Northwestern

Hyperbaric Oxygen Therapy for Inflammatory Bowel Diseases

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Disclosures

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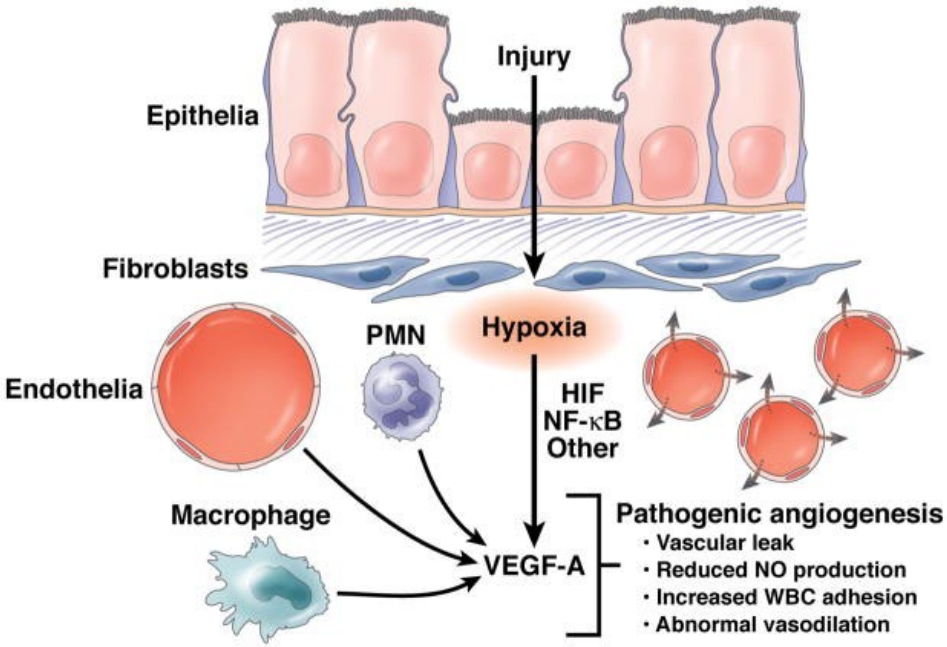
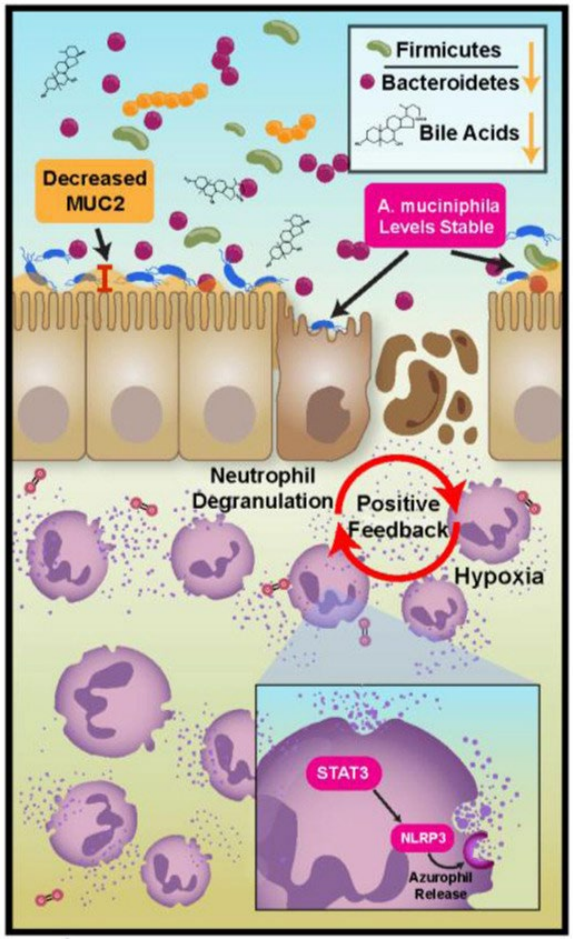
Off Label Discussion: Hyperbaric oxygen therapy is not FDA approved for use in inflammatory bowel disease

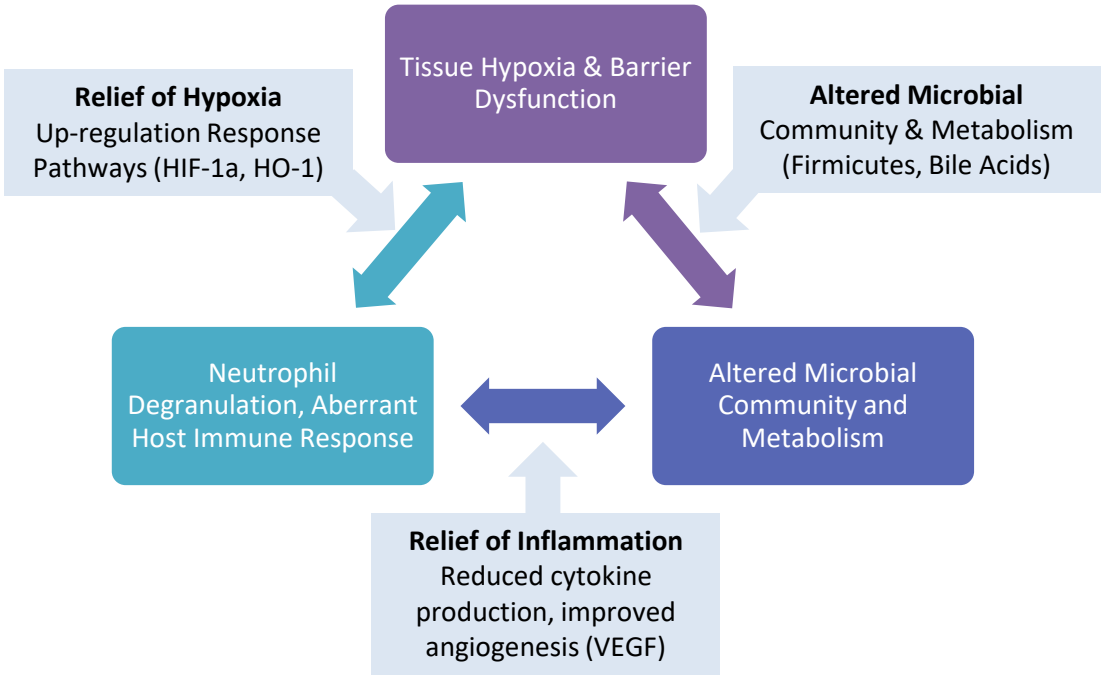
Inflammatory Bowel Diseases – Background and Pathogenesis





Glover L et al. *Gastroenterology* 2011; Gonzalez CG et al. *Cellular and Molecular Gastroenterology and Hepatology* 2023

Does Hyperbaric Oxygen Therapy Have a Role in Treating IBD?



Safety and Efficacy HBOT in IBD

Adverse Events	Rate
Overall	10/10,000 sessions
Serious AE	6.7/10,000 sessions

IBD Type	Response Rate
Ulcerative Colitis	85%
Crohn's Disease	88%

Event	IBD	Other Indications	IRR (95% CI)
Middle Ear Barotrauma	1.1/10,000 sessions	29/10,000 sessions	0.04 (0.01 – 0.23)
Psychological Intolerance	6.7/10,000 sessions	30/10,000 sessions	0.23 (0.08 – 0.54)

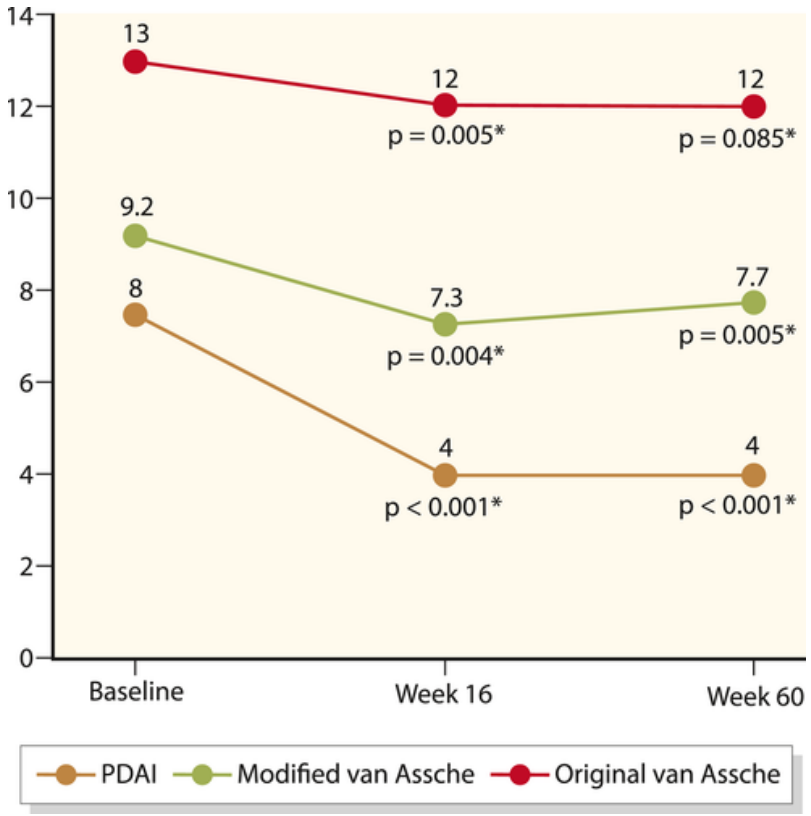
Gaps in Evidence to Support Integration of HBOT for IBD?

- Limitations in measurement of disease activity
  - Imaging for fistulae healing
  - Endoscopy for mucosal (intestinal) healing

- High-quality clinical trials
  - Blinded to intervention and outcome
  - Sham hyperbaric treatment

Crohn's Disease – Perianal Fistulae

- Prospective observational cohort study
  - 21 Crohn's disease
  - Active perianal fistulae
  - 40 daily HBOT sessions
  - MRI based assessment
  - Biomarkers of inflammation
  - Clinical assessment (PDAI)



Crohn's of the Pouch

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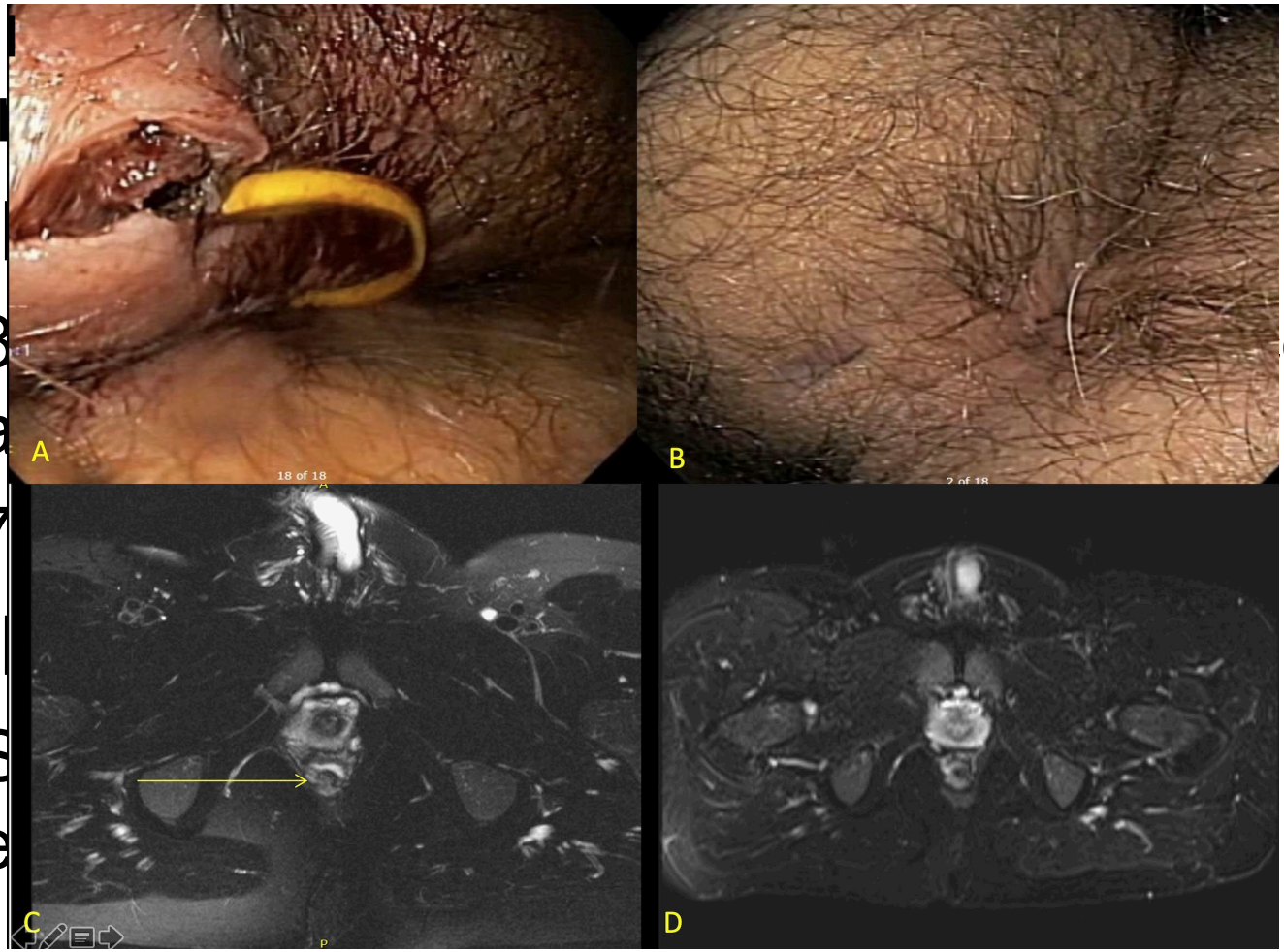


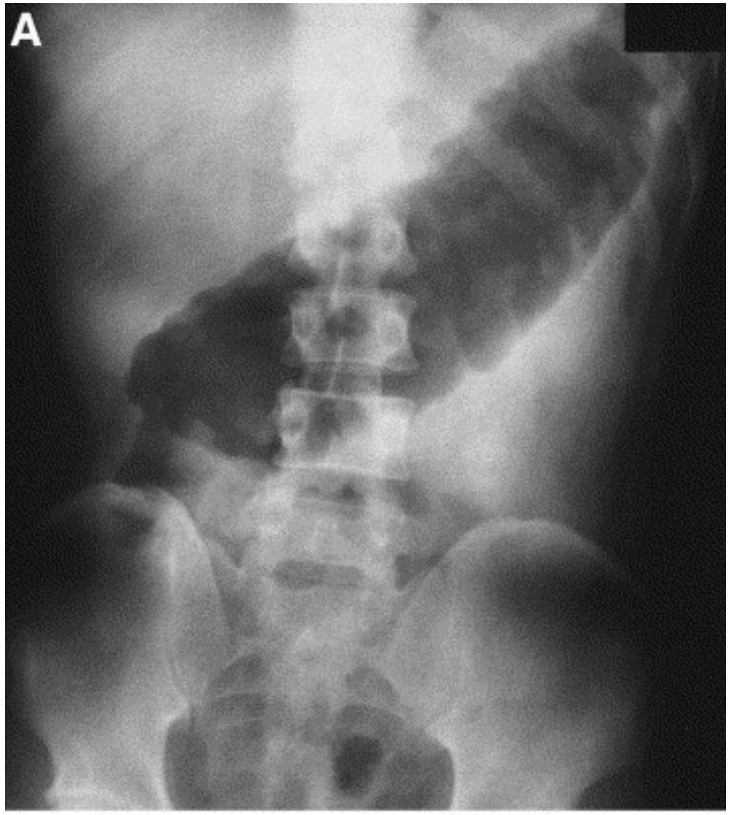
Dulai et al. *AP&T* 2014; Fahad H, Dulai PS, et al *CGH* 2020; Hasan B et al. *IBDJ* 2020

Treatment of UC patients hospitalized for acute flares in ~~2005~~ 2023

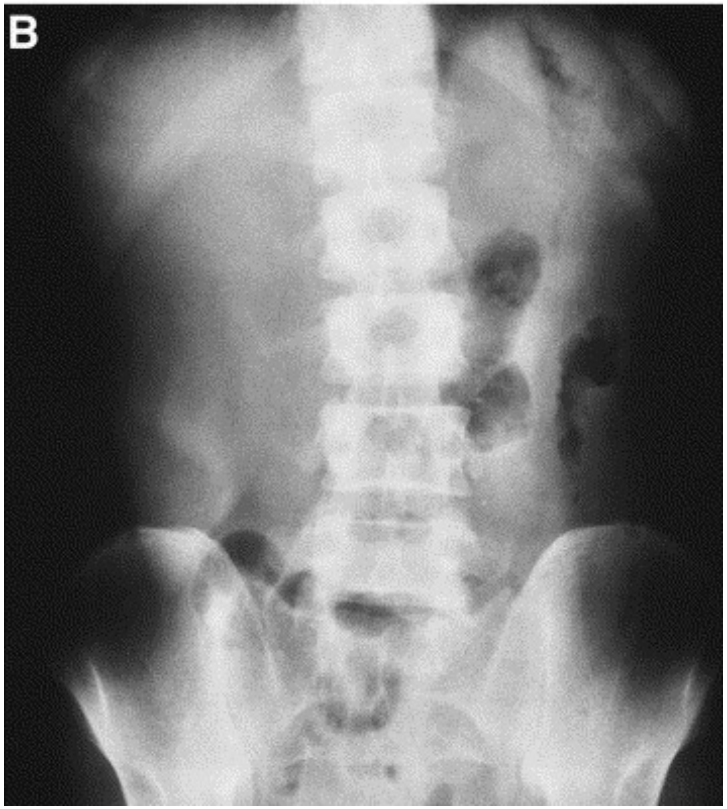
- 50% of UC patients will be hospitalized
- ~40% will fail to respond to IV steroids
- 2nd line therapies (infliximab, cyclosporine, colectomy) associated with significant costs, adverse events, and mortality of up to 5%
- Excluded from traditional pharmaceutical trials
- Need exists for novel therapeutic strategies

Dulai PS, Jairath V. *Ther Adv Chronic Disease* 2018

Hyperbaric oxygen for toxic megacolon (1998)



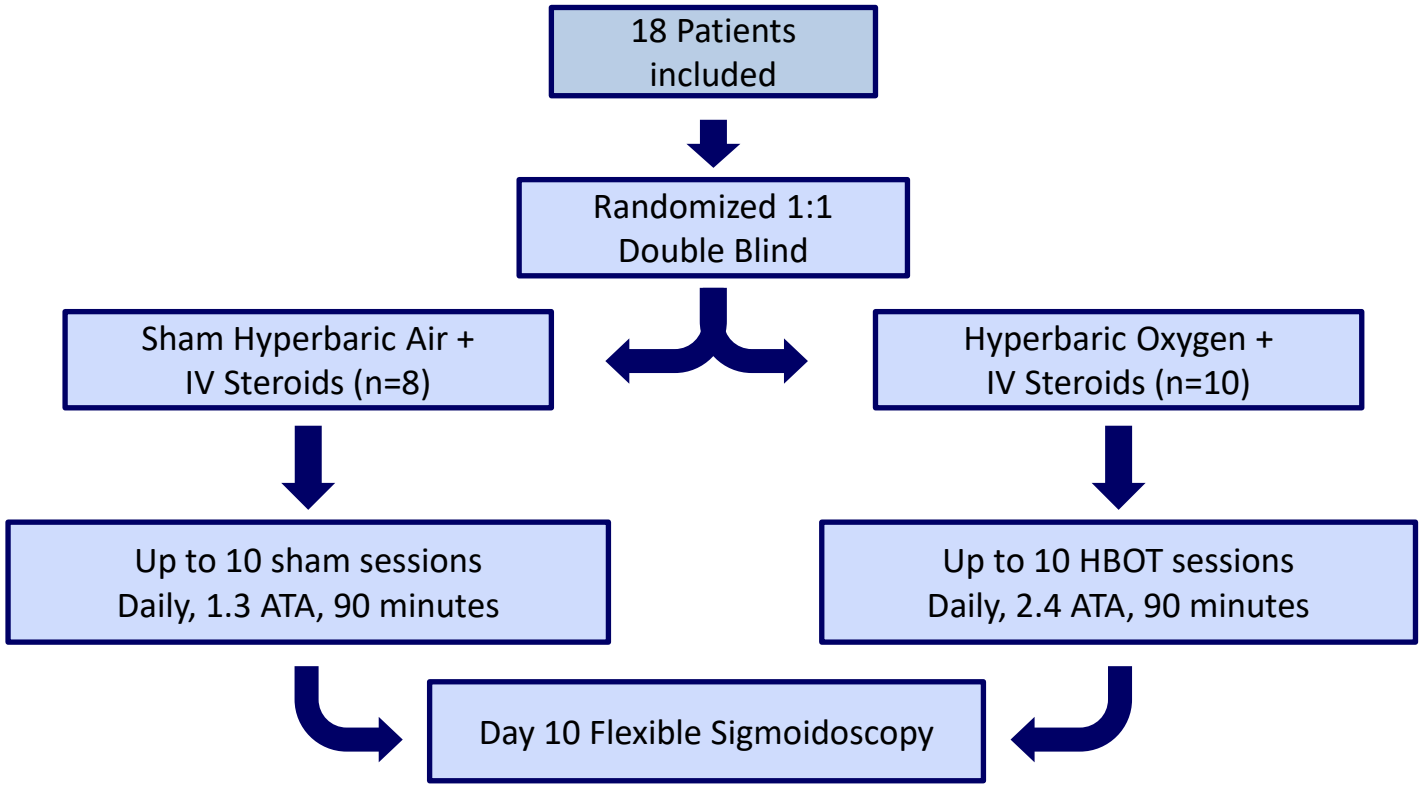
Before Hyperbaric Oxygen



After Hyperbaric Oxygen

Katsuro K et al. *Lancet* 1998

Phase 2A Sham-Controlled, Double-Blind, Clinical Trial Hospitalized UC Patients with Moderate-Severe Flares



Dulai et al. *AJG* 2018

Patient Demographics

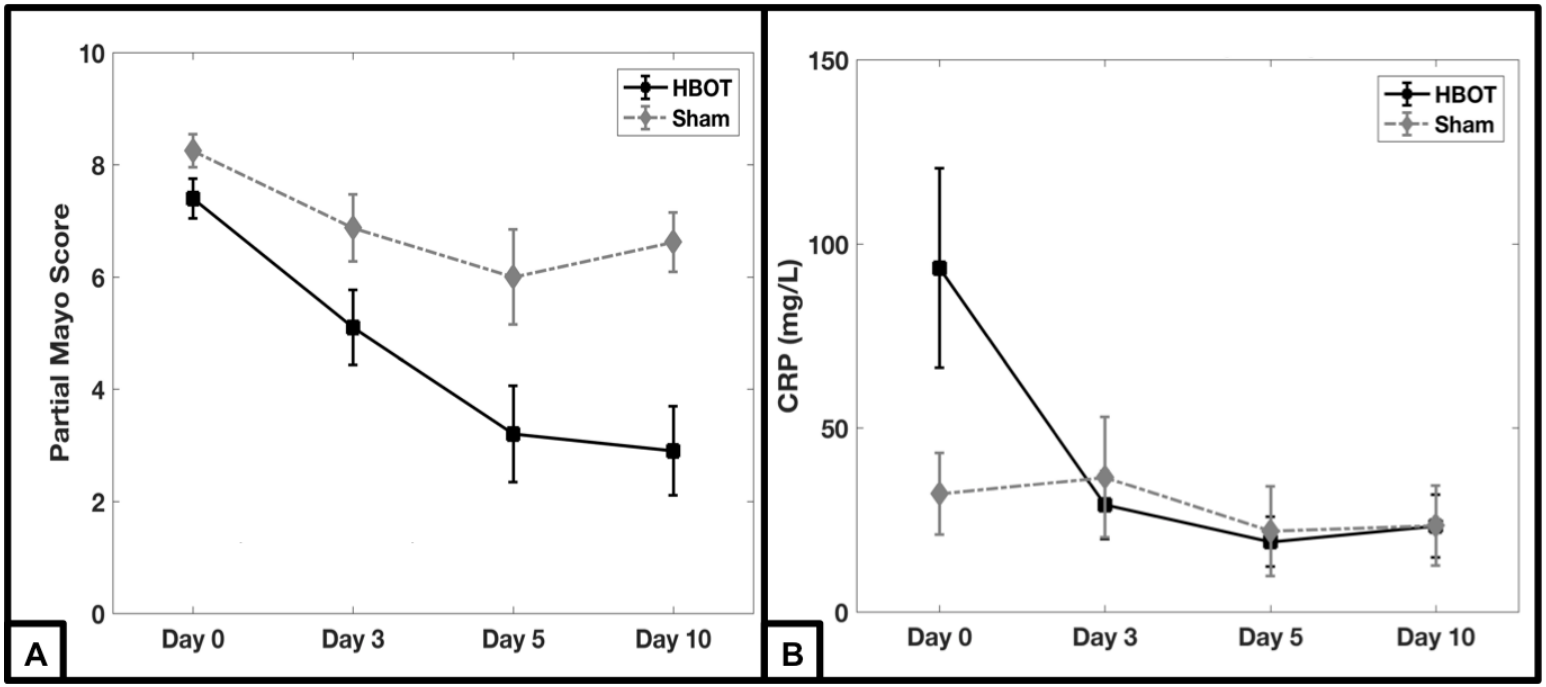
	HBOT (n=10)	Sham (n=8)	p value
Gender, male	4 (40%)	5 (63%)	0.64
Age, median (IQR)	47 (40 – 57)	31 (22 – 43)	0.26
Treatment upon enrollment			
High dose steroids (> 20mg/day)	8 (80%)	7 (88%)	1.00
Immunomodulator	5 (50%)	2 (25%)	0.37
Anti-TNF	5 (50%)	5 (63%)	0.66
Baseline Labs			
Hg, mean (± SD)	11.7 (± 1.1)	12.1 (± 2.6)	0.72
Platelets, median (IQR)	314 (252 – 495)	413 (341 – 508)	0.40
Albumin, mean (± SD)	3.3 (± 0.45)	3.5 (± 0.45)	0.23
CRP, median (IQR)	81 (14 – 143)	10 (7 – 66)	0.13
ESR, median (IQR)	38 (31 – 68)	39 (28 – 42)	0.48
Baseline Clinical Assessment			
Full Mayo, mean (SD)	9.9 (± 1.5)	10.9 (± 1.1)	0.14
Partial Mayo, mean (SD)	7.4 (± 1.2)	8.3 (± 0.9)	0.10
Severe Endoscopy (Mayo endoscopy sub-score 3), n	5 (50%)	5 (63%)	0.66

Treatment Outcomes	HBOT (n=10)	Sham (n=8)	P value
Day 5 Clinical Remission	50%	0%	**0.04**
Day 10 Clinical Remission	50%	0%	**0.04**
Day 10 Clinical Response	80%	25%	0.05
Day 10 Endoscopic Remission	50%	13%	0.15
In-hospital 2nd line therapy (biologics or colectomy)	10%	63%	**0.04**

Day 5 clinical remission: partial Mayo score ≤2 points, no sub-score > 1 point.
Day 10 clinical remission: Full Mayo score ≤2 points, no sub-score > 1 point which includes the endoscopic sub-score.
Day 10 endoscopic remission: Mayo endoscopic sub-score 0 or 1.

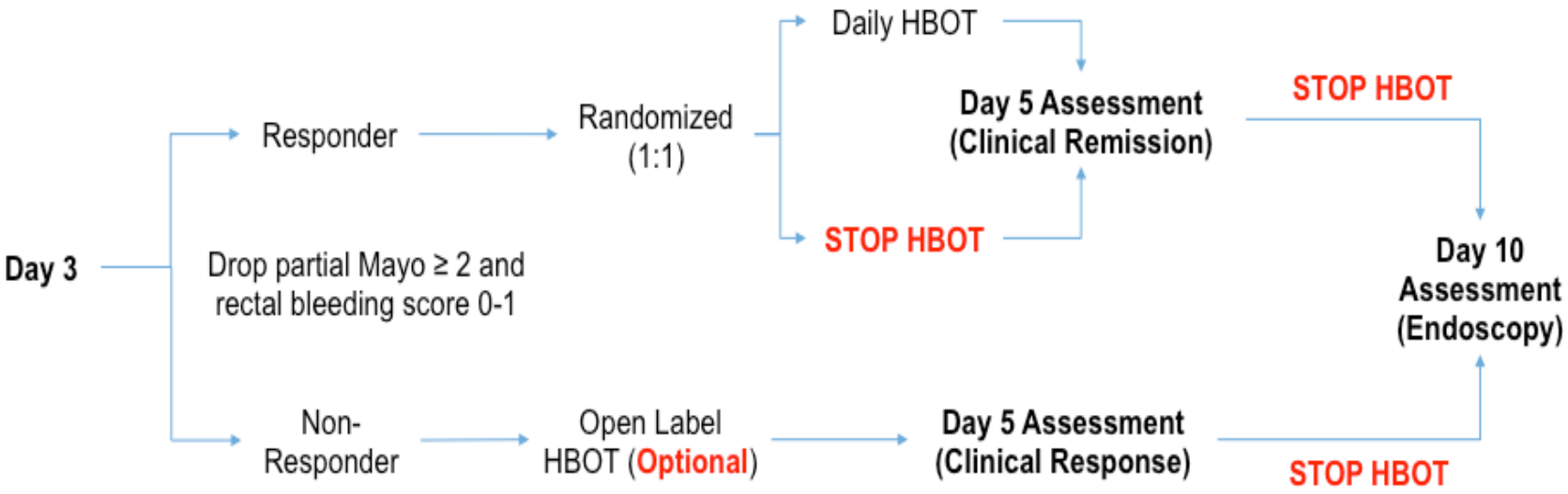
Dulai et al. *AJG* 2018

Maximum Benefit at Day 5



Dulai et al. *AJG* 2018

Phase 2B Dose-Finding Trial

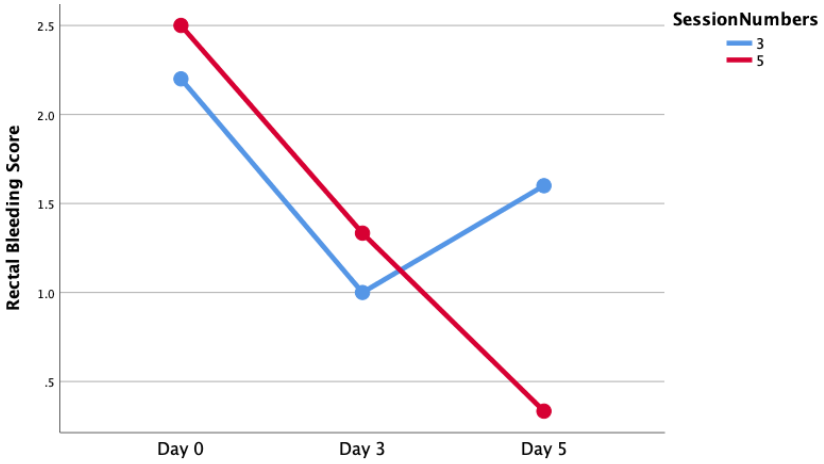


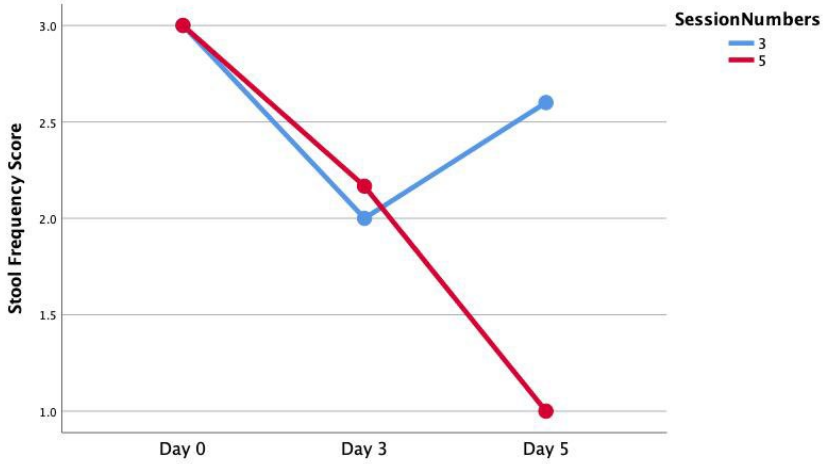
Dulai et al. *AP&T* 2020

Demographics

	HBOT treated UC (n=20)
Age, mean years (SD)	37 (15)
Male gender, n (%)	10 (50%)
Pancolitis*, n (%)	17 (85%)
Prior IM, n (%)	18 (90%)
Prior TNF antagonist, n (%)	15 (75%)
Prior Vedolizumab, n (%)	7 (35%)
Prior Tofacitinib, n (%)	5 (25%)
Mayo endoscopic sub-score of 3, n (%)	17 (85%)
CRP, median mg/dL (IQR)	14.4 (3-51)
Albumin, median mg/dL (IQR)	3.5 (3.1-3.6)

5 days superior to 3 days for response





Rate of re-hospitalization at 3 months: 10% for day 3 responders
(expected rate of 26% based on literature)

Dulai et al. *AP&T* 2020

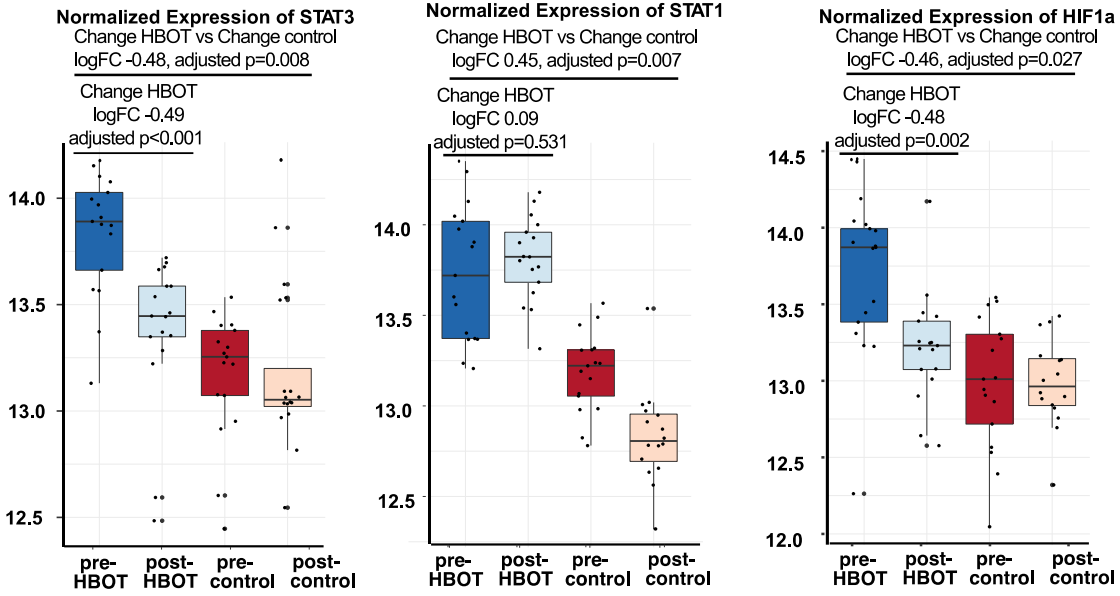
HBOT Cost-Effective in UC

- Microsimulation Model
- 5-year horizon with modeling of uncertainty for efficacy and natural history
- HBOT Cost-Effective ($43,000 per QALY)
- Significant reduction in use of inpatient second line therapies and disease modification
  - colectomy, re-hospitalization, and mortality

Dulai et al. *Dig Dis Sci* 2021

B

Neutrophil Gene Expression Changes for STAT and HIF Mediated Signaling



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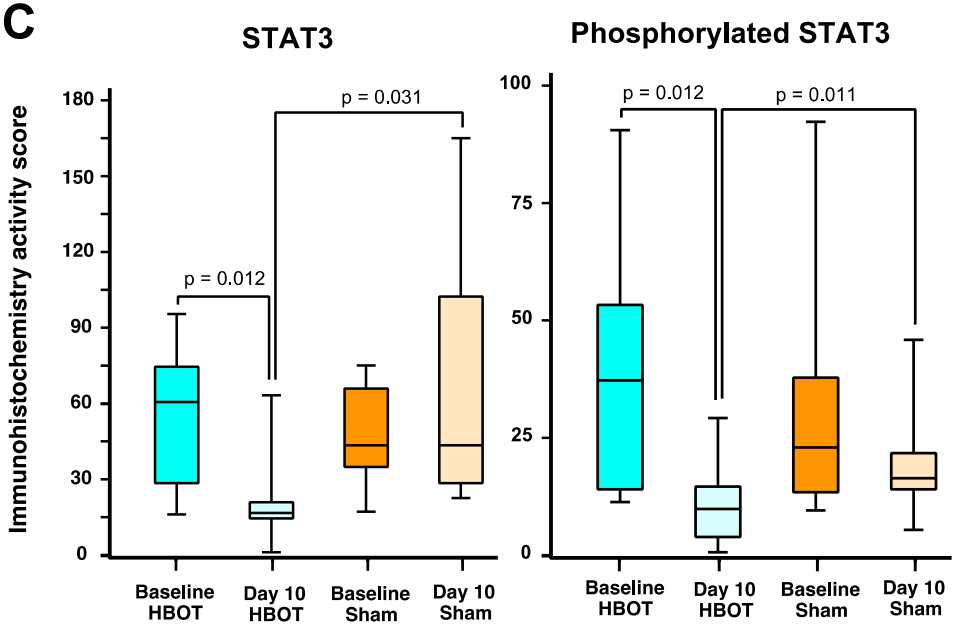
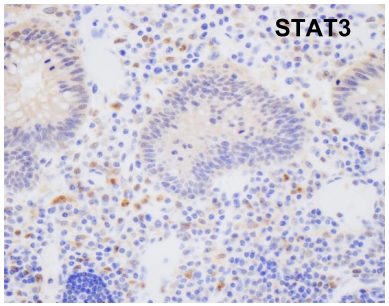
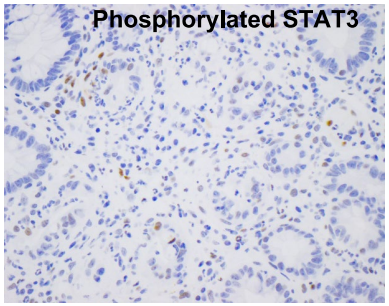
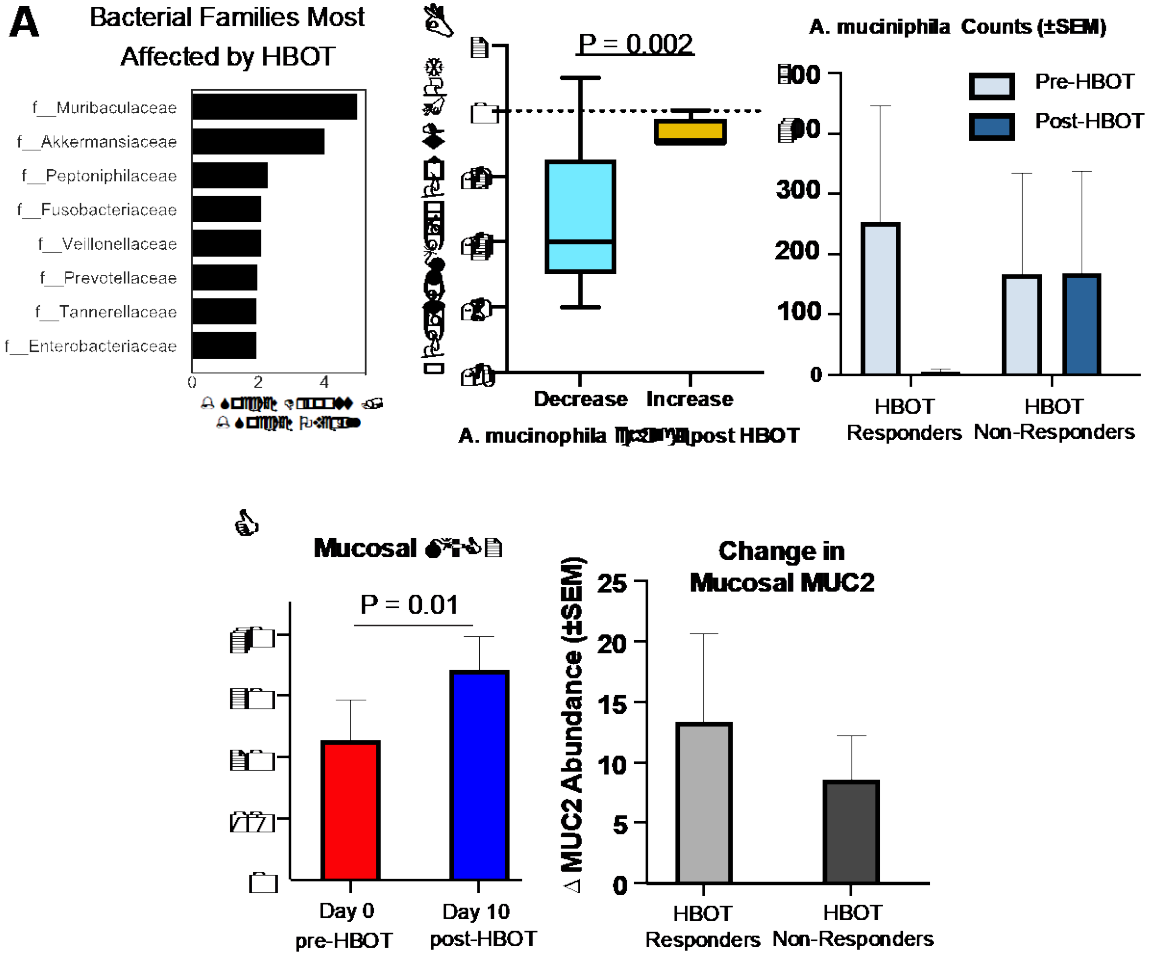


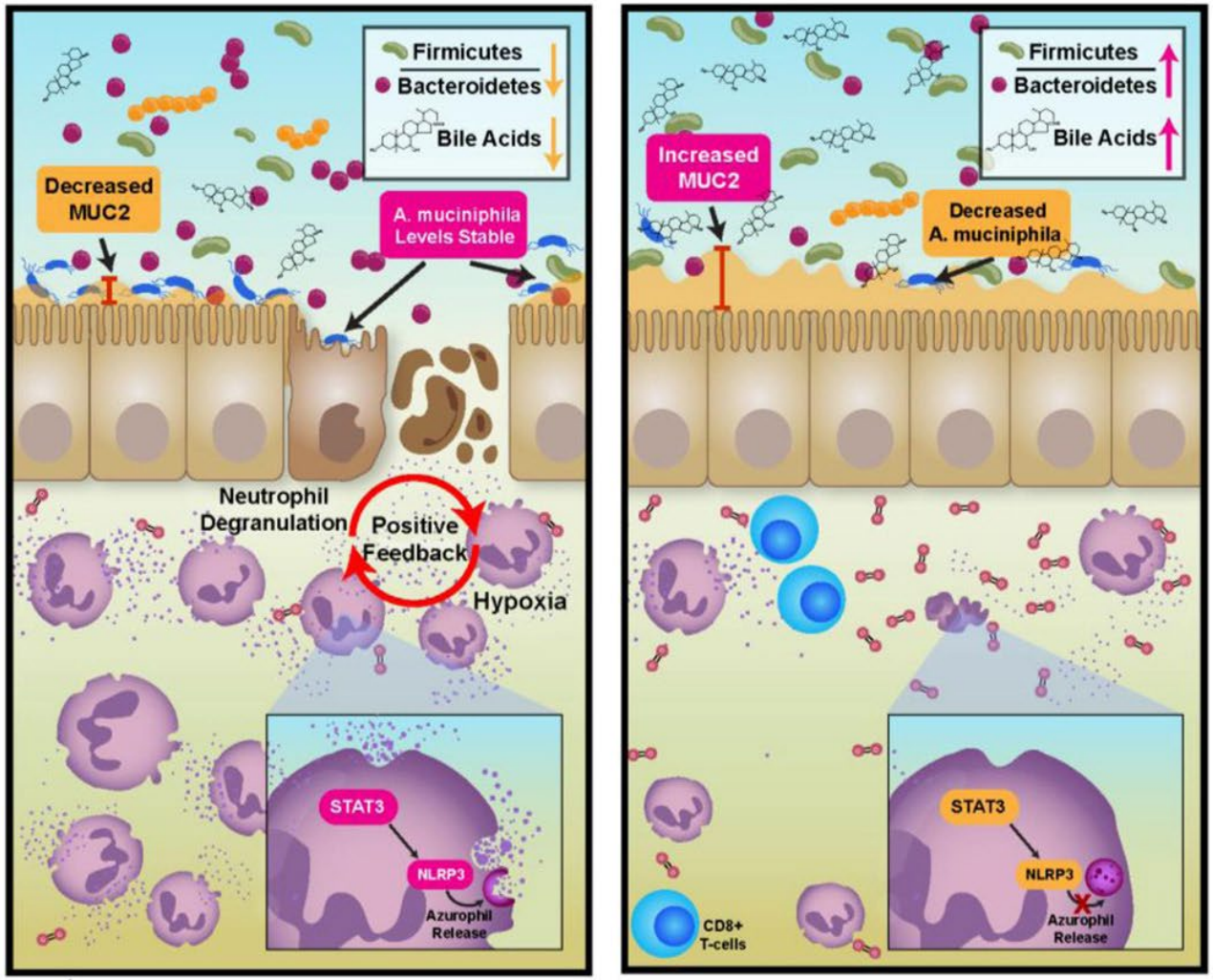




Reduction in Mucinophiles



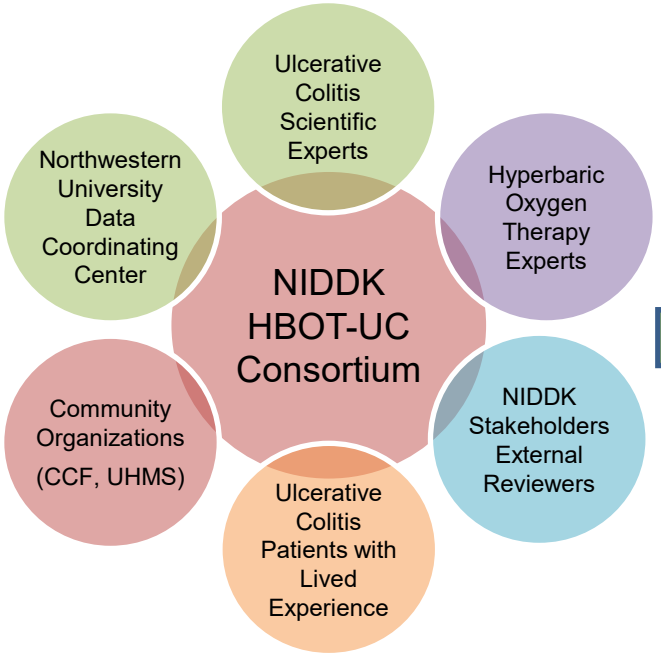
Gonzalez C…Dulai PS. *Cellular and Molecular Gastroenterology and Hepatology* 2022



cmgh CELLULAR AND MOLECULAR GASTROENTEROLOGY AND HEPATOLOGY

Gaps for ASUC Trials

Clinical trial design considerations for hospitalized patients with ulcerative colitis flares and application to study hyperbaric oxygen therapy in the NIDDK HBOT-UC consortium



PRECIS-2 Framework

ASUC Trial Design Recommendations

- Endoscopy required for enrollment (Mayo endoscopic sub-score 2-3)
- PROs: Rectal Bleeding, Stool Frequency, Urgency, Nocturnal Bowel Movements
- Competing risks of rescue therapy requires early escape design
- RAND Panel Statement for standardized steroid dosing, discharge criteria, follow-up
- Primary endpoint: resolution of bleeding, improvement in stool frequency, avoidance rescue therapy
- Stratification for advanced therapy exposures in outpatient setting
- Biomarkers and Endoscopy require exploration as secondary outcomes to define response criteria

Dulai PS, et al. *Aliment. Pharmacol. Ther.*

AP&T

1:1 RANDOMIZATION (HBOT:sham)

Site A

Site B

Site C

Site D

Site E

Site F

PRIMARY END-POINT (Day 5 Response – resolution of bleeding and improvement in stool frequency without colectomy, biologics, or small molecules)

HBOT ARM (n=63)

VERSUS

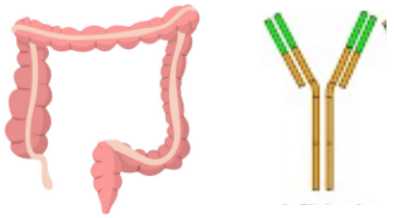
SHAM ARM (n=63)

Multiplace Sham

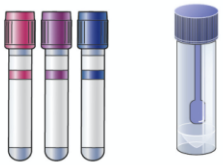
Monoplace Sham

SECONDARY

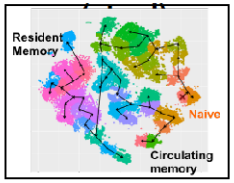
Endoscopic and histologic remission, blinded central reads



Progression to biologic, small molecules, or colectomy



Multi-omics microbial sequencing



Single-cell tissue immune and microbe sequencing (spatial transcriptomics)

Multiplace Chamber	Multiplace HBOT	Multiplace Sham	Monoplace Chamber	Monoplace HBOT	Monoplace Sham

HBOT (Multi-place or monoplace) – 2.4 ATA, 100% O2; Multiplace Sham – 2.4 ATA, 21% O2; Monoplace Sham – 1.3 ATA, 21% O2

HBOT for IBD

- Safe and well tolerated
- Evidence exists for efficacy, particularly for Crohn's fistulae and hospitalized UC
- High quality RCTs underway for ASUC