Evidence in Context

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Health research — synthesized and contextualized for use in Newfoundland & Labrador

2019 Evidence Update:

Hyperbaric Oxygen Therapy for Difficult Wound Healing in Newfoundland & Labrador

Wendy Lasisi, Pablo Navarro

Newfoundland & Labrador Centre for APPLIED HEALTH RESEARCH
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Glossary

Adjunctive Hyperbaric Oxygen Therapy	Hyperbaric Oxygen Therapy that is used to supplement or to add to other treatment modalities rather than being the sole treatment used.
Adverse events	An unexpected medical problem that happens during treatment with a drug or therapy.
AMSTAR	An 11-item instrument used to assess the methodological rigor of systematic reviews.
Bone continuity	Unbroken connection of bone.
Brachial plexopathy	Disease arising from damage to the nerves that extend to the shoulder, arm and hand.
Delayed radiation-induced injury (DRII)	Injury arising from any form of radiation therapy for cancer.
Diabetic foot ulcer (DFU)	Common foot problems in persons with Diabetes Mellitus, caused by a combination of factors that often lead to severe foot ulceration, gangrene and amputation.
Graft survival	Probability of graft functioning after transplant.
Hyperbaric oxygen treatment (HBOT)	The therapeutic intermittent administration of oxygen in a chamber at greater than sea-level atmospheric pressures (three atmospheres).
Implant failure	Loss of dental implant or failure to fulfil its purpose.
Ischemic DFU	Diabetic foot ulcer in patients with restriction in blood supply to the affected tissue.
Major amputation	Removal of all or part of a limb above the wrist or ankle.
Minor amputation	Removal of all or part of a hand or foot.
Mucosal cover	Mucous membrane that covers cavities in the body.
Non-Ischemic DFU	Diabetic foot ulcers in patients with adequate blood circulation to the affected tissue.
Osteoradionecrosis	Necrosis/tissue death of bone as a result of exposure to radiation.
Post-implantation complication	Unexpected problem that arises after implantation.
Post-organ transplantation revascularization	Restoration of blood flow following organ transplantation.
Pressure ulcer	Ulcerations caused by prolonged pressure on the skin and tissues when one stays in one position for a long period of time.
Radiation proctitis	Inflammation and damage to the lower parts of the colon after exposure to x-rays and radiation.
Radiation rectitis	Another term for radiation proctitis.
Skin graft	Skin for grafting that is wholly removed from one part of the body and transferred to another site.
Skin flap	Skin from grafting that is only partially removed from one part of the body so that it retains its own blood supply during transfer to another site.
SF-36	36-item health survey used to measure quality of life.
SOMA-LENT	A scale used to measure Late Effects on Normal Tissue (LENT) from radiation therapy, from several perspectives: Subjective, Objective, Management, and Analytical (SOMA).
Thermal burns	Injury resulting from the skin making contact with heated objects.
Transcutaneous oxygen tension	Oxygen level of the tissue under the skin.
Unknown perfusion DFU	Diabetic foot ulcer in patients in which blood circulation is undetermined.
Wagner Grade	Grading systems used to score severity of diabetic foot ulcers.
Wound dehiscence	Rupturing of wound along a surgical incision.

Background

In 2012, the Contextualized Health Research Synthesis Program (CHRSP), in partnership with health system partners in Newfoundland and Labrador and the Canadian Agency for Drugs in Technology and Health (CADTH), published a contextualized health evidence synthesis report on the clinical and cost effectiveness of hyperbaric oxygen therapy (HBOT) for difficult wound healing in Newfoundland and Labrador (1). For the 2012 study, the Project Team was led by Pablo Navarro, Research Officer and CHRSP Project Coordinator at the Newfoundland and Labrador Centre for Applied Health Research (NLCAHR) and by Rhonda Boudreau, Research Officer at CADTH. That report is published online.[1]

To provide decision makers with more recent evidence on this topic, the current report updates our original synthesis with evidence from moderate to high quality systematic reviews[2] published since 2010. Furthermore, this study was undertaken with an updated version of the CHRSP methodology (2), including a new CHRSP Evidence Rating System (ERS).

The CHRSP Evidence Rating System assesses the strength of the combined body of evidence for a particular intervention to achieve a given outcome for a defined population. The strength of the body of evidence increases with the quality of the systematic reviews included in the analysis, the number of unique primary research studies included within the reviews, and the consistency of the findings. We use the AMSTAR instrument (3,4) to appraise the methodological quality of systematic reviews (5) and to categorize systematic reviews in terms of their methodological quality: An AMSTAR Score of 0 to 3 indicates Low Quality; an AMSTAR Score of 4 to 7 indicates Moderate Quality; and an AMSTAR Score of 8 to 11 indicates High Quality.

Largely inconsistent findings, regardless of the number and quality of systematic reviews, are interpreted as a "Very Weak" body of evidence by default (see Table 1).

Strength of the Body of Evidence	# of Systematic Reviews	# of Primary Studies included in the review literature
Strong	2 or more High Quality reviews	10+
Moderate	1 or more High Quality reviews	10+
Weak	1 or more High Quality reviews	5+
Very Weak	1 review with moderate or inconsistent findings	1-4

Table 1: CHRSP ERS: Evidence thresholds for strength of body of evidence

The CHRSP Evidence Rating System also considers whether the body of evidence: favors the intervention (i.e., the evidence indicates that the intervention works effectively enough to consider implementing it); indicates no benefit when the intervention is compared to the control (i.e., the intervention is no better than usual care); or is unable to indicate whether the intervention achieves better outcomes than the control (i.e., the report authors cannot draw any conclusions because there is a lack of evidence or there is conflicting evidence).

[1] https://www.nlcahr.mun.ca/CHRSP/HBOT.php

[2] A systematic review is a summary of results from available primary research studies (e.g., controlled trials) that provides decision makers with a high level of evidence on the effectiveness of healthcare interventions.

Research Question

The following research question was posed in the original 2012 *Evidence in Context* report on this topic and it remains the research question for this 2019 Evidence Update:

"What does the scientific literature tell us about the clinical and economic effectiveness of hyperbaric oxygen therapy for difficult wound healing (i.e., diabetic and non-diabetic pressure ulcers, delayed radiation-induced injury, thermal burns, skin grafts, and post-organ transplantation revascularization) considering the expected patient populations and given the social, geographic, economic and political contexts of Newfoundland and Labrador?"

Summary of key findings and their implications for decision makers

The findings of this update are consistent with those of the original report and indicate that, overall, more high-quality research is needed in this area. The following summarizes our key findings:

- As a treatment for diabetic foot ulcers, a strong body of evidence indicates that HBOT does not reduce minor amputations whereas weak evidence points to its effectiveness in reducing major amputations. These findings may be attributed to the fact that those undergoing a minor amputation will no longer require a major amputation (as a result, minor amputations do not decrease but major amputations do). A strong body of evidence shows that HBOT, as adjunctive therapy, is significantly more effective than usual care to reduce the severity of non-healing diabetic foot ulcers.

- HBOT has been shown to be clinically-effective in the treatment of delayed radiation-induced injuries of the head and neck and of the pelvic regions by improving wound healing and quality of life. The economic effectiveness of HBOT for treating these wounds is unknown.

- The benefits of HBOT for wound healing will depend on the severity of the injury and on the timeliness of treatment.

- There is insufficient evidence to determine the clinical or economic effectiveness of HBOT for the treatment of non-diabetic pressure ulcers, thermal burns, skin grafts and flaps, and post-organ transplantation revascularization.

- More research is needed to determine the effectiveness of HBOT for healing a variety of wounds and decision makers can expect future studies to have an impact on the body of evidence for the effectiveness of HBOT to treat conditions for which there is insufficient evidence at present.

- Monitoring and documenting patient outcomes at the St. John's Hyperbaric Oxygen facility in Eastern Health will support future decisions about the most suitable patient populations for Hyperbaric Oxygen Therapy.

Evidence included in this report

This report includes the results from 19 systematic reviews and one health technology assessment. Eight of the included studies were rated as being of "High Quality" and twelve were of "Moderate Quality." We also found 18 reviews that were rated as being of "Low Quality" and were therefore excluded from our synthesis. The inter-rater reliability for appraising methodological quality was 0.81, which is considered high (6). Table 2 below summarizes our appraisal of the evidence for this update.

Methodological Quality	Reference	AMSTAR Score	Was it a Cochrane Review?
High Quality (8 included studies)	**Bennett 2016** (7)	81.82	Yes
	Elraiyah 2016 (8)	90.91	No
	Eskes 2013 (9)	100.00	Yes
	Esposito 2013 (10)	90.91	Yes
	Kranke 2015 (11)	81.82	Yes
	Liu 2013 (12)	72.73	No
	Rollason 2016 (13)	90.91	Yes
	van de Weterring 2016 (14)	90.91	Yes
Moderate Quality (12 included studies)	**Cardinal 2018** (15)	54.44	No
	Game 2016 (16)	54.55	No
	Hoggan 2014 (17)	63.64	No
	Huang 2015 (18)	45.45	No
	HQO 2017 (19)	54.55	No
	Lauvrak 2015 (20)	54.55	No
	O'Reilly 2013 (21)	63.64	No
	Peters 2016 (22)	54.55	No
	Reddy 2015 (23)	45.45	No
	Santema 2015 (24)	45.45	No
	Stoekenbroek 2014 (25)	63.64	No
	Zhao 2017(26)	63.64	No
Low Quality (18 excluded studies)	Allen 2013 (27)	9.09	No
	Borab 2017 (28)	36.36	No
	Braun 2014 (29)	0.00	No
	Craighead 2011 (30)	18.18	No
	Dauwe 2014 (31)	27.27	No
	Fox 2015 (32)	18.18	No
	Fritz 2010 (33)	0.00	No
	Gibson 2013 (34)	18.18	No
	Hanson 2012 (35)	27.27	No
	Hunt 2011 (36)	36.36	No
	Jensen 2011 (37)	18.18	No
	Lovelace 2014 (38)	9.09	No
	Nabil 2010 (39)	36.36	No
	Nelamangala 2016 (40)	0.00	No
	Payne 2013 (41)	9.09	No
	Peterson 2010 (42)	9.09	No
	Ravi 2017 (43)	9.09	No
	Spiegelberg 2010 (44)	0.00	No

Table 2: Critical appraisal results for eligible systematic reviews

Please see the Online Companion Document for details about our methodology for searching and filtering, data extraction and synthesis.

Overview of the evidence

In the original 2012 report on this topic, we noted that the systematic review evidence summarized relatively few primary research studies on HBOT for difficult wounds; moreover, we noted that the included research could be characterized as having methodological weaknesses, small sample sizes, and inadequate follow-up. Overall, the evidence in 2012 pointed to the need for more high-quality primary research and subsequent systematic reviews / meta-analyses to support any firm conclusions.

When searching for systematic reviews to include in this 2019 update, we noted that the number of reviews about HBOT for difficult wounds had increased significantly between 2010 and 2018:

- the 2012 report included studies from 2005 to 2010 and identified **13** systematic reviews (2.2 publications/year);
- this 2019 update spans the period from 2011 to 2018 and identified **38** systematic reviews (4.2 publications/year), almost twice the rate of systematic review publications per year.

We analyzed the new systematic review evidence to find out whether this dramatic increase in publications reflects an actual increase in primary research studies on this topic or if it represents an increase in systematic reviews that summarize many of the same primary studies (i.e., we asked if more original primary research had been carried out on the topic or if there were simply more reviews of the same research). Figures 1 and 2 below show our analysis of the number of unique primary research studies included in reviews included in the 2012 report and the number of primary studies included in this 2019 Evidence Update (45).

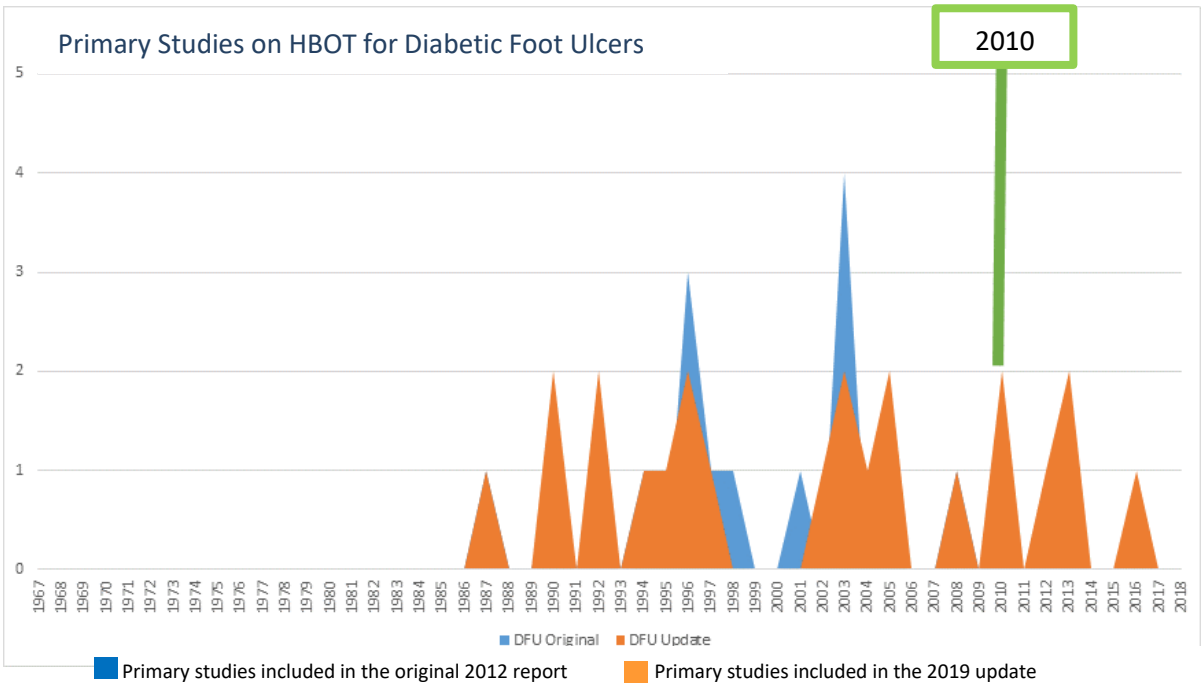

Figure 1: Number of unique primary studies of HBOT for Diabetic Foot Ulcers from included systematic reviews.

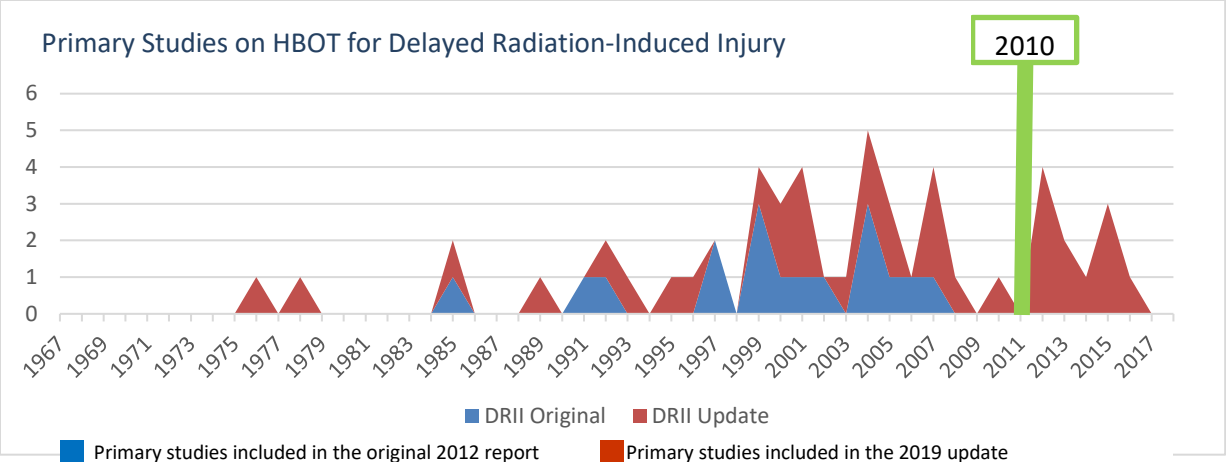

Figure 2: Number of unique primary studies of HBOT for Delayed Radiation-Induced Injuries from included systematic reviews.

Unfortunately, our analysis indicates that the increase in systematic review publications was **not** the result of a similar increase in the number of primary research studies since 2010. While we found some new primary research studies in the review literature, most studies that were included in the new systematic reviews were published prior to 2010; this seems to indicate that systematic review authors have gotten better at identifying primary research: by more thorough search techniques; by improved access to journals and/or trials; and, possibly, by having fewer restrictions on the language of publication.

Wound types studied in 2012 and in this update

The 2012 report studied HBOT for treating five different types of difficult wounds:

1. diabetic and non-diabetic pressure ulcers,
2. delayed radiation-induced injury,
3. thermal burns,
4. skin grafts and flaps, and
5. post-organ transplantation revascularization.

This update will address the first four types of wounds. Post-organ transplantation revascularization is excluded: this procedure is not carried out in Newfoundland and Labrador and is, therefore, not directly relevant. There was also a lack of evidence on this topic.

HBOT for Diabetic and Non-Diabetic Pressure Ulcers

For this update, we identified thirteen new systematic reviews studying the effectiveness of HBOT to treat diabetic and non-diabetic pressure ulcers. Three of the reviews were AMSTAR-rated as being of "High Quality" and ten as being of "Moderate Quality." In the original report, we noted some inconsistencies in the terminology: PubMed does not include a Medical Subject Heading (MeSH) for 'diabetic pressure ulcer' but does include the terms 'pressure ulcer' and 'diabetic foot ulcer.' These two

terms describe different wounds, produced by different mechanisms. The literature still refers almost exclusively to *diabetic foot ulcers* as defined by PubMed.[3] Ultimately, we used combinations of these terms, along with others that are descriptive of skin ulcers, to identify evidence for this category of wound healing (see the Online Companion Document for details). The available literature for this update focuses mainly on diabetic foot ulcers (DFU), as it did when the original report was carried out.

The main clinical outcomes of interest for diabetic foot ulcers were major amputation, minor amputation,[4] wound healing, and wound-size reduction. Other outcomes lacked robust evidence, but they included cost effectiveness, adverse events, resolution of infections, time to heal, length of stay, mortality, quality of life and transcutaneous oxygen tensions. The findings for these outcomes are updated below.

HBOT to reduce major amputation in diabetic foot ulcers

We identified ten systematic reviews: three high-quality studies (8,11,12) and seven moderate-quality studies (18–22,25,26) that reported on HBOT as an intervention to reduce major amputation from diabetic foot ulcers. All but one of these reviews (25) considered all types of diabetic foot ulcers together. Overall, we found a very weak body of evidence showing HBOT as having a positive effect in reducing major amputation from diabetic foot ulcers. This "very weak" rating results from numerous disagreements between the high-quality and moderate-quality reviews.

The highest-rated Cochrane Review on this topic (11) reported no difference between HBOT and a control group. The two other high-quality reviews (8,12) favored HBOT over usual care. While the Cochrane Review based its conclusions on five randomized controlled trials (RCTs), the two other reviews (8,12) based their conclusions on the same trials plus nine additional observational studies. Moreover, using the rationale that one trial had not employed a control group and had a high risk of bias, the Cochrane Review authors weighted the RCT with the largest number of participants considerably lower than the other reviewers (8, 12) weighted the same study. Compounding this disagreement, the moderate-quality reviews (18–22,26) produced a weak body of evidence showing no difference in major amputation between HBOT and usual care. It is also worth noting that three reviews (11,18,25) categorized diabetic foot ulcers by their mechanisms or by Wagner Grades and that these reviews also produced a weak body of evidence showing no difference in major amputation rates, with the exception of Wagner Grade 2 or lower, where HBOT was favored over usual care to reduce major amputations. As a result of so many conflicting findings, all reviews taken together can produce only a very weak body of evidence that HBOT decreases major amputations caused by diabetic foot ulcers (See Table 3).

Overall, we found a very weak body of evidence showing HBOT as having a positive effect in reducing major amputation from diabetic foot ulcers.

[3] Pubmed's Medical Subject Heading defines diabetic foot ulcers as *"common foot problems in persons with diabetes mellitus, caused by any combination of factors,"* but does not include pressure as one of the causes.

[4] A *major* amputation is the removal of all or part of a limb from above the wrist or ankle. A *minor* amputation is defined as the removal of all or part of a hand or foot.

As in the original report, this finding may be subject to change once more high-quality primary research is undertaken on this issue.

Evidence Summary: HBOT to reduce major amputation in diabetic foot ulcers (DFU)		
Population	**Strength of body of evidence**	**Finding**
Diabetic Foot Ulcers	**Very weak**	**Positive effect**
Ischemic DFU	Weak	No difference
Non-Ischemic DFU	Weak	No difference
Unknown Perfusion	Weak	No difference
Wagner Grade 2 or lower	Weak	Positive effect
Wagner Grade 3 or higher	Weak	No difference

Table 3: Evidence for clinical effectiveness of HBOT for major amputation in diabetic foot ulcers

HBOT to reduce minor amputation from diabetic foot ulcers

We identified nine systematic reviews, consisting of two high-quality studies (11,12) and seven moderate- quality studies (18–22,25,26) that reported on minor amputation from diabetic foot ulcers. Eight reviews (11,12,18–22,26) considered all types of diabetic foot ulcers and produced a strong body of evidence showing no difference between HBOT and usual care to reduce the likelihood of minor amputation. Two reviews (12,25) categorized diabetic foot ulcers by their mechanisms or Wagner Grades, and produced a weak body of evidence also showing no difference in minor amputation with HBOT, with the exception of Wagner Grade 2 or lower where it favors HBOT (See Table 4).

The 2012 report indicated a possible *increase* in the risk of minor amputation as a paradoxical consequence of the reduction in the risk for major amputation.[5] Again, this finding was sensitive to change with further research.

The 2019 update differs from the original report in this regard: the most up-to-date research provides a strong body of evidence showing that there is *no difference* in minor amputation rates with HBOT in diabetic foot ulcers.

Evidence Summary: HBOT to reduce minor amputation in diabetic foot ulcers		
Population	**Strength of body of evidence**	**Finding**
Diabetic Foot Ulcers	**Strong**	**No difference**
Ischemic DFU	Weak	No difference
Non-Ischemic DFU	Weak	No difference
Unknown Perfusion DFU	Weak	No difference
Wagner Grade 2 or lower DFU	Weak	Positive effect
Wagner Grade 3 or higher DFU	Weak	No difference

Table 4: Evidence for clinical effectiveness of HBOT for minor amputation in diabetic foot ulcers

HBOT for healing wounds in diabetic foot ulcers

Our update identified ten systematic reviews, consisting of three high quality studies (8,11,12) and six moderate quality studies (16,18,19,21,24–26) that reported on HBOT for wound healing in diabetic foot ulcers. Six reviews (11,12,16,19,21,26) considered all types of diabetic foot ulcers and produced a strong

[5] The paradoxical consequence from the original report stated that, possibly and plausibly, having undergone HBOT treatment, a patient who might otherwise have required a major amputation would now require only a minor amputation. As a result, HBOT, as a therapy, might have been seen as linked statistically to an increased incidence of minor amputations because it had decreased the incidence of major amputation.

body of evidence showing a positive effect of HBOT in wound healing, although there were some disagreements between the high-quality and moderate-quality reviews.

Two high-quality reviews (11,12) found a positive effect for HBOT to improve wound healing, but four moderate-quality reviews (16,19,21,26) were split, with two finding a positive effect (16,19) and two finding no difference (21,26). When all the reviews are considered together, they produce a strong body of evidence showing a positive effect for HBOT in healing wounds from diabetic foot ulcers. This positive effect is reported as most evident at up to six months post-treatment as shown by two high-quality reviews (11,12). Four reviews (11,18,24,25) categorized diabetic foot ulcers by their mechanisms or Wagner Grades, and produced a weak body of evidence showing a positive effect in most categories, with the exception of non-ischemic diabetic foot ulcers and mixed ulcers where they showed no difference (See Table 5).

This update re-affirms the findings from our original 2012 report by providing a strong body of evidence that finds that HBOT improves wound healing in diabetic foot ulcers.

Evidence Summary: HBOT for wound healing in diabetic foot ulcers		
Population	**Strength of body of evidence**	**Finding**
Diabetic Foot Ulcers	**Strong**	**Positive effect**
Ischemic DFU	Weak	Positive effect
Non-Ischemic DFU	Weak	No difference
Unknown Perfusion DFU	Weak	Positive effect
Wagner Grade 2 or lower DFU	Weak	Positive effect
Mixed Ulcers	Weak	No difference
Wound healing at 6 months or less		
Diabetic Foot Ulcers	**Strong**	**Positive effect**
Venous Ulcers	Weak	Positive effect
Wound healing at 1 year or less		
Ischemic DFU	Weak	Positive effect
Wagner Grade 3 or higher DFU	Weak	Positive effect

Table 5: Evidence for clinical effectiveness of HBOT for wound healing in diabetic foot ulcers

HBOT to reduce wound size in diabetic foot ulcers

We found five systematic reviews, consisting of one high-quality study (11) and four moderate-quality studies (19,21,25,26) that reported on wound-size reduction in diabetic foot ulcers. Four reviews (11,19,21,26) considered all types of diabetic foot ulcers and produced a weak body of evidence showing a positive effect, but no difference at six months or fewer, post-treatment. Two reviews (11,25) categorized diabetic foot ulcers by their mechanisms or Wagner Grades, and also produced a weak body of evidence showing a positive effect (i.e. a reduction in wound size) in mixed ulcers and venous ulcers at up to six months but no difference in ischemic and non-ischemic ulcers at up to six months (See Table 6).

The original report did not include wound-size reduction as a distinct outcome; rather, it was grouped together with wound healing. However, the systematic reviews included in this 2019 update have reported wound healing and wound-size reduction as individual outcomes, indicating a weak body of evidence that favors HBOT for reducing wound size in diabetic foot ulcers (See Table 6).

Evidence Summary: HBOT for wound-size reduction in diabetic foot ulcers		
Population	**Strength of body of evidence**	**Finding**
Diabetic Foot Ulcers	**Weak**	**Positive effect**
Mixed Ulcers	Weak	Positive effect
Wound-size reduction at 6 months or less		
Diabetic Foot Ulcers	**Weak**	**No difference**
Ischemic DFU	Weak	No difference
Non-Ischemic DFU	Weak	No difference
Venous Ulcers	Weak	Positive effect

Table 3: Evidence for clinical effectiveness of HBOT for wound size reduction in diabetic foot ulcers

New for this update: HBOT for other outcomes in diabetic pressure ulcers

The systematic reviews included in this update reported on other outcomes for diabetic pressure ulcers that are not found in the original report. They include:

- cost effectiveness (12,24),
- adverse events (12,19,20,26),
- resolution of infections (12,18,22),
- length of stay (22),
- mortality (19–21),
- quality of life (11,12,19–21),
- time to heal (19), and
- transcutaneous oxygen tensions (11).

The body of evidence for each of these outcomes is characterized as weak. The body of evidence for two outcomes, cost effectiveness and resolution of infections, indicated a positive effect (i.e., favoring HBOT). The body of evidence for the remaining outcomes indicated no difference when HBOT was compared to the control (Table 7).

Evidence Summary: HBOT for other outcomes in diabetic pressure ulcers		
Outcomes	**Strength of body of evidence**	**Finding**
Adverse events	Weak	No difference
Cost Effectiveness	Weak	Positive effect
Length of stay	Weak	No difference
Mortality	Weak	No difference
Quality of Life	Weak	No difference
Resolution of Infections	Weak	Positive effect
Time to Heal	Weak	No difference
Transcutaneous Oxygen Tensions	Weak	No difference

Table 4: Evidence for clinical effectiveness of HBOT for other outcomes in diabetic foot ulcers

HBOT for delayed radiation-induced injury (DRII)

This update identified seven systematic reviews, consisting of four high-quality (7,10,13,14) and three moderate-quality (15,17,20) that reported on HBOT for DRII generally, and for the treatment of delayed radiation-induced injury (DRII) in two cancer types: soft tissue injuries from pelvic region cancers and bone-related injuries from radiation treatment of head and neck cancers.

HBOT for DRII generally

Two reviews (17,20) reported on delayed radiation inducted injuries generally. They produced a weak body of evidence showing no difference for HBOT in mortality or quality of life using the SF-36 health survey (Table 8). One review (20) included only one primary study and was unable to draw any conclusions, while the other review (17) reported only on the safety of HBOT, stating that no deaths were attributed to the therapy. (Table 8)

HBOT for pelvic region soft tissue DRII

This update is consistent with the original report as it provides a weak body of evidence favoring HBOT for the treatment of pelvic region soft tissue injury by showing improved healing. The main clinical outcomes for pelvic region soft tissue injury reported in in the original study and in this update are:

- quality of life,
- resolution of symptoms,
- scores based "Subjective, Objective, Management, and Analytical" measurements of "Late Effects on Normal Tissue" (i.e., SOMA-LENT), and
- wound healing.

Five reviews (10,13–15,20) reported on soft tissue injuries from pelvic region cancer radiation treatments, specifically on radiation rectitis and proctitis. They produced a very weak to weak body of evidence showing a positive effect of HBOT on all outcomes. The weak evidence favors HBOT by showing improved quality of life, resolution of symptoms and wound healing (Table 8).

HBOT for head and neck soft tissue DRII

The updated findings for head and neck soft tissue injury are also consistent with the original report, as they show some improvement, but the findings are still of limited strength (See Table 8).
The main clinical outcomes for HBOT in for head and neck soft tissue injury examined in the original report were:

- implant failure,
- mucosal cover,
- symptom resolution,
- wound dehiscence, and
- wound healing.

This update reports on the same outcomes, and includes three new outcomes:

- bone continuity,
- pain, and
- complications after dental implantation.

Two reviews (7,20) reported on bone-related injuries from head and neck cancer radiation treatment, specifically osteoradionecrosis and brachial plexopathy. They produced a weak body of evidence showing either a positive effect or no difference for HBOT. This weak body of evidence also favors HBOT by showing improved bone continuity, mucosal cover, wound dehiscence and wound healing at 6

months or less. The evidence also shows no difference for HBOT in implant failure or loss of dental implant, pain, post-implantation complication and resolution of symptoms (Table 8).

Evidence Summary: HBOT for delayed radiation-induced injury (DRII)		
Outcome	**Strength of body of evidence**	**Finding**
HBOT for DRII generally		
Mortality (safety)	Moderate	Positive effect
Mortality (1 year)	Weak	No difference
Quality of Life (SF-36)	Weak	No difference
HBOT for DRII in pelvic region soft tissue (proctitis, rectitis. etc.)		
Quality of Life	Weak	Positive effect
Resolution of Symptoms	Very weak	Positive effect
SOMA-LENT	Weak	Positive effect
Wound Healing	Weak	Positive effect
HBOT for DRII in head and neck soft tissue (osteoradionecrosis, brachial plexopathy, etc.)		
Bone Continuity	Weak	Positive effect
Implant Failure/Loss of Dental Implant	Weak	No difference
Mucosal Cover	Weak	Positive effect
Pain	Weak	No difference
Post-Implantation Complication	Weak	No difference
Resolution of Symptoms	Weak	No difference
Wound Dehiscence	Weak	Positive effect
Wound Healing (6 months or less)	Weak	Positive effect

Table 5: Evidence for clinical effectiveness of HBOT for delayed radiation-induced injury.

HBOT for thermal burns

This update identified one moderate-quality systematic review that reported on HBOT for the treatment of thermal burns (24). The main clinical outcomes in the original report were graft success, mortality, sepsis and wound healing. Evidence from this update does not include findings for these outcomes; instead, it reports on two new outcomes: cost effectiveness and length of stay.

The evidence from this update produced a weak body of evidence for HBOT showing no difference in cost but a reduced length of stay (24). This update agrees with the original report, as there is still insufficient evidence to determine the clinical effectiveness of HBOT for the treatment of thermal burns (See Table 9).

Evidence Summary: HBOT for Thermal Burns		
Outcome	**Strength of body of evidence**	**Finding**
Cost Effectiveness	Weak	No difference
Length of Stay	Weak	Positive effect

Table 6: Evidence for clinical effectiveness of HBOT for thermal burns

HBOT for skin grafts and flaps

This update identified one high-quality Cochrane review that reported on HBOT for the treatment of skin grafts and flaps (9). While the main clinical outcome in the original report was wound healing, this update reports on all of the following outcomes:

- wound healing,
- adverse events,
- amputation,
- graft survival,
- length of stay, and
- time to heal.

The only review included in the original report discussed three primary studies and produced a weak body of evidence showing no difference for HBOT in adverse events, amputation, graft survival, length of stay and time to heal, but HBOT as having a positive effect for wound healing (9).

This update's findings are consistent with the original report as we found that there is still insufficient evidence to support or contradict the use of HBOT to treat skin grafts and flaps (Table 10)

Evidence Summary: HBOT for Skin Grafts and Flaps		
Outcome	**Strength of body of evidence**	**Finding**
Adverse Events	Weak	No difference
Amputation	Weak	No difference
Graft Survival	Weak	No difference
Length of Stay	Weak	No difference
Time to Heal	Weak	No difference
Wound Healing	Weak	Positive effect

Table 7: Evidence for clinical effectiveness of HBOT for skin grafts and flaps

Summary of key findings from the evidence

…the evidence we found for this update suffers from the same limitations as the evidence we found in 2012 – a lack of high-quality primary research studies on HBOT for the treatment of difficult wounds.

This update seeks to add to the synthesis of the body of evidence studied in the 2012 *Evidence in Context* report on the clinical and economical effectiveness of HBOT for difficult wound healing by providing decision makers with new evidence from systematic reviews published since 2010.

Overall, the findings of this update are consistent with those of the original report. For the most part, the evidence remains weak for the effectiveness of HBOT as an adjunctive treatment for diabetic/non-diabetic pressure ulcers, delayed radiation-induced injuries, thermal burns and skin grafts/flaps. This can be attributed to the fact that, although we found an increase in the number of systematic reviews

published in recent years, the newer systematic reviews mostly cover primary studies that had already been included in the original report (or that *should* have been included but were not identified in the older systematic reviews). In essence, the systematic reviews included in our original report and the newer systematic reviews included in this evidence update are largely assessing the same body of original evidence with a few new inclusions. Consequently, the evidence we found for this update suffers from the same limitations as the evidence we found in 2012 – a lack of high-quality primary research studies on HBOT for the treatment of difficult wounds.

Post-organ transplantation revascularization is excluded from this update for two reasons: because organ transplantation is not carried out in Newfoundland and Labrador and is, therefore, not directly relevant and there was a lack of evidence on this topic.

We wish to point out that this update focuses on the *clinical* effectiveness of HBOT, and not the economical effectiveness, due to a lack of economic evidence.

The largest body of evidence in this report relates to HBOT for diabetic/non-diabetic foot ulcers:

A strong body of evidence indicates that HBOT *does not* reduce the likelihood of minor amputations in diabetic foot ulcers. However, as in the original report, it is both possible and plausible that this finding is the result of a paradox: having undergone HBOT treatment, a patient who might otherwise have required a major amputation would now require only a minor amputation. As a result, HBOT, as a therapy, might be seen as being linked to having no effect on reducing the incidence of minor amputations *because* it has decreased the incidence of major amputations. Unfortunately, the available evidence cannot support or refute this possibility.

As a result of disagreements between high-quality and moderate-quality systematic reviews assessed in this update, the evidence for the effectiveness of HBOT to reduce major amputations in diabetic foot ulcers must be characterized as being very weak. Such divergence in the findings precludes drawing any firm conclusions on the effectiveness of HBOT in reducing the likelihood of major amputations.

A strong body of evidence shows that HBOT as adjunctive therapy is significantly more effective than usual care to reduce the severity of non-healing diabetic foot ulcers. Although there is no strong evidence for reducing the likelihood of amputation, there is strong evidence for improved wound healing. This could mean that improved wound healing could make a major amputation become a minor amputation, or that improved wound healing is a more favorable outcome for patients whose ulcers are not so severe as to result in amputation.

This update also reports on HBOT for Delayed Radiation-Induced Injury (DRII):

As the result of weak evidence, it is difficult to judge the clinical effectiveness of HBOT in treating delayed-radiation induced injuries in general. Overall, further research is needed in this area, although existing studies do indicate that HBOT is safe for treating DRII.

Weak evidence also indicates that adjunctive HBOT could be beneficial for treating osteoradionecrosis, radiation rectitis, and radiation proctitis by resulting in improved wound healing and quality of life.

This update also reports on the clinical effectiveness of HBOT for treating other difficult wounds:

When considering HBOT to treat thermal burns, skin grafts and flaps, the findings of this update are largely consistent with the original report: the research is limited and there is still insufficient evidence to support or contradict the effectiveness of HBOT in treating these conditions.

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