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SUMMARY WITH CRITICAL APPRAISAL

Continuously Diffused Oxygen Therapy for Wound Healing: A Review of the Clinical Effectiveness, Cost-Effectiveness, and Guidelines

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Abbreviations

CDO	continuously diffused oxygen
DFU	diabetic foot ulcer
ITT	intention-to-treat
IWGDF	International Working Group on the Diabetic Foot
RCT	randomized controlled trial
SOC	standard of care
SR	systematic review
TCOT	topical continuous oxygen therapy
TOT	topical oxygen therapy
TPOT	topical pressurized oxygen therapy
TWO2	topical wound oxygen
UTWCS	University of Texas Wound Classification System

Context and Policy Issues

Patients with chronic wounds pose a significant and growing challenge for healthcare as populations increase in age and as the prevalence of diabetes, obesity, and atherosclerosis continue to increase worldwide.[1] In addition, failure to heal these wounds is associated with additional burdens of infection, sepsis, amputation, and recurrence complications as well as death from direct complications of the wounds themselves.[2] In Ontario wound care accounts for up to half of home care services, with 31 000 patients admitted to home wound care each year resulting in $108.7 million in service costs alone.[3] The challenging management and rising costs associated with chronic wounds and related complications in many health care settings requires that interventions for chronic wound healing be supported by clinical efficacy and cost-effectiveness evidence to improve outcomes.

A key modulator in the healing of normal wounds is oxygen, which is a requirement for the physiological wound healing processes of collagen deposition, epithelialization, fibroplasia, angiogenesis, and resistance to infection.[1] Delivery of oxygen through systemic circulation is often impeded in a chronic wound environment which limits the physiological wound healing processes. Topical wound oxygen (TWO2) therapy is aimed at increasing local oxygen concentrations to support wound healing processes without depending on systemic circulation for oxygen delivery. TWO2 can be categorized into two related interventions, continuously diffused oxygen (CDO) therapy (also known as topical continuous oxygen therapy (TCOT)), and topical pressurized oxygen therapy (TPOT).[4] A defining difference is that while TPOT uses local pressurized humidified oxygen, CDO uses a continuous flow of non-humidified oxygen at atmospheric pressure over the wound. Generally, TWO2 therapies are relatively portable, suitable for use in a home care setting, avoid possible

complications of related systemic oxygen therapies, and can be used in addition to standard wound care.[3]

The purpose of this report is to retrieve and review the existing evidence on the clinical effectiveness and cost-effectiveness of the use of CDO therapy in comparison to standard wound care alone for patients with chronic wounds. In addition, this report aims to retrieve and review the evidence-based guidelines on the use of CDO for patients with chronic wounds.

Research Questions

1. What is the clinical effectiveness of continuously diffused oxygen (CDO) therapy for wound healing compared with conventional wound care?

2. What is the cost-effectiveness of CDO therapy for wound healing compared with conventional wound care?

3. What are the evidence-based guidelines regarding the use of CDO therapy for wound healing?

Key Findings

Evidence regarding the clinical efficacy of continuously diffused oxygen was identified in three unique randomized controlled trials and a systematic review. The key contributions to the findings of this report were from two recently published, double-blinded, placebo controlled, randomized controlled trials associated with few methodological limitations, however both observed high patient attrition. These two studies had conflicting findings which prevented evidence-based conclusions regarding clinical efficacy of continuously diffused oxygen for patients with diabetic foot ulcers. Limited evidence from these studies suggested that the patient population most likely to benefit from continuously diffused oxygen treatment of diabetic foot ulcers has yet to be defined. Two smaller unblinded randomized controlled trials, one identified in the systematic review, observed benefits of continuously derived oxygen for diabetic foot ulcers but both were associated with methodological limitations. While consensus was reached in all identified evidence that continuously diffused oxygen is safe, the best safety evidence was from patients with diabetic foot ulcers and limited comorbidities. For patients with other chronic wounds, evidence for the efficacy of continuously diffused oxygen was generally favourable however this evidence consisted of two small case series identified by the systematic review included in this report. No evidence regarding the cost-effectiveness of continuously diffused oxygen therapy was identified. Relevant guidelines from the International Working Group of the Diabetic Foot were published in 2020. The guideline development group recommended not to use topical oxygen therapy, of which continuously diffused oxygen is a subtype, as a primary or adjunctive intervention for diabetic foot ulcers. The strength of this recommendation was weak, and it rated the supporting evidence as low quality. Further studies to resolve the conflicting evidence identified in this report, and further studies on patients with chronic wounds other than diabetic foot ulcers, are required before an evidence-based assessment of the potential role for continuously diffused oxygen therapy in wound healing can be well established.

Methods

Literature Search Methods

A limited literature search was conducted by an information specialist on key resources including Medline, the Cochrane Library, the University of York Centre for Reviews and Dissemination (CRD) databases, the websites of Canadian and major international health technology agencies, as well as a focused internet search. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were continuously diffused oxygen and wound healing. No search filters were applied to limit retrieval. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 01, 2011 and June 16, 2020.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Population	Patients with wounds (e.g., diabetic foot ulcers, burns, frostbite) Subgroups: patients with diabetes, patients with ischemia
Intervention	Continuously diffused oxygen (CDO) (may be known as topical wound oxygen therapy (TWO2))
Comparator	Q1,2: Standard wound care (e.g., traditional dressings); Q3: Not applicable
Outcomes	Q1: Clinical Effectiveness: time to wound healing, percentage of wound healing, need for surgical closure or debridement, infection rate, pain control, quality of life, Q2: Cost-effectiveness: cost per quality adjusted life years Q3: Recommendations regarding the use of CDO for wound healing
Study Designs	Health technology assessments, systematic reviews, randomized controlled trials, non-randomized studies, economic evaluations, and evidence-based guidelines.

CDO = continuously diffused oxygen; TWO2 = topical wound oxygen therapy

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, they were duplicate publications, or were published prior to 2011. Systematic reviews in which all relevant studies were captured in other more recent or more comprehensive systematic reviews were excluded. Primary studies retrieved by the search were excluded if they were captured in one or more included systematic reviews. Guidelines with unclear methodology were also excluded.

Critical Appraisal of Individual Studies

The included publications were critically appraised by one reviewer using the following tools as a guide: A Measurement Tool to Assess Systematic Reviews 2 (AMSTAR 2) for the included systematic review (SR),[5] the Downs and Black checklist for the randomized controlled trials (RCT), and the Appraisal of Guidelines for Research and Evaluation (AGREE) II instrument[6] for guidelines. Summary scores were not calculated for the

included studies; rather, the strengths and limitations of each included publication were described narratively.

Summary of Evidence

Quantity of Research Available

A total of 332 citations were identified in the literature search. Following screening of titles and abstracts, 315 citations were excluded and 17 potentially relevant reports from the electronic search were retrieved for full-text review. Six potentially relevant publications were retrieved from the grey literature search for full-text review. Of these 23 potentially relevant articles, 17 publications were excluded for various reasons, and six publications met the inclusion criteria and were included in this report. These comprised one SR,[4] four RCTs,[7-10] and one evidence-based guideline.[2] Appendix 1 presents the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[11] flowchart of the study selection.

Two of the RCT publications reported on the same study cohort and therefore are considered a single RCT for the purposes of this report.[9,10] This RCT (Niederauer et al., 2017/2018)[9,10] along with another RCT (Driver et al., 2017)[7] are included in this report and are also cited by the included guidelines as clinical efficacy evidence of TWO2 therapy.[2] There is overlap in the primary study evidence summarized by the systematic review by Sayadi et al., the primary study evidence used to formulate the International Working Group on the Diabetic Foot (IWGDF) recommendations, and the RCT evidence included in this report.[2,4,7,9,10] This overlap of evidence included in this report is outlined in Appendix 5.

Summary of Study Characteristics

Details regarding the characteristics of included publications are tabulated in Appendix 2.

Study Design

One SR met the inclusion criteria outlined in Table 1 and is included in this report. Sayadi et al., 2018,[4] narratively summarized relevant systematically identified evidence from two case series,[12,13] and one RCT,[14] without conducting a meta-analysis.

Two identified studies were double-blinded, placebo controlled RCTs.[7,9,10] The results of one of these RCTs was published twice, one reported the per-protocol analysis in 2017,[9] and one reported the intent-to-treat analysis in 2018.[10]

One guideline formulated relevant recommendations based on evidence from two double-blind RCTs[7,10] both of which are also included in this report.[2] These guidelines were developed by the IWGDF in 2019 using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) system to develop consensus-based expert recommendations with methodology provided in a separate publication.[2,15] Quality of evidence was rated high, moderate, or low based on study design and risk of bias while the strength of recommendations were graded as strong or weak based on expert consensus weighing of factors including quality of evidence, benefits and harms, patient values and preferences, feasibility, and resource utilization.[15]

Country of Origin

The SR and the three RCTs included in this report were authored in the United States.[4,7-10] Driver et al., 2017 reported that at least one of the 22 participating wound clinics was in Canada.[7]

The primary author of the IWGDF guidelines was located in the Netherlands, however other contributing authors were located in Australia, the United Kingdom, Sweden, and the United States, reflecting the international scope of these guidelines.[2]

Patient Population

The SR did not strictly define a patient population and searched for evidence on patients of unspecified age with unhealed wounds in addition to preclinical evidence.[4]

All of the RCTs examined patients with diabetic foot ulcers (DFUs), and provided inclusion and exclusion criteria to examine a defined population with limited comorbidities.[7-10] Inclusion criteria of the RCTs defined patient age range,[7-10] DFU size,[7-10] DFU age,[7,9,10] and circulatory parameters,[7-10] while exclusion criteria limited acceptable comorbidities including uncontrolled hyperglycemia,[7-10] malignancy,[7-10] pregnancy,[7-10] alcohol or substance abuse,[7-10] and recent history of radiation or chemotherapy.[7,9,10] Two RCTs excluded patients that had more than 30% wound size reduction in the week prior to randomization with standard of care (SOC) to ensure that non-chronic DFUs were excluded.[7,9,10] The most recently published RCT, Niederauer et al., treated 146 randomized patients, Driver et al. (2017) randomized 130 patients, and Driver et al. (2013) enrolled 17 patients.[7-10]

The IWGDF guidelines were intended for use by clinicians, other health care professionals, public agencies, and policymakers. The recommendations were applicable to patients with diabetic foot ulcers.[2]

Interventions and Comparators

Sayadi et al. focused on evidence for micro/nanobubbles and TWO2 therapy interventions in patients with unhealed wounds, and did not require any comparator.[4] CDO therapies, also called TCOT, can be considered a subcategory of TWO2 therapies that also includes TPOT.[3,4] This report examines only the CDO relevant evidence from the included SR. Sayadi et al. clearly distinguished between CDO and TPOT interventions providing separate conclusions for these interventions.[4] A specific commercially available CDO device, Epiflow (Neogenix LLC, Beachwood, OH), was cited for two included primary clinical studies however evidence for a specific device was not examined in isolation.[4]

The three RCTs examined a CDO device intervention that delivered pure oxygen at a rate of 3 mL/hour to the wound uninterrupted except for scheduled assessments and wound care. The two larger and more recent RCTs included a sham device control treatment group to which patients and investigators were blinded to assignment. The sham devices either did not generate pure oxygen[7] or the generated pure oxygen was not directed towards the wound.[9,10] Standard of care that included moist wound therapy (MWT) was also used by both larger RCTs in addition to the intervention or sham device.[7,9,10] The smaller RCT published in 2013 used SOC that included debridement once per week, boot offloading, and moisture as a comparator.[8] Niederauer et al. used consistent dressings for all patients,[9,10] and Driver et al., 2017 used a dressing selection guide and clinical judgement to determine the best dressing (hydrocolloid or alginate and foam dressing).[7] While the RCT by Driver et al. in 2017 did not specifically name the device intervention, the

prior study published in 2013 by Driver et al. used Epiflow (Neogenix LLC, Beachwood, OH) devices.[7,8] The RCT by Niederauer et al. used the TransCu O_2 System (EO_2 Concepts, San Antonio, TX).[9,10]

The guidelines from IWGDF included all interventions that may accelerate the healing of DFUs, and required that primary study evidence included any controlled comparator.[2] These guidelines did not distinguish between CDO therapies and TPOT, however CDO evidence was examined and the working group of international experts grouped these TWO2 therapies for the purposes of formulating relevant recommendations.[2]

Outcomes

Sayadi et al. did not define outcomes as part of an evidence search criteria. Reported outcomes of the evidence identified by this SR relevant to CDO therapy consisted of percentage of wounds healed, wound size, and wound infection checklist scores.[4]

Two RCTs reported well defined outcomes of proportion of complete wound closure, rate of wound closure, and adverse events occurring within the follow-up time of 12 weeks.[7,9,10] The smaller RCT reported wound volume reduction during the four week study along with biomarkers of wound healing and the cellular inflammatory response.[8]

IWGDF guidelines aimed to ensure inclusion of evidence on outcomes with critical importance to the healing of DFUs using a set of outcomes defined by Jeffcoate et al. in 2016.[2,16] These outcomes were ulcer healing, amputation, failure to heal, survival, health-related quality of life (HRQOL), and ulcer area change.[16] Outcomes considered when grading strength of recommendations consisted of benefits and harms, costs, and patient preferences.[15]

Summary of Critical Appraisal

Systematic Reviews

The SR included in this report conducted a comprehensive systematic literature search but did not justify a lack of meta-analysis, did not assess of publication bias, did not provide quantitative analysis of the identified evidence, lacked PICO formulated study questions and inclusion criteria, did not justify exclusion of studies, did not provide a list of excluded studies, or use an appropriate critical appraisal tool to evaluate the identified evidence. Sayadi et al. also failed to report funding sources or provide a conflict of interest statement.[4] The SR did provide a table of characteristics of included studies although it was not sufficiently detailed, conducted study selection in duplicate, and provided a PRISMA flowchart of literature selection. Importantly, unlike other SRs identified by the literature search strategy that were subsequently excluded for examining TWO2 as a single intervention, Sayadi et al. distinguished between CDO and TPOT interventions.

Clinical Studies

The three included primary clinical studies were RCTs,[7-10] two of which were sufficiently powered, double-blind, and sham device controlled.[7,9,10] All three studies were funded by device manufacturers and had an acknowledged conflict of interest.[7-10] The two more recently published and sufficiently powered RCTs also had significant loss-to-follow up but accounted for missing data with appropriate intention-to-treat (ITT) analysis.[7,9,10] It is not clear that ITT analysis sufficiently accounted for the significant loss to follow-up. Niederauer et al. reported 27% and Driver et al. reported 49% patient attrition. The most common reason for attrition in Neiderauer et al. was adverse event related while in Driver et al. the

most common reason was categorized as 'discontinued intervention.' Similar attrition from both treatment groups was observed in both studies.[7,9,10] Driver et al. did not justify including dropouts in the per-protocol analysis, and excluded only patients that had a major protocol violation. Neiderauer et al. did not comment on the potential impact of attrition and Driver et al. stated that the loss to follow-up was found acceptable. Both RCTs anticipated high attrition and according to their analysis the studies remained sufficiently powered, despite the observed high attrition. These studies also did not report how compliance was determined or if patients were provided training for the use of the study device intervention. In all other respects, both Driver et al. (2017) and Niederauer et al. were well conducted RCTs, with well reported and complete methodology provided on randomization, blinding, allocation concealment, intervention, outcomes, statistical methods, CONSORT diagrams for patient recruitment and follow-up, tabulated baseline patient characteristics and sufficient adverse event reporting and discussion.[7,9,10] Both multicenter studies were conducted with methodologies that may make findings relevant to the Canadian healthcare system, however the enrollment criteria of both studies may limit the applicability to patient populations with DFUs and without other commonly associated comorbidities. Driver et al. also included device malfunction data.[7]

The smaller unblinded RCT reported by Driver et al. in 2013 had some additional limitations including a lack of CONSORT diagram, insufficient statistical power, and no adverse event data or discussion. This RCT however provided tabulated baseline patient characteristics, statistical methods, randomization methods, defined patient eligibility, defined intervention, defined outcomes, and a discussion on the limitations of the study. Additionally, this small RCT observed no loss to follow-up.

Guidelines

The IWGDF guidelines,[2] were supported by a separately published systematic review published by Vas et al.[17]Additional methodology for the development of the IWGDF guidelines were also published separately.[15] The methodology described in these three publications was critically appraised using the AGREE II instrument.[6] The IWGDF guidelines provided specific objectives, health questions, patient population, and target audience for the formulated guidelines. The guideline also provided clear, unambiguous, easily identifiable recommendations that were linked to the supporting evidence. Much of the methodology was described generally, including in the separately published methodology, without specific information such as search terms however a systematic literature search was described. General methodology was also provided for the formulation of recommendations, consideration of benefits and harms, external review by experts, guideline updating, and consideration of potential resource implications. Methodology for seeking views and preferences of the population of interest, input from relevant professional groups, alternative options for management, facilitators and barriers to application, information on implementation, monitoring or auditing were not described. The IWGDF guidelines were developed with unrestricted grant support from several industry sponsors that did not have any communication with the working group during guideline development, nor access to any guidelines prior to publication. Competing interests of individual authors however were reported elsewhere and it was unclear if conflicts, if any existed, were addressed.[2]

Additional details regarding the strengths and limitations of included publications are provided in Appendix 3.

Summary of Findings

A tabulated summary of findings is also provided in Appendix 4.

Clinical Effectiveness of CDO

The identified evidence on the clinical efficacy of CDO included in the SR by Sayadi et al. consisted of three primary clinical studies. The SR included and discussed a small RCT that enrolled 20 patients and was published in 2016 by Yu et al. Patients with DFUs were randomized to receive CDO or SOC and assessed weekly for eight weeks.[14] Sayadi et al. summarized the percentage of all wounds completely healed at eight weeks noting that 90% of CDO treated wounds were completely healed as compared to only 30% of SOC treated wounds. Additionally, Sayadi et al. reported that there was a statistically significant decreased mean wound size from baseline in CDO patients but not in SOC treated patients.[4] Sayadi et al. also included and discussed two additional small case series.[4] Woo et al. examined a series of patients with DFUs, postsurgical ulcers, or venous leg ulcers. This study observed statistically significant decreases in wound surface area and wound infection checklist score following four weeks of CDO treatment of nine patients.[4,13] Banks and Ho observed an improvement in dimensions and volume of stage IV pressure ulcers in three patients that received CDO treatment.[4,12] Based upon the identified evidence Sayadi et al. concluded that larger studies were required to make conclusions regarding CDO.[4,12]

The two double-blind RCTs retrieved and reviewed for this report conflicted in their clinical efficacy findings and author's conclusions regarding CDO treatment of DFUs.[7,9,10] Neiderauer et al. observed statistically significant increases in the proportion of full wound closure, a greater rate of closure, and no increased adverse events following 12 weeks of CDO treatment as compared to patients treated with a sham device.[9,10] Driver et al. examined comparable12-week outcomes in a similar patient population and did not observe statistically significant differences in the proportion of closed wounds, rate of wound closure, or adverse events in patient DFUs treated with CDO as compared to sham device.[7] The reason for these conflicting findings is unclear. Subgroup analysis by Driver et al. found a statistically significant improved DFU closure rate for patients over 65 years old with CDO treatment while subgroup analysis by Niederauer et al. found a statistically significant improved DFU closure rate for weight-bearing DFUs but not non-weight-bearing DFUs, as well as limited evidence that more chronic wounds may be more effectively treated with CDO.[7,9,10] These findings suggest that future studies could focus on more specific patient populations that are more likely to benefit from CDO treatment of DFUs.

A smaller RCT that enrolled 17 patients with DFUs was reported by Driver et al. in 2013. This study observed a statistically significant decrease in wound volume following four weeks of CDO as compared to SOC.[8]

Cost-Effectiveness

No cost-effectiveness evidence for CDO were identified.

Guidelines

The IWGDF guidelines utilized evidence from a SR authored by Vas et al. published in 2020 to formulate recommendations. The strength of the recommendation on TWO2 was graded as weak and was based upon a quality of evidence rated as low. The IWGDF suggests not using TWO2 therapy as a primary or adjunctive intervention for DFUs.[2] The authors noted that the best quality of evidence comes from recently published double-blind

RCTs,[7,10] and that these studies observed conflicting results regarding the clinical efficacy of CDO for patients with DFUs.[2,17]

Limitations

The body of evidence included in this report was limited by a lack of identified consensus in the primary clinical study evidence. The majority of the identified evidence on CDO was as treatment for patients with DFUs and high-quality evidence for clinical efficacy of CDO on patients with other chronic wounds was lacking. Additionally, the guidelines did not distinguish between CDO and TCOT when formulating recommendations based upon the combined evidence. While the lack of distinction between CDO and TCOT conclusions was possibly appropriate, no rationale was provided and therefore there is some uncertainty to the degree to which conclusions are relevant to CDO as compared generally to TWO2 therapy for wound healing. The identified guidelines were international in scope however their applicability to the Canadian healthcare system was not clear.

Conclusions and Implications for Decision or Policy Making

This report identified one SR that retrieved and reviewed the evidence regarding CDO clinical efficacy.[4] The identified evidence in this SR by Sayadi et al. identified evidence published as recently as 2016 which included a small RCT (n = 20) and two small case series (n = 9 and n = 3).[12-14] These studies demonstrated that CDO improved healing of chronic wounds, including DFUs, stage IV pressure ulcers, postsurgical ulcers, and venous leg ulcers. The authors concluded that larger studies were required to evaluate the limitations of CDO. Two larger well-conducted RCTs (n = 146 and n = 130) were subsequently published in 2017 and 2018 that examined the clinical efficacy of CDO for the treatment of patients with DFUs. These two double-blinded RCTs studies were similar with regard to all PICO elements in addition to follow-up time and sample size. Both studies were industry funded studies that suffered from patient attrition of over 25%, greatly increasing the probability of attrition bias. Otherwise these RCTs had few limitations. A prior unblinded RCT with more significant limitations was published by Driver et al. in 2013 and observed a higher average wound closure with CDO as compared to SOC for DFUs. The findings of these studies conflicted with regard to the clinical efficacy of CDO for the treatment of DFUs. While the results suggest potential sources of the conflicting findings, including wound severity and patient attrition bias, more studies are required to resolve this conflicting efficacy evidence. Both large RCTs observed evidence that the subset of patients with DFUs most likely to benefit from CDO therapy could be better defined in future studies. Ad-hoc analyses suggested that patients over 65 years old and patients with weight-bearing DFUs experienced statistically significant improved outcomes with CDO treatment.[7,9,10] With regard to the safety of DFU treatment, both large RCTs demonstrated that CDO was safe when compared to a sham device in this patient population with limited comorbidities.[7,9,10]

Prior CADTH research on TWO2 therapy from 2012 identified a lack of RCT evidence from which to base an assessment of its role in wound treatment.[18] In this report additional evidence was identified that included evidence from two well conducted RCTs that enrolled over 100 patients.[7,10,17] These studies both examined CDO in patients with DFUs and the conflicting findings did not support any conclusions regarding the role of CDO in wound treatment. Further high-quality studies are required in order to resolve this conflicting evidence.

One relevant set of guidelines on TWO2for DFU healing was identified and included in this report.[2] Based on evidence that included the same two double-blind RCTs identified by in this report,[7,9,10] the IWGDF guidelines did not recommend the use of TWO2 for primary or adjunctive treatment of DFUs including for difficult to heal DFUs in a recommendation graded as weak.[2] No rationale was provided for the failure to distinguish between CDO and TPOT however clinical evidence of both TWO2 interventions for the treatment of DFUs was used in formulating the evidence-based recommendation.

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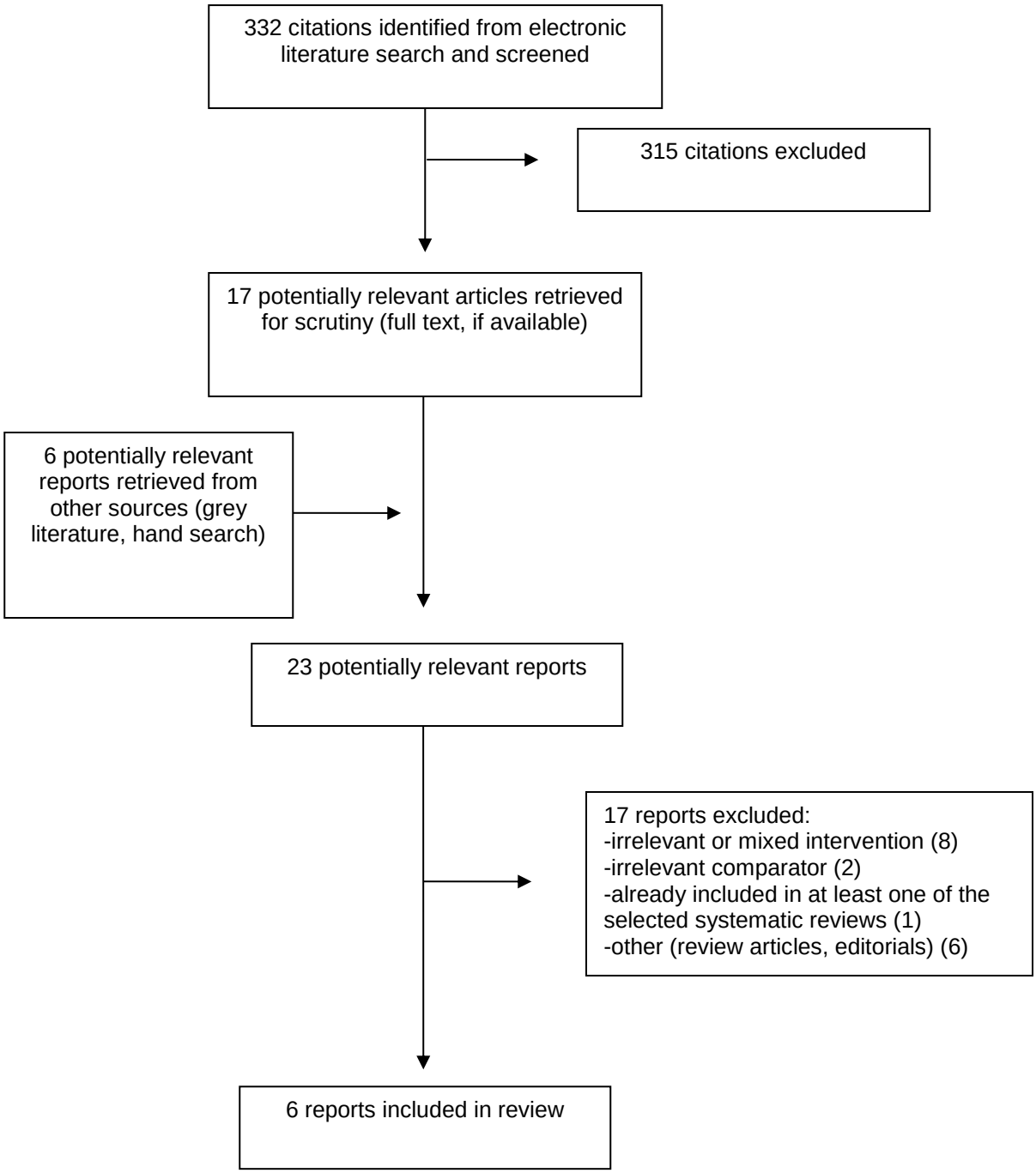
Appendix 1: Selection of Included Studies



Appendix 2: Characteristics of Included Publications

Table 2: Characteristics of Included Systematic Reviews

Study citation, country, funding source	Study designs and numbers of primary studies included	Population characteristics	Intervention and comparator(s)	Clinical outcomes
Systematic Review				
Sayadi et al. (2018)[4], US, funding not reported	CDO studies: 1 RCT[14] 2 Case series[12,13] 3 Pre-clinical studies	Patients with unhealed wounds	Micro/nanobubbles and TWO2 No comparator required	Undefined

CDO = continuously diffused oxygen; TWO2 = topical wound oxygen therapy; RCT = randomized controlled trial;

Table 3: Characteristics of Included Primary Clinical Studies

Study citation, country, funding source	Study design	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow-up
Neiderauer et al., 2017/2018[9,10], US, Industry funded study Two publications reported on the same study cohort. Neiderauer et al., 2017[9] reported the per-protocol analysis while Neiderauer et al., 2018[10] reported the intention-to-treat analysis	Double-blind, multicentre RCT (n = 146)	Patients (30 to 90 years old) with DFUs > 30 days, < 1 year old. DFUs > 1.5cm^{2,} < 10 cm^2 UTWCS Class 1A only TcO_2 and skin perfusion pressure > 30 mmHg, absolute toe pressure >30mmHg ABI>0.7 Able and willing to comply with off-loading regimen Exclusions: Malignancy, uncontrolled hyperglycaemia, unknown wound etiology, renal disease, alcohol or substance abuse, allergy to dressings, pregnancy, DVT, Hx or radiation or chemotherapy within 3 months or > 30% ulcer size decrease in run-in period	Intervention: TransCu O2 system (EO_2 Concepts, San Antonia, TX) **w/ O_2 flow rate to the wound at 3 mL/hr.** plus dressings and offloading which was preceded by SOC dressings, and debridement Weekly visits included assessment, debridement, dressing change, and reapplication of device. Dressings changed as needed by patient or caregiver Comparator: TransCu O2 system (EO_2 Concepts, San Antonia, TX) **w/ O_2 flow rate to the wound at 0 mL/hr**. plus dressings and offloading which was preceded by SOC dressings, and debridement Weekly visits included assessment, debridement, dressing change, and reapplication of sham device. Dressings changed as needed by patient or caregiver	● Complete wound closure ● Rate of closure ● Adverse Events Follow-up of 12 weeks with weekly assessments
Driver et al., 2017[7], US, Industry funded study	Double-blind, multicentre RCT (n = 130)	Patients (20 to 90 years old) with DFUs > 30 days, < 1 year old. DFUs > 1.0cm^{2,} < 10 cm^2	Intervention: TCOT device with MWT	● Complete wound closure ● Rate of closure ● Adverse Events

Study citation, country, funding source	Study design	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow-up
		TcO_2 and skin perfusion pressure > 40 mmHg, absolute toe pressure 40mmHg ABI>0.7 Able and willing to comply with off-loading regimen Exclusions: Malignancy, infection, uncontrolled hyperglycaemia, creatinine > 3mg/dL, unknown wound etiology, renal disease, alcohol or substance abuse, exposed bone, pregnancy, Hx or radiation or chemotherapy within 3 months or > 30% ulcer size decrease in run-in period	Device was changed every 15 days along with assessment and wound care treatment Dressings changed every 3 to 7 days Comparator: TCOT sham device (not oxygen generating) with MWT Device was changed every 15 days along with assessment and wound care treatment Dressings changed every 3 to 7 days	Follow-up of 12 weeks assessments every 15 days
Driver et al., 2013[8], US, Industry funded study	RCT (n = 17)	Patients (18 to 90 years old) DFUs > 0.5 cm^2, < 15 cm^2 TcO_2 and skin perfusion pressure > 30 mmHg ABI>0.6 Exclusions: Malignancy, infection, uncontrolled hyperglycaemia, end stage renal disease, severe liver disease, alcohol or substance abuse, pregnancy.	Intervention: TCOT device - Epiflo (Neogenix, LLC, Beachwood, OH) with SOC Device was changed every 15 days Comparator: SOC	● Wound volume reduction ● Biomarkers of healing by multiplex immunoassay ● Immuno-histochemistry of inflammatory response Follow-up of 4 weeks with weekly assessment

ABI = ankle/brachial index; DVT = deep vein thrombosis; MWT = moist wound therapy; RCT = randomized controlled trial; SOC = standard of care; TcO_2 = transcutaneous oxygen; TCOT = topical continuous oxygen therapy; UTWCS = University of Texas Wound Classification System

Table 4: Characteristics of Included Guidelines

Intended users, target population	Intervention and practice considered	Major outcomes considered	Evidence collection, selection, and synthesis	Evidence quality assessment	Recommendations development and evaluation	Guideline validation
IWGDF (2019)[2]						
Intended users: Clinicians, public agencies,	All interventions to enhance healing of chronic DFUs	● Ulcer healing ● Amputation ● Failure to heal	PICO-based systematic search and selection, working group	GRADE system using expert opinion in the absence of evidence	Recommendations based on quality of evidence and careful weighing of benefits and harms, patient	Reviewed by international experts and members of

Intended users, target population	Intervention and practice considered	Major outcomes considered	Evidence collection, selection, and synthesis	Evidence quality assessment	Recommendations development and evaluation	Guideline validation
policymakers, and other health care professionals **Target population:** Patients with diabetic foot ulcers		● Survival ● Adverse events ● HRQOL ● Ulcer area change	selection and synthesis of the included evidence	Rated: high, moderate, or low	preferences, and financial costs (resource utilization) Graded: strong or weak	the IWGDF Editorial Board

GRADE = Grading of Recommendations, Assessment, Development and Evaluation; DFU = diabetic foot ulcer; HRQOL = health-related quality of life; IWGDF = International Working Group on the Diabetic Foot; PICO = population, intervention, comparator, outcomes;

Appendix 3: Critical Appraisal of Included Publications

Table 5: Strengths and Limitations of Systematic Reviews Using AMSTAR 2[5]

Strengths	Limitations
Sayadi et al. (2018)[4]	
● Comprehensive systematic literature search performed ● Study selection and data extraction not performed in duplicate ● PRISMA flowchart of literature selection ● Distinction between pressurized and non-pressurized TWO2 interventions ● A table of limited study characteristics provided	● No meta-analysis ● No clear PICO formulated study questions and inclusion criteria ● Limited inclusion and exclusion criteria ● No reasons provided for study exclusion ● No list of excluded studies provided ● No critical appraisal conducted ● Limited synthesis of body of evidence and accounting for risk of bias ● No assessment of publication bias ● Findings described narratively with limited quantification ● Funding sources not provided ● No statement on potential conflicts of interest

PICO = population, intervention, comparator, outcomes; PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses; PROSPERO = International Prospective Register of Systematic Reviews

Table 6: Strengths and Limitations of Clinical Studies Using the Downs and Black checklist[19]

Strengths	Limitations
Neiderauer et al., 2017/2018[9,10]	
● Multicenter study ● CONSORT diagram for patient recruitment/enrollment ● Patient characteristics tabulated - no statistically significant differences between groups ● Allocation concealment methodology described ● Statistical methods described and appropriate ● Randomization methodology described ● Role of blinded investigators outlined ● Clearly defined patient eligibility ● Clearly defined intervention ● Clearly defined outcomes ● Statistical power determined a priori, unclear where outcome estimates are from ● Provided ITT analysis (included all drop-outs in primary outcome analysis) ● Adverse events discussed and quantified ● COI statement	● Industry funded study ● Significant loss to follow-up ● Very brief discussion on study limitations ● Unclear monitoring of compliance or information on patient device training
Driver et al., 2017[7]	
● Multicenter study ● CONSORT diagram for patient recruitment/enrollment ● Patient characteristics tabulated - no statistically significant differences between groups ● Allocation concealment methodology described ● Statistical methods described and appropriate	● Industry funded study ● Intervention not entirely consistent within treatment group (different dressings) ● Significant loss to follow-up ● Unclear monitoring of compliance or information on patient device training

Strengths	Limitations
● Randomization methodology described ● Role of blinded investigators outlined ● Clearly defined patient eligibility ● Clearly defined intervention ● Clearly defined outcomes ● Statistical power determined a priori, based upon cited prior studies ● Provided ITT analysis (included dropouts with at least one assessment in primary outcome analysis) ● Adverse events discussed and quantified ● Good discussion on study limitations ● COI statement	
Driver et al., 2013[8]	
● Patient characteristics tabulated - no statistically significant differences between groups ● Statistical methods described and appropriate ● Randomization methodology described ● Clearly defined patient eligibility ● Clearly defined intervention ● Clearly defined outcomes ● No loss to follow-up ● Good discussion on study limitations ● COI statement	● Industry funded study ● Single center study (perhaps limiting external validity) ● No CONSORT diagram for patient recruitment/enrollment ● Unblinded, open-label trial ● Underpowered study (no statistical power calculation) ● No discussion or quantification of adverse events ● Unclear monitoring of compliance or information on patient device training

COI = conflict of interest; CONSORT = Consolidated Standards of Reporting Trials

Table 7: Strengths and Limitations of Guideline Using AGREE II[6]

Item	Guideline
	IWGDF, 2019[2,15]
1. The overall objective(s) of the guideline is (are) specifically described.	Yes
2. The health question(s) covered by the guideline is (are) specifically described.	Yes
3. The population (patients, public, etc.) to whom the guideline is meant to apply is specifically described.	Yes
4. The guideline development group includes individuals from all relevant professional groups.	Unclear
5. The views and preferences of the target population (patients, public, etc.) have been sought.	No
6. The target users of the guideline are clearly defined.	Yes
7. Systematic methods were used to search for evidence.	Yes
8. The criteria for selecting the evidence are clearly described.	No
9. The strengths and limitations of the body of evidence are clearly described.	No
10. The methods for formulating the recommendations are clearly described.	Yes
11. The health benefits, side effects, and risks have been considered in formulating the recommendations.	Yes
12. There is an explicit link between the recommendations and the supporting evidence.	Yes
13. The guideline has been externally reviewed by experts prior to its publication.	Yes

Item	Guideline
	IWGDF, 2019[2,15]
14. A procedure for updating the guideline is provided.	Yes
15. The recommendations are specific and unambiguous.	Yes
16. The different options for management of the condition or health issue are clearly presented.	No
17. Key recommendations are easily identifiable.	Yes
18. The guideline describes facilitators and barriers to its application.	No
19. The guideline provides advice and/or tools on how the recommendations can be put into practice.	No
20. The potential resource implications of applying the recommendations have been considered.	Yes
21. The guideline presents monitoring and/or auditing criteria.	No
22. The views of the funding body have not influenced the content of the guideline.	Unclear
23. Competing interests of guideline development group members have been recorded and addressed.	No

AGREE II = Appraisal of Guidelines for Research and Evaluation II; IWGDF = International Working Group of the Diabetic Foot;

Appendix 4: Main Study Findings and Authors' Conclusions

Table 8: Summary of Findings Included Systematic Reviews

Main study findings	Authors' conclusion
Sayadi et al. (2018)[4]	
Yu et al., 2016 RCT (n = 20) NATROX (InotecAMD, Burlington, ON, Canada)[14] Percentage wounds healed at 8 weeks CDO 90% SOC 30% Statistically significant decrease in mean wound size compared with baseline measurements in CDO patients but not in SOC treated patients. **Woo et al., 2012 Case series (n = 9) Epiflo (Ogenix Corporation, Cleveland OH)[13]** Chronic wound surface area after 4 weeks ($P < 0.05$) Before 12.03 cm^2 After 9.60 cm^2 Chronic wound infection checklist score after 4 weeks ($P < 0.05$) Before 5.3 After 2.7 **Banks and Ho., 2008 Case series (n = 3) Epiflo (Ogenix Corporation, Cleveland OH)[12]** Improvement in dimensions and volume of stage IV pressure ulcers in three patients.	"Several small studies demonstrate that TCOT improves wound healing. However, much like TPOT, larger studies are needed to thoroughly investigate and assess its limitations. (p. 369)"[4]

CDO = continuously diffused oxygen; TCOT = topical continuous oxygen therapy; ITT = intention-to-treat; SOC = standard of care; TPOT = topical pressurized oxygen therapy; UTWCS = University of Texas wound classification system;

Table 9: Summary of Findings of Included Primary Clinical Studies

Main study findings	Authors' conclusion
Neiderauer et al., 2017/2018[9,10]	
Full wound closure at 12 weeks ITT - all treated ($P = 0.033$) CDO (n = 74) 32.4% Sham (n = 72) 16.7% RR (95% CI) 1.95 (1.05 to 3.59) ITT - all completed ($P = 0.016$) CDO (n = 52) 46.2% Sham (n = 53) 22.6% RR (95% CI) 2.04 (1.14 to 3.63) Per protocol ($P = 0.016$) CDO (n = 50) 46.0% Sham (n = 50) 22.0%	"In a fully blinded study, we report a significantly greater percentage of, and rate of, healing in patients receiving CDO therapy compared with a placebo device providing standard wound therapy with identical dressings, debridement and offloading. … Relative performance did not vary significantly with wound size but revealed better relative performance in more chronic wounds and in weight-bearing wounds." (p. S44)

Main study findings	Authors' conclusion
RR (95% CI) 2.09 (1.15 to 3.82) **Rate of closure** Days to 50% closure - all treated (*P* = 0.001) CDO (n = 40) 18.4 Sham (n = 37) 28.9 Days to 75% closure - all treated (*P* = 0.04) CDO (n = 34) 46.0% Sham (n = 25) 22.0% **Adverse Events** All Adverse Events - ITT (*P* = 0.66) CDO (n = 74) 14.9% Sham (n = 72) 18.1% Related to study wound - ITT (*P* = 0.30) CDO (n = 74) 8.1% Sham (n = 72) 13.9% Requiring hospitalization - ITT (*P* = 0.054) CDO (n = 74) 2.7% Sham (n = 72) 11.1% Gangrene - ITT (*P* = 0.24) CDO (n = 74) 0.0% Sham (n = 72) 2.8% **Subgroup analysis** **Weight-bearing DFUs** **Full wound closure at 12 weeks** ITT - all treated (*P* = 0.003) CDO (n = 59) 33.9% Sham (n = 53) 7.55% RR (95% CI) 4.49 (1.64 to 12.3) **Non-weight-bearing DFUs** **Full wound closure at 12 weeks** ITT - all treated (*P* = 0.37) CDO (n = 15) 26.67% Sham (n = 19) 42.11% RR (95% CI) 0.63 (0.24 to 1.71) "There was increasing significant beneficial effect of the CDO arm at 25%/40% PWAR (p=0.017) and 20%/30% PWAR (p=0.008)." (p. S39) PWAR is the run-in wound closure rate and lower PWAR indicates a more chronic wound.	
Driver et al., 2017[7]	
Full wound closure at 12 weeks ITT - all treated (*P* = 0.4167) CDO (n = 65) 53.8% Sham (n = 63) 49.2%	"The TCOT device tested in a well-conducted, blinded, RCT in conjunction with SC does not appear to offer added benefit over SC in the healing of small, nonsevere DFUs in relatively healthy patients. However, the device may offer a greater benefit to older patients. Future research should concentrate

Main study findings	Authors' conclusion
ITT - age ≥ 65 years (*P* = 0.0723) CDO (n = 19) 78.9% Sham (n = 16) 50.0% PP - all treated (*P* > 0.05) CDO (n = 61) 55.7% Sham (n = 61) 50.8% PP - age ≥ 65 years (*P* = 0.049) CDO (n = 17) 82% Sham (n = 16) 50% **Rate of closure** Days to 100% closure - PP Kaplan-Meier estimate (*P* > 0.05) CDO (n = 61) 63 Sham (n = 61) 77 Days to 100% closure - PP age ≥ 65 years Kaplan-Meier estimate (*P* = 0.139) CDO (n = 19) 35 Sham (n = 16) 70 **Adverse Events** All Adverse Events - Safety population (*P* > 0.05) CDO (n = 64) 27 Sham (n = 66) 14	on patients with larger, more severe wounds and more severe comorbidities to determine whether TCOT would benefit the healing of their wounds." (p. 28) "It is worth noting that in calculating the sample size for the trial, a standard 30% healing rate for DFU was used based on 6 different prior publications. In this study, approximately 50% of wounds healed in both treatment arms. Safety analysis demonstrated no significant differences in the AEs between the 2 arms; the TCOT device was safe." (p. 26)
Driver et al., 2013[8]	
Wound volume reduction at 4 weeks Percentage of volume remaining compared to baseline ± SD (*P* ≤ 0.05) CDO (n = 9) 21.8 ± 20.0% SOC (n = 8) 49.2 ± 52.3%	"The results of this study show that TCOT may facilitate healing of DFUs by reversing the inflammatory process through reduction in pro-inflammatory cytokines and tissue-degrading proteases. Additional research to elucidate the effects of this treatment on complete healing and increase understanding about the role of wound fluid analysis is needed." (p 19)

CDO = continuously diffused oxygen; CI = confidence interval; ITT = intention-to-treat; PP = per protocol; PWAR = percentage wound area reduction; SD = standard deviation; TCOT = topical continuous oxygen therapy

Table 10: Summary of Recommendations in Included Guideline

Recommendations and supporting evidence	Quality of evidence and strength of recommendations
IWGDF, 2019[2]	
"**We suggest not using topical oxygen therapy as a primary or adjunctive intervention in diabetic foot ulcers including those that are difficult to heal**" (pp. 2) While two earlier nonrandomized studies demonstrated apparent benefit,[20,21] two subsequently published larger, blinded RCTs at low risk of bias observed conflicting results.[7,10]	Quality of Evidence: Low Strength of Recommendation: Weak

RCT = randomized controlled trial;

Appendix 5: Overlap of Evidence between Included Articles

Table 11: Overlap in Relevant Primary Studies between Included SRs and Guidelines

Primary clinical study citation	Systematic Review and Guideline citation	
	Sayadi et al., 2018[4]	IWGDF Guidelines[2]
CDO		
Niederauer et al., 2018[10]		✓
Niederauer et al., 2017[9]		✓
Driver et al., 2017[7]		✓
*Yu et al., 2016[14]	✓	
**Driver et al., 2013[8]		
*Woo et al., 2012[13]	✓	
*Banks and Ho, 2008[12]	✓	

* these studies were not included in this report as separate studies as they were included in the systematic review by Syadi et al.

** this study was not included in either the systematic review or guidelines but is included as an individual primary study in this report.