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Adjunctive Hyperbaric Oxygen
Therapy for Diabetic Foot Ulcer:
An Economic Analysis



Supporting Informed Decisions

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CADTH
600-865 Carling Avenue
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Tel. (613) 226-2553
Fax. (613) 226-5392
Email: pubs@cadth.ca

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Canadian Agency for Drugs and Technologies in Health

**Adjunctive Hyperbaric Oxygen Therapy for
Diabetic Foot Ulcer: An Economic Analysis**

David Hailey¹
Philip Jacobs²
Douglas C. Perry³
Anderson Chuck²
Andra Morrison⁴
Rhonda Boudreau⁴

March 2007

¹ Department of Community Health Sciences, University of Calgary, Calgary AB

² Department of Public Health Sciences, University of Alberta, Edmonton AB

³ Misericordia Hospital, Edmonton AB

⁴ Canadian Agency for Drugs and Technologies in Health, Ottawa ON

Reviewers

These individuals kindly provided comments on this report.

External Reviewers

Craig Mitton, PhD
Assistant Professor, University of
British Columbia
Vancouver BC

Kenneth M. LeDez, MB ChB FRCPC
Associate Professor
Memorial University of Newfoundland
St. John's NL

CADTH's Scientific Advisory Panel Reviewers

Charles Wright, MD MSc
Consultant in Medical & Academic Affairs
Program Planning & Evaluation
Toronto ON

Robert C. Lee, Bsc BscEd MSc
Director, Calgary Health Technology
Implementation Unit
Foothills Medical Centre
Calgary AB

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CADTH takes sole responsibility for the final form and content of this report. The statements and conclusions in this report are those of CADTH and not of its Panel members or reviewers.

Authorship

David Hailey, Philip Jacobs, and Andra Morrison participated in planning the project, which was coordinated by David Hailey. David Hailey drafted the clinical review and conclusions, and reviewed and revised all sections of the report. Philip Jacobs directed the analyses of cost effectiveness and health services impact, drafted the sections on these topics, assisted with the selection of clinical studies, and reviewed all sections of the report. Douglas Perry provided clinical content expertise and reviewed manuscript drafts. Anderson Chuck developed and implemented the decision model used in the economic analysis. Andra Morrison designed and performed the literature search, wrote material in the report related to literature searching, and verified bibliographic references. Rhonda Boudreau assisted with data extraction and study quality scoring for the clinical review.

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Conflicts of Interest

No conflicts of interest were declared by any of the authors.

Dr. Kenneth LeDez declared that a small portion (less than 15%) of his income is derived from treating patients in a hyperbaric chamber. Of that income, less than 5% is derived from treating diabetic wounds. There is a possibility that a report favourable to hyperbaric treatment of diabetics could lead to a modest increase in referrals of such patients.

Adjunctive Hyperbaric Oxygen Therapy for Diabetic Foot Ulcer: An Economic Analysis

Technology and Condition

Adjunctive hyperbaric oxygen therapy (HBOT) for diabetic foot ulcer (DFU), a complication of diabetes mellitus, in adults and children.

The Issue

An estimated 240,000 to 300,000 Canadians will have a DFU in their lifetime. DFU is associated with major morbidity, in many cases leading to lower extremity amputation (LEA). Use of HBOT may increase the success of healing DFU, and decrease the risk of infection and LEA. There is uncertainty regarding the cost effectiveness of using this technology versus standard care.

Methods

Controlled studies that compared adjunctive HBOT for DFU with standard wound care in patients of all ages were identified through a literature search. Summary estimates were derived for proportions of LEAs and healed ulcers in patients who received adjunctive HBOT, and those who had standard care only. Using a decision model, the cost effectiveness of adjunctive HBOT was compared with that of standard care alone for the treatment of 65-year-old patients. A health services budget impact analysis was conducted using prevalence data from the literature, and utilization data from Alberta and Canada.

Implications for Decision Making

- **Adjunctive HBOT for DFU is more effective than standard care alone.** The proportion of major LEAs can decrease from 32% among patients receiving standard care to 11% among those receiving adjunctive HBOT. There was a decrease in the proportion of unhealed wounds with HBOT; the reverse was true for minor LEAs.
- **HBOT for DFU is cost effective compared with standard care.** The 12-year cost for a patient receiving HBOT was C\$40,695 compared to C\$49,786 for standard care alone, with an associated increase of 0.63 quality-adjusted life years (QALYs) (3.01 QALYs for standard care to 3.64 QALYs for those receiving HBOT).
- **HBOT requires additional resources and planning.** The estimated costs to treat all prevalent DFU cases in Canada is C\$14 million per year for four years. An estimated 179 additional monoplace chambers or 19 seven-person multiplace HBOT chambers would be required.
- **Optimal use will require additional considerations.** Guidelines would need to be applied to identify those patients most appropriately treated with HBOT. As standard care evolves and better quality studies become available, the estimated comparative advantage of HBOT may change.

This summary is based on a health technology assessment available from CADTH's web site (www.cadth.ca): Hailey D, Jacobs P, Perry DC, Chuck A, Morrison A, Boudreau R. *Adjunctive Hyperbaric Oxygen Therapy for Diabetic Foot Ulcer: An Economic Analysis*.

EXECUTIVE SUMMARY

The Issue

Diabetes mellitus is a widespread chronic disease among Canadians, and diabetic foot ulcers (DFU) are a common complication. They are associated with major morbidity, in many cases leading to lower extremity amputation (LEA). The use of hyperbaric oxygen therapy (HBOT) in the management of DFU has been suggested as an adjunct to standard methods of care. Its use may increase the success of healing DFU, and decrease the risk of infection and LEA.

Limited information is available on the economic aspects of adjunctive HBOT for the management of DFU, particularly in the Canadian population. There is a need to assess its cost effectiveness, to provide health care decision makers with information to assist with policy formulation.

Objective

Our objective was to determine if adjunctive HBOT is a cost-effective option compared with standard care for treating patients with DFU in Canada. The objective was achieved by:

- synthesizing data on the clinical efficacy of HBOT as an adjunctive treatment for DFU
- undertaking a cost-effectiveness analysis of the use of HBOT in this application, using Canadian data where possible.

Clinical Review

Published and unpublished literature was searched to identify controlled studies that compared adjunctive HBOT for DFU with standard wound care in patients of all ages with type 1 or type 2 diabetes. The search included electronic databases, selected journals, CADTH's health technology assessment checklist, and the Internet.

Two reviewers independently selected abstracts and relevant articles, and used a data extraction form to record clinical data from selected studies. The study quality was evaluated using an approach that takes into account study design and performance, and links these to judgements on study reliability. Any disagreements were resolved by consensus.

Seven relevant studies were identified. There was a lower proportion of major LEAs reported in groups of patients who received adjunctive HBOT, as opposed to standard care alone (i.e., 11% versus 32%). Wound healing occurred in 83% patients who had HBOT, compared with 43% of the controls. The proportion of patients with wounds remaining unhealed, but who did not require amputation was 6% (HBOT) and 24% (controls). The evaluation of study design and performance suggested that the available evidence of efficacy was of fair quality, with some limitations that should be considered in any implementation of study findings.

Economic Analysis

A decision model was developed to determine the cost effectiveness of adjunctive HBOT compared with standard care alone for the treatment of DFU. The patient population was a 65-year-old cohort with DFU, and the care setting included inpatients and outpatients. The time horizon was 12 years, and the perspective was one of a ministry of health. The health states in the model were a healed wound with or without a minor LEA, an unhealed wound with no related surgery, and a major LEA. Two sensitivity analyses were conducted to assess the stability of the model.

The 12-year cost for patients receiving HBOT was C\$40,695, compared with C\$49,786 for standard care alone. Outcomes were 3.64 quality-adjusted life years (QALYs) for those in the HBOT arm, and 3.01 QALYs for controls. Because outcomes were better and costs were less in the HBOT arm, adjunctive HBOT used with standard care is the dominant strategy. This remained the case in the sensitivity analyses.

Health Services Impact

A health services budget impact analysis was conducted for Alberta, and for Canada. Using prevalence data from the literature; and utilization data from an Alberta hospital, and from a previous assessment conducted in Québec, we estimated the cost and capacity needs for treating all eligible DFU patients in Alberta and in Canada during a period of one to four years.

The estimated cost to treat all prevalent DFU cases in Canada is \$57 million in one year or \$14 million per year over four years. About 179 additional monoplace HBOT chambers would be required nationally for the four year scenario.

Conclusions

The results of the clinical review corroborate findings in previous assessments that adjunctive HBOT for DFU is more effective than standard care, although the available evidence remains limited. Good quality studies are needed to confirm the comparative benefits of the technology in this application. The results of our economic evaluation show that, based on available data, adjunctive HBOT for DFU is cost effective compared with standard care.

Guidelines would need to be applied to identify those patients for whom HBOT would be the most appropriate treatment. The severity of ulceration and the delay in response to treatment using standard care are important considerations.

ABBREVIATIONS

AÉTMIS	Agence d'évaluation des technologies et des modes d'intervention en santé
ATA	one atmosphere absolute
DFU	diabetic foot ulcer
DM	diabetes mellitus
DRG	diagnosis related group
HBOT	hyperbaric oxygen therapy
HTA	health technology assessment
LEA	lower extremity amputation
MSAC	Medical Services Advisory Committee
NHS	National Health Service
NRCT	non-randomized controlled trial
QALY	quality-adjusted life year
RCT	randomized controlled trial
SEK	Swedish krona

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APPENDIX 4: Wagner Grading System for DFU Classification

APPENDIX 5: HBOT Procedures in Selected Studies

1 INTRODUCTION

1.1 Background

Diabetes mellitus (DM) is a widespread chronic disease caused by the body's inability to sufficiently produce or properly use insulin. Type 1 diabetes occurs in approximately 10% of patients with DM, when the pancreas can no longer produce insulin. Other patients have type 2 diabetes, which results from the pancreas not producing enough insulin, or from the body not effectively using the insulin that is produced. Many complications are associated with type 1 and type 2 diabetes, and DM is a leading cause of death in Canada. The number of Canadians with DM is expected to reach three million by 2010.¹

Diabetic foot ulcers (DFUs) are a common manifestation of DM. In the US, the prevalence of DFUs in adults with DM is reported to range from 12% to 15%.^{2,3} Factors in their occurrence include mechanical changes in the conformation of the bony architecture of the foot, peripheral neuropathy, and atherosclerotic peripheral arterial disease, all of which occur with higher frequency and intensity among those with diabetes. Non-enzymatic glycosylation predisposes ligaments to stiffness. Furthermore, neuropathy causes the loss of protective sensation and coordination of muscle groups in the feet and legs, both of which increase mechanical stresses during ambulation.³

Approximately 12% of patients with DFU will need lower extremity amputation (LEA). Major LEAs are amputations of the leg above or below the knee, whereas minor LEAs involve amputation of the toes or the forefoot.² A study of diabetes-related LEAs in Ontario from 1987 to 1988 found a crude rate of 40 LEAs per 10,000 patients with DM annually.⁴ There was a wide range among regions in the province (i.e., 30 to 60 per 100,000 annually).⁴ Major LEAs accounted for 45% of the total.⁴ LEA is a major adverse event for those with DM, and is associated with considerable costs to the health care system.

The standard of care for treating DFU includes the maintenance of optimal blood glucose control; use of débridement, antibacterials, and dressings; administration of antibiotics to control infection; and pressure relief in the areas of the foot that are most subject to weight bearing. There has been increasing interest in the use of hyperbaric oxygen therapy (HBOT) as an adjunctive treatment for DFU. It has been suggested that the use of adjunctive HBOT will improve the healing of DFU, and decrease the risk of LEA.

Several health technology assessments,⁵⁻⁸ conducted between 1998 and 2001, were supportive of the use of HBOT as an adjunctive treatment for DFU, but there was only limited evidence of efficacy from a few studies.

1.2 Overview of the Technology

HBOT is an established technology that has been used to treat various medical conditions. It involves the inhalation of 100% oxygen while the patient is in a compression chamber under pressure greater than one atmosphere absolute (ATA). Single-place compression chambers are pressurized with 100% oxygen. Multiplace chambers are pressurized with air, and the patient breathes 100% oxygen through a mask or a hood. The increased pressure, which is associated with the inspiration of high levels of oxygen, increases the level of oxygen dissolved in the blood plasma. The immune system, wound healing, and vascular tone are all affected by the oxygen supply.⁹

For wound healing applications, HBOT sessions are typically conducted during a 45 to 120 minute period, once or twice daily, at pressures between 1.5 and 3.0 ATA. The number of sessions needed to treat a chronic wound is usually 20 to 30.¹⁰

2 THE ISSUE

DM is widespread in the Canadian population, and DFU is a common complication. DFUs are associated with major morbidity, and in many cases lead to a LEA. The use¹¹ of HBOT in the management of DFU has been suggested as an adjunct to standard methods of care. HBOT may increase the success of healing DFUs, and decrease the risk of infection and LEA.

There is limited information available on the economic aspects of adjunctive HBOT for the management of DFUs, particularly in the Canadian population. There is a need to assess the cost effectiveness of HBOT in this application, to provide health care decision makers with relevant and timely information to assist with policy formulation.

3 OBJECTIVES

The objective of this economic assessment was to determine if adjunctive HBOT is a cost effective option compared with standard care for treating patients with DFU in Canada. The objective was achieved by:

- synthesizing data on the clinical efficacy of HBOT as an adjunctive treatment for DFU
- undertaking a cost effectiveness analysis of HBOT use in this application, using Canadian data where possible.

4 CLINICAL REVIEW

A protocol for the review of the clinical and economic literature was written a priori, and was followed throughout the project.

4.1 Methods

4.1.1 Literature search strategy

Published literature was searched to identify studies that compared adjunctive HBOT used in the treatment of DFU with standard wound care (Appendix 1). Bibliographic databases searched included PubMed; Cochrane Library; CINAHL; HEED economic database; HORAD outcomes database; Oxford University HERC database; and the DIALOG® system, which incorporates OneSearch on MEDLINE® (1966 to present), EMBASE® (1974 to present), BIOSIS Previews® (1969 to present), TOXFILE, and PASCAL. Journals such as *Health Economics*, *Diabetes Care*, *Journal of Diabetes Complications*, and *Clinics in Podiatric Medicine and Surgery* were hand searched for information. Grey and unpublished literature was searched using CADTH's health technology assessment (HTA) checklist to identify articles relating to HBOT and DFU. An open

search was performed on the Internet to identify additional information. DIALOG, PubMed, and CINAHL searches were updated in June 2005.

4.1.2 Selection criteria and method

a) Selection criteria

Included studies were controlled trials that reported clinical outcomes in patients with DFU treated with adjunctive HBOT and standard care only (i.e., débridement, dressings, antibiotics, and minimization of pressure on the wound). The outcomes considered were the number of major and minor amputations performed, number of wounds that healed, changes in wound size, recurrence of ulceration, and length of hospital stay. The study population included patients of all ages with type 1 or type 2 diabetes. Studies of patients who were previously non-responsive to HBOT, and of those improving well with conventional therapies were excluded, because they were inappropriate for the appraisal of the intervention.

b) Selection method

Two reviewers (DH and PJ) independently selected studies, and any discrepancies were resolved by consensus.

4.1.3 Data extraction strategy

A structured data extraction form was used (Appendix 2). The information extracted from selected studies included details of study design, number of subjects in each group, patient characteristics, clinical outcomes, any reported adverse events attributable to treatment, and details of the HBOT intervention. Two reviewers (DH and RB) independently extracted data, and any disagreements were resolved by consensus.

4.1.4 Strategy for quality assessment

The quality of the selected studies was evaluated using an approach that accounts for study design and study performance, and links both to judgements on study reliability.¹² Studies were rated on a scale of one to 15 (i.e., five for design, and 10 for performance) (Appendix 3). On the basis of their quality scores, each study was assigned to one of five categories:

A=high quality (high degree of confidence in study findings)

B=good quality (some uncertainty regarding the study findings)

C=fair quality (some limitations that should be considered in any implementation of study findings)

D=poor to fair quality (substantial limitations in the study, findings should be used cautiously)

E=poor quality (study findings have unacceptable uncertainty).

4.1.5 Data analysis methods

For each selected study, the outcomes of interest (number of major and minor LEAs, number of healed wounds, and number of unhealed wounds) for the HBOT and control groups were recorded. Totals for each outcome are expressed as proportions of the number of patients in the HBOT and control groups.

4.2 Results

4.2.1 Quantity of research available

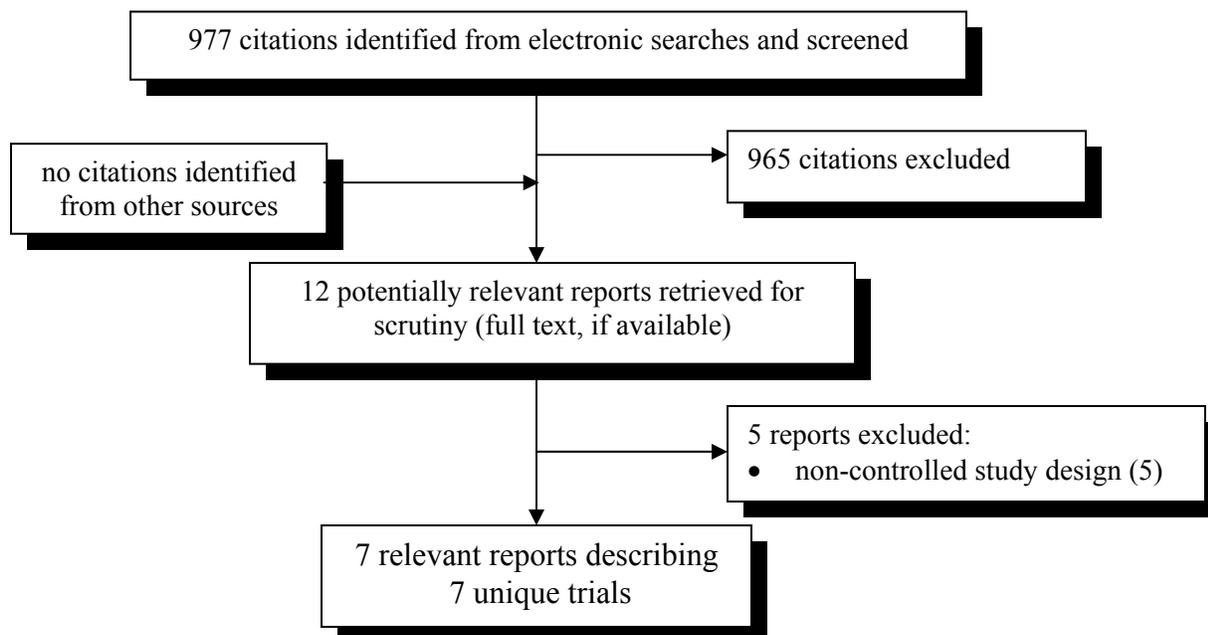
The literature search identified 930 citations (Figure 1). A further 47 citations were identified in the updated search. Among the total of 977, 12 articles were retrieved for scrutiny. Five articles were excluded, resulting in a total of seven articles reporting results from seven unique trials that met the selection criteria. The selected studies included those considered in earlier HTA assessments of HBOT.

4.2.2 Trial characteristics

The characteristics of the seven trials are shown in Table 1. Three were RCTs,^{11,13,14} and four were non-randomized comparative studies.¹⁵⁻¹⁸ Control groups received only standard care for DFU, without HBOT. The study by Abidia *et al.*¹⁴ differed from the others, because the control group was exposed to 100% air in a single-place chamber, to provide sham adjunctive treatment.

Study participants had DM for many years, and were insulin-dependent or non-insulin dependent, although the proportions were not always stated. Ulcer severity varied in the treatment groups, but only two studies^{13,14} provided details in terms of Wagner grades (Appendix 4). Details of the HBOT treatments used in each study are given in Appendix 5.

Figure 1: Selected studies for clinical review



4.2.3 Assessment of study quality

Details of the quality and reliability scores for the selected studies are shown in Appendix 3. Reliability for two studies was rated as B,^{13,14} three had a score of C,^{15,16,18} and the remaining two had a score of D.^{11,17} When the studies are considered together, taking into account study numbers, the

weighted reliability score was C, which suggests that the available evidence of efficacy was “fair quality (some limitations should be considered in any implementation of study findings).”

4.2.4 Data analyses and synthesis

The duration of hospital stay and the length of follow-up after treatment are shown in Table 2. In the three trials^{11,13,15} that reported duration of hospital stay, the number of days spent in hospital were shorter for the HBOT groups than for the control group.

a) Amputations

The number of major LEAs was reported in all seven studies, providing results for 149 patients who received HBOT and for 156 in the control groups (Table 3). Results indicate a lower proportion of major LEAs in patients who received adjunctive HBOT as opposed to standard care alone (i.e., 11% versus 32%). It is assumed in the study by Kalani *et al.*¹⁸ that the amputations occurred before the deaths recorded during the follow-up.

Study	Study Design	Study Quality	Patients	Comments
Baroni ¹⁵	NRCT	C	28 DM patients with foot gangrene (23) or perforating ulcer (5); consecutive series admitted to hospital; HBOT 18, controls 10	controls were patients who refused HBOT; 5 controls were stable (unhealed) in hospital, but lost to follow-up after discharge
Doctor ¹¹	RCT	D	30 DM patients with chronic foot lesions; all in this category admitted to hospital for treatment; HBOT 15, controls 15	no information on randomization method; specific wound healing details for 12 HBOT patients and 11 controls
Faglia ¹³	RCT	B	68 consecutive DM patients hospitalized for foot ulcer; Wagner grade 2, HBOT 4, controls 5; grade 3, HBOT 9, controls 8; grade 4, HBOT 22, controls 20	no information on randomization method
Zamboni ¹⁶	NRCT	C	10 consecutive patients with long-term DM; non-healing lower extremity wounds; treated as outpatients; HBOT 5, controls 5	controls were patients who refused HBOT
Faglia ¹⁷	NRCT	D	115 consecutive patients with DM, hospitalized with foot ulcers; HBOT 51, controls 64	controls were patients who refused HBOT; brief details of HBOT; only major LEA data presented
Kalani ¹⁸	NRCT	C	38 patients with DM; chronic non-healing foot ulcers, treated as outpatients; HBOT 17, controls 21	started as RCT (first 14 patients) but completed as non-randomized study; 2 deaths in HBOT group, and 3 in controls group, unrelated to treatment
Abidia ¹⁴	RCT	B	16 patients with DM; ischemic ulcers >1 cm and <10 cm maximum diameter with no signs of healing despite optimum management for >6 weeks since presenting; treated as outpatients; HBOT 8, controls 8; Wagner grades HBOT: all grade 2; controls: 7 grade2 and 1 grade 1	randomized to 100% oxygen or 100% air; sealed envelope, single blind; 2 dropouts, 1 from each group

NRCT=non-randomized controlled trial; RCT=randomized controlled trial; DM=diabetes mellitus; HBOT=hyperbaric oxygen therapy.

The number of minor LEAs was reported in six of the seven studies, providing results for 98 patients treated with HBOT and 92 in the control groups (Table 4). The rate of minor LEAs was higher in HBOT-treated patients when compared with controls in three studies where such amputations occurred.^{11,13,14} The six studies also provided data on wound healing for 96 HBOT and 89 control patients (Table 5).

b) Wound healing

The details of wound healing are presented in Table 5. The totals for “wounds healed” are based on the assumption that all minor LEAs were followed by wound healing, as was the case in the study of Faglia *et al.*¹³ In this study, the authors considered the limb to be salvaged when the plantar support was preserved and the ulcer healed, despite minor amputation.¹³

c) Other outcomes

Zamboni *et al.* found that over seven weeks, the reduction in wound surface area was significantly greater in the HBOT group than in the control group ($p < 0.05$).¹⁶ Abidia *et al.* reported 100% reduction in wound size with HBOT at six weeks compared with 52% at six weeks, and 95% at six months in controls.¹⁴ Kalani *et al.* found that the mean healing time was 15 months for the HBOT and control groups.¹⁸

Table 2: Hospital stay and length of follow-up			
Study	Treatment	Hospital Stay (days)	Length of Follow-up
Baroni ¹⁵	HBOT	62.2	13.5 months
	Control	81.9	NR
Doctor ¹¹	HBOT	40.6	only hospital stay given
	Control	47	
Faglia ¹³	HBOT	43.2	only hospital stay given
	Control	50.8	
Zamboni ¹⁶	HBOT	NR	7-week study, 4 to 6 months follow-up
	Control		
Faglia ¹⁷	HBOT	NR	unclear
	Control		
Kalani ¹⁸	HBOT	NR	3 years
	Control		
Abidia ¹⁴	HBOT	NR	1 year
	Control		

NR=not reported.

Table 3: Number of major LEAs						
Study	HBOT			Controls		
	n	Number of LEAs	%	n	Number of LEAs	%
Baroni ¹⁵	18	2	11	10	4	40
Doctor ¹¹	15	2	13	15	7	47
Faglia ¹³	35	3	9	33	11	33
Zamboni ¹⁶	5	0	0	5	0	0
Faglia ¹⁷	51	7	13	64	20	33
Kalani ¹⁸	17	2	13	21	7	39
Abidia ¹⁴	8	1	13	8	1	13
Totals	149	17	11	156	50	32

LEAs=lower extremity amputations.

Table 4: Number of minor LEAs

Study	HBOT			Controls		
	N	Number of LEAs	%	n	Number of LEAs	%
Baroni ¹⁵	18	0	NA	10	0	NA
Doctor ¹¹	15	4	27	15	2	13
Faglia ¹³	35	21	60	33	12	37
Zamboni ¹⁶	5	0	NA	5	0	NA
Kalani ¹⁸	17	0	NA	21	0	NA
Abidia ¹⁴	8	1	13	8	0	NA
Totals	98	26	27	92	14	15

LEAs=lower extremity amputations; NA=not applicable.

Table 5: Number of patients with healed and non-healed wounds*

Study	HBOT					Controls				
	n	Wounds healed		Wounds unhealed		n	Wounds healed		Wounds unhealed	
		Number	%	Number	%		Number	%	Number	%
Baroni ¹⁵	18	16	89	0	NA	10	1	10	5	50
Doctor ¹¹	15	10	67	3	20	15	4	27	4	27
Faglia ¹³	35	32	91	0	NA	33	22	67	0	NA
Zamboni ^{16†}	5	4	80	1	20	5	1	20	4	80
Kalani ^{18‡}	15	13	87	0	0	18	10	56	1	6
Abidia ¹⁴	8	5	63	2	25	8	0	0	7	88
Totals	96	80	83	6	6	89	38	43	21	24

*Number of cases with wounds healed includes those where there was a minor LEA; †HBOT group had four wounds heal spontaneously and one with surgical coverage using a flap; ‡number of patients are those who were alive at the end of the follow-up period; NA=not applicable.

Treatment-related adverse effects were reported in two studies. Two HBOT patients in the study by Faglia *et al.* had symptoms of barotrauma, but treatment was not interrupted.¹³ One patient in the Kalani *et al.* study developed a cataract, which was attributed to HBOT, although no rationale for this conclusion was given.¹⁸ Doctor *et al.*¹¹ and Abidia *et al.*¹⁴ reported that no adverse effects were recorded during the study periods.

d) Summary of outcomes

A summary of reported outcomes, using the means of the values reported for each study, is provided in Table 6.

Table 6: Summary of reported outcomes

	Number of Studies	HBOT	Controls
Major LEAs (%)	7	11	32
Minor LEAs (%)	6	27	15
Wounds healed, no minor LEA (%)	6	56	27
Total with wounds healed (%)	6	83	43
Total with wounds unhealed (%)	6	6	24
Hospital stay (range) in days	3	47.1 (43.2 to 57.6)	56.9 (50.8 to 72.8)

LEAs=lower extremity amputations.

4.3 Discussion

There is clinical evidence provided in the included studies that HBOT is effective in the treatment of DFU, although there are few comparative studies, and all have limitations. The summary of outcomes presented in Table 6 must be regarded as provisional, given the disparate nature of the studies that were reviewed. We adopted a pragmatic approach to obtain summary measures for use in the economic analysis.

All the studies found lower rates of major LEAs in patients whose treatment included HBOT. In three studies where minor LEAs were reported, they were more common in the HBOT groups.^{11,13,14} Minor LEAs seemed to be associated with subsequent wound healing. The proportion of patients whose wounds healed, either subsequent to a minor LEA or without amputation, were higher for those receiving HBOT.

5 ECONOMIC ANALYSIS

5.1 Review of Economic Studies

5.1.1 Methods

The literature search strategy used for the clinical review was also used to locate studies that included economic evaluations of adjunctive HBOT for DFU. Economic outcomes of interest included costs of drug acquisition and dispensing, hospitalization costs, procedure fees, facility costs in operating the HBOT unit, and indicators of cost effectiveness.

5.1.2 Results

Limited comparative data on the costs and benefits of HBOT treatment for DFU were found. In the British study by Abidia *et al.*,¹⁴ which was included in the clinical review, it was suggested that cost savings may be realized from a reduction in the number of visits for ulcer dressings. The mean number of patient visits for ulcer dressing changes was 33.75 annually (HBOT) compared with 136.5 annually (controls).¹⁴ The associated estimated annual costs were £4,972 (HBOT) versus £7,946 (controls) (C\$1=£0.504 as of February 27, 2006).¹⁴ Estimates were based on costs obtained from the National Health Service (NHS) Executive of £58 per outpatient visit for ulcer dressings, and £100 per patient per session for HBOT. The authors note that this is a “crude and not an accurate figure,” and that “savings will vary between units.”¹⁴

In the Kalani *et al.* study,¹⁸ which was included in the clinical review, the cost of HBOT treatment is given as SEK60,000 to SEK90,000 (1997 prices) (C\$1=SEK6.998 as of February 27, 2006). It was stated that HBOT is “approximately one fourth to one tenth of the cost of an amputation,” but no other details were provided.¹⁸

In a report by Cianci,¹⁹ an estimate for the cost of HBOT treatment of US\$15,900 (C\$1=US\$0.877 as of February 27, 2006), with total hospital charges of US\$32,000 for an average length of stay of 27 days, was reported. Primary amputation costs were given as more than \$US40,000, and rehabilitation costs between US\$40,000 and US\$50,000.¹⁹ No details were provided on the derivation of these cost estimates.

An Australian assessment by the Medical Services Advisory Committee (MSAC) used data from a pooled analysis of comparative studies, and Australian Diagnosis Related Group (DRG) data to estimate the cost effectiveness of HBOT.⁷ The hospitalization cost of A\$14,805 (C\$1=A\$1.189 as of February 27, 2006) for a major amputation was used to approximate the cost of a major LEA. The report notes that this may be an inaccurate cost for major amputations specifically associated with diabetes, and may be an overestimate for patients already admitted for a diabetic wound.⁷ The costs of rehabilitation after discharge from hospital were included in the analysis.

The incremental cost of HBOT treatment per major amputation avoided was estimated at A\$34,705, assuming that 20% of amputations were avoided through treatment.⁷ When the cost offsets of major amputations were considered, the incremental cost per major amputation avoided was A\$11,142, taking into account only acute hospitalization costs.⁷ It was suggested by the MSAC that if outpatient rehabilitation costs were included, the HBOT treatment of diabetic wounds could be a cost saving option in terms of major amputations.⁷ When major and minor amputation risks were considered, the estimated incremental cost per amputation avoided by using HBOT in the treatment of diabetic wounds was A\$22,054.⁷

An assessment conducted by the Agence d'évaluation des technologies et des modes d'intervention en santé (AÉTMIS) of Québec considered the cost benefit of HBOT from the perspective of the hospital system for various medical conditions, including DFU.⁸ Estimates were made of the reduction in length of stay that would have to occur for HBOT costs to be offset by cost savings in hospitalization. In the case of DFU, HBOT treatments would have to result in a reduction in hospital stay of at least 29% in the full capacity scenario, or 62% in the status quo scenario, to yield a favourable hospital cost per benefit ratio.⁸

5.2 Cost Effectiveness Analysis

5.2.1 Methods

A decision model was developed to determine the cost effectiveness of adjunctive HBOT for the treatment of DFU. The analysis was based on that of Guo *et al.*,²⁰ applied in a Canadian context, and altered to allow for a wider range of outcomes and Canadian data.

The patient population was a 65-year-old cohort with DFU, and the care setting included inpatients and outpatients. The perspective was that of a ministry of health. The comparative interventions are HBOT plus standard care, and standard care alone. The time horizon is 12 years, which is equal to the expected lifetime (18 years) of a person in Alberta (i.e., male or female composite at age 65), according to Alberta Health and Wellness.²¹ This time horizon is adjusted for the expected lifetime of a person with diabetes (i.e., 0.67 according to Gu *et al.*).²² There are four health states in the model: healed wound without a minor LEA, a healed wound with a minor LEA, an unhealed wound with no related surgery, and a major LEA.

The first year of the decision tree is shown in Figure 2. The cohort will receive one of the two interventions. With either intervention, there can be four outcomes: patients can be healed with a minor LEA, they can be healed without a minor LEA, they can have a major LEA, or they can remain unhealed. The probabilities of the four outcomes for each intervention are shown in Table 7. Several assumptions were made in the model: LEAs occur in the first year; if patients are healed in

the first year, they will not have a subsequent LEA; and patients who are unhealed in the first year will remain so for the remainder of their lifetime, and will receive wound care intermittently.

Mortality is based on life expectancy, and is expressed in terms of the number of deaths annually (i.e., 0.083 deaths per person). This measure is consistent with a life expectancy of 12 years. The mortality rate (i.e., deaths divided by survivors) will therefore increase with each passing year.²² There is a 5% addition to the mortality rate in the first year only for persons who have a major LEA.²³ After the first year, the number of deaths annually is the same for all persons with DFU, including those who have had a minor or major amputation.²⁴

Utilities and costs for each year, in each health state, and health-related outcomes for those who receive or do not receive HBOT are shown in Table 7. HBOT costs include overhead and amortized machine costs. For patients receiving HBOT, all relevant costs occur in the first year. The efficacy estimates are derived from the analysis in the earlier part of this report. The cost of HBOT is derived from Alberta operating data. The medical costs of diabetic persons with foot ulcers are based on Saskatchewan data supplemented by estimates on subgroups (minor LEA, major LEA) that were obtained from the literature. Sources are presented in Table 7. Utility data for the various conditions of diabetic persons with foot ulcers were obtained from Ragnarson Tennvall and Apelqvist²⁵ who conducted a survey of persons with diabetic foot ulcers using the Euroquol EQ-5D measure.

Based on the model, a cost-utility ratio is measured, which is the ratio of the difference in costs to the difference in utilities. The cost-utility measure is gauged against generally used standards. In cases where costs and outcomes are preferable for one arm, the most commonly used standard is C\$50,000 per QALY.²⁶ This standard was selected to assess the results from the model. Nonetheless, if one arm is dominant (i.e., lower costs, better outcomes), such a standard is unnecessary as the outcome will automatically be superior.

a) Sensitivity analysis

Two sensitivity analyses were conducted to assess the stability of the model. In the first analysis, the outcome probabilities were changed to make them more favourable to routine care. The new probabilities are shown in Table 8. The probability of healing was reduced by 10%, and the probability of not being healed was increased by 10%.

In the second sensitivity analysis, the cost of HBOT was increased until the total costs of the two interventions were the same. This allows for the assessment of the relation between the break-even and current cost (i.e., the price at which HBOT is no longer the dominant strategy).

5.2.2 Results

The 12-year cost for patients receiving HBOT was C\$40,695 compared with C\$49,786 for patients receiving standard care alone. The outcomes of the two arms were 3.64 QALYs (HBOT) and -3.01 QALYs (controls). Adjunctive HBOT used with standard care is the dominant strategy, because outcomes are better, and costs are less in the HBOT arm.

Figure 2: Decision tree model (first year)

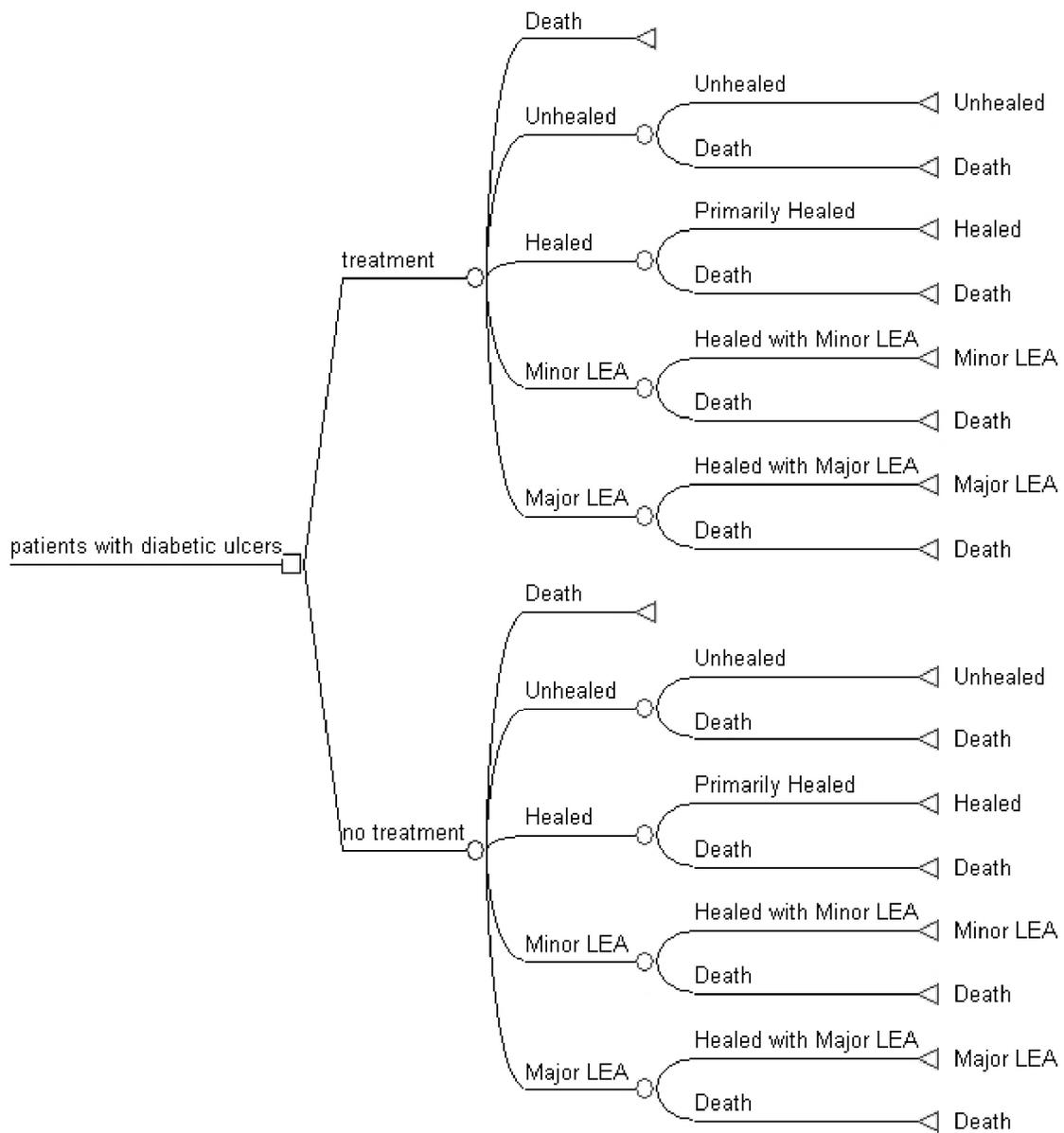


Table 7: Assumptions in decision model

Variable	HBOT	Controls	Data Source
Mortality, deaths in year 1(annual)			
healed	0.083	0.083	Gu <i>et al.</i> , ²² Ramsey <i>et al.</i> ²⁴
minor LEA, healed	0.083	0.083	
unhealed	0.083	0.083	
major LEA	0.133	0.133	deaths due to major surgery are 0.05. Eckman <i>et al.</i> ²³
Mortality annual deaths, subsequent years			
healed	0.083	0.083	Gu <i>et al.</i> , ²² Ramsey <i>et al.</i> ²⁴
minor LEA, healed	0.083	0.083	
unhealed	0.083	0.083	
major LEA	0.083	0.083	
Utility of health state (QALY per year)			
healed	0.6	0.6	Ragnarson Tennvall and Apelqvist ^{25,27}
minor LEA, healed	0.61	0.61	
unhealed	0.44	0.44	
major LEA	0.31	0.31	
Probability of outcome in first year			
healed	0.56	0.24	see section 5.2.1
minor LEA, healed	0.27	0.16	
unhealed	0.06	0.28	
major LEA	0.11	0.33	
Cost of HBOT (C\$)	\$3,652		facility costs: estimated 30 dives @ C\$110 per dive (cycle of pressurization in HBO chamber), Misericordia Hospital, Edmonton AB; physician fees for first day only, minor consult, and additional time, \$352 (Alberta Health and Wellness, Schedule of Medical Benefits) ²⁸
Annual cost per patient			
First year			
healed	\$4,228	\$4,228	
minor LEA (including operation)	\$10,823	\$10,823	
unhealed	\$9,386	\$9,386	
major LEA (including operation)	\$19,195	\$19,195	base value is annual cost in Saskatchewan for all persons with diabetes ^{29,30} adjusted for relative ratio of costs for persons with diabetes and with or without DFU (2.61 first year, 1.56 subsequent years), ²⁴ ratio costs of first and subsequent years for persons with foot problems with no LEA (ratios are 1 and 0.92), minor LEA (ratios are 2.22 and 2.23), and major LEA (ratios are 4.54 and 2.77), ³¹ all costs adjusted to 2004 values using Consumer Price Index (www.statcan.ca); annual wound care costs based on Netherlands costs, adjusted for time in healed, non-infected, and infected states; ³² euro values converted to Canadian values using 2004 exchange rate (C\$1.60=1 euro, www.finance.yahoo.com)
Subsequent years			
healed	\$3,890	\$3,890	
minor LEA (including operation)	\$10,484	\$10,484	
unhealed	\$9,428	\$9,428	
major LEA (including operation)	\$11,712	\$11,712	

Table 8: Variable values used in sensitivity analysis

Variable	Ranges Tested	Explanation
Probability of alternative outcomes	base case: probabilities for healed minor LEA, healed LEA, unhealed LEA, and major LEA are HBOT 56%, 27%, 6%, 11%; standard care 25%, 16%, 28%, 33%; sensitivity analysis probabilities are HBOT 46%, 27%, 16%, 11%; standard care 25%, 16%, 28%, 33%	outcomes for HBOT made 10% worse
Cost of HBOT	increased until break-even between 2 treatments	not applicable

Much of the difference in outcomes can be attributed to the dramatic probabilities of being healed that were found in the literature, with the large increase in QALYs when comparing healed and unhealed persons. The life expectancy in the HBOT arm was 5.96 life years, and 5.84 life years in the control arm. The probability of being healed with HBOT increased to 56% from 24%, while the probabilities of being unhealed or having a major LEA fell to 6% and 11% respectively. The utilities of individuals who were healed were almost 0.2 greater than those for persons who were unhealed, and 0.3 greater than those for patients with major LEAs.

a) Sensitivity analysis

In the first sensitivity analysis (i.e., where the probability of alternative outcomes was varied), HBOT remained the dominant strategy. The difference in the cost-effectiveness ratio was narrowed by approximately one-third, which indicates that the outcomes were well into the dominant range. The same is true for the second sensitivity analysis (i.e., varying the cost of HBOT). The break-even point would occur when the cost of HBOT was above C\$17,000. Given that the current cost is C\$3,652 (Table 7), HBOT remains dominant.

5.2.3 Discussion

An economic model, which was developed using efficacy measures obtained from the clinical review, indicates that HBOT is a cost-saving intervention when compared with standard wound care. A sensitivity analysis, applied to key variables, shows that the model is robust.

The data (notably cost) on which the variables in the model were based, are not of high quality, and in some cases, estimates from foreign resources had to be used. For example, the utility measures were based on a Swedish study in which the number of observations of persons who had major amputations was small. The number of such amputations has fallen, so it will be difficult to obtain a large number of subjects. The cost data for HBOT were based on data from only a few centres, and the reporting was not standardized. Nevertheless, because the sensitivity analyses showed the results to be robust, there is confidence in the finding that adjunctive HBOT used for the treatment of DFU is economically attractive.

6 HEALTH SERVICES IMPACT

We conducted a health services budget impact analysis for Alberta, and for Canada. The purpose of this analysis was to determine the net impact on the health care budget of providing HBOT to patients with DFU, who are eligible for such services, following the approach used by AÉTMIS.⁸ In the AÉTMIS report, the proportion of DFU cases that could benefit from HBOT was derived by first estimating the number of hospitalized DFU cases in Québec, and then adjusting this value upwards by a factor obtained from the literature to account for patients treated solely on an outpatient basis during the previous 12 months.^{5,8}

The budget impact analysis considers the demand for adjunctive HBOT, based on the prevalence of DFU, and gives estimates of the budget impact in meeting this demand during periods of one to four years. The analysis has two components—a demand analysis, and a capacity or cost analysis. In the demand analysis, we estimate the number of persons who could have benefited from HBOT treatment, whereas in the capacity or cost analysis, we estimate the present costs, future capacity, and cost of meeting demand.

6.2.1 Methods

a) Demand analysis

The potential demand for adjunctive HBOT for patients with DFU, at a given period, is calculated as the product of three variables:

- number of patients with diabetes
- percentage of patients with diabetes who have DFU at any one time (i.e., prevalence)
- percentage of patients with DFU whose conditions warrant HBOT.

Data for Canada, for Alberta, and for each of the three variables, and the corresponding data sources are presented in Table 9.

b) Capacity and cost analysis

The capacity of HBOT is a function of the number of chambers available, the time that they are operating, and the number of dives (cycles of pressurization in the HBO chamber) required for a complete treatment. In our analysis, we assumed that each chamber has a capacity of 2,000 operating hours annually (i.e., operating eight hours daily for 250 days a year).

Variables	Canada	Alberta	Data source
Number of patients with diabetes	1,195,000	86,000	National Diabetes Surveillance Strategy ³³
Prevalence of DFU in patients with diabetes	6%	6%	Ramsey <i>et al.</i> ²⁴
Percentage of patients with DFU whose condition warrants HBOT	22% to 30%	22% to 30%	Reiber <i>et al.</i> , ³⁴ AÉT MIS ⁸
Demand for prevalent cases	15,774 to 21,510	1,135 to 1,548	not applicable

DFU=diabetic foot ulcer; HBOT=hyperbaric oxygen therapy.

A complete treatment was assumed to range from 30 dives, based on data from the Misericordia Hospital in Edmonton, to 40 dives as per the AÉT MIS report.⁸ Each dive is between two and 2½ hours in duration (1½ hours for treatment and a half hour to one hour for set-up and post-treatment). Therefore, the total number of DFU cases that could be treated with one chamber annually, using a mid-point of 2¼ hours, ranges from 22 to 30 complete treatments (Québec and Misericordia Hospital data respectively), if there were no other uses for the HBOT machines.

HBOT machines are used for many indications. In Québec, DFU cases account for 52.6% of HBOT machine capacity.⁸ If one assumes that the proportion of machine time spent on DFU is similar to that in Québec, then one HBOT machine would only be used to treat 11.5 DFU cases annually. The machine could be used to treat 10.5 (22–11.5) cases for other indications, with the same treatment patterns. If the other indications (non-diabetes cases) required more or fewer dives per case, then the number of non-diabetes cases would change; however, our results would remain unchanged. In our base case analysis, we assumed that the HBOT machines are used for DFU cases only.

In our base case analysis, we focused on the additional cost of HBOT care that is needed to treat all eligible DFU cases. The cost per patient treated is C\$3,652 (i.e., assuming 30 dives per treatment as per Misericordia Hospital data). If 40 dives are required, using the estimates from the AÉT MIS report, then the cost is C\$4,752 per complete treatment. These costs include amortized equipment costs.

We also used different assumptions about how many years it will take to clear the current number of cases, making estimates for timeframes of one to four years. We assumed equal annual depreciation charges for all scenarios; that is, even if the backlog were cleared in one year, the machine would have other purposes for its remaining life. In the Canada analysis, we did not have Canadian data on total current machine capacity.

6.2.2 Results

The immediate impact of adjunctive HBOT for DFU treatment on the provincial budget is the cost of providing HBOT. Post-HBOT downstream costs, which include treatment costs for unhealed wound care, and major and minor LEAs have not been considered in our analysis. We have conducted an immediate budget impact analysis for Alberta, and for Canada, and have considered HBOT costs only (i.e. costs of acquiring and operating machines).

The results of several patient treatment scenarios for Alberta and Canada are provided in Table 10. The most relevant variable in this analysis is the number of years that it will take to treat the entire disease-prevalent group. We considered four scenarios in which the target group of patients is treated during periods of one to four years.

Using Alberta data and the lower prevalence rates from Table 9, we conclude that it would cost C\$4.1 million (C\$3,652 per case \times 1,135 cases) to treat the entire prevalent group in one year as detailed in Table 10. If treatments were spread over four years, the annual cost would be C\$1 million, due to only 284 patients being treated annually.

The cost to treat all eligible patients in Canada is C\$57 million (C\$3,652 per case \times 15,774 cases) in one year as per Table 10. If treatments were spread over four years, the annual cost would be \$14.4 million.

In Alberta, there is public funding for the operation of three monoplace chambers (Misericordia Hospital in Edmonton has two chambers, and a contracted private facility in Calgary has one). If these machines were dedicated to DFU cases, they could be used to treat 66 cases annually. If 52% of machine capacity is used to treat DFU (as in Québec), then 34 cases would be treated annually. The capacity in Alberta is 1½ machine-years (52% \times 3 chambers). Therefore, additional needs would range from 13 machines (i.e., if all cases are treated over four years with 100% of capacity used for the DFU cases) to 51 fully utilized monoplace machines (i.e., if all cases are treated in one year).

This analysis is predicated on the use of monoplace machines. In the AÉTMIS report,⁸ the use of a seven-person, multiplace machine was analyzed. This machine had a maximum capacity of 14,000 hours annually (7 places \times 8 hours daily \times 250 days annually). If a full course of treatment is assumed to be 67.5 hours (30 dives per patient \times 2¼ hours per dive), then a multiplace machine that operates at full capacity can be used to treat 207 DFU cases annually. The estimated (2000) costs in Québec, at maximum capacity, were C\$156 per dive, which includes physician fees, but excludes capital costs, amounting to C\$4,500 per treatment.⁸ A machine costs approximately C\$2 million, and depreciation costs would be roughly C\$600 (extra) per treatment.⁸ Total costs (i.e., C\$5,100 per treatment) in the AÉTMIS report were considered to be lower than for treatments using a monoplace machine; however, no calculations were given.⁸

Table 10: Budget impact of expanding HBOT

Scenario	Total Number of Patients	Years to Complete Backlog	Monoplace Machines Needed	Total Annual Cost (C\$)
Alberta Costs				
All patients treated in 1 year*	1,135	1	51	\$4,145
All patients treated in 1 year*	1,548	1	70	\$5,653
All patients treated in 2 years*	1,135	2	26	\$2,072
All patients treated in 3 years*	1,135	3	17	\$1,381
All patients treated in 4 years*	1,135	4	13	\$1,036
Canada Costs				
All patients treated in 1 year*	15,774	1	717	\$57,606
All patients treated in 1 year*	21,510	1	977	\$78,554
All patients treated in 2 years*	15,774	2	358	\$28,803
All patients treated in 3 years*	15,774	3	239	\$19,202
All patients treated in 4 years*	15,774	4	179	\$14,401

*Alberta cost of \$3,652 per treatment, and 22 patients treated annually per monoplace machine.

If the capacity data for a seven-person multiplace machine are applied to the estimated Canadian demand for HBOT, and 100% of machine time is used for DFU cases, then additional national needs would range from 19 machines (i.e., if all 15,774 cases are treated during four years) to 76 machines (i.e., if all cases are treated in one year). In the first case, there would be excess capacity after the first year, and in the latter case, there would be some, but less, excess capacity after the fourth year. From a clinical perspective, it could be difficult to use a multiplace chamber to maximum efficiency. Different protocols are used for the conditions that are treated with HBOT. Therefore, it would not always be possible to mix patients with different diagnoses in the chamber at the same time to fill it to capacity.

Additional costs are incurred with poor wound healing that are not associated with HBOT. Nonetheless, as shown in the modelling analysis, the overall health care system costs will be lower with the use of adjunctive HBOT for DFU, so there may be a potential for cost savings in the system, if the use of the technology in this application is routinely adopted.

6.2.3 Discussion

In our analysis, we estimated the cost of providing adjunctive HBOT to treat all patients with DFU in Alberta and in Canada, based on prevalence rates obtained from the literature. Our results show that if all Canadian patients were treated over four years, with monoplace machines, approximately 179 additional machines would be needed nationally. In our analysis, we only considered the costs of HBOT. If downstream costs were also included, overall cost savings to the health care system would likely result. The quality of the data in most studies was poor, but despite this, our results indicate that HBOT warrants attention.

7 CONCLUSIONS

The results of our clinical review corroborate findings in previous assessments that adjunctive HBOT for DFU treatment is more effective than standard care alone, although the available evidence remains limited. Data from a few clinical studies suggest that adjunctive HBOT results in a reduction

in the proportion of patients with DFU undergoing a major LEA from 32% to 11%, and in those with continuing non-healed ulcers from 24% to 6%. If such reductions were applicable to the Canadian population, many major amputations would be avoided, with consequent benefits to patients and their families, and to the health care system.

The results of our economic evaluation show that, based on available data, adjunctive HBOT for this application is cost effective when compared with standard care. To achieve the possibility of reductions in major LEA commensurate with what was found in our clinical review, it would be necessary for health authorities to ensure that there was sufficient HBOT capacity to cope with the DFU caseload and that patients had reasonable access to HBOT facilities. To treat all Canadian patients with DFU during a four-year period with monoplace chambers, we estimate that an additional 179 HBOT machines would be required nationally.

These conclusions are subject to several qualifications that should be considered by health care service providers in the decision-making process.

- Most patients with DFU are managed successfully using standard care. Guidelines would need to be applied to identify those patients who would be most appropriately treated with HBOT. The severity of ulceration and delay in response to treatment using standard care are considerations in deciding who should receive therapy.
- Newer types of dressings and other technologies are becoming available for the treatment of ulcers, so that the comparative advantage of adjunctive HBOT may change.
- The consequences of recurring ulceration and treatment required have not been considered in this analysis.

The clinical data supporting the effectiveness of adjunctive HBOT for DFU remain limited. Good quality studies are required to confirm the comparative benefits of this technology in Canadian health care.

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APPENDICES

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