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Systematic review: the safety and efficacy of hyperbaric oxygen therapy for inflammatory bowel disease

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SUMMARY

Background
Hyperbaric oxygen therapy (HBOT) provides 100% oxygen under pressure, which increases tissue oxygen levels, relieves hypoxia and alters inflammatory pathways. Although there is experience using HBOT in Crohn's disease and ulcerative colitis, the safety and overall efficacy of HBOT in inflammatory bowel disease (IBD) is unknown.

Aim
To quantify the safety and efficacy of HBOT for Crohn's disease (CD) and ulcerative colitis (UC). The rate of adverse events with HBOT for IBD was compared to the expected rate of adverse events with HBOT.

Methods
MEDLINE, EMBASE, Cochrane Collaboration and Web of Knowledge were systematically searched using the PRISMA standards for systematic reviews. Seventeen studies involving 613 patients (286 CD, 327 UC) were included.

Results
The overall response rate was 86% (85% CD, 88% UC). The overall response rate for perineal CD was 88% (18/40 complete healing, 17/40 partial healing). Of the 40 UC patients with endoscopic follow-up reported, the overall response rate to HBOT was 100%. During the 8924 treatments, there were a total of nine adverse events, six of which were serious. The rate of adverse events with HBOT in IBD is lower than that seen when utilising HBOT for other indications ($P < 0.01$). The risk of bias across studies was high.

Conclusions
Hyperbaric oxygen therapy is a relatively safe and potentially efficacious treatment option for IBD patients. To understand the true benefit of HBOT in IBD, well-controlled, blinded, randomised trials are needed for both Crohn's disease and ulcerative colitis.

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INTRODUCTION

The inflammatory bowel diseases (IBD), Crohn's disease and ulcerative colitis, are chronic relapsing illnesses characterised by recurrent inflammation of the gastrointestinal tract, bloody diarrhoea, abdominal pain and constitutional symptoms such as fever and weight loss. Although there has been great progress in the treatment of IBD over the past decade, even with anti-tumour necrosis factor (TNF) agents there is still significant room for improvement.[1–5] Furthermore, corticosteroids have significant long-term consequences and the steroid sparing immunomodulators, and anti-TNF agents have been associated with serious adverse events including life-threatening infections and lymphomas.[6–9]

Hyperbaric oxygen therapy (HBOT) involves breathing 100% oxygen under pressure. This increases plasma and tissue oxygen levels, which relieves hypoxia, and increases the oxygen content of blood reaching inflamed bowel or chronic nonhealing fistulas. HBOT has also been shown to alter signalling pathways involved in the tissue response to hypoxia and wound repair, notably Hypoxia Inducible Factor (HIF) and heme-oxygenase (HO) pathways.[10–13] More directly, HBOT suppresses the production of pro-inflammatory cytokines and chemokines (IL-1, IL-6, TNF-α) responsible for the metabolic stress created during active inflammation.[14–20] These pathways and inflammatory cytokines contribute significantly to the local microenvironmental cues responsible for IBD activity, and there is great interest in targeting these pathways for therapy in IBD.[21–23]

Several authors have advocated for the use of HBOT as an adjunct to standard medical therapy in patients with refractory IBD. The majority of data supporting the use of HBOT for IBD, however, comes from small case series or from IBD cohorts undergoing therapy for non-enteric symptoms. To better understand the overall impact of HBOT on Crohn's disease and ulcerative colitis, we performed a systematic review of the literature to quantify the safety and efficacy of HBOT for IBD.

METHODS

Search strategy

The following databases were searched on 12/10/2013: MEDLINE (PubMed, 1946 to 12/2013); Cochrane Library (Wiley, 2013 issue 1); Web of Knowledge (Web of Science, 1900 to 12/2013); Embase (Embase.com, 1947 to 12/2013). The search included indexed terms and text words to capture the concepts of: *inflammatory bowel disease* and *hyperbaric oxygen*. There were no language or study design restrictions. The search strategy was adjusted for the syntax appropriate for each database. The reference lists of included papers and review articles were examined for additional relevant studies. The full search strategy is available at the international prospective register of systematic reviews PROSPERO (#CRD42013006099).

Study selection and data extraction

Published articles or meeting abstracts were included for analysis if they met the following criteria: the study design was a randomised controlled trial, case–control study, cohort study, case series or case report; the treatment included hyperbaric oxygen for Crohn's disease or ulcerative colitis; the outcomes and follow-up were clearly reported. Review articles were excluded and studies were excluded if the primary indication for HBOT was not IBD. Studies with insufficient data for outcomes and/or follow-up were excluded only after attempting to contact the primary author(s). The reviewer (P.S.D) attempted to contact the primary author(s) as required to obtain any necessary missing data from the original publications. No language restrictions were applied and publications were translated into English as required. Two reviewers (P.S.D and D.T) independently evaluated each of the articles for eligibility. Inclusion decisions for each paper were made independently based on the eligibility criteria with disagreements being resolved by a third reviewer (C.A.S) and consensus. The reviewers followed the PRISMA standards for systematic review.

Data were abstracted by D.T. using a pre-designed data abstraction tool and were verified by P.S.D. This electronic data collection form (Excel; Microsoft, Redmond, WA, USA) included study design, patient demographics (age, gender), disease characteristics (duration, extent and severity of involvement, endoscopic findings, fistula characteristics), treatment history, hyperbaric oxygen protocol (depth, duration, frequency, number of sessions), follow-up and adverse events. Two reviewers (P.S.D and D.T) independently evaluated the reported endoscopic findings from each study and categorised disease activity according to the Crohn's Disease Endoscopic Index of Severity (CDEIS) or the Mayo endoscopic sub-score for ulcerative colitis. We followed the American Gastroenterological Association (AGA) classification of fistulas and categorised fistulas as simple or complex.[24, 25]

Risk of bias assessment

Risk of bias was assessed independently by two reviewers (P.S.D and D.T), with disagreements being resolved by a

third reviewer (C.A.S) and consensus. Risk of bias was assessed as described in the Cochrane handbook and the AHRQ methods guide for comparative effectiveness research. Given the inherit risk of bias in case reports, these studies were excluded from this analysis. Case-series/cohort studies, case–controls and randomised control trials were assessed for: selection bias (method of selection, control for confounders, matching of controls, randomisation and sequence generation, allocation concealment), performance bias (types of co-interventions or additional interventions, balancing of interventions between cases and controls, blinding of providers and patients deciding additional interventions), detection bias (definition and method of outcome assessment, blinding of outcome assessors, reliability of outcome measure), attrition bias (completeness of outcome and follow-up data), reporting bias (selective reporting of outcomes) and other potential biases. Review Manager version 5.0.23 (RevMan for Windows 2008; the Nordic Cochrane Center, Copenhagen, Denmark) was used to generate risk of bias graphs and summaries.

Outcomes and analysis

Pooled summary estimates and sensitivity analyses. Our primary outcome of interest was to quantify the rate of response to therapy. Patients were considered responsive if they had objective radiological or endoscopic evidence of improving disease control, were documented to have a significant reduction in disease activity indexes, or were noted to be clinically responsive by the primary author (s). Given the subjectivity in physician-reported response to therapy, sensitivity analyses were performed including only studies reporting endoscopic follow-up of disease activity. Our secondary outcome of interest was to quantify the rate of serious and nonserious adverse events with HBOT in IBD. These rates were calculated based on the total number of events occurring during total hyperbaric sessions. Adverse events were categorised as serious if they were categorised as serious by the original investigator(s) or resulted in discontinuation of therapy, hospitalisation or death.

Comparison of adverse events to prior data and the general population. We further aimed to compare the rate of adverse events with HBOT for IBD to the expected rate of adverse events with HBOT and to those seen when using HBOT for another gastrointestinal indication, radiation proctitis. The expected rate of adverse events with HBOT was derived from a large prospective single centre observational cohort of 782 patients undergoing a total of 11 376 HBOT sessions for various indications.[26] The rate of adverse events with HBOT for radiation proctitis was derived from a prospective randomised double-blind crossover trial enrolling 120 patients with radiation proctitis who received a total of 3600 HBOT sessions.[27] Relative rates for adverse events were calculated as incidence rate ratios (IRR), using the STATA 'IR' command (STATA 10.0; College Station, TX, USA).

RESULTS

Study and patient characteristics

The initial search strategy yielded 313 publications. Of those, 271 were excluded after reviewing titles and abstracts. Subsequently, 42 papers were retrieved in full text of which 17 studies were included in our final analysis.[28–44] (Figure 1) Eleven were case reports (<5 patients),[28–38] three were case series (≥5 patients) or cohort studies,[39–41] two were case–control studies[42, 43] and one was a randomised controlled trial.[44]

These studies reported on a total of 327 ulcerative colitis patients and 286 Crohn's disease patients. Forty ulcerative colitis patients had endoscopic disease activity reported prior to undergoing HBOT and based on the Mayo endoscopic sub-score, flares were categorised as: mild (n = 10), moderate (n = 19) or severe (n = 11). Forty-four Crohn's disease patients had disease extent reported, of which 40 (91%) had perineal disease for a median of 2 years prior to initiating HBOT. Twenty-one (48%) patients had fistulas with the majority of fistulas (91%) being categorised as complex. Fistulas were entero-cutaneous (n = 8), vaginal (n = 7), perianal (n = 3), intersphinteric (n = 2) and entero-enteric (n = 1) in location. Baseline disease activity indices or endoscopic severity was infrequently reported for Crohn's disease patients. The majority of IBD patients had failed 5-ASA, steroids and immunomodulator therapy prior to initiating HBOT (Tables 1 and 2).

Hyperbaric oxygen efficacy

The 613 patients underwent a total of 8924 HBOT treatments with protocols varying across studies. (Tables 1 and 2) The overall response rate to HBOT for patients with IBD was 86%. When only including studies reporting endoscopic follow-up of disease activity, the overall response rate to HBOT for ulcerative colitis patients was 100%. HBOT was attempted in one ulcerative colitis patient for toxic megacolon to avoid surgery. After 27 sessions, the patients' toxic megacolon resolved and he was eventually discharged home with out-patient

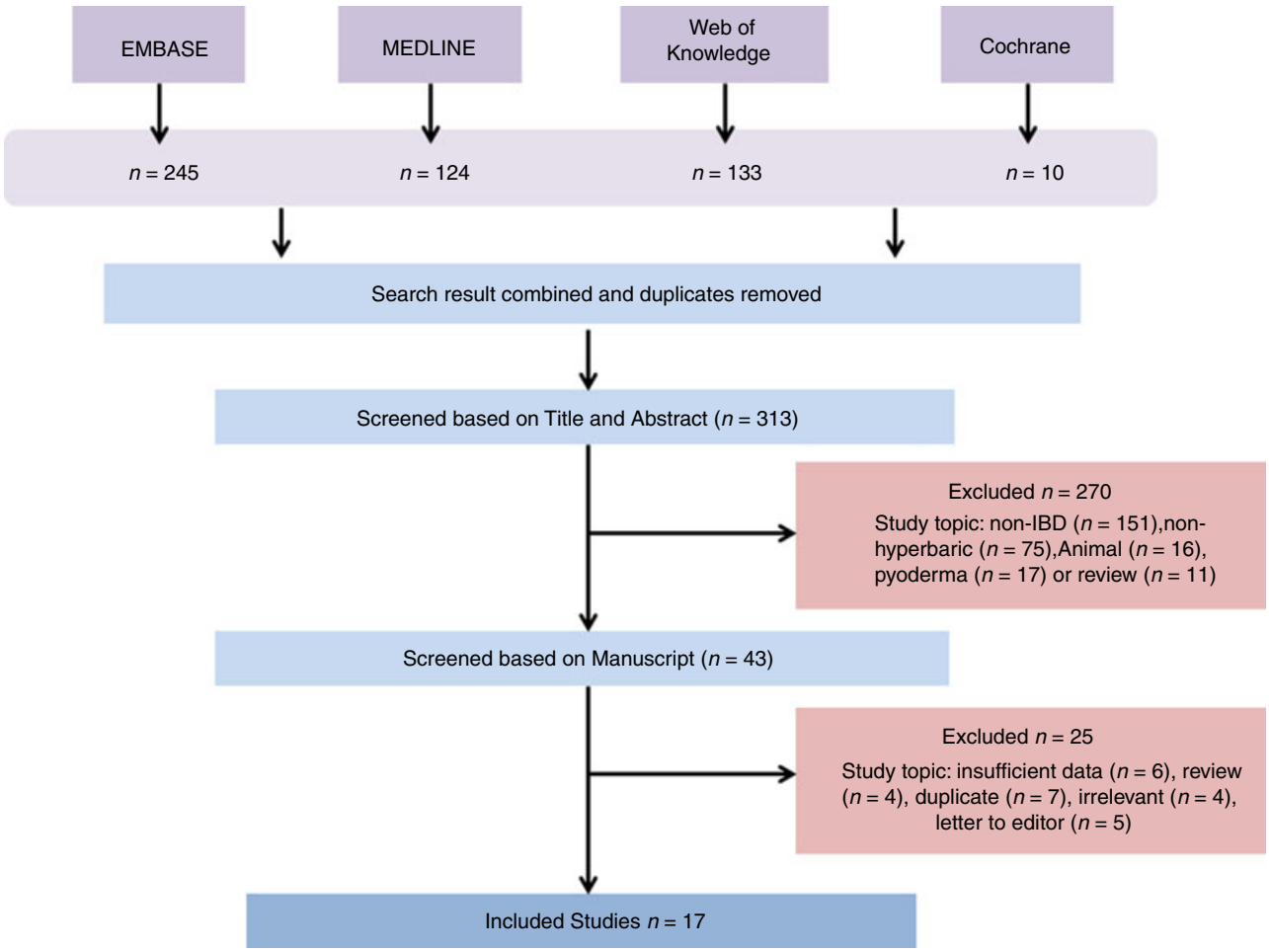

Figure 1 | Flow diagram of the studies identified in search, and reasons for study exclusion.

follow-up.[37] Endoscopic follow-up of disease activity was infrequently reported for Crohn's disease patients and therefore a meaningful sensitivity analysis could not be performed for this group. Of the 42 patients with perineal and/or fistulising Crohn's disease, 18 (43%) had complete healing of lesions and 17 (41%) were noted to have partial healing at the end of therapy. Five patients (12%) were unresponsive to therapy and two discontinued therapy prior to a response due to adverse events (see below).[40]

We identified a single randomised controlled trial investigating the impact of HBOT in IBD. This study enrolled hospitalised UC patients suffering from severe (Mayo score >10) flares. Participants were randomised to standard medical therapy alone (IV steroids, oral mesalazine, suppository prednisolone, enema prednisolone) or standard medical therapy in combination with HBOT (90 min/session, 2.4 ATA, 5 days/week, 6 consecutive weeks). The primary outcomes were change in Mayo score, laboratory studies and faecal weight at study day 180. Secondary outcomes included prevention of colectomy, impact on health-related quality of life and overall safety. Only four patients received a complete course of HBOT. The median full Mayo score declined more in the HBOT group (control group = 11 points pre-treatment to 3 points post-treatment, HBOT group = 11 points pre-treatment to 0.5 points post-treatment), but this difference was not statistically significant. There were no differences in faecal calprotectin, health-related quality of life, or other study parameters.[44]

Risk of bias analysis

After excluding case reports from the risk of bias analysis, six studies were evaluated for risk of bias across five parameters. The overall risk of bias was high with attrition bias and reporting bias being the highest. (Figures 2 and 3) The studies by Grigoreva *et al.*[43] (277 CD, 242 UC) and Karkumov *et al.*[42] (34 UC) accounted for the

Table 1 | Hyperbaric oxygen for ulcerative colitis

Author, year	Patients	Severity and Location	Previous Treatment	HBOT protocol†	HBOT Sessions	Response	Response Criteria	Comments
Grigoreva*, 2011	277	Not reported	5-ASA, antibiotics, steroids, IM	Induction: 1.7 ATA for 40 min; Consecutive for 12 sessions Maintenance: 1.7 ATA for 40 min; once yearly	12–32 based on follow-up duration (up to 20 years)	238/277	Symptoms, Endoscopic	Improved response compared to a control group (nonrandomised and no control data presented)
Karkumov*, 1994	34	Mild (n = 10) Moderate (n = 19) Severe (n = 5)	n/a	2.4 ATA for 120 min; Consecutive treatments	12	34/34	Symptoms, Labs, Endoscopic	Ulcerations completely healed, ESR normalised, reduced hospital stay by 8–10 days vs. control (control data not presented)
Pagoldh, 2013	10	Severe pancolitis (n = 8), Severe left sided (n = 2)	n/a	2.4 ATA for 90 min; 5 days/ week	30	2/10	Full Mayo score, Labs, PMSS, HRQoL	Randomised Open-Label Control trial; no improvement when compared to controls; only negative study to date
Demirturk, 2002	2	Severe Pancolitis	5-ASA, steroids, TPN, IM	2.0 ATA for 120 min; Consecutive treatments	30	2/2	Truelove-Witts, Endoscopic	
Gurbuz, 2003	1	Severe Descending colon	5-ASA, steroids, IM	2.0 ATA for 120 min; Consecutive treatments	30	1/1	Symptoms, Truelove-Witts, Endoscopic	Clinical remission; continued endoscopic activity
Buchman, 2001	1	Severe Rectosigmoid	5-ASA, steroids, IM	2.0 ATA for 120 min; 5 days/ week	30	1/1	Truelove-Witts, Endoscopic	
Kuroki, 1998	1	Toxic Megacolon	Steroids, antibiotics	2.0 ATA for 60 min; Consecutive treatments	27 based on clinical response	1/1	Symptoms, Imaging, Endoscopic	Avoided colectomy
Bouali*, 1990	1	Severe Pancolitis	5-ASA, steroids, antibiotics, TPN	2.5 ATA for 90 min; consecutive for 12 sessions	12	1/1	Symptoms, Truelove-Witts, Endoscopic	Surgery sparing, weaned off steroids

HBOT, hyperbaric oxygen therapy; ATA, atmospheric pressure; 5-ASA, 5-aminosalicylic acid; TPN, total parentral nutrition; IM, immunomodulators (Azathioprine, mercaptopurine, Methotrexate); min, minutes; PMSS, patient medical safety score: this score is a nonvalidated scoring system created by the authors to assess clinical deterioration between the two groups; HRQoL, health-related quality of life, n/a, data not available.

* Study translated.

† All hyperbaric oxygen therapies used 100% oxygen.

majority of patients included in our analysis, and both studies carried a high or uncertain risk of bias across all five parameters. This was due to the lack of published data within these studies, missing data on control patients used for comparison, unclear study design, poorly described research methods and inadequate description of outcomes. Given the large degree of uncertainty in risk of bias for these studies, we attempted to contact the

Table 2 | Hyperbaric oxygen for Crohn's disease

Author, year	Patients	Disease extent	Previous Treatment	HBOT protocol†	HBOT Sessions	Response	Response Criteria	Comments
Grigoreva*, 2011	242	Not reported	5-ASA, antibiotics, steroids, IM	Induction: 1.7 ATA for 40 min; Consecutive for 12 sessions Maintenance: 1.7 ATA for 40 min; once yearly	12–32 based on follow-up duration (up to 20 years)	208/242	Symptoms, Colonoscopy, Biopsies	Improved response compared to a control group (nonrandomised and no control data presented)
Iezzi, 2011	14	Entero-cutaneous fistula (n = 6), Perineal (n = 10), pyoderma gang. (n = 2)	Unknown	2.4 ATA for 120 min; Consecutive treatments	10–50 based on clinical response	11/14	Symptoms	
Colombel, 1995	10	Colorectal (n = 7) Ileocolonic (n = 2) Small bowel only (n = 1) Perineal (n = 10)	5-ASA (n = 6), antibiotics (n = 6), TPN (n = 4), IM (n = 5), surgery (n = 10)	2.5 ATA for 120 min; 5 days per week	40	6/10	Cardiff Classification and Global assessment	Two patients intolerant and two unresponsive to therapy
Lavy, 1994	10	Perineal disease	5-ASA, antibiotics, steroids, IM	2.5 ATA for 90 min; 6 days per week	20–60 based on clinical response	8/10	Perineal healing, Symptoms	
Di Girolamo, 2013	4	Ileocolonic, perineal, penis	Anti-TNF-α	1.9–2.5 ATA for 90 min; twice daily for 10 days followed by daily for 10 days then 2–3 per year maintenance	33	4/4	Symptoms	
Green, 2013	2	Ileitis, perianal	5-ASA, antibiotics, steroids, IM	2.4 ATA for 90 min; consecutive treatments	20	2/2	MRI, Symptoms	
Takeshima, 1999	1	Colon, rectum	5-ASA, steroids, TPN	2.8 ATA for 120 min	20	1/1	CDAI, Endoscopic, Symptoms	
Sipahi, 1996	1	Colon, oral, vaginal, perianal	Antibiotics, TPN, steroids	2.4 ATA for 90 min; 7 days/week for 14 days followed by 3 days/week for 3 months	60	1/1	Fistula healing, Symptoms	
Nelson, 1990	1	Colon, perineal, inguinal	5-ASA, antibiotics, steroids, IM, surgery	Stage I: 2 ATA for 120 min; 18 in-patient sessions (perioperative) Stage IIa: 2.8 ATA for 90 min; 30 out-patient sessions Stage IIb: 2.0 ATA for 120 min; 12 in-patient sessions (perioperative) Stage III: 2 ATA for 120 min; 14 in-patient sessions (perioperative)	74	1/1	Perineal healing, Symptoms	
Brady, 1989	1	Descending colon, perirectal, perianal, pelvis, abdominal wall	5-ASA, antibiotics, steroids, TPN, IM, Surgery	2.4 ATA for 120 min; 6 days per week	67 based on clinical response	1/1	Symptoms	Four recurrences re-treated with HBOT

HBOT, hyperbaric oxygen therapy; ATA, atmospheric pressure; 5-ASA, 5-aminosalicylic acid; TPN, total parentral nutrition; IM, immunomodulators (azathioprine, mercaptopurine, methotrexate), Anti-TNF-α, anti-tumour necrosis factor alpha inhibitor; min, minutes.

* Study translated.

† All hyperbaric oxygen therapies used 100% oxygen.

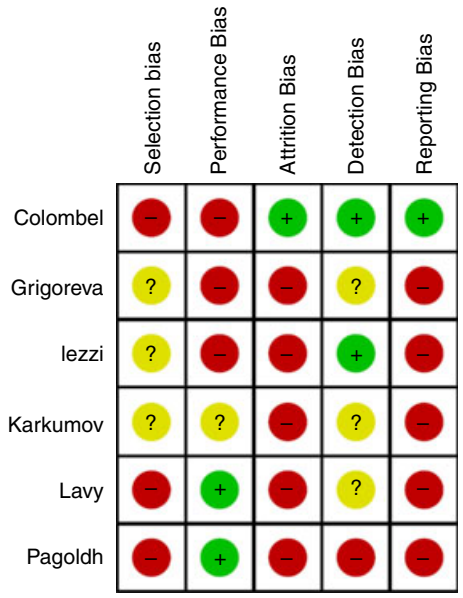

Figure 2 | Risk of bias for included studies across five domains. The red circles indicate a high risk of bias within that domain for a given study, the yellow circles indicate an unclear risk of bias and the green circle indicates a low risk of bias.

authors but were unsuccessful. Of the three remaining CD studies, the study by Colombel *et al.*[40] carried the lowest risk of bias. This study, however, had a high risk of performance bias due to the concomitant use of other treatments, including surgery.

The one remaining UC study by Pagoldh *et al.*[44] carried the highest risk of bias among included studies. Although this study had a randomised, open-label controlled trial design; the study lacked blinding and allocation concealment. Key baseline characteristics of the control and treatment groups were not provided. Much of the study outcome data were not reported, the sample size was very low (only four patients completed the HBOT protocol). These factors, and the early study termination despite inadequate power, give the study a high risk of bias, which significantly limits the conclusions that can be drawn from the results.

Hyperbaric oxygen safety

Nine adverse events occurred during the 8924 HBOT treatments equating to an incidence of 10/10 000 treatments. Six patients suffered serious adverse events necessitating discontinuation of therapy (6.7/10 000 treatments). One patient required discontinuation of therapy due to bilateral ear drum perforations within the first few treatments (1.1/10 000 treatments) and another patient discontinued therapy due to difficulty equalising middle ear pressures (1.1/10 000 treatments), but this patient had no reported damage to the tympanic membrane or middle ear. The rate of middle ear barotrauma with HBOT in IBD patients (1.1/10 000 treatments) is significantly lower than the expected rate with HBOT for radiation proctitis (22/10 000 sessions; IRR: 0.05, $P < 0.001$, 95% CI 0.001–0.38), and when HBOT is used for other indications (29/10 000 sessions; IRR: 0.04, $P < 0.001$, 95% CI 0.001–0.23).

Six patients suffered from psychological intolerance (6.7/10 000 treatments), four of which had to discontinue therapy due to intolerance (4.5/10 000 treatments). Two discontinued therapy within the first few treatments and the remaining two stopped therapy after 33 and 36 sessions. These two patients had demonstrated complete healing of perineal lesions prior to discontinuation. The rate of psychological intolerance with HBOT for IBD is similar to that seen with radiation proctitis (5.6/10 000

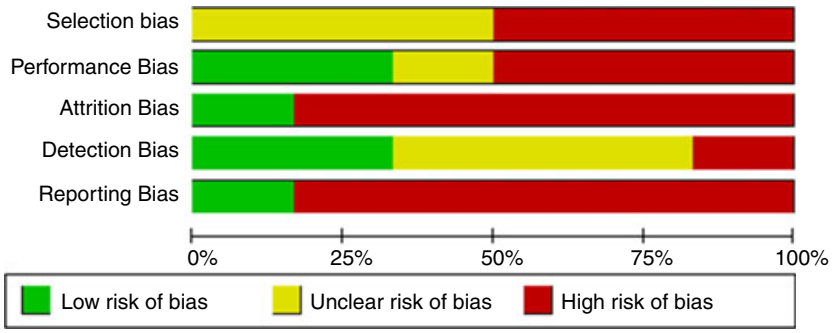

Figure 3 | Summary risk of bias across five domains. The risk of bias across the five domains (*y*-axis) was aggregated between studies to achieve an overall risk of bias. The *x*-axis represents the percentage of studies according to the risk of bias within a given domain. The red bar indicates a high risk of bias, the yellow bar indicates an unclear risk of bias and the green bar indicates a low risk of bias.

treatments; IRR: 1.2, $P = 0.87$, 95% CI 0.22–12.3) but significantly lower than the expected rate when used for other indications (30/10 000 treatments; IRR: 0.23, $P < 0.001$, 95% CI 0.08–0.54).

One patient developed temporary blurred vision during prolonged therapy >60 sessions (1.1/10 000 treatments).[36] This resolved without intervention and she successfully underwent another 55 sessions during the following year. The risk of myopia and vision changes increases with the number of HBOT sessions administered. Given the variability in HBOT protocols among studies included in our analysis, and short-term use of HBOT for the majority of IBD patients, we are unable to accurately compare the rate of vision changes with HBOT in IBD to those expected with the use of HBOT for other indications which typically require prolonged therapy. There were no reported episodes of pneumothorax, seizure, bowel perforation or other serious adverse events.

DISCUSSION

The management of IBD has made great advances over the past decade with the advent of biologics. Although these agents are effective in Crohn's disease and ulcerative colitis, many patients remain unresponsive to therapy or require frequent treatment adjustments. Furthermore, the initiation of these agents is often met with hesitancy from patients and providers due to concerns surrounding their safety profile and long-term risks. With growing evidence that the pathogenesis of IBD is multi-factorial and involves a complex interaction of genetic and environmental factors, newer treatment modalities are needed that optimise patient outcomes while minimising treatment-related risks. Our pooled analysis demonstrates that hyperbaric oxygen therapy is a safe and well-tolerated treatment option for both Crohn's disease and ulcerative colitis. It may be a potentially efficacious treatment option for patients suffering from refractory perineal and/or fistulising Crohn's disease and moderate to severe ulcerative colitis flares.

Pathogenesis of IBD

The destructive inflammatory response in IBD takes place at the interface of intestinal epithelia with the bowel contents, along a steep oxygen gradient from the oxygen-rich arterial blood supplying the mucosa to the anaerobic lumen of the gut. It is at this boundary where the immune system is actively protecting the body from both pathogenic and commensal organisms of the gut microbial community while at the same time attempting to maintain tolerance to self. Emerging research is revealing the interplay between tissue hypoxia, epithelial integrity and innate and adaptive immune cell function.[23, 45, 46] Investigations into the role of oxidative stress in IBD, stimulated by the long-puzzling observation that cigarette smoking is protective in ulcerative colitis, led to the observation that oxidative stress response genes heme-oxygenase-1 (HO-1) and hypoxia inducible factors (HIFs) are upregulated by carbon monoxide exposure or tissue hypoxia and both play a protective role in animal models of IBD.[20, 47] HO-1 appears to potentiate monocyte clearance of bacteria, while HIF-1α enhances epithelial integrity and may quiet the immune response via induction of regulatory T-cells.[13, 47]

Potential mechanism of action for HBOT in IBD

Hyperbaric oxygen therapy (HBOT) involves breathing 100% oxygen under increased atmospheric pressure; typically twice to three times standard sea level pressure (2.0–3.0 ATA). This dramatically increases the amount of oxygen dissolved in blood plasma which in turn helps to promote wound healing by increasing oxygen delivery to hypoxic tissues. The immediate hypoxia-reducing effect of hyperbaric oxygen only persists while the patient is in the hyperbaric chamber and for a short time thereafter. The high levels of oxygen, however, also produce a variety of biochemical effects that persist after the patient leaves the chamber. The beneficial effects of HBOT on IBD disease activity may be due not only to reduced hypoxia, but also to changes in inflammatory and immunological mediators responsible for the dysregulated inflammation.[48]

In other human studies and model systems, HBOT has been demonstrated to inhibit neutrophil adhesion and pro-inflammatory cytokine (IL-1, IL-6, TNF-α) production, improve hypoxia tolerance through upregulation of response pathways (HIF-1α, HO-1), and enhance wound healing through increased growth factor synthesis and migration of stem cell progenitors from the bone marrow.[10–19, 49–51] Furthermore, the reactive oxygen and reactive nitrogen species generated by brief hyperbaric oxygen exposures may function as intermediates in the nitric oxide synthase, and vascular endothelial growth factor (VEGF) signalling pathways. The net effect of these various influences could be blunting of the inflammatory cascade, skewing of immune cell responses and enhancing epithelial integrity, all of which may be responsible for the demonstrated efficacy of HBOT in IBD.

Gaps in current literature

Although these data appear promising, this analysis has several limitations. The variability in study design among included studies, and the subjectivity in determining

responsiveness to HBOT, limit the conclusiveness of these results, particularly for nonperineal Crohn's disease. Furthermore, although several studies commented on comparisons to control groups, data on control patients were often not reported making it difficult to compare HBOT outcomes with standard medical therapy. The single randomised trial investigating the impact of HBOT for UC carried a significant risk of bias and was underpowered to make any definitive statements regarding the utility of HBOT for severe UC flares. Another limitation of this review is the variation in treatment protocols used in the included studies. Several adverse events increase in frequency and severity with treatment pressure and number of sessions. This limits our ability to comment on an ideal treatment pressure or frequency. Finally, most patients were only followed during the treatments or for a short time thereafter. Thus, the long-term safety and impact on disease severity remain unclear.

CONCLUSIONS

Hyperbaric oxygen therapy appears to be a potentially efficacious treatment option for IBD patients. Patients suffering from perineal Crohn's disease and moderate to severe ulcerative colitis derive the greatest benefit from this treatment. There is a high risk of bias within these studies and further well-controlled, blinded, randomised trials are needed to understand the true benefit of HBOT in IBD. Studies focusing on the molecular impact of hyperbaric oxygen in IBD will enhance our understanding of the disease mechanisms and may allow for the identification of new treatment targets.

AUTHORSHIP

Guarantor of the article: Parambir S. Dulai.

Author contributions: Parambir S. Dulai: study concept and design; acquisition, analysis, review and interpretation of data; manuscript preparation and critical revisions. Michael W. Gleeson: manuscript preparation and critical revisions. Dean Taylor: acquisition, analysis, review and interpretation of data. Stefan D. Holubar: critical revisions of the manuscript. Jay C. Buckey Jr.: study concept and design; critical revisions of the manuscript; study supervision. Corey A. Siegel: study concept and design; critical revisions of the manuscript; study supervision. All authors approved the final version of the manuscript.

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REFERENCES

1. Rutgeerts P, Sandborn WJ, Feagan BG, *et al.* Infliximab for induction and maintenance therapy for ulcerative colitis. *N Engl J Med* 2005; **353**: 2462–76.
2. Hanauer SB, Feagan BG, Lichtenstein GR, *et al.* Maintenance infliximab for Crohn's disease: the ACCENT I randomised trial. *Lancet* 2002; **359**: 1541–9.
3. Sandborn WJ, van Assche G, Reinisch W, *et al.* Adalimumab induces and maintains clinical remission in patients with moderate-to-severe ulcerative colitis. *Gastroenterology* 2012; **142**: 257–65.e1-3.
4. Rutgeerts P, Van Assche G, Sandborn WJ, *et al.* Adalimumab induces and maintains mucosal healing in patients with Crohn's disease: data from the EXTEND trial. *Gastroenterology* 2012; **142**: 1102–11.e2.
5. Sandborn WJ, Feagan BG, Stoinov S, *et al.* Certolizumab pegol for the treatment of Crohn's disease. *N Engl J Med* 2007; **357**: 228–38.
6. Siegel CA, Marden SM, Persing SM, *et al.* Risk of lymphoma associated with combination anti-tumor necrosis factor and immunomodulator therapy for the treatment of Crohn's disease: a meta-analysis. *Clin Gastroenterol Hepatol* 2009; **7**: 874–81.
7. Siegel CA, Hur C, Korzenik JR, *et al.* Risks and benefits of infliximab for the treatment of Crohn's disease. *Clin Gastroenterol Hepatol* 2006; **4**: 1017–24.
8. Dulai PS, Siegel CA, Dubinsky MC. Balancing and Communicating the Risks and Benefits of Biologics in Pediatric Inflammatory Bowel Disease. *Inflamm Bowel Dis* 2013; **19**: 2927–36.
9. Dulai PS, Thompson KD, Blunt HB, *et al.* Risks of serious infection or lymphoma with anti-tumor necrosis factor therapy for pediatric inflammatory bowel disease: a systematic review. *Clin Gastroenterol Hepatol* 2014; doi: 10.1016/j.cgh.2014.01.021 [Epub ahead of print].
10. Speit G, Dennog C, Eichhorn U, *et al.* Induction of heme oxygenase-1 and adaptive protection against the induction of DNA damage after hyperbaric oxygen treat-ment. *Carcinogenesis* 2000; **21**: 1795–9.
11. Gu GJ, Li YP, Peng ZY, *et al.* Mechanism of ischemic tolerance induced by hyperbaric oxygen preconditioning involves upregulation of hypoxia-inducible factor-1alpha and erythropoietin in rats. *J Appl Physiol* 2008; **104**: 1185–91.
12. Peng Z, Ren P, Kang Z, *et al.* Up-regulated HIF-1alpha is involved in the hypoxic tolerance induced by hyperbaric oxygen preconditioning. *Brain Res* 2008; **1212**: 71–8.
13. Furuta GT, Turner JR, Taylor CT, *et al.* Hypoxia-inducible factor 1-dependent induction of intestinal trefoil factor

protects barrier function during hypoxia. *J Exp Med* 2001; **193**: 1027–34.
14. Tjarnstrom J, Wikstrom T, Bagge U, *et al.* Effects of hyperbaric oxygen treatment on neutrophil activation and pulmonary sequestration in intestinal ischemia-reperfusion in rats. *Eur Surg Res* 1999; **31**: 147–54.
15. Yang ZJ, Bosco G, Montante A, *et al.* Hyperbaric O2 reduces intestinal ischemia-reperfusion-induced TNF-alpha production and lung neutrophil sequestration. *Eur J Appl Physiol* 2001; **85**: 96–103.
16. Yamashita M, Yamashita M. Hyperbaric oxygen treatment attenuates cytokine induction after massive hemorrhage. *Am J Physiol Endocrinol Metab* 2000; **278**: E811–6.
17. Benson RM, Minter LM, Osborne BA, *et al.* Hyperbaric oxygen inhibits stimulus-induced proinflammatory cytokine synthesis by human blood-derived monocyte-macrophages. *Clin Exp Immunol* 2003; **134**: 57–62.
18. Weisz G, Lavy A, Adir Y, *et al.* Modification of in vivo and in vitro TNF-alpha, IL-1, and IL-6 secretion by circulating monocytes during hyperbaric oxygen treatment in patients with perianal Crohn's disease. *J Clin Immunol* 1997; **17**: 154–9.
19. Alex J, Laden G, Cale AR, *et al.* Pretreatment with hyperbaric oxygen and its effect on neuropsychometric dysfunction and systemic inflammatory response after cardiopulmonary bypass: a prospective randomized double-blind trial. *J Thorac Cardiovasc Surg* 2005; **130**: 1623–30.
20. Karhausen J, Furuta GT, Tomaszewski JE, *et al.* Epithelial hypoxia-inducible factor-1 is protective in murine experimental colitis. *J Clin Invest* 2004; **114**: 1098–106.
21. Colgan SP, Curtis VF, Campbell EL. The inflammatory tissue microenvironment in IBD. *Inflamm Bowel Dis* 2013; **19**: 2238–44.
22. Naito Y, Takagi T, Yoshikawa T. Heme oxygenase-1: a new therapeutic target for inflammatory bowel disease. *Aliment Pharmacol Ther* 2004; **20** (Suppl. 1): 177–84.
23. Glover LE, Colgan SP. Hypoxia and metabolic factors that influence inflammatory bowel disease pathogenesis. *Gastroenterology* 2011; **140**: 1748–55.
24. American Gastroenterological Association medical position statement. perianal Crohn's disease. *Gastroenterology* 2003; **125**: 1503–7.
25. Sandborn WJ, Fazio VW, Feagan BG, *et al.* AGA technical review on perianal Crohn's disease. *Gastroenterology* 2003; **125**: 1508–30.
26. Plafki C, Peters P, Almeling M, *et al.* Complications and side effects of hyperbaric oxygen therapy. *Aviat Space Environ Med* 2000; **71**: 119–24.
27. Clarke RE, Tenorio LM, Hussey JR, *et al.* Hyperbaric oxygen treatment of chronic refractory radiation proctitis: a randomized and controlled double-blind crossover trial with long-term follow-up. *Int J Radiat Oncol Biol Phys* 2008; **72**: 134–43.
28. Sipahi AM, Damiao AO, de Sousa MM, *et al.* Hyperbaric oxygen: a new alternative in the treatment of perianal Crohn's disease. *Rev Hosp Clin Fac Med Sao Paulo* 1996; **51**: 189–91.
29. Takeshima F, Makiyama K, Doi T. Hyperbaric oxygen as adjunct therapy for Crohn's intractable enteric ulcer. *Am J Gastroenterol* 1999; **94**: 3374–5.
30. Di Girolamo M. Hyperbaric oxigen (HBO) therapy in Crohn's cutaneous disease (CCD): our experience in patients non responder at biological therapy. *Dig Liver Dis* 2013; **45S**: S146–7.
31. Ben Bouali A, Burtin P, Delaby J, *et al.* Indications of hyperbaric oxygen for the treatment of severe ulcerative colitis? [French] Place De L'oxygene Hyperbare Dans Le Traitement Des Colites Ulcereuses Graves? *Medecine et Chirurgie Digestives* 1990; **19**: 340.
32. Buchman AL, Fife C, Torres C, *et al.* Hyperbaric oxygen therapy for severe ulcerative colitis. *J Clin Gastroenterol* 2001; **33**: 337–9.
33. Demirturk L, Ozel M, Yazgan Y, *et al.* Therapeutic efficacy of hyperbaric oxygenation in ulcerative colitis refractory to medical treatment. *J Clin Gastroenterol* 2002; **35**: 286–7.
34. Gurbuz AK, Elbuken E, Yazgan Y, *et al.* A different therapeutic approach in patients with severe ulcerative colitis: hyperbaric oxygen treatment. *South Med J* 2003; **96**: 632–3.
35. Nelson EW Jr, Bright DE, Villar LF. Closure of refractory perineal Crohn's lesion. Integration of hyperbaric oxygen into case management. *Dig Dis Sci* 1990; **35**: 1561–5.
36. Brady CE 3rd, Cooley BJ, Davis JC. Healing of severe perineal and cutaneous Crohn's disease with hyperbaric oxygen. *Gastroenterology* 1989; **97**: 756–60.
37. Kuroki K, Masuda A, Uehara H, *et al.* A new treatment for toxic megacolon. *Lancet* 1998; **352**: 782.
38. Green MS, Purohi M, Sadacharam K, *et al.* Efficacy of hyperbaric oxygen in patients with Crohn's disease: two case reports. *Undersea Hyperb Med* 2013; **40**: 201–4.
39. Iezzi LE, Feitosa MR, Medeiros BA, *et al.* Crohn's disease and hyperbaric oxygen therapy. *Acta Cir Bras* 2011; **26** (Suppl. 2): 129–32.
40. Colombel JF, Mathieu D, Bouault JM, *et al.* Hyperbaric oxygenation in severe perineal Crohn's disease. *Dis Colon Rectum* 1995; **38**: 609–14.
41. Lavy A, Weisz G, Adir Y, *et al.* Hyperbaric oxygen for perianal Crohn's disease. *J Clin Gastroenterol* 1994; **19**: 202–5.
42. Karkumov M, Nikolov N, Georgiev L, *et al.* Hyperbaric oxygenation as a part of the treatment of chronic ulcerohemorrhagic colitis. *Vutr Boles* 1991; **30**: 78–80.
43. Grigor'eva GA, Poliakova LV, Golysheva IV. Experience of preservation remission in inflammatory bowel diseases. *Eksp Klin Gastroenterol* 2011; **9**: 132–5.
44. Pagoldh M, Hultgren E, Arnell P, *et al.* Hyperbaric oxygen therapy does not improve the effects of standardized treatment in a severe attack of ulcerative colitis: a prospective randomized study. *Scand J Gastroenterol* 2013; **48**: 1033–40.
45. Nizet V, Johnson RS. Interdependence of hypoxic and innate immune responses. *Nat Rev Immunol* 2009; **9**: 609–17.
46. Clambey ET, McNamee EN, Westrich JA, *et al.* Hypoxia-inducible factor-1 alpha-dependent induction of FoxP3 drives regulatory T-cell abundance and function during inflammatory hypoxia of the mucosa. *Proc Natl Acad Sci USA* 2012; **109**: E2784–93.
47. Hegazi RA, Rao KN, Mayle A, *et al.* Carbon monoxide ameliorates chronic murine colitis through a heme oxygenase 1-dependent pathway. *J Exp Med* 2005; **202**: 1703–13.
48. Al-Waili NS, Butler GJ. Effects of hyperbaric oxygen on inflammatory response to wound and trauma: possible mechanism of action. *ScientificWorldJournal* 2006; **6**: 425–41.
49. Thom SR. Hyperbaric oxygen: its mechanisms and efficacy. *Plast Reconstr Surg* 2011; **127**(Suppl. 1): 131S–41S.
50. Thom SR. Effects of hyperoxia on neutrophil adhesion. *Undersea Hyperb Med* 2004; **31**: 123–31.
51. Rothfuss A, Radermacher P, Speit G. Involvement of heme oxygenase-1 (HO-1) in the adaptive protection of human lymphocytes after hyperbaric oxygen (HBO) treatment. *Carcinogenesis* 2001; **22**: 1979–85.