Joint Conference on

**Oxygen and Tissue Repair**

organized by

**European Committee for Hyperbaric Medicine**
and
**European Tissue Repair Society**

Ravenna, 27 – 28 October, 2006

Recommendations by the International Jury

**Members of the Jury:**

J. Niinikoski, Finland (Chairman)

ECHM

D. Bakker, The Netherlands
F. Cronjé, South Africa
F. Lind, Sweden
D. Mathieu, France
J. Schmutz, Switzerland

ETRS

T. Hunt, USA
R. Mani, United Kingdom
M. Romanelli, Italy
L. Téot, France
T. Wild, Austria

A. Marroni, Italy (Secretary)

**Questions to be answered by the Jury**

1. What are the incidence and the costs of wounds with delayed healing?
2. What tissue changes induced by hypoxia lead to delayed wound healing?
3. What methods are available in clinical practice to evaluate tissue hypoxia as a factor responsible for delayed wound healing?
4. What is the rationale to add HBO to the conventional treatment of delayed wound healing?
5. Which patients are most likely to benefit from adjunctive HBO?
6. Is HBO cost-effective in the management of patients with delayed wound healing?
7. What actions and studies have to be conducted in the near future to solve the remaining controversies?
**Recommendations**

After having listened the expert reports and with the assistance of the literature reviewers, the jury met to discuss all the presented evidence and came to recommendations for clinical practice.

To assess the quality of the existing evidence, the jury used the following scale:

- Level 1: strong evidence,
- Level 2: convincing evidence,
- Level 3: existing but weak evidence,
- Level 4: anecdotal evidence.

In order to indicate its evaluation of the strength of evidence supporting each statement, the jury graded its recommendations using the following scale:

- Type I: Strongly recommended. Recommendations or Standards are supported by level 1 evidence.
- Type II: Recommended. Recommendations or guidelines are supported by level 2 evidence.
- Type III: Optional. Statements are supported only by level 3 evidence.

1. **What are the incidence and the cost of wounds with delayed healing?**

   1. **Diabetic foot ulcer:**
      Diabetic foot ulcers affect 6.8% of the diabetic population per year (USA). The total cost over a three year period amounts to $26,700 per case with ischaemia; $16,100 without ischaemia; $43,100 with minor amputation; and $63,000 with amputation (Sweden).
   2. **Venous stasis ulcer:**
      The incidence increases with age approaching, 3-5% above 65 and 12% above 70 years (Sweden). The national costs implications are assessed to be in the order of 5 Billion Euros (Germany).
   3. **Arterial insufficiency-related ulcer:**
      Approximately 4.5% of the population over 40 years has peripheral vascular disease / chronic limb ischemia (CLI) affecting the lower extremity (USA). The prevalence of CLI approaches 0.1-0.24% inhabitants in Western countries (Germany, Norway). The projected costs are $17,000 per CLI case (hospital costs only); at 5 years (with prior reconstruction): $111,000 per case with major amputation; $77,600 per case without amputation; $213,000 per case with immediate major amputation.
   4. **Pressure ulcers:**
      These ulcers are a function of hospitalization, immobility and institutionalization. The incidence is projected at 16.8% of in-patients per year (Japan). The national cost implications amount to 1.4 to 2.1 Billion Pounds (UK).
   5. **Radionecrosis:**
      The incidence for bone and soft tissue radionecrosis is in the order of 5%. The projected costs, although unspecified, are surely high.
2. What tissue changes induced by hypoxia lead to delayed wound healing?

1. Oxygen is an important factor in wound healing.
2. Hypoxia interferes with many components of wound healing. Many of these can be modelled or expressed numerically.
3. There is in vitro, in vivo and clinical evidence of a relationship between the available amount of oxygen in the wound to healing processes. Oxygen is specially needed in the inflammatory phase (level 1).
4. The presence of oxygen reduces wound oedema (level 1).
5. Bacterial killing is oxygen dependent. It is maximal at several hundred mm Hg pO2, and goes almost to zero in hypoxic patients. There is evidence for the relationship between hypoxia to wound infection at the cellular, animal, and human level (level 1). Questions remain on the type of bacteria most sensitive to hypoxia and which clinical parameters are involved (CRP, fibrin, procollagen, leukocytes, neutrophils).
6. Angiogenesis, although previously thought to be induced by hypoxia, seems to be directly sensitive to oxygen as a function of local lactate delivery. Angiogenesis is reduced to zero at tissue tensions of 10 mm Hg. In clinically oxygen deficient situations, the granulation tissue is not formed. There is evidence for an effect of oxygen on angiogenesis in basic studies (level 1) and for animals and humans (level 2).
7. Collagen production is maximal at 250 mm Hg and falls to almost zero in severe clinical hypoxia (Km= 25 mm Hg pO2). Cell motility falls with loss of cell energy production that occurs at or below 10 mm Hg pO2. There is evidence for the need of oxygen in collagen synthesis and strength in basic, animal and human wounds (level 1).
8. No data exists on oxygen and apoptosis of myofibroblasts in the remodelling phase.

3. What methods are available in clinical practice to evaluate tissue hypoxia as a factor responsible for delayed wound healing?

1. Currently there is a lack of technology to assess tissue hypoxia and cell metabolism in clinical practice. The Near Infra Red Reflectance Spectrophotometry (NIRO) has the potential to measure both tissue pO2 and cellular cytochrome a-a3 redox state. However validation of the hypoxic state of cells using NIRO is yet to be reported.
2. Several techniques are available for research rather than for clinical application:
   a.- Imaging techniques including PET scans, and MRI derived techniques.
   b.- Direct measurements of tissue pO2 using e.g., subcutaneous polarographic needle electrodes. These are invasive and therefore unappealing in clinical practice.
3. Clinical techniques that assess altered perfusion state thereby permitting comments on tissue hypoxia include:
   a.- Clinical assessment including ankle and toe pressure measurements using portable Doppler are part of routine evaluation of patients.
   b- Imaging techniques including Duplex ultrasonography, arteriography, MRI techniques. These techniques are recommended part of the workup for revascularisation.
   c.- Techniques that assess local perfusion include:
      1. Clearance methods.
      2. Thermal clearance including thermography.
3. Laser Doppler flowmetry and imaging.
The techniques permit interpretation of altered perfusion states. Each technique offers subtly different information of microvascular function. All the techniques require strict protocol to derive reliable data. Evidence for the use of \( P_{tcO2} \) to assess viability of diabetic foot is at least level 3, possibly level 2.

4. What is the rationale to add HBO to the conventional treatment of delayed wound healing?

1. HBO is not required in situations where normal wound healing is anticipated. Its primary role is restricted to certain situations of impaired or delayed wound healing.
2. Delayed wound healing implies an acute wound not healing in the normal time frame (4-6 weeks) under conditions of standard care or conventional treatment in an uncompromised patient.
3. Among the factors that can cause delayed wound healing there are many both systemic and local factors which impair oxygen delivery to the wound.
4. A key factor to achieve normal wound healing is to optimize the oxygen concentration in or around the wound.
5. HBO can be used when standard care fails to achieve oxygen levels necessary for normal wound healing.
6. The rationale for the use of HBO is because it has the potential, not only to correct hypoxia, but also to improve tissue perfusion, to stimulate tissue repair and to prevent and treat infection.

Level of evidence:
- Basic studies: level 1.
- Animal studies with control group: level 2 to 1.
- Human studies: level 3 to 2.

Recommendation for adding HBO to conventional treatment in delayed wound healing is a type II recommendation.

5. Which patients are most likely to benefit from adjunctive HBO?

1. Prior to considering a patient for HBO, there shall be a complete clinical evaluation with correction of systemic and local factors responsible for the delayed healing. These include cessation of smoking, pressure measures, glycaemic control and so on. (type I recommendation).
2. The possibilities of revascularisation must be considered and either performed or the possibility excluded (type I recommendation).
3. The two main conditions that prompt the possibility of using adjunctive HBO are infection (i.e., periwound cellulitis, bone and joint infection) and ischaemia. When HBO is planned to correct wound ischaemia (hypoxia), wound hypoxia and its correction under hyperbaric condition should be measured using objective methods. (type I recommendation).
4. Presently there is reliable evidence that HBO is effective in reducing major amputations in patients with diabetic foot ulcers (level 2). In cases of patients with lower extremity wounds of other aetiologies, there is a paucity of reliable evidence of the value of HBO treatment.
6. Is HBO cost-effective in the management of patients with delayed wound healing?

1. In determining the cost-effectiveness of HBO in the management of delayed wound healing, certain assumptions have had to be made to simplify calculations. Prospective research is recommended, but for the time being, the jury has confidence that these approaches rival the economic basis for decisions made in other fields of healthcare.
2. Based on projections using Persels formula applied to the currently available data, a significant saving can be achieved using HBO as a standard adjunct in treating necrotising infections, diabetic ulcers, and radiation necrosis as currently recommended by the ECHM and UHMS. The number of HBO treatments has a significant impact on cost-effectiveness ratios. Clinical guidelines are recommended to assure optimal cost effectiveness (type I recommendation).
3. Based on this data, HBO for the problem wounds listed in the analysis, not only appears to be clinically effective, but also likely to reduce the general costs of a nation's healthcare, reduce the social impact of related illnesses and offer better quality of life.

7. What actions and studies are required in the near future to solve the remaining controversies?

1. Measure oxygen concentration in the wound and in the normal tissues (type I recommendation);
2. Colleagues working in HBO interested in wound healing would be properly trained in wound healing and use tools already developed in order to quantify clinical results (type I recommendation).
3. Hyperbaric personnel should be associated into multi-disciplinary teams with specialist in other fields and basic scientists (type I recommendation).
4. Medical staff involved in Wound Care and Hyperbaric Medicine should receive training in basic and clinical research methods on a continuously regular base (e.g. CME). (type I recommendation).
5. The relationship between the European Committee for Hyperbaric Medicine and the European Society of Tissue Repair should continue with the 2 following objectives:
   1. - establishing a network of centres and teams involved in clinical and basic research related to oxygen and wound healing.
   2. - organizing seminars and workshops dedicated to clinical and basic research training.
   (type I recommendation).
6. Information and personnel exchange policies should be implemented between hyperbaric and wound care facilities (type I recommendation).