

Hyperbaric Oxygen Therapy for Non-Healing Ulcers in Diabetes Mellitus

An Evidence-Based Analysis

September 2005



Medical Advisory Secretariat
Ministry of Health and Long-Term Care

Suggested Citation

This report should be cited as follows:

Medical Advisory Secretariat. Hyperbaric oxygen therapy for non-healing ulcers in diabetes mellitus: an evidence-based analysis. *Ontario Health Technology Assessment Series* 2005; 5(11)

Permission Requests

All inquiries regarding permission to reproduce any content in the *Ontario Health Technology Assessment Series* should be directed to MASinfo@moh.gov.on.ca.

How to Obtain Issues in the Ontario Health Technology Assessment Series

All reports in the *Ontario Health Technology Assessment Series* are freely available in PDF format at the following URL: www.health.gov.on.ca/ohtas.

Print copies can be obtained by contacting MASinfo@moh.gov.on.ca.

Conflict of Interest Statement

All analyses in the Ontario Health Technology Assessment Series are impartial and subject to a systematic evidence-based assessment process. There are no competing interests or conflicts of interest to declare.

Peer Review

All Medical Advisory Secretariat analyses are subject to external expert peer review. Additionally, the public consultation process is also available to individuals wishing to comment on an analysis prior to finalization. For more information, please visit http://www.health.gov.on.ca/english/providers/program/ohtac/public_engage_overview.html.

Contact Information

The Medical Advisory Secretariat
Ministry of Health and Long-Term Care
20 Dundas Street West, 10th floor
Toronto, Ontario
CANADA
M5G 2N6
Email: MASinfo@moh.gov.on.ca
Telephone: 416-314-1092

ISSN 1915-7398 (Online)
ISBN 1-4249-0124-3 (PDF)

About the Medical Advisory Secretariat

The Medical Advisory Secretariat is part of the Ontario Ministry of Health and Long-Term Care. The mandate of the Medical Advisory Secretariat is to provide evidence-based policy advice on the coordinated uptake of health services and new health technologies in Ontario to the Ministry of Health and Long-Term Care and to the healthcare system. The aim is to ensure that residents of Ontario have access to the best available new health technologies that will improve patient outcomes.

The Medical Advisory Secretariat also provides a secretariat function and evidence-based health technology policy analysis for review by the Ontario Health Technology Advisory Committee (OHTAC).

The Medical Advisory Secretariat conducts systematic reviews of scientific evidence and consultations with experts in the health care services community to produce the *Ontario Health Technology Assessment Series*.

About the Ontario Health Technology Assessment Series

To conduct its comprehensive analyses, the Medical Advisory Secretariat systematically reviews available scientific literature, collaborates with partners across relevant government branches, and consults with clinical and other external experts and manufacturers, and solicits any necessary advice to gather information. The Medical Advisory Secretariat makes every effort to ensure that all relevant research, nationally and internationally, is included in the systematic literature reviews conducted.

The information gathered is the foundation of the evidence to determine if a technology is effective and safe for use in a particular clinical population or setting. Information is collected to understand how a new technology fits within current practice and treatment alternatives. Details of the technology's diffusion into current practice and information from practicing medical experts and industry, adds important information to the review of the provision and delivery of the health technology in Ontario. Information concerning the health benefits; economic and human resources; and ethical, regulatory, social and legal issues relating to the technology assist policy makers to make timely and relevant decisions to maximize patient outcomes.

If you are aware of any current additional evidence to inform an existing Evidence-Based Analysis, please contact the Medical Advisory Secretariat: MASInfo@moh.gov.on.ca. The public consultation process is also available to individuals wishing to comment on an analysis prior to publication. For more information, please visit http://www.health.gov.on.ca/english/providers/program/ohnac/public_engage_overview.html.

Disclaimer

This evidence-based analysis was prepared by the Medical Advisory Secretariat, Ontario Ministry of Health and Long-Term Care, for the Ontario Health Technology Advisory Committee and developed from analysis, interpretation and comparison of scientific research and/or technology assessments conducted by other organizations. It also incorporates, when available, Ontario data, and information provided by experts and applicants to the Medical Advisory Secretariat to inform the analysis. While every effort has been made to do so, this document may not fully reflect all scientific research available. Additionally, other relevant scientific findings may have been reported since completion of the review. This evidence-based analysis is current to the date of publication. This analysis may be superceded by an updated publication on the same topic. Please check the Medical Advisory Secretariat Website for a list of all evidence-based analyses: <http://www.health.gov.on.ca/ohnas>.

Table of Contents

Table of Contents.....	4
Executive Summary	6
Objective	6
Clinical Need.....	6
The Technology	6
Review Strategy.....	6
Summary of Findings	7
Conclusions.....	8
Abbreviations	9
Objective.....	10
Background	10
Clinical Need: Target Population and Condition	10
Non-Healing Wounds and Diabetes Mellitus.....	10
Treatment of Chronic Ulcers in Diabetes	11
Technology Being Reviewed: Hyperbaric Oxygen Therapy for Ulcers in Diabetes	12
Regulatory Status.....	12
Insurance Coverage	12
Literature Review.....	13

Objective	13
Questions Asked.....	13
Methods.....	13
Summary of Health Technology Reports.....	14
Summary of Literature Review	20
Existing Guidelines.....	20
Economic Analysis.....	22
Ontario Context	22
Direct Costs of Hyperbaric Oxygen Therapy and Chronic Wounds.....	23
Appraisal	23
Demographics.....	23
Patient Outcomes – Medical, Clinical	23
Cost.....	24
Stakeholder Analysis	24
System Pressures.....	24
Conclusions	24
Appendices	26
Appendix 1: Codes Extracted From Ontario Hospital Discharge Abstracts at the Ontario Ministry of Health and Long-term Care 2005	26
References	27

Executive Summary

Objective

To examine the effectiveness and cost-effectiveness of hyperbaric oxygen therapy (HBOT) to treat people with diabetes mellitus (DM) and non-healing ulcers. This policy appraisal systematically reviews the published literature in the above patient population, and applies the results and conclusions of the review to current health care practices in Ontario, Canada.

Although HBOT is an insured service in Ontario, the costs for the technical provision of this technology are not covered publicly outside the hospital setting. Moreover, access to this treatment is limited, because many hospitals do not offer it, or are not expanding capacity to meet the demand.

Clinical Need

Diabetes mellitus is a chronic disease characterized by an increase in blood sugar that can lead to many severe conditions such as vision, cardiac, and vascular disorders. The prevalence of DM is difficult to estimate, because some people who have the condition are undiagnosed or may not be captured through data that reflect access to the health care system. The Canadian Diabetic Association estimates there are about 2 million people in Canada with diabetes (almost 7% of the population). According to recent data, the prevalence of DM increased from 4.72% of the population aged 20 years and over in 1995, to 6.19% of the population aged 20 years and over in 1999, or about 680,900 people in 1999. Prevalence estimates expanded to 700,000 in 2003.

About 10% to 15% of people with DM develop a foot wound in their lifetimes because of underlying peripheral neuropathy and peripheral vascular disease. This equals between 70,000 and 105,000 people in Ontario, based on the DM prevalence estimate of 700,000 people. Without early treatment, a foot ulcer may fester until it becomes infected and chronic. Chronic wounds are difficult to heal, despite medical and nursing care, and may lead to impaired quality of life and functioning, amputation, or even death.

The Technology

Hyperbaric oxygen therapy has been in use for about 40 years. It is thought to aid wound healing by supplying oxygen to the wound. According to the Hyperbaric Oxygen Therapy Association, HBOT acts as a bactericidal, stops toxin production, and promotes tissue growth to heal difficult wounds.

During the procedure, a patient is placed in a compression chamber with increased pressure between 2.0 and 2.5 atmospheres absolute for 60 to 120 minutes, once or twice daily. In the chamber, the patient inhales 100% oxygen. Treatment usually runs for 15 to 20 sessions.

Noted complications are rare but may include claustrophobia; ear, sinus, or lung damage due to pressure; temporary worsening of short sightedness; and oxygen poisoning. Careful monitoring during the treatment sessions and follow-up by a trained health care provider is recommended.

Review Strategy

The aims of this health technology policy appraisal were to assess the effectiveness, safety, and cost-effectiveness of HBOT, either alone, or as an adjunct, compared with the standard treatments for non-healing foot or leg ulcers in patients with DM. The following questions were asked:

- Alone or as an adjunct therapy, is HBOT more effective than other therapies for non-healing foot or leg ulcers in patients with DM?
- If HBOT is effective, what is the incremental benefit over and above currently used strategies?
- When is the best time in a wound treatment strategy to use HBOT?
- What is the best treatment algorithm with HBOT?

The Medical Advisory Secretariat searched for health technology assessments in the published and grey literature. The search yielded 4 reports, which were published from 2000 to 2005. The most recent from the Cochrane Collaboration had a literature review and analysis of randomized control trials to 2003.

As an update to this review, as per the standard Medical Advisory Secretariat systematic review strategy, the abstracts of peer-reviewed publications were identified using Ovid MEDLINE, EMBASE, MEDLINE in-process and not-yet-indexed citations, Cochrane Database of Systematic Reviews, Cochrane CENTRAL, and INAHTA using key words and searching from January 1, 2003 to 2004.

The criteria for inclusion were as follows:

- Patients with diabetes
- Live human study
- English-language study
- HBOT as adjunctive therapy or alone
- Randomized control trial

The number of excluded studies included the following:

- 2 animal studies
- 13 focus on condition other than DM
- 8 review/protocol for HBOT use
- 3 HBOT not focus of report
- 2 health technology assessments (2)
- 1 non-RCT

Outcomes of interest were wound healing and prevention of amputation.

The search yielded 29 articles published between 2003 and 2004. All 29 of these were excluded, as shown beside the exclusion criteria above. Therefore, this health technology policy assessment focused exclusively on the most recently published health technology assessments and systematic reviews.

Summary of Findings

Four health technology assessments and reviews were found. Cochrane Collaboration researchers published the most recent review in 2005. They included only randomized controlled trials and conducted a meta-analysis to examine wound healing and amputation outcomes. They found that, based on findings from 118 patients in 3 studies, HBOT may help to prevent major amputation (relative risk, 0.31; 95% confidence interval [CI], 0.13–0.71) with a number needed to treat (NNT) of 4 (95% CI, 3–11). They noted, however, that the point estimates derived from trials were not well reported, and had varying populations with respect to wound severity, HBOT regimens, and outcome measures. These noted limitations rendered the comparison of results from the trials difficult. Further, they suggested that the evidence was not strong enough to suggest a benefit for wound healing in general or for prevention of minor amputations.

The Medical Advisory Secretariat also evaluated the studies that the Cochrane Collaboration used in their analysis, and agreed with their evaluation that the quality of the evidence was low for major and minor amputations, but low to moderate for wound healing, suggesting that the results from new and well-conducted studies would likely change the estimates calculated by Cochrane and others.

Conclusions

In 2003, the Ontario Health Technology Advisory Committee recommended a more coordinated strategy for wound care in Ontario to the Ministry of Health and Long-term Care. This strategy has begun at the community care and long-term care institution levels, but is pending in other areas of the health care system.

There are about 700,000 people in Ontario with diabetes; of these, 10% to 15% may have a foot ulcer sometime in their lifetimes. Foot ulcers are treatable, however, when they are identified, diagnosed and treated early according to best practice guidelines. Routine follow-up for people with diabetes who may be at risk for neuropathy and/or peripheral vascular disease may prevent subsequent foot ulcers. There are 4 chambers that provide HBOT in Ontario. Fewer than 20 people with DM received HBOT in 2003.

The quality of the evidence assessing the effectiveness of HBOT as an adjunct to standard therapy for people with non-healing diabetic foot ulcers is low, and the results are inconsistent. The results of a recent meta-analysis that found benefit of HBOT to prevent amputation are therefore uncertain. Future well-conducted studies may change the currently published estimates of effectiveness for wound healing and prevention of amputation using HBOT in the treatment of non-healing diabetic foot ulcers.

Although HBOT is an insured service in Ontario, a well conducted, randomized controlled trial that has wound healing and amputation as the primary end-points is needed before this technology is used widely among patients with foot wounds due to diabetes.

Abbreviations

AHRQ	Agency for Healthcare Research and Quality
CI	Confidence interval
DM	Diabetes mellitus
HBOT	Hyperbaric oxygen therapy
ICES	Institute for Clinical Evaluative Sciences
MSAC	Medical Services Advisory Committee
NNT	Number needed to treat
OR	Odds ratio
QUALY	Quality adjusted life year
RCT	Randomized controlled trial
RR	Relative risk
SD	Standard deviation

Objective

To examine the effectiveness and cost-effectiveness of hyperbaric oxygen therapy (HBOT) to treat people with diabetes mellitus (DM) and non-healing ulcers. This policy appraisal systematically reviews the published literature in the above patient population, and applies the results and conclusions of the review to current health care practices in Ontario, Canada.

Although HBOT is an insured service in Ontario, costs for the technical provision of this technology is not covered publicly outside the hospital setting. Moreover, access to this treatment is limited, because many hospitals do not offer it, or are not expanding capacity to meet the demand.

Background

Clinical Need: Target Population and Condition

Diabetes mellitus is a chronic disease characterized by an increase in blood sugar that can lead to many severe conditions such as vision, cardiac, and vascular disorders. The prevalence of DM is difficult to estimate, because some people who have the condition are undiagnosed or may not be captured through data that reflect access to the health care system. According to the Canadian Diabetes Association, (www.diabetes.ca/Section_About/feet.asp; accessed May 26, 2005) there are about 2 million people in Canada with diabetes (almost 7% of the population). According to a specialized dataset created by researchers at the Institute for Clinical Evaluative Sciences (ICES) in Toronto, Ontario, (1) the prevalence of DM increased from 4.72% of the population aged 20 years and over in 1995, to 6.19% of the population aged 20 years and over in 1999, or about 680,900 people in 1999. Prevalence estimates expanded to 700,000 in 2003 (Personal communication, 2005). The researchers suggested that the increase in the overall number of cases over time was because people are living longer with DM (prevalence), rather than because more people were acquiring the condition each year (incidence).

Non-Healing Wounds and Diabetes Mellitus

People with DM are prone to foot ulcers, owing to loss of sensation in their feet due to peripheral neuropathy, which can occur if blood sugar levels are not controlled. Because of the neuropathy, a foot injury and subsequent infection cannot be felt. Without treatment, such a foot ulcer may fester until it becomes infected and chronic. Peripheral vascular disease has also been implicated in the development of foot ulcers in people with DM.

Many chronic wounds are difficult to heal, despite medical and nursing care. Chronic wounds may lead to impaired quality of life and functioning, amputation, or even death. Of those with DM, it is estimated that about 10% to 15% will develop foot ulcers sometime in their lifetimes. This translates to about 105,000 people in Ontario (www.diabetes.ca/Section_About/feet.asp; accessed May 26, 2005), based on an Ontario prevalence of 700,000 people with DM.

According to the ICES report cited above, the rate of inpatient hospitalization for skin and soft tissue infections among people with diabetes decreased by about 25% from 807 per 100,000 people aged 20 years and over in 1995, to 602 per 100,000 people aged 20 years and over in 1999. (2) Although these data could not discern the specific cause of the infections, the authors speculated that most of these hospitalizations were due to foot ulcers. They suggested that the decrease might have been due to an active awareness campaign on diabetic foot care among Ontario physicians during this time.

Similarly, as reported in the ICES report, the rate of minor amputations for people with DM dropped by 29% from 1995 to 1999 (158 to 112 per 100,000 people with DM). (2) However, people with DM were 24-fold more likely to have a minor amputation than were people without DM, after adjusting for the age and sex distribution in the populations. The rate of major amputations in the diabetic population also dropped over the study period, but not as drastically as that for minor amputations (202 per 100,000 people with DM in 1995 to 179 per 100,000 in 1999). Despite this drop, people with DM had a 14-fold-higher likelihood of major amputation than did people without DM, after adjusting for age and sex. (2)

According to Ontario hospital discharge abstracts, 1,065 people were admitted primarily for a foot ulcer due to DM (152 per 100,000 people with DM). A further 1,305 (186 per 100,000 people with DM) were admitted to hospital with a foot ulcer as a secondary diagnosis, complication, or comorbid condition in 2003. There were 67 minor amputations of the toe or toe/phalanx in patients identified as having DM reported in the hospital discharge abstract (9.57 per 100,000 people with DM) and 357 major amputations at the foot, ankle, or leg (51 per 100,000 people with DM) in 2003. The 1999 data reported by ICES and the 2003 data cited above cannot be compared because of changes in the administrative data coding systems for both diagnoses and procedures.

Various diagnostic grading systems are routinely used to stratify the severity of foot ulcers. The Wagner system, published in 1981, (3) is widely used to assess the degree and severity of ulcers in people with DM. Many clinical and treatment management guidelines and study protocols use this system to stratify patients with foot ulcers. The system is as follows:

- Grade 1: partial or full thickness ulcer
- Grade 2: probing tendon or capsule
- Grade 3: deep ulcer with osteitis
- Grade 4: partial foot gangrene
- Grade 5: whole foot gangrene

Treatment of Chronic Ulcers in Diabetes

Little is known about the wound-healing process, and this makes treating chronic wounds challenging. Usually, a DM foot ulcer takes between 12 and 20 weeks to heal. (4) Many therapies exist for treating wounds in persons with DM, such as: (4)

- Identification and correction of the etiological cause of the wound (e.g., ensuring good nutrition and maintaining normal blood glucose)
- Current best practices for the treatment of chronic wounds including debridement and infection control
- Preventive and therapeutic strategies such as orthopedic shoes/devices and shoe fitting to resist blisters and wounds, and off-loading to relieve pressure on the foot.
- Amputation in very severe cases.

Technology Being Reviewed: Hyperbaric Oxygen Therapy for Ulcers in Diabetes

Hyperbaric oxygen therapy has been in use for about 40 years. It is thought to aid healing by supplying oxygen to the wound. The Hyperbaric Oxygen Therapy Association (www.hotaweb.org/HBOT.asp) notes that HBOT acts as a bactericidal, stops toxin production, and promotes tissue growth.

During the procedure, a patient is placed in a compression chamber with increased pressure between 2.0 and 2.5 atmospheres absolute (ATA) for 60 to 120 minutes, once or twice daily. In the chamber, the patient inhales 100% oxygen. Each treatment cycle consists of 15 to 20 treatment sessions.

Noted complications of HBOT may include ear, sinus, and lung damage; temporary worsening of shortsightedness; claustrophobia; and oxygen poisoning. (5;6) The incidence of aural barotraumas is the most frequently cited complication. (7) The complications are reportedly rare. Careful monitoring during the treatment sessions and follow-up by a trained health care provider are recommended.

Regulatory Status

Health Canada lists 2 manufacturers who are licensed to sell hyperbaric oxygen chambers in Canada:

- Sechrist Industries, Inc. (Anaheim, California)
 - Monoplace hyperbaric chamber (licence 440, Class 3)
- Perry Baromedical Corp. (Rivera Beach, Florida)
 - Sigma 34 monoplace hyperbaric system (licence 26990; Class 3)
 - Sigma plus series hyperbaric chamber (licence 27313; Class 3)
 - Sigma II series hyperbaric chamber (licence 28094; Class 3)
 - Sigma MP series hyperbaric chamber (licence 28304; Class 3)

Insurance Coverage

Hyperbaric oxygen therapy has been an insured service in Ontario since 1992 under the Health Insurance Act (codes G800–G806 in the Ontario schedule of benefits for physician services). (http://www.health.gov.on.ca/english/providers/program/ohip/sob/physserv/J_diagth.pdf).

It may be used under special circumstances for these indications (Personal communication, 2004):

- Air or gas embolism
- Carbon monoxide complicated by cyanide poisoning, carbon monoxide poisoning, or smoke inhalation
- Clostridial myonecrosis (gas gangrene)
- Crush injury, compartment syndrome, and other acute traumatic ischemia
- Decompression sickness
- Enhancement of healing in selected problem wounds, including diabetic wounds
- Exceptional blood loss (e.g., due to anemia)
- Intracranial abscess
- Necrotizing soft tissue infections (e.g., of the subcutaneous tissue, muscle, or fascia)
- Treatment-resistant osteomyelitis (i.e., an acute or chronic bone infection)

- Radiation tissue damage and osteoradionecrosis (i.e., the death of bone tissue due to radiation)
- Skin grafts and flaps (compromised)
- Thermal burns

Other Canadian provinces and territories offer HBOT either as a general insured service or by special provision.

In the United States, reimbursement for HBOT has been covered by the Centers for Medicaid & Medicare Services since 2003 for diabetic wounds. It is covered if a patient has type 1 or 2 diabetes, a Wagner grade III or higher (please see above explanation), and if traditional wound treatment has failed. (8) If the wound does not show signs of healing after 30 days of HBOT, coverage is discontinued. (8) The Centers for Medicaid & Medicare Services (<https://www.cms.hhs.gov/>) is doing a full review of wound care to determine the burden of illness, to outline and review the knowledge base for chronic wound treatment, and to develop and promote the use of standard outcomes and measures in order to bolster the quality of clinical research initiatives in this area. Specific products and timelines for this initiative have yet to be defined.

Literature Review

Objective

To assess the effectiveness, safety, and cost-effectiveness of HBOT, either alone, or as an adjunct, compared with the standard treatments for non-healing foot or leg ulcers in patients with DM.

Questions Asked

- Alone or as an adjunct therapy, is HBOT more effective than other therapies for non-healing foot or leg ulcers in patients with DM?
- If so, what is the incremental benefit over and above currently used strategies?
- When is the best time in a treatment strategy to use HBOT?
- What is the best treatment algorithm with HBOT?

Methods

The Medical Advisory Secretariat searched for health technology assessments in the published and grey literature. The search yielded 4 reports, which were published from 2000 to 2005. The most recent report from the Cochrane Collaboration had a literature review and analysis of randomized control trials (RCTs) to 2003.

As an update to this review, and as per the Medical Advisory Secretariat's standard review strategy, the abstracts of peer-reviewed publications were identified through Ovid MEDLINE, EMBASE, MEDLINE in-process and not-yet-indexed citations, the Cochrane Database of Systematic Reviews, Cochrane CENTRAL, and INAHTA using the following key words from January 1, 2003 to 2004.

- hyperbaric oxygenation, oxygen
- HBOT
- wound healing
- diabetic foot
- osteomyelitis or diabetic chronic osteomyelitis

- gas gangrene or diabetic gas gangrene
- fasciitis, necrotizing/or diabetic necrotizing fasciitis
- diabetic thermal burn
- skin ulcer or exp decubitus ulcer or exp leg ulcer or exp foot ulcer or varicose ulcer
- wounds and injuries or chronic wound.

The criteria for inclusion were as follows:

- Patient population comprising people with diabetes
- Live human study
- English-language study
- HBOT as adjunctive therapy or alone
- RCT

The number of excluded studies were as follows:

- 2 animal studies
- 13 focus on condition other than DM
- 8 review/protocol for HBOT use
- 3 HBOT not focus of report
- 2 Health technology assessments
- 1 Non-RCT

The outcomes of interest were wound healing and prevention of amputation.

The search yielded 29 citations of papers published between 2003 and 2004. All 29 of these articles were excluded, as shown beside the criteria above. Therefore, this health technology policy appraisal focused exclusively on the most recently published health technology assessments and systematic reviews.

Summary of Health Technology Reports

The Medical Advisory Secretariat retrieved 4 recent health technology assessments or systematic reviews that examined the effectiveness of HBOT to treat ulcers due to diabetes compared with other therapies (Table 1).

The most recent systematic review, (7) which was published in 2005 by German and Australian researchers in the Cochrane Collaboration, extended a previous Cochrane Collaboration health technology assessment (5) that was published in 2005. The extended review aimed to elucidate the best evidence on the impact of HBOT to manage diabetic, venous, arterial, and pressure ulcers, because the available evidence was “sparse and difficult to interpret.” This systematic review followed the Cochrane method to search and assess the literature. Their inclusion criteria were as follows:

- Comparison of effect of HBOT (adjunctive) with no HBOT or sham therapy
- Diabetic, venous, arterial, and pressure ulcers
- RCT with random allocation
- Chronic wounds that had not responded to other therapy

The exclusion criteria were as follows:

- Animal studies
- Topical HBOT

The literature search spanned 1966 to 2003 using the standard medical search databases (MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials) and DORCTHIM (a specialized hyperbaric medicine database); results were cross-referenced to the Cochrane Wounds Group Special Trials register. Six studies with 191 patients were included. Out of 6 RCTs included in the review, 5 focused on HBOT for non-healing wounds due to diabetes, and 4 focused on the outcomes of interest for the Medical Advisory Secretariat's health technology policy assessment.

The methods used in this assessment were rigorous. The Jadad score (9) for RCT quality was used to assess each study, and homogeneity was assessed for pooled analyses across stratified outcome measures (wound healing, minor or major amputation, transcutaneous oxygen tension measurements). These RCTs are discussed in more detail further in this report.

The conclusions from this extended health technology assessment and from the previous Cochrane report were that there was no evidence of the effectiveness of HBOT for wound healing in general, or for prevention of minor amputation (Table 1). However, their analysis found that HBOT might decrease the risk of major amputation compared with a control treatment (relative risk [RR], 0.31; 95% confidence interval [CI], 0.13–0.71). The calculated number needed to treat (NNT) to prevent 1 amputation was 4 (95% CI, 3–11). Further, the transcutaneous oxygen tensions monitored before and after treatment in some of these studies may have provided support for this finding. Caveats to these conclusions were stated as inconsistent study quality, inclusion and exclusion criteria, and HBOT treatment regimens; and small sample sizes. The RCTs from this health technology assessment are discussed in more detail further in this report.

In 2003, the Alberta Heritage Foundation (10) and Agency for Healthcare Research and Quality (AHRQ) (11) published reviews of the use of HBOT to heal wounds in diabetes. Neither did an analytic synthesis of the data. The Alberta Heritage Foundation suggested that there might be some benefit, but that the benefit had yet to be established in the published literature. AHRQ suggested that more research is needed to determine how and where HBOT fits in wound care for diabetes.

In 2000, the Medical Services Advisory Committee (MSAC) (6) in Australia reviewed the effectiveness of HBOT for many indications, including the following:

- Thermal burns
- Diabetic and other chronic wounds
- Necrotizing soft tissue infections and necrotizing fasciitis (a rare bacterial infection also called flesh-eating disease)
- Fournier's gangrene (a bacterial skin infection that affects the genitals and perineum)
- Osteomyelitis
- Osteoradionecrosis
- Skin grafting

The MSAC found that HBOT was effective at healing wounds based on a pooled analysis of 38 patients across 2 comparative studies (odds ratio [OR], 39.39; 95% CI, 5.54–280.32; $P < .0001$) with no apparent heterogeneity ($P = .462$). The confidence in this result is, however, questionable, because the confidence intervals are wide.

Based on a pooled 251 patients from 2 RCTs and 2 comparative studies (no apparent heterogeneity [$\chi^2_{df=3}$, 0.87; $P = .833$]), the MSAC found that HBOT was effective at preventing major amputations (OR, 0.25 (95% CI, 0.13–0.50; $P < .0001$). Their analysis of minor amputations was not statistically significant.

The authors also analyzed the cost of treating diabetic wounds. They found a cost savings of \$63,100 (AU) or less per amputation avoided with the use of HBOT based on 15 to 40 sessions that cost \$6,941 (AU). A caveat about these estimates, however, is that the conclusion of the effectiveness of HBOT was based on limited evidence.

The MSAC accepted recommendations for public funding of HBOT to treat chronic wounds due to diabetes, necrotizing soft tissue infection, decompression illness, gas gangrene, and air or gas embolism, despite the limitations of the studies reviewed and the scant evidence of effectiveness. They did not develop standards for the therapy, but they encouraged Standards Australia to do so.

Table 1: Summary of Health Technology Assessments and Systematic Reviews on Hyperbaric Oxygen Therapy for People With Diabetes*

Assessment or Review	Years Searched	Inclusion Criteria	Exclusion Criteria	Results	Conclusions
Roeckl-Wiedmann, Bennett & Kranke, for Cochrane Collaboration, 2005 (7) Update from Kranke, Bennett, Roeckl-Wiedmann, Debus, 2005 (5) and Kranke,	1966–2003	- RCT (adjunctive HBOT with sham or no HBOT) - Random allocation - Chronic wounds that did not respond to other therapy - 5 RCTs on patients with DM evaluated with some study limitations	- Animal study - Topical HBOT	Patients healed right after and within 2 weeks, % (46 patients pooled, 2 studies; (12;13) no heterogeneity [$I^2=0$]) <u>Overall</u> RR: 4.78 (95% CI, 0.94–24.24) <u>Best-case scenario</u> RR: 6.04 (95% CI, 1.23–9.80) <u>Worst-case scenario</u> RR: 2.89 (95% CI, 0.83–10.14) Major amputation 7 wks, 1 year combined (118 patients pooled, 3 studies; (12;14;15) no heterogeneity [$I^2=0$]) <u>Overall</u> RR: 0.31 (95% CI, 0.13–0.71) <u>Best-case scenario</u> RR: 0.28 (95% CI, 0.12–0.64) <u>Worst-case scenario</u> RR: 0.41 (95% CI, 0.19–0.86) NNT: 4 (3,11)	- No evidence to suggest HBOT is effective in ulcer healing or in minor amputation (not shown). - Patients with treatment-resistant leg ulcers due to diabetes are 1/3 less likely to have a major amputation after treatment with HBOT compared with controls. - 4 patients need to be treated to avoid 1 amputation. - No adverse events reported.
Alberta Heritage Foundation, 2003 (10)	1998–2003 update of 1998 report Not an HTA	- 3 HTAs, 1 review, 1 non-RCT, 1 case series - Ulcers due to diabetes and other indications	Not stated	No analysis or synthesis performed	- Conditional support for HBOT treatment of wounds due to diabetes, but lack of quality studies; lack of quality evidence of benefit does not mean there is no benefit

Assessment or Review	Years Searched	Inclusion Criteria	Exclusion Criteria	Results	Conclusions
Centers for Medicaid/Medicare and AHRQ, 2001 (11)	mid-1998–2001	- Original data, 5 human subjects, clinical outcomes, RCTs, non-RCTs and case series For diabetes: 2 RCTs (14;15) and 4 non-RCTs	Not stated	No analysis or synthesis performed	- More research necessary to assess effectiveness in diabetic patients - The best timing for optimum outcomes using HBOT is not known
Medical Services Advisory Committee (MSAC), 2000 (6)	1966–1999 Two-stage search strategy: first for HBOT, then for indications	All studies focusing on wounds due to diabetes, other chronic wound and skin conditions, and other indications 5 studies on wounds due to diabetes, 2 RCTs (14;15) of unclear quality	Not stated	Risk of major amputation (251 pooled, 2 RCTs, (14;15) 2 comparative (16;17); no heterogeneity [$\chi^2_{df=3}, 0.87; P = .833$]) OR: 0.25 (95% CI, 0.13–0.50; $P < .0001$) Pooled risk difference: 20% (95% CI, 11%–30%; $P < .0001$) Risk of minor amputation (toe or forefoot) (155 patients; 2 RCTs; (14;15) no heterogeneity [$P = .722$]) OR: 1.76 (95% CI, 0.68–4.59; $P = .245$) Pooled risk difference: 9% (95% CI, -8%–25%; $P = .295$) Wound healing (38 patients in 2 comparative; (16;17) no heterogeneity [$P = .462$]) OR: 39.39 (95% CI, 5.54–280.32; $P < .0001$)	- 1 major amputation avoided with every 5 patients treated with HBOT (N = 251) - 1 minor amputation will be done for every 11 patients treated by HBOT (N = 155) - 3 of 4 patients treated with HBOT will have lesions healed compared with other therapies (N = 38) “Evidence that HBOT effective in promoting wound healing and reducing length of hospital stays and likelihood of major amputations.”

* CI indicates confidence interval; DM, diabetes mellitus; HBOT, hyperbaric oxygen therapy; HTA, health technology assessment; NNT, number needed to treat; OR, odds ratio; RCT, randomized controlled trial; RR, relative risk.

Studies Included in the Recently Published Cochrane Review

Tables 2 and 3 (on the next 2 pages) show summaries of the designs and quality of the studies included in the Cochrane pooled analyses on HBOT. (7) There were 4 studies (12-15) that focused on the outcomes of interest to the Medical Advisory Secretariat. All of the studies compared HBOT as an adjunct to standard treatment with the control arm as standard treatment. The studies included in the pooled analysis were not well described, with the exception of one high-quality study (12) that was given a Jadad score (9) of 5 by the Cochrane authors. However, the sample size of this high-quality study was small (8 people in each arm) and therefore, the results might be subject to a type II error where a negative result was found. Moreover, the method of the sample size calculation for this study was not explicit.

Despite an analysis of heterogeneity performed by Cochrane, the studies reviewed were comprised of patients with varying degrees of wound severity, HBOT protocols and control interventions, follow-up durations, and outcome measures. As a result, the validity of the obtained results of the Cochrane pooled analysis may be uncertain.

Table 2: Summary of Randomized Controlled Trials in the 2005 Cochrane Systematic Review (7)

Author (Jadad Score)*	N	Inclusion Criteria (Recruitment)	Comparator	Hyperbaric Oxygen Therapy Course†	Follow-up	Outcomes
Doctor, 1992 (14) (Jadad 2)	30	DM patients with chronic foot lesions (Over 2 years)	HBOT + standard treatment Standard treatment	3 ATA for 45 minutes, 4 sessions over 2 weeks	Not stated	Major amputation HBOT: 13% (2/15) Control: 46% (7/15) (<i>P</i> < .05)
Faglia, 1996 (15) (Jadad 2)	70	Consecutive DM patients with foot ulcers; Wagner scale II – IV; almost 2/3 in Wagner grade IV in each arm (1993–1995)	HBOT + aggressive treatment (N = 35; 1 refused treatment) Aggressive treatment only (N = 33; 1 died) (aggressive debridement, antibiotic therapy, intravenous insulin where necessary, provision of orthopedic devices)	Phase 1: 2.5 ATA, 90 minutes daily Phase 2: 2.4–2.2 ATA, 5/7 sessions for average of 38 (SD, 8) sessions	Not stated	Major amputation HBOT: 9% (3/35) Control: 31% (11/35) (<i>P</i> = .016) RR, 0.26 (95% CI, 0.08–0.84) Amputation rate correlated with more severe wound (<i>P</i> = .002 in Wagner scale IV; not significant in Wagner scale II or III across study arms) Unadjusted logistic regression model suggests HBOT: OR, 0.84 (95% CI, 0.008–0.821; <i>P</i> = .033) High Wagner grade OR, 11.199 (95% CI, 1.41– 89.15; <i>P</i> = .022)
Abidia, 2003 (12) (Jadad 5)	18	- Ulcers for longer than 6 weeks - Wounds 1–10 cm in diameter - Vascular assessment by angiography (1999–2001)	HBOT + medical treatment (N = 9; 1 needed surgery, dropped out) Sham: compressed air in chamber + medical treatment (N = 9; 1 dropped out)	-2.4 ATA, 90 minutes x 30 treatments over 6 weeks Plus: off-loading, debridement, dressings, and infection control if necessary	Baseline 5 treatments 30 treatments 6 months 1 year	Healed at 1 year HBOT: 75% (5/8) Control: 13% (1/8) (<i>P</i> = .026) Major amputation HBOT: 13% (1/8) Control: 13% (1/8) Minor amputation HBOT: 13% (1/8) Control: 0% (0/8) No adverse effects
Kessler, 2003 (13) (Jadad 2)	28	Consecutive patients with type 1 or 2 DM with chronic Wagner grade I–III foot ulcers lasting more than 3 month with standard treatment -Clinical signs of neuropathy -No arteriopathy -No infection (1999–2000)	HBOT + standard treatment (N = 15) Standard treatment (N = 13)	2.5 ATA, twice daily, 90 minutes x 5 days/ week for 2 weeks	All patients hospitalized for 2 weeks during treatment and then followed-up for 2 weeks as outpatients	Wound ulcer surface area reduction, baseline to 2 weeks HBOT: 41.8% (SD, 25.5%) Control: 21.7% (SD, 16.9%) (<i>P</i> = .037) Wound ulcer surface area reduction, baseline to 4 weeks HBOT: 61.9% (SD, 23.3%) Control: 55.1% (SD, 21.5%) (not significant)

* Jadad score for study quality, 1996 (9)

†ATA indicates atmospheres absolute.

Table 3: The Medical Advisory Secretariat's Assessment of the Quality of RCTs* in the 2005 Cochrane Systematic Review (7)

Author	Randomization/ Concealment	Sample Size Calculation	Blinding	Inclusion/ Exclusion/ Criteria	Intention- To-Treat Analysis	Medical Advisory Secretariat Comments
Doctor, 1992 (14)	Method and concealment not stated No differences across treatment arms	Not stated	Not stated	Not stated	Not stated	Study not well described
Faglia, 1996 (15)	Method and concealment not stated No differences across treatment arms	Not stated	Not stated	No	No	Adjusted multivariate analysis not reported; severe and non-severe patients included
Abidia, 2003 (12)	Sealed envelopes No differences across study arms, but very small sample size to make adequate comparison	Reportedly based on similar work but not explicit	Yes: double- blinded (all carers and providers blind) Treatment & sham regimen the same in both groups	Yes	Yes	Well-conducted but very small sample size; type II error possible
Kessler, 2003 (13)	Randomization table used; concealment not stated No differences across treatment arms	Not stated	Not stated	Yes	Not stated	Study not well described

*RCT indicates randomized controlled trial.

Table 4: GRADE (18) Analysis of Studies in the 2005 Cochrane Systematic Review (7)

Outcomes	Study Design, RCTs*	Quality	Consistency	Directness	Overall assessment
Wound healing rate	High	Low to moderate	Yes	No	Low-moderate
Major amputation rate	High	Low	Yes	- Severity of patients recruited - Intensity of HBOT* - Aggressiveness of adjunct/comparison regimen - Small number of patients recruited	Low
Minor amputation rate	High	Low	No	-Small sample sizes may lead to type II error	Low

*RCT indicates randomized controlled trial; HBOT, hyperbaric oxygen therapy.

Summary of Literature Review

The Cochrane health technology assessment focused only on RCTs, whereas the MSAC assessment included all study designs. The MSAC assessment pooled all study designs and treatment protocols; thus, the uncertainty around their estimates is high.

The pooled results from the Cochrane assessment suggests that HBOT plus adjunct treatment might prevent amputation compared with adjunctive treatment alone in people who have DM and non-healing wounds (RR, 0.31; 95% CI, 0.13–0.71). They also found an NNT of 4 (95% CI, 3–11). The effect of HBOT plus adjunctive therapies compared to adjunctive therapy alone is not known for wound healing in general, or for minor amputation, according to the Cochrane review.

The Medical Advisory Secretariat examined the quality of the studies that were included in the Cochrane review, using the recently published GRADE Assessment, (18) a tool designed by international study design experts. GRADE provides a systematic approach to judge the certainty or confidence of results, based on the quality of the available evidence, and provides advice on recommendations surrounding a body of literature. According to this rubric, the overall certainty of the outcomes gleaned from the HBOT literature is low to moderate for the outcome of wound healing, and low for the outcomes of major and minor amputation. (See Table 4.)

According to the GRADE criteria, (18) the judgement of low to moderate quality evidence suggests that further research will likely have an important impact on the confidence in the estimate of effect and may, in fact, change the estimate.

Existing Guidelines

There are many guidelines from various organizations on the treatment of DM foot ulcers:

- American Diabetes Association
- International Working Group on the Diabetic Foot
- Canadian Diabetes Association
- Canadian Association of Wound Care
- American College of Foot and Ankle Surgeons
- Wound Healing Society

Recently, Frykberg (4) summarized these guidelines and concluded that the assessment and treatment of foot ulcers in DM should include the following:

- Taking a detailed patient history: trauma to foot, neuropathy, previous ulcer, infection, hypoxia, and protein glycosylation
- Assessing the wound and cause of wound cause: kidney function, depth, location, area, odour, neurological exam, vascular exam, infection
- Classifying the wound: no universally accepted system
- Addressing treatment: correct causal etiology, treatment of comorbidities, debridement, total contact cast for ‘off-loading,’ topical cream, gel, antimicrobials, dressings, etc.
- Focusing on prevention: provider/patient education, protective/therapeutic footwear, appropriately fitted shoes, prophylactic surgery Adopting a multidisciplinary approach.

The Canadian Diabetes Association’s guidelines (www.diabetes.ca) suggest 10 steps to prevent foot

ulcers for people with DM, as follows:

- Check feet regularly, either with a caregiver or using hand mirror. Any change in the skin should be examined by a health care provider.
- Keep feet clean.
- Apply moisturizer or medicated ointment to damaged skin.
- Avoid heat, like heating pad or hot water bottle.
- Follow directions from health care providers.
- Wear loose clothing.
- Be careful with sharp instruments, such as nail clippers or scissors.
- Maintain a healthy weight.
- Don't walk barefoot.
- Quit smoking.
- Visit a health care professional regularly.

Economic Analysis

Disclaimer: This economic analysis represents an estimate only, based on assumptions and costing methodologies that have been explicitly stated. These estimates will change if different assumptions and costing methodologies are applied for the purpose of developing implementation plans for the technology.

A literature review was conducted to examine the costs and cost-effectiveness of HBOT plus standard treatment for lower-limb diabetic wounds. The MSAC (6) assessment analyzed cost, as did 1 RCT (12) that was included in the recent Cochrane review, and one stand-alone article by Guo. (19) The MSAC assessment and the Guo article emphasized that the costing analyses were based on uncertain estimates of effectiveness.

Table 5: Costs and Cost-Effectiveness of Hyperbaric Oxygen Therapy

Study	Cost Analysis	Savings	Assumptions	Caveats
MSAC (6)	\$6,341 (AU) per patient for HBOT* course	Cost per amputation avoided: \$63,100 (AU)	- Based on 11% mean risk difference in amputations - Would be cost saving if rehabilitation costs included	Stated assumption that the clinical magnitude of effect is correct based on the studies included.
Abidia (12)	<p>HBOT group £3000: HBOT course £1972: outpatient dressing changes (£58 x 33.75 visits) Total: £4972</p> <p>Control group £58 x 136.6 dressing changes Total: £ 7946</p>	£2974 saved using HBOT		Only included cost of dressing changes; other treatments were included in HBOT and control groups.
Guo (19)	Incremental cost per QALY* (US): 1 year: \$27,310 5 years: \$5,166 12 years: \$2,255		- Payer and societal perspective - Hypothetical cohort of 1000 patients with severe foot ulcers (Wagner scale III or >) - Cost of best-care treatment not factored in since HBOT is adjunctive treatment	Estimate of effectiveness from small, poorly conducted trials that would affect cost-effectiveness outcomes.

*HBOT indicates hyperbaric oxygen therapy; QALY, quality adjusted life year.

Ontario Context

According to estimates, (1) there are about 700,000 people with diabetes in Ontario; of these, from 70,000 to 100,00 may have a foot ulcer in their lifetime (10%–15% of prevalent cases). According to current Ontario hospital discharge abstracts, in 2003, 1,065 cases were admitted primarily for a foot ulcer due to DM (152 per 100,000 people with DM), and a further 1,305 (186 per 100,000 people with DM) were admitted to hospital with a diagnosed foot ulcer as a secondary diagnosis, complication, or comorbid condition. There were a reported 67 minor amputations of the toe or toe/phalanx in patients identified as having DM from the hospital discharge abstracts (9.57 per 100,000 people with DM), and 357 major amputations at the foot, ankle, or leg (51 per 100,000 people with DM) in 2003. The Ontario codes used are in Appendix 1.

There are 6 hyperbaric oxygen chambers in Ontario, which are located in the Greater Toronto area, Ottawa, and Hamilton. The abstracting of HBOT by Ontario hospital health records coders is not mandatory; therefore, the use as indicated in the provincial hospital discharge abstracts may underestimate the true use. Nonetheless, the data suggest that only 17 patients identified as having DM received HBOT in 2003.

Direct Costs of Hyperbaric Oxygen Therapy and Chronic Wounds

All costs are in Canadian currency. The cost to lease a hyperbaric oxygen chamber is about \$275,000 plus \$315,000 in variable and fixed costs annually (e.g., maintenance, staff resources, medical supplies, etc.). The cost of HBOT per treatment cycle for a patient that has DM and an ulcer is estimated at \$5,200 based on 100 patients treated each year with 1 chamber (Personal communication, 2005), plus amortization of the cost of the machine (about \$1,000). Thus, the total cost per patient is about \$6,200.

It is estimated that the hospital cost for a patient that has DM and an ulcer, and that does not require amputation, is \$58,500 (based on 78 days in the hospital at \$750 per day). The estimated system cost for an amputation is \$60,000 per patient (Personal communication, 2005). To determine the possible cost avoidance of HBOT, the following analysis was done:

- Cost avoidance for 1 amputation: \$ 60,000 (cost amputation) - \$6,200 (HBOT) = \$53,800
- Cost avoidance in Ontario:

Low estimate: One-third of amputations avoided with HBOT (Cochrane estimate)
357 major amputations in Ontario x 0.30 = 107.1 x \$53,800
= \$5.8 million

High estimate: All amputations avoided with HBOT
357 major amputations in Ontario x \$53,800
= \$19.6 million

Thus, between \$5.8 million and \$19.6 million in costs could be avoided based on current estimates if HBOT was deemed effective at preventing amputations in patients who have DM and foot ulcers.

Appraisal

Demographics

- About 700,000 people may have diabetes in Ontario.
- About 10% to 15% of these people may have a foot wound in their lifetime.
- At least 67 minor and 357 major amputations were done in people with diabetes in 2003 in Ontario.
- Fewer than 20 patients with DM were treated with HBOT in 2003, according to Ontario hospital discharge abstracts.

Patient Outcomes – Medical, Clinical

- Pooled data found a potential benefit of HBOT for preventing major amputation but not for prevention of minor amputation or for wound healing overall.

- These pooled estimates reported in a previously published health technology assessment are uncertain, because there is a dearth of good quality studies.
- The Medical Advisory Secretariat's synthesis of the quality of the studies included in the pooled data found that more research of higher quality likely would change the current estimates and certainty around the estimates.

Cost

All costs are in Canadian currency:

- In Ontario, a hyperbaric oxygen chamber costs about \$275,000 plus \$315,000 in variable and fixed costs.
- The cost per patient with DM treated with HBOT is \$6,200 in Ontario.
- The system cost of an amputation is estimated at \$60,000.
- The cost per amputation avoided using HBOT may be estimated as \$5.8 million to \$19.6 million if HBOT was deemed effective at avoiding amputation in patients who have DM and foot ulcers.

Stakeholder Analysis

- Significant patient burden is associated with diabetic foot ulcers.
- A registered hyperbaric technician should operate the chamber.

System Pressures

- A previous Medical Advisory Secretariat health technology policy assessment on wound care highlighted the need for a coordinated wound care effort across providers in Ontario.

There are 6 HBOT chambers in 3 sites in Ontario, with limited access for wound treatment.

Conclusions

The quality of the evidence assessing the effectiveness of HBOT as an adjunct to standard therapy for people with non-healing diabetic foot ulcers is low, and the results are inconsistent. The results of a recent meta-analysis that found benefit of HBOT to prevent amputation are therefore uncertain. Future well-conducted studies may change the currently published estimates of effectiveness for wound healing and prevention of amputation for HBOT in the treatment of non-healing diabetic foot ulcers. This health technology policy assessment could not determine when the best time to provide HBOT in the treatment cycle or what the best algorithm for effective treatment would be.

Based on the level of evidence, a well-conducted study may change the currently published estimates of effectiveness for wound healing and prevention of amputation for HBOT in the treatment of non-healing diabetic foot ulcers.

There are about 700,000 people in Ontario with diabetes, and 10% to 15% of these people may have a foot ulcer sometime in their lives. Foot ulcers are treatable when they are identified, diagnosed, and treated early, according to best-practice guidelines. Routine follow-up for people with diabetes who may be at risk for neuropathy and/or peripheral vascular disease may prevent subsequent foot ulcers.

HBOT is an insured service in Ontario; however, fewer than 20 people with DM were treated with this

therapy in 2003, according to hospital discharge abstracts. There are 3 centres housing 6 hyperbaric oxygen chambers in Ontario.

In 2003, the Ontario Health Technology Advisory Committee recommended a more coordinated strategy for wound care in Ontario to the Ministry of Health and Long-term Care. This strategy has begun at the community care and long-term care institution levels, but is pending in other areas of the health care system.

Appendices

Appendix 1: Codes Extracted From Ontario Hospital Discharge Abstracts at the Ontario Ministry of Health and Long-term Care 2005

	ICD-10 CA Diagnosis Codes	Canadian Classification of Interventions
Diabetic foot ulcer	E10700-10709 E11700-E11709 E13700-E13709 E14700-E14709	
Unspecified skin condition - diabetes	E10610-E10619 E11610-E11619 E13610-E13619 E14610-E14619	
<u>Oxygenation wound therapy:</u> Monoplace hyperbaric chamber (or chamber NOS)		1.YZ.12.JA-MS
Multiplace hyperbaric chamber		1.YZ.12.JA-MT
Amputation of toe/phalanx		1.WL.93
Amputation of toe at joint		1.WM.93
Amputation of tarsometatarsal, metatarsal bones and metatarsophalangeal joints		1.WJ.93
Amputation at ankle		1.WA.93
Amputation of femur		1.VC.93
Amputation through knee joint		1.VG.93
Amputation through tibia-fibula		1.VQ.93
Amputation through mid-foot		1.WE.93

References

1. Hux JE, Tang M. Patterns of prevalence and incidence of diabetes. In: Hux JE, Booth GL, Slaughter PM, Laupacis A, editors. Diabetes in Ontario. Practice atlas [monograph on the Internet]. Toronto: Institute for Clinical Evaluative Sciences; 2003. [cited 2005 June 1] Available from: http://www.ices.on.ca/file/DM_Chapter1.pdf
2. Booth GL, Fang J. Acute complications of diabetes. In: Hux JE, Booth GL, Slaughter PM, Laupacis A, editors. Diabetes in Ontario. Practice atlas [monograph on the Internet]. Toronto: Institute for Clinical Evaluative Sciences; 2003. [cited 2005 June 6] Available from: http://www.ices.on.ca/file/DM_Chapter2.pdf
3. Wagner FW. The dysvascular foot: a system of diagnosis and treatment. *Foot Ankle* 1981; 2: 64-181
4. Frykberg RG. A summary of guidelines for managing the diabetic foot. *Adv Skin Wound* 2005; 18(4): 209-214
5. Kranke P, Bennett M, Roeckl-Wiedmann I, Debus S. Hyperbaric oxygen therapy for chronic wounds. *Cochrane Database Syst Rev* 2004; Issue 1(Art.No.: CD004123.DOI: 10.1002/14651858.CD004123.pub2)
6. Medical Services Advisory Committee. Hyperbaric oxygen therapy [report on the Internet]. 2001. Canberra: Medical Services Advisory Committee (MSAC). [cited 2005 June 15]. Available from: <http://www.msac.gov.au/reports.htm>.
7. Roeckl-Wiedmann I, Bennett M, Kranke P. Systematic review of hyperbaric oxygen in the management of chronic wounds. *Br J Surg* 2005; 92(1): 24-32
8. Schaum KD. Hyperbaric oxygen therapy 2003 Medicare coverage decision. *Adv Skin Wound Care* 2003; 16(5): 244
9. Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Control Clin Trials* 1996; 17: 1-12
10. Hailey D. Hyperbaric oxygen therapy - recent findings on evidence for its effectiveness [report on the Internet]. IP13: Information Paper. March 2003. Edmonton: Alberta Heritage Foundation for Medical Research (AHFMR). [cited 2005 June 20]. Available from: <http://www.ahfmr.ab.ca/publications.html>.
11. Wang C, Schwaitzberg S, Berliner E, Zarin DA, Lau J. Hyperbaric oxygen for treating wounds: a systematic review of the literature. *Arch Surg* 2003; 138(3): 272-279
12. Abidia A, Laden G, Kuhan G, Johnson BF, Wilkinson AR, Renwick PM et al. The role of hyperbaric oxygen therapy in ischaemic diabetic lower extremity ulcers: a double-blind randomised-controlled trial. *Eur J Vasc Endovasc Surg* 2003; 25(6): 513-518
13. Kessler L, Bilbault P, Ortega F, Grasso C, Passemard R, Stephan D et al. Hyperbaric oxygenation

accelerates the healing rate of nonischemic chronic diabetic foot ulcers: a prospective randomized study. *Diabetes Care* 2003; 26(8): 2378-2382

14. Doctor N, Pandys S, Supe A. Hyperbaric oxygen therapy in diabetic foot. *J Postgrad Med* 1992; 38: 112-114
15. Faglia E, Favales F, Aldghi A, Calia P et al. Adjunctive systemic hyperbaric oxygen therapy in treatment of severe prevalently ischemic diabetic foot ulcer. A randomized study. *Diabetes Care* 1996; 19: 1338-1343
16. Baroni G, Porro T, Faglia E, et al. Hyperbaric oxygen in diabetic gangrene treatment. *Diabetes Care* 1987; 10: 81-86
17. Zamboni WA, Wong HP, Stephenson LL, Pfeifer MA. Evaluation of hyperbaric oxygen for diabetic wounds: a prospective study. *Undersea Hyperb Med* 1997; 24: 175-179
18. GRADE Working Group. Grading the quality of evidence and strength of recommendations. *BMJ* 2004; 328: 1-8
19. Guo S, Counte MA, Gillespie KN, Schmitz H. Cost-effectiveness of adjunctive hyperbaric oxygen in the treatment of diabetic ulcers. *Int J Technol Assess Health Care* 2003; 19(4): 731-737