2024 MID-ATLANTIC CONFERENCE

12th ANNUAL CURRENT CONCEPTS IN VASCULAR THERAPIES

2024

Hyperbaric Oxygen: Its Role in the Treatment of Complex Wounds

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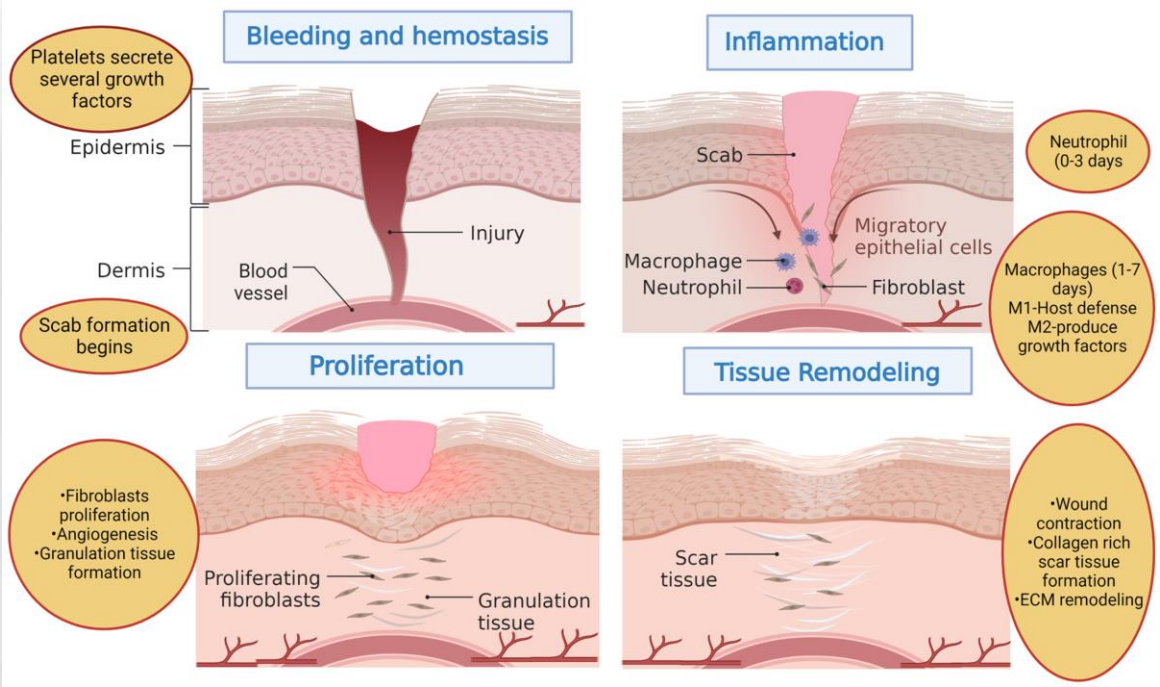
Wound Healing: Overview

- Normal Healing
  - Hemostasis
  - Inflammation
  - Proliferation
  - Remodeling



Wound Healing: Overview

- Essential Steps

Ensure adequate perfusion
Manage nonviable tissue
Assess for infection
Manage inflammation
- **Primary vs secondary**

Manage edema
Evaluating for unusual etiologies (Ca, vasculitis)

Optimize wound bed
- **Moisture, bacteria, biofilm**

Offloading
Manage host factors
- **DM, CHF, smoking**

Enhance tissue growth
- **Tissue grafts, growth factors**
- **NPWT**
- **HBO**

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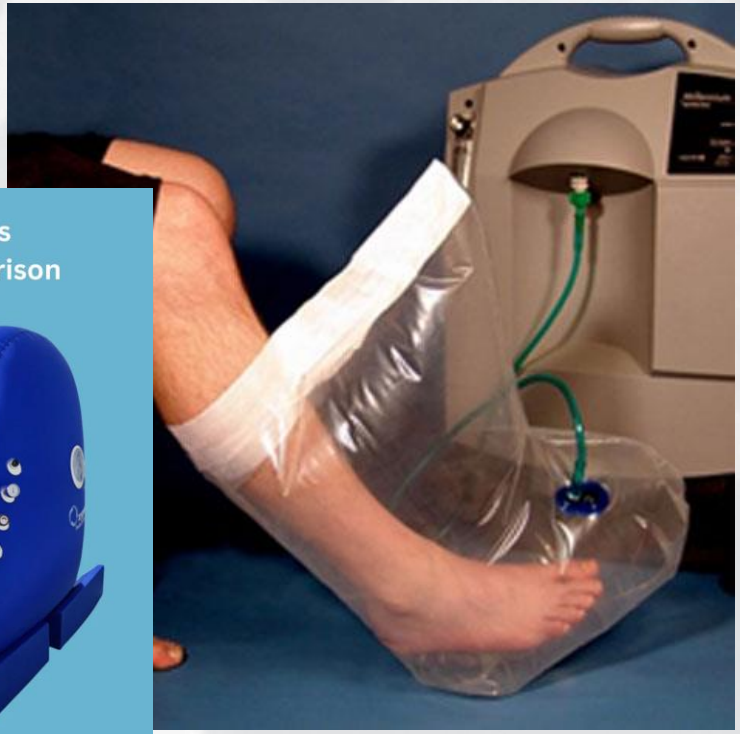
HBO: What is it?

- Defined
  - A therapeutic treatment whereby medical grade O2 is given in a chamber pressurized to at least 2.0 ATA
- What it is not
  - Topical oxygen
  - Mild hyperbaric treatments
    - Treatment pressures 1.3-1.4 ATA
    - Wellness centers, home soft sided units

HBO: What is it?

HBO: What is it Not?



Oxygen Health Systems
Wheelchair Ready Comparison

MC 4500
63 width x 81"tall
and 71" length
Door-31" width x 57" tall

MC 4400
63 width x 72" tall
and 71" length
Door-31" width x 57" tall

MC 4000
52" width x 66" tall
and 61" length
Door-32" width x 52" tall

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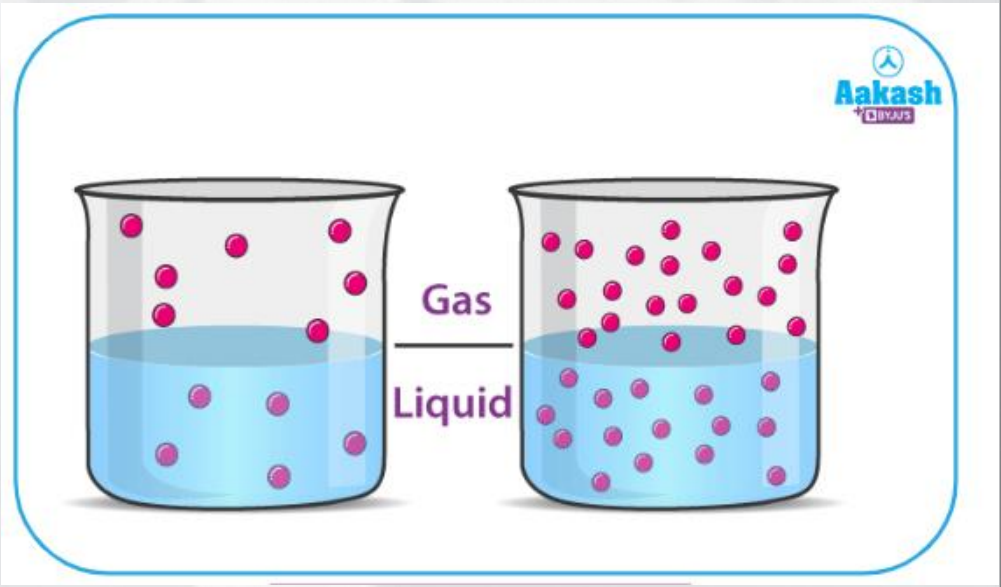
HBO: How it Works

- Boyle's Law : $P_1V_1 = P_2V_2$
- Henry's Law: $C = kP$
  - (C- concentration in solution,

    P- pressure, k - constant)
  - At 2.5 ATA and 100% FiO2, plasma has 17-20x more dissolved O2 in solution.



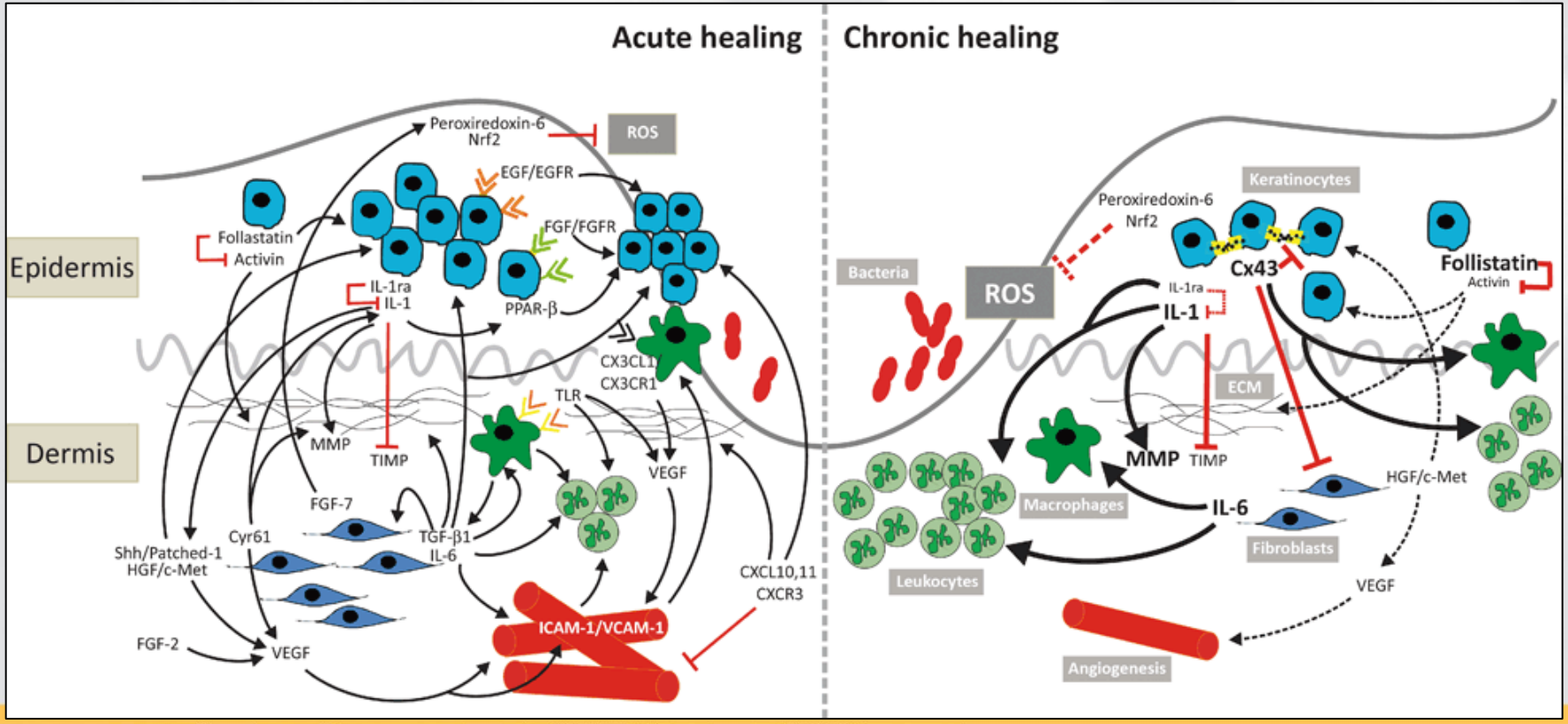
HBO : How it Works

- Diffusion distance of O2 in tissue is increased
- Tissue hyperoxia induces vasoconstriction
  - Decreased edema (compartment syndrome, crush injuries, inflamed tissue)
- Antimicrobial effects
  - Toxic to anaerobic bacteria
  - Oxygen derived free radicals are bactericidal
  - Stimulates PMN phagocytosis in tissue
  - Increases effectiveness of antibiotics
    - Increases active transport of abx across bacterial cell wall
  - Prevents the production of clostridial α toxin and impairs pseudomonas growth

HBO : How it Works

- Supplies O2 which is a fundamental need of mitochondria (ox phos for ATP)
- Increases efficacy of WBC activity (chemotaxis, cell signaling)
- Downregulates cytokine production (ILs, TNF)
- Upregulates growth factor production (PDGF, VEGF, TGF-b)
- Increased neovascularization / angiogenesis
- Reduces leucocyte adhesion in reperfusion injury
- Improves fibroblast activity (collagen production, growth factors)

HBO : Why not every Wound?



HBO : When to use it

- UHMS – Undersea and Hyperbaric Medicine Society
  - International organization serving as the primary worldwide source for scientific information for diving physiology and hyperbaric medicine physiology
  - Publishes Hyperbaric Medicine Indications Manual q3 yrs
  - Serves as a resource to CMS
  - Sets accreditation standards for HBO treatment centers
    - Standards for safety and effectiveness

HBO : UHMS List of Indications

- Air / gas embolization
- CO poisoning +/- cyanide
- Clostridial myonecrosis (gas gangrene)
- Acute traumatic ischemias
- Decompression illness
- Central retinal artery occlusion
- Arterial inefficiencies : enhanced healing for problem wounds
- Necrotizing soft tissue infections
- Severe anemia
- Intracranial abscess
- Acute thermal injury (burns)
- Idiopathic sudden sensorineural hearing loss
- Aseptic avascular necrosis
- Compromised flaps / grafts
- Refractory osteomyelitis
- Delayed radiation injury (soft tissue, bone)

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HBO : CMS List of Indications

- Air / gas embolization
- CO poisoning
- Cyanide poisoning
- Clostridial myonecrosis (gas gangrene)
- Acute traumatic ischemias
- Limb reattachment
- Decompression illness
- Refractory actinomycosis
- Acute peripheral arterial insufficiency
- Necrotizing soft tissue infections
- Compromised flaps / grafts
- Refractory osteomyelitis
- Delayed radiation injury (soft tissue, bone)
- Diabetic foot ulcer Wagner grade III or greater

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HBO : Diabetic Foot Ulcer

Wagner classification of diabetic foot ulcers

Grade 0	Grade 1	Grade 2
No ulcer in a high-risk foot 	Superficial ulcer involving the full skin thickness but not underlying tissues 	Deep ulcer, penetrating down to ligaments and muscle, but no bone involvement or abscess formation 
Grade 3	**Grade 4**	**Grade 5**
Deep ulcer with cellulitis or abscess formation, often with osteomyelitis 	Localized gangrene 	Extensive gangrene involving the whole foot 

HBO : Diabetic Foot Ulcer

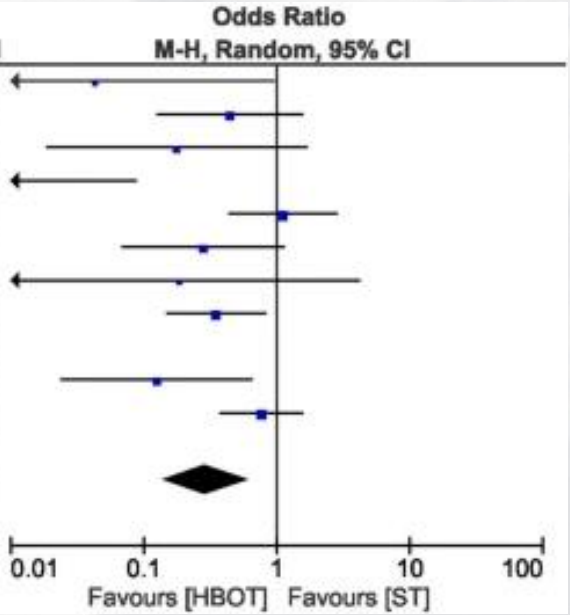
- DFU – most studied indication for response to HBO
- Still much heterogeneity of response seen in studies
  - Studies limited by variation in inclusion criteria, outcomes measurements, HBO treatment protocols, rates of debridement
- 2014 Meta analysis (Stoekenbroek) – 669 trials reviewed, 7 met inclusion
  - Two RCTs : NNT 1.8 , NNT 4.1 but no difference in amputation rates
  - Third trial w/ lower amputation rate with NNT 4.2.
- 2021 Meta analysis (Sharma *et al*) 12 RCTs, 2 CCTs: 768 patients
  - Complete healing OR HBO vs ST 0.29 (95% CI 0.14-0.61)
  - Major amputation RR 0.60 (95% CI 0.39-0.92)

HBO : Diabetic Foot Ulcer

Study or Subgroup	ST Events	ST Total	HBOT Events	HBOT Total	Weight	Odds Ratio M-H, Random, 95% CI
Abidia, 2003	0	9	5	9	4.4%	0.04 [0.00, 0.96]
Chaudhary, 2013	8	20	12	20	12.3%	0.44 [0.13, 1.57]
Chen, 2017	1	18	5	20	6.9%	0.18 [0.02, 1.69]
Duzgun, 2008	0	50	33	50	5.0%	0.01 [0.00, 0.09]
Fedorko, 2016	12	54	10	49	14.6%	1.11 [0.43, 2.87]
Kalani, 2002	10	21	13	17	11.3%	0.28 [0.07, 1.15]
Kessler, 2003	0	13	2	14	4.3%	0.19 [0.01, 4.25]
Londahl, 2010	12	45	25	49	15.2%	0.35 [0.15, 0.83]
Ma, 2013	0	18	0	18		Not estimable
Salama SE, 2019	3	15	10	15	9.7%	0.13 [0.02, 0.66]
Santema, 2018	29	60	33	60	16.3%	0.77 [0.37, 1.57]
Total (95% CI)		**323**		**321**	**100.0%**	**0.29 [0.14, 0.61]**
Total events	75		148			

Heterogeneity: Tau² = 0.73; Chi² = 23.65, df = 9 (P = 0.005); I² = 62%

Test for overall effect: Z = 3.26 (P = 0.001)



(Sharma 2021)

HBO : Diabetic Foot Ulcer

- Global rate of DFU in diabetics is appx 18.6 million per year.
- Lifetime risk of DFU in diabetics is about 25%.
- DFU carries 2.5 mortality risk c/t diabetics without DFU.
- Up to 50% of DFU patients undergo amputation in their lifetime.
- Five-year survival rate after amputation is 40-48%.
- High rates of polymicrobial infection
- High rates of coincident macrovascular and microvascular arterial disease

HBO : DFU Clinical Pearls

- Look for evidence of infection in Wagner grade II patients
  - Deep wound Cx (tissue sample)
  - Clinical findings – static or worsening wound, odor, edema, new pain in neuropathic foot
  - Probe to bone : PPV 94% for osteomyelitis (Morales Lozano 2010)
  - Labs (ESR, CRP), Xray, MRI
  - Bone Bx
  - Wound duration >4 weeks without healing
    - Healing rate decreased by 50% for duration > 52 days (Hilde Smith-Strom 2017)

HBO : Compromised Flap / Graft

- Graft
  - Single or multiple tissue types
  - Lacks its own blood supply, relies on its recipient bed for nutrients, revascularization
  - Normal progression of graft take: pale > bluish hue (congestion) > pink blush
  - Threatened graft : dusky > epidermolysis > desiccation and necrosis
    - Initial signs visible 24-48hrs
    - Occurs when metabolic demand > vascular capacity of the recipient bed

HBO : Compromised Flap / Graft

E Hand: The Electronic Textbook of Hand Surgery.

HBO : Compromised Flap / Graft

- Flap
  - Unit of tissue with its own inherent blood supply
  - Ischemia is usually distal at the area furthest from the source of vascular perfusion
  - Arterial compromise - pale, cool, decreased CR
  - Venous compromise – blue/purple color, warm, increased turgor
  - Treatment
    - Surgical correction of cause if possible
    - HBO to enhance flap survivial

HBO : Compromised Flap / Graft

HBO : Compromised Flap / Graft

(Ernst 2020)

Transcutaneous Oximetry (TCOM)

- Contact method to measure tissue O2 content
- Directly assesses oxygen delivery to tissue
- Limitations: operator dependent, nonspecific as to cause, high variability of normal readings
- <40mmHg predicts poor healing

HBO : Compromised Flap / Graft

- Many animal studies
  - Experimentally induced devascularized wounds: HBO at 2.0 ATA improved healing to compromised wounds, no benefit to similar wounds w intact vascular supply (Kivisaari 1975)
  - Pig models of impaired flap, 90mins HBO at 2.0 ATA decreased flap necrosis by 35% (Pellitteri 1992)
- Flap survival highly dependent on when HBO initiated : ideal is in first 72hrs after surgery

HBO : Compromised Flap / Graft

- Early recognition is paramount
  - Early exam postop is needed
- Early TCOM if suspicious
- Consider empiric HBO
- HBO is an adjunct to surgical evaluation and Tx for compromised flaps
- Initial HBO treatment is BID until either clinical improvement or TCOM >40mmHg, then qday, average is 20 treatments
- Meta analysis (Zhou 2014) 23 clinical trials : 957 HBO vs 583 controls
  - 62-100% survival w HBO
  - 35-86.5% survival in controls

HBO : Chronic PAD

- Not a covered indication under CMS
- Last CMS review 2002
  - Hypoxia not found to be a unique wound identifier
  - Some studies did show TcPO2 to be predictive of poor healing if < 40mmHg and predictive of good healing if >200mmHg in chamber.
- CMS : Literature does not adequately demonstrate that TcPO2 can reliably predict a wound's outcome with HBO treatment.
- We can sometimes get approval (private insurers) for HBO to treat refractory wounds with demonstrable periwound hypoxia by TCOM

Chronic Refractory Osteomyelitis

- Infection of bone or bone marrow that recurs or fails to respond to accepted management techniques
- Limitations in identifying response after initial Tx:
  - Imaging
  - Postop patients (orthopedic)
  - Serum inflammatory markers
- No randomized trial data
- CMS : the majority of animal data, human case series, and non-randomized prospective trials suggests the addition of HBO improves the ultimate rate of resolution of infection.

Chronic Refractory Osteomyelitis

- In OM : O2 tension in bone is low. PMNs require pO2 30-40mmHg minimum for oxidative killing of bacteria
- O2 augments transport of abx across bacterial cell wall. Active transport is impaired if pO2 is < 20-30mmHg
- HBO plus antibiotics are synergistic
  - Cefazolin plus HBO produces 100-fold greater decrease in bacterial counts than either intervention alone
- Similar effects in soft tissue - important since soft tissue can act as a conduit for sustaining cortical bone infection

CROM : Clinical Pearls

- HBO is an adjunct to surgery and antibiotics
- HBO duration is 6-8 weeks along with antibiotics
- Markers for endpoint reached
  - Imaging (limited for ~6 mos)
  - Inflammatory markers, ancillary findings (CBC)
  - Wound response
- A note about acute OM
  - Under-recognized in chronic wounds
  - DFU, chronic wounds, post orthopedic surgery, exposed hardware, probe to bone, PUs (contamination), exposed bone (periosteum vs desiccated bone)

HBO : Delayed Radiation Injury

- STRN : soft tissue radionecrosis / ORN : osteoradionecrosis
- Radiation exposure >6 mos ago (ie not acute or subacute injury)
- Total exposure dose typically > 6000cGy
- May or may not have experienced an associated acute or subacute injury
- Tissue characteristics
  - Obliterative endarteritis with capillary dropout
  - Fibro-atrophic effect : depletion of stem cells with increased release of fibrogenetic cytokines
- Wide range of patient tolerance to XRT but no good measurable predictors for delayed radiation injury

HBO : Delayed Radiation Injury

- HBO : increased vascularity and cellularity
- Most data is from treatment of mandibular ORN
  - Robert Marx DDS established many of the key findings of ORN
    - Avascular, Aseptic
    - Showed that treatment required HBO to be paired with surgical resection
    - 30/10 HBO treatment protocol with surgical treatment in between the two groups
    - Series of 268 patients (Marx) with 100% successful resolution, though 68% required treatment as stage III
  - Subsequent studies mixed but many did not adhere to Marx's protocols : low HBO treatment counts, leaving out surgical resection
  - Marx 20/10 protocol for prophylaxis (extraction w XRT Hx) – sometimes for non-CMS

HBO : Delayed Radiation Injury

- STRN
  - At sites of prior XRT given for a primary skin indication or for other indications
  - Spontaneous wound or non-healing after trauma
  - Can be associated w underlying ORN (tibia, ribs)
    - Bone imaging can mimic chronic OM. Sometimes need bone Bx to exclude.
    - Gum ulceration in mandibular ORN is an example of concomitant STRN
  - Radiation cystitis, enteritis, proctitis
    - Potential for hemorrhage from mucositis
    - Functional symptoms can respond to HBO as well as bleeding
    - Radiation cystitis covered when prior treatments (fulguration, laser) ineffective
    - Our LCD for CMS does not approve coverage for radiation proctitis

HBO Practical Issues

- Absolute contraindication – untreated PTX
- Relative contraindications
  - Poorly controlled, brittle DM
  - Seizure disorder
  - URI, chronic sinusitis
  - Implanted devices (need clearance)
  - Decompensated congestive heart failure
  - COPD with air trapping or severe architectural parenchymal distortion
  - Active malignancy is NOT a contraindication – no data to show acceleration of cancer behavior

HBO Practical Issues

- Possible side effects
  - Temporary myopia
  - Hyperoxic seizure
  - Hypoglycemia
  - Confinement anxiety
  - Barotrauma – middle ear, sinuses, pulmonary
  - Cataract maturation
  - Pulmonary oxygen toxicity

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