Management of Hospitalized Patients with IBD: Pain Control and Dietary Therapy

Jason Harper, MD

Clinical Associate Professor, University of Washington

Disclosures

- Advisory Boards: None relevant to this presentation to disclose

Outline

- Multimodal inpatient pain management in IBD
- Inpatient nutritional therapy and IBD

Inpatient Proactive Pain Management in IBD

- Opiate use among patients with IBD is highly correlated with poor outcomes, including mortality.[1]
- Opiates are prescribed to ~30-50% of IBD patients at hospital discharge.[2]
- 30-day readmission rates are higher in opiate-exposed IBD patients.[3]

1. Liechtenstein et al. *Serious infections and mortality in association with therapies for Crohn's disease: TREAT registry.* Clin Gastro Hepatol, 2006.
2. Berry et al. *Pain in inflammatory bowel disease is not improved during hospitalization: The impact of opiates on pain and healthcare utilization.* Dig Dis Sci, 2020
3. Hazratjee et al. *Hospital readmission in patients with inflammatory bowel disease.* Am J Gastroenterol, 2013

A Multimodal Intervention Using Nonopioid Analgesics Is Associated With Reduced Intravenous Opioid Exposure Among Hospitalized Patients With Inflammatory Bowel Diseases

Rahul S. Dalal, MD[1], Sonali Palchaudhuri, MD[2], Christopher K. Snider, MPH[3], Yevgeniy Gitelman, MD[4], Mihir Brahmbhatt, MD[4], Nikhil K. Mull, MD[4], Shivan J. Mehta, MD, MBA, MSHP[2,3], Christopher Klock, MBA[5], James D. Lewis, MD, MSCE[2,3,4] and Gary R. Lichtenstein, MD[2]

Am J Gastroenterol, 2020

Methods/Target Population

- Prospective cohort study (control ➔ pre-implementation data) of 4 targeted interventions:
  - 1) Access to IV acetaminophen for IBD patients
  - 2) GI consult “smartphrase”
  - 3) Inpatient pain pathway published to intranet
  - 4) Text message “alerts” to admitting providers

Pain Management Pathway

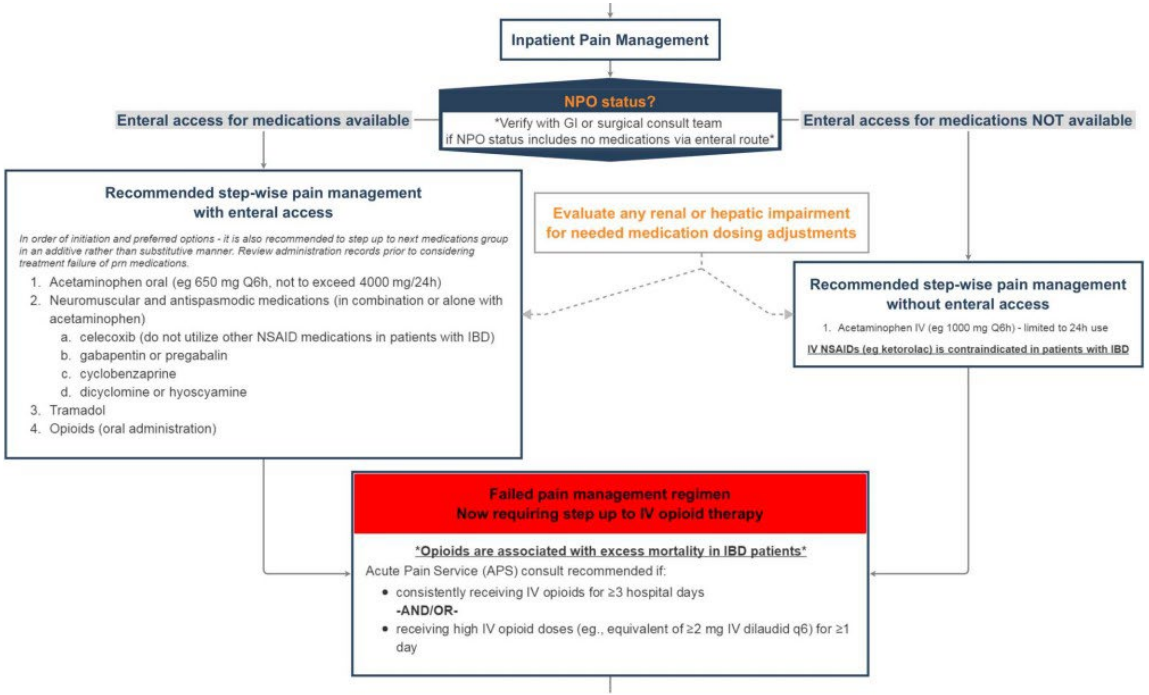
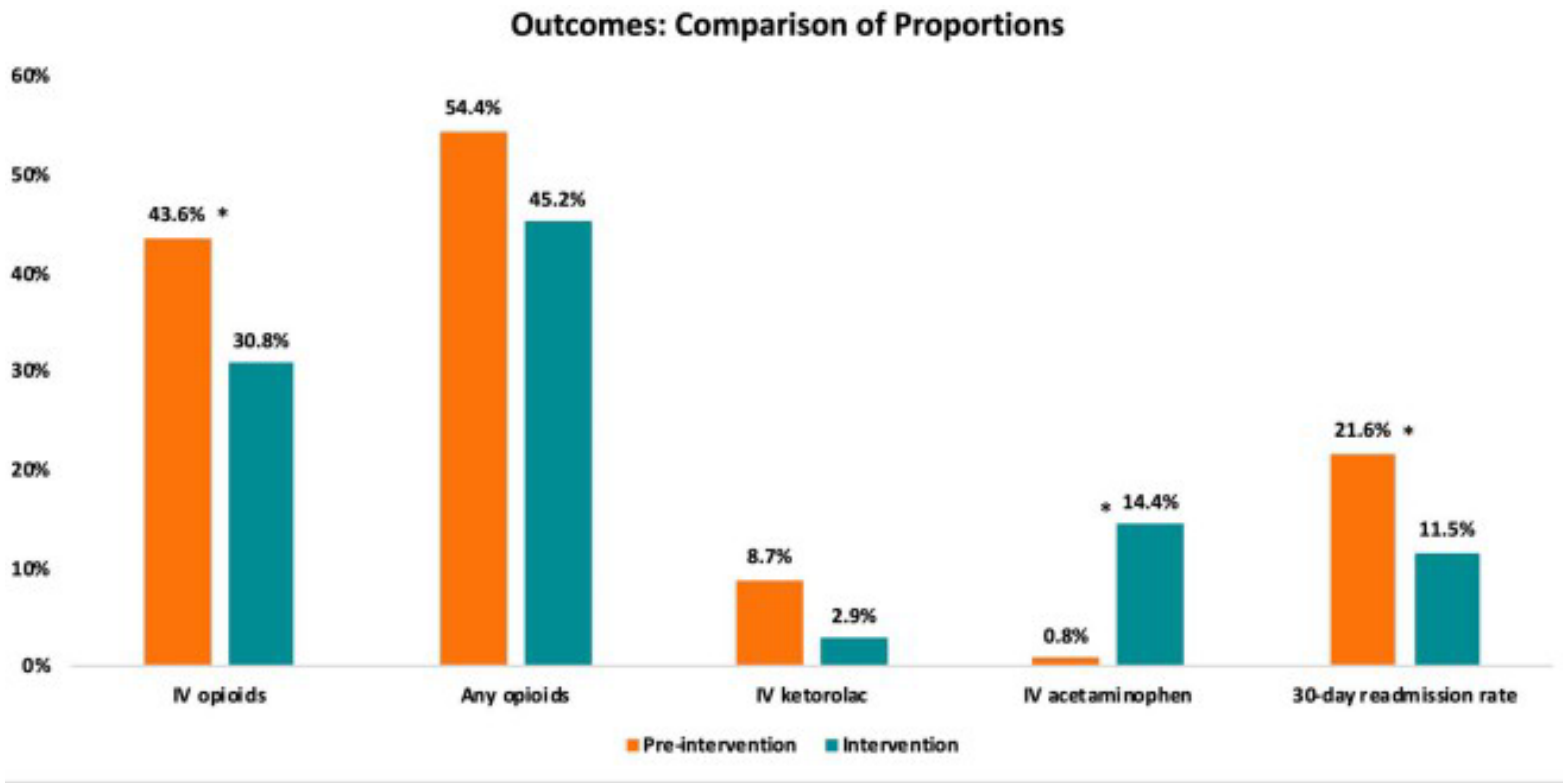


Figure 1. Inflammatory bowel disease pain management pathway. GI, gastroenterology; IBD, inflammatory bowel disease; IV, intravenous; NPO, nothing by mouth; NSAID, nonsteroidal anti-inflammatory drug.

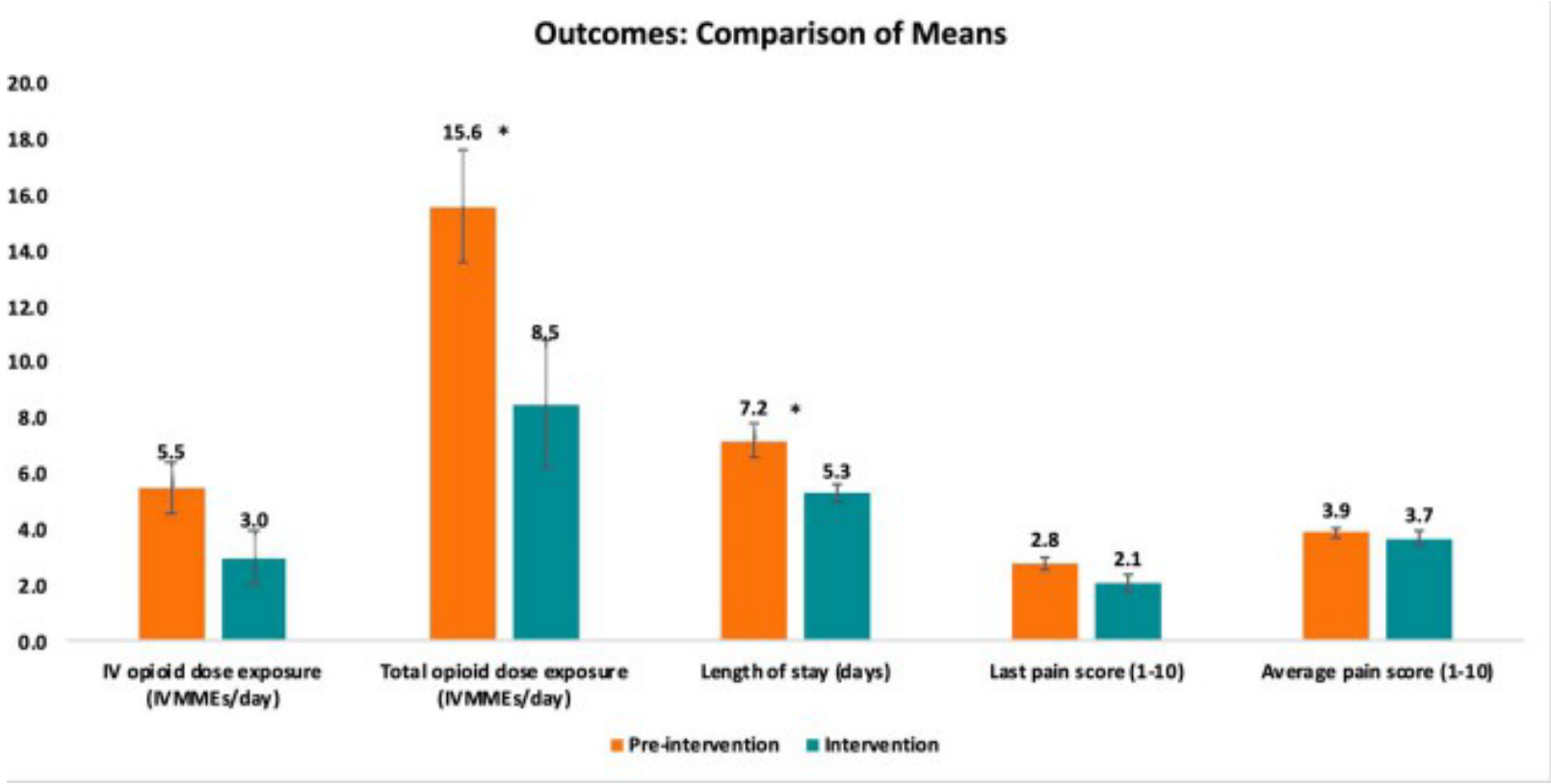
Table 1. **Baseline characteristicsof primary analysis**

Primary analysis: patient characteristics (January-December 2018 n January-June 2019)	Pntintervention (Jan1111 ember 2018) N = 241	Intervention (Jan1111ry–June 2019) N = 104	Pvalue•
Proportion 18D type			0.87
UC	29.9%	30.8%	
CD	70.1%	69.2%	
Proportion on biologic therapyb	53.5%	49.0%	0.44
Proportion admitted for 18D flare	66.8%	69.2%	0.66
Proportion with fistula, abscess, or bowel obstruction	25.7%	21.2%	0.36
Proportion bowel resection surgery performed	25.7%	26.0%	0.96
Proportion with opioids on home medication list	29.1%	28.9%	0.97
Proportion female	58.5%	47.1%	0.05
Proportion race			0.15
White	64.3%	57.7%	
Black	27.4%	29.8%	
Asian	1.7%	0.0%	
Other or unknown	6.6%	12.5%	
Proportion Hispanic ethnicity	4.2%	3.9%	0.90
Mean age (yr)	42.5	41.5	0.60
Mean BMI	25.4	25.5	0.90
Mean first pain score 0-10)	6.0	6.6	0.18

Primary Outcomes



Primary Outcomes



Targeted housestaff intervention reduces opioid use without worsening patient-reported pain scores and improves outcomes among patients with IBD: the "IBD pain ladder"

Pavlos Kaimakliotis[1] · Ajit Ramadugu[1] · Jennifer Kang[1] · Timothy McGorisk[2] · Anne Polick[1] · Effrosyni Votta-Velis[3] · Itishree Trivedi[2]

International Journal of Colorectal Disease (2021) 36:1193–1200

INITIAL MANAGEMENT

1. Start IV hydration; replete lytes
2. Ensure treatment with anti• Inflammatory (IV or PO steroids) after discussion with GI feUow (SI
3. For patients with evidence of rectal-Involvement of Clohn's and all patients with UC, consJder rectal stl!l'olds
4. Consider neuromodulator (SNRI or 1abilpentlnl *for* neuropathlc **pain**
5. **Pain** Control
   1. *II THE MTIINT IS* **A** IMll1 *CH/IONIC 11/GH-OOSE* OPI0/0 *U$EII, IIEFER TO* **:if'**
   2. Ac,etamlnophen: *Start 625mg* ***q4H*** *(consider PR if not tolerating PO)*
   3. Antispasmodics: *If no contraindication -* 2e ***revrrse***
      1. Hvascyamine: *o.usmg-0.25mg q4H PRN*
      2. Dlcydomlne: *20mg q6H* ***PRN***
   4. *Con:sider pain comult* lo *start opioid.sparing analgesia*

ADDITIONAL CONSIDERATIONS I -

1. If tolerating PO solid diet, ensure patient is on a low-residue diet
2. Antiemetics PRN to allow for intake of PO analgesics

OPIOID DEPENDENT MANAGEMENT IN CHRONIC USER

1. Acetaminophen with hydrocodone: *Start 315mg/5mg* ***q 6*** *hours,* maJ(*hydrocodoM 6Dmg/day*
2. ConJlder *pain consult to* Jtort *opioid sporing onalgeslo*

If non-opioid therapy not llontrolling pain, attempt the following

OPIOID DEPENDENT MANAGEMENT

1. Tramadol: *Start .ISmg q6H, max 400mg dally .. consider CYP Interactions If patient also started on 1CAfor neuropathlc pain••*
2. Acetaminophen with hydrocodone: *Start 325mg/5mg q 6 hours, max hydracodone 60mg/day*

Characteristic	Pre-intervention (*n* =40)	Post-intervention (n =41)	*p* value
Age	39.5	40.5	0.7
Mean disease duration (years)	8.9	10.8	0.43
Female sex	61%	57%	0.81
UC	22.5%	24%	
CD	77.5%	76%	
Most common Montreal phenotype in Crohn's disease	A2L3B3	A2L3B3	
Current tobacco use	26%	24.3%	
Home biologic use*	35%	34%	1
Home corticosteroid use	28%	15%	0.28
Chronic/outpatient opioid use	12.5%	10%	1
Mean admission CRP level (mg/L)	52	36	0.16
Mean admission fecal calprotectin level (µgig)	385	616	0.1
Mean admission hemoglobin level (g/dL)	11.8	12.1	0.5

*Biologics use in order of frequency of use included in:fliximab, adalimumab, vedolizumab, and ustekinumab

Outcomes	Pre-intervention (n =40)	Post-intervention (n=41)	*p* value
Opioid-related outcomes			
Mean total motphine equivalents during admission (mg)	43.4	7.7	0.01
Opioids administered during admission (yes/no)	65%	41%	0.001
Discharge opioid prescription	3.7%	0%	0.03
Quality of care outcomes			
Mean pain scores on admission	4.7	5.4	0.41
Mean pain scores on discharge	1.4	1.6	0.67
Length of hospitalization (days)	5.3	3.7	0.04
90-day readmission rate	25%	7%	0.04

Targeted ER Intervention Works As Well

- Park et al., AJG 2021 (abstract)
- Pilot study of educational intervention for ER providers (EMR smart-set, GI consult smart-phrase, intra-net guideline)
- Post-intervention, rate of **any** opiate being given in ER for IBD patients fell by 33% and total amount of opiates given by 50% (in MME)
- Rate of GI consultation fell by 23% and rate of hospital admission by 17% (P = 0.058)
- Average pain scores unchanged pre-/post-intervention

Sci Rep. 2023; 13: 22396.
Published online 2023 Dec 16. doi: 10.1038/s41598-023-48126-0

PMCID: PMC10725490
IPMID: 38104145

A randomized controlled trial of a proactive analgesic protocol demonstrates reduced opioid use among hospitalized adults with inflammatory bowel disease

Sameer K. Berry,[1] Will Takakura,[1] Devin Patel,[1] Rajalakshmi Govalan,[1] Afsoon Ghafari,[2] Elizabeth Kiefer,[3] Shao-Chi Huang,[3] Catherine Bresee,[4] Tend K. Nuckols,[1] and Gil Y. Melmed[02]

Outline

- Single center RCT (un-blinded) of “usual care” vs opiate-sparing pain protocol
- Small study (~15 ppl per arm)
  - Most excluded due to imminent surgery or refusal to participate

Pain Protocols

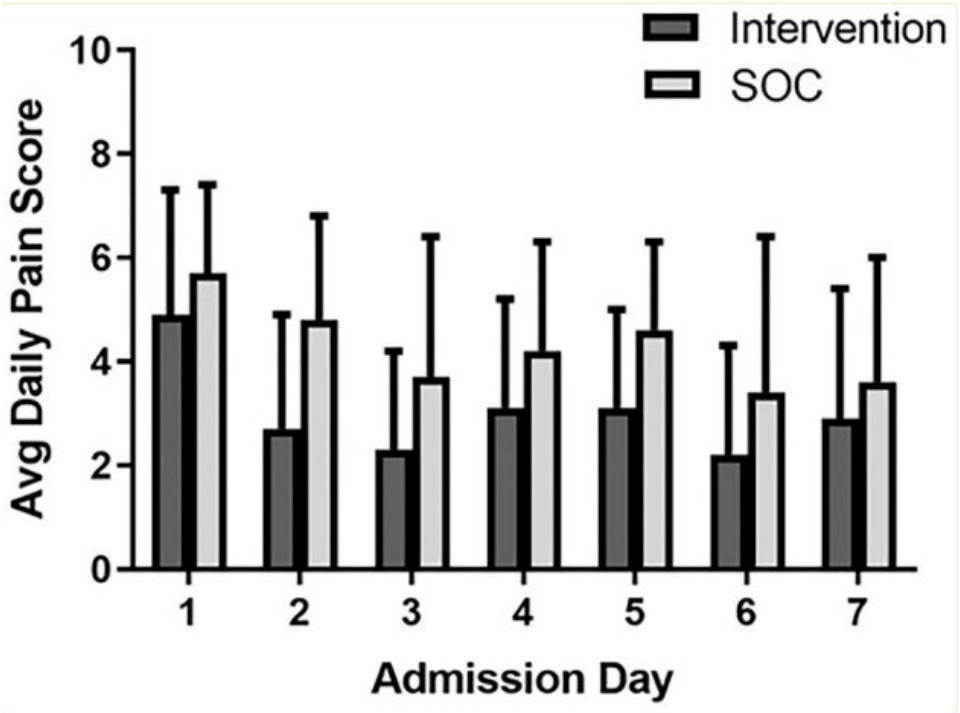
Mild Pain (VRS 1 - 3)
- PO Acetaminophen 1000 mg q8hr

Moderate Pain (VRS 4 - 6)
- PO Acetaminophen 1000 mg q8hr
- PO Gabapentin **400** mg qhs — *hold for sedation*
- PO Lorazepam **1** mg q8hr PRN — *hold for sedation*
- PO Celecoxib **200** mg on day 1, then 100 mg BID **(4 days total - automatic end date)**
- sequential compression device + SQ heparin (auto order)

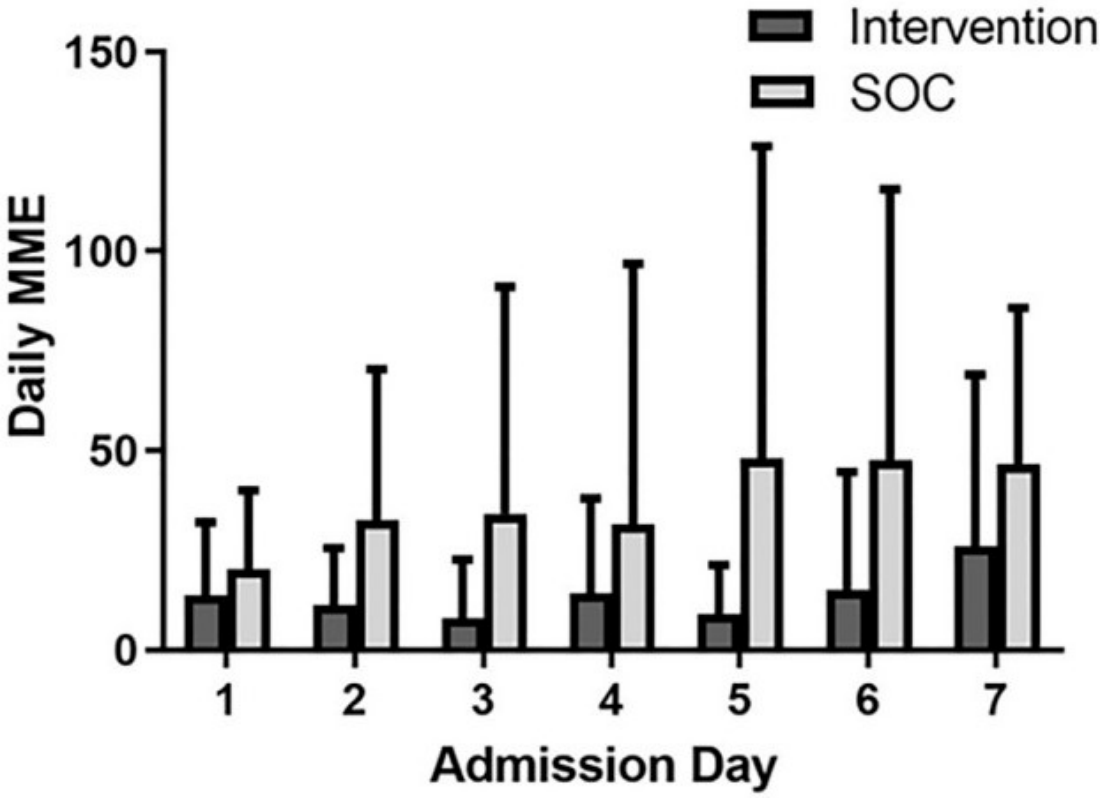
Severe Pain (VRS 7 > 10)
- PO Acetaminophen 1000 mg q8hr
- PO Gabapentin **600** mg qhs — *hold for sedation*
- PO Lorazepam **2** mg q8hr PRN — *hold for sedation*
- PO Celecoxib **400** mg on day 1, then 100 mg BID **(4 days total - automatic end date)**
- sequential compression device + SQ heparin (auto order)

Breakthrough Pain
- PO Tramadol 50 mg q6hr PRN
- IVPB Morphine 2 mg q4hr PRN (opiate naive)
- IVPB Morphine 4 mg q4hr PRN (opiate tolerant - may adjust)

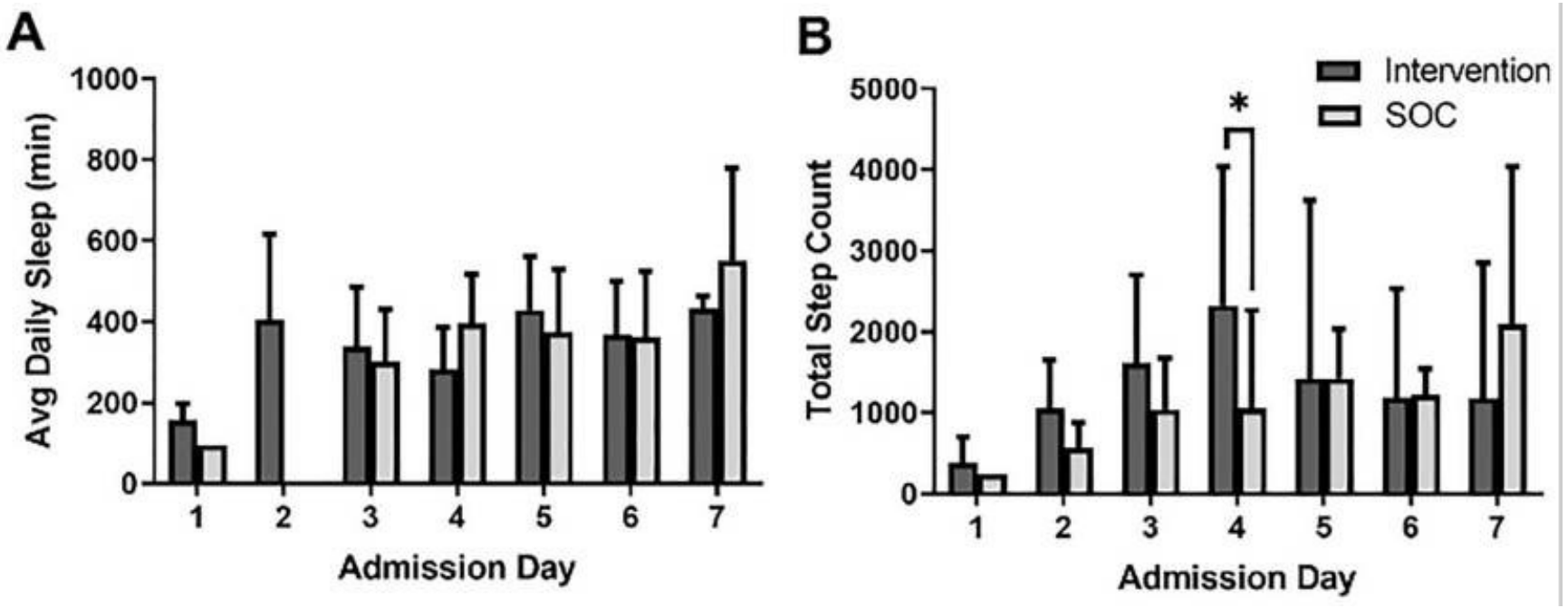
Average Pain By Day



Opiate Usage



Sleep Quantity and Daily Step Counts



NSAIDs and IBD : Fact or Fiction?

- Older case control studies looking at NSAID usage and risk of IBD flare problematic
- Extended (4 weeks) use of non-selective NSAIDs **may** increase risk of IBD flare[1]
- Temporal association between IBD flares and NSAID prescriptions heavily affected when adjusting for **baseline level of disease pre-exposure[2]**
- Blinded short term usage of celecoxib (14 days) ≠ UC flare compared to placebo[3]

1. Takeuchi K et al. Clin Gastroenterol Hepatol. 2006
2. Cohen-Mekelburg S et al. Am J Gastroenterol. 2022
3. Sandborn WJ et al. Clin Gastroenterol Hepatol. 2006

Takeaways

- Paucity of literature about pain management in hospitalized IBD patients
- Opiate sparing protocols are feasible and potentially effective
  - Caution re: scheduled acetaminophen in high risk populations
    - EtOH abuse, elderly, malnourished, pre-existing liver disease
- Expectation matters in analgesia (high placebo response): scheduled > PRN
  - Anxiety vs pain

Inpatient Nutritional Management in IBD

- Malnutrition is simultaneously under-recognized, under-defined and under-treated among IBD patients despite high prevalence.[1]
- Malnutrition is an independent risk factor for adverse IBD outcomes.[2]
- Nutritional optimization protocols have shown improved perioperative outcomes.[3]

1. Massironi S et al. *Inflammation and malnutrition in inflammatory bowel disease.* Lancet Gastroenterol Hepatol, 2023
2. Hashish J, et al. *AGA Clinical Practice Update on Diet and Nutritional Therapies in Patients With Inflammatory Bowel Disease: Expert Review*. Gastroenterology, 2024.
3. Ljungqvist O et al. *Enhanced recovery after surgery: a review*. JAMA Surg, 2017

Frequency and Variables Associated with Fasting Orders in Inpatients with Ulcerative Colitis: The Audit of Diet Orders –Ulcerative Colitis (ADORE-UC) Study

Zane R. Gallinger, MD, Amir Rumman, MD, Kevin Pivovarov, MD, Kyle J. Fortinsky, MD, A. Hillary Steinhart, MD, and Adam V. Weizman, MD

Inflamm Bowel Dis • Volume 23, Number 10, October 2017

TABLE 1. Criteria for Appropriate Nutritional Delivery and Unjustified NPO or CLO Orders

Determination	Definition
Appropriate nutrition provided	Regular diet
	EN
Justified NPO or CLD orders	Awaiting endoscopic or other diagnostic procedure
	Acute pancreatitis
	Bowel obstruction
	Toxic megacolon
	Intractable nausea or vomiting
Unjustified NPO or CLD orders	NPO or CLD orders with the absence of a clear justification and without alternative nutrition provided (TPN or EN)

- Single center review of ~180 admissions for severe UC (LOR 2-30 days)
  - Total of 252 NPO/CLD orders
  - 112 of these (45%) were considered unjustified
    - Average duration **3 days** ➔ over 300 missed patient-meals
    - Most common reason ➔ initial diet order placed
      - Patients on prolonged NPO status were **less** likely to undergo endoscopic restaging

Efficacy of exclusive enteral nutrition in complicated Crohn's disease

Qingfan Yang[a,b], Xiang Gao[a,b], Huiping Chen[a,b], Miao Li[a,b], Xiaojian Wu[a,b], Min Zhi[a,b], Ping Lan[a,b] and Pinjin Hu[a,b]

SCANDINAVIAN JOURNAL OF GASTROENTEROLOGY, 2017
VOL. 52, NO. 9, 995–1001

- Single center observational trial of 12 weeks of EEN (through NGT) in adults with B2/B3 Crohn's disease
- **No** concurrent medical therapy was allowed
  - Exception: antibiotics for IAA after drainage
- Total of 41 patients recruited
  - 33 with some form of complex fistulizing disease
  - 10 with inflammatory strictures

Table 2. Inflammatory Index before and after EEN.

	Before EEN	4 week EEN	12 week EEN	Before EEN vs. 12 weeks of EEN (*p* value)
Hs-CRP(mg/L)	9.75± 3.57	3.69± 3.87 (2 weeks EEN) 3.27± 3.69 (4 weeks EEN)	3.74± 3.27	<.01
PLT(*10E9/L)	324.34± 108.64	247.25± 83.46	238.96± 59.59	<.01
ESR(mm/h)	45.55± 27.36	19. 33± 14.02	19. 95±14.27	<.01
CDAI	223.43± 65.53	129.00± 32.05	106.77± 42.73	<.01

Table 3. Nutritional Index before and after EEN.

	Before EEN	4 week EEN	12 week EEN	Before EEN vs. 12 week EEN (*p* value)
NRS2002	3.54± 1.45		2.23± 1.48	<.01
BMI(Kg/m2)	16.64± 1.79	17.72±1.74	18.26± 1.74	<.01
ALB(g/L)	35.69±5.41	39.19± 4.81	42.17±3.02	<.01
Hb(g/L)	105.95 ± 18.64	110.56± 11.87	127.04± 13.31	<.01

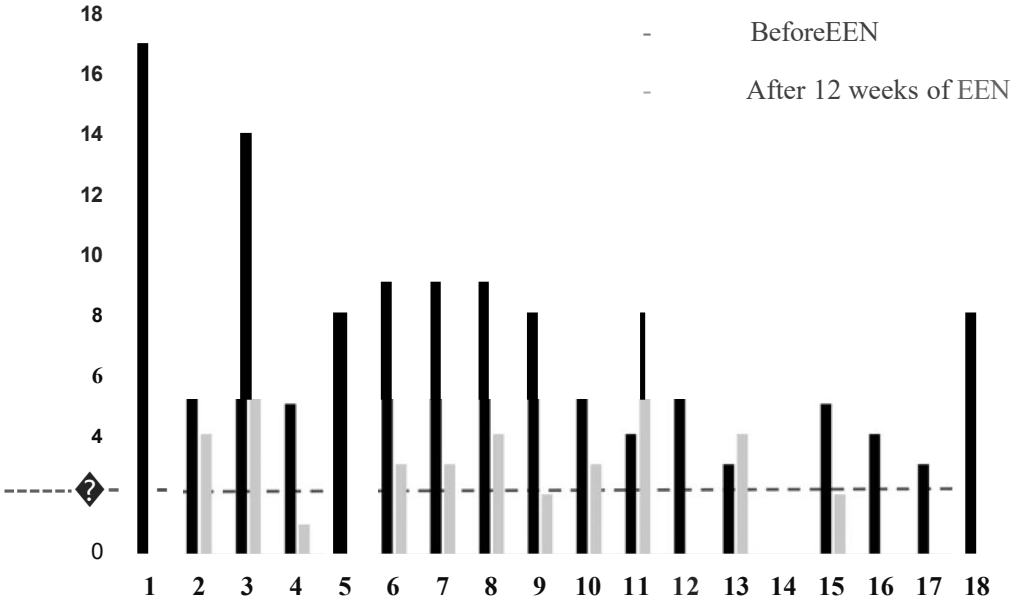


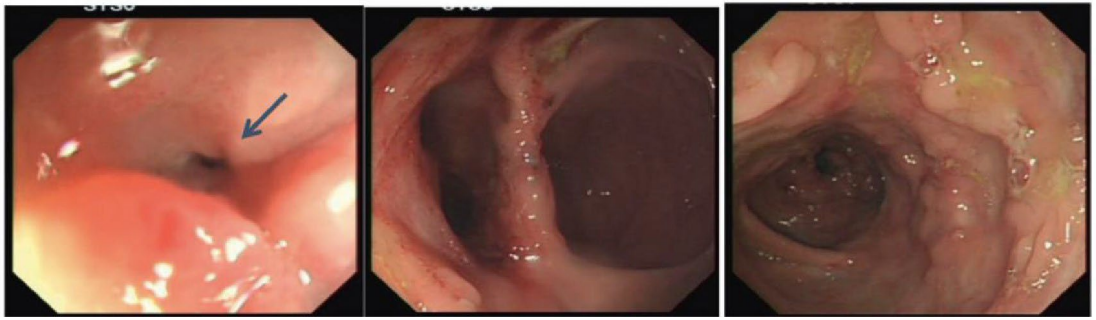
Figure 2. SES-CD before and after EEN. In our study, 23 out of 41 patients underwent paired endoscopy before and after EEN treatment. Among them, 5 patients were excluded because of colostomy. The scores of SES-CD were calculated in the remaining 18 patients with intact ileocolon. The SES-CD score of case 14 was 0 both before and after EEN.

Fistula in terminal ileum

Ulcers in ileocecal valves

Ulcers in descending colon

Before EE

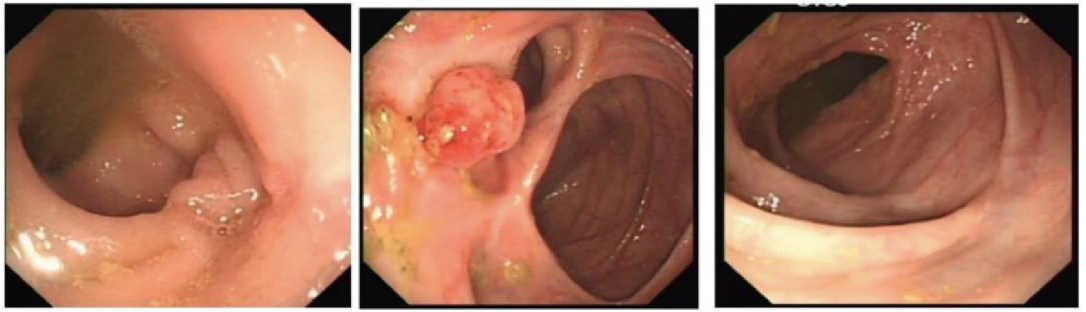


Fistula in terminal ileum closed

Ulcers healed

Ulcers healed

AfterEEN



- Of 33 patients with internal fistula and/or IAA, 3 required surgery during the study period
- Resolution of enterocutaneous fistulae seen in 3 of 4 individuals
- BWT in stenotic disease segments decreased by ~1.5 mm (*P* = NS)

Inflammatory Bowel Diseases, 2024, XX, 1-10
https://doi.org/10.1093/ibd/izae204
Advance article publication 2 July 2024
Review Article

CROHN'S &COLITIS FOUNDATION

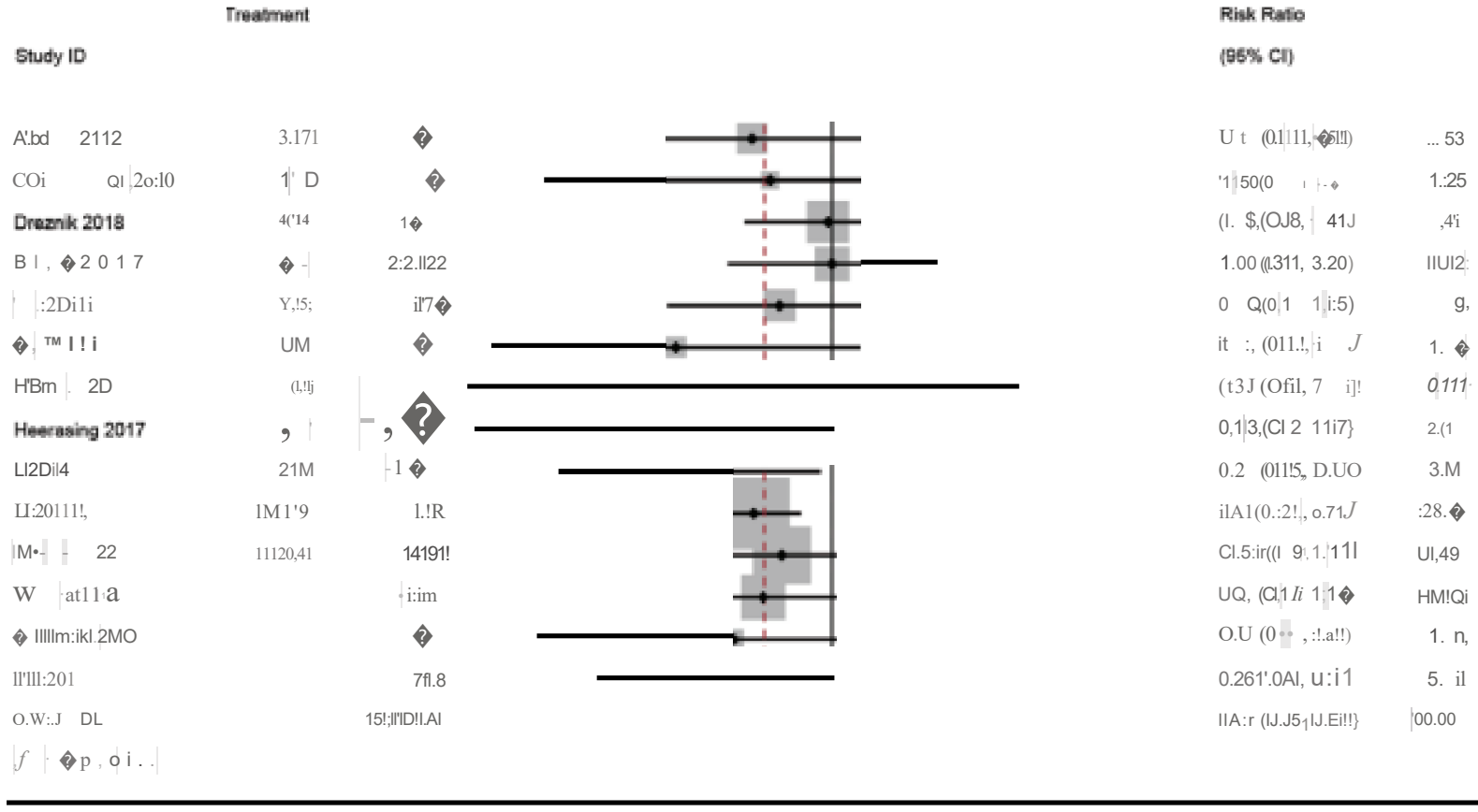
Preoperative Exclusive Enteral Nutrition Is Associated With Reduced Skin and Soft Tissue and Intra-abdominal Infections in Patients With Crohn's Disease Undergoing Intestinal Surgery: Results from a Meta-Analysis

Lev Krasnovsky, BA, Andrew T. Weber, MD, Victoria Gershuni, MD, MTR, MSGM, Elisa Petlake, MD, MPH,[1] and James O. Lewis, MD, MSCE[1]

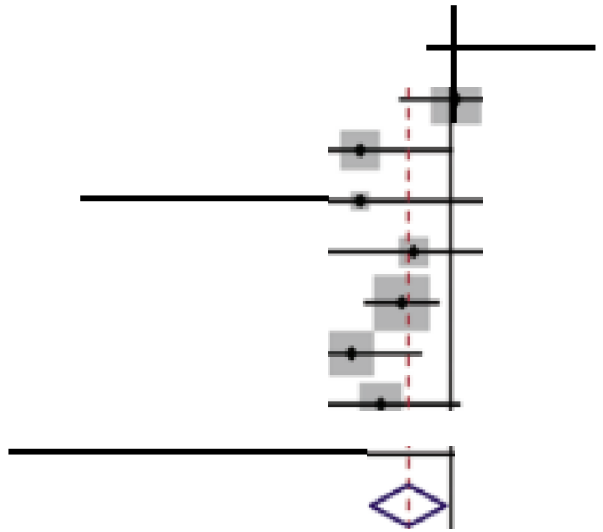
Outline

- 20 included studies (1982-2022)
  - All but 1 retrospective cohorts
- Duration of EEN ➔ 7-90 days
- TPN exposure considered separately

ntra-abdominal Septic Complications



Skin and Wound Infections



Tr.irtrna.m:

Risk Ratio

Study ID

(95% CI)

Dreznik 201

El-Hussuna 2017

e 2019 4/45

anis 2020 0/8

Heerasing 2017 2/38

0.00781125 1 1 B

Tl:ible 2. Swnmall"p' •of posts:ul'gim.J outc ◆e:s betw.ee11 IBD patients:with Dl' wilt1Du . EEN prior ro surgery.

Outiilomc-	No. StudiC!S!	Co1i1im:1ls	EE	Pooled Estimate (95% Confidc,nc,c lnt:c:nalf		Eggir's .P
]nl:ra-abdorninal septic comlP!icatiDD.:!l (	14	152/1044	65"l974	0.47 (O.l5"; 0.61)	0.0%	(U.17
SkiOJ and soft 1:is:m.c-iri:fc-ctioOJ (ri/N)	9	160/919	*711638*	0.63 (0.42; 0.94)	42.7%	0.42.9
DuratioOJ o:f sucw:I"Y	4	lO'i'	**34:!:l**	-0.96 (-2.01; 0.09)	96.7%	0.4.29
lc:n.g.1:h of rci;c:ctc:dl bow.c-l	4	473.	272	-0.08 (-0.34. 0.19)	rn.5%	iJ.799
lc:ngm of .smr	*5"*	*557*	367	-0.13 (-0.30. 0.04)	15.2%	0.941
Blood! losi;	3.	211	3JO	0.03 {-0.15"◆0.20)	0.0%	0.6:!:16
Comrccs.ion horn laparoscopic to open (n/N)	*3*	l0/104.	14/,6"1	0.9-0 {0_3.9 2.11)	17.0%	0.372

"'.Rd:ia\'i::ri◆k **for** dii:hmomom CJI!l.toon1c.s: **and!** mmdar.dizcd mc.:11.1 d:iffc-l'CJ.10: fur ccmr:inLJOLJ!S:O'l!ICCOJneg_

Recehred: 10 OcltobN 2020 | First decision: 26 Oc.ro'ber 2020 | Accepted: 19 December- 2020

001: il!0..1111(.apt.t6249'

AP&T Alimentary Ph.:irmacolo& Therapeutics WI LEY

Randomised clinical trial: exclusive enteral nutrition versus standard of care for a,cute sever,e ulc,erativ,e colitis

Pabitra Sahu[1] fl | Saurabh Kedia[1] fl | Sudheer K.. Vu-yyuru[1] | Aditya l Bajaj[1]
MainasV1ini Markandey[1] | Namrata s1·ngh[1] | Mukesh Singh[1] | Bhaskar Kant-e'[1] |
Peeyush Kumar[1] | Muke-sh Ra1njan[1] | Peush Sahni[2] | Raj-esh P.anwa1r[2] | Raju Sharma1[3]
Prasenjit Das[4] | Govind Makharia[1]8 | Simon P. L. Tl'aviis[5]8 | Vineet Ahuja[1]

Protocol/Methods

- All patients with ASUC (defined by T&W criteria) admitted to single center over ~2 year time period offered enrollment
- 7 days of IV CS given to each arm, with salvage decision (IFX/CsA or colectomy) made by day 5 according to Oxford criteria
- Intevention ➔ 7 days of **exclusive** Peptamen vs ad libitum oral diet
- Originally intended to recruit ~50-60 people per arm but halted due to COVID-19

TABLE 1 Baseline demographics and clinical parameters

	EEN group (n = 32)	Standard of care (SOC) group (n = 30)	*P* value
Age (years)	32.8 ± 10.8	37.9 ± 13.1	0.82
Sex	M-12 (37%) F-20 (63%)	M-13 (43%) F-17 (57%)	0.63
Disease duration (months)	36 (12-72)	36 (9-84)	0.81
Extent	E2-8 (25%) E3-24 (75%)	E2-10 (33%) E3-20 (67%)	0.77
Prior ASUC[a]	6 (19%)	8 (27%)	0.81
Steroid use in 1st year of diagnosis	18 (56%)	21 (70%)	0.64
Prior use of azathioprine	18 (56%)	17 (57%)	0.91
Prior anti -TNF[b] therapy	4 (12%)	2 (7%)	0.75
Extra-intestinal manifestations (EIM)	7 (22%)	8 (27%)	0.83
Number of Truelove and Witts' criteria on admission in addition to bloody stool frequency > 6			
1	8 (25%)	9 (30%)	0.82
2	15 (47%)	14 (47%)	
3 or more	9 (28%)	7 (23%)	
Pulse rate (/min)	84 (70-110)	84(72-108)	0.92
Day 1 stool frequency	10 (8-20)	11 (8-16)	0.91

TABLE 2 Comparison of laboratory parameters between EEN and SOC groups at admission

	EEN group (n = 32)	Standard of care (SOC) group (n = 30)
Day 1 haemoglobin (g/L)	98 ± 20	94 ± 19
Total leucocyte count (/μL)	8735 ± 3166	8190 ± 3898
Platelet (/μL)	3.2 ± 1.3	2.7 ± 0.9
Creatinine (micromole/L)	53 ± 18	53 ± 9
Sodium (mmol/L)	138.7 ± 4.3	139.4 ± 3.3
Potassium (mmol/L)	4 ± 0.5	4.1 ± 0.5
Serum protein (g/L)	62 ± 8	61 ± 7
Serum albumin (g/L)	31 ± 7	30 ± 7
ESR (mm/hr)	46 ± 13.7	41 ± 14.1
CRP (mg/L)	24.2 (11.4-51.3)	21.7 (11.2-59.5)
FCP μg/g	1356.1 (880.1-1794.3)	1398.1 (744.7-2126.7)
UCEIS on admission	5 (4-7)	6 (4-7)
Positive CMV tissue PCR	16/30 (53%)	13/26 (50%)

lntl!fltion to treat analysis

	Exclusive enhm1I nutrition IEEN)(n =32)	**Standard of care** (SOCI In =30)	**Pvalue**
S.teroid failure	S (25%l	13f43%l	0.051
CoJectomy	3 (9%]	4 (13%1	0.41
Response to n!SOJe medical tr.erapy	4/5(801)6)	10/12 (83%}	0.72
Duration of hospitalisation (daysl	10(8-171	13 (8-241	0.04
Adverse effects	7t22%}	4(13'b)	0.00
Per protocol **.anah,sis**			
	EEN §fOUp fn =271	'Standard of care (SOC) group fn =30)	P ....alue
Co:rbirnsteroid failure	5 (19'%1	13 {43%)	0.04
CoJectomy	2 (7%}	4(13%}	0.32
Response to n!SOJe medical tr.erapy	3/3(100%1	10/12(83%1	0.41
Duration of ho spitalisation fdays}	9 (7-1.6)	13 (8-24}	<.0.01

Note: Values provided as mean ±standard deviation. median (IQR})or n (%}asappropri:at:e.

	EEN gm14> (n＝32)	**Standard** of care (SOC) group (n = 30)	**Pvalue**
Day 7 liaemo◆lol:J1n h:::IL)	**9'9** _ lB	97± '12	
Day 7 [Protein {g/U	6 4 ± 7	58,± 7	<0.01
Day 7 albumin [g/LJ	3 4 ± 4	29 ±:3	<0.01
Day 5 CRP {mg/U	5.7◆1.1•3'9.3); **n** = 27	11.7 (4.3•55.4); **n** = Zo,	O.OJ
Delta CRP (clayl--clay.5) !mgll)	23..4 !6..S•:3B.9l	11_4 (1.9-2.Sl	Ou04
Day 3 CRP {mg/ U	10.1 (1.3·54.1)	12.a U.2-n.2◆	0.13
Day 3 E-SR tmm/h)	3 4 _ :il.1.5	:37± '12.5	Oi.41
Day 3 FI:P{pg/g◆	720 {415•1126); n＝28.	1103 (676•1552◆; ㎖＝29	O.OJ
Delta fC P Wayl◆day. Jl (µig/g}	31:5 (;1.29-797)	1'40 (-.JB6➔59l	

Note◆fail..l'Es.prm1iided as mean ±standard deviation. median OQRl or n (%l as appro;p:riate.

Other Findings

- Average daily kcal/protein intake similar between groups
- Intolerance to EEN seen in ~16% of EEN group
- Lower composite rates of re-admission/colectomy within 6 months seen with EEN
- Changes in beta diversity on EEN noted with relative increase in *Erysopelotrichiae spp.*
  - No changes in alpha diversity

Takeaway

- Attention to malnutrition and its treatment is an emerging quality metric in IBD care
- Oral nutritional support (including EEN) is **risk free** in almost any non-obstructed patient and may offer measureable clinical benefits
  - Compare against $$$ and risks of PEN (TPN)
  - Patient buy-in ➔ improved adherence
- If the gut works, use it!
- Mechanism of action of EEN remains unknown
  - May **not** be translatable through the microbiome