

Hyperbaric Oxygen Therapy:
A White Paper on effectiveness and safety
in inflammatory bowel disease

A new lease of life:
Healing
Inflammatory
Bowel Disease

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Executive summary

- An estimated 75,000 Australians live with inflammatory bowel disease.¹
- Australia has amongst the highest reported incidence of inflammatory bowel disease worldwide. The latest figures estimate that there are more than 1622 new cases diagnosed every year (776 with Crohn's disease and 846 with ulcerative colitis).²
- Conventional medical treatment such as corticosteroids, immunomodulators and anti-inflammatory medications may not achieve remission alone, with poor fistulae healing rates and relapsing flares.³⁻⁵
- There is high quality evidence that fistulising Crohn's disease and ulcerative colitis flares refractive to conventional treatment can be successfully treated by adjunctive hyperbaric oxygen therapy.^{3,5,6}
- Hyperbaric oxygen therapy works by markedly increasing tissue oxygenation of inflamed bowel or chronic non-healing fistulas which changes inflammatory pathways and promotes healing.^{3,5,6}
- Hyperbaric oxygen therapy has been shown to have continued biochemical benefits after the patient leaves the chamber.⁵
- Reported side effects include difficulty equalising middle ear pressures, middle ear barotrauma and temporary effects on visual acuity,⁵ which are rare and usually temporary.
- Wesley Hyperbaric provides 3700 hyperbaric oxygen treatments a year. We are actively involved in research to prevent late radiation tissue injury. We were involved in sponsoring and participating in venous leg ulcers trial and are currently undertaking a Xerostomia trial for patients experiencing dry mouth following radiation.

The challenge

Crohn's disease and ulcerative colitis are chronic relapsing inflammatory bowel diseases characterised by recurrent inflammation of the gastrointestinal tract, bloody diarrhoea, abdominal pain and symptoms such as fever and weight loss.⁷ Crohn's disease and ulcerative colitis have a significant impact on patients' lives beyond intestinal symptoms with no prospect of a cure.

There is a steady annual increase in the prevalence of inflammatory bowel disease in New South Wales and Queensland (Figure 1).¹ In 2018, estimates showed that there were 43,418 people with inflammatory bowel disease in New South Wales and Queensland combined,¹ more than half the national total.

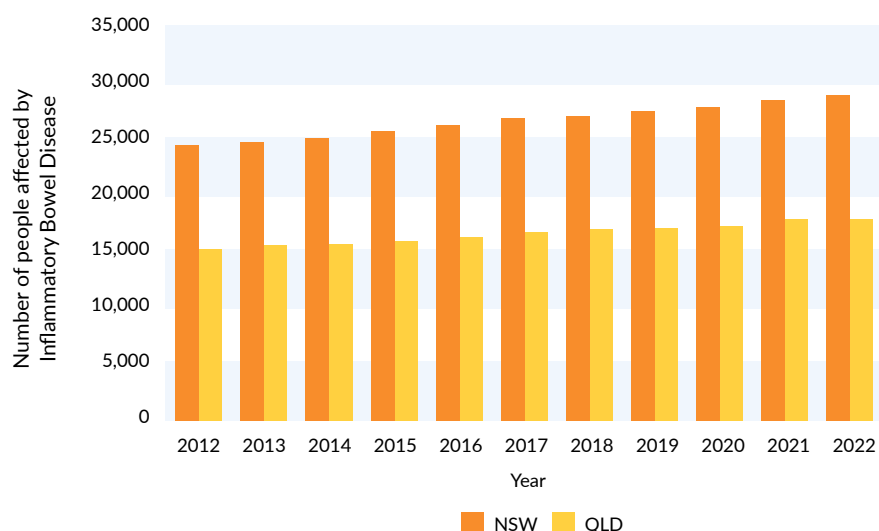


Figure 1. Current and projected prevalence of inflammatory bowel disease 2012-2022 in New South Wales and Queensland. Adapted from Crohn's & Colitis.¹

Crohn's disease: Crohn's disease can affect any part of the gastrointestinal tract. Approximately 20–40% of patients with Crohn's disease develop perianal fistulae⁷ which rarely heal untreated and are resistant to treatment. Conventional treatment with immunomodulatory agents such as infliximab is reported to achieve initial healing rates of 60% with uncertainty of long-term effectiveness.⁷ Crohn's disease is incurable and is associated with a 47% increase in the mortality risk.⁸

Ulcerative colitis: Ulcerative colitis is characterised by continuous inflammation and ulceration in the mucosa of the colon and rectum with no segments of normal tissue. One quarter of patients with ulcerative colitis will develop a severe acute exacerbation of disease during their lifetime.⁹ Despite high dose corticosteroids, half of these patients will fail subsequent medical rescue therapy (open-label administration of active drug e.g. infliximab).⁹ Half will require colectomy within five years.⁹ Second line therapies (infliximab, cyclosporine, colectomy) are associated with significant costs, adverse events, and post-operative morbidity and mortality.⁹

Unmet need: The current model of care for Crohn's disease and ulcerative colitis is reactive in that treatment occurs only when the condition flares. This fails to address the chronic relapsing nature of inflammatory bowel disease. On average, about 50% of patients not on effective maintenance therapy have a relapse in any given year.² There is an unmet need for novel therapeutic strategies. This is why Wesley Hyperbaric is an active partner in scientific research to increase understanding of how hyperbaric oxygen therapy works to assist patients with non-healing lesions.

The solution: Hyperbaric Oxygen Therapy

Hyperbaric oxygen therapy is increasingly indicated for inflammatory bowel disease with burgeoning research evidence on efficacy and safety. Hyperbaric oxygen therapy involves breathing 100% oxygen under increased atmospheric pressure; typically, 2 to 3 times atmospheric pressure at sea level (2.0–3.0 atmospheres absolute). This dramatically increases the amount of oxygen in blood plasma delivered to inflamed bowel or chronic non-healing fistulae. High levels of oxygen produce a variety of biochemical, physiological and cellular effects such as reducing hypoxia, infection and cell death, maintains tissue viability while healing occurs and promotes angiogenesis.⁵

Other applications of hyperbaric oxygen therapy include decompression sickness, arterial gas embolism, and carbon monoxide poisoning, arterial insufficiency, chronic osteomyelitis, compartment syndrome, crush injury, diabetic wounds, limb salvage, necrotising fasciitis and radiation injury.¹⁰

Protocols vary but in general, patients are treated daily for the majority of treatments, although some may require treatments up to three times per day. Treatments are about 1.5 to 2 hours long, depending on the indication.⁶ Treatment programs can last from 20 to 40 days.^{9,11} Chambers designed to treat one patient are usually compressed to a pressure of 2.4 – 2.8 atmospheres absolute,



for the majority of treatments. Chambers for multiple patients are pressurised with air and patients breathe pure oxygen¹⁰ through a tight-fitting face mask, a hood, or an endotracheal tube.¹⁰ During treatment, the arterial oxygen tension often exceeds 2000 mmHg and levels of 200 to 400 mmHg occur in tissues.¹¹

Reported side effects of hyperbaric oxygen treatment include difficulty equalising middle ear pressures, the risk of bilateral ear drum perforation, myopia and temporary vision changes which may increase with the number of

An additional \$2.7 billion of financial and economic costs have been associated with the management of inflammatory bowel disease.¹

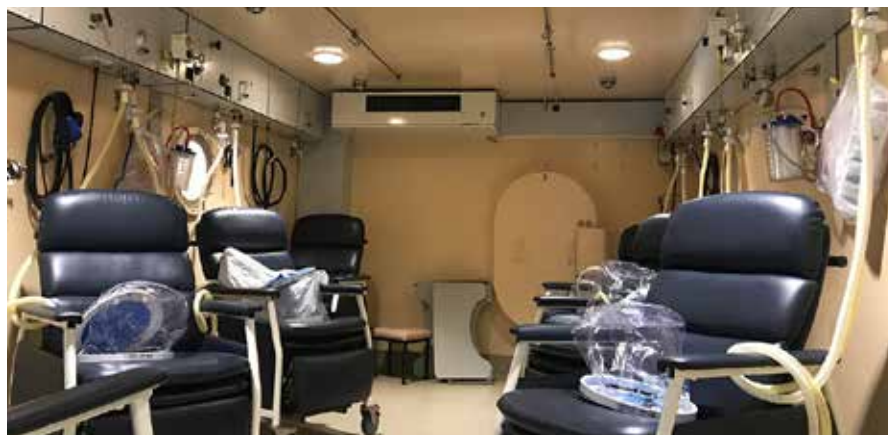
hyperbaric oxygen therapy sessions administered.⁵ The majority of patients do not experience side effects. Any effects are usually temporary with a full return to pre-treatment levels once the program is complete.

The Wesley Hyperbaric advantage

In 1998, Wesley Hyperbaric became the world's first square, triple lock chamber. Wesley Hyperbaric treats patients from all areas of Queensland and Northern New South Wales. On average Wesley Hyperbaric treats 150 patients per year. This represents an average of 3700 treatments a year or 313 patient treatments per month.

The hyperbaric chamber at Wesley Hyperbaric is a triple lock multi-place chamber which means that more than one person can be treated at any one time. The facility has the capability to treat any patient that is likely to require hyperbaric oxygen. One compartment, called The Lounge, can be pressurised to 3 atmospheres absolute and can treat up to eight patients with a hyperbaric nurse in attendance in the chamber. The other compartment, known as The Study, is a high-pressure compartment with the capacity to pressurise to 6 atmospheres absolute. It is used for emergencies such as patients transferred from the intensive care unit and patients that need special oxygen delivery systems including decompression sickness (the bends).

In March 2003, Wesley Hyperbaric contributed to the International Hyperbaric Oxygen Radiation Tissue Injury Study (HORTIS)



trial.¹² This trial was a multi-centre international study investigating the potential of hyperbaric oxygen therapy to prevent late radiation tissue injury. The trial found that

hyperbaric oxygen therapy significantly improved the healing responses in patients with refractory radiation proctitis.¹² We have also contributed to the setting up of the Bert Turner Fund, which assists patients who are

not properly insured to obtain treatments. Over the past 20 years we have funded treatments through this trust for approximately 190 patients.

In 2005, we helped to set up the Australasian Hyperbaric and Diving Medicine Research Trust which has funded several small preliminary research studies. Prior to 2010, Wesley Hyperbaric was the only chamber in South East Queensland

that served both private and public health communities. Wesley Hyperbaric has continued to be pro-active. In conjunction with Queensland University of Technology we were sponsors of the Venous Leg Ulcer trial in 2012. Currently, we are sponsoring the Xerostomia trial for patients experiencing dry mouth following radiation.

Looking ahead

Wesley Hyperbaric looks forward to embracing new challenges in regard to evolving understanding of the mechanisms of action of hyperbaric oxygen therapy, continuing to contribute to the body of research in our field, and maintaining our flexibility to deal with changing funding models through continuing to support the Bert Turner Fund, maximising the number of patients we continue to assist.

In 1998, Wesley Hyperbaric became the world's first square, triple lock chamber.

On average Wesley Hyperbaric conducts 3,700 treatments a year or 313 a month.

Safety and efficacy profile of hyperbaric oxygen therapy in inflammatory bowel disease

Recently, systematic reviews and randomised sham-controlled trials have supported evidence from case series for efficacy and safety of hyperbaric oxygen therapy for inflammatory bowel disease. Systematic reviews and randomised sham-controlled trials are considered a high level of evidence.¹³ Two systematic reviews^{5,6} demonstrated strong evidence that hyperbaric oxygen therapy is a safe, effective and acceptable treatment option for both Crohn's disease and ulcerative colitis. In particular, they demonstrated that hyperbaric oxygen therapy may be potentially efficacious for patients with refractory perineal or fistulising Crohn's disease and moderate to severe ulcerative colitis flares.

Systematic review 1

A systematic review⁵ of 613 patients with inflammatory bowel disease who underwent a total of 8924 hyperbaric oxygen therapy treatments demonstrated an overall response rate of 86%.⁵ Protocols varied across studies but all studies used 100% oxygen and atmospheric pressure ranged from 1.7 to 2.5 atmospheres absolute. There were a total of nine adverse events across the 8924 treatments, equal to an incidence of 10/10,000 treatments. Six events were serious e.g. perforated ear drum, and these patients discontinued treatment.⁵

Crohn's disease

- 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.⁵
- Five patients (12%) were unresponsive to therapy and two discontinued therapy prior to a response due to adverse events (difficulty equalising middle ear pressure, barotrauma to the middle ear, blurred vision).⁵

Ulcerative colitis

- The response rate to hyperbaric oxygen therapy for the 40 ulcerative colitis patients was 100%⁵ amongst studies that reported endoscopic follow-up of disease activity. Endoscopic follow-up is considered to be sensitive to evidence of improving disease control.⁵



Systematic review 2

Another systematic review⁶ identified thirteen studies of hyperbaric oxygen therapy in Crohn's disease and six studies in ulcerative colitis. In all studies, participants had severe disease refractory to standard medical treatments, including corticosteroids, immunomodulators and anti-inflammatory medications:

Crohn's disease

- In patients with Crohn's disease, 31/40 (78%) had significant clinical improvements with hyperbaric oxygen therapy at a pressure ranging from 2.0 to 2.8 atmospheres absolute.⁶
- One study in Crohn's disease reported a significant decrease in proinflammatory cytokines (IL-1, IL-6 and TNF-alpha).⁶

Ulcerative colitis

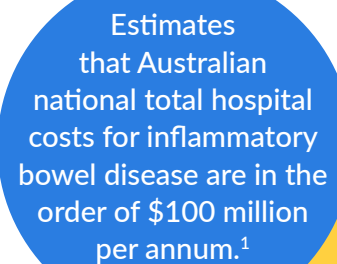
- All 39 patients with ulcerative colitis improved with pressure delivered at 2.0 atmospheres absolute.⁶
- One study in ulcerative colitis reported a decrease in IL-6 with hyperbaric oxygen therapy.⁶

Efficacy of hyperbaric oxygen therapy in patients hospitalised with acute active ulcerative colitis

A randomised sham-controlled double-blind multi-centre study^{3,4} of hyperbaric oxygen therapy on 18 patients with severe ulcerative colitis demonstrated significantly higher rates of response and remission compared to steroids alone. Ten patients received steroids plus hyperbaric oxygen therapy and eight received steroids plus sham treatment. Sham patients breathed normal air and were pressurised to 1.34 atmospheres absolute to mimic pressure changes observed with hyperbaric oxygen therapy, and then decompressed to 1.2 atmospheres absolute for the remainder of the treatment.

Outcomes

- Amongst the hyperbaric oxygen therapy patients, there was a reduction in the need for progression to second line therapy such as colectomy during hospitalisation.^{3,4}
- Response to hyperbaric oxygen therapy was observed as early as day 3.^{3,4}
- Half of the intervention patients significantly achieved clinical remission by day 5 and day 10 compared to zero patients in the controlled arm.^{3,4}
- Hyperbaric oxygen therapy patients required progression to second line therapy or specifically, colectomy, significantly less often while hospitalised.^{3,4}
- Efficacy was measured by flexible sigmoidoscopy at day 10.^{3,4}
- There were no adverse events.^{3,4}



Estimates that Australian national total hospital costs for inflammatory bowel disease are in the order of \$100 million per annum.¹

A case study: Hyperbaric oxygen treatment of Crohn's disease

A 24-year-old male with long-standing Crohn's disease presented with multiple rectum-to-rectum fistulae and inflammatory changes and was reported as part of a case series of nine patients.⁷ He had failed to heal fistulae on conventional treatment. His conventional treatment was azathioprine, examination under anesthesia and seton drainage, metronidazole, infliximab, and mesalazine.⁷ MRI confirmed the presence of multiple (>3) perirectal abscesses, the largest of these being 1 cm in diameter.⁷ His combination treatment was 30 hyperbaric oxygen therapy sessions and three infusions of infliximab.⁷

Outcomes

- At 3 months post-combination therapy, the patient was in asymptomatic clinical remission, with no fistulae and abscesses detectable on MRI.⁷
- Complete healing of mucosa persisted at 20-month review.⁷
- The patient remained well at two-year review with maintenance anti-mycobacterium avium ss paratuberculosis (anti-MAP) therapy alone.⁷

This patient was part of a case series⁷ of nine patients which reported 100% fistulae healing rates on adjunctive hyperbaric oxygen therapy combined with infliximab and anti-MAP therapy. The nine patients were treated with 18–30 courses of hyperbaric



Before (fistulae) and after (healed) photos of this case study patient.

Images credit: Prof Thomas J Borody & Dr Gaurav Agrawal, Centre for Digestive Diseases, Sydney, NSW, Australia.

oxygen therapy. After hyperbaric oxygen therapy, continuation with anti-MAP therapy alone maintained healing although one patient who ceased the anti-MAP therapy had a relapse.⁷ 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.⁷

Almost
75,000 Australians
have Crohn's disease or
ulcerative colitis, with
this number projected to
increase to 100,000
by 2022.¹

Summary

Hyperbaric oxygen therapy delivers 100% oxygen to the tissues under increased atmospheric pressure which promotes healing and reduces hypoxia in lesions. Robust research evidence indicates that adjunctive hyperbaric oxygen therapy increases response and remission rates of refractory Crohn's disease and ulcerative colitis compared to conventional treatment alone. It has also been shown to reduce the need to progress to surgical treatment associated with high morbidity and mortality in severe ulcerative colitis. Research suggested that hyperbaric oxygen therapy is an effective adjunctive therapy for Crohn's disease and ulcerative colitis with a good safety profile. Research to date suggested that further well-powered trials with larger numbers of participants are required to confirm these effects.



References

1. Pricewaterhouse Coopers Australia. Improving inflammatory bowel disease care across Australia. Commissioned by Crohn's & Colitis Australia (CCA); 2013.
2. The Gastroenterological Society of Australia. Clinical Update for General Practitioners and Physicians – Inflammatory Bowel Disease, 2018. 2018.
3. Dulai P, Buckey J, Raffals L, et al. Hyperbaric Oxygen Therapy is safe and effective for ulcerative colitis patients hospitalized for moderate-severe flares: A multi-center, randomized, double-blind, sham-controlled trial. *Journal of Crohn's and Colitis* 2017;11:S12-S3.
4. Dulai P, Buckey J, Raffals L, et al. Hyperbaric oxygen therapy is well tolerated and effective for ulcerative colitis patients hospitalized for moderate-severe flares: a phase 2A pilot multi-center, randomized, double-blind, sham-controlled trial. *American Journal of Gastroenterology* 2018.
5. Dulai PS GM, Taylor D, Holubar SD, Buckey JC, Siegel CA,. Systematic review: The safety and efficacy of hyperbaric oxygen therapy for inflammatory bowel disease. . *Alimentary Pharmacology and Therapeutics* 2014;39:1266-75.
6. Rossignol DA. Hyperbaric oxygen treatment for inflammatory bowel disease: a systematic review and analysis. *Medical Gas Research* 2012;2:1-11.
7. Agrawal G, Borody T, Turner R, Leis S, Campbell J. Combining infliximab, anti-MAP and hyperbaric oxygen therapy for resistant fistulizing Crohn's disease. *Future Science* 2015;1:FSO77.
8. Access Economics. The Economic Costs of Crohn's Disease and Ulcerative Colitis. 2007:4.
9. Jairath V. Hyperbaric Oxygen for Hospitalized patients with Ulcerative Colitis. *The American Journal of Gastroenterology* 2018:1-3.
10. Shaha J. Hyperbaric Oxygen Therapy. *Journal of the American College Certification in Wound Specialists* 2010;2:9-13.
11. Thom S. Hyperbaric oxygen – its mechanisms and efficacy. *Plastic and reconstructive surgery* 2011;127:131S-41S.
12. Clarke RE, Tenorio C, 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. *International Journal of Radiation Oncology* 2008;72:134-43.
13. National Health and Medical Research Council. NHMRC levels of evidence and grades for recommendations for developers of guidelines Australian Government: NHMRC 2009.

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