HYPERBARIC OXYGEN THERAPY IN REFRACTORY OSTEOMYELITIS IN ADULTS & PEDIATRIC PATIENTS

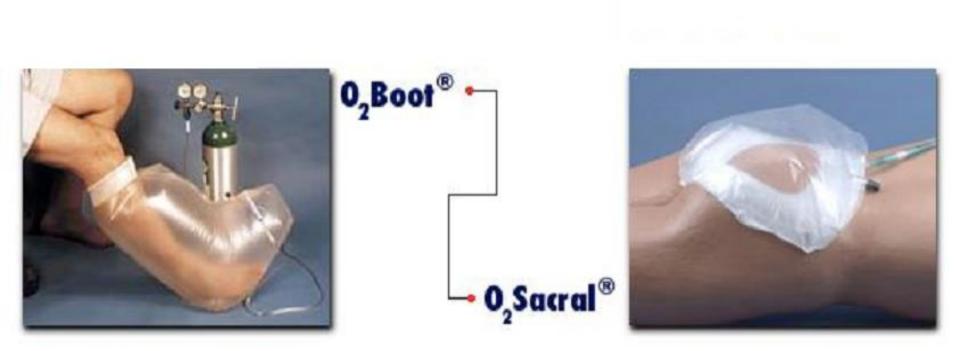
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Objectives

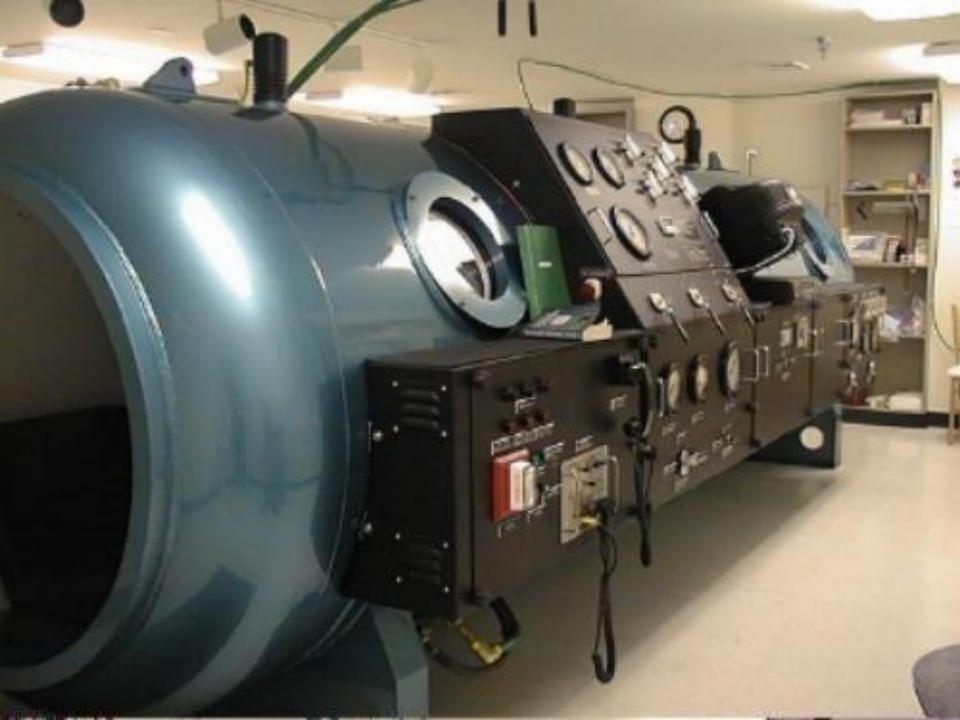
- To introduce Hyperbaric Medicine and its indications and contraindications to the audience, with particular focus on refractory osteomyelitis.
- Review Osteomyelitis management in Pediatrics
- To present a case series of six pediatric patients highlighting role of hyperbaric oxygen therapy as an adjunctive treatment in managing refractory osteomyelitis .

This is not Hyperbaric Oxygen!



What is Hyperbarics

- Hyperbaric oxygen (HBO₂) is a treatment, in which a patient breathes 100% oxygen intermittently while inside a treatment chamber at a pressure higher than sea level pressure.
- Treatment can be carried out in either a mono- or multiplace chamber.





Another multiplace model.

Patients enter rectangular door. The transfer lock door is the circular door on the left background (circular door)



BREATHING GAS SYSTEMS IN A MULTIPLACE CHAMBER

 a chamber occupied by more than one person must be pressurized with air (or other inert gases) with the oxygen or other therapy gases delivered to the pulmonary system through a breathing gas system.





Monoplace Chamber

- Chamber is filled with 100% oxygen as the compression and breathing gas.
- About 8 feet long and about 3-4 feet in diameter, permitting only single occupancy.
- The patient is moved in and out of the chamber by means of a sliding stretcher cart with which it interlocks. The chamber walls are of clear heavy duty acrylic plastic.





DEL 2000 DO

Subtraction of the second seco

Solace 210

Most popular selling Chamber in the world Ready for Home Use Extremely Safe

more info

This "soft shell" mono is NOT HBO2

11

Monoplace vs Multiplace

Advantages vs Disadvantages

Monoplace

- •Improved infection control (i.e spread)
- Increased
 claustophobia/reduced
 compliance potential
 Increased risk of fire,
- environment is 100% oxygen.

Multiplace

- •Critical care treatments are possible in this chamber
- •Tender present in case of emergency
- •More individuals, more infection risks.
- •Increased comfort and compliance due to space

Effects of Hyperbaric Oxygen

- Diffusion of inert gas from bubbles
- Suppressed alpha-toxin production (gangrene)
- Enhanced leukocyte-dependent killing
- Decreased adhesion of white cells
- Vasoconstriction of normal vessels
- Restoration of fibroblast growth
- Increased production of superoxide dismutase

Effects of Hyperbaric Oxygen

- Preservation of ATP in membranes (and secondary reduction of edema)
- Suppression of selected immune responses (experimental porcine encephalomyelitis)
- Enhanced osteoclast activity (bone absorption)
- Angiogenesis
- Nervous pathology
- Decreased pulmonary function
- Reduced lenticular flexibility

Osteomyelitis

- infection of bone or bone marrow
- Refractory osteomyelitis defined as a chronic osteomyelitis that persists or recurs after appropriate interventions have been performed or where acute osteomyelitis has not responded in spite of extensive antibiotic therapy.
- Osteomyelitis is a common problem in the pediatric population and can be difficult to treat.

Historic Perspective

Advances in diagnostic Management, antibiotic and surgical techniques have reduced mortality from 15-25% pre antibiotic age to 2%

The incidence of bone infections have seem to remain constant over the last 3 decades hospital osteomyelitis to about 1% incidence

Osteomyelitis in Children

Bacteria may reach bone through direct inoculation from traumatic wounds, by spreading from adjacent tissue affected by cellulitis or septic arthritis, or through hematogenous seeding.

In children, an acute bone infection is most often hematogenous in origin. The most common site is the highly vascular metaphysis. The apparent slowing of blood flow as The vessels make sharp angles at the distal metaphysis predisposes the vessels to thrombosis and the bone itself to localized necrosis & bacterial seeding. When osteomyelitis is diagnosed, it is classified:

- Acute = less than 2 weeks
- Subacute = 2 weeks to 3 months
- Chronic = longer duration.

Chronic Osteomyleitis (CROM)

Infection of both the cortical & medullary bone that has persisted or recurred after treatment has been given.

- Specific CROM tx includes one or more of the following:
- Antibiotics IV, impregnated beads
- debridement
- ostectomy
- segmental bone resection
- free flaps
- hyperbaric oxygen

Host Predispositions

Certain underlying disease states predispose a patient to acquiring bone & joint infections. These conditions include diabetes mellitus, sickle cell disease, AIDS, alcoholism, IV drug abuse, steroid use, preexisting joint disease, & immunosuppressed States

Common to most of the diseases that predispose to osteomyelitis are a decreased ability to mount an inflammatory & immune response, impaired bacterial killing, & poor vasculature.

CIERNY-MADER STAGING SYSTEM FOR OSTEOMYELITIS

Anatomic type

Stage 1: Medullary osteomyelitis

Stage 2: Superficial osteomyelitis

Stage 3: Localized Osteomyelitis

Stage **4**: Diffuse osteomyelitis

Note - Stage 3 can be surgically excised w/o instability, whereas Stage 4 cannot be excised.

Cierny G, Mader JT, A clinical staging system for adult osteomyelitis. Contemporary Orthopedics 1985;10(5):17-37

CIERNY-MADER STAGING SYSTEM FOR OSTEOMYELITIS

- **Physiologic class**
- A Host: healthy
- **B Host: compromised**
- Bs: systemic
- Bl : local
- Bls: local & systemic
- C Host: tx worse than disease

CIERNY-MADER STAGING SYSTEM FOR OSTEOMYELITIS

Bacteriology

- In all age groups except neonates, *Staph aureus is the* leading cause of osteomyelitis.
- In the elderly, gram-negative bacteria account for a higher percentage of infections.
- Methicillin-resistant *S. aureus & Vancomycinresistant* enterococci have emerged as a significant problem.
- Multiresistant enterococci pose the greatest potential danger as no regimens are reliably bactericidal.

Bacteriology

• Anaerobes can complicate polymicrobial infection & are present more often than is commonly recognized.

- In chronic osteomyelitis, anaerobic bacteria may be present in up to 40% of cases.
- Certain types of trauma are assoc w/ special infections.

Bateriology (Continued)

Patients who are wounded or receive open fractures in fresh water are susceptible to *Aeromonas hydrophila*.

Animal bites, particularly dogs & cats, are at risk for developing osteomyelitis from *Pasteurella multocida*.

Pseudomonas is responsible for infections in 3 settings:
(1) Puncture wounds to the foot while wearing shoes.
(2) Orthopedic prosthetic devices are at risk.
(3) IV drug users may develop hematogenous osteo, often in the spine, from Pseudomonas.

Bacterial Pathology review in Pediatric Osteomyelitis

- Staphylococcus aureus is by far the most common causative agent in osteomyelitis,
- followed by the respiratory pathogens *Streptococcus pyogenes and S. pneumoniae*.
- For unknown reasons, Haemophilus influenzae type b is more likely to affect joints than bones.
- Salmonella species are a common cause of osteomyelitis in developing countries and among patients with sickle cell disease.
- Infections due to *Kingella kingae* are increasing and are most common in children younger than 4 y/o

Microbe Identification

The likelihood of establishing a bacteriologic diagnosis in acute osteomyelitis is 80% to 90%, but in some cases, even resected bone cultures yield no organism.

Possible reasons for this are:

- Poor culture techniques
- Inadequate preparation of recovered tissue for culture
- Previous antibiotic treatment
- Culturing from necrotic ischemic regions that may be devoid of bacteria

Lab Studies

- Generally not helpful in establishing a diagnosis. Elevation of the WBC count is variable. Typical values in osteomyelitis range from normal to 15,000/mm3.
- ESR is a sensitive marker for bone infection; many report elevated ESRs in more than 90% of cases mm/hr). Less 8% will have an ESR < 15 mm/hr.
- C-reactive protein, increases within the first 24 hours infection, peaks within approximately 48 hours,

ESR is most valuable in following treatment response. Typically, the ESR falls steadily as osteomyelitis resolves & increases if it recurs.

Comparison of Imaging StudiesSensitivitySpecificityMRI

99%

81%

Plain Xray 62%

64%

Triple Phase 86%

45%

78%

Bone Scan

89%

Signs & Symptoms

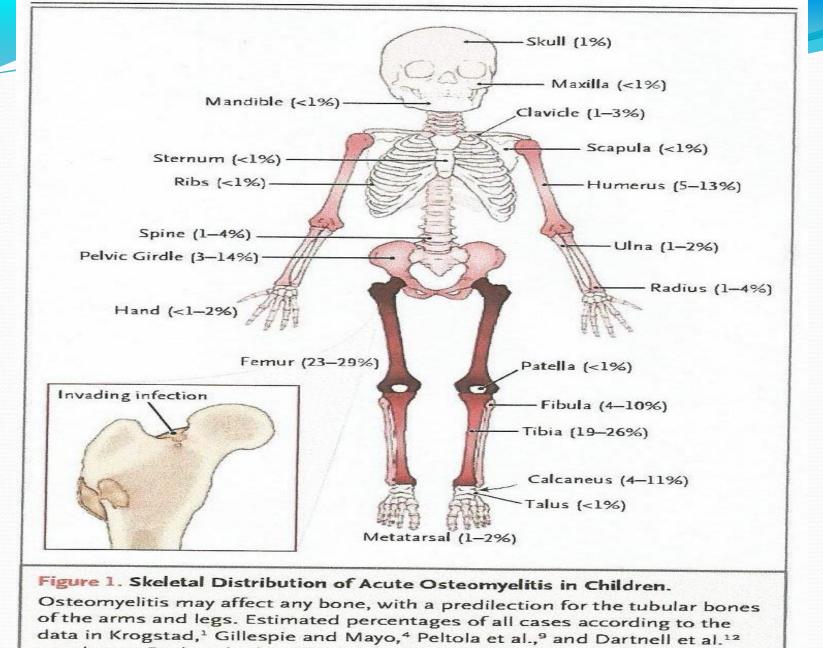
Classic clinical manifestations in children are limping or an inability to walk, fever and focal tenderness, and sometimes visible redness and swelling around a long bone, more often in a leg than in an arm

Spinal osteomyelitis is characteristically manifested as back pain.

whereas pain on a digital rectal examination suggests sacral osteomyelitis.

Acute osteomyelitis should be considered in any patient who presents with a fever of unknown origin. Acute cases occur in all age groups, with a small peak in incidence among prepubertal boys, presumably because of strenuous physical activity and microtrauma. (1)

Children with methicillin-resistant *S. aureus (MRSA) osteomyelitis have a high temperature,* tachycardia, and a painful limp more often than those with methicillin susceptible *S. aureus (MSSA).* (1)



are shown. Darker shades of red denote a higher burden of infection.

Conservative Therapy

- Treatment of acute osteomyelitis is almost always instituted empirically before the causative agent and its resistance pattern are known.
- Antibiotic must have an acceptable side-effect profile when administered orally because the doses are unusually large.
- Absorption and penetration into the bony structure should be satisfactory

Table 1. Antibiotic Treatment for Acute Osteomyelitis in Children.*

Antibiotic	Dose	Maximal Daily Dose†	Bone Penetration:	Reference
	mg/kg/day		%	
Empirical treatment				
First-generation cephalosporin, if prevalence of MSSA in community >90%§	≥150 administered in 4 equal doses¶	2–4 g	6–7	Dose: Peltola et al., ⁹ Peltola et al. ²⁰ ; extent of bone penetration: Tetzlaff et al. ²¹
Antistaphylococcal penicillin (cloxa- cillin, flucloxacillin, dicloxacillin, nafcillin, or oxacillin), if prevalence of MSSA in community >90%	≤200 administered in 4 equal doses	8–12 g	15–17	Dose: Jagodzinski et al. ⁸ ; extent of bone penetration: Tetzlaff et al. ²¹
Clindamycin, if prevalence of MRSA in community ≥10% and prevalence of clindamycin- resistant S. <i>aureus</i> <10%	≥40 administered in 4 equal doses	Approximately 3 g	65–78	Prevalence of microorganisms: Liu et al. ¹⁴ ; dose: Peltola et al., ⁹ Liu et al., ¹⁴ Peltola et al. ²⁰ ; extent of bone penetration: Feigin et al. ²²
Vancomycin, if prevalence of MRSA in community ≥10% and prev- alence of clindamycin-resistant <i>S. aureus</i> ≥10%	≤40 administered in 4 equal doses	Dosing adjusted ac- cording to trough level, with a target of 15 to 20 µg per milliliter	5–67	Prevalence of microorganisms: Liu et al. ¹⁴ ; dose: Liu et al. ¹⁴ ; extent of bone penetration: Landersdorfer et al. ²³
Linezolid, if no response to vancomycin	30 administered in 3 equal doses	1.2 g for no more than 28 days	40-51	Dose: Kaplan et al., ²⁴ Chen et al. ²⁵ ; extent of bone penetration: Landersdorfer et al. ²³
Alternatives for specific agents				
Ampicillin or amoxicillin for group A beta-hemolytic streptococcus, <i>Haemophilus influenzae</i> type b (beta-lactamase-negative strains), and <i>S. pneumoniae</i>	150–200 admin- istered in 4 equal doses	Approximately 8–12 g	3–31	Dose: Peltola et al. ⁹ ; extent of bone penetration: Landersdorfer et al. ²³
Chloramphenicol, if safer agents not available or affordable	75 administered in 3 equal doses	2–4 g	39	Dose: Krogstad ¹ ; extent of bone penetration: Summersgill et al. ²⁶

* When relevant, the same dose may be used parenterally and orally. MRSA denotes methicillin-resistant Staphylococcus aureus, and MSSA methicillin-susceptible S. aureus.

† The maximal daily dose is not always well defined, but the maximal adult dose should not be exceeded.

‡ Bone penetration is the ratio of the bone concentration to the serum concentration.

§ Data on antistaphylococcal penicillins, first-generation cephalosporins, and clindamycin^{21,22} are from in vivo studies involving children; the remaining data were derived from studies involving adults or from experimental models.

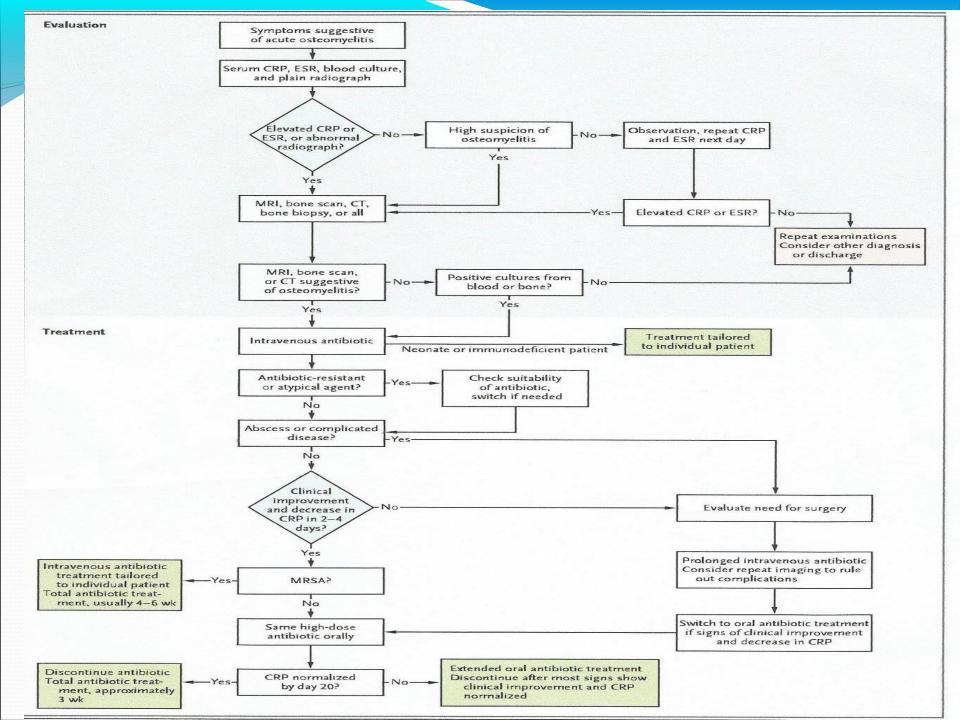
¶ Cephalothin and cefazolin are administered intravenously, cephalexin and cefadroxil are administered orally, and cephradine is administered by either route. If no parenteral first-generation agent is available, cefuroxime can be used for parenteral administration.

Chloramphenicol at a dose of 100 mg per kilogram of body weight per day in four equal doses is generally used in bacterial meningitis.

Conservative Therapy

Conservative treatment is effective in up to 90% of cases of *acute* osteomyelitis if it is diagnosed early in the course of the illness

Current clinical-practice guidelines of the Infectious Diseases Society of America recommend individualized therapy and typically a minimum of 4 to 6 weeks of medication for children with acute osteomyelitis



Role Of Surgery

Since data are lacking from randomized trials of surgery for osteomyelitis in children, questions about the timing and extent of surgery and the overall need for surgical intervention other than biopsy remain unanswered.

Role Of Surgery

In a series of 68 pediatric patients who underwent aggressive primary surgery, 17% of the patients had chronic osteomyelitis after the procedure

HBO2 & Refractory Osteomyelitis

- Increased oxygen tension in osteomyelitic bone results in improved leukocyte mediated oxidative killing of aerobic organisms including *Staphylococcus aureus*
- Osteomyelitic bone typically has a pO2 < 20 mm Hg, whereas normal bone has a pO2 of 45 mm Hg. *Mader 1978*
- HBO impedes anaerobes.
- Antibiotics (HBO Synergy) augments transport of antibiotics across cell walls (e.g. aminoglycoside)
- reduces tissue edema leading to improved collagen formation and capillary angiogenesis.
 - Vascular damage may impair the immune system and limit beneficial effects of antibiotics

Osteomyelitic bone typically has a pO2 < 20 mm Hg, whereas normal bone has a pO2 of 45 mm Hg. - *Mader 1978*

HBO2 utilized in Refractory Osteomyelitis in Adults

Regarding Hyperbaric Medicine with Adults, PICO format was utilized and Pubmed All studies identified through on-line searches using the terms "hyperbaric oxygen" and "osteomyelitis" were abstracted. This search methodology returned a total of 201 articles, spanning the period from 1965 through the present

HBO2 utilized in Refractory Osteomyelitis in Adults

Eltorai et. al. described results in managing 44 spinal cord injured patients with osteomyelitis secondary to pressure sores.

Infection resolution was achieved in 30 of 44 (68%) of patients. None of these patients underwent surgical debridement in conjunction with their course of HBO2 therapy

HBO2 utilized in Refractory Osteomyelitis in Adults

Reporting more definitive data on concurrent surgical management, Morrey et. al. detailed HBO2 in 40 patients with surgery and antibiotic refractory long bone osteomyelitis.

HBO2 has been associated with remission in about 80% of cases of RO T 23 month f/u and also reduction in the risk of amputation in diabetic foot ulcers. 75% of the patients sustained remission at 7-10 year reevaluation.

Refractory Osteomyelitis in Adults

Davis et. al. In a subsequent series of 38 patients, reported All patients had failed at least one or more previous attempts at sterilization with combined surgery and antibiotics.

An average of 45 HBO2treatments were provided in conjunction with debridement and antibiotics. After nearly three years of mean follow up, 34 of 38 (89%) remained infection free.

RECAP HBO2 and Refractory Osteomyelitis in Adults

human data on refractory osteomyelitis was abstracted from retrospective clinical case series, the overwhelming majority of available studies supported the use of HBO2 as a beneficial adjunct

Specifically, the highest reported osteomyelitis cure rates were obtained when HBO2 therapy was combined with culture-directed antibiotics and concurrent surgical debridement.

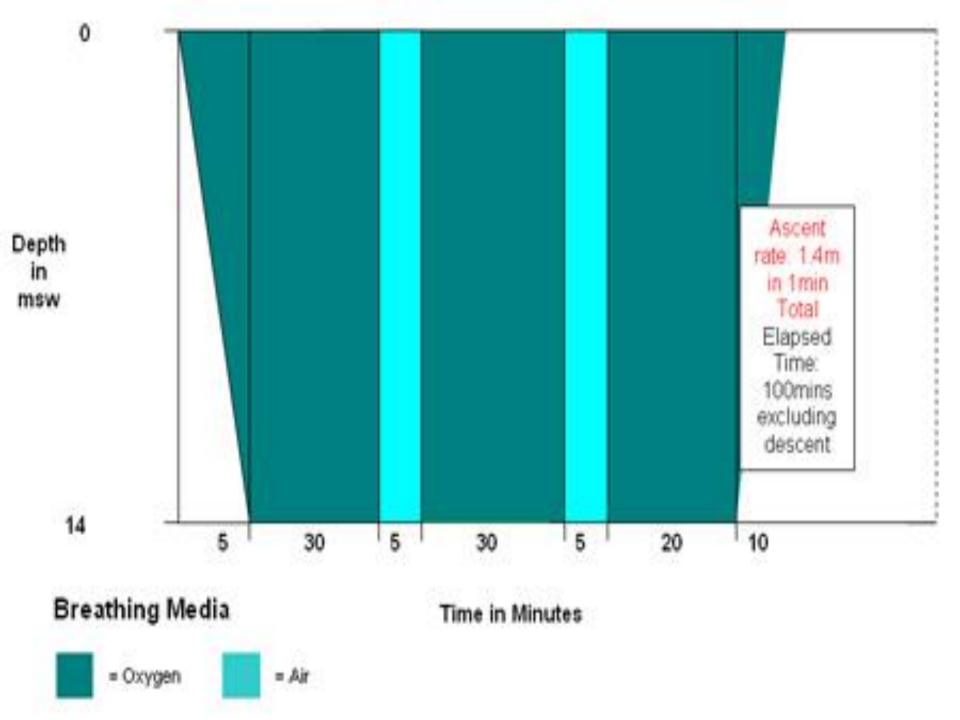
Data in Pediatrics

- data in pediatrics employing HBO2 in refractory osteomyelitis is limited
 - Hyperbaric Oxygen Therapy in the Pediatric Patient: The Experience of the Israel Naval Medical Institute Waisman, et al. Pediatrics; 1998
 - 139 pediatric patients age 2 months to 18 years, variety of indications for HBO2
 - 5 pediatric patients with refractory osteomyelitis
 - median age: 9 years (range, 5 to 13); 4 boys and 1 girl

An overall literary search was perfromed using PICO format on Pubmed utilizing **US National Library of Medicine** 18 articles.

Case Series

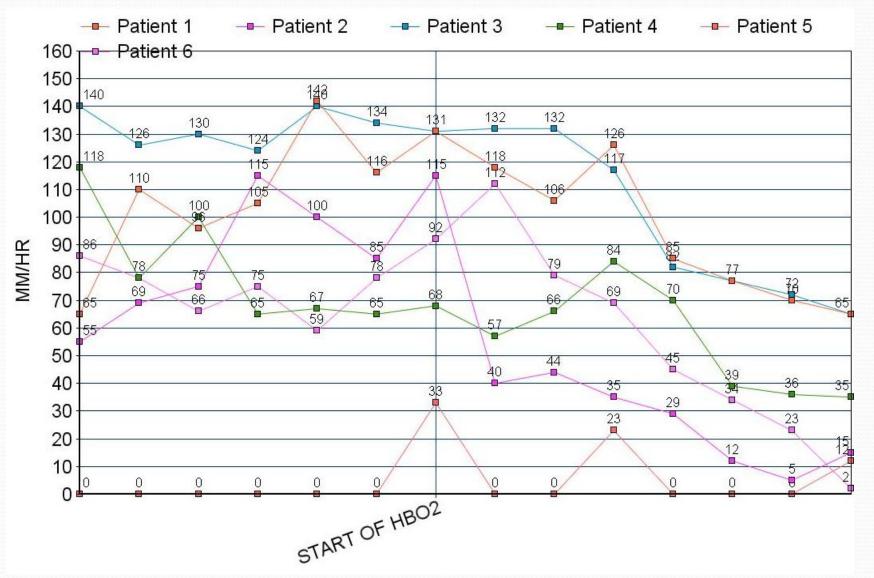
- Six patients, age 10 to 18 years, received hyperbaric oxygen therapy for refractory osteomyelitis.
- MRI showed osteomyelitis in all of these cases
- All patients received IV antibiotics, wound debridement and/or wound care
- After at least 4 weeks of traditional treatment with no sustained improvement, HBO2 was initiated using US Navy Table 66 protocol consisting of 90 minute treatments, 5x/week.



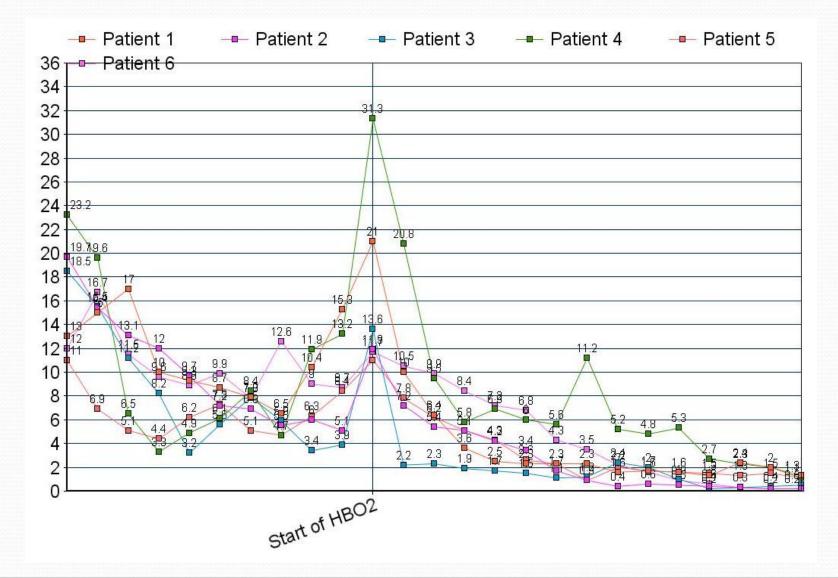
Patient demographics and clincial course

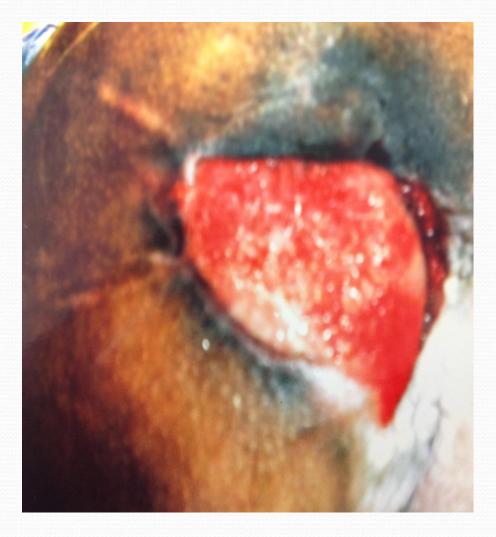
Age/Gender	Medical Condition	Infection Site	Duration	Admisson ESR/CRP*	Debridement/ Wound Care	Culture	Antibiotics	Wks of abx/ESR & CRP* prior to HB02	# HBO2 sessions	ESR/CRP* at hospital d/c
10/M	none	R hip	9.5 weeks	65/21.9	Yes	MSSA	Cefazolin	4/142/21	20	65/1.3
14/F	Spina bifida	R distal fibula	10.5 months	67/19.7	Yes	Pseudomonas Proteus	Ceftazidime Gentamicin	6/35/11.9	45	25/0.2
18/F	Spina bifida CP ^β ,DD ^γ	Pelvis	7.5 months	140/18.6	Yes	Pseudomonas	Ceftazidime Gentamicin	6/117/13.6	60	65/0.5
15/M	Spina bifida CP ^β	Pelvis	1.5 year	118/23.2	Yes	Pseudomonas Proteus	Pip-Tazo Gentamicin	6/100/31.3	60	35/1.1
16/M	Trauma/ paraplegia	Sacrum Pelvis	8 months	33/11	Yes	Pseudomonas	Ceftazidime Gentamicin	6/33/11	36	12/1.1
17/F	CP ^{β,} DD ^γ	L iliac wing	1 year	86/12	Yes	Pseudomonas	Ceftazidime	4/95/11.7	40	2/0.2

ESR trend



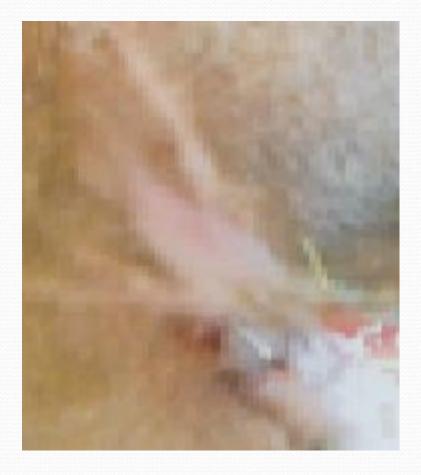
CRP trend





20th Treatment

35th Tx



Completion of HBO2



Pt 2 at 40 Treatments



Side effects of HB02 therapy

- Barotrauma
- CNS- Seizures (seen on further slides)
- Pulmonary System substernal burning, cough, and if no removal of Oxygen when symptoms initially seen, can cause lasting fibrosis.
- Ocular- Progressive myopia has been observed in some patients undergoing prolonged periods of daily HBO₂ therapy. Although the exact mechanism remains obscure, it is apparently lenticular in origin and usually reverses completely within a few days to several weeks after the last therapy
- Cardiovascular Experienced if patient has low EF.
- Hypoglycemia Drops up to 60 pts in Blood sugar.
- Confinement anxiety -which appears to be present in about 2% of the general patient population
- Hypothermia and hyperthermia Due to Gay-Lussac's Law

Side effects of HBO2 Therapy

Cardiovascular responses to hyperbaric hyperoxia include a rate-dependent reduction in cardiac output and systemic vasoconstriction with an increase in peripheral vascular resistance.

Although these effects are well tolerated by normal individuals, the occurrence of acute pulmonary edema in three patients during hyperbaric oxygen therapy, with one related fatality

All three patients had cardiac disease with reduced left ventricular ejection fractions

Side effects of HB02 therapy

- Pulmonary barotrauma most dangerous side effect
 - if patients do not exhale on ascent back to surface ambient pressure the risk of overexpansion of the lungs can occur.
- Seizure induced by oxygen toxicity
 - Pulmonary and neurological manifestations of oxygen poisoning are often cited as major concerns. Oxygen tolerance limits that avoid these manifestations are well defined for continuous exposures in normal men. Pulmonary symptoms are not produced by daily exposures to oxygen at 2.0 or 2.4 atm abs for 120 or 90 min, respectively. Partial pressure oxygen utilizing a Table 66 protocol and duration of oxygen in minutes (with airbreaks given also in protocol) reduces this risk.

Oxygen Toxicity (Seizures)

estimates of the seizure rate during therapeutic oxygen exposures at 2.0-3.0 ATM reported a convulsion incidence of about 1 per 10,000 therapies or 0.01%

This side effect is seen at depths of 66 fsw or greater This is for the treatment of CO, DCS, and AGE, not the depth utilized for Osteomyelitis protocol. Among 900 patients who received HBO2 therapy for carbon monoxide poisoning, 16 or 1.8% had

for carbon monoxide poisoning, 16 or 1.8% had seizures. . Even when oxygen convulsions do occur, there are no residual effects if mechanical trauma can be avoided.

Middle ear & sinus barotrauma

- Most common side effect
- mild and self-limiting
- placement of tympanostomy tube placement may facilitate continuation of HBO2
- consider ear tube placement prior to HBo2 in patients who may not be able to follow instructions well (eg very young patients, with certain neurologic conditions)

Middle ear & sinus barotrauma

Incidence of middle ear barotrauma Study done by Sheffield (0.4%)

Preventing middle ear barotrauma

- Avoid treatment if patients have upper respiratory infection
- Teach valsalva maneuver
- Use decongestants/anti-histamines if necessary

Treatment of Middle ear barotrauma

• HBO₂ break (days- weeks)

Barotrauma

Barotrauma of descent

- Middle ear squeeze
- > Inner ear squeeze
- > External auditory
- Sinuses
- Mask Squeeze

Barotrauma of ascent

- > Ear
- > Teeth (decayed tooth, loose fillings)
- Pulmonary overinflation syndromes
- Local injury
- Interstitial emphysema
- > Pneumothorax
- Air embolism



Absolute Contraindications

Untreated pneumothorax

Untested pacemakers

Select medications

Doxorubicin (Adriamycin)- anticancer, cardiac toxicity

<u>Bleomycin</u>- Anticancer, pulmonary toxicity

so consider 1 ATA trial followed by PFTs w/ CO2 diffusion capacity

<u>Cis-Platinum</u>- Anticancer, interferes w/ DNA synthesis to delay fibroblast and collagen production

Mefenide Acetate (Sulfamylon)- Antibacterial burn cream

Carbonic anhydrase inhibitor promotes CO2 increase with vasodilation may cause hypotension in large amounts.

Relative Contraindications

- URI/Chronic sinusitis
- Seizure disorder
- Emphysema w/ CO2 retention
- High fever
- History of spontaneous pneumothorax
- History of thoracic surgery
- History of surgery for otosclerosis
- Congenital spherocytosis
- History of optic neuritis

HBO Observations:

- 1.) HBO Pretreatment improves the peri- CROM environment. Recommendation for 2 wks of HBO before repeat surgery & antibiotics. Esp in septic nonunion & diffuse sclerosing varieties. Decreased wound edema, induration, drainage & better demarcation of infected vs.noninfected tissue.
- 2.) HBO demarcates viable vs nonviable bone. This aids the surgeon in establishing viable infection-free margins at the time of debridement

HBO Observations:

3.) HBO preferentially stimulate the osteoclast. The osteoclast removes dead or infected bone that often remains after debridement.

4.) The osteoclast cannot function in a hypoxic environment. This cell has an O2 requirement 100 x greater than an osteocyte.

HBO Observations:

- 5.) Optimal protocols must be followed to achieve success.
- 2.5 ATA x 90 min QDAY

6.) The duration of CROM does not have an adverse effect on the outcomes, which appear to be independent of duration.

Conclusion

- HBO₂ is underutilized and should be considered in patients that have been unresponsive to at least 4-6 weeks of antibiotic and surgical intervention.
- Should be considered in Pediatric Patients
- HBO₂ is relatively safe, with the most common side effect being middle ear and sinus barotrauma

References

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6.) Cierny G, Mader JT, A clinical staging system for adult osteomyelitis. Contemporary Orthopedics 1985;10(5):17-37