Anerobic and Mixed Soft Tissue Infections

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A Critical Appraisal of Hyperbaric Oxygen Therapy in Modern Medical Practice Lecture Series

Gas Gangrene & Necrotizing Skin & Soft Tissue Infections

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Disclosures

- K30 Program Alumnus
- BJH and WUSM Foundations
- Merck, Inc.----research funding for intra-abdominal infections
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- Musculoskeletal Transplant Foundation—research in AWR
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- Wendi Gordon Shelist Foundation—NF, Surg Infections & WH
- Bard, Lutronix, Inc. photographic analyses

None of these disclosures represent conflicts of interests for this presentation on NSSTI & HBO & are offered for better complete transparency

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What are more relevant are my Biases

- Critical Care Wound Healing – Critical Skin & Soft Tissue Integrity Care
  - *Burns: thermal, electrical, chemical & desquamating skin conditions, even radiation*
  - *NSSTI's & NF*
  - *Soft tissue traumatic injuries*
  - *Limb threatening wounds*
  - *Sepsis in association with soft tissue defects*
- These are all Surgical Critical Care Imperatives & all patients get better outcomes with multidisciplinary care teams & providers and their sponsoring institutions are better off for that care in a well functioning team as well
- However, as care improves it also must be better, not just more expensive
- HBO must meet & exceed these challenges via further study in NSSTI's

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Critical Appraisal Preview in considering HBO for GG & NSSTI's

1. Your fundamental orientation and capabilities re HBO matters – but we should be more open to more collaborative study and optimization on how HBO might be used in the treatment of GG and NSSTI's
2. GG, NF, NSSTI have a problem in terms of incidences, magnitudes and classifications to be captured and then studied
3. The care of NSSTI has hallmarks that have improved mortality already - so the added value of HBO is more difficult to show and in the current era needs more overall savings to pts, to clinicians and healthcare delivery entities - how to capture it?
4. And more research is needed both for clinical comparative effectiveness AND basic science of HBO's value & effects
5. A possible solution may lie in EMR data registries
6. HBO remains an opportunity to leverage and coordinate better care

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Why Clostridial Myonecrosis, Gas Gangrene & Necrotizing Soft Tissue Infections?

- Infrequent, but severe - even "rare" in next slides discussions
- Topping out responses with resuscitation, antibiotics & surgery
- HBO offers better improvements in care
  - *Interestingly NSSTI immunomodulatory and vaccine like approaches continue to generate funded development*
  - *Unlikely that material improvements in either resuscitation, critical care, available antibiotics or surgery will revolutionize care - most likely all will incrementally evolutionarily improve care outcomes*
  - *And HBO is ready to be that next incremental improvement to shift toward better outcomes*

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Recent European Review [1]


Clinical Microbiology and Infection

Necrotizing skin and soft-tissue infections in the intensive care unit

- NSSTI's are "rare"
- 4 per 100,000 per year
- 1.2% of all patients admitted to an ICU with sepsis
- CDC tracks via microbiological isolates--Active Bacterial Core Surveillance

1. *Peetermans, et al. Necrotizing skin and soft-tissue infections in the intensive care unit, Clin Micro and Infection 26 (2020) Elsevier pp 8 - 17*

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CDC SEER, ABC, other surveillance programs organize DATA by isolated microbiological organism annually [2]

- For example
  - *group A Streptococcus*
  - *group B Streptococcus*
  - *Haemophilus influenza*
  - *Legionellosis*
  - *Methicillin-resistant Staphylococcus aureus*
  - *Neisseria meningitidis*
  - *Streptococcus pneumoniae*
- But if incidence around 4 per 100,000 & St Louis

2 https://www.cdc.gov/abc/reports-findings/surv-reports.html

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Critical Appraisal 1 - NSSTI's & NF are underdiagnosed & under-reported

- 2018 population of St Louis 302,838
- If 4-5/100,000 than
- So, we should be seeing 12 - 16 cases of NSSTI's per year
- We see 1 - 2 consults for S&STI's per 24 hrs. & 1- 2 high level septic shock NSSTI per week at Barnes – Jewish Hospital in St Louis, MO

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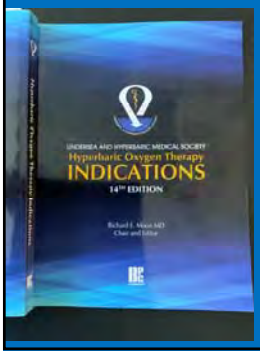
Critical Appraisal Challenge #2 Capturing & Classifying is also part of the problem



Note in the 14th Ed UHMS Indications Manual [3]
- #4 Clostridial Myonecrosis, myositis and Gas Gangrene
- #11 Necrotizing Soft Tissue Infections – meaning Streps and Gram Positives & others
- Invasive fungal infections---more addressing in sections on intra-cranial abscesses

So…there is a very heterogeneous range of infections and pathogens causing these soft tissue infections & necrosis & systemic sepsis

Problem we have is in comparing Apples to Apples

And many of our basic science assumptions are still being questioned…for example:

3 UHMS Hyperbaric Oxygen Therapy Indications 14th Richard E Moon, MD, Chair & Editor, Best Publications North Palm Beach FL

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HBO Community Dogma under review [4,5]

Clostridia spp are a semi-obligate anaerobes – high oxygen tensions may be more bacteriostatic than bactericidal

Obligate Aerobic Bacteria - may be regarded by some as more limited to
- *Pseudomonas aeruginosa*
- *Bacillus subtilis*

Facultative Anaerobic Bacteria:
- *Streptococcus pyogenes*
- *Staphylococcus aureus*
- *Escherichia coli*
- *Aeromonas hydrophilia*
- Obligate, semi-obligate, facultative, spore form, dormancy, invasive, elaborating---all evolving over time and further study---HBO must evolve

4. Prescott LM, Harley JP, Klein DA (1996). Microbiology (3rd ed.). Wm. C. Brown Publishers. pp. 130–131. ISBN 0-697-29390-4
5. Brooks GF, Carroll KC, Bulel JS, Morse SA (2007). Jawetz, Melnick & Adelberg's Medical Microbiology (24th ed.). McGraw Hill. pp. 307–312. ISBN 978-0-07-128735-7.

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If classification schema, basic science assumptions under re-review---

- **Clinically we also have a moving target** –in this case this is good
- Advances are decreasing mortality
  - *1980's to 1999 28%* [6]
  - *After 2000 and with timely care <24hrs—10%* [7,8]
  - **I still** quote 50% to pts & families
- Earlier diagnoses – remain problematic
- Even With Lineic type scoring schema, and
- Efforts to organize, prioritize care on-going

6. May AK. *Surg Clin North Am.* 2009; 89:403-420
7. Gelbard RB. *J Trauma Acute Care Surg.* 2018; 85:208-214
8. Zhao JC. *BMC Infectious Diseases.* 2017; 17:792

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Earlier Dx remains problematic

- Wong C-H, *et al*. The LRINEC (Laboratory Risk Indicator for Necrotizing Fasciitis) score: a tool for distinguishing necrotizing fasciitis for other soft tissue infections, Crit Care Med 2004 Jul; 32(7): 1535-41
- And other attempts to better protocolize diagnosis for earlier recognition and treatments
- But earlier triumvirate of therapies (other than HBO) are making an impact:
  - *Better resuscitations & critical care*
  - *Better & earlier antibiotics*
  - *Better & more timely surgical debridements*

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An interim critical appraisal conclusion: HBO studies in NSSTI will need to

- Include resuscitation & control or contrast differences in those critical care resuscitations
  - As when deliberate resuscitation protocols are bundled mortality decreases [9]
  - 57% to 37%---see 9. Castellanos-Ortega, A Crit Care Med 2010: 38: 1036 – 1043.
  - But to continue to ratchet down on that mortality –
  - You need bundle in resuscitation guidelines & antibiotics from the SCCM surviving Sepsis Campaign [10] & timely debridements as often stressed in reviews by surgeons [11]

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One of the challenges in GG, NSSTI's

- Many stakeholders are trying to improve care methods
- Many professional societies trying to facilitate the care of these complex patients from the Society of Critical Care Medicine[10] to the Surgical Infection Society to the American College of Surgeons[11], as well as the UHMS just to name a few
- In the Fall of 2019, the Wendi Gordon Shelist Necrotizing Fasciitis Foundation sponsored a speaker who has contributed to the care of these patients, Dr. Addision May to have a session at the Midwest Chapter meeting on HBO and its impact on NSSTI's
- Profession societies can stimulate discussions & build the collaborations necessary for further study needs and goals
- We should continue to try and be inclusive to make progress in HBO

10. Society of Critical Care Medicine (SCCM) and the European Society of Intensive Care Medicine (ESICM) – Surviving Sepsis Campaign: www.sccm.org/SurvivingSepsisCampaign-home
11. ACS Clinical Congress 2015
12. Kumar A, et al. Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock. Crit Care Med. 2006;34(6):1589-96

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One of the challenges is that when an NSSTI goes to sepsis & septic shock

- Timing of interventions becomes more of a factor to be controlled for and tracked
- So even timing of antibiotics is an issue [12]
- 2731 pts with septic shock (56% mortality)
- Time to AB Rx most strongly associated with outcome-- Each 1 hr delay ---could translate into -- a 12% increase in risk of death

12. Kumar A, Roberts D, Wood KE, et al. Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock. Crit Care Med. 2006;34(6):1589-96

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Our colleagues, outside of HBO…

- Will be looking for accounting of, control for, tracking of….
- *Co-morbidities*
- *Timing of dx*
- *Timing and character of resuscitation – note we have some guidelines in Surviving Sepsis Campaign from SCCM*
- *Antibiotic timing and adequacy*
- *And timing of surgery and adequacy*
- *The good news is we are still dealing with a 50% mortality to 10% - to drop the last 10% will need something*
- *And that something still could be HBO*
- *But we must be able to compare apples to apples…*

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Some HBO's efficacy may also be linked to the patient's actual microbiology NSTI: Empiric AB therapy based upon presentation

Is the S&STI not rapidly progressing?

- *We typically train our staff to mark any zones of erythema*
- *How do you know if necrotizing or non necrotizing (less virulent – pus forming) or*
- *Polymicrobial or*
- *MRSA - all effect initial antimicrobial choices*

- **Is the S&STI complex or rapidly progressing?**
- Clinical evidence of toxin production and sepsis?
- Beyond gm pos or neg - are their atypical pathogens, Vibrio? Fungii? Aeromonads? *et al.*
  - **Antibiotic stewardship may offer opportunities for HBO to be focus on better practices AND** synergistically improve - again an opportunity to collaborate with ID, Surgery, & Crit Care Colleagues

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Timing & adequacy of debridement remain confounding issues

- Note we still struggle with how to quantify debridement's adequacy
  - *Digital photos*
  - *Back wall biopsies for vasculature adequacy, bioburden of bacteria*
  - *Enhanced infrared and other technologies*
- Initial debridement within 12 hours has been demonstrated to improve outcomes, mortality, odds ratios of dying [13]
- Coordination with patients' co-morbidities & critical care resuscitation as well [14-19]

13. Gelbard RB J Trauma Acute Care Surg. 2018; 85: 208-214
14. McHenry CR Ann Surg. 1995; 221: 558 -565
15. Bosshardt TL Arch Surg. 1996; 131: 846 – 52
16. Elliott DC Ann Surg 1996; 224: 672 – 83
17. Bilton BD, Am Surg. 1998: 64: 397 – 400
18. Bhilders BJ Am Surg. 2002: 68: 109 – 116
19. Wong CH J Bone Joint Surg 2003; 85!: 1454 - 1460

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And evidence data gets murkier

- And seems dependent upon sources with access to HBO or without access to HBO
- However, even outside of HBO based sources:
- Literature exists for increased oxygen's effects on enhancement of leukocyte pathogen killing, where bacterial growth is suppressed, where antimicrobials have increased efficacy & where toxin production and its effects are suppressed [20, 21]
- It is hard to completely catalog all the HBO effects as improvements in measuring them evolve

- 20. Brummelkamp WH. The importance of administration of oxygen under atmospheric positive pressure in the treatment of gas phlegmon. Ned Tijdschr Geneeskd, 1961;105; 2430 – 2432
- 21. Kaide CG. Hyperbaric Oxygen: applications in infectious disease, Emerg Med Clin North Am. 2008; 26; 571-595

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HBO has

- Evolving basic science evidence for its value in GG and NSSTI
- Previous animal studies for its value as well as basic science

- 22. Demello FJ: Comparitive Study of experimental clostridium perfringens infections in dogs treated with antibiotics, surgery and HBO, Surgery 1973; 73; 936 -941
- 23. Stevens DL: Evaluation of therapy with hyperbaric oxygen for experimental infection with Clostridium perfringens, Clin Infect Dis 1993; 17: 231 – 232.

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HBO may---and HBO sources cite

- HBO may have mechanisms of action harder to quantify or appreciate by those unfamiliar with it [24, 25]
- Oxygen delivery via dissolved, non-Hgb bearing effects of pressure into tissues &
- Its ensuring anti-microbial
- Anti-ischemic, anti-microthombosis, anti-inflammatory effects
- Enhanced micro-circulatory support of marginal tissue

- 24. Bonne SL. *Infect Dis Clin North Am.* 2017; 31:497-511
- 25. Stevens DL. *NEJM*. 2017; 377:2253-2265

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UHMS Indication Manual: HBO Captures many of the Clinical Effects in NSSTI & NF

- Direct anti-pathogenicity on pathogens, less growth, less elaboration of toxins & antibiotic synergistics– for example, certain Clostridia spp are toxogenic and proteolytic contributing to both the local severities of spreading tissue necrosis as well as the systemic septic toxicities leading to mods, sirs, mof & mortalities [26, 27] & direct decreases in alpha and other toxin elaborations [28]
- HBO may helpfully form free O_2 radicals in relative absences of free radical degrading enzymes such as superoxide dismutases, catalases and then a net effect is stopping or limiting alpha-toxin and other toxin elaboration and effects [29]
- High tissue oxygen tensions at 250 mmHg may also be bacteriostatic and achievable at 3.0 ATA …UHMS Manual, 14th Ed. [3]

26. Abella BS, Kuchinic P, Hiraoka T Howes DS. Atraumatic Clostridial myonecrosis: case report and literature review. J. Emer. Med. 2003; 24 (4): 401-405
27. Verherstraeten S, Goossens Evalgaeren B, et al Perfringolysin O: The Underrated Clostridium perfringens Toxin: Toxs (Basel), 2015; 7(5): 1702-1721
28 Aldape MJ, Bryan AE, Steves DL, Clostridium sordellii infections: epidemiology, clinical findings, and current perspectives on diagnosis and treatment. Clin Infect Dis. 2006; 43(11): 1436 -1446
29. Van U Inhibition of Toxin Production in Clostridium Perfringens in Vitro By Hyperbaric Oxygen Antie Van Leeuwenhoek. 1965;31 181-186

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Further catalog of HBO Effects

- Increased host immunity, oxygen related and antimicrobial synergistic effects in killing of pathogens [30]
- Improved balance between harmful excessive inflammation and cellular and tissue recovery and support so that less tissue is lost [31]
- Pro-healing effects from better ischemic-reperfusion responses - including direct dissolved oxygen supporting tissues, even those highly sensitive to perfusion flow, that are otherwise deprived of blood flow,[31] better perfusing flow in & out of tissue beds to improved neo-angiogenesis & re-epithelialization [32]
- Challenge: Levels of Evidence for these & other statements

- 30. Thom, SR, *et al*. Vasculogenic stem cell mobilization and wound recruitment in diabetic patients: increased cell number and intracellular regulatory protein content associated with hyperbaric oxygen therapy Wound Repair Regen. 2011; 19(2): 149 – 161
- 31. Patz A. Oxygen inhalation in retinal arterial occlusion. Am J Opthlalmol. 1955;40: 789-795.
- 32. Hopf HW, *et al*. Hyperoxia and angiogenesis. Wound Repair Regen. 2005; 13(6): 558-564.

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HBO has to grow beyond mixed results

- Pro HBO
  - *Wilkinson D in Arch Surg 2004; 138: 1339 – 1345: 44 patients with lower mortality in HBO treated patients*
  - *Shaw in Surg Infections 2014; 15: 323 – 325: 1583 patients over 14 centers with increased survival in the few centers with HBO*
  - *Meta-analysis in determinant in many clinicians' opinions*
- HBO essentially not worth the effort to add transfer or install
  - *George ME in Surg Infect. 2009;101:21-28*
  - Professional society recommendations
  - For HBO also mixed

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And additional adjuncts may further muddy conclusions

- Newer vaccine & immune modulation trials – not yet shown to influence outcomes – studies on-going
- Better imaging to quantify
  - *Tissue ischemia and tissue resected at debridement*
  - *Selected bacterial bio-burdens*
  - *Also not yet shown to influence outcomes*
- All these may further cloud or refine HBO utility in NSSTI & NF
- Future clinical use and research will need interest from multiple intersection professional societies: UHMS, ACHMD's, SIS, SCCM, ABA, WHS, SHOCK, amongst others
- And on-going collaboration between clinical and research thought leaders

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Critical Appraisal for HBO in NSSTI - Data is Mixed - but sufficiently positive to merit further study & use

- Those utilizing HBO should be as rigorous as possible with this in mind
- Although NSSTI's may be infrequent – the calls for better cooperative studies, if not RCT's and more data, are frequent
- Various professional societies continue to try and work together
- This could be where enhanced EMR use could make a difference between institutions & data registries

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My strongest critical appraisal for HBO in NSST – is that as a fulcrum to leverage ooordinated care

- Ferreira, APP, *et al*. Hyperbaric oxygen therapy as an adjuvant to source control in necrotizing soft tissue infections, Undersea Hyperb Med Nov-Dec 2017;44(6):535 - 542
- Better coordination – through institutions that are now coordinating with HBO - may have more successful execution of all the previous hallmarks of better care & then
- HBO shortens and lessens the septic period with less impact upon patients for complications

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There are opportunities for HBO here

- How can comparative effectiveness academic work be done between institutions with different habits & capabilities to improve evidence-based practices?
- Will a limited data registry or enhanced patient de-identified EMR help us all collaborate & advance?
- Basic science and animal studies for HBO still deserve study to delineate HBO's effects - in some colleagues' minds
- The time is now as we have data justifying use, and yet equipoise

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What might that look like in practice

- Earlier presentations of NSSTI & NF due to public & clinician education – earlier diagnoses & earlier aggressive treatments
- Resuscitation, tissue culture sampling, antibiotics & surgery –
- EMR capture of whether 2, 2.4 or 3 ATA HBO is offered early, later or not at all in nonrandomized retrospective & prospective data registries
- Minimize delays for initial triumvirate treatment (resuscitation, antibiotics & surgery) AND HBO referral in risk stratified patients (age, severity, co-morbidities…)
- Longer timeframes at any level will need to be accounted for in any outcome data analysis

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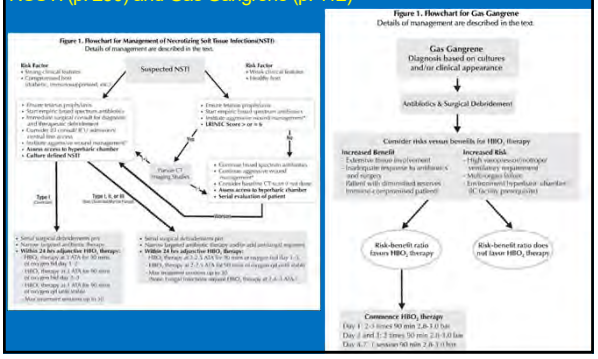
UHMS Indications Manual 14th ED has nice flow decision-diagrams for NSSTI (p. 250) and Gas Gangrene (p. 112)



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Follow markers for clinical quality, costs and overall mortality

NSSTI Multidisciplinary Team with HBO	NSSTI Multidisciplinary Team without HBO
Age – severity - comorbidity match controls	• Age - severity - comorbidity match controls
Higher HBO Tx Pressures: 2.0 to 3.0 ATA	• Fewer intra- and inter hospital transfers so that triumvirate treatment goals reached more smoothly & at lower cost
Tissue preservation for fewer trips to OR, fewer ostomies, fewer amputations & easier reconstructions, fewer plastic surgery consultations, less micro-surgery, earlier staged reconstruction & discharge	• Equally good clinical outcomes at lower costs
Or more complete resolution at discharge	

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Single payer international healthcare delivery systems may advance

- Further, faster as fewer losses to follow up
- May assist with problems in previous studies where the reconstructive phase was included where patients received HBO - elongating initial hospitalization with HBO, but missing the savings to the system as more completely treated at first discharge [32,33]
- Potential for better vertical integration with or without HBO for comparisons not clouded by economically driven access
- Standardization for earlier, better comparisons

- 32. Wilkions D, Doolette D Hyperbaric oxygen treatment and survival from necrotizing soft tissue infections. Arch Sug. 2004; 139: 1339-1345.
- 33. Brown DR *et al.* A multicenter review of the treatment of major truncal necrotizing infections with and without HBO. Am J Surg. 1994; 167; 485-489.

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In the US in the current era – can HBO not just

- Give better value (quality of outcomes/cost)
- But --Lower costs---?
  - *Shorter ICU stays, shorter hospitals stays, earlier discharge & fewer unplanned returns to the OR, or repeated hospital admissions*
  -
- Reconstruction phases will need to be addressed so that if easier to reconstruct & done at the index admission - the reconstructive care times do not contribute to increasing length of stays and overall costs [34]
- Better basic science delineation of these HBO associated claims

- 34. Soh CR, *et al.* Hyperbaric oxygen therapy in necrotizing soft tissue infections: a study of patients in the US Nationwide Inpatient sample. Intensive Care Med. 2012; 38: 1143.

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It remains notable that even

- Articles that do not find a benefit for HBO - see Thrane JF. Scarce evidence of efficacy of hyperbaric oxygen therapy in necrotizing soft tissue infection: a systematic review Infect Dis (Lond). 2019 Jul;51(7): 485 -492
- Are still calling for : **"There is a strong need for randomized controlled trials (RCT's) to shed light on a potential life-saving treatment"**

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And in the contemporary era

- Are we asking the right study or research
  - *In stead of looking for overall mortality differences not adding HBO*
  - *Perhaps we should be looking at other surrogate*
  - *Colostomy rates in Fournier's Gangrene cases with or wit*
  - *Complex reconstruction in men or women?*
  - *If with or without Colostomies associated rates of sacral-coccygeal osteomyelitis rates in Fournier's Gangrene or other wounds that convert over to more active NSSTI's?*
- Enhanced EMR has buried in it: days on a ventilator, time in the ICU, duration of pressors, length and severity of sepsis/septic response MOF/MOI, amputation rates and functional outcomes, earlier or later complex reconstructive surgery, number of trips to the OR, - but that clinical data is still hard to extract for either QI or clinical research purposes

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In short

- Can we transform our use of HBO to
- Focus studies on how to continue to improve care & better comparative effectiveness trials?
- Maintain academic equipoise - rather than trying to "prove" HBO should be used?
- Can we take the best of the decision trees from major societies & accumulate data in the EMR for later study?
- That would allow us to compare and contrast outcomes for better evidence-based medicine - this is where HBO
- Could contribute……

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Summary Critical Appraisal Conclusions

1. On going work is needed to recognize NSSTI's early and capture their severity by established and refined definitions—currently we may underestimate their frequencies in clinical practice
2. Better achievement of early diagnosis, earlier goal directed resuscitation as per the Surviving Sepsis Guidelines, aggressive antibiotic treatment and surgery so that better treatment and better treatment studies can be done
3. This will allow better comparisons and collaborations between
   - *Institutions that have HBO programs and those without—possibly RCT's as well*
   - *Professional Society Stakeholders and Clinician – Researchers can continue their academic rigor and equipoise to study patient centered value-based care with or without HBO*
4. Onus will be on the interested clinicians and thought leaders to get this done in the modern EMR era
5. HBO remains an opportunity to improve outcomes in GG and NSSTI and for study, and could be the fulcrum to really coordinate care between clinicians

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And we have great evolving partnerships to do this - So I wish to THANK

- The Wendi Gordon Shelist Foundation for supporting our work and for sponsoring events like Dr. May's presentation and discussion session at the UHMS Midwest Chapter, Milwaukee, 2019
- To the UHMS for updating their guidelines and facilitating discussions
- Increased interest by the SIS, SCCM and the UHMS in studying GG and NF and NSSTI - and increased commercial interests as well
- And to Dick Clarke's efforts like this Critical Appraisal Series as well!

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THANK YOU

To my section partners who continue to support our work and day to day take care of our patients with GG and NSSTI

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