Patient JM

• Chief Complaint
  – 48 y/o referred for evaluation of right anterior tonsil/retromolar trigone mass
• History of Present Illness
  – Patient noticed the mass one month prior to presentation. Has trismus and dysphagia. Has ear pain. No weight loss, good activity level.
• Past Medical History
  – Liver cirrhosis and recurrent pancreatitis
• Social History
  – 30 pack year smoking history, current
  – 24 ounces of beer daily
• Family History
  – Father died of prostate cancer, Mother died of lung cancer.
• Allergy to Penicillin
• No current medications
• Review of systems is non contributory
Physical Exam

- **Vital Signs**
  - 6ft 1 in, 188 lbs., Pulse 75, BP 157/97
- **Head and Neck Examination**
  - CN 2-12 intact
  - Good dentition
  - 2.0 cm jaw opening
  - OP/OC exam demonstrated 3.0x3.0 cm ulcerative, firm, mass centered on anterior tonsillar pillar extending into retromolar trigone to posterior molar and lingual gingiva.
  - No other findings
Assessment and Plan

• Assessment
  – Mass in OP/OC suspicious for malignancy

• Plan:
  – Plan for biopsy in office and PET
  – Evaluation by Medical and Radiation Oncology
  – Tooth extraction, Port-a-cath placement and PEG tube placement.
  – Staged as T4 N1 M0
Treatment

• Treated with Brizel Protocol
• Post treatment
  – Post treatment mucositis
  – PEG and Port removed
  – PET
• Lost to follow-up secondary to insurance issues for 2 years
Recurrence

• 6 months prior to his second presentation he noted a growing mass in the anterior portion of his oral cavity. MRI performed by a missionary healthcare facility found a mass eroding the cortical bone of his right anterior mandible.

• Assessment and Plan
  – PET scan
  – Biopsy in the office
  – Surgical resection
Hospital Course

• Operation
  – Tracheostomy, composite resection of ventral tongue, floor of mouth, segmental mandiblectomy, bilateral neck dissections sparing all structures. The area was reconstructed with a right fibula free flap.

• Pathology

• Post-operative course
  – POD 1 Right fibula free flap venous congestion and hematoma
  – POD 2 revision of the anastomosis
  – Orocutaneous Fistula development
  – POD 8 Flap failure, taken for debridement
  – Consideration for HBO
  – POD 15 Left Fibula Free Flap reconstruction and left pectoralis flap
  – Started HBO POD 17
  – POD 20 Failure of left fibula free flap, anastomosis revised
  – POD 35 Right Pectoralis flap reconstruction
  – Discharged on POD 50
Right Tonsillar Carcinoma Axial PET-CT Images - 2007
Recurrent tumor in the floor of the mouth: PET-CT 2010
Recurrent tumor involving the mandible - PET-CT 2010
Right submental lymph node metastasis
07-S-18888, Right tonsillar mass
10-S-4271, Right Anterior Gingiva
10-S-5940, Composite anterior mandible, floor of mouth and glossectomy: Anterior soft tissue
Vascular and perineural invasion
Mandibular invasion
Separately submitted margins
Anterior chin margin - Right lateral gingival margin
10-S-6757, Anterior chin resection
Separate anterior chin margin #1
(right and left anterior chin margins, #6 and 7 free of tumor)
The Role of HBOT in Management of Head and Neck Cancer Patients

Ziad Mirza MD CMD FACP MBA
ABIM
ABPM in Dive & HBOT
Disclosures

• Dr Mirza is an employee of GBMC and Genesis Health Care. He owns and operates Baltimore Medical and Surgical Associates PA and has no other affiliations nor does he own stock in any company that produces equipment or products discussed in this presentation.
Goals

• Describe the mechanism of action of HBOT and its effect on cellular function.
• List HBOT indications and identify usage in Head and Neck Cancer Patients:
  - Radiation Injury.
  - Compromised Grafts and Flaps.
  - Infections.
• Side effects and Contraindications to HBOT.
• Future Applications.
Acknowledgements

• Diversified clinical services.

• The HBO Team @GBMC.

• Peter Golueke, M.D., FACS, Medical Director.
Hyperbaric oxygen treatment

HBOT is a treatment with 100% oxygen at 1.4 ATA or above.

HBOT is of interest to Internist, Infectious disease, Pharmacology, Emergency Physicians, Dentist, Orthopedics, Plastic surgery, Head & Neck surgery, General surgery, Pulmonary, Critical care, Radiation oncology and Aerospace medicine.
Hyperbaric Oxygen History

• Henshaw 1662 “the Domicilium”.
• Priestley 1775 Discovered oxygen.
• Paul Bert 1878 CNS oxygen toxicity
• Fontaine 1879 “mobile Hyperbaric operating room”- Air @ 2 ATA.
• Corning 1891 introduced compressed air therapy to the US.
• J. Lorrain-Smith 1899 Pulmonary oxygen toxicity.
• Cunningham 1918-1930 clinical uses.

Kindwall, Hyperbaric Medicine Practice
Mechanical Effects of Pressure

Bubble size/pressure “Boyles Law”

Solubility/pressure “Henry’s Law”

Diffusion & Counter diffusion

Boerema “life without blood” 1960 ; Basis for current HBOT.
## Oxygen Delivery to Lung

<table>
<thead>
<tr>
<th>Total pressure ATA</th>
<th>Total pressure mmHg</th>
<th>PO2 Breathing (Alveolar 21%)O2 mmHg</th>
<th>Alveolar PO2 Breathing (100%)O2 mmHg</th>
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<tr>
<td>1</td>
<td>760</td>
<td>102</td>
<td>673</td>
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<tr>
<td>1.5</td>
<td>1140</td>
<td>182</td>
<td>1053</td>
</tr>
<tr>
<td>2</td>
<td>1520</td>
<td>262</td>
<td>1433</td>
</tr>
<tr>
<td>2.5</td>
<td>1900</td>
<td>342</td>
<td>1813</td>
</tr>
<tr>
<td>3</td>
<td>2280</td>
<td>422</td>
<td>2193</td>
</tr>
</tbody>
</table>
Hemodynamic Effect of HBOT

- Decrease in Heart Rate: autonomic, vagal.
- Increase in Blood Pressure: vasoconstriction.
- Increase in Cardiac After load: 30-60%.
- Decrease in cardiac output: 24-35%.
- Tissue oxygenation is maintained secondary to dissolved oxygen and hyperoxic state.

(Kindwall, Hyperbaric Medicine Practice, Page20)
Cellular Effect Of HBOT

- Improved leukocyte function: mobility, phagocytosis, and bacterial killing.
- Enhanced collagen synthesis and cross-linking.
- Blunting of systemic inflammatory responses.
- Prevention of leukocyte activation and adhesion-Beta2 integrin inhibition (CD-11).
- PDGF-BB receptor stimulation with VEGF release and angiogenesis.
- Stem Cell Mobilization by increasing nitricoxide NO.

(Dr Thom group, Stem Cells. 2006;24:2309-18)
Pharmacological Effects of HBOT

- Direct antimicrobial effects – anerobes.
- Toxin synthesis suppression – clostridium alpha toxin.
- Antibiotic potentiation – aminoglycosides.
- Detoxification (CO, CN, H2S).
UHMS Approved HBOT

- AGE & Symptomatic VGE
- Carbon Monoxide Poisoning
- Clostridial Myonecrosis
- Crush Injury
- Compromised Flaps/Grafts
- Decompression Sickness
- Hypoxia and Wound Healing
- Severe Anemia
- Intracranial abscess
- Necrotizing Infection
- Refractory Osteomyelitis
- Delayed Radiation Injury
- Acute Retinal Artery Occlusion
- Acute Thermal Injury
HBOT indications Head and Neck patients

- Delayed Radiation Injury:
  - Osteoradonecrosis (Active and Prophylaxis).
  - Laryngeal necrosis.
  - Soft tissue injury.

- Compromised Flaps/Graft

- Infections:
  - Necrotizing Infection.
  - Mucormycosis.
  - Refractory Osteomeylitis.
Radiation Injury
Radiation Injury

- Classified as Acute, Sub acute or Delayed Complications.
- **Acute** is mainly mitotic cellular death 2\textsuperscript{nd} to damaged DNA.
- **Sub acute** identified in few organs “lung and spine” with onset of 2-3 mo after radiation.
- **Delayed** is 6 mo to several years after radiation.
- Radiated tissue gets worse with time.
Delayed Radiation Injury- Etiology

- Biochemical process not well understood.
- Vascular changes characterized by obliterative endarteritis.
- Release of fibrogenetic cytokines with fibro-atrophic effect.
- Depletion of parenchymal and stem cell.
- Review by Feckenstein et al found TGF-beta is the most frequent cytokine associated with radiation injury.
- IL-1,2,4,5,6,7,8,10,12,13,17 and TNF-alpha.
Complication of radiation injury on Head and Neck

• Osteoradiodnecrosis (ORN).
• Xerostomia.
• Trismus.
• Dysphagia.
• Aspiration.
• Fibrosis.
• Laryngeal Necrosis.
Osteoradionecrosis
Osteoradionecrosis (ORN)

• Incidence increase above 6000cGY.
• Avascular, aseptic bone necrosis.
• Principles of management set by Dr Robert Marx DDS- Marx Protocol.
• Stages I, II, III ORN.
• Treatment starts with 30 HBOT sessions for Stage I with 10 additional sessions post operative.
• An additional 10 sessions will be needed for any reconstructive surgery- post operative.
Literature Review for ORN

• Feldmeier and Hampton published in 2002 a review of HBOT and Radiation injury:
  - Cumulative data reveals 371 cases ORN with 83% positive outcome on HBOT

• Only two trials had negative outcome:
  - 53 patients (22 Gal report & 31 Annane trial)
HBOT for Prophylactic Rx of ORN

- Marx RPCT of HBOT vs Penicillin (JADA, 1985)
  - 37 patients in each arm with >6800 cGY.
  - HBOT arm 20 pre 10 post dental extraction.
  - ORN developed in 5.4% of HBOT vs 29.9%

  - 1 of 29 patients had ORN on HBOT.

- David et al (J Can Den Assc, 2001)
  - 1 of 24 patients had ORN on HBOT.
ORN Prophylaxis Controversy

  - Retrospective study.
  - 187 patients with radiation between 6-7 Gy, only 3 received HBOT.
  - ORN developed in 4 patients only. 2.2%

- Michael Wahl (Int J Rad Onc Biol Phys 2006):
  Review published with recommendation not to treat for ORN prophylaxis.

  Web Based survey, 410 responded, 78% reported Rx for Preventive ORN.
Laryngeal & Soft Tissue Delayed Radiation Injury
HBOT for Laryngeal Necrosis

• Laryngeal Radionecrosis (Chandler)
  – Grade 1: Slight hoarseness, laryngeal edema and telangectasia.
  – Grade 2: Moderate hoarseness, slight impairment of vocal cord mobility and moderate edema.
  – Grade 3: Severe hoarseness with dyspnea and dysphasia, severe impairment of cord mobility.
  – Grade 4: Respiratory distress, fistula, laryngeal obstruction.

• 5 reports (1987-2005) with patients Chandler grade 3 or 4.

• Total of 43 cases reported with 6 patients failing HBOT and requiring laryngectomy.
HBOT for Head and Neck Soft Tissue Necrosis

- Controlled, not randomized study by Dr Marx Kindwall; 160 patients total:

<table>
<thead>
<tr>
<th></th>
<th>HBOT</th>
<th>No HBOT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wound Infection</td>
<td>6 %</td>
<td>24%</td>
</tr>
<tr>
<td>Dehiscence</td>
<td>11%</td>
<td>48%</td>
</tr>
<tr>
<td>Delayed Healing</td>
<td>11%</td>
<td>55%</td>
</tr>
</tbody>
</table>

- Davis & colleagues 15 out of 16 improved on HBOT.
- Neovius & colleagues 12/15 on patients versus 7/15.
- Feldmeier & colleagues:
  - 60% complications from surgery in radiated fields.
  - 87% healed with HBOT.
Cochrane Review of Delayed Radiation Injury

- RCTs HBOT vs No HBOT updated in August 2008.
- Eight trials contributed to this review (566 participants).
- Surgical flaps: RR 8.7, 95% CI 2.7 to RR 27.5, P = 0.0002
- Hemimandibulectomy: RR 1.4, 95% CI 1.1 to RR 1.8, P = 0.001
- Healing irradiated tooth sockets following dental extraction: RR 1.4, 95% CI 1.1 to RR 1.7, P = 0.009
Summary of Delayed Radiation Injury

- Need at least 5-6 Gy with a latency period of >6 Month.
- ORN and STRI are I B/A AHA recommendation.
- Prophylactic treatment for ORN is not approved by CMS.
- Potential treatment for prevention of STRI is underway.
“One must always hope when one is desperate, and doubt when one hopes.”
Gustave Flaubert
Compromised Flaps/Grafts
Etiology of Compromise

- Arterial Occlusion.
- Venous Congestion.
- Random Ischemia.
- Ischemia-reperfusion injury (Free Flaps):
  PMNs enter tissues from post capillary venules with mediation by ICAM-1, PECAM, VCAM-2 and VLA-4.
  Role of Nitric Oxide production is mediated by NOS I (neuro), NOS II (induced) and NOS III (Endothelial).
Nitric Oxide Synthetase (NOS) and HBOT

**nNOS** (NOS-1 from neurons).

**iNOS** (NOS-2 inducible from macrophages upon stimulus).

**eNOS** (NOS-3 from endothelial cells that line the lumen of blood vessels and membranous structures).

**Protective Effects** (Physiological Level):
Vasodilation, Inhibit platelet aggregation, Inhibit leukocyte adhesion, Immune defense.
Reduced oxygen radical and Favorable cellular signaling

**Harmful Effects** (Pathological Levels):
Produce peroxynitrite ONOO-, Endothelial dysfunction, Leukocyte adhesion and Increase vessel permeability.

**HBOT** seems to increase NOS III activity. (UHMSuppl,Abst89,2005)
Ischemic Preconditioning (IP)

• First studied in Canine Model with myocardial Ischemia.

• In myocardial tissue, IP preserves ATP, reduces Lactic acidosis, decreases ROS and protects against stunning.

• HBOT is theoretically a potential preconditioning agent (not proven yet).
Evidence Based Animal Studies (Extensive)

- Zhang et al, composite skin graft in rabbit ear, 82% survival with HBOT vs 26% without.
- Li et al, harvest and reattach 0.5/1.0/2.0 cm graft in rabbit ear, the 2cm grafts had 85.5% survival with HBOT vs 51.3% without.
- Pillitteri et al, random flaps in pigs with measured necrosis, 77% mean survival on HBOT with 35% less necrosis.
Evidence Based Human Studies (Limited)

- Perrins and Colleagues,
  - RPCT 48 patients with compromised skin grafts.
  - 64% complete survival on HBOT vs 17%.
- Greenwood and Gilchrist  HBOT effect on post irradiated compromised wounds in laryngectomy patients.
- Barr et al, favorable case reports on composite flaps and HBOT.
Evidence Based Appraisal

• Freidman and colleagues review:
  - Composite grafts: AHA IV, historic non randomized cohort or case control studies.
  - Skin graft: AHA IB, one or more RCT.
  - Random flaps: AHA IV.
  - Distant flaps: AHA V, human case series.
  - Free flaps: AHA VI.

Summary of Compromised Grafts & Flaps

• Treatment is indicated for compromised Grafts.

• For compromised flaps need to treat underlying etiology for compromise; HBOT is an adjunct treatment only.

• Failed flaps will qualify for pre treatment prior to further surgical intervention.
Infections
Other HBOT indication for Head and Neck cancer patients

- Necrotising infections including non- Clostridial myonecrosis (Peptococcus, Peptostreptococcus, Bacteroides).
- Mucormycosis: Whitish cottony exudates. Multiple retrospective trials with significant improvement in mortality on HBOT making it unethical to perform a prospective trial.
- Refractory Osteomyelitis Mandible: Failure to respond to antibiotic therapy for 1 month; if combined with antibiotics and surgery AHA lib.
Side Effect & Contraindications
Side Effect of HBOT

• Barotrauma (Dental, Ear and Sinus, Pulmonary).
• Claustrophobia.
• Oxygen toxicity (CNS, Pulmonary).
• Vision (progressive myopia, cataracts).
• Other (fatigue, paresthesias).
Contraindications to HBOT

• Certain Chemotherapy
  – Adriamycin (Doxorubicin).
  – Bleomycin:
    • Both cause cardiac toxicity/sudden death.
  – Cis-Platinum:
    • Superoxide dismutase antagonist.
  – Sulfamyelon (Mafenide Acetate)
    • Weakend tensil strength in healing wounds.

• Antabuse (Disulfiram)
  – Superoxide dismutase agonist.

• Amiodarone:
  -Pulmonary fibrosis, dosage > 200mg/day.

• Untreated Pneumothorax.
New & Future Applications
HBOT for Radiation Injury Prophylaxis

- Early HBOT for reducing radiotherapy side effect:
  - 19 patients with tumors on radiotherapy.
  - Randomized to receive HBOT or not.
  - Swallowing, Dry mouth, Sticky saliva, Eating in public and pain in mouth had better Qol score in HBOT group.

Int J Radiat Oncol Biol Phys. 2009 Nov 1;75(3):711-6
HBOT as a Radiosensitizer

- HBOT as a radiation sensitizer for locally advanced squamous cell carcinoma of Head and Neck (SCCHN):
  - 12 subjects with SCCHN any site stage III & IV M0, 2 dropped (non-compliance & mets)
  - 3 Cohort groups: 2, 3 & 5 days/wk HBOT
  - Average time between HBOT and radiation: 10’
  - 100% response on HBOT. Cleared for Phase II & III.
  
  J Clin Oncol 28, 2010 (suppl; abstr e16002)
Advancement is Cancer Treatment

• Effect of HBOT & 5FU on Human Nasopharyngeal Carcinoma:
  Four Groups of cell lines; Significant Synergism @ 48 hrs between 5FU and HBOT.
  UHM 2010, Vol. 37, No. 3

• Auto Transplantation of Cryo-perserved minor salivary glands:
  Cryo-preserved salivary glands 2 wks prior to radio therapy. 20 HBOT prior to re implantation and 10 post surgery.
“We now can see a clear path to what we call “the 4 P’s of Medicine”: medicine that will be more Predictive, Personalized, Preemptive, and Participatory.”

Elias A. Zerhouni, M.D.
Director, National Institutes of Health
March 5, 2008