
2021 SCSG
GI SYMPOSIUM

Best of DDW 2021: IBS

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Boston, MA Subtitle

Disclosures

- Honorarium
  - Ironwood
  - Takeda
  - Mylan
  - Bayer
  - Shire
  - Arena
  - Orphomed
  - Gemelli Biotech

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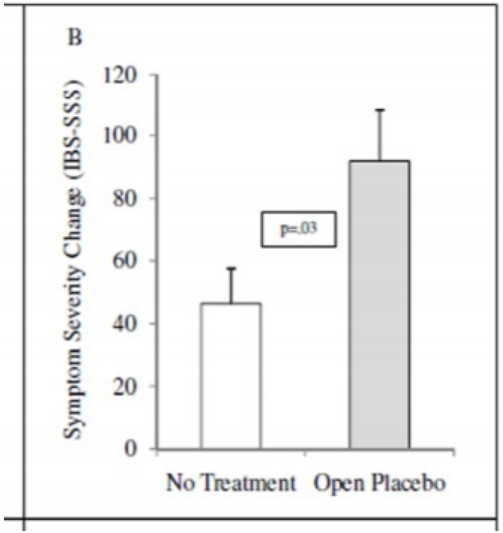
PLoS one

Placebos without Deception: A Randomized Controlled Trial in Irritable Bowel Syndrome

Ted J. Kaptchuk[1,2*], Elizabeth Friedlander[1], John M. Kelley[3,4], M. Norma Sanchez[1], Efi Kokkotou[1], Joyce P. Singer[2], Magda Kowalczykowski[1], Franklin G. Miller[5], Irving Kirsch[6], Anthony J. Lembo[1]

IBS-SSS



Research Paper

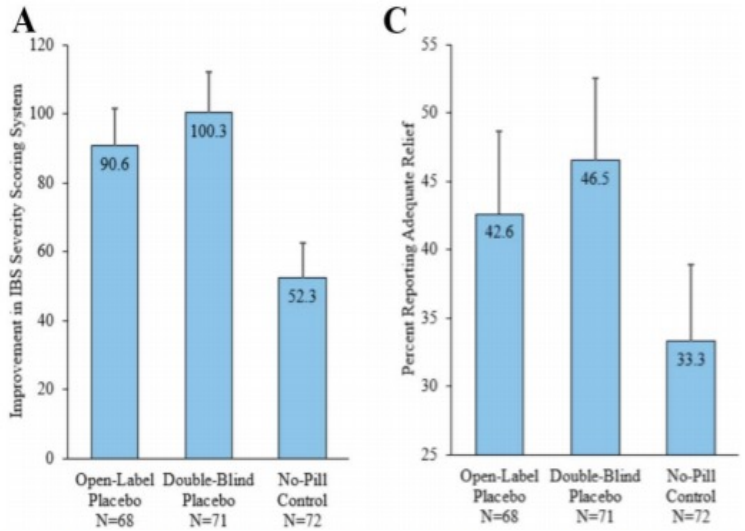
PAIN

Open-label placebo vs double-blind placebo for irritable bowel syndrome: a randomized clinical trial

Anthony Lembo[a,*], John M. Kelley[b,c], Judy Nee[a], Sarah Ballou[a], Johanna Iturrino[a], Vivian Cheng[a], Vikram Rangan[a], Jesse Katon[a], William Hirsch[a], Irving Kirsch[c], Kathryn Hall[c,d], Roger B. Davis[c,e], Ted J. Kaptchuk[c,e]

IBS-SSS

Adequate Relief



Are They Side Effects? Non-specific Symptoms Reported At The End Of A Randomized Controlled Trial Are Often Present At Baseline

Rafla Hassan[1], Sarah Ballou[1], Vanessa Yu[1], Vikram Rangan[1], Nee, Judy[1] Johanna Iturrino[1], Ted J. Kaptchuk[1], Anthony Lembo[1]
[1] Division of Gastroenterology, Department of Medicine, Beth Israel Deaconess Medical Center, Boston, MA, USA

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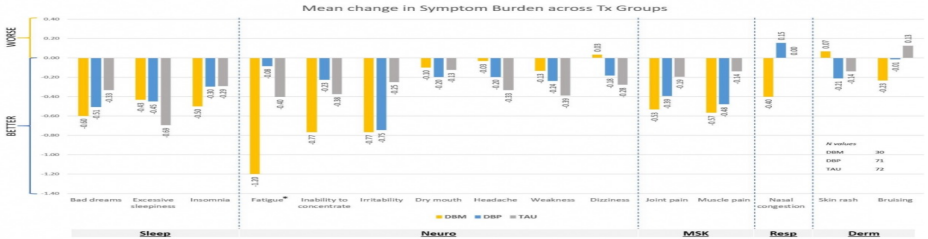
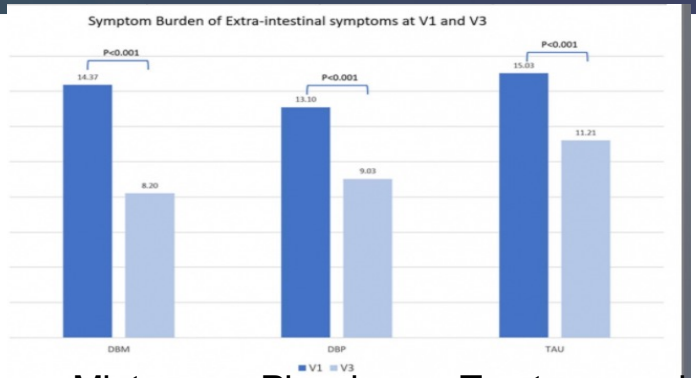
- Adverse events (AEs) clinical trials often use open-ended questions to assess AEs
- This approach is not validated, is prone to bias, can underestimate the number of actual symptoms and does not account for symptoms present at baseline
- We aimed to evaluate now extraintestinal symptoms (EIS) change over time in a RCT
- 15 nonspecific EIS assessed baseline and end of study (week 6). Symptom burden: summing severity (0-5).
- 219 IBS patients (73% women)





Mint Placebo Treat as usual

Double-blind groups

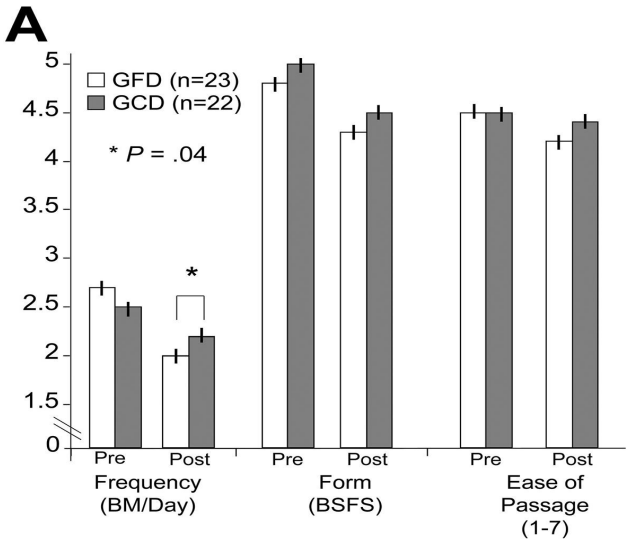
Conclusions: Non-specific symptoms are common and usually more severe at baseline.

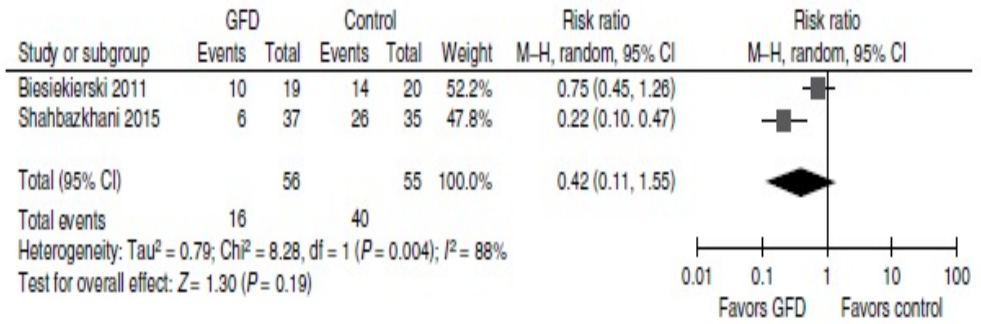
Commonly reported AEs should be assessed at baseline to better assess their relationship to treatment

Dietary Considerations for IBS

- "Traditional IBS diet"
  - 3 meals and ≤3 snacks /day : do not over eat!
  - Reduce fatty or spicy foods, coffee, alcohol, onions, cabbage and beans
  - Avoid soft drinks, chewing gum, sweeteners that ends in –ol
  - Soluble fibers - intake evenly during the day
- Low-FODMAP
- Gluten Free

Gluten Free Diet for IBS: Clinical Trials





Study or subgroup	GFD Events	GFD Total	Control Events	Control Total	Weight	Risk ratio M–H, random, 95% CI
Biesiekierski 2011	10	19	14	20	52.2%	0.75 (0.45, 1.26)
Shahbazkhani 2015	6	37	26	35	47.8%	0.22 (0.10. 0.47)
Total (95% CI)		56		55	100.0%	0.42 (0.11, 1.55)
Total events	16		40			

Heterogeneity: $Tau^2 = 0.79$; $Chi^2 = 8.28$, df = 1 ($P = 0.004$); $I^2 = 88\%$

Test for overall effect: $Z = 1.30$ ($P = 0.19$)

- Patients who responded to a GFD randomized to continue GFD or receive diet “spiked” with gluten

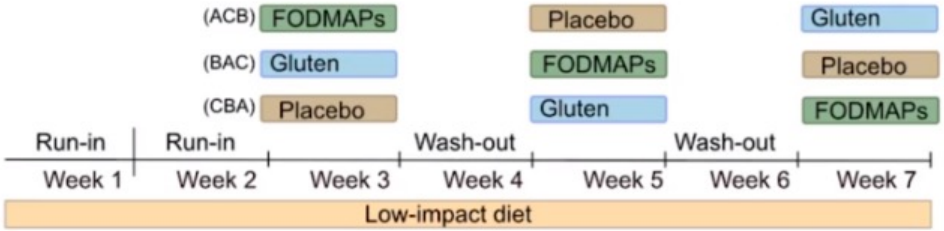
There is insufficient evidence to recommend a GFD to reduce IBS symptoms

Vazquez0Roque, M, et al. Gastroenterology 2013 144903-911.

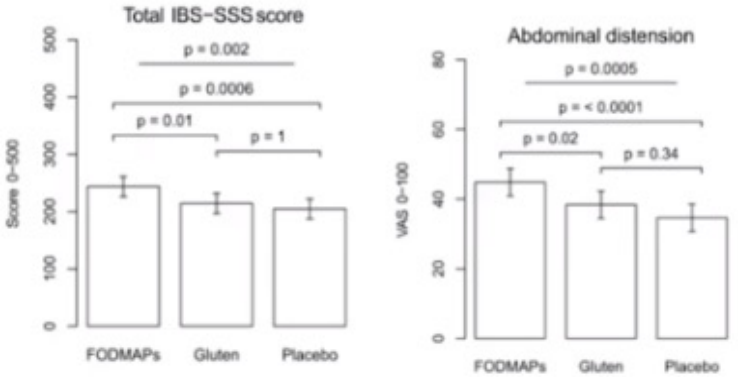
Dionne et al. Am J Gastroenterol 2018,

FODMAPs, but not Gluten, Elicit Modest Symptoms of IBS: Double-Blind, Placebo-Controlled, Randomised 3-way Crossover Trial

Per M. Hellström, Elise Nordin,
Carl Brunius, Rikard Landberg



110 IBS patients(96 women; all subtypes)



- Daily exposure
  - FODMAPs: 50 gram
  - Gluten: 17.3 gram

FODMAPs	Gram
- Lactose	15.7
- Fructose	19.5
- Sorbitol	4.5
- Mannitol	1.8
- Galactooligo - saccharide (GOS)	1.5
- Fructooligo- saccharide (FOS)	7

Approximately 50% higher amounts than typical Swedish diet

No difference in other components of IBS-SSS

Conclusions:

Modest symptom increase with FODMAP,
No significant increase with gluten

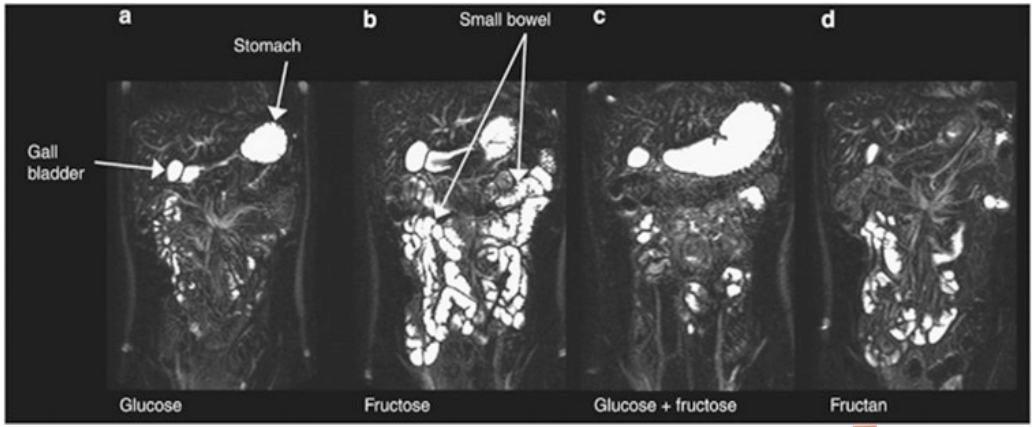
What are FODMAPs?

- **Fermentable oligo-, di-, monosaccharides and polyols**
- **Fruits with fructose exceeding glucose**
  - Apples, pears, watermelon
- **Fructan containing vegetables**
  - Onions, leeks, asparagus, artichokes
- **Wheat based products**
  - Bread, pasta, cereal, cake, biscuits
- **Sorbitol and lactose containing foods**
- **Raffinose containing foods**
  - Legumes, lentils, cabbage, brussels sprouts

Eswaran & Chey, GI Cl North Am 2011;40:141
Shepherd, et al, Clin Gastro Hepatol 2008;6:765
Gibson & Shepherd. J Gastro Hepatol 2010;25:252

Differing Effects of FODMAPs in the GI Tract

Fructose distends the small bowel with water



Fructan distends the colon with gas

Common fructans

Wheat including bread, pasta, etc., onions,, garlic, barley, brussels sprouts, cabbage, broccoli,, artichoke, inulin

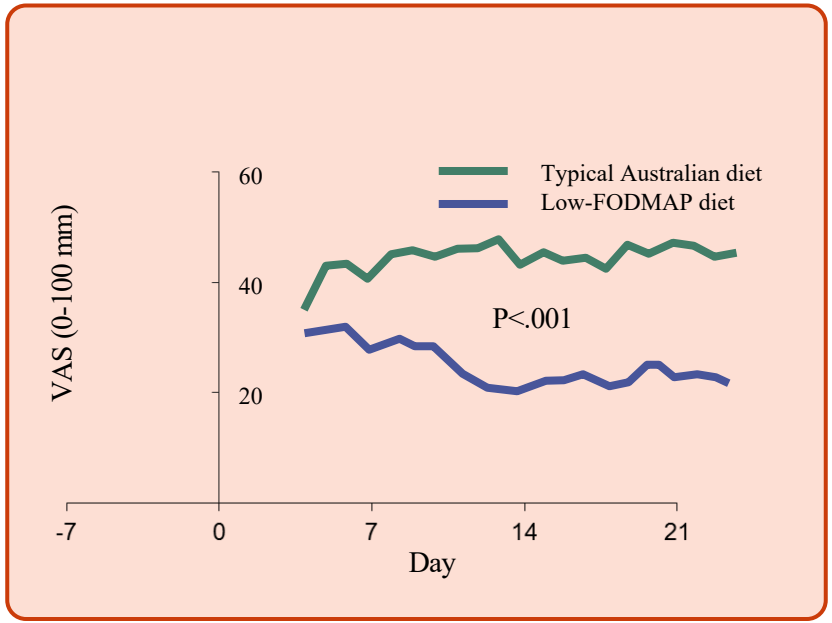
Murray et al. Am J Gastroenterol 2014 Jan;109(1):110-9

3 Phases of the Low-FODMAP Diet

Chey WD. Am J Gastroenterol 2016:111;366
Dolan R, et al. Exp Rev Gastroenterol Hepatol 2018;12:607

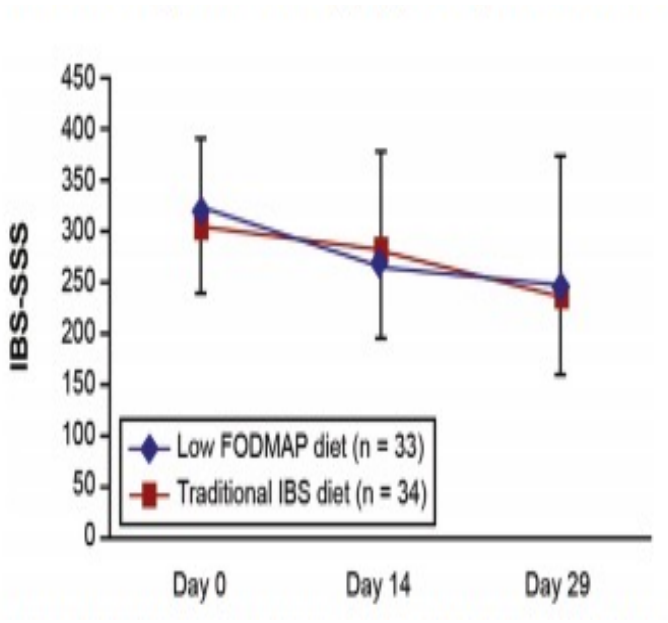
Examples of Studies Assessing the Elimination Phase of the Low-FODMAP Diet in IBS

Low FODMAP vs. Typical Australian Diet



Halmos EP, et al. Gastroenterology. 2014;146:67-75.

Low FODMAP vs. Traditional IBS Diet



Böhn L, et al. Gastroenterology. 2015. doi: 10.1053/j.gastro.2015.07.054.

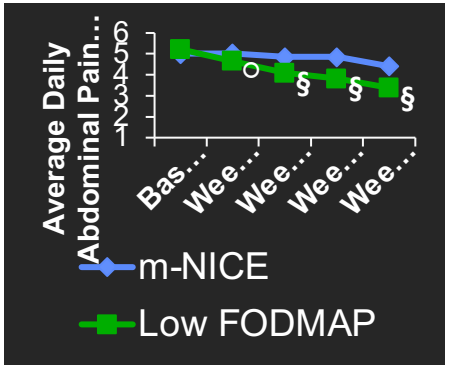
Low-FODMAP vs. mNICE Diet: IBS-D

No Differences between Low FODMAP and mNICE

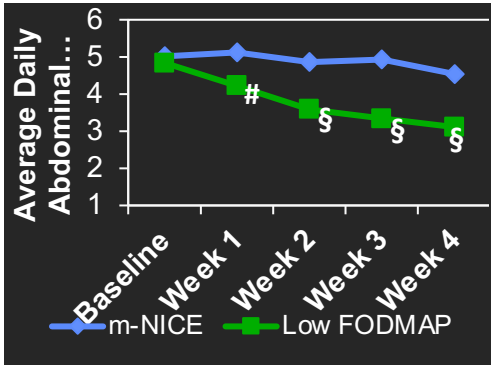
Adequate Relief (≥50% of the weeks)
52% vs. 41% (P=0.31)

Composite responders (abdominal pain and stool consistency) (P=0.13)

Abdominal Pain



Bloating

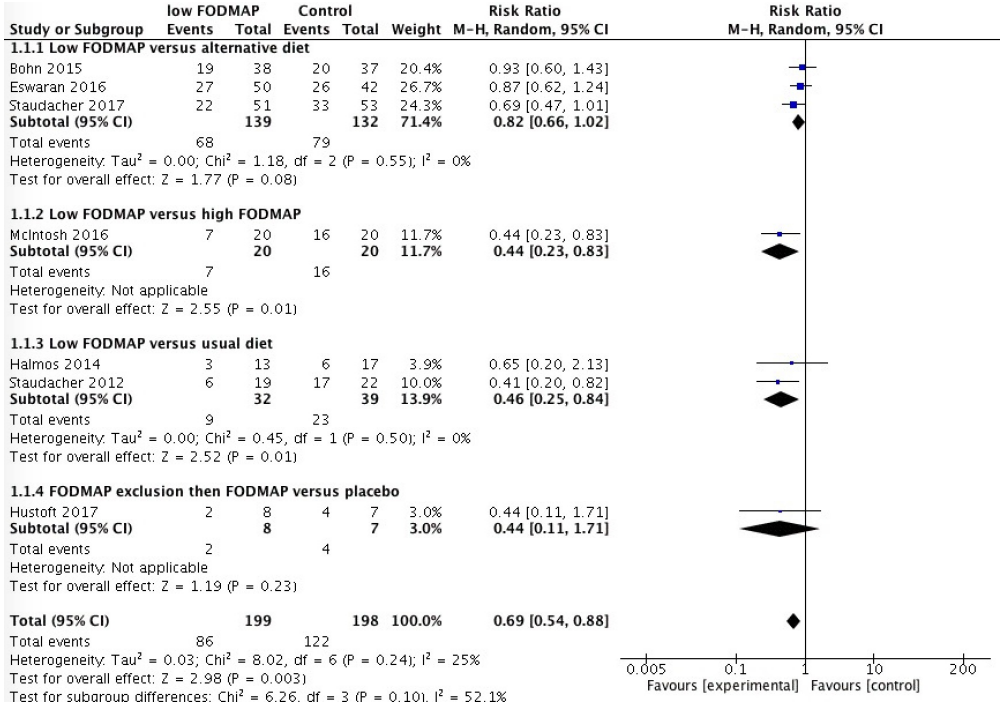


P values refer to the change WITHIN group comparing to baseline score

Eswaran, et al, Am J Gastroenterol 2016;111:1824

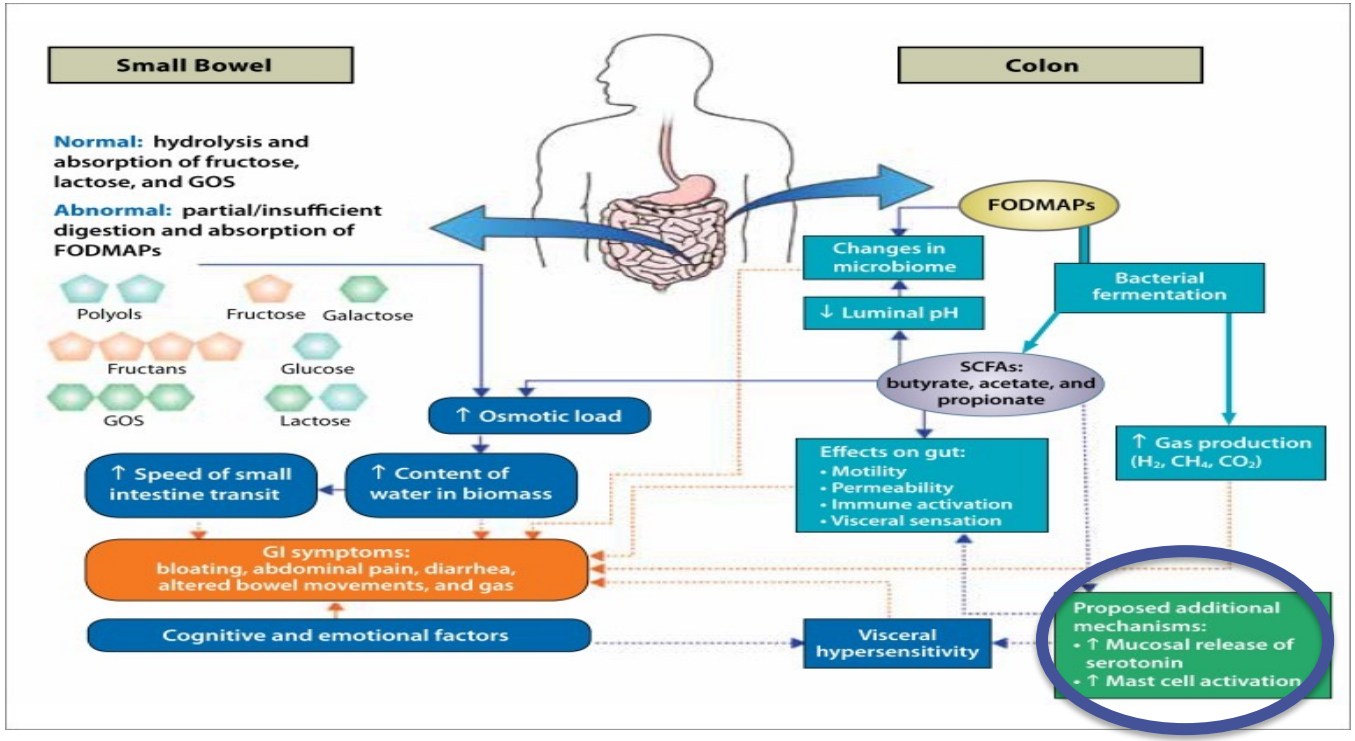
RCTs Evaluating the Low-FODMAP Diet for IBS

- 7 RCTs (n=397)
- Overall reduction in symptoms (RR 0.69; 95% CI 0.54, 0.88)
- RCTs comparing low FODMAP with control diets had the least magnitude of effect
- Overall quality of the data = “very low”
  - Most studies were high risk of bias
  - Heterogeneity between study designs
  - Imprecision in the estimate of effect



Dionne et al. Am J Gastroenterol 2018, online early.

How Do FODMAPs Cause IBS Symptoms?



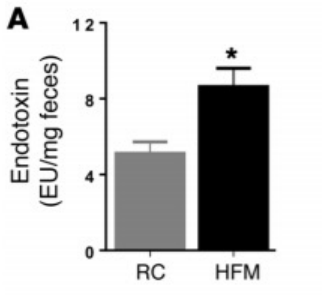
Werlang, Palmer, Lacy. Gastroenterol Hepatol (N Y).

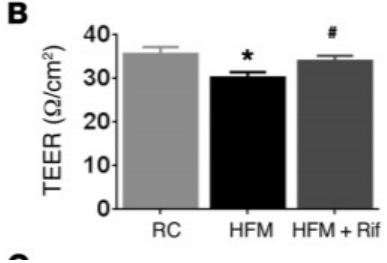
JCI The Journal of Clinical Investigation

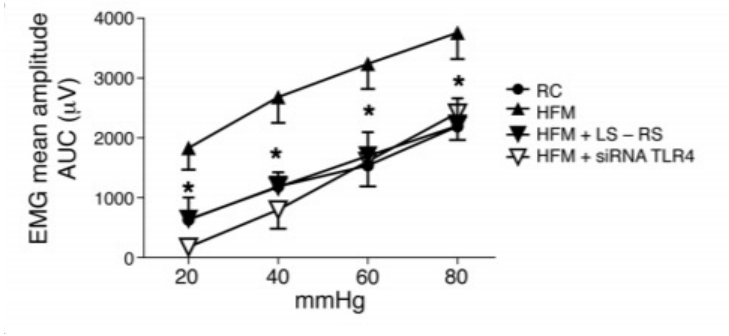
FODMAP diet modulates visceral nociception by lipopolysaccharide-mediated intestinal inflammation and barrier dysfunction

Shi-Yi Zhou, … , Yuanxu Lu, Chung Owyang

J Clin Invest. 2018;128(1):267-280. https://doi.org/10.1172/JCI92390.







Mast Cell Activation Leading to Colonic Barrier Dysfucntion Following High FODMAP Diet is Mediated via Lipopolysaccharide

Prashant Singh, **Gintautas Grabauskas**, **Shi-Yi Zhou**, Yawen Zhang, **Chung Owyang**

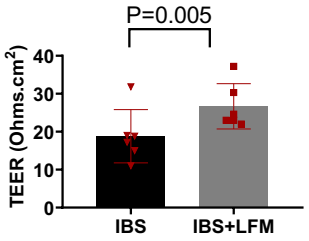
- In the rodent Model:

High FODMAP causes intestinal barrier dysfunction through mast cell recruitment and activation

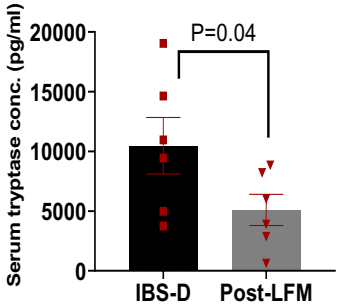
Mast cells are critical - mice deficient in Mast cells do not show intestinal barrier dysfunction to High FODMAP

In IBS-D, low-FODMAP improves:

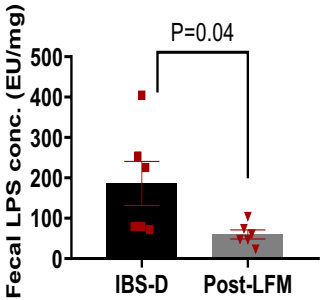
barrier dysfunction



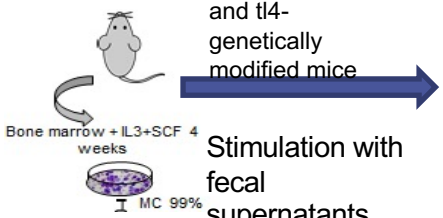
mast cell activation



fecal LPS levels

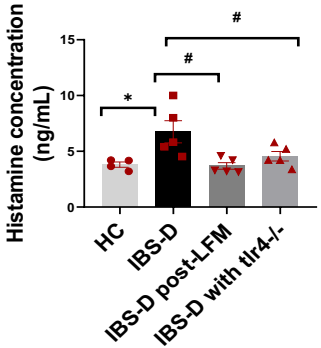


Low-FODMAP diet decreases mast cell activation via TLR4



Mast Cells from wild type mice and tl4-genetically modified mice

Stimulation with fecal supernatants



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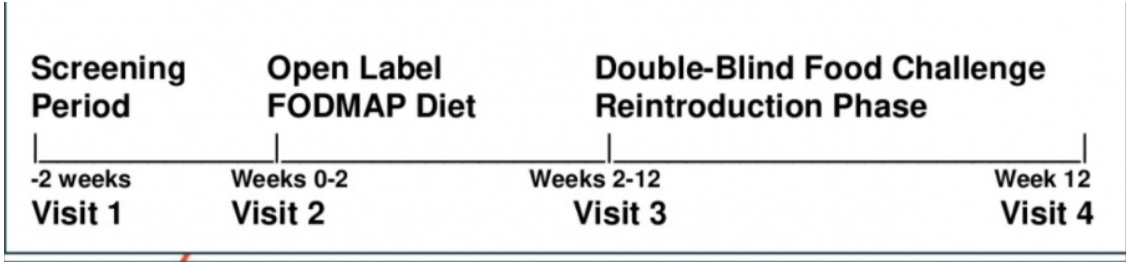
Limitations of the Low FODMAP Diet

- High level of restriction
- Difficult to follow (best done with an expert dietitian)
- Potential nutritional deficiencies (i.e, removes many ‘healthy’ foods such as fruits and vegetables)
- Significant gut microbiota reduction
- No current predictors of response

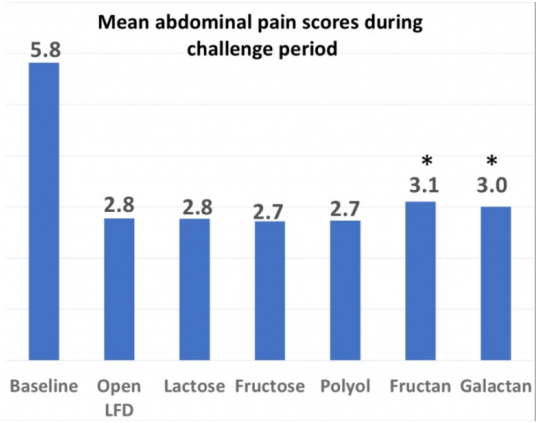
Does the low-FODMAP diet need to be so restrictive?

Are all FODMAPs created equal? A blinded, randomized reintroduction trial to determine which FODMAPs drive clinical response in IBS patients

Shanti Eswaran; Prashant Singh; Samara Rifkin; Theresa Han-Markey, William D Chey
[1] Division of Gastroenterology, Department of Internal Medicine, Michigan Medicine



45 IBS patients (95% women; all subtypes)



Double-blind Food Challenge

5 sequences over 7 days; 7 day washout

3 days of moderate FODMAP followed by 4 days higher FODMAP

FOS 0.75 g/day -> 1.5 g/day

fructose 10 g/day -> 21 g/day

lactose 10 g/day -> 20 g/day

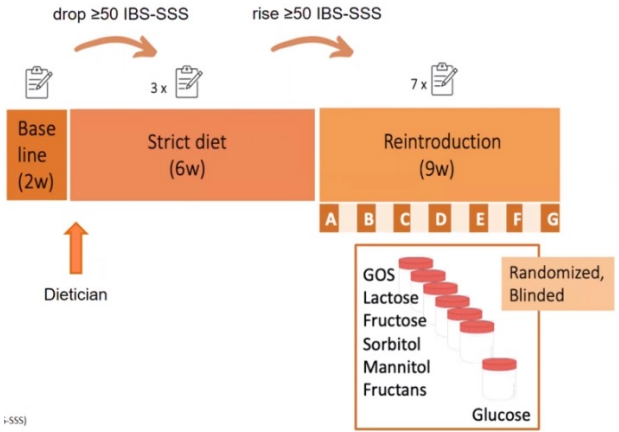
sorbitol 5g/day -> 10g/day

CONCLUSIONS

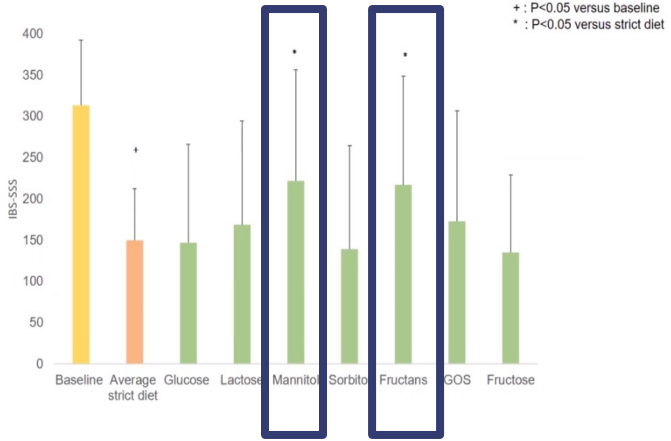
- Blinded reintroduction of fructans and galactans was associated with worsening of abdominal pain and/or bloating.
- These findings suggest that all FODMAPs are not equal and opens the door to trials evaluating the clinical benefits of a simplified low FODMAP diet in IBS patients.

Efficacy of a new approach to the reintroduction phase of the low-FODMAP diet in IBS patients

Karen Van den Houte, Esther Colomier, Zoë Mariën, Jolien Schol, Jasmien Van den Bergh, Julie Vanderstappen, Nelle Pauwels, Christophe Matthys, Tim Vanuytsel, Florencia Carbone, Jan Tack



46 IBS patients (85% women all subtypes)
IBS-SSS (baseline vs. 6 w Low-FODMAP: 305 -> 150
95% reported decrease IBS-SSS ≥ 50 points



FODMAP	% of patients
Lactose	42
Mannitol	54
Sorbitol	29
Fructans	54
GOS	33
Fructose	25
Glucose	29

Mannitol and fructans are most likely to increase symptoms
Average number FODMAPs to increase symptoms = 2.7

Sucrase-Isomaltase Deficiency (SID)

- Often occurs together since *Sucrase -isomaltase* is synthesized in the enterocyte as a single glycoprotein chain and, after insertion in the brush-border membrane, is cleaved by pancreatic proteases into sucrase and isomaltase
- Prevalence of deficiency is not well know
  - Primary deficiency is inherited as autosomal recessive (CSID)
    - Prevalence of CSID: estimated to 0.05% to 0.2%, higher in Greenland, Alaska and Canada up to 10%
  - Secondary deficiency of SID : not well studied

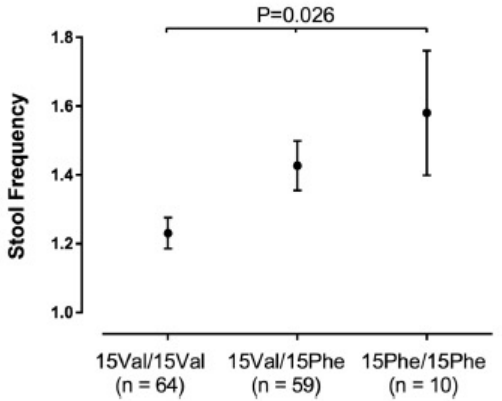
- One study 35% (11/31) of patients with undergoing EGD for an evaluation of chronic diarrhea and/or abdominal pain had a decrease in sucrase-isomaltase enzyme activity on duodenal biopsies
- Kim S, et al Digestive Diseases and Sciences (2020) 65:534–540

CSID Mutations are Associated with IBS

Two studies found CSID mutations more often in patients with IBS than controls

IBS	Controls
22/1031 (2.1%)	10/856 (1.2%)
88/2207 (4.0%)	928/33,370 (2.8%)

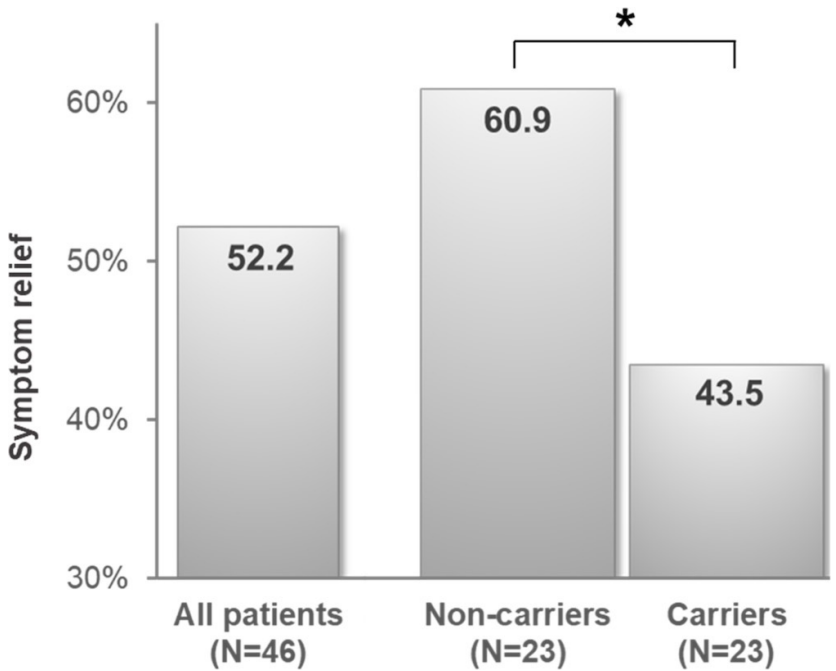
A common SI variant (Val15Phe), which shows reduced enzymatic activity in vitro, is strongly associated with increased risk of IBS



Henström M, et al. Gut 2016;0:1–8. doi:10.1136/gutjnl-2016-312456
Garcia-Etxebarria, et al. Clin Gastroenterol Hepatol 2018;16:1673
Husein & Naim. Gut 2019, doi:10.1136/gutjnl-2019-319411

,

Reduced efficacy of Low FODMAP diet in patients with SID



- 46 pts from US RCT randomized to LFD
- Primary endpoint: Adequate relief of IBS symptoms
- SI gene variants analyzed
- In a separate analysis the number of gene variants present predicted non-response to LFD or mNICE

Zheng et al. *Gut* 2020;**69:**397-398

Prevalence of Sucrase-Isomaltase Deficiency in adults with Irritable Bowel Syndrome and Diarrhea: An interim analysis from a prospective US trial

SW Chey MPH[1], SL Eswaran MD[1], and WD Chey MD[1]
[1] Division of Gastroenterology, Department of Internal Medicine, Michigan Medicine

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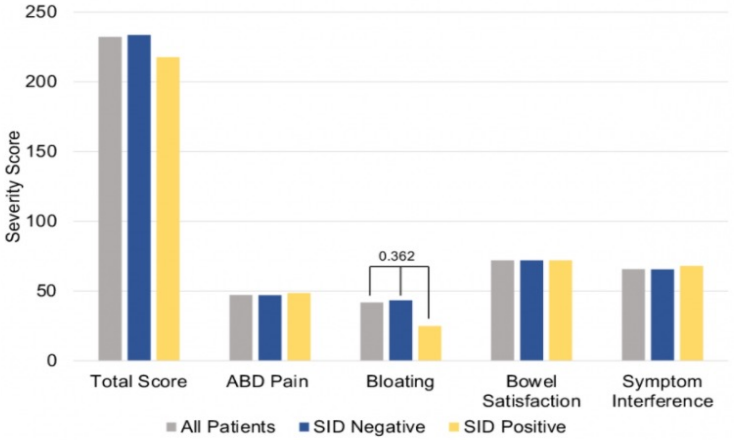
- AIM: Determine prevalence of SID in IBS-D using diasaccharidase enzyme activity

Table 1. Demographics and Baseline of Study Participants

Characteristic	Study Population (n:58)	SID-positive Population (n: 5)
Average Age (years)	42.6	48.6
Gender - n (%)		
Female	43 (74)	3 (60)
Male	15 (26)	2 (40)
Race - n (%)		
White/Caucasian	54 (93)	5 (100)
Black/African American	1 (2)	0
Hispanic/Latino	1 (2)	0
Asian	1 (2)	0
Other	1 (2)	0
Diagnosis - n (%)		
IBS-D	39 (67)	3 (60)
Functional Diarrhea	19 (33)	2 (40)
Average BMI (kg/m^2)	30.4	26.5
Treatment Naïve	29 (50)	0

Figure 1. IBS-SSS Questionnaire Data for Study Population and Domains**



Conclusions:

1. SID was present in 9% of adults with IBS-D or Functional Diarrhea

2. Demographics/symptoms similar in those with and without SID

Exhaled Hydrogen Sulfide is Increased in Patients with Diarrhea: Results of a Novel Collection and Breath Testing Device

Mark Pimentel MD[1,3], Ava Hosseini BS[1], Christine Chang RN[1], Ruchi Mathur MD[1,2], Mohammed Rashid MD[1], Rashin Sedighi PhD, RN[1], Halley Fowler BS[1], Jiajing Wang MS[1], Ali Rezaie MD MSc[1,3]

[1]Medically Associated Science and Technology (MAST) Program, Cedars-Sinai, Los Angeles, CA.
[2]Division of Endocrine, Diabetes, and Metabolism, Department of Medicine, Cedars-Sinai, Los Angeles, CA.
[3] Karsh Division of Gastroenterology and Hepatology, Department of Medicine, Cedars-Sinai, Los Angeles, CA.

- H2 and CH4 are currently measured on breath tests
- New detection device (Gemelli Biotech) measures H_2S
- IBS-C (n=124); IBS-D (n=15); healthy (n=47)
- H_2S ≥5ppm

	Sensitivity	Specificity
– IBS-D vs. healthy	68%	98%
– IBS-D vs. IBS-C	67%	95%

Table 1: Symptom severity based on elevated H_2S

	H_2S Negative (<5ppm)	H_2S Positive (≥5 ppm)	P-value
Symptoms	**Mean±SD**	**Mean±SD**	
Abdominal pain	9.2±20.0	50.8±42.6	**0.0001**
Bloating	12.2±22.7	56.3±39.2	0.0016
Constipation	5.8±9.6	26.9±31.3	0.0171
Diarrhea	9.3±23.7	61.6±33.6	**0.0005**
Discharge of mucus from rectum	5.5±16.0	38.7±37.2	0.0015
Excess gas	10.5±21.0	53.1±40.5	0.0001
Incomplete evacuation	10.0±22.1	33.6±29.2	0.0021
Straining during bowel movement	4.8±10.7	30.7±36.5	0.0005
Urgency with bowel movement	11.8±27.0	74.8±28.5	**0.0003**
Symptom Combinations			
Diarrhea + Urgency with bowel movement	21.1±49.0	130.2±55.1	**0.0004**
Abdominal pain + Diarrhea	18.4±43.2	112.3±68.4	**0.0001**
Abdominal pain + Diarrhea + Urgency with bowel movement	30.3±67.9	175.9±87.3	**<0.0001**

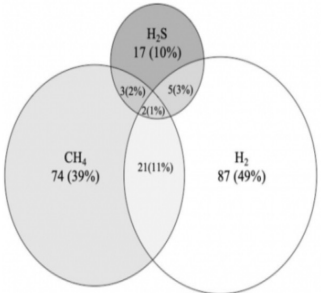
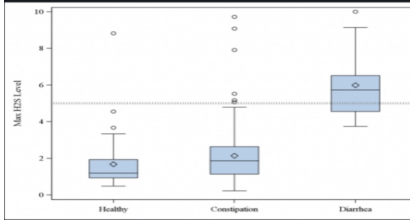


Figure 1: Comparing maximum H_2S between groups (P<0.001)



1. A new gas collection system and novel 4-gas detection device was capable of measuring levels of H_2, CH_4, and H_2S (in addition to CO_2) in humans during clinical breath testing.
2. H_2S of ≥5ppm during breath testing was associated with diarrhea, abdominal pain, and urgency during breath testing.
3. H_2S was uncommonly found in patients with CH_4.
4. A cutoff of 5ppm for H_2S was the best predictor of diarrhea. However, normal subjects almost never exceeded 2 ppm of H_2S.

Predictors of Health Care Utilization in Patients with Functional Bowel Disorders

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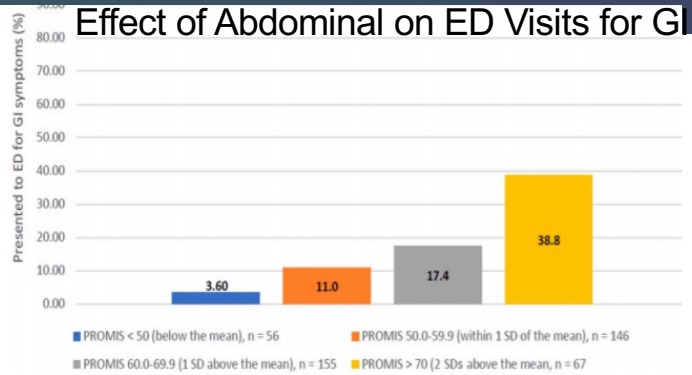
[2] Tufts University School of Medicine, Boston, MA, USA

- ✓ Patients with disorders of gut-brain interactions are high utilizers of health care.
- ✓ Direct and indirect costs related to disorders of gut-brain interactions are estimated to be $21.0 and $37.4 billion, respectively.
- ✓ Previous health care utilization studies lacked patient-level predictors.

434 patients completed the health care utilization questionnaire and met the criteria for IBS, FC, or RD (mean age 44 years, 79.5% female, and 73.5% IBS).

Effect of Abdominal on ED Visits for GI symptoms



Patient-Reported Outcomes Measurement Information System (PROMIS) standardized t-score. Higher scores more severe symptoms.

Table 4. Multivariate regressions

Linear regression predicting GI outpatient utilization			
	β	SE	*P*
Age	0.01	0.01	0.18
Sex	−0.16	0.33	0.63
Abdominal pain	0.03	0.02	**0.02**
Constipation	0.01	0.02	0.44
Diarrhea	−0.004	0.02	0.81
Anxiety	−0.02	0.02	0.32
Depression	0.07	0.02	**0.001**
Sleep	0.03	0.02	**0.04**
R^2		0.11	
F		6.12, $P < 0.0001$	

WHAT IS NEW HERE

- ✓ Abdominal pain was a primary predictor of health care utilization.
- ✓ Severity of depressive symptoms was also a strong predictor.
- ✓ Altered bowel habits did not predict health care utilization.

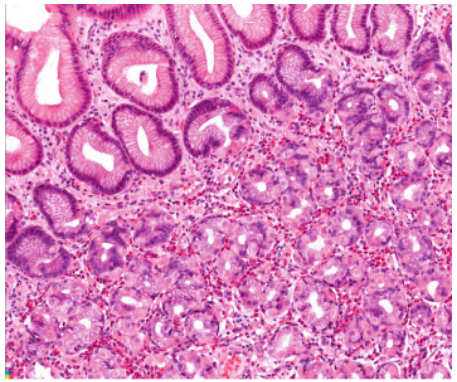
Eosinophilic Gastrointestinal Diseases

Associated with activated eosinophils and mast cells

Eosinophilic GI disease are considered to rare however emerging evidence suggests that they may be more common

Symptoms are non-specific and overlaps with functional bowel disorders

Definition:
Presence of > 30 eosinophils/hpf in at least five HPFs



Endoscopy and Systematic Biopsy of Patients with Chronic Gastrointestinal Symptoms Leads to High Discovery Rate of Patients Who Meet Histologic Criteria for Eosinophilic Gastritis and/or Eosinophilic Duodenitis

Nicholas J. Talley MD PhD[*1], Amol P. Kamboj MD[2], William D. Chey MD[3], Henrik S. Rasmussen MD PhD[2], Brian E. Lacy MD PhD[4], Ikuo Hirano MD[5], Mirna Chehade MD MPH[6], Nirmala Gonsalves MD[5], Kathryn A. Peterson MD[7], Anthony Lembo MD[8], Colleen M. Schmitt MD MHS[9], Marc E. Rothenberg MD PhD[10], Robert M. Genta MD[11], Maria A. Pletneva MD PhD[7], Kevin O. Turner DO[12], Malika Pasha MBA[2], Evan S. Dellon MD MPH[*13], William J. Sandborn MD[*14]

Prospective, multi-center trial using blinded centralized pathologists

Patients:

Chronic functional symptom (6 months) pain, n/v, diarrhea, bloating or early satiety

IBS/Functional Dyspepsia

Controls:

Asymptomatic individuals

Protocol

8 biopsies stomach; 4 duodenum

EG/EoD: ≥ 30 eos/hpf in 5 gastric or 3 duodenal hpf

Mast cells: > 30 mast cells/hfp in 5 gastric and 3 duodenal hpf

Results

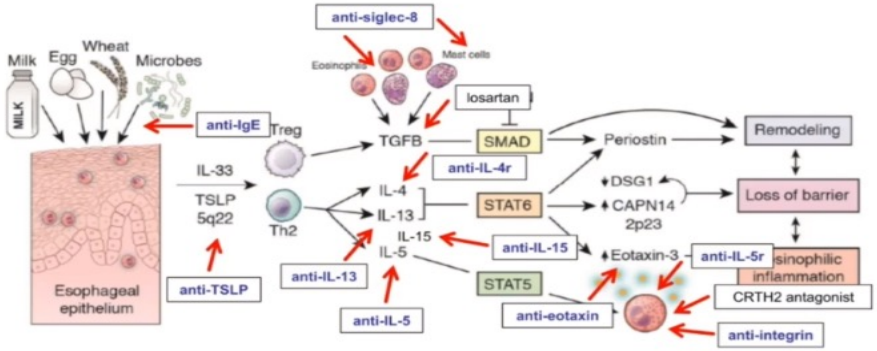
Histologic criteria for EG or EoD

45% (181/405) patients vs. 6% (2/33) asymptomatic contro

Patient Characteristics		Met Histologic[a] Criteria for EG and/or EoD n=181
Mean age, years (range)		45 (19-78)
Female sex, %		73%
White, %		85%
Weight, median, kg		83
Blood eosinophils	Cells/μL, median (IQR)	170 (100-250)
	Blood eos ≥250 cells/μL, %	27%
	Blood eos ≥500 cells/μL, %	4%
	Blood eos ≥1500 cells/μL, %	0%
Immunoglobin E	kU/μL, median (IQR)	34 (14-103)
	IgE ≥70 kU/μL, %	36%
TSS [0-80], mean ±SD		31.3 ±11.2
History of	GI symptoms, mean years	11
	Atopy[b], %	48%
	EoE, %	2%

EG and/or EoD appear to be more common than previously thought, and should be considered in patients with moderate-severe unexplained GI symptoms

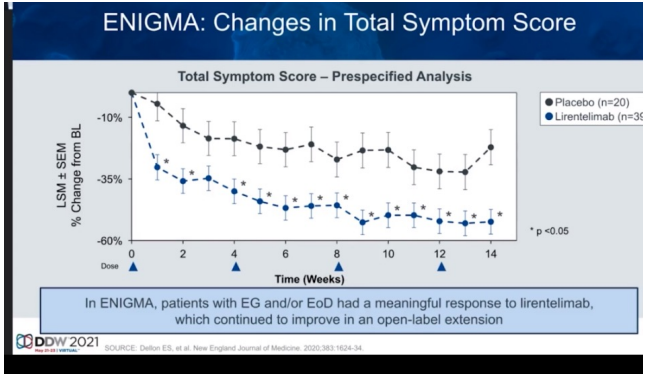
Emerging Treatments for Eosinophilic Disease



From: Evan Dellon, MD: Refractory EoE DDW 2021

- Anti-IL5 - mepolizumab; reslizumab (approved eosinophilic asthma; investigator-initiated EoE)
- Anti-IL13 – RPC4046 (phase 2 EoE complete)
- Anti-IL4r/IL-13 – dupilumab (approved for atopic dermatitis, asthma, CRSNP; phase 3 EoE)
- Anti-siglec-8 – AK002 (EG/EGE phase 3; EoE phase 2/3)
- Anti-IL-5r – benralizumab (approved for eosinophilic asthma; investigator-initiated EG/EGE; phase 2/3 EoE)
- Anti-TSLP – tezepelumab (asthma phase 2)
- Anti-IL-15 – proof of concept *(Vicari, mABs, 2017)*
- Anti-α4β7 integrin (vedolizumab; approved IBD) – case reports in EoE/EGID *(Kim, CGH, 2018; Nhu, AJG, 2018; Taft, CGH, 2018; Grandinette, DDS, 2019; Beales, DDS, 2019 but for natulizumab)*

AK002 (lirentelimab)



Thank you