

**Health
Technology
Assessment**

Hyperbaric Oxygen Therapy (HBOT)

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LOW Yen Sia, LIM Woan Wui, Jeremy LIM

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For more information, please contact SingHealth CHSR at:
 Web: <http://www.singhealth.com.sg/research/hsr>
 Email: hsr@singhealth.com.sg
 Fax: (65) 6323 2901
 Mail: SingHealth Centre for Health Services Research
 226 Outram Road
 #03-01 Block A
 Singapore 169030

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Summary

Hyperbaric oxygen therapy (HBOT) is safe, efficacious, cost-effective in reducing amputation rates among patients with diabetic foot ulcers (DFU). The evidence is supported by several systematic reviews, HTAs and cost-effectiveness analyses. HBOT should be considered as a limb-salvaging option and be made widely available to suitable patients (those with severe wounds unresponsive to standard wound care alone).

Introduction

Objective

1. To review existing literature for the safety, efficacy and cost-effectiveness of hyperbaric oxygen therapy (HBOT) for diabetic foot ulcers (DFU)
2. To perform a cost-effectiveness analysis to estimate the incremental costs of adjunctive HBOT to a person with diabetic foot and to the society at large in a year in Singapore.

Population	Patients with diabetic foot ulcers (DFU)
Intervention	Hyperbaric oxygen therapy (HBOT)
Comparison	Standard wound care without HBOT
Outcomes	Amputation rates

About the Technology

Hyperbaric oxygen therapy (HBOT) has been used in chronic wounds for about 40 years (Kulonen 1968). During therapy, 100% oxygen is delivered to a chamber under high pressure (2 to 2.5 ATA) for periods between 45 and 120 minutes. A typical course involves 15 to 30 such treatments (Kranke 2004). Unlike topical or localised HBOT, the patient and not just the wound is exposed to a hyperbaric oxygen environment.

As insufficient oxygen supply may impede normal healing, administering oxygen to hypoxic tissue may aid healing. Wound healing proxies include hyper-oxygenation of tissue, vasoconstriction, fibroblast activation, down-regulation of inflammatory cytokines, up-regulation of growth factors, antibacterial effects and reduction in leukocyte chemotaxis (Kranke 2004). HBOT is always presented as an adjunctive therapy to normal wound care measures and is not proposed as an alternative therapy (Kranke 2004).

Burden of Disease

Worldwide, up to 70% of all leg amputations happen to someone with diabetes. In the UK, up to 15% of diabetics suffer from foot ulceration at some point in their lives. A leg is lost to diabetes every 30 seconds worldwide (International Working Group on the Diabetic Foot 2005).

Diabetic foot ulcer (DFU) is the leading cause of lower extremities amputation (LEA) in Singapore. Almost 60% of limb amputations in SGH Department of Orthopaedics are attributed to diabetes (Tan 1983). Some 700 LEAs due to diabetes are performed in Singapore each year (Ministry of Health Annual Report 2001). The prevalence of diabetics in Singapore is 8.2% (National Health Survey 2004).

Geographic Distribution

In addition to the navy chambers, there are 3 hyperbaric medical facilities available for civilian use in Singapore (Camden, Singapore General Hospital and Tan Tock Seng Hospital).

Methodology

Search terms: 'hyperbaric oxygen* diabet*'

Databases: Pubmed, NHS Centre for Reviews and Dissemination Database (CRD) and the National Guidelines Clearinghouse

Search date: May 2007

Non-English papers and those without abstracts were excluded. Search results were also checked for clinical relevance.

In the cost effectiveness analysis (CEA), there are 3 key components:

1. differences in outcomes due to the intervention
2. cost differences as a result of the intervention,
3. probabilistic component to account for the effectiveness of the intervention

Only outcomes (amputation rates) shown to be statistically and clinically significant were considered. Cost differences were retrieved from the inpatient charges of 2 major restructured hospitals in which amputation for diabetic foot (DRG R.520, S.8415 or S.8417) was carried out in 2006. Non-resident charges (n=3) were excluded from the analysis. The HBOT cost is estimated from the charges offered by the only hyperbaric medical facilities opened for civilian use (Hyperbaric Medical Services Pte Ltd). The risk reduction in the outcomes of interest were taken from meta-analyses of published literature. Two cost estimates will be calculated: one from the point of view of the individual patient and another from the society.

Results

Literature search using Medline retrieved 9 health technology assessments and systematic reviews of HBOT. One systematic review was located through a local conference. Zero new randomized controlled studies not included in previous reviews were found. Seven sets of clinical guidelines were found from the National Guidelines Clearinghouse.

Systematic reviews

Systematic reviews generally acknowledged the role of HBOT in reducing major amputations despite few small RCTs with study flaws (Table 1). HBOT was assessed on several outcome measures (major amputations, minor amputations, ulcers healed, time to complete healing, wound size reduction, quality of life, transcutaneous oxygen tensions and recurrence rates). Of them, amputation rates consistently reached statistical significance. The lower major amputation rates in the HBOT group were sometimes augmented by higher minor amputation rates, suggesting HBOT downgrades the amputation from a major (above foot) to a minor (below foot) one.

Economic Evaluations

All the economic evaluations found HBOT to be cost-effective for diabetic wounds (Table 4). Previous cost-effectiveness analyses of HBOT put cost savings of preventing an amputation in a person from £2974 to A\$63100. Depending on the size of the population, total societal costs savings can range from C\$19.6m in Canada. Such estimates are not necessarily applicable to Singapore as the health financing structure is different. See Annex 1 for details of the cost-effectiveness analysis of HBOT in Singapore.

Clinical Guidelines

Most guidelines recommend that HBOT be used adjunct to standard wound care for severe wounds. NICE (UK) guidelines did not recommend HBOT due to limited trial evidence. See Table 2.

Conclusion

There is strong albeit small body of evidence supporting HBOT as treatment for diabetic wounds. CEAs have also shown that HBOT is cost-effective. The cost-effectiveness improves with better selection of patients with serious wounds (Wagner III and above recommended by most insurers).

In Singapore, our CEA estimates HBOT will cost society S\$1,900 to prevent each major LEA. Applying sensitivity analysis to account for the varying efficacy of HBOT, this figure ranges from S\$7,000 savings to S\$68,000 costs to prevent each major LEA. Taken in aggregate, this translates to S\$1.6 million savings to S\$4.3 million costs to prevent the 9-33% of the 700 LEAs in Singapore each year. Preventing amputations reduces inpatient stay (882 to 3234 beds-days prevented per year).

There are also numerous substantial benefits of salvaging limbs (remaining employed, better quality of life, less burden to caregiver, etc) which are not considered in the CEA. Other than costs and risk of barotrauma and oxygen toxicity, HBOT presents minimal harm.

Most HTAs conclude that HBOT remain a complement to good wound care and urge careful patient selection to improve cost-effectiveness. HBOT has not been widely adopted in Singapore largely due to the perceived high cost (S\$260/session) and lack of referrals. While up to S\$100 of Medisave can be used each session, the out-of-pocket cost (S\$160/session) is substantial. As HBOT requires intensive capital investment, optimising services to reduce prices will be the best approach to make HBOT accessible to the large number of patients who stand to benefit from HBOT.

Regulatory and Healthcare Financing Information

Insurance coverage of HBOT for diabetic foot is provided in Canada, Australia and the US but was denied in Germany (Welslau 2001) . In Singapore, up to \$100 from Medisave may be used to pay for each session of HBOT (regardless of indication).

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Tables

Table 1: Systematic reviews and health technology reports

Study	Methods	Conclusion
Hailey et al. CADTH (2007) Ottawa, Canada	Literature review of evidence regarding the use of HBOT for the diabetic foot ulcers. Comparators include other wound care interventions. Studies included were 3 RCTs, 4 comparative studies between 1966 and 2005.	<ul style="list-style-type: none"> • % major amputations reduced from 32% to 11% (7 studies, n=305) • % minor amputations up from 15 to 27% (6 studies, n=190) • % of patients with wounds healed up from 43 to 83% (6 studies, n=185) • Length of hospital stay reduced from 56.9 to 47.1 days (3 studies) HBOT is more effective than standard care. Limited evidence; need more large trials.
Chew (2007) Singapore	Literature review of evidence regarding the use of HBOT for the diabetic foot ulcers. Comparators include other wound care interventions. Studies included were 4 RCTs between 1966 and 2005.	<ul style="list-style-type: none"> • Fewer major amputations (RR = 0.32 [0.11-0.91], 2 RCTs, n=43) • More minor amputations (RR = 1.70 [1.01-2.87], 2 RCTs, n=43) • Smaller wound area (SMD=0.65 [0.10-1.19], 2 RCTs, n=27) HBOT is more effective than standard care. Limited evidence; need more large trials.
Kranke et al. (2004) Updated in 2006 Cochrane Collaboration Hyperbaric oxygen therapy for chronic wounds Germany	Literature review of evidence regarding the use of HBOT for the treatment of chronic wounds (diabetic, vascular, pressure). Comparators include other wound care interventions. Studies included were 5 RCT between 1966 and 2003.	<ul style="list-style-type: none"> • Fewer major amputations (RR = 0.31 [0.13-0.71], 3 RCTs, n=118) • More wounds healed after 1 year (RR=2.25, [1.08-4.67], 1 RCT, n=18) • Higher transcutaneous oximetry (WMD=11.76 [5.68-17.84], 3 RCTs, n=113) HBOT more effective than standard care alone in reducing amputations. Limited evidence; need more large trials. Major amputation rate reduced by HBOT is largely driven by 1 RCT of 70 pts (Faglia 1996 Jadad=2 as control was weak and pts were not blinded). A better study (Abidia 2003, 18 pts, Jadad=5) which compared HBOT against sham therapy showed no reduction in major amputation rate.

Study	Methods	Conclusion
Roeckl et al. (2005) Munich, Germany	Literature review of evidence regarding the use of HBOT for the treatment of chronic wounds (diabetic, vascular, pressure). Comparators include other wound care interventions. Studies included were 6 RCT between 1966 and 2003.	<ul style="list-style-type: none"> • Smaller wound area (WMD=20.10-33.00 [3 RCTs, n=44]) • Fewer major amputations (RR=0.31 [0.13-0.71], 3 RCTs, n=118) • More wounds healed after 1 year (RR=2.25 [1.08-4.67], 1 RCT, n=18) • Higher transcutaneous oximetry (WMD=11.76 [5.67-17.84], 3 RCTs, n=117) HBOT is more effective than standard care. Limited evidence; need more large trials.
Ontario (2005) Ontario, Canada	Literature review of evidence regarding the use of HBOT for the treatment of diabetic wounds. Comparators include other wound care interventions. Studies included were 4 HTAs between 2000 and 2005.	Inconsistent and low level evidence supporting the use of HBOT for DFUs. Limited evidence; need more better and quality trials
Wang (2003) Boston, US	Literature review of evidence regarding the use of HBOT for the treatment of hypoxic wounds. Comparators include other wound care interventions. Studies included were 7 RCTs, 16 comparative studies, 34 case series between 1998 and 2001.	HBOT is beneficial in management of diabetic wounds. It significant reduced wound size, increased healing rates, and reduced major amputation rates (2 RCTs, 4 comparative studies, 2 case series, n=392). Adjunctive HBOT is effective for some wounds. Limited evidence; need more and better quality trials.
Alberta Heritage Foundation (2003) Alberta, Canada	Literature review of evidence regarding the use of HBOT for the treatment of ulcers. Comparators include other wound care interventions. Studies included were 3 HTAs, 1 review, 1 comparative study, 1 case series between 1998 and 2003.	Conditional support for HBOT for diabetic wounds. Lack of quality evidence does not mean there is no benefit.
Centres for Medicaid/Medicare and AHRQ (2001) US	Interviewed physicians, insurers, medical directors of chambers, analysed Medicare payments between 1995 and 1998, sampled 378 medical records for review regarding the use of HBOT.	Coverage decisions for HBOT lacking in the US. More research is required to assess effectiveness in diabetic patients.

Study	Methods	Conclusion
<p>Medical Services Advisory Committee (2000)</p> <p>Australia</p>	<p>Literature review of evidence regarding the use of HBOT. Comparators are other interventions depending on disease condition. Studies included were RCT between 1966 and 1999.</p>	<p>Fewer major amputations (RD=20%, [11-30%]) More wounds healed.</p> <p>HBOT is effective in promoting wound healing, and reducing the length of hospital stays and the likelihood of major amputations in patients with diabetic wounds. There may also be cost savings associated with these treatment benefits.</p>
<p>O'Meara et al. NHS (2000)</p> <p>UK</p>	<p>Literature review of evidence of HBOT for diabetic foot ulcers. Comparators include other wound care interventions. Studies included was 1 RCT between 1966 and 1999.</p>	<p>Fewer major amputations (OR=0.22, [0.07-0.72]) More minor amputations (OR=2.54, [0.99-6.53, 1RCT, n=68]) Impossible to draw any firm conclusions for practice based on 1 trial.</p>

Table 2: Clinical Practice Guidelines

Issuing organization	Methodology	Recommendation
<p>Department of Veterans Affairs, US 2007</p> <p>VA/DoD clinical practice guideline for rehabilitation of lower amputation.</p>	<p>The guideline is supported by the literature in a majority of areas, with evidence-based tables and references through the document..Where existing literature is ambiguous or conflicting, or where scientific data are lacking on an issue, recommendations are based on the expert panel's opinion and clinical experience.</p>	<p>Hyperbaric oxygen can be considered as an adjunct treatment for impaired wound healing</p>
<p>Registered Nurses' Association of Ontario (RNAO) Mar 2007</p> <p>Assessment & management of stage I to IV pressure ulcers</p>	<p>Guidelines group comprised of mainly RN. Guidelines were adapted from previous guidelines.</p>	<p>Chronic pressure ulcers may be treated by HBOT (Level of Evidence = IV (expert consensus))</p>
<p>Frykberg et al, Sep 2006</p> <p>Diabetic foot disorders: a clinical practice guideline.</p>	<p>Guidelines group comprised of mainly physicians and surgeons.</p>	<p>HBOT has shown promise in the treatment of diabetic foot wounds with hypoxia severe enough to interfere with healing. However, most of the HBO studies were hampered by methodological errors that preclude any definite role for this modality in the routine treatment of diabetic foot ulcers. Nevertheless, in 2003, Medicare and Medicaid coverage for HBO extended to ulcers classified as Wagner grade 3 or higher that failed standard wound care therapy. Clearly, a large multicenter randomized clinical trial is needed to properly test the efficacy of this expensive modality</p>
<p>Lipsky et al, Oct 2004</p> <p>Diagnosis and treatment of diabetic foot infections.</p> <p>Clin Infect Dis 1;39(7):885-910</p>	<p>Guidelines group comprised of M.D, nurses, podiatrists.</p>	<p>Studies have not adequately defined the role of most adjunctive therapies for diabetic foot infections, but systematic reviews suggest that granulocyte colony-stimulating factors and systemic hyperbaric oxygen therapy may help prevent amputations (B-I, Moderate evidence from at least 1 RCT). These treatments may be useful for severe infections or for those that have not adequately responded to therapy, despite correcting for all amenable local and systemic adverse factors.</p>

Issuing organization	Methodology	Recommendation
<p>National Collaborating Centre for Primary Care (NICE, UK). Jun 2004</p> <p>Clinical guidelines for type 2 diabetes. Prevention and management of foot problems.</p>	<p>Guidelines group consists of diabetologists, podiatrists, patient representative</p> <p>In addition to these evidence-based recommendations, the guideline development group also identifies recommendations drawn from the NICE 2003 technology appraisal of patient education models for diabetes.</p>	<p>Currently, there is a lack of trial evidence on the use of the following interventions in the treatment of foot ulcers and they are not recommended: cultured human dermis (or equivalent), hyperbaric oxygen therapy, topical ketanserin, or growth factors.</p>
<p>National Collaborating Centre for Chronic Conditions (NICE, UK) (2004)</p> <p>Type 1 diabetes in adults. National clinical guideline for diagnosis and management in primary and secondary care.</p>	<p>Guidelines group consists of diabetologists, podiatrists, patient representative</p> <p>In addition to these evidence-based recommendations, the guideline development group also identifies recommendations drawn from the NICE 2003 technology appraisal of patient education models for diabetes.</p>	<p>For people with an ulcerated foot: Do not use cultured human dermis (or equivalent), hyperbaric oxygen therapy, topical ketanserin, or growth factors I routine foot ulcer management.</p>
<p>Wound, Ostomy, and Continence Nurses Society (WOCN). (2004)</p> <p>Guideline for management of wounds in patients with lower-extremity neuropathic disease.</p>	<p>Guidelines group comprised of mainly nurses.</p>	<p>Consider hyperbaric oxygen therapy (HBOT) for Wagner grades III and IV ulcers.</p>

Table 3: Primary Studies

No new primary study found following the previous systematic review (CADTH 2007).
The list of primary studies included in the CADTH systematic review is reproduced below.

Table 1: Characteristics of selected studies				
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 grade 2 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.

Table 4: Economic Evaluations

Study	Methodology	Results	Remarks
Ontario (2005)	Calculate incremental price difference 33% less risk of major amputation Amputation cost = C\$30,000 HBOT cost = C\$6,200	C\$53,800 <u>saved</u> per amputation avoided	
MSAC (2000)	Calculate incremental price difference 11% less risk of major amputation Amputation cost = AU\$14,805 HBOT cost = AU\$6,941 Rehabilitation cost = AU\$8,758	AU\$11,142 <u>spent</u> per amputation avoided	MSAC concludes that HBOT is cost-effective for diabetic wounds
Guo (2003)	Markov model simulation of cost-effectiveness of HBOT vs without for 100 60-year old patients with DFU. Considered 3 outcomes (major amputations, minor amputation, healed)	Incremental cost per QALY: 1 yr – US\$27,310 (\$41,831) 5 yr – US\$5,166 (\$7,913) 12 yr – US\$2,255 (\$3,453)	An intervention is considered cost-effective if it costs less than €50,000 (or US\$50,000 or £25,000) per QALY.
Abidia (2003)	103 fewer dressing changes Dressing cost = £58 HBOT cost = £3000	£2974 saved	

Annex 1: Cost Effectiveness Analysis of HBOT for DFU in Singapore

Method

In the cost effectiveness analysis, there are 3 key components:

1. differences in outcomes due to the intervention,
2. cost differences as a result of the intervention, and
3. probabilistic component to account for the effectiveness of the intervention.

To keep the cost-effectiveness analysis simple, of the statistically significant outcomes, only proportion of patients requiring major amputation was considered, similar to methods used in previous cost-effectiveness analyses (Ontario 2005, MSAC 2000). As the Cochrane review was highly stringent with the selection of studies, its estimated range of absolute risk reduction (9-33%) was the widest and was adopted by this CEA for sensitivity analysis.

Cost differences were retrieved from the inpatient charges of 2 major restructured hospitals in which amputation for diabetic foot (DRG R.520, S.8415 or S.8417, n=226) was carried out in 2006 (Table 2). Non-resident charges (n=3) were excluded from the analysis. The HBOT cost is estimated from the charges offered by the main hyperbaric medical facilities opened for civilian use. The risk reduction in the outcomes of interest were taken from meta-analyses of published literature. Two cost estimates will be calculated - one from the point of view of the individual patient and another from the society.

Results

From Table 7, average amputation (without rehabilitation) charges range from \$2098 (C class, n = 96) to \$7396 (A class, n=3). The overall average amputation charge of \$2473 was taken to estimate the amputation cost to the patient. Average amputation with rehabilitation charges range from \$4182 (C class, n=16) to \$12138¹(B2 class, n=2). The overall average amputation and rehabilitation charges of \$4900 was ultimately used to estimate the amputation and rehabilitation cost to the patient.

Major LEA cost (n = 188, ALOS ² = 14)	:	\$2,473	≈	\$2,500
Major LEA and rehabilitation cost (n = 34, ALOS=35)	:	\$4,923	≈	\$4,900
Major LEA and rehabilitation cost if without government subsidy (n = 34)	:	\$18,877	≈	\$18,900

Patient's perspective

To the typical patient, HBOT will cost \$300 more than amputation and rehabilitation in B2 or C class for 35 days.

Cost to <i>patient</i> on HBOT who avoids a major LEA (patient's viewpoint)	=	Major amputation cost	+	Rehabilitation cost	-	HBOT cost
	=			\$4900	-	\$5200
	=	- \$300				

Society's perspective

After considering the subsidy, a major LEA and rehabilitation cost society \$18,900 per patient. Recall that adjunctive HBOT reduces the risk of a major amputation by 25%. Therefore, not everyone on HBOT will necessarily preserve his legs. This works out to HBOT costing \$1900 more in order to prevent a lower limb amputation.

Table 5: CEA of HBOT for 100 hypothetical patients

Basis: 100 patients	With HBOT	Without HBOT	Incremental
Number of major LEA	75	100	25 LEAs prevented
HBOT cost (\$260/session)	\$520,000	\$0	
LEA & rehabilitaton cost (\$18,900/LEA)	\$1,417,500	\$1,890,000	
Total cost	\$1,937,500	\$1,890,000	\$47,500
Cost per LEA avoided			\$1,900

¹ The wide range is due to the uncharacteristically long average length of stay of 110 days observed in TTSH B2 class.

² ALOS: Average length of stay

Sensitivity analysis

Recall that on average, HBOT costs society \$1,900 to prevent a LEA. This figure ranges from -\$7,000 savings to \$67,000 costs per LEA prevented after sensitivity analysis. On an annual basis, HBOT will *cost* society \$4.3 million in the *worst* case and *save* society \$1.6 million in the *best* case to prevent 9-33% of the 700 LEAs in Singapore each year.

Table 6: Sensitivity analysis adjusting for variances in risk and number of HBOT sessions required¹

	Assumptions	Cost per LEA avoided	Annual costs
Base case	20 HBOT sessions, 25% LEA avoided	\$1,900	\$332,500
Best case	15 HBOT sessions, 33% LEA avoided	-\$7,082	-\$1,635,900
Worst case	30 HBOT sessions, 9% LEA avoided	\$67,767	\$4,269,300

Table 7: Inpatient charges/bill sizes of amputation for diabetic foot (DRG R.520, S.8415 or S.8417, n=226) in 2006

Procedure	Institution	Class	Number of episodes	Average inpatient charge	Average length of stay	Average inpatient charge without subsidy
Amputation	Hospital A	B2	3	\$3641	20.3	\$10402
	Hospital B	A	3	\$7396	8.0	\$7396
	Hospital B	B1	10	\$6370	12.1	\$7963
	Hospital B	B2	76	\$2192	12.1	\$6264
	Hospital B	C	96	\$2098	15.6	\$10491
Amputation Total			188	\$2473	13.9	\$8597
Amputation and rehabilitation	Hospital A	B2	14	\$4772	22.6	\$13635
	Hospital A	C	16	\$4182	34.3	\$20911
	Hospital B	B2	2	\$12138	111.0	\$34680
	Hospital B	C	2	\$4698	51.5	\$23490
Amputation and rehab Total			34	\$4923	35.0	\$18877

¹ Risk reduction in LEA by HBOT: 25% [95% CI: 9-33%] (Kranke 2004)
Number of HBOT sessions required: 15-30 (Kranke 2004)