

Emergency Medicine – Foot Ulcer

A 45 y/o male with a PMHx of HIV/AIDS (CD4 <17), and uncontrolled T2DM presents with complaints of left ankle ulcer. The patient admits that he has not taken his HIV medication in months and states that he is homeless, without insurance and is unable to care for the wound himself. He states that the wound has been ongoing for the past 6 months. On exam the wound appears to be a stage 2 ulcer and has increased to double its original size with new granulation tissue present. The patient was eventually admitted because of the complexity of his situation (lack of access to care, lack of insurance, chronic wound, uncontrolled HIV/AIDS infection etc.)

Clinical Question: Is Hyperbaric oxygen therapy effective (and as add on therapy) for treating chronic ulcers in immunocompromised patients?

PICO search terms:

P	I	C	O
Immunocompromised patients with ulcers	Hyperbaric Oxygen therapy	Standard wound care	Improved wound healing
Patients with HIV and ulcers			Shortened duration of wound healing
Patients with T2DM and ulcers			

SEARCH TOOLS & LIMITS

Database	Filter	Terms Searched	Articles Returned
PubMed	1. English, Clinical Trials/ Meta-analysis/ RCT/ Systematic review 2. English, 2017-2022 Clinical Trials/ Meta-analysis/ RCT/ Systematic review	“Hyperbaric oxygen secondary ulcer” “Hyperbaric oxygen secondary ulcer”	<ul style="list-style-type: none">• 10• 5

PMC/NCBI	1. Open access/ 10 years 2. Open access/ 5 years	“Is hyperbaric oxygen beneficial for foot ulcer” “Hyperbaric oxygen secondary ulcer”	<ul style="list-style-type: none"> • 268 • 457
Cochrane library	1. Title, abstract, Keyword/ English 2014-2022	“Is hyperbaric oxygen beneficial for foot ulcer”	<ul style="list-style-type: none"> • Cochrane (0) • Reviews (0) • Trials (2)
Wiley Online Library	1. Open access 2. 2014-2022	“Is hyperbaric oxygen beneficial for foot ulcer”	<ul style="list-style-type: none"> • 28

My clinical question for this study was general because I wanted to try to increase the range of results I would retrieve during my research on this topic. Although the patient in question suffers from a chronic foot ulcer which is also due to the patients immunodeficient status (uncontrolled HIV and T2DM), I chose to use broader search terms that simply explored the effectiveness of hyperbaric oxygen therapy for treating ulcers. I chose to use the 4 databases above for my search because they have been good resources and have tools that make it easier to narrow down my search results even further. I found a fairly good number of results during my search and skimmed through these article titles and abstracts. I eventually selected the following 4 articles below for my PICO as they relate to my clinical question in different ways. Most of the articles were from PubMed and Wiley library. I chose to use articles that were systematic review, meta-analyses and RCT as they would provide more reliable evidence for my research.

Article 1: The effectiveness of hyperbaric oxygen therapy for healing chronic venous leg ulcers: A randomized, double-blind, placebo-controlled trial

Citation: Thistlethwaite KR, Finlayson KJ, Cooper PD, et al. The effectiveness of hyperbaric oxygen therapy for healing chronic venous leg ulcers: A randomized, double-blind, placebo-controlled trial. <i>Wound Repair Regen.</i> 2018;26(4):324-331. doi:10.1111/wrr.12657
Type of Study: A randomized, double-blind, placebo-controlled trial
<p>Abstract</p> <p>Over 30% of venous leg ulcers do not heal despite evidence-based treatment. This study aimed to determine the effectiveness of Hyperbaric Oxygen Therapy (HBOT) as an adjunct treatment for nonhealing venous leg ulcers. A randomized, double-blind, parallel group, placebo-controlled trial was undertaken in three hyperbaric medicine units. Adults with a venous leg ulcer, Transcutaneous Oxygen Measurement indicative of a hypoxic wound responsive to oxygen challenge, and without contraindications for HBOT; were eligible. Of 84 eligible patients, 10 refused and 74 enrolled. 43 participants achieved over 50% ulcer Percent Area Reduction (PAR) after four weeks of evidence-based care and were thus excluded from the</p>

intervention phase. Thirty-one participants were randomized to either 30 HBOT treatments (100% oxygen at 2.4 atmospheres absolute (ATA) for 80 minutes), or 30 “placebo” treatments, receiving a validated “sham” air protocol, initially pressurized to 1.2ATA, then cycled between 1.05–1.2ATA for eight minutes before settling at 1.05ATA. The primary outcome was numbers in each group completely healed. Secondary outcomes were ulcer PAR, pain and quality of life, 12 weeks after commencing interventions. The participants’ mean age was 70 years (standard deviation (SD) 12.9) and median ulcer duration at enrolment was 62 weeks (range 4–3120). At 12 weeks, there was no significant difference between groups in the numbers completely healed. The HBOT intervention group had a mean of 95 (SD 6.53) ulcer PAR, compared to 54 (SD 67.8) mean PAR for the placebo group ($t = -2.24$, $p = 0.042$, mean difference -40.8 , SE 18.2) at 12 weeks. HBOT may improve refractory healing in venous leg ulcers, however patient selection is important. In this study, HBOT as an adjunct treatment for nonhealing patients returned indolent ulcers to a healing trajectory.

Reason for Selection: I chose this article because it is RCT and focuses also on non-healing leg ulcers and the use of HBOT as an add on therapy. It is also a recent study and could provide more recent data.

Key points:

- This is a RCT consisting of 74 original participants (limitation- small sample size). Patients were included if the ulcer was proven to be of venous etiology.
- The mean duration of the ulcers was 48 weeks.
- Participants spent as much as 120 mins/day in a hyperbaric oxygen chamber and spent a treatment time of 80 mins of oxygen at 2.4 ATA, plus compression and decompression time. This was done as 30 treatments (5 days/ week for 6 weeks) or until the ulcer was healed.
- Participants who were randomized to the HBOT group received compression for 6-8 mins following the treatment, and 100% oxygen was delivered for two 40-minute periods at 2.4 ATA with a 5-minute break on air after the first period and a 30 min decompression period. Those randomized to the placebo group received air that was initially pressurized to 1.2 ATA and then the pressure was cycled up and down between 1.05 ATA to 1.2 ATA for 8 mins and then settling at 1.05 ATA.
- Primary outcome was percent of participants completely healed within each group at the end of the study at 12 weeks. Secondary outcomes were percent area reduction (PAR) of the ulcer, pain, and quality of life 12 weeks after treatment
- The HBOT group had a mean of 95 (SD 6.53) ulcer PAR, while it was 54 (SD 67.8) mean PAR for the placebo group ($t = -2.24$, $p = 0.042$, mean difference -40.8 , SE 18.2) at 12 weeks.
- The HBOT group had a significant reduction of ulcer PAR from enrollment period down to the end of the study with mean PAR of 95 and a mean of 54 in the placebo group. In terms of secondary outcomes pain scores reduced for both groups during the study
- Ultimately HBOT had positive healing outcomes for patients with non-healing ulcers.

PDF Link: <https://onlinelibrary-wiley-com.york.ezproxy.cuny.edu/doi/pdfdirect/10.1111/wrr.12657>

Article 2: The Role of hyperbaric oxygen Therapy in orthopedics and Rheumatological Diseases

Citation: Barilaro, Francesco Masala, I., Parracchini, R., Iesu, C., Caddia, G., Sarzi-Puttini, P., & Atzeni, F. (2017). The Role of Hyperbaric Oxygen Therapy in Orthopedics and Rheumatological Diseases. The Israel Medical Association Journal, 19(7), 429–434.

Type of Study: Review

Hyperbaric oxygen therapy (HBOT) has been investigated as a primary/adjunctive treatment for a number of injuries and medical conditions including traumatic ischemia, necrotizing soft tissue injuries, non-healing ulcers and osteoradionecrosis, but the results are controversial. There is insufficient evidence to support or reject the use of HBOT to quicken healing or to treat the established non-union of fractures. However, in patients with fibromyalgia, HBOT reduces brain activity in the posterior cortex and increases it in the frontal, cingulate, medial temporal and cerebellar cortices, thus leading to beneficial changes in brain areas that are known to function abnormally. Moreover, the amelioration of pain induced by HBOT significantly decreases the consumption of analgesic medications. In addition, HBOT has anti-inflammatory and oxygenatory effects in patients with primary or secondary vasculitis. This review analyzes the efficacy and limitations of HBOT in orthopedic and rheumatologic patients

Reason for article: I chose this article because it also explores the use of HBOT in treating different rheumatological conditions and discusses non-healing skin ulcers.

Key Points:

- HBOT may improve clinical outcomes like acute and chronic pain.
- HBOT also has anti-inflammatory effects
- In a study referenced under secondary and primary vasculitis (Efrati and Co-authors) involving 35 patients, the baseline treatment protocol consists of administration of 100% ATA a pressure of 2 ATA for 90 mins times 5 times a week for 4 weeks. After HBOT treatment 80% of patients (28 patients) showed complete healing. 4 patients had partial healing, and 3 showed no response without side effects from the HBOT treatment.
- Note that this article is the least beneficial of the four choices as it only briefly discusses the use of HBOT in treating non-healing skin ulcers based on findings from other studies.

Pdf link: <https://www.ima.org.il/FilesUploadPublic/IMAJ/0/247/123626.pdf>

Article 3: Systematic review and meta-analysis of clinical trials examining the effect of hyperbaric oxygen therapy in people with diabetes-related lower limb ulcers

Citation: Golledge J, Singh TP. Systematic review and meta-analysis of clinical trials examining the effect of hyperbaric oxygen therapy in people with diabetes-related lower limb ulcers. *Diabet Med.* 2019;36(7):813-826. doi:10.1111/dme.13975

Type of Study: A Systematic review and Meta-analysis

Abstract:

Aim To examine the efficacy of hyperbaric oxygen therapy in healing diabetes-related lower limb ulcers through a meta-analysis of randomized clinical trials.

Methods A literature search was conducted to identify appropriate clinical trials. Inclusion required randomized study design and reporting of the proportion of diabetes-related lower limb ulcers that healed. A meta-analysis was performed to examine the effect of hyperbaric oxygen therapy on ulcer healing. The secondary outcomes were minor and major amputations.

Results Nine randomized trials involving 585 participants were included. People allocated to hyperbaric oxygen therapy were more likely to have complete ulcer healing (relative risk 1.95, 95% CI 1.51–2.52; $P < 0.001$), and less likely to require major (relative risk 0.54, 95% CI 0.36–0.81; $P = 0.003$) or minor (relative risk 0.68, 95% CI 0.48–0.98; $P = 0.040$) amputations than control groups. Sensitivity analyses suggested the findings were dependent on the inclusion of one trial. Adverse events included ear barotrauma and a seizure. Many of the trials were noted to have methodological weaknesses including absence of blinding of outcome assessors, lack of a justifiable sample size calculation and limited follow-up.

Conclusions This meta-analysis suggests hyperbaric oxygen therapy improves the healing of diabetes-related lower limb ulcers and reduces the requirement for amputation. Confidence in these results is limited by significant design weaknesses of previous trials and inconsistent findings. A more rigorous assessment of the efficacy of hyperbaric the efficacy of hyperbaric oxygen therapy is needed.

Reason for Selection:

I chose this article because it is a recent article and a systematic review/ meta-analysis which would provide a higher level of evidence. It also draws data from different databases and includes RCTs only. The study also tries to obtain up to date data on the topic studied and addresses the variability seen with different studies about the effectiveness of HBOT in treating non-healing ulcers.

Key Points:

- This study includes only 9 RCTs involving 585 participants.
- The control group was treated with either sessions of sham HBOT in which participants were administered air only or were provided with standard care (dressings, revascularization, control of hyperglycemia etc.) only.

- The HBOT regimen included delivery of 100% oxygen at ~2.5 ATA in sessions that lasted up to 90 mins
- The primary outcome for this study was the percentage of participants that had complete healing of their lower limb ulcer.
- Secondary outcomes included minor and major amputations (% of patients), time to ulcer complete healing, quality of life was also assessed.
- Findings showed 2 studies reported that patients in the HBOT group had significant improvement in the percentage of completely healed ulcers. The main findings of the study overall showed that HBOT improved the healing of diabetes related lower limb ulcers and reduced the risk of major amputations however there is only moderate confidence in this finding as there were some methodological flaws of some of the RCTs.
- There were lower rates of amputation in the HBOT groups compared to the control groups.
- Side effects of the HBOT reported included ear barotrauma and one seizure case.

PDF link: <https://onlinelibrary-wiley-com.york.ezproxy.cuny.edu/doi/pdf/10.1111/dme.13975>

Article 4: Adjuvant Hyperbaric Oxygen Therapy Enhances Healing of Nonischemic Diabetic Foot Ulcers Compared with Standard Wound Care Alone

Citation: Salama SE, Eldeeb AE, Elbarbary AH, Abdelghany SE. Adjuvant Hyperbaric Oxygen Therapy Enhances Healing of Nonischemic Diabetic Foot Ulcers Compared With Standard Wound Care Alone. *Int J Low Extrem Wounds*. 2019;18(1):75-80. doi:10.1177/1534734619829939

Type of Study: Prospective Study

Abstract:

Recent systematic reviews and meta-analyses have produced conflicting results about the efficacy of hyperbaric oxygen therapy (HBOT) in improving the healing rate for chronic diabetic foot wounds. This study aimed to assess the efficacy of systemic HBOT in healing of chronic nonischemic diabetic foot ulcer. Thirty adult patients having Wagner's grade 2 or 3 chronic diabetic foot ulcers, in whom the response to 30 days of standard wound care was not favorable, were prospectively randomized to have either HBOT (20-40 sessions) plus conventional treatment (n = 15) or conventional treatment alone (n = 15). Ischemic wounds and patients with contraindications to systemic HBOT were excluded. The primary end point was complete healing of the target ulcer. Secondary endpoints included the following: rate of ulcer healing at the end of treatment period and at 4 and 8 weeks thereafter as well as rate of amputation. A significantly greater percentage of HBOT-treated wounds (33.3%, 5/15)

achieved complete closure than conventional therapy-treated wounds (0%, 0/15; P = .014) at the end of treatment. This significant difference was maintained throughout the 8 weeks of follow-up. Complication's frequency was non-significantly different between both groups. Our study showed that HBOT plus conventional therapy appears as safe as and probably more effective than conventional therapy alone for the healing of chronic nonischemic diabetic foot wounds. Larger studies are required to confirm its specific indications.

Reason for Selection:

I chose this article because it is a recent prospective study and compares HBOT to standard wound care for chronic diabetic ulcers.

Key Points:

- This study includes 15 patients randomized to receive HBOT and 15 randomized to receive 2 months of conventional treatment only. (Limitation -small sample size)
- The HBOT protocol involved patients receiving one daily session for 5 days a week with 2 days off which results in a total of 20-40 sessions. The session starts with a gradual increase in treatment pressure up to 2.5 ATA over 10-15 mins in a 100% oxygen environment. The treatment period at pressure lasts for 1 hour followed by gradual decompression over another 10-15 mins.
- The conventional treatment involved initial surgical debridement (of the stage 2/3 ulcers) and antibiotic application based on a culture and sensitivity. Topical moist saline dressing w/ antiseptic was also used.
- The primary outcome for this study was complete healing of the target ulcer.
- Secondary outcomes included the rate of ulcer healing by weeks 4 and 8, and the rate of amputation.
- The study showed that an addition of HBOT to conventional therapy had more significant rate of ulcer size reduction and complete healing compared to conventional therapy alone.
- They also concluded that there was positive correlation between the number of HBOT sessions and the rate of ulcer healing based on the findings from the study.
- There were no major amputations in both groups but one minor amputation of toes in one case from each group.

PDF link: <https://journals.sagepub.com/doi/pdf/10.1177/1534734619829939>

Article 5: Efficacy of hyperbaric oxygen therapy for diabetic foot ulcer, a Systematic review and Meta-analysis of controlled clinical trials

Citation: Sharma, Sharma, S. K., Mudgal, S. K., Jelly, P., & Thakur, K. (2021). Efficacy of hyperbaric oxygen therapy for diabetic foot ulcer, a systematic review and meta-analysis of

controlled clinical trials. *Scientific Reports*, 11(1), 2189–2189. <https://doi.org/10.1038/s41598-021-81886-1>

Type of Study: Systematic Review and Meta-analysis

Abstract:

Studies have suggested that hyperbaric oxygen therapy (HBOT) is effective in the healing of diabetic foot ulcer (DFU); however, there is a lack of consensus. Therefore, to assess the efficacy of HBOT on diabetic foot ulcer among diabetic patients, controlled clinical trials were searched through PubMed, EMBASE, Clinical key, Ovid Discovery, ERMED, Clinical Trials.gov databases for randomized controlled trials (RCTs) and other sources until 15 September 2020. Studies that evaluated the effect of HBOT on diabetic foot ulcer, complete healing, amputation, adverse events, ulcer reduction area, and mortality rate were included. Of 1984 study records screened, 14 studies (768 participants) including twelve RCTs, and two CCTs were included as per inclusion criteria. The results with pooled analysis have shown that HBOT was significantly effective in complete healing of diabetic foot ulcer (OR = 0.29; 95% CI 0.14–0.61; I₂ = 62%) and reduction of major amputation (RR = 0.60; 95% CI 0.39–0.92; I₂ = 24%). Although, it was not effective for minor amputations (RR = 0.82; 95% CI 0.34–1.97; I₂ = 79%); however, less adverse events were reported in standard treatment group (RR = 1.68; 95% CI 1.07–2.65; I₂ = 0%). Nevertheless, reduction in mean percentage of ulcer area and mortality rate did not differ in HBOT and control groups. This review provides an evidence that hyperbaric oxygen therapy is effective as an adjunct treatment measure for the diabetes foot ulcers. These findings could be generalized cautiously by considering methodological flaws within all studies.

Reason for Selection:

I chose this article because it is a systematic review and meta-analysis which are higher levels of evidence and provide data on the efficacy of hyperbaric oxygen as an adjunct treatment in the management of diabetic foot ulcers. It is also a fairly new study which helps to provide more up to date data on the topic.

Key Points:

- The Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines were used for this study.
- 14 controlled trials/studies (12 RCT and 2 controlled trials) were included which involved a total of 768 participants with 384 in HBOT and 384 in standard therapy
- The HBOT exposure time for most studies was a total of 90 minutes, 120 in two studies and 45-85 mins in 4 studies.

- 11 trials reported ulcers that were completely healed. 4 studies reported complete healing by 12 months and 7 reported below 12 months. The number of completely healed ulcers following HBOT was higher than standard therapy.
- Outcomes explored in the trials include, complete healing, amputation rate, mortality, reduction in ulcer size, adverse events,
- Patients treated with HBOT had a lower rate of major amputation (below the knee or above the ankle) compared to those treated with standard therapy. There was however no difference in amputation rates with minor amputations. There was a reduction in ulcer size.
- The number of adverse events (e.g., oxygen toxicity, ocular effects, **barotrauma**, ear injury, cataracts etc. was higher in patients treated with HBOT compared to standard therapy.

PDF

link: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7838311/pdf/41598_2021_Article_81886.pdf

Article 6: Hyperbaric oxygen therapy for nonischemic diabetic ulcers: A systematic review

Citation: Lalieu, Brouwer, R. J., Ubbink, D. T., Hoencamp, R., Bol Raap, R., & van Hulst, R. A. (2020). Hyperbaric oxygen therapy for nonischemic diabetic ulcers: A systematic review. *Wound Repair and Regeneration*, 28(2), 266–275. <https://doi.org/10.1111/wrr.12776>

Type of Study: Systematic Review

Abstract:

Diabetic foot ulcers are a common complication of diabetes, which affects 25% of patients and may ultimately lead to amputation of affected limbs. Research suggests hyperbaric oxygen therapy improves healing of these ulcers. However, this has not been reflected in previous reviews, possibly because they did not differentiate between patients with and without peripheral arterial occlusive disease. Therefore, we performed a systematic review of published literature in the MEDLINE, Embase, and Cochrane CENTRAL databases on nonischemic diabetic foot ulcers with outcome measures including complete ulcer healing, amputation rate (major and minor), and mortality. Seven studies were included, of which two were randomized clinical trials. Two studies found no difference in major amputation rate, whereas one large retrospective study found 2% more major amputations in the hyperbaric oxygen group. However, this study did not correct for baseline differences. Two studies showed no significant difference in minor amputation rate. Five studies reporting on complete wound healing showed no significant differences. In conclusion, the current evidence suggests

that hyperbaric oxygen therapy does not accelerate wound healing and does not prevent major or minor amputations in patients with a diabetic foot ulcer without peripheral arterial occlusive disease. Based on the available evidence, routine clinical use of this therapy cannot be recommended. However, the available research for this specific subgroup of patients is scarce, and physicians should counsel patients on expected risks and benefits. Additional research, focusing especially on patient selection criteria, is needed to better identify patients that might profit from this therapy modality.

Reason for Selection:

I chose this article because it is a systematic review and another higher-level evidence that can provide data on the efficacy of hyperbaric oxygen as an adjunct treatment in the management of non-ischemic diabetic foot ulcers. It is also a new study with more likely to have up to date data on the topic.

Key Points:

- The Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines were used for this study.
- The overall study showed that there was not faster wound healing with HBOT and there is no protection against major or minor association,
- Patients undergoing HBOT treatment may undergo the risk of adverse effects.

PDF link: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7079107/pdf/WRR-28-266.pdf>

Author (Date)	Level of Evidence	Sample/Setting (# of subjects/ studies, cohort definition etc.)	Outcome(s) studied	Key Findings	Limitations and Biases
1. Thistle Thwaite, KR, Finlayson KJ (2018)	Randomized, double-blind, placebo-controlled trial	<p>1. 74 participants included in the study of which only 64 completed the standard care phase) (9 changed their mind and withdrew from the study, 3 were hospitalized and lost to follow up and one was withdrawn late after it was realized they did not meet inclusion criteria</p> <p>2. The timeline was broken into the standard care phase (week 1-4) where patients were given evidence-based treatment and the healing process was assessed weekly. Patients who did not have at least 50% PAR (Percent area reduction) were randomized to HBOT or placebo group (Intervention phase weeks 5-10). Lastly there was the follow up phase where patients were followed for 6 weeks after the intervention phase.</p> <p>3. Participants spent as much as 120 mins/day in a hyperbaric oxygen chamber and spent a treatment time of 80 mins of oxygen at 2.4 ATA, plus compression and decompression time. This was done as 30</p>	<p>1. The primary outcome of the study was the proportion of each group that was healed at the conclusion of the study.</p> <p>2. The secondary outcome was ulcer PAR and pressure ulcer scale for healing (PUSH) scores.</p>	<p>1. Ulcer healing: Using ITT principles there was no difference between groups in participants healed at 12 weeks with 40% of placebo and 39% of HBOT groups healed.</p> <p>2. Reduction in ulcer area: In the HBOT group there was significantly greater ulcer PAR from the start of enrollment to the end of the study. Mean PAR was 95 (SD 6.53) in comparison to placebo (mean of 54, SD 67.8), $t = -2.24$, $p = 0.045$.</p> <p>3. Pain and QoL: Pain scores were reduced in both groups from a mean of 50.2 (SD 24.4) to 35.9 (sd 23.4) for the placebo group and from 48.6 (SD 16.9) to 26.4 (SD 18.4) for the HBOT</p>	<p>1. Small number of participants reducing the power for statistical analysis and randomization of confounding factors.</p> <p>2. There was also inadequate follow up time.</p>

		<p>treatments (5 days/ week for 6 weeks) or until the ulcer was healed.</p> <p>4. Participants who were randomized to the HBOT group received compression for 6-8 mins following the treatment, and 100% oxygen was delivered for two 40-minute periods at 2.4 ATA with a 5-minute break on air after the first period and a 30 min decompression period. Those randomized to the placebo group received air that was initially pressurized to 1.2 ATA and then the pressure was cycled up and down between 1.05 ATA to 1.2 ATA for 8 mins and then settling at 1.05 ATA.</p>		<p>group although change was not statistically significant</p> <p>4. Adverse effects: There were 12 serious adverse events that occurred during the intervention but 10 were unrelated to the study. There were however 2 otic barotrauma episodes related to the intervention occurred.</p>	
2. Barilaro, Francesco Masala, I., Parracchini, R. et. al (2017)	Review	<p>1. A search was conducted on MEDLINE database (PubMed, National library of Medicine, Bethesda, md USA) and used a combination of search terms like “hyperbaric oxygen therapy”, “ulcers, vasculitis”, “fractures”, “rheumatological disease”, “pain” and “fibromyalgia”. Search included</p>	<p>1. The goal of the review is to analyze the efficacy and limitations of HBOT in orthopedic and rheumatologic patients.</p>	<p>1. They note 2 RCTs that showed that HBOT improves arterial flow and local skin reperfusion. It also increases the rate of complete healing and reduces the need for further surgery in comparison</p>	<p>1. A major limitation of this article is that it is not an actual study but rather a general review but not as in depth as that of a systematic review. Therefore, it only contributes very limited data on the effectiveness of HBOT and may provide a biased opinion.</p>

		studies from 1990-2016.		to standard treatment. 2. HBOT has showed promising results in relieving pain in conditions such as chronic headache, fibromyalgia etc. 3. They discuss that although HBOT has been used as an additional treatment to antibiotics, debridement in chronic non-healing ulcer it is still unclear the effectiveness of HBOT.	
3. Golledge J, Singh TP. (2019)	Systematic Review & Meta-Analysis	<p>1. The systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-analysis protocols. This study includes only 9 RCTs involving 585 participants</p> <p>2. The control group was treated with either sessions of sham HBOT in which participants were administered air only or were provided with standard care (dressings, revascularization,</p>	<p>1. The primary outcome for this study was the percentage of participants that had complete healing of their lower limb ulcer.</p> <p>2. Secondary outcomes included minor (amputation below the ankle) and major amputations (amputation above the ankle) % of patients, time to ulcer complete healing, quality of</p>	<p>1. Findings showed 2 studies reported that patients in the HBOT group had significant improvement in the percentage of completely healed ulcers. The main findings of the study overall showed that HBOT improved the healing of</p>	<p>1. Some of the studies included in the review had methodological weaknesses (e.g., absence of a reported blinded outcomes assessment in 5 of the trials) which included the absence of blinding, limited follow-up, lack of sample size.</p> <p>2. The included trials were all small (120 participants or less)</p>

control of hyperglycemia etc.) only.
3. The HBOT regimen included delivery of 100% oxygen at ~2.5 ATA in sessions that lasted up to 90 mins

life was also assessed.

diabetes related lower limb ulcers and **reduced the risk of major amputations** however there is only moderate confidence in this finding as there were some methodological flaws of some of the RCTs.

2. There were lower rates of amputation in the HBOT groups compared to the control groups.

3. Side effects of the HBOT reported included ear barotrauma and one seizure case.

Author (Date)	Level of Evidence	Sample/Setting (# of subjects/ studies, cohort definition etc.)	Outcome(s) studied	Key Findings	Limitations and Biases
4. Salama SE, Eldeeb AE et al. (2019)	Prospective Study	<p>1. This study includes 15 patients randomized to receive HBOT and 15 randomized to receive 2 months of conventional treatment only. (Limitation - small sample size)</p> <p>2. The HBOT protocol involved patients receiving one daily session for 5 days a week with 2 days off which results in a total of 20-40 sessions. The session starts with a gradual increase in treatment pressure up to 2.5 ATA over 10-15 mins in a 100% oxygen environment. The treatment period at pressure lasts for 1 hour followed by gradual decompression over another 10-15 mins.</p> <p>3. The HBOT protocol involved patients receiving one daily session for 5 days a week with 2 days off which results in a total of 20-40 sessions. The session starts with a gradual increase in treatment pressure up to 2.5 ATA over 10-15 mins in a 100% oxygen environment. The treatment period at pressure lasts for 1 hour followed by gradual decompression over another 10-15 mins.</p>	<p>1. The primary outcome for this study was complete healing of the target ulcer.</p> <p>2. Secondary outcomes included the rate of ulcer healing by weeks 4 and 8, and the rate of amputation.</p>	<p>1. The study showed that an addition of HBOT to conventional therapy had more significant rate of ulcer size reduction and complete healing compared to conventional therapy alone.</p> <p>2. They also concluded that there was positive correlation between the number of HBOT sessions and the rate of ulcer healing based on the findings from the study.</p> <p>3. There were no major amputations in both groups but one minor amputation of toes in one case from each group</p>	<p>1. Small number of participants reducing the power for statistical analysis and randomization.</p>

	<p>4. The conventional treatment involved initial surgical debridement (of the stage 2/3 ulcers) and antibiotic application based on a culture and sensitivity. Topical moist saline dressing w/ antiseptic was also used.</p>		
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Author (Date)	Level of Evidence	Sample/Setting (# of subjects/ studies, cohort definition etc.)	Outcome(s) studied	Key Findings	Limitations and Biases
5. Rakesh, S, Suresh S, et. al (2021)	Systematic Review and Meta-analysis	<p>1. The Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines were used for this study. PubMed, EMBASE, Clinical key, Ovid Discovery, ERMED, Clinical Trials.gov database and other sources were used to conduct the data search.</p> <p>2. The goal of this study is to assess the efficacy of systematic HBOT in healing of chronic non-ischemic diabetic foot ulcer.</p> <p>3. Controlled clinical trials were searched through PubMed, EMBASE, Clinical key, Ovid Discovery, ERMED, Clinical Trials.gov databases for randomized controlled trials (RCTs) and other sources until 15 September 2020.</p> <p>4. 14 controlled trials/studies (12 RCT and 2 controlled trials) were included which involved a total of 768 participants with 384 in HBOT and 384 in standard therapy</p> <p>5. The HBOT exposure time for most studies was a total of 90 minutes, 120 in two studies and 45-85 mins in 4 studies.</p>	1. The primary outcomes of the study include, complete healing, amputation rate, mortality, reduction in ulcer size, adverse events,	<p>1. Patients treated with HBOT had a lower rate of major amputation (below the knee or above the ankle) compared to those treated with standard therapy. There was however no difference in amputation rates with minor amputations. There was a no difference noted in the reduction in ulcer size between the standard and HBOT groups.</p> <p>2. 11 trails reported ulcers that were completed healed (644-HBOT =321, and ST= 323). 4 studies reported complete healing by 12 months and 7 reported below 12 months. The number of completely</p>	<p>1. Of 14 trials only 6 performed sample size calculation</p> <p>2. Observation times and techniques used for the HBOT group were not uniform for most studies.</p>

				<p>healed ulcers following HBOT was higher than standard therapy.</p> <p>3. The number of adverse events (e.g., oxygen toxicity, ocular effects, barotrauma, ear injury, cataracts etc. was higher in patients treated with HBOT compared to standard therapy.</p> <p>4. There was a higher rate of mortality reported with the standard group compared to the HBOT group, but this was seen in only 3 trials that explored mortality rate.</p>	
6. Laliou, Brouwer, R. J., Ubbink, D. T.S, et. al (2020).	Systematic Review	1. The Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines were used for this	1. The primary outcomes of the study include complete healing, amputation rate, and mortality.	1. The studies showed no difference in amputation rate and 5 studies	1. There was limited amount of data/ literature on non-ischemic diabetic ulcers.

		<p>study. MEDLINE, Embase, and Cochrane CENTRAL are the databases that were used to explore the published literature from inception to 2018.</p> <p>2. 7 studies were included of which (2 are RCTs, 2 prospective studies, and 2 retrospective studies) including a total of 6,438 participants.</p> <p>3. HBOT protocols varied between 60-120 mins. Pressure was between 2.0 and 2.5 ATA, for three to 6 days a week</p>		<p>reporting on complete wound healing showed no significant difference between the study groups.</p>	<p>2. The small size and number of RCTs and non-randomized studies.</p>
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Summary of the Evidence

Article 1 (2018): Is a **double blind RCT** which is a higher level of evidence and explores the effectiveness of **HBOT in treating chronic venous leg ulcers**. The study is a recent one and includes a small number of participants (75). During the standard care phase of the study participants were provided standard care for foot ulcers which include pressure relief, glycemic control, antibiotics etc. Patients without complete ulcer healing were then randomized to the HBOT or the placebo group and followed afterward. The overall evidence from this study shows that there was **no difference in ulcer healing between the HBOT and Placebo groups at 12 weeks**, however there was much more **significant reduction in ulcer area in the HBOT group** compared to the placebo group. In both groups there was reported reduction in pain, but it was not statistically significant.

Article 2 (2017): This article is a **review** of the role and effectiveness of HBOT in orthopedic and rheumatologic disease. Although brief, there is a discussion of the role of HBOT in treating diabetic foot ulcer. This review discusses the mechanism by which HBOT works which includes improved arterial blood flow and local skin reperfusion and improve the rate of complete healing and reduce the need for surgery following standard care. It has also been noted to be beneficial with pain relief in some other conditions as well.

Article 3 (2019): Is a systematic review and Meta-analysis which is one of the highest levels of evidence. Of all the articles included in my CAT, this review has the second most numbers of participants. This review consists of only RCTs which are also a higher level of evidence, and explores the benefits and effectiveness of HBOT as an adjunct for treating diabetic lower limb ulcerations. The findings from the review and meta-analysis show that participants in the **HBOT group have significant improvement in the percentage of completely healed ulcers** compared to those given standard treatment of sham HBOT. HBOT was also noted to be associated with **decreased risk of major amputation**.

Article 4 (2019): This study is a prospective study which is a weaker source of evidence. It studies the role of HBOT as an adjuvant treatment for diabetic non-ischemic ulcers in comparison to standard care. The study showed that **the addition of HBOT to standard care improved the rate of ulcer size reduction and complete healing** compared to standard care alone. There was no occurrence of major amputation but there were cases of minor amputation in both groups.

Article 5 (2021): This is another systematic review and meta-analysis which is a higher level of evidence. It is a recent article and is more likely to have up to date data from the literature on HBOT and diabetic foot ulcers. This study also contains the most number of participants which may contribute to the power of the study. The findings from this study show that participants receiving **HBOT had a significant decrease in the number of major amputations**. There was however no difference in the rate of minor amputations. The findings also showed no difference in the reduction in ulcer size between both groups. It was noted however that the **number of completely healed ulcers following HBOT was greater** than with standard therapy. Lastly there were more adverse effects seen with HBOT compared to standard therapy.

Article 6 (2020): This is a **systematic review and** focuses on the use of hyperbaric oxygen therapy in treating chronic diabetic ulcers. The findings of this study showed **no difference in the amputation rate in both groups and no significant difference in complete wound healing** with treatment with HBOT.

Conclusion:

Based on the findings from the studies/literature that were used for my PICO/ CAT, it seems the evidence is somewhat inconclusive on the effectiveness of HBOT as an adjunct for treating chronic diabetic ulcers. Although there are many articles that advocate for the use of HBOT in treating chronic ulcers, it appears that the response to treatment varies between individuals. The differences in findings from the studies may be in part due to a lack of uniform protocols between the RCTS, and clinical studies. Some studies are more reliable than others which can affect the reliability of the overall findings and make it difficult to draw a final conclusion.

PICO Question: Is Hyperbaric oxygen therapy effective (and as add on therapy) for treating chronic ulcers in immunocompromised patients?

Clinical bottom line

HBOT has been seen to show promise in wound healing and in the case of the patient discussed in this scenario my pico was based on curiosity about the effectiveness of hyperbaric oxygen therapy as an adjunct in treating chronic ulcers (wounds). The patient in this case presentation is quite immunocompromised which can alter their ability to heal following a wound. This patient has been in and out of the hospital following standard wound care, however, the wound has persisted for months causing much discomfort to the patient as he is unable to fully care for the wound alone. The presence of ulcers such as that experienced by the patient in this case scenario can cause discomfort and a decrease in quality of life for those affected especially when chronic. In a worst-case scenario, the ulcer may progress and reach the point of requiring amputation. The patient was eventually admitted and since the patient is in need of more attention and care I was curious about whether an adjunct therapy with HBOT may be beneficial to the healing process for this patient.

There has been conflicting evidence on the effectiveness of HBOT treatment with some studies arguing that it is beneficial while few reports no difference following HBOT. The articles included in my CAT for the most part advocate that HBOT may be effective in treating chronic wounds/ ulcers in patients such as those with venous insufficiency, or immune deficiency as in the case of patients with diabetes. The studies show that HBOT alone may be beneficial for a reduction in wound size, increasing, the rate of healing and potentially reducing the time taken for full recovery. HBOT is believed to have several physiological effects beneficial for healing including promoting angiogenesis, and leukocyte activity, reduction in edema and increased collagen deposition. HBOT added on to conventional therapy may be more effective than conventional therapy alone particularly when conventional therapy alone has not been quite effective. With this knowledge I would advocate for a trial of HBOT as an adjunct for treating this patient's foot ulcer.

However, I would keep in mind that there are some adverse effects that may be associated with HBOT which include short term pressure damage to the ears, sinuses, and lungs such as a pneumothorax. A limitation to its use can also be claustrophobia during therapy. Oxygen poisoning may also occur acutely after a neurological event. It may also not be recommended for pregnant patients. HBOT is also a quite expensive procedure so the benefits and risk of its use should be weighed. Contraindications to the use of HBOT should also be considered as well as the cost-effectiveness of the therapy.

Weight of Evidence:

Article 5 > Article 3 > Article 6 > Article 1 > Article 2 > Article 4

Based on the hierarchy/ strength of evidence I think Article 5 would be the highest level of evidence as it is a systematic review / meta-analysis and is the most recent study amongst the list of literature. In addition, it also includes more studies (12 RCT and 2 controlled trials) in comparison article 3. Article 3 is also a recent systematic review and meta-analysis and would also be high on the hierarchy of evidence. I believe article 3 provides more reliable evidence than article 6 as it also contains a meta-analysis and has a larger sample size than Article 6 which is a

systematic review. Article 1 is a double blind RCT which on the hierarchy of evidence is superior to a prospective study (article 2) and general review (article 4).

Magnitude of Effects:

Article 1: Thistle Thwaite, KR, Finlayson KJ (2018)

Ulcer healing: Undertaking a PP analysis of the proportion of participants in each group healed at 12 weeks, 36% (5/14) of the placebo group, and 46% (5/11) of the HBOT group fully healed (I² 0.24, p = 0.62), relative risk 0.85 (95% CI 0.44–1.65). **Reduction in Ulcer area:** The HBOT group had a significantly greater ulcer PAR from enrolment to the end of the study, with a mean PAR of 95 (SD 6.53), compared to the placebo group mean of 54 (SD 67.8), t = 12.24, p = 0.045, mean difference 40.3, SE 18.2. **Ulcer severity:** On a scale from 0 – 17, where 0 = completely healed, and 17 = worst possible score; the placebo group went from a mean of 12.46 (SD 2.22) to 7.62 (SD 5.53) at the end of the study, and the HBOT group from a mean of 12.17 (SD 2.02) to 3.38 (SD 4.09). **Pain and QoL:** Pain scores reduced for both groups over the study, from a mean of 50.2 (SD 24.4) to 35.9 (SD 23.4) for the placebo group; and from 48.6 (SD 16.9) to 26.4 (SD 18.4) for the HBOT group, although the change was not statistically significant (two-way ANOVA within group change F = 4.55, p = 0.059; between groups effect F = 0.22, p = 0.53).

Article 2: Barilaro, Francesco Masala, I., Parracchini, R. et. al (2017): N/A

Article 3: Golledge J, Singh TP. (2019)

Analysis suggested that HBOT approximately doubled the likelihood of an ulcer healing (RR 1.95, 95% CI 1.51–2.52; P<0.001), and approximately halved the risk of major amputation (RR 0.54, 95% CI 0.36–0.81; P=0.003) and reduced the likelihood of minor (RR 0.68, 95% 0.48–0.98; P=0.040) amputation.

Article 4: Salama SE, Eldeeb AE et al. (2019)

At the end of all HBOT sessions and 2 months of conventional treatment, the median ulcer surface area was significantly reduced in the HBOT group but not in the control group. The median pretreatment ulcer surface area in the HBOT group was 7.5 cm², with a range of 1.5 to 15.5 cm², which was reduced to 2 cm², with a range of 0 to 4.5 cm², P= .0001*, at the end of treatment period. In the control group, the median pretreatment ulcer surface area was 8 cm², with a range of 2 to 16.5 cm², which was reduced to 7.5 cm², with a range of 1.8 to 10.5 cm², P= .126. On bivariate analysis, it was found that a significantly higher wound healing rate was associated with more HBOT sessions completed (r= 0.888, P= .0001, 95% confidence interval= 0.6904-0.9626).

Article 5: Rakesh, S, Suresh S, et. al (2021)

Complete ulcer healing: The number of complete healed ulcer after HBO therapy (148/321) were significantly higher compared to standard treatment (75/323) (OR = 0.29, 95% CI 0.14–0.61; I² = 62%; p < 0.001. **Major amputation:** pooled effect size from the fixed-effect model shows DFUs patients treated with HBOT had a significant lower major amputation rate as compared to ST and the difference was statistically significant as shown after analysis (HBOT 27/232 vs. ST 46/231; RR=0.60; 95% CI 0.39–0.92; I² = 24%; p = 0.02) **Minor amputations:** Pooled result by a random effect model demonstrated that there was no significant difference in the numbers of minor amputations between HBOT and ST group. (RR=0.82; 95% CI 0.34–1.97;

I² = 79%; p = 0.66.). **Adverse events:** After pooled proportion of result, it was reported that RR was 1.68 (95% CI: 1.07–2.65; I² = 0%; p = 0.02) which was statistically significant. **Mortality rate:** Pooled data results by the fixed effect model showed that there was no significant difference (p = 0.15) in HBOT and ST group in mortality rate (RR = 0.55; 95% CI 0.25–1.24; I² = 0%). **Reduction in ulcer area (%):** Forest plot reveals that pooled data from the completion of therapy found no significant differences (p=0.18) in the percentage mean reduction ulcer size of patients in HBOT and ST group (Mean Difference (Md) = 11.61; 95% CI – 5.36 to 28.58; I² = 72%).

Article 6: Laliou, Brouwer, R. J., Ubbink, D. T.S, et. al (2020): N/A

Clinical Significance

Diabetic foot ulcers are ulcers present in the lower limbs of patients with diabetes and are often associated with neuropathy and or peripheral arterial disease. These ulcers when infected can become non-healing and can lead to amputations, mortality, and a reduction in quality of life for those affected. Some of the standard treatment modalities that are available are surgical debridement of the ulcer, pressure relief, antibiotics, and glucose control. With chronic wounds affected tissues may become hypoxic which can hinder healing and cause pain and discomfort for patients. There may be a clinical role in the use of HBOT as an adjunct to promote wound healing in diabetic foot ulcers and it may be beneficial in non-healing wounds that have proven difficult to manage with standard therapy alone. With standardized and efficient study protocols it may be possible to determine if HBOT can play more of an important role as an adjunct for treating diabetic foot ulcers.

Other considerations important in weighing this evidence to guide practice

I think it would be important consider that although the data is inconclusive on the effectiveness of HBOT as an adjunct in treating chronic ulcers, there are studies that have shown benefit in some individuals. There are few side effects that have been mentioned in the studies above such as otic barotrauma, oxygen toxicity, ear injury, cataracts etc. but they are not very common. With HBOT being a fairly safe treatment option with low risks for severe adverse effects there could be benefit in providing trials of HBOT to patients that have been unable to be effectively managed on standard therapy alone.