the Diabetic Foot (IWGDF) 2023³

“Consider 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”

A new algorithm for the management of diabetic foot ulcer 2023⁴

Clinical experts in Europe agree that adjunctive treatments with a clear evidence base (cTOT) should be included in the treatment algorithm and “All hard-to-heal wounds are likely to benefit from TOT, even after revascularization”

Expert led Delphi consensus document in South America 2023⁵

“..expert consensus supports the efficacy and safety of continuous transdermal oxygen in the treatment of chronic and/or difficult-to-heal ulcers”

Positive Health Technology Guidance – Wales UK 2022⁶

“cTOT should be adopted in Wales and if not justify why it has not been followed”

WHS (Wound Healing Society) guidelines update: Diabetic foot ulcer treatment guidelines 2023⁷

‘Level 1 Evidence’ recommendation for topical oxygen therapy - “Topical oxygen has been shown to increase the incidence of healing and decrease the time to heal”



1. ElSayed, N. A. *et al.* 12. *Diabetes Care* **46**, S203–S215 (2023)
2. ElSayed, N.A. *et al.* 12. *Diabetes Care* **47** (Suppl. 1):S231–S243 (2024)
3. Chen, P. *et al.* www.iwgdfguidelines.org (2023)
4. Bem, R. *et al.* *Journal of Wound Care* **32**, 264–272 (2023)
5. Pacheco YJ, *et al.* *JWC LATAM Supplement Oct 2;32(LatAm sup 10):1-37* (2023)
6. Health Technology Assessment guidance Wales, September 2022
7. Lavery, L. A. *et al.* WHS (Wound Healing Society) guidelines update: Diabetic foot ulcer treatment guidelines. *Wound Repair and Regeneration* (2023)



Oxygen is essential for multiple critical functions during wound healing

- Many chronic wounds have low oxygen levels which can be supplemented with Topical Oxygen Therapy (TOT).
- TOT use is supported by **high level evidence** and is recognised in multiple **expert guidelines** globally.
- NATROX[®] O₂ cTOT is a **simple, easy to use evidence-based technology** that can support **improved wound healing** and allow patients to return to **everyday activities**.

