Issue: Hyperbaric Oxygen Therapy
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Evidence *in* Context

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

Hyperbaric Oxygen Therapy for Difficult Wound Healing in Newfoundland & Labrador

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Newfoundland & Labrador Centre for APPLIED HEALTH RESEARCH
www.nlcahr.mun.ca

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Canadian Institutes of Health Research
Instituts de recherche en santé du Canada

Canadian Agency for Drugs and Technologies in Health

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Additional Online Resources

See our website **www.nlcahr.mun.ca/chrsp** for further background materials relating to this document, including a companion report by the Canadian Agency for Drugs and Technologies in Health (CADTH), "Hyperbaric Oxygen Therapy for Difficult Wound Healing: A Systematic Review of Clinical Effectiveness and Cost Effectiveness" 26 May 2010 © CADTH (May 2010) and a listing of hyperbaric oxygen therapy treatment centres in Canada.

About this Report

About NLCAHR

The Newfoundland & Labrador Centre for Applied Health Research, established in 1999, contributes to the effectiveness of health and community services in Newfoundland and Labrador and to the physical, social, and psychological wellbeing of its population. NLCAHR accomplishes this mandate by building capacity in applied health research, supporting high-quality research, and fostering the effective use of research evidence by decision makers and policy makers in the provincial healthcare system.

About the Contextualized Health Research Synthesis Program

In 2007, NLCAHR launched the Contextualized Health Research Synthesis Program (CHRSP) to provide research evidence that would help guide decision makers in the provincial health system on issues of pressing interest to Newfoundland and Labrador. Instead of conducting original research, CHRSP analyzes findings from high level research already conducted in the subject area, such as systematic reviews, meta-analyses and health technology assessments. Findings are then synthesized and subjected to a systematic process of contextualization: they are analyzed in terms of their applicability to the conditions and capacities of the unique context of Newfoundland and Labrador. Our contextual analysis includes assessing the specific forms an issue may take in this province as well as the applicability of any proposed solutions and methods to locally available resources, infrastructure, human resources, cultural conditions and financial capacities. CHRSP uses a combination of external experts and local networks to carry out and contextualize the research synthesis and to facilitate the uptake of the results by research users. CHRSP focuses on three types of projects: health services/ health policy projects, health technology assessment (HTA) projects, and projects that combine the two to examine processes for the organization or delivery of care involving a health technology.

About Our Partners

For this project, NLCAHR partnered with Eastern Health and the Canadian Agency for Drugs in Technology and Health (CADTH). Senior administrators from Eastern Health proposed the research topic while CADTH helped the research team refine the research question. CADTH also identified relevant research literature, appraising and synthesizing the evidence in a peer-reviewed report. The work by CADTH has been published independently and is available for viewing on the NLCAHR website: www.nlcahr.mun.ca/chrsp. The CHRSP Project Team, with input from key stakeholders throughout the province, provided additional analysis and contextualization of the CADTH results for Newfoundland and Labrador. This project was funded in part by the Canadian Institutes of Health Research (CIHR)- Institute of Health Services and Policy Research (IHSPR).

Who Should Read This Report?

This report provides a synthesis of the relevant research-based evidence on the clinical and cost effectiveness of hyperbaric oxygen therapy for difficult wound healing, including diabetic foot ulcers, pressure ulcers, delayed radiation-induced injury, thermal burns, skin grafts and flaps, and revascularization after organ transplantation.

This report is intended to inform and assist decision makers in the Eastern Health Regional Health Authority, the Newfoundland and Labrador Department of Health and Community Services and the province's three other Regional Health Authorities on the treatment and management of patients with certain non-healing (i.e., difficult) wounds. The findings of our synthesis are specifically interpreted for the context of Newfoundland and Labrador. Decision makers from other jurisdictions, especially those with similar potential clients, geography and resources, may also find the content helpful. The report includes explanations of research terms and technical language; as such, there is no need to have a specialized medical or health background to understand its content.

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Hyperbaric Oxygen Therapy for Difficult Wound Healing in Newfoundland & Labrador

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Acronyms

AMSTAR	Assessment of Multiple Systematic Reviews
CADTH	Canadian Agency for Drugs and Technology in Health
CI	Confidence Interval
CIHR-ISPR	Canadian Institutes of Health Research – Institute of Health Services and Policy Research
DHCS	Department of Health and Community Services (Government of Newfoundland and Labrador)
DRII	Delayed Radiation Induced Injury
ECHM	European Committee for Hyperbaric Medicine
HBOT	Hyperbaric Oxygen Therapy
HIF	Hypoxia-Inducible Factors
HTA	Health Technology Assessment
HTIS	Health Technology Information Systems (CADTH)
ICU	Intensive Care Unit
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care) Germany
KTE	Knowledge Transfer and Exchange
MEDICOR	Centre for Offshore and Remote Medicine (Memorial University)
MeSH	Medical Subject Headings
MUN	Memorial University
NLCAHR	Newfoundland and Labrador Centre for Applied Health Research
NNT	Number Needed to Treat
PR	Primary Research
QALY	Quality Adjusted Life Years
QoL	Quality Of Life
RCT	Randomized Controlled Trials
RHA	Regional Health Authority
RR	Relative Risk
RT	Respiratory Therapist
SOMA-LENT	Subjective, Objective, Management, and Analytic (SOMA) measures of Late Effects on Normal Tissue (LENT) from radiation therapy
UHMS	Undersea and Hyperbaric Medical Society

Glossary

Adjunctive therapy	A supplementary therapy that improves the outcomes of a primary therapy or procedure.
Adjunctive treatment	An assistive treatment that does not act directly on the target pathology.
AMSTAR	An 11-item instrument used to assess the methodological rigor of systematic reviews.
Apoptosis	Programmed cell death.
Collagen synthesis	Cellular formation of collagen, a common connective tissue in the body.
Confidence interval (CI)	A measure of the reliability of an estimate. A CI specifies a range within which the true value of the estimated parameter is expected to lie. For ratios, if the CI spans the 1 value, e.g. 0.8 to 1.3 for a relative risk, the comparison in question is not statistically significant. Likewise, if the CI spans the 0 value, e.g. -2.4 to 3.2 for the difference in a test score, than the comparison in question is also not statistically significant. When the CI spans those critical values, the studied groups cannot be considered different from one another on the measure in question.
Costs-effectiveness study	A study in which the monetary costs of an intervention are considered in terms of a single common health outcome that is measured in natural units. Examples of such outcomes include: the number of years with full mobility gained or the number of placements in long-term care deferred.
Cost-utility study	A study in which the monetary costs of an intervention are considered in terms of a single outcome, or considered in terms of multiple outcomes that are weighted or valued in relative terms. The combined outcome is measured in units that capture both the quantity and quality of the effects of the intervention, with the most common measure being the quality-adjusted life-year or QALY.
Cytokine	A type of protein that acts as a signal between cells involved in immune response.
Dive	A single treatment session in a hyperbaric oxygen chamber. A treatment course for hyperbaric oxygen therapy may involve multiple dives taken over a period of time.
Effect size	A measure of the strength of a relationship between two variables, for example between a treatment for a health condition and recovery from that health condition. Effect sizes may be quantified by a range of different measures, including correlations, differences in means and relative risks.
Effectiveness	The ability of an intervention to produce the desired beneficial effect in actual usage.
Efficacy	The ability of an intervention to produce the desired beneficial effect in expert hands and under ideal circumstances.
Fibroblast	Cells that make connective tissues, e.g., collagen.
Grey literature	Research that is published non-commercially, that may include reports carried out by governments, health authorities and not-for-profit associations.
Health Technology Assessment (HTA)	A multidisciplinary field of policy analysis that studies the medical, social, ethical and economic implications of development, diffusion, and use of health technology.
Hemoglobin	A blood-protein that contains iron and serves as the principal carrier of oxygen in the blood.
HIF	Hypoxia-inducible factors, proteins that bind to specific DNA sequences to promote cell survival in hypoxic conditions.
Hyperbaric	Of, relating to, producing, operating, or occurring at pressures higher than normal atmospheric pressure.
Hypoxia	A deficiency of oxygen reaching the tissues and cells of the body.
Incidence	A measure of the number of new cases of a disease in a population over a period of time.
Ischemia	Restriction of blood supply, and therefore oxygen, to tissue that leads to damage and/or dysfunction.
Meta-analysis	A type of systematic review that uses statistical techniques to quantitatively combine the findings from previous primary research studies.

Monocyte	A white blood cell involved in immune responses; during an immune response, monocytes will become macrophages or dendritic cells . Macrophages destroy damaged tissue and pathogens, and stimulate additional immune responses. Dendritic cells process and display proteins from pathogens, and coordinate additional immune responses.
Neutrophil	A white blood cell involved in immune responses; during an immune response, neutrophils will congregate at the site of inflammation, attack micro-organisms and stimulate additional immune responses.
Number needed to treat (NNT)	A measure of treatment effectiveness. NNT is the number of patients that need to be treated in order to prevent one additional adverse outcome among those patients. An ideal treatment would have a NNT equal to 1, meaning that each patient treated will not experience the adverse outcome in question. The greater the NNT, the less effective the treatment in question.
Osteoradionecrosis	Necrosis/tissue death of bone as a result of exposure to radiation.
Partial pressure	The pressure exerted by one component gas in a mixture of gasses. A gas may also be partly dissolved in a liquid; in this case, the partial pressure is the pressure exerted by the un-dissolved or gaseous component of the gas when in a state of equilibrium (where the concentration of the dissolved gas is constant).
Prevalence	A measure of the number of existing cases of a disease in a population at a particular time.
Proctitis	Inflammation of the rectum or anus.
Progenitor	The originator of a type of cell, a stem cell.
Primary research	Research that involves the collection and analysis of data from actual participants, as opposed to the combination of such research (i.e. higher level studies) or secondary analyses of previously collected data.
QALY	A measure that combines time and an assessment of quality of life. QALY stands for "quality adjusted life year." A QALY unit is based on a scale that considers one year of life lived in perfect health worth 1 QALY. A year of life that is lived in a state of less than perfect health is worth less than 1 QALY. The quality of life is quantified as "the utility value," a measure of the state of health of the person in question. To get a QALY value, the utility value is multiplied by the years lived in that state: UTILITY x TIME = QALY. QALYs are expressed in terms of "years lived in perfect health." For example, half a year lived in perfect health is equivalent to 0.5 QALYs, the same as 1 year of life lived in a compromised state of health with utility 0.5 (Drummond, Sculpher, Torrance, O'Brien, & Stoddart, 2005).
Randomized controlled trial	A type of primary research in which participants are randomized with regards to treatment, with the objective of balancing the impacts of confounding factors that may exist among the participants.
Rectitis	Another term for proctitis.
Relative risk (RR)	A measure of the likelihood that an exposure will have a particular outcome. In the case of health treatments, RR is the ratio of the probability of an outcome occurring in a treated group compared to the probability of its occurring in an untreated group. For example, for diabetic foot ulcers treated with HBOT and major amputation as the outcome, RR is expressed as the ratio of the probability that a treated patient will not require a major amputation to the probability that an untreated patient will require an amputation: ○ RR of 1 means that there is no difference between the treated and untreated groups; ○ RR of less than 1 means the patients who received the treatment are less likely to require a major amputation; ○ RR of greater than 1 means patients are more likely to require a major amputation.

Skin graft	Skin for grafting that is wholly removed from one part of the body and transferred to another site.
Skin flap	Skin for 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.
SOMA-LENT	A scale to measure Late Effects on Normal Tissue (LENT) from radiation therapy, from several perspectives: Subjective, Objective, Management, and Analytic (SOMA).
Systematic review	A literature review, focused on a specific and explicit research question that tries to identify, appraise, select and synthesize published and unpublished research evidence relevant to that question.
Tension	The partial pressure of a gas that is dissolved in blood.
Units of measurement	○ **atm** (atmosphere): a unit of pressure equal to the average pressure of the atmosphere at sea level. One atmosphere is defined as 101.325 kPa or 760 mm Hg. ○ **bar** (bar): a unit of pressure used to describe compressed air equipment, including that used in HBOT. One bar is defined as 100.0 kPa and is also referred to as standard pressure. ○ **Gy** (gray): unit of absorbed energy from ionizing radiation. One gray is defined as the absorption of one joule of ionizing radiation by one kilogram of matter (usually human tissue). ○ **kPa** (kilopascal): a unit of pressure. One kilopascal is defined as 1000 pascals or 1000 N/m^2 (newtons per square meter, a measure of force applied over an area). ○ **mm Hg** (torr): a unit of pressure. One torr is defined as 133.3 pa. The 'mm' refers to millimeters and the 'Hg' refers to mercury. This is a holdover from measuring devices that used a column of mercury to measure pressures, for example, barometers or sphygmomanometers (the arm-cuff blood pressure instrument).

The Research Question

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

Key Messages from this Report

1. Research evidence supports HBOT as both clinically-effective and cost-effective (from a societal perspective) for diabetic foot ulcers.
2. Research evidence supports HBOT as clinically-effective for delayed radiation-induced injuries in the head, neck and pelvic regions.
3. There is insufficient evidence to support or contradict HBOT treatment for pressure ulcers, delayed radiation-induced injuries other than those in the head, neck and pelvic regions, severe thermal burns, skin grafts and skin flaps, or revascularization after organ transplantation.
4. The cost effectiveness of HBOT for appropriate non-healing wounds will increase as the number of patients treated increases. The incidence of health conditions that can result in non-healing wounds is expected to increase in Newfoundland and Labrador, producing a greater number of patients who would be appropriate candidates for HBOT.
5. For difficult wounds shown to be responsive to HBOT (e.g., diabetic foot ulcers and radiation proctitis) the appropriate and timely referral of patients is expected to improve with greater integration of wound-care management into existing chronic and acute health services programs. This, in turn, is expected to increase the clinical and cost-effectiveness of HBOT treatment for those conditions.
6. Overall, research evidence for the clinical and cost-effectiveness of HBOT for difficult (non-healing) wounds is limited. As a result, future studies are expected to have a significant impact on the evidence base for or against HBOT for a number of non-healing wound conditions. Furthermore, Eastern Health may benefit from establishing liaisons with other more established HBOT units across the country to share evidence and clinical expertise.

Background

The hyperbaric oxygen therapy (HBOT) facilities for Newfoundland and Labrador were originally located in, and administered by, the Centre for Offshore and Remote Medicine (MEDICOR). MEDICOR was established in 1982 as a research centre within the Faculty of Medicine at Memorial University. The initial mandate of MEDICOR was to conduct health research related to diving and related industries. The main focus of operation for its HBOT facilities was research. Over time, HBOT was increasingly used for clinical emergency cases such as decompression illness and carbon monoxide poisoning. The recommended clinical applications of HBOT for non-emergency cases also increased, resulting in significant additional demand. (1,2)

The shift in focus from research activity to clinical applications was conducted on an *ad hoc* basis with limited staff and resources. By 2008, research involving HBOT had decreased effectively to nothing. Staffing issues then forced the closure of the HBOT facility in February 2009. In September 2009, Eastern Health and Memorial University announced the transfer of ownership of the HBOT facilities to Eastern Health. Eastern Health and Memorial University established an agreement in March 2010 whereby Eastern Health would take formal responsibility for the HBOT facility for all clinical case work, while Memorial University would still have access to the equipment for research and educational purposes. (1,2)

As a result, Eastern Health is now developing policy for the clinical use of the HBOT facility. It has increased HBOT capacity, in terms of both infrastructure and dedicated human resources. Eastern Health intends to continue to increase capacity to meet the expected growth in demand for clinical HBOT services. In partnering with CHRSP, Eastern Health is seeking research-based evidence that will provide guidance about the clinical and cost effectiveness of HBOT for difficult wounds, health conditions that require attention in the province.

For this project, NLCAHR partnered with Eastern Health and the Canadian Agency for Drugs in Technology and Health (CADTH). The CHRSP Project Team included senior administrators from Eastern Health (who proposed the topic), local clinical and research experts in HBOT and difficult wound healing, and CHRSP staff at NLCAHR (see "The Research Team," page 2, for details). The CHRSP Project Team and CADTH refined the original research question for this project and produced the following:

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

CADTH was tasked with searching for and identifying the relevant research literature (see "What research did we look for?" on page 15), critically appraising the evidence, producing a report synthesizing the evidence, and having the results peer-reviewed. The work by CADTH has been published as an independent report and it forms the basis of the NLCAHR project. (3) The CHRSP Project Team took the CADTH results and, with input from key stakeholders throughout the province, provided additional analysis and contextualization for Newfoundland and Labrador.

What is hyperbaric oxygen therapy?

In essence, hyperbaric oxygen therapy (HBOT) consists of delivering to patients pure oxygen gas (O_2) at pressure levels higher than normal pressure. HBOT delivers 100% O_2 to the patient, compared with the average O_2 concentration in air at sea level, which is 21%. Hyperbaric oxygen therapy is used to treat both emergency and chronic health conditions. HBOT was first used and developed for emergency conditions such as decompression illness or carbon monoxide poisoning (see Table 1. Page 12 for more examples). Emergency HBOT is immediately administered to the patient and generally consists of one dive[1] that may last several hours. HBOT is also used to treat chronic health conditions such as diabetic foot ulcers or some types of radiation-induced necrosis. In these cases, HBOT is an adjunctive therapy that typically consists of many shorter dives (60-90 minutes) administered once daily or less, over weeks or months. New research suggests, though does not yet prove, that HBOT may be used for the pre-treatment of tissue and organs prior to surgery in order to improve their resistance to ischemic and other trauma. (7-9)

Airtight chambers are used to produce the higher pressures and they come in two basic types of construction.

The first type is a multi-place chamber that can accommodate one or more patients at a time. Multi-place chambers are designed as sealed rooms. The space inside the chamber is pressurized with compressed normal air to maintain the higher than normal pressures. Patients then breathe pure pressurized oxygen through a mask or a hood. In this design, patients absorb oxygen exclusively through the lungs by breathing. Most of the equipment and attendant staff are located inside the multi-place chamber along with the patients. The additional space for staff makes multi-place chambers a good option for patients with complex case management and multiple co-morbidities requiring monitoring by specialists. By virtue of involving several individuals working together, multi-place chambers provide an effective opportunity for team training.

All HBOT regulatory bodies recommend limits on hyperbaric exposure, time for decompression, and restrictions on certain activities, such as flying or travel in mountainous regions, for attendant staff. (4) In practice, this usually means that attendant staff does not participate in more than one dive per day (E. Carew, Patient Care Co-ordinator, Hyperbaric Medicine, Eastern Health, personal communication, 2011).

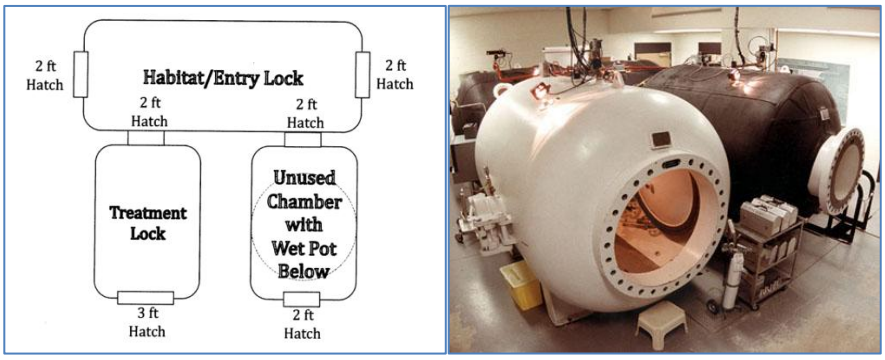

Figure 1: Schematic layout of HBOT multi-place chamber in the Health Sciences Centre, St. John's (Wood, 2009) and photo of actual chamber (Memorial University of Newfoundland)

[1] Hyperbaric medicine often refers to an individual treatment as a 'dive.' For the purposes of this report, a single course of hyperbaric oxygen therapy is referred to as a 'treatment.' A 'full course of HBOT' refers to the number of treatments prescribed to patients for particular health condition(s).

The second type of construction is a mono-place chamber, or mono-chamber, that can accommodate only one patient. In some special cases, the chamber will accommodate two people (for example, a child and parent). Mono-chambers are typically designed as an enclosed bed on which the patient reclines. No hoods or masks are worn by the patient as with multi-place chambers; instead, pure O_2 is pumped directly into the chamber at elevated pressure. The patient absorbs oxygen through the lungs by breathing (5) and by passive diffusion through the skin and open wounds. (6) Equipment and staff are located outside the mono-chamber.

With both constructions, the combination of elevated pressure and the higher concentration of inhaled O_2 causes an increase in the amount of oxygen that is absorbed by the patient. The principal transport mechanism for oxygen is blood. Approximately 98.5% of inhaled oxygen is bound to the blood-borne protein hemoglobin. Hyperbaric oxygen does not increase the amount of hemoglobin-bound oxygen, since hemoglobin is normally saturated with oxygen already. The remaining 1.5% of oxygen in the blood is dissolved in the liquid component of blood, plasma. At 1 atm[2] of pressure, and breathing 100% O_2, the dissolved amount of oxygen in blood plasma is approximately 1.5 g/dL. An increase in pressure to 3 atm will raise this to 6.0 g/dL, which, by itself, is enough oxygen to support resting cellular metabolism. (5)

Oxygen plays multiple critical roles in wound metabolism. Research has advanced to the point where complex biochemical and physiologic pathways can be investigated at the molecular level. These analytic methods provide evidence for ways in which HBOT effects wound metabolism.

In mono-chamber HBOT, the body surface of the patient is also exposed to 100% O_2. In normal conditions, the O_2 tension in wounds typically drops from 60 mm Hg to 20-35 mm Hg after one week. A standard HBOT treatment of 100% O_2 at 3 atm for 20 minutes will raise O_2 in wounds, on average, to nearly 400 mm Hg. (6)

Oxygen plays multiple critical roles in wound metabolism. Research has advanced to the point where complex biochemical and physiologic pathways can be investigated at the molecular level. These analytic methods provide evidence for ways in which HBOT effects wound metabolism. The most important mechanisms are related to how oxygen influences the levels of cytokines, which are intercellular mediators of immune function. Recent evidence indicates that particular combinations of cytokines, or 'cytokine signatures,' trigger the production of specific proteins and the expression of specific genes involved in wound metabolism. The oxygen level influences the body's subsequent immune reaction to a wound. The oxygen level may also affect tissues and the immune system prior to sustaining a wound: it may reduce the severity of tissue damage and the degree of immune-related inflammation. HBOT influences cytokine signatures in several complex and inter-related ways that are described schematically in Figure 2. (5-13)

Very few adverse effects from HBOT have been reported. Barotrauma, damage as a result of sudden pressure changes, may affect the middle ear (less than 2% of cases), cranial sinuses, teeth or lungs (very rare). Reversible myopia is the most common side-effect and is normally a temporary result of the effects of oxygen on the ocular lens. Other types of oxygen toxicity are possible, but very rare. The remaining adverse effects involve discomfort, including claustrophobia, chest tightness and cough. (5,14)

[2] Gas pressure is measured in several different units depending on the context. Definitions for the units used in this report may be found in the Glossary under "Units of measurement," on page 6.

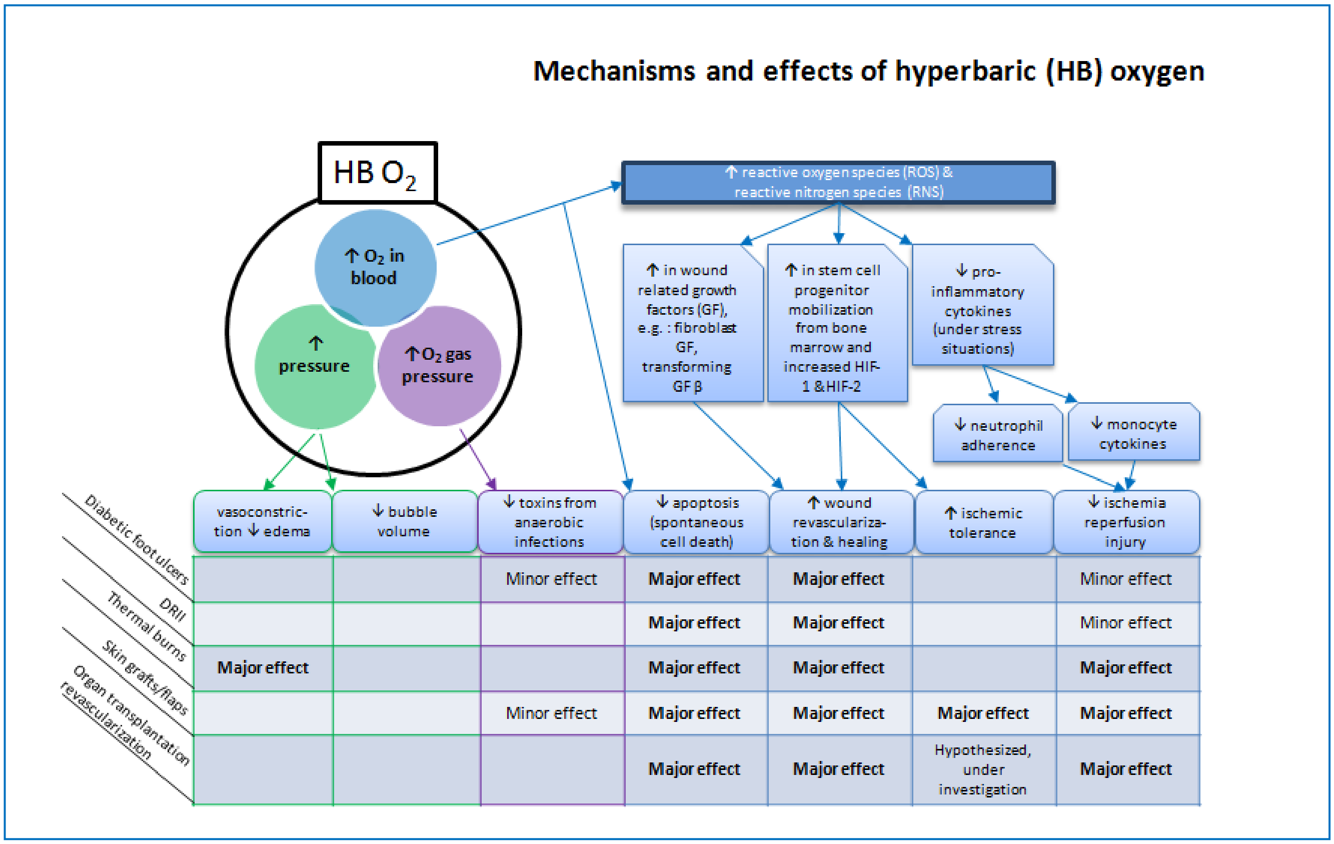

Figure 2: Mechanisms and effects of HBOT on non-healing wounds. (5-13)

Hyperbaric oxygen therapy in Canada

At present, the principal regulatory process for HBOT in Canada is the issuing of medical device licenses by Health Canada. (15,16) Such licenses are required to import or sell HBOT chambers. According to Health Canada, (17) HBOT medical device licenses will only be issued if the chamber(s) will be used to treat one or more health conditions approved by the US-based Undersea and Hyperbaric Medical Society (UHMS) (See Table 1). UHMS considers research evidence in developing the list of approved conditions through a committee-based approval process. Multiple Canadian and international jurisdictions, including national ministries of health and multi-national organizations, have a high level of agreement (though not unanimity) with the UHMS list of conditions.

List of Approved Health Conditions for Hyperbaric Oxygen Therapy: Multiple Jurisdictions

	Condition	Case	UHMS	ECHM	BE	NL	FR*	UK**	US	AU
UHMS approved	Clostridal myositis and myonecrosis (gas gangrene)	E	Y	Y	Y	Y	Y*	Y**	Y	Y
	CO poisoning	E	Y	Y	Y	Y	Y*	Y**	Y	Y
	Decompression illness & gas embolism	E	Y	Y	Y	Y	Y*	Y**	Y	Y
	Diabetic foot ulcers	**A**	**Y**	**Y**	**Y**	**Y**	**Y***	**Y****	**Y**	**Y**
	Hemorrhagic cystitis after irradiation	**A**	**Y**	**Y**	**Y**	**Y**	**Y***	**Y****	**Y**	**Y**
	Osteoradionecrosis	**A**	**Y**	**Y**	**Y**	**Y**	**Y***	**Y****	**Y**	**Y**
	Radiation proctitis & enteritis	**A**	**Y**	**Y**	**Y**	**Y**	**Y***	**Y****	**Y**	**Y**
	Chronic refractory osteomyelitis	A	Y	Y	Y	Y	Y*	Y**	Y	
	Crush injuries, compartment syndromes, traumatic ischemias	E	Y	Y	Y	Y	Y*	Y**	Y	
	Larynx radionecrosis	**A**	**Y**	**Y**	**Y**	**Y**	**Y***	**Y****		**Y**
	Necrotizing soft tissue infections (flesh-eating disease)	E	Y	Y		Y	Y*	Y**	Y	Y
	Skin grafts and myocutaneous flaps	**A**	**Y**	**Y**	**Y**	**Y**	**Y***	**Y****	**Y**	
	Soft tissue radionecrosis	**A**	**Y**	**Y**	**Y**		**Y***	**Y****	**Y**	**Y**
	Intracranial abscess	A	Y	Y			Y*	Y**		
	Pressure ulcers	**A**	**Y**	**Y**		**N**	**Y***	**Y****	**N**	
	Thermal burns	**A**	**Y**	**Y**		**N**	**Y***	**Y****	**N**	
	Exceptional blood loss or anemia	E	Y				Y*	Y**		
Conflicting approval	Acute deafness	A		Y	Y	N				
	Re-implantation of fingers/extremities	P				Y				
	Acute peripheral arterial insufficiency	E							Y	
	Anoxic encephalopathy	E		Y		N				
	Chronic critical ischemia in case of arteriosclerosis	A			Y				N	
	Cyanide poisoning	E							Y	
	Ischemic ocular disorders/abnormalities	A		Y		N				
	Neuroblastoma Stage IV	A		Y						
	Pneumatosis Cystoides Intestinalis	A		Y						
Not approved or disapproved	**Organ storage or transplantation**	**P**							**N**	
	Acute cerebral oedema, Acute or chronic cerebral vascular insufficiency, Aerobic or anaerobic septicemia & infection (non-clostridial), Arthritic Diseases, Cardiogenic shock, Chronic peripheral vascular insufficiency, Exceptional blood loss anaemia, Hepatic necrosis, Myocardial infarction, Nonvascular causes of chronic brain syndrome, Pulmonary emphysema, Senility, Sickle cell anaemia, Smoke inhalation, Systemic aerobic infection, Tetanus	n/a							N	
	Acute coronary syndrome, Acute traumatic brain damage, Cerebral hypoxia, traumatic or after a stroke, Malign otitis externa, Multiple Sclerosis, Radionecrosis of the central nervous system, Tinnitus	n/a				N				

Legend:

- **Bold**: Condition is studied in this report
- **Y**: Condition is eligible for HBOT treatment (and public system reimbursement)
- **N**: Condition is specifically designated on exclusion list (and ineligible for public system reimbursement)
- **[blank]**: Condition is not indicated as eligible for HBOT (and ineligible for public system reimbursement)

Cases:

- **E**: Emergency treatment cases
- **A:** Adjunctive therapy cases
- **P:** Pre-treatment cases

Jurisdictions:

- **UHMS**: Undersea and Hyperbaric Medical Society
- **ECHM**: European Committee for Hyperbaric Medicine
- **Countries**: **BE** Belgium | **NL** Netherlands | **Fr** France | **UK** United Kingdom | **US** United States (Medicare) | **AU** Australia

Notes:

- **Fr*** : No restrictive list in place, any condition is potentially eligible for HBOT treatment;
- **UK** :** No explicit list of eligible conditions in place at national level, District Health Authorities determine the health conditions that will be covered and these are usually based on UHMS

Table 1: List of approved health conditions for HBOT from multiple jurisdictions

Within Canada, the provinces have authority over which health conditions will be insured for HBOT through their public health plans. In practice, the provinces follow Health Canada's UHMS-based guidelines. Private clinics must claim that any imported HBOT chamber will be used to treat one or more of the UHMS-based approved conditions. However, once the HBOT chamber has been set up and is operational, private clinics are largely unregulated.[3] There is little to no oversight as to which conditions are being treated with HBOT, and private clinics are not obliged to follow any particular clinical guidelines or standards of practice.

An exhaustive listing of hyperbaric facilities in Canada does not seem available at present. A compilation of partial listings originating from hyperbaric medicine organizations, the Canadian Armed Forces, and business directories, indicates that there are at least forty-seven HBOT facilities operating across the country (see Figure 3 and the online Companion Document for details). Fourteen facilities exist in hospitals or are otherwise part of the public healthcare system. Several significant investments have reportedly been made to existing facilities across Canada in the past ten years, namely at: Vancouver General Hospital (2004), Toronto General Hospital (2005), and Hôtel-Dieu de Lévis (2012). These investments indicate an increased demand for HBOT capacity for clinical and research uses (Evans, W., Chair, Ontario Medical Association & Assistant Professor - Department of Anaesthesia, Faculty of Medicine, University of Toronto, personal communication, 2010). Other HBOT facilities in Canada include six that are operated by the Canadian Armed Forces and two located in university research centers.

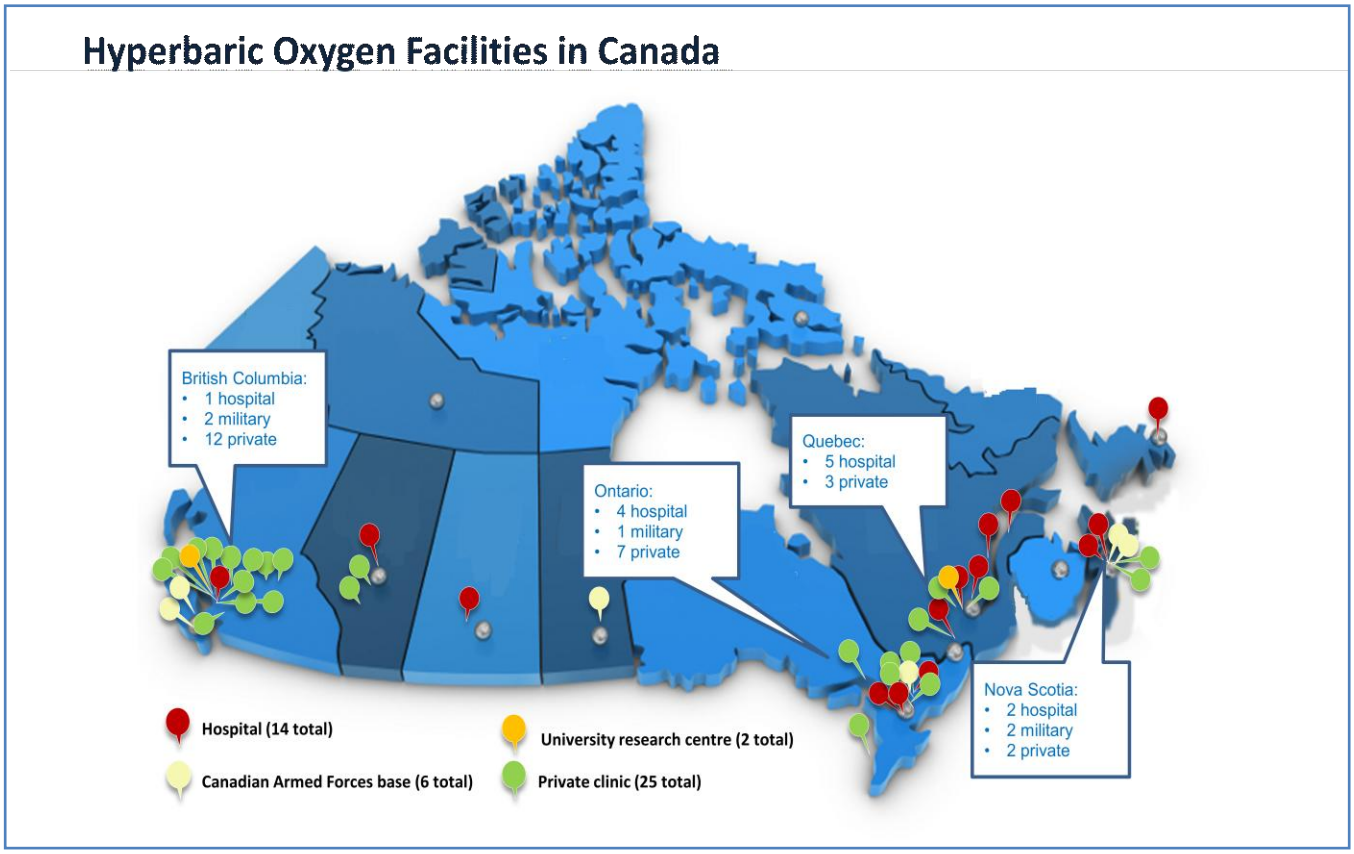

Figure 3: HBOT facilities in Canada

[3] Private HBOT clinics are regulated only with respect to the operational standards of their HBOT chambers, not what conditions their chambers are used to treat.

The remaining twenty-five identified facilities are in private clinics that may or may not treat patients on behalf of the public healthcare system. Medical groups have voiced concern that private clinics are using HBOT to treat a number of non-UHMS approved conditions (see "Not approved" section in Table 1). Additional concerns about private clinics include: lack of adequately trained medical staff at the clinics, lack of informed consent from patients as to the experimental nature of some treatments, increased risk of side effects from multiple treatments, and the financial exploitation of patients with conditions that have been shown consistently to not improve with HBOT, e.g., autism, cerebral palsy, or Alzheimer's disease. (18)

Unlike most medical sub-specialties in Canada, there is currently no formal certification for physicians to practice hyperbaric medicine. A Canadian chapter of UHMS was recently established and one of its first objectives is to initiate a diploma program that will be recognized by the Royal College of Physicians and Surgeons. Local training is available in provinces with HBOT facilities and is usually required by regional health authorities. A similar situation exists with respect to nurses and respiratory therapists involved with HBOT. Hyperbaric safety directors and supervisors, key non-medical staff at every HBOT facility, are required to be certified by the Canadian Standards Association (K. LeDez, President, Undersea & Hyperbaric Medical Society—Canadian Chapter, personal communication, 2011).

Hyperbaric oxygen therapy in Newfoundland and Labrador

The HBOT facilities for Newfoundland and Labrador are located in the Health Sciences Center (HSC) in St. John's. Eastern Health administers HBOT through the Cardiac/Critical Care Program, with a mandate to serve the whole province. Facilities currently include one multi-place chamber that can take up to six patients and two mono-place chambers. The multi-place chamber is located in the northeast corner of the ground floor of the HSC, next to the medical school and MEDICOR. However, the multi-place chamber was not operational between 2009 and 2012.[4] Until recently, the two mono-place chambers were housed in custom trailers located outside the northeast exit; they have now been moved inside the facility.

At present, core staff serving the HBOT facilities consists of two physicians, a treatment or dive supervisor, a technical analyst and a patient care coordinator. Additional clinicians from other units within Eastern Health, such as respiratory therapists (RT) or Intensive Care Unit (ICU) nurses, participate on a case-by-case basis. At time of writing, HBOT capacity is limited to the two mono-place chambers and consists of approximately six treatments per week. With additional staff support, full use of the multi-place chamber and the relocation of the mono-place chambers inside the HSC, the facilities could, we have been advised, provide up to seventy treatments per week.

[4] The multi-place chamber was first closed as the result of trained staff shortages, and later due to a contamination episode.

There have been some gaps in HBOT record-keeping and in the monitoring of clinical data. The data that do exist are not considered reliable. Nevertheless, HBOT staff members are confident that the number of appropriate elective patients with non-healing wounds, as well as the cumulative number of treatments they are receiving, is significantly higher than the number of patients and treatments for emergency cases. Emergency patients typically undergo one to three HBOT treatments in total. The average number of emergency patients is reported to be no more than twenty per year. Elective patients, including patients with non-healing wounds, average twenty treatments for a full course of hyperbaric oxygen therapy. The number of elective patients treated has varied considerably over the past ten years, for two key reasons. The first is the intermittent availability of staff to oversee and administer the multi-place chamber. The second involves closures of the multi-place chamber for significant periods as the result of technical problems or contamination. In Newfoundland and Labrador, patients with non-healing wounds are referred for HBOT most often through specialists, such as dermatologists or orthopedic surgeons, involved in the treatment of the wound and/or treating underlying medical condition(s). Primary care physicians may also refer patients directly. In practice, most patients will be seen first by a specialist in order to assess the wound, any underlying medical conditions, and any additional co-morbidity. Nurses, especially wound-care and community health nurses, may act as catalysts for referral by bringing potential HBOT patients to the attention of their primary care physicians (Wells, C. Research Coordinator, Western Regional School of Nursing, personal communication, 2010). Although a provincial committee on wound care has recently been established, at present there are few standardized wound-care protocols for non-healing wounds.

Despite the lack of data, there is broad consensus amongst healthcare professionals that a significant number of patients with the types of difficult wounds suitable for hyperbaric oxygen therapy are not currently receiving this treatment. Furthermore, cases requiring hyperbaric oxygen therapy for difficult wounds are expected to increase in future as a result of various trends: an aging population; expected increased prevalence of diabetes and obesity; and other medical factors such as the introduction of higher intensity radiotherapy treatments that are more likely to cause delayed radiation-induced injuries (DRII).

What research did we look for?

The health conditions included in this project were selected through consultation among the project team, our health system partners, and CADTH. Of particular interest was the fact that HBOT is not included in the standard of care for so-called elective uses of HBOT for chronic conditions. This contrasts with emergency conditions (e.g., carbon monoxide poisoning, gas embolism or gas gangrene) where HBOT *is* the standard of care.

Standards of care for difficult wounds in general do not include HBOT, despite many types of wounds being approved by hyperbaric medicine organizations. The specific forms of difficult wound healing that are included in this report are: diabetic foot ulcers, pressure ulcers, delayed radiation-induced injury, thermal burns, skin grafts and flaps, and revascularization after organ transplantation.

The search for, and identification of, evidence for this project were carried out by CADTH's Health Technology Inquiry Service (HTIS). Their methodology for identifying evidence, like the approach traditionally used by CHRSP, focuses primarily on high level research, including systematic reviews, meta-analyses, health technology assessments (HTA), and very recent high quality primary studies such as randomized controlled trials. Like CHRSP, HTIS's methodology includes searching periodical indexes for published articles as well as grey (not commercially published) literature sources. A list of the health evidence databases used is available on the CADTH website.[5]

The main difference in methodology between CHRSP and CADTH is that HTIS will exclude a given review paper where a more recent paper has been published that captures the same evidence as the older paper, and where the more recent review is judged to be as good, or better, in terms of methodological rigor (CADTH Report, "Hyperbaric Oxygen Therapy for Difficult Wound Healing: A Systematic Review of Clinical Effectiveness and Cost Effectiveness" p 21).

For this project, CADTH carried out the following searches (see CADTH report "Hyperbaric Oxygen Therapy for Difficult Wound Healing: A Systematic Review of Clinical Effectiveness and Cost Effectiveness" for details of the search, pp 15-20, available at www.nlcahr.mun.ca/chrsp):

- Key word and MeSH term searches were conducted for the health indicators of interest, for 2005 to 2010, of the following periodical indexes and databases: OVID Medline, OVID Medline In-Process & Other Non-Indexed Citations, EMBASE, PubMed, and the Cochrane Library.
- Grey literature was identified by searching the websites mentioned above, as well as by web searches of related professional associations and additional specialized databases.
- The foregoing searches were supplemented by general web searches (e.g., using Google Scholar), hand searching the bibliographies of identified references, and consultation with individuals and agencies involved with the topic in question.
- Search results were screened based on information in the title and abstract of the article, and articles were then selected based on a full reading of the entire article. Both stages were carried out by two independent reviewers based on the following criteria (CADTH Report, "Hyperbaric Oxygen Therapy for Difficult Wound Healing: A Systematic Review of Clinical Effectiveness and Cost Effectiveness" p5):

    - the study had to assess the clinical effectiveness, efficacy or economic effectiveness of HBOT for one or more of the eligible criteria;
    - the study design had to include a systematic review component (i.e., health technology assessment, systematic review or meta-analysis) with at least two reviewers selecting studies and/or analyzing the data, or it could be a randomized clinical trial, or an economic evaluation;
    - the study had to be in English, peer-reviewed, and published within the last five years.

Searches by HTIS initially identified 314 references (see Figure 4). Screening reduced the number of references to sixty-three potentially relevant ones, from which thirteen were finally selected.

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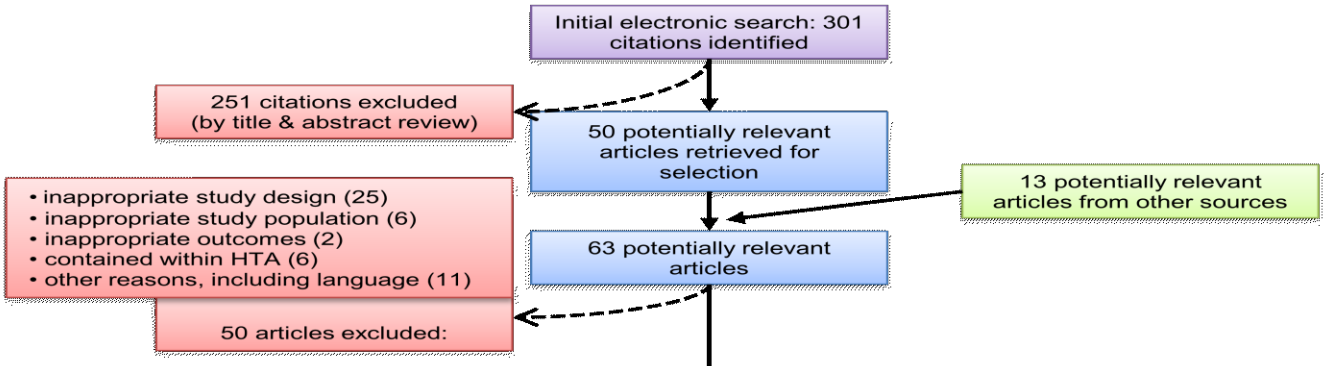
[5] http://www.cadth.ca/index.php/en/cadth/products/grey-matters



13 articles included

Type	Article	Reference	Diabetic Foot Ulcers	DRII	Thermal Burns	Skin Grafts & Flaps	PT Revascularization	Economic Analysis	Full report (English)	AMSTAR
HTA	de Laet *et al.* (2008)	19	X	X	X	X		X	X	8/11
	Hailey *et al.* (2007)	20	X					X	X	8/11
	IQWG (2007)	21			X					n/a
	MAS (2005)	22	X					X	X	7/11
	Pichon Riviere *et al.* (2006)	23	X	X	X					n/a
	Ritchie *et al.* (2008)	24	X	X	X	X		X	X	7/11
	Rouleau *et al.* (2008)	25	X	X	X	X				n/a
Systematic Review	Bennet *et al.* (2005)	26		X					X	9/11
	Chow *et al.* (2008)	27	X					X	X	4/11
	Denton *et al.* (2009)	28		X					X	8/11
	Hinchliffe *et al.* (2008)	29	X						X	7/11
	HOTWG (2005)	30	X	X					X	2/11
RCT	Duzgun *et al.* (2008)	31	X							n/a

Figure 4: Article selection flow-chart for project and summary of topic focus for included articles

Of the thirteen included studies, seven were HTAs, (19-25) five were systematic reviews, (26-30) and one was a randomized controlled trial (see Figure 4). (31) Three of the HTAs were in languages other than English, for which only an English version of the executive summary was used in the synthesis. (21,23,25) Four HTAs studied HBOT as adjunctive therapy for multiple categories of health indications. (19,23-25) The remainder of the included studies focused on a single category of health indications. Following is a breakdown of the types of review identified, according to health condition:

- Diabetic foot ulcers: two HTAs, (20,22) two systematic reviews, (27,29) and one RCT; (31)
- Delayed radiation-induced injury: three systematic reviews; (26,28,30)
- Thermal burns: one HTA; (21)
- Skin grafts & flaps: no exclusive references;
- Revascularization after organ transplantation: no exclusive references.

The results of this literature search were synthesized by HTIS and independently reviewed by a clinical expert in the field.

What is the evidence?

General comments about the evidence

The existing systematic review literature for hyperbaric oxygen therapy for difficult wound healing has several inherent limitations. The first, and most significant, is the lack of large-scale randomized controlled trials. Interviews with local experts suggest two key reasons for this: difficulties coordinating the multi-site studies that would be required to provide an adequate number of research participants, and gaps in funding opportunities for both HBOT research and wound healing research (K. LeDez, President, Undersea & Hyperbaric Medical Society—Canadian Chapter, personal communication, 2011). The gap in research funding in Canada is an ongoing issue, since none of the Canadian Institutes of Health Research have an explicit mandate for hyperbaric medicine or wound healing (K. LeDez, personal communication, 2011).[6]

Applying the findings from existing research to the HBOT facilities in St. John's also has inherent limitations based on variability in the delivery of services. For this study, the most important sources of variability involve differences in the degree to which HBOT is integrated into a wound-care program and the availability of support services for patients undergoing weeks or months of treatment. The greater the degree of integration, the more likely it becomes that patients will be treated in a timely manner, that they will be suitable patients for HBOT, that relevant patient information will be shared among health service providers, and so forth. The availability of support services will increase the likelihood that a patient will complete his or her full course of treatment, which is a key determinant of positive health outcome.

For example, at Hôtel Dieu de Lévis outside Quebec City, the HBOT facility contains modern mono-chambers that are accessible by acute-care patients and patients with limited mobility. The HBOT facility is located adjacent to a 'complex wound clinic' and shares with it a referral and booking system as well as some medical staff. The intensive care unit is located in the same wing of the hospital, two floors down. For accommodations, patients are referred to a non-profit hospice that is directly across the street from the hospital. The hospice offers low-cost rooms for extended stays and access to a common kitchen area for guests to keep food and prepare meals (C. Boutin, Head of the Respiratory and Hyperbaric Department, Centre de médecine de plongée du Québec, personal communication, 2011). As a result, research that relies on data from this facility and others like it may result in health outcomes that are better than what can be reasonably expected from the St. John's HBOT facility, where there is less service integration and fewer supports are offered to patients.

Pressure ulcers and diabetic foot ulcers

The incidence of foot ulcers among people with diabetes is estimated to range from 1.0% to 4.1%, while the lifetime risk ranges from 15% to 25%. (27,32) The most severe health outcome from diabetic foot ulcers is amputation, which is estimated to occur in approximately 0.2% of adults with diabetes or about 3,000 in Canada.(33) Approximately 85% of amputations carried out in Canada are the result of a non-healing foot ulcer and an estimated 50% to 69% of amputees with diabetes die within five years.(34)

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[6] In contrast, a significant amount of HBOT research is supported by the armed forces, both in Canada and the U.S.A. Accordingly, the topics that are studied tend to be quite different, with a focus on young healthy men in combat, peacekeeping and other related situations.

Article Analysis

The number of times individual references were cited by the included review studies, by type of reference cited:

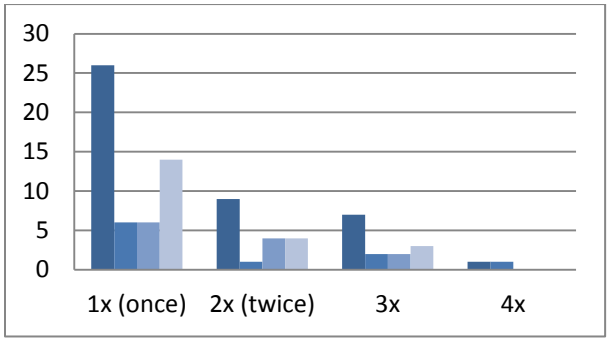


Figure 5: Article analysis for HBOT for diabetic foot ulcers.

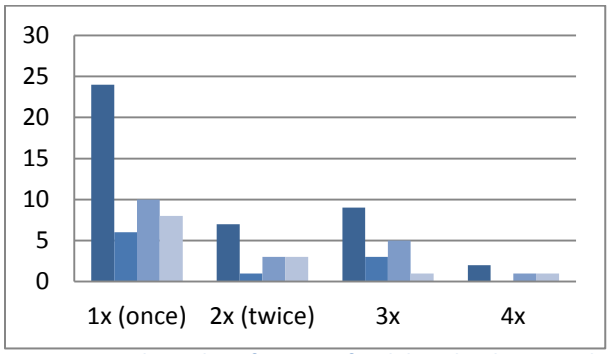


Figure 6: Article analysis for HBOT for delayed radiation-induced injury (DRII).

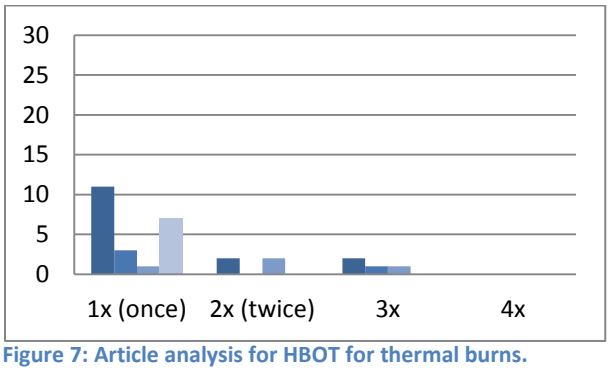


Figure 7: Article analysis for HBOT for thermal burns.

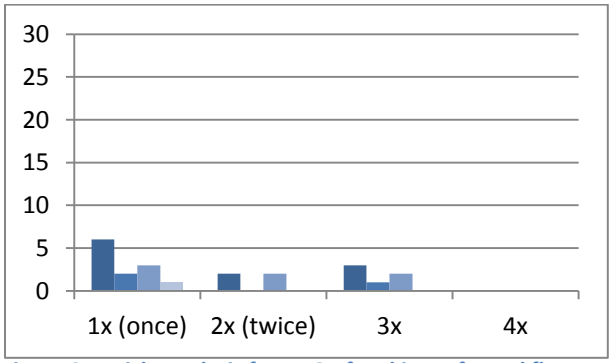
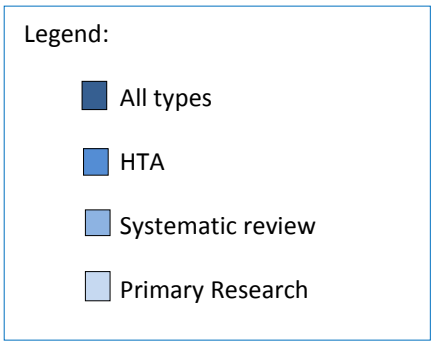


Figure 8: Article analysis for HBOT for skin grafts and flaps.



About the Article Analysis Figures:

These article analyses indicate the degree of overlap of evidence among the included systematic reviews and HTAs included in this report.

Systematic reviews with a high degree of overlap are synthesizing the same primary studies and would be expected to have convergent findings.

Systematic reviews with a low degree of overlap are synthesizing different primary studies, and may or may not be convergent.

Each bar cluster in the graphs indicates the number of times that a primary research study article was cited by the included systematic reviews.

Articles that are only cited once represent no overlap; articles cited twice or more represent overlap.

Patients who have amputations also experience a significant decrease in quality of life and increased risk of injury.(35) The main cost drivers for diabetic foot ulcers are treatment, co-morbidity, injuries related to an amputation, and subsequent amputations. (36) Research from Ontario estimates the average cost of treating a diabetic foot ulcer to have risen to $8,000 in 2007, up from a cost of $4,595 in 1998. The average cost of treating an infected diabetic foot ulcer is estimated to be $17,000. (37,38)

Newfoundland and Labrador has the highest prevalence rate of diabetes in Canada, with an estimated 47,000 cases in 2010.(39) An estimated 26,000 new cases are expected between 2010 and 2020.(39) Based on the predicted rates cited above, an estimated 7,050 people with diabetes in the province will experience some form of foot ulcer during their lifetime, and nearly 100 will require some type of amputation. Data from the Newfoundland and Labrador Centre for Health Information (NLCHI) indicate that, on average, 158 patients with diabetes are admitted to hospital for diabetic foot ulcers each year. Statisticians at NLCHI report that this number is understood to represent the most severe cases and accounts for only a portion of the estimated 15% of persons with diabetes who will develop lower-extremity ulcers over their lifetime (J. Dowden, Statistician, NL Centre for Health Information, personal communication, 2010). The burden of disease represented by diabetic foot ulcers in Newfoundland and Labrador, in terms of either clinical or cost outcomes, has not been estimated.

CADTH identified eight review papers, including six HTAs (19,20,22-25) and two systematic reviews (27,29) as well as one RCT (31) that addressed diabetic foot ulcers. The eight review papers cited a total of sixty-five individual publications. Forty-two of these publications studied clinical health outcomes and twenty-three studied economic outcomes. CADTH also identified one review paper (24) that addressed pressure ulcers. This review paper cited a total of three individual publications based on one RCT. Figure 5 provides an article analysis of references for diabetic foot ulcers cited among the included studies for this report.

Three CADTH references are English abstracts of French, German or Spanish language HTAs which did not contain enough information to be assessed for this report in terms of methodological quality.(21,23,25)

Five of the remaining reviews had high quality methodologies, as rated by the AMSTAR[7] scale:

- De Laet et al. 8/11(19)
- Ritchie et al. 7/11(24)
- Hailey et al. 8/11(20)
- MAS 7/11(22)
- Hinchliffe et al. 7/11(29)

Some references received low AMSTAR scores:

- Chow et al. 4/11(27)
- Cancer Care Ontario's Hyperbaric Oxygen Therapy Working Group (HOTWG) 2/11(27,30)

[7] AMSTAR scores range from 0 to 11, with the following score categories: Low=0 to 4, Middle=5 to 7, High=8 to 11

Before reviewing the findings, an issue concerning terminology should be addressed. The body of the text in the original CADTH report refers to 'diabetic pressure ulcers.' This term is a misnomer that requires correction.

PubMed does not include a Medical Subject Heading (MeSH) for 'diabetic pressure ulcer.' However, the MeSH term 'Pressure Ulcers' is defined as: *"ulceration[s] caused by prolonged pressure on the skin and tissues when one stays in one position for a long period of time"* (PubMed, 1963/2006).

In contrast, the MeSH term 'Diabetic foot ulcer' is defined as: *"[a] common foot problem in persons with diabetes mellitus, caused by any combination of factors such as diabetic neuropathies; peripheral vascular disease; and infection. With the loss of sensation and poor circulation, injuries and infections often lead to severe foot ulceration…"* (PubMed, 1994).

Thus, 'Pressure Ulcer' and 'Diabetic Foot Ulcer' represent two distinct types of wounds produced by different mechanisms. As a result, there is ambiguity in the terminology 'diabetic pressure ulcer' as used by CADTH.

An analysis of the search strings, including systematic reviews and HTAs, as well as the individual studies synthesized by those reviews, indicates that the term 'diabetic pressure ulcer' refers exclusively to 'Diabetic Foot Ulcer' as defined by PubMed. Accordingly, for purposes of clarity and consistency, this report refers to diabetic foot ulcers and does not use the term 'diabetic pressure ulcers.'

The CADTH report finds sufficient evidence to indicate that HBOT is "clinically beneficial and cost-effective as adjunctive therapy" for diabetic foot ulcers, but not for uncomplicated pressure ulcers (p. 10). The main clinical outcomes of interest for diabetic foot ulcers are: wound healing, minor amputation and major amputation[8] (see Table 2). For diabetic foot ulcers, there is broad agreement that HBOT is an effective adjunctive treatment that reduces the risk of major amputation. The available evidence, however, is limited in sample size and power. Nonetheless, one high-quality and frequently cited Cochrane systematic review (40) quantifies the estimated relative risk (RR)[9] of major amputation for patients treated with HBOT, compared with those who do not receive this treatment, to be 0.31 [95% CI 0.13, 0.71], resulting in less than half the number of major amputations. Further, the estimated number needed to treat[10] (NNT) is 4 [95% CI 3, 11] which is very low. The authors of this review paper caution that current findings are likely to change with further research. However, they state this caution with regard to the effect size, not the characterization of the treatment as beneficial in terms of clinical and cost outcomes. (20,31,41)

The CADTH report finds sufficient evidence to indicate that HBOT is ***"clinically beneficial*** and cost effective as ***adjunctive therapy" for*** diabetic foot ulcers, but not for uncomplicated pressure ulcers.

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

[9] Relative risk (RR) is the ratio of the probability of an outcome occurring in a treated or exposed group compared to the untreated or unexposed group (see Glossary).

[10] Number needed to treat (NNT) is the number of patients who need to be treated in order to prevent one additional adverse health outcome (see Glossary).

Diabetic Foot Ulcers: Clinical Outcomes and Effectiveness of HBOT		
Outcome	**Quality of Review (AMSTAR)**	**Evidence** **Conclusion:** finding
Major Amputation		
Clinical Effectiveness	8	**Decrease in risk:** statistically significant evidence RR 0.31 [95%CI 0.13, 0.71]. (19)
	8	**Caution**: sensitive to change with further research, lacking robust RCT evidence. (19)
	8	**Decrease in risk**: HBOT 11% vs controls 32%, "more effective than standard care." (20)
	7	**Decrease in risk:** "therapeutic efficacy [is] suggested." (24)
	7	**Decrease in risk**: statistically significant evidence RR 0.31 [95%CI 0.13, 0.071]. (22) Number Needed to Treat (NNT) to avoid amputation = 4 [95% CI 3 to 11]. (22)
	7	***Caution***: sensitive to change with further research, lacking robust RCT evidence. (22)
	7	**Decrease in risk:** systemic HBOT reduced rates of major amputation, but not topical HBOT.
	7	***Caution:*** sensitive to change with further research, lacking robust RCT evidence.(29)
	n/a	**Decrease in risk**: convergent evidence that HBOT was good for lesions. (25)
	n/a	***Caution***: sensitive to change with further research, lacking robust RCT evidence. (25)
Economic/ Quality of Life Impacts	8	**Unclear:** Potential cost savings, requires better research. (19)
	8	**More cost-effective**: than standard of care (societal perspective), with nearly 20% less costs; if outcomes for HBOT were 10% worse it would still remain dominant therapy. (20)
	8	**Breakeven point**: $17,000 (CND), current cost $3,652. (20)
	8	**Positive impact on QoL**: significant increase in QoL (HBOT, 3.64, Standard care, -3.01). (20)
	7	**More cost-effective**: consistently cost-effective (societal perspective) compared to standard care or HBOT plus placebo. (24)
	7	**More cost-effective**: nearly 90% less costs compared to amputation, saving approximately $54,000 (CND). Relatively cost-effective from both payers' and societal perspective (US research) with an incremental cost per additional QALY gained of approximately $27,310, $5,166, and $2,255 at the 1, 5, and 12-year periods. (22)
	4	**More cost-effective**: if used long term (societal perspective); Incremental costs per QALY for 1 year, $27,310 (USD), 12 years $2,255. (USD). (27)
	4	***Caution***: Number of HBOT treatments/case, costs of amputations/case, costs of HBOT treatment had significant impact on cost-effectiveness. (27)
Minor Amputation		
Clinical Effectiveness	8	**Possible increase in risk**: indications for increased risk RR 2.20 [95%CI 0.56, 8.72], not statistically/clinically significant. (19)
	8	***Caution***: sensitive to change with further research, lacking robust RCT evidence. (19)
	8	**Possible increase in risk**: HBOT 27% vs controls 15%, , not statistically or clinically significant. (20)
	8	**Possible increase in risk**: not statistically or clinically significant. (24)
	7	**Possible increase in risk:** estimates 1 minor amputation for every 11 patients treated with HBOT. (22)
	7	***Caution***: sensitive to change with further research, lacking robust RCT evidence. (22)
Wound Healing		
Clinical Effectiveness	8	**Improved wound healing**: 33% greater decrease in wound size, [95%CI 18.97, 47.03]. (19)
	8	***Caution:*** very sensitive to change with further research, drawn from single study with N=16. (19)
	8	**Improved wound healing**: HBOT 83% vs controls 43% (significance not calculated). (20)
	7	**Insufficient evidence.** (24)
	7	**Improved wound healing.** (22)
	7	**Insufficient evidence.** (29)
Economic/ Quality of Life Impacts	8	**Possible shorter hospital stay**: HBOT: 47.1 days (range 43.2 - 57.6 days)|Control: 56.9 days (range 50.8 -72.8 days). (20)
	7	**Insufficient evidence.** (24)
Pressure Ulcers: Clinical Outcomes and Effectiveness		
General		
Clinical Effectiveness	7	**Insufficient evidence.** (24)
	n/a	Not recommended (23)

Table 2: Evidence for clinical and cost effectiveness of HBOT for diabetic foot ulcers

One paradoxical consequence of the reduction in risk for major amputation in patients with diabetic foot ulcers treated with HBOT appears to be an increase in the risk for minor amputation. It is widely interpreted that this documented (but not statistically significant) increase in minor amputations is reflective of the mitigating effect of HBOT on diabetic foot ulcers. While HBOT reduces the degree of severity of the wound, it does not entirely reduce the risk for any amputation.

The main economic outcomes of interest for the treatment of diabetic foot ulcers with HBOT are those of cost effectiveness[11], cost utility[12] and length of hospital stay. The literature reviewed was consistent in finding HBOT to be cost-effective from a societal perspective when compared with standard of care or placebo. The quantification of cost effectiveness is complicated by factors including differences in health insurance systems between countries and access to additional care within regions and population sub-groups. Estimates from Canada suggest that HBOT for diabetic foot ulcers results in 20% lower costs overall compared to standard treatment and 90% lower costs compared to amputation.(20,22,24,27) Chow et al. caution that the cost of amputations and the number of treatments per case have a significant impact on cost effectiveness.(27) However, Hailey and colleagues (20) find that HBOT would still be the most cost-effective treatment for diabetic foot wounds, even if clinical outcomes were 10% less beneficial to the patient. The same authors also found that the costs of HBOT would need to rise to $17,000 per patient in order for HBOT to be deemed less cost-effective than the current standard of care, which they estimated to be an average of $3,652 per patient. Fewer reviews studied cost utility but, among those that did, there is convergent evidence indicating that HBOT provides greater quality of life (QoL) outcomes than the standard of care. In one high-quality HTA from Canada, (20) the authors found a statistically significant improvement in QoL scores resulting from HBOT. Research evidence from the U.S.A. indicates that, for HBOT treatment of diabetic foot ulcers, the additional costs per QALY range from $27,310 for the first year to $2,255 over a 12-year period. Fewer still of the included studies considered length of hospital stay as a distinct health economic variable, but in considering the effectiveness of HBOT in wound healing for diabetic foot ulcers, Hailey and colleagues found a decrease in hospital stay of 17% or 9.8 days.(27)

Insufficient evidence was available to evaluate the clinical or economic benefits of HBOT for pressure ulcers.

Delayed radiation-induced injuries

Delayed radiation-induced injuries (DRII) may arise from any form of radiation therapy for cancer. These injuries are categorized as a form of 'radiological disorder' and accounted for 291 patients and 439 hospital separations in Newfoundland and Labrador between 2002-2003 and 2007-2008. A detailed analysis of the specific types of delayed radiation-induced injuries encountered in the province is not available. Interviews with local experts indicate that the number of admitted patients underestimates the total number of patients with DRII since many, if not most, are treated as outpatients (K. LeDez, President, Undersea & Hyperbaric Medical

[12] Costs-effectiveness study: the monetary costs of an intervention are considered in terms of a single common health outcome that is measured in natural units. In the case of HBOT, outcomes may include: wound resolution, major amputation, and graft revascularization.

[13] Cost-utility study: the monetary costs of an intervention are considered in terms of a single outcome or of multiple outcomes that are valued in relative terms. The combined outcome is measured in units that capture both the quantity and quality of the effects of the intervention. The most common measure is the quality-adjusted life-year or QALY (see Glossary).

Society, Canadian Chapter, personal communication, 2011). In addition, predicting the number of potential DRII patients who will be eligible for HBOT is complicated by various factors, including new developments in oncology treatment, changes in survival times for treated patients, and increases in rates of diagnosis. Our interviews also revealed that the number of specific HBOT referrals for DRII appears to have risen recently due to some increases in the dosage of radiation being used to treat certain cancers and a higher level of awareness about using HBOT as an adjunctive therapy for DRII.

HBOT research has focused mainly on DRIIs in two types of cancers: soft tissue injuries from pelvic region cancer radiation treatments and bone-related injuries from head and neck cancer radiation treatments.

Pelvic region DRIIs include radiation proctitis and radiation rectitis, which may occur as a result of radiation treatments for cancer of the prostate, testis, ovary, cervix, uterus, urinary bladder or rectum. The incidence of radiation proctitis/rectitis is strongly influenced by the type of radiation therapy used and the amount of radiation absorbed by the patient. Depending on the specific technique, incidence rates have been estimated from 5% to 20%.(42,43) Incidence rates of many pelvic-region cancers, such as prostate or ovary cancer, increase with age. Consequently, rates of these cancers and related side-effects such as radiation proctitis/rectitis are expected to increase with the aging of the population in Newfoundland and Labrador.

Head and neck region DRIIs mainly affect the jaw and teeth. Similar to radiation proctitis/rectitis, head and neck DRIIs are strongly influenced by the type of radiation treatment and the amount of absorbed radiation. The incidence of mandibular osteoradionecrosis,(44,45) (i.e., degeneration of the jaw bone following radiation treatment) has been estimated to range between 1.8% at doses of 6,000 cGy to 9% at 7,000 cGy.(44)

CADTH identified four HTAs (19,23-25) and three systematic reviews (26,28,30) that addressed HBOT for the treatment of a broad range of DRII. The seven review papers cited a total of forty-four individual studies. Forty-three studies examined clinical health outcomes and three examined health economic outcomes (Figure 6). Two of the publications referred to by CADTH are English summaries of French and Spanish language HTAs and were not assessed in terms of methodology. (23,25) The two remaining HTAs and two systematic reviews scored high on the AMSTAR scale:

- De Laet et al. 8/11(19)
- Ritchie et al. 7/11(24)
- Denton et al. 8/11(28)
- Bennett et al. 9/11(26)

One systematic review scored low: HOTWG, 2/11(30).

A range of DRIIs are possible candidates for adjunctive HBOT (Table 3). The main clinical outcomes of interest across these conditions are: decreased inflammation and/or infection, successful resolution of injury, and improved quality of life scores.

The CADTH report finds evidence that adjunctive HBOT is “beneficial” for osteoradionecrosis and radiation rectitis/proctitis; however the report does not find the strength of the evidence to be sufficient to call for the *routine* use of HBOT for these conditions. However, our local experts pointed out that ‘routine use’ of HBOT in Newfoundland is quite rare: most patients with non-healing wounds are referred for HBOT only after having undergone a series of other unsuccessful treatments.

Delayed radiation-induced injury		
Outcome	**Quality of Review (AMSTAR)**	**Evidence Conclusion:** finding
General		
Clinical Effectiveness	n/a 2	**"Controversial."** (23) **Insufficient evidence:** Limited research available and conflicting evidence. (30)
Radiation rectitis/proctitis		
Clinical Effectiveness	9 8 8 7 n/a	**Improved healing:** compared to placebo across several primary outcome measures including symptoms and resolution, secondary measures included mortality, co-morbidity and QoL scores (RR: 2.7, [95%CI 1.2 to 6.0] p = 0.02). Number Needed to Treat (NNT) = 3. (26) **Improved healing:** compared to placebo. (28) ***Caution***: sensitive to change with further research, lacking robust RCT evidence. (28) **Improved healing**: statistically significant greater likelihood of healing or improvement of proctitis (RR=2.67; 95% CI: 1.19, 5.99; p=0.02), significantly improved SOMA-LENT scores (5.00 in the HBOT group versus 2.61 in the sham HBOT group (p=0.0019)). (24) **Improved healing.** (25)
Osteoradionecrosis, head & neck soft tissue (*as treatment)*		
Clinical Effectiveness	9 9 8 8 7 7 2	**Improved healing**: despite negative findings in most recent RCT, evidence indicates better outcomes with HBOT treatment. (26) ***Caution:*** Limited research available, and differences in measuring clinical health outcomes falsely indicating divergent conclusions. (26) **Improved healing**: complete resolution (RR 1.41 [95% CI 1.14, 1.75]); head and neck wound dehiscence (RR 8.67 [95% CI 2.73, 27.49]), complete mucosal cover healing (RR 1.38 [95% CI 1.19, 1.61]), healing of tooth sockets after tooth extraction (RR 1.35 [95% CI 1.08, 168]); further research to clearly establish clinical effectiveness (from one SR with 6 RCTs [447 patients]). (19) ***Caution***: further research needed to clearly establish clinical effectiveness. (19) **Improved healing**: head and neck wound dehiscence. (24) ***Caution***: sensitive to change with further research, lacking robust RCT evidence. (24) **Insufficient evidence**: Limited research available. (30)
Economic/ Quality of Life Impacts	8 7	**Possibly cost-effective**: available evidence indicates decreased costs, but insufficient to generalize (from two studies). (19) **Possibly cost-effective**: available evidence indicates decreased costs, but insufficient to generalize (from two studies). (24)
Osteoradionecrosis, head & neck soft tissue *(as prevention*)		
Clinical Effectiveness	7 7 7	**Effective prophylaxis**: more effective than antibiotics (RR=1.4, 95% CI: 1.1, 1.7; p=0.009). (24) **Effective for dental implants:** fewer failures with HBOT compared to controls (8.1% versus 53.7%; p=0.0009). (24) ***Caution***: sensitive to change with further research, lacking robust RCT evidence. (24)
Urinary Bladder		
Clinical Effectiveness	9 7 2	**No available evidence.** (26) **Insufficient evidence** (interstitial cystitis). (24) **Insufficient evidence**: Limited research available (interstitial cystitis). (30)
Breast/chest wall		
Clinical Effectiveness	7 2	**No available evidence.** (24) **Insufficient evidence**: Limited research available. (30)
Bowel		
Clinical Effectiveness	7	**No available evidence.** (24)
Neurological tissues		
Clinical Effectiveness	7 7	**Insufficient evidence and/or no significantly improved healing** (brain irradiation).(24) **No significantly improved healing** (brachial plexopathy). (24)

Table 3: Evidence for clinical and cost effectiveness of HBOT for delayed radiation-induced injury

The evidence cited by the CADTH report for HBOT treatment of radiation proctitis/rectitis indicates consistent, statistically significant improvements across a range of clinical outcomes, including degree of healing, resolution of injury, quality of life and improved SOMA-LENT[13] scores (see Table 3). Similarly, the evidence for HBOT treatment for prevention of head and neck injuries to soft and bony tissue indicates improvement, but the findings are of limited strength. For example, De Laet and colleagues (19) found improved healing with HBOT treatment of osteoradionecrosis across several clinical health outcomes; however, the evidence is taken from a limited number of studies with few participants and sometimes incommensurate outcome measures.

It should also be noted that the research studies on adjunctive HBOT for other types of DRII are consistent in finding no significant negative effects. Instead, where data is available, there are consistent and repeated findings of small improvements in wound healing. The lack of statistically significant positive findings should not be interpreted as evidence that the treatment is not effective; rather, it may be the case that the existing studies have too few research participants to statistically detect an actual treatment effect. In other words, while there is insufficient evidence to indicate HBOT is an effective adjunctive treatment for other forms of DRII, it should not yet be ruled out as ineffective.

The literature included in the CADTH synthesis sought out evidence for other forms of delayed radiation-induced injuries, including to the bowel, urinary bladder, breast and chest wall, and to neurological tissue. In these cases, there was either insufficient evidence or no evidence at all due to a lack of published research. Very little health economic research has been carried out on the cost-effectiveness of HBOT for DRII. Ritchie et al. and De Laet et al. published findings on cost effectiveness from the same studies, (24,45) and both suggested that using HBOT for osteoradionecrosis would generate savings from the societal perspective as compared to a "conservative" treatment option. Reduced hospital stays and fewer future health complications were the main drivers for these savings.

Thermal burns

When compared with other injuries, relatively few cases of severe thermal burns occur in Canada. One study estimated the number of children admitted to hospital for burns at 12.6/100,000.(46) Among the adult population admitted to hospital for burn treatment, North American estimates are 30 per 100,000 patients, with approximately 4.2/100,000 requiring specialized burn treatment/ admission to a burn-care centre.(47) However, costs for treating severe burns are often estimated to be among the highest for all injuries.(48)

Interviews with local experts indicate that severe burns are now less prevalent in Newfoundland and Labrador than they were twenty years ago, and that the drop in numbers can be attributed mostly to the decrease in use of deep fat fryers in the home (M. Cashin, Wound Care Consultant, Acute Care, Eastern Health, personal communication, 2011). Data for severe burns in the province are limited mainly to children. Between 1995 and 2001, NLCHI reports that there were 157 hospital separations for children aged 0 to 16 years with severe burns. (49) Burns were more common among aboriginal children - 84.3 per 100,000 - than among those of European descent- 19.0 per 100,000.

CADTH identified five HTAs (19,21,23-25) that studied HBOT for the treatment of thermal burns (Table 4). The five review papers cited a total of seventeen individual references. Sixteen references studied clinical outcomes and one studied health economic outcomes only (Figure 7).

[13] SOMA-LENT is a scale to measure Late Effects on Normal Tissue (LENT) from radiation therapy, from several perspectives: Subjective, Objective, Management, Analytic (SOMA).

Thermal burns		
Outcome	**Quality Of Review (AMSTAR)**	**Evidence Conclusion:** finding
General		
Clinical Effectiveness	7 n/a n/a n/a	**Insufficient evidence.** (24) **Insufficient evidence.** (25) **Insufficient evidence**: Evidence of reduced wound healing time, but not conclusive. (21) **Not recommended.** (23)
Graft success		
Clinical Effectiveness	8	**No improvement**: No evidence for graft success (RR 2.00 [95%CI 0.50, 8.00]). (19)
Mortality		
Clinical Effectiveness	8 n/a	**No improvement**: No evidence for reducing mortality (RR 0.98 [95%CI 0.37, 2.64]). (19) **No improvement.** (21)
Sepsis		
Clinical Effectiveness	n/a	**Unclear**: contradictory findings from two studies, neither significant. (21)

Table 4: Evidence for clinical and cost effectiveness of HBOT for thermal burns

Three of the CADTH references are English summaries of other language HTAs and could not be assessed in terms of methodology. (21,23,25) The two remaining HTAs scored high on the AMSTAR scale: De Laet et al. 8/11(19) and Ritchie et al. 7/11. (24) In agreement with each of the included HTAs, the CADTH report finds insufficient evidence to support HBOT as a treatment for thermal burns.

The most relevant evidence comes from a high-quality and thrice-cited (19,24,25) Cochrane review by Villanueva and colleagues (50) that specifically focuses on HBOT for thermal burns. This systematic review searched for RCTs that compared HBOT for thermal burns against a control group and that reported on at least one out of nine possible health outcomes.[14] Only two studies were identified that met the eligibility criteria; both studies were poor in methodological quality and had small sample sizes. Consequently, they did not provide adequate evidence to support or contradict the use of HBOT for thermal burns. This result is similar to that found in the other included systematic reviews. CADTH found what little research exists to be characterized by poor methodological quality and small study groups that do not provide the evidence base required to determine the clinical effectiveness of HBOT treatment for thermal burns.

Skin grafts & flaps

CADTH identified three HTAs that looked at HBOT for the treatment of skin grafts and skin flaps. (19,24,25) The three review papers cited a total of eleven individual references, all of which studied clinical health outcomes (Figure 8).

[14] The studied health outcomes were: mortality, major morbidity, healing time, need for grafts and/or debridement, length of stay, pain scores, activities of daily living, and adverse effects from HBOT.

One of the CADTH references is an English summary of a French HTA and was not assessed in terms of methodology. (25) The two remaining HTAs scored high on the AMSTAR scale: De Laet et al. 8/11, (19) Ritchie et al. 7/11. (24) In agreement with the included HTAs, the CADTH report concluded there is insufficient evidence to support or contradict HBOT treatment for skin grafts or for skin flaps (Table 5).

Skin grafts and flaps		
Outcome	**Quality of Review (AMSTAR)**	**Evidence Conclusion:** finding
General		
Clinical Effectiveness	8 7 n/a	**Improved healing**: compared to standard care, for acute soft tissue ischemia (based on 1 RCT) ***Caution****:* very sensitive to change with further research, lacking robust RCT evidence to form conclusion.(19) **Insufficient evidence.** (24) **Not more effective**: except in cases of radio-necrosis, as mentioned above.(25)

Table 5: Evidence for clinical and cost effectiveness of HBOT for skin grafts and flaps

Revascularization after organ transplantation:

CADTH did not identify any research-based evidence for HBOT for post-transplantation revascularization (Table 6). Published articles in this field of research consist mainly of animal models or human case studies, neither of which provides an adequate evidence base for the purposes of this report. Nonetheless, there is growing basic bio-medical evidence that suggests that HBOT should trigger biochemical, proteomic and genomic processes that would "condition" the donor's organ to better withstand the stresses of the transplant procedures. (54)

Revascularization after organ transplantation		
Outcome	**Quality of Review (AMSTAR)**	**Evidence Conclusion:** finding
General		
Clinical Effectiveness	7	**Insufficient evidence.** (24)

Table 6: Evidence for clinical and cost effectiveness of HBOT for post-organ transplantation revascularization

The Newfoundland and Labrador Context

Throughout the course of this project, the specific characteristics of the province have been considered in relation to the research topic. Through individual interviews, as well as a panel discussion, we have identified contextual factors that may influence the relevance and applicability of the research-based evidence. Some of these factors have already been described and addressed in the body of the text.

Following is a comprehensive and categorized table that lists factors of relevance to contextualization.

Client-related factors	
Demographics	Demographic trends in NL indicate an increase in the prevalence of risk factors for diabetic foot ulcers, including: an aging population, increasing rates of diabetes and overweight, and persistent high rates of smoking. The number of prospective NL patient referrals to HBOT for wound healing is expected to increase.
Geographic/ cost factors for patients	Patients who live significant distances from St. John's must travel a long way to access HBOT for wound healing. These same patients also require accommodations in St. John's for weeks or months at a time. Lost time from work can be another significant out-of-pocket expense for patients. As a result of these geographic and cost factors, patients may leave St. John's before their full course of HBOT treatment has been completed, which can be expected to decrease the effectiveness of the hyperbaric oxygen therapy. ○ The local HBOT team is experimenting with different treatment protocols for out-of-town patients that would reduce requirements for length of stay in St. John's. One new protocol would see patients being treated twice a day instead of once a day, reducing length of stay by 50%. ○ Tele-health services may be a useful means to consult with out-of-town patients about HBOT services prior to their arrival.
Awareness	The public is learning more about HBOT independently through media, hyperbaric and patient advocacy groups, and online sources. Elevated awareness of HBOT as a treatment option may increase the rate of patients self-referring or directly requesting referrals from their physicians. Some of these patients may not be good candidates for HBOT and might put additional work demands on staff while decreasing the overall effectiveness of the facility.

Table 7: Factors of Relevance in Contextualization for Newfoundland and Labrador

Factors related to site of service/service design	
Location	The HBOT facilities in the Health Sciences Centre are located outside of the patient-care areas of the hospital. This may make accessing the HBOT chambers problematic for patients with limited mobility and especially challenging for patients arriving from outside the Health Sciences Centre: ○ Travel through public areas increases the risk of infections, especially for immune-compromised patients. Since many patients with non-healing wounds are immune-compromised, this is a serious concern for HBOT. ○ Increased travel, in general, for patients with non-healing wounds can exacerbate the wounds or worsen co-morbid conditions. This is especially the case for patients who are far from St. John's or who are in-patients at other care centres in the city and require inter-facility transportation. ○ Entering and leaving the multi-place chamber is physically challenging and may exacerbate non-healing wounds.
Design	Problems in the design of the main oxygen line for the hospital are interfering with the delivery of oxygen to the mono-place chambers. As a result, the mono-place chambers are currently using replaceable oxygen canisters, a more expensive option.
Directing patients	Differing signage protocols between Eastern Health and Memorial University have presented challenges in providing adequate directional signs to guide patients to the hyperbaric oxygen facilities. As a result, cost efficiency is compromised in two ways: (a) Patients are more likely to get lost and be late for appointments and (b) employees at the facility are required to spend valuable treatment time guiding patients through the Health Sciences Centre to locate the facility.
Factors related to health human resources	
Capacity	At current available health human resource levels, capacity for HBOT operations exceeds actual utilization levels. Cost efficiencies will improve when utilization of the facility increases to meet its operating capacity.
Availability	In the past, availability of appropriate human resources was a major factor in the ability to deliver HBOT services. As a result, past systems of service delivery saw a significant proportion of HBOT delivered at the end of the standard working day, which increased costs because personnel were working overtime hours. There are now four additional physicians who have been trained to deliver and oversee HBOT treatments. This development is expected to alleviate previous human resource capacity problems.

Table 7: (continued) Factors of Relevance in Contextualization for Newfoundland and Labrador

Factors related to health human resources (continued from previous page)	
Training and Safety	There is currently a shortage of appropriately trained nurses and respiratory therapists to accompany unstable, intensive care, or critical care patients into the HBOT multi-place chamber. This particular issue is compounded by the fact that, due to safety issues, personnel accompanying patients inside the multi-place chamber are limited to participating in one hyperbaric treatment per day. As a result, cost effectiveness of the multi-place chamber, which can treat up to six patients per session, is limited. The cost effectiveness of the two mono-place chambers is also limited by the lack of specialized personnel available to attend patients. However, unlike the multi-place chamber, personnel can attend multiple sessions throughout a day for the mono-place chambers, which may result in increased cost effectiveness for this option.
Pediatric cases	Additional health human resources are required when treating pediatric patients with HBOT. Currently, there are no specialized pediatric personnel or equipment available for the HBOT facilities.
Record-keeping	The efficiency of local HBOT is undermined by gaps in record-keeping and data collection that will require additional human resources support. The ability to better monitor treatments will enable HBOT staff to identify strengths and weaknesses in facility operations and to tailor services to be more effective and cost-efficient.
Education/Orientation	There are challenges to raising awareness and building expertise for appropriate wound-care management among referring physicians, patients and health system administrators. There may be a requirement for increased human resources to support initiatives that will educate and orient relevant groups about HBOT in the province.

Table 7: (continued) Factors of Relevance in Contextualization for Newfoundland and Labrador

Factors related to organization and delivery of services	
Appropriateness of referrals	While most referrals to the HBOT service are appropriate, a significant minority are not. Inappropriate referrals can be expected to decrease the clinical effectiveness and/or cost effectiveness of HBOT: ○ In some cases, physicians in the province are either uneducated or misinformed about the approved medical conditions for HBOT or the clinical indications used to assess eligibility for HBOT. As a result, they may make inappropriate referrals or fail to make referrals in cases where HBOT is explicitly indicated. ○ Bed shortages can arise in acute-care facilities (particularly in St. John's) due to a lack of appropriate wound-care beds or alternative discharge options. As a result, admitted patients who have had extended hospital stays without noticeable progress in wound recovery may be referred for HBOT on the basis of mitigating bed shortages rather than being referred on the basis of their particular clinical indications. ○ Increased exposure to HBOT in medical school and through continuing medical education may improve levels of knowledge concerning appropriate referrals.
Integration with wound-care management	HBOT for non-healing wounds is expected to be most effective when integrated into a standardized wound-care management program. Eastern Health and some of the other RHAs have established wound-care clinics, but lack a standardized wound-care program. As a result, the effectiveness of HBOT may be lower than reported in the research literature.
Acute-care vs. Chronic-care approaches	The current administration of HBOT in Newfoundland and Labrador places a dual acute-care/chronic-care service solely within an acute-care program (Emergency Ambulatory Care Services, Eastern Health). Acute-care programs have mandates and objectives that are different from, and may be in conflict with, the chronic-care needs and goals of HBOT. Furthermore, the chain of command between program administrators and the HBOT staff is not as robust as it could be and may need strengthening.[15] These organizational factors may influence the implementation and delivery of HBOT services and consequently the clinical effectiveness and/or cost efficiency of the therapy.
Service efficiencies	Past systems for dealing with wound care, including the streamlining of products and services that were expected to improve cost efficiency and the integration of wound-care management with other services, appear to have been lost in the transition to the present regional health authority system.

Table 7: (continued) Factors of Relevance in Contextualization for Newfoundland and Labrador

[15] Local administrators identified a lack of knowledge about HBOT and expressed interest in a having a half-day seminar to explain the results of this study and to learn more about HBOT.

Other system factors	
Effective communications	There are challenges in communication between family physicians and specialists treating patients with non-healing wounds. In particular, information related to previous and ongoing treatments is not always accurately shared and a common platform to share this information is lacking. As a result, treatment planning may be less than optimal and the clinical outcomes less robust than expected. In addition, where some tests, treatments or consultations are repeated unnecessarily, the costs per patient may be higher than necessary.
Capacity and chamber issues	An increase in referrals, even if for appropriate patients, will not be absorbed into the present system easily. Increased capacity and a resolution to chamber functionality issues will be required to meet increased demand.
Impact of emergency cases	Emergency cases are unpredictable and have an impact on elective cases in terms of wait times and processing. Emergency cases can delay HBOT for elective treatments and decrease its efficiency.
Economic factors	
Remuneration for multi-place chamber vs. mono-place chamber use	A significant challenge to the cost effectiveness of HBOT services has been the existence of remuneration inequities in treating multiple patients simultaneously vs. treating one patient at a time. The multi-place chamber is more cost-effective than the mono-place chambers since it can treat several patients simultaneously. However, until recently, physicians were remunerated at the full rate for only the first patient treated in the multi-place chamber and thereafter at a fractional rate for additional patients. As a result, the more efficient HBOT chamber had been underutilized.
Overtime	Until recently, HBOT was typically delivered after standard work hours, requiring non-medical staff to be remunerated at overtime rates. This issue arose from a disincentive to supervising physicians when it came to offering treatment during normal work hours; namely, they earned less administering HBOT than they did carrying out other clinical duties. In turn, the overtime issue made the service less cost-effective, with the facilities being under-utilized during regular hours and patients being required to remain in hospital for longer than necessary.
Costs borne by patients	Out-of-pocket costs, including travel, accommodations and lost work time, may dissuade patients from obtaining timely and effective HBOT wound care (as mentioned above).

Table 7: (continued) Factors of Relevance in Contextualization for Newfoundland and Labrador

Political factors	
Requirement for a Canadian HBOT indications system	In Canada, indications for HBOT are determined by the US-based UHMS. The UHMS does not use a strictly evidence-based system to include/exclude HBOT indications, and may be influenced by political factors within the US health system. A newly formed Canadian Chapter of the UHMS could provide a more flexible and appropriate set of indications for HBOT.
Credentials	Provincial credentialing for hyperbaric medicine is expected to increase the level of expertise, competencies and skill for relevant health professionals, which in turn is expected to increase the effectiveness of HBOT for all conditions, including non-healing wounds.
Public expectations for services	The original impetus behind the recent upgrading of the facilities was public outcry over the unavailability of services. As the new HBOT services are implemented, public expectations for continued access to those services are likely to be high.
Public awareness about HBOT uses	Due to a lack of professional awareness about HBOT for chronic conditions, in particular, non-healing wounds, significant demand is expected to be consumer-directed. Non evidence-based claims of HBOT effectiveness for some conditions, (e.g., HBOT for cerebral palsy or autism) have been reported despite conclusive debunking (28 in WE). Awareness initiatives directed to the public are expected to help counterbalance these claims and mitigate public expectation for services.
Impact of private services	There have been rumors of a private facility being opened in Central Newfoundland and Labrador that may offer HBOT services for conditions that lack an evidence base or for which HBOT is not an indicated treatment. Such privately provided services could increase demand on publicly provided HBOT for conditions that are not supported by clinical evidence. At present, there is no credentialing system for HBOT that would serve to protect the public from unqualified private service providers.

Table 7: (continued) Factors of Relevance in Contextualization for Newfoundland and Labrador

Implications for Decision Makers

Evidence for the clinical and cost effectiveness of HBOT for difficult wounds, and the contextualization of this evidence for Newfoundland and Labrador, reveal several implications for decision makers:

1. Hyperbaric oxygen therapy is expected to be a clinically effective adjunctive therapy for non-healing diabetic foot ulcers for patients in Newfoundland and Labrador, in terms of both *health* outcomes (such as a reduction in major amputation) and *quality of life* outcomes. HBOT is also expected to be cost-effective from a societal perspective in treating such conditions.
2. HBOT is expected to be a clinically-effective adjunctive therapy for delayed radiation-induced injuries for patients in Newfoundland and Labrador who have been treated for cancers in the head, neck, and pelvic regions. It is unclear, however, whether HBOT for these difficult wounds is cost-effective.
3. Existing research evidence does not support or contradict HBOT for other difficult wounds included in this study, namely: pressure ulcers, delayed radiation-induced injuries in parts of the body other than the head, neck and pelvic regions, severe thermal burns, skin grafts and skin flaps, or post-transplantation revascularization.
4. The overall incidence of difficult wounds is expected to increase as a result of various trends, including increased life expectancies, higher prevalence of chronic disease, and improvements and/or changes in the treatment of cancer, diabetes and other chronic diseases. An increase in the number of patients that can be treated both effectively and efficiently with HBOT will improve its overall cost effectiveness. This economic impact will result from the fixed costs of HBOT being divided among a greater number of patients. Cost effectiveness also improves with faster and/or more complete healing of non-healing wounds. Improved healing decreases both direct and indirect costs to the healthcare system that would otherwise be incurred in treating such wounds.
5. Clinical and cost benefits of HBOT for diabetic foot ulcers and DRII are contingent on the appropriate and timely referral of patients. Physician education will play a major role in maximizing appropriate referrals which, in turn, will have a positive impact on the clinical and cost effectiveness of the therapy.
6. Implementing an integrated wound-care management program is expected to result in significant improvements to the clinical and cost effectiveness of HBOT. Establishing HBOT within an integrated wound-care program would also influence several contextual factors that are expected to have beneficial health and economic outcomes. These contextual factors include: the site and design of the service (e.g., the distance between in-patient areas, admitting, and the HBOT facilities), organization and delivery of services (e.g., appropriateness of treatment programs/referrals), and other system factors (e.g., more effective communications among healthcare providers). The review literature draws on evidence that tends to come from jurisdictions where wound management is an integrated service within the healthcare system. The lack of integration of wound management within other healthcare services and programs is expected to reduce overall clinical effectiveness and cost efficiency of HBOT for non-healing wounds when compared with reports from the review literature.

7. The overall scarcity of research on HBOT for non-healing wounds implies that future studies will have a significant impact on the evidence base. For health conditions with insufficient evidence to support or contradict HBOT as effective, new research may provide more definitive answers. Decision makers should expect evidence for new applications of HBOT for chronic conditions and non-healing wounds.

Our interviews with local experts and decision makers also revealed some problems related to governance in terms of HBOT in Newfoundland and Labrador. Specifically, there were concerns from both practice and policy stakeholders that there is no obvious and appropriate administrative locus for HBOT within Eastern Health. HBOT is not yet adequately utilized to warrant its own program within the health authority, serving only a small number of emergency cases and increasing numbers of patients with chronic conditions, while being administered through Ambulatory Acute Care. At several meetings, it was suggested that education and orientation sessions for decision makers should be undertaken in an effort to explore the full range of HBOT services available and to identify any future problems and challenges anticipated for hyperbaric oxygen therapy in Newfoundland and Labrador.

References

(References 19-31 are the articles that were included in the synthesis of this report)

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