
2018
NCSCG
15TH ANNUAL
POST-DDW
SYMPOSIUM
Rehoboth McKinley Christian Health Care Services
Northern California Society for Clinical Gastroenterology
Jointly provided by the New Mexico Medical Society (NMMS) through the joint providership of Rehoboth McKinley Christian Health Care Services (RMCHCS) and the Northern California Society for Clinical Gastroenterology.

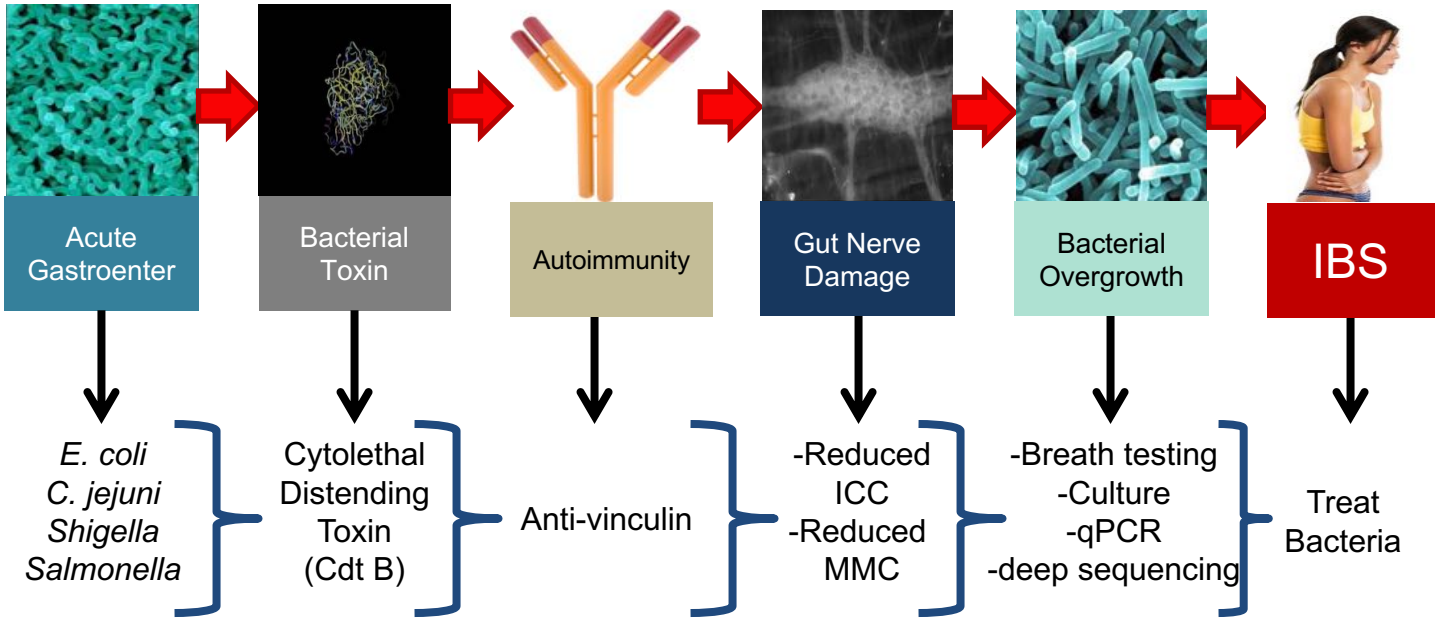
2018 NCSCG 15TH ANNUAL POST-DDW SYMPOSIUM

The Microbiome and IBS

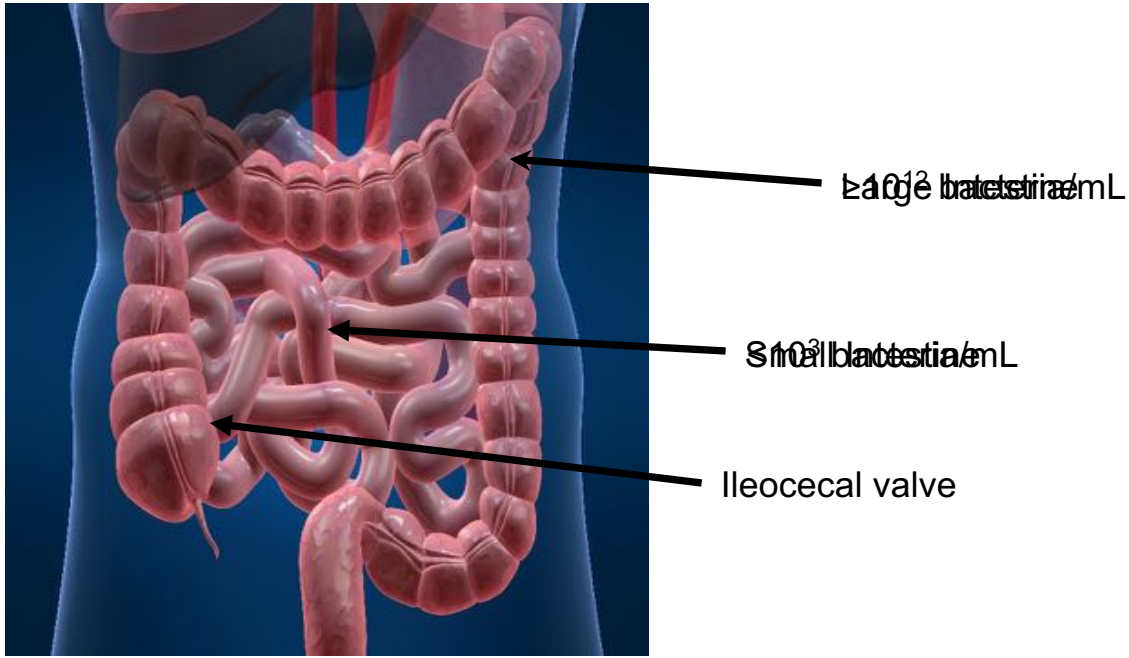
Mark Pimentel, MD, FRCP(C)
Executive Director, Medically Associated Science and Technology (MAST) Program
Cedars-Sinai

CEDARS-SINAI

IBS Microbiome Sequence

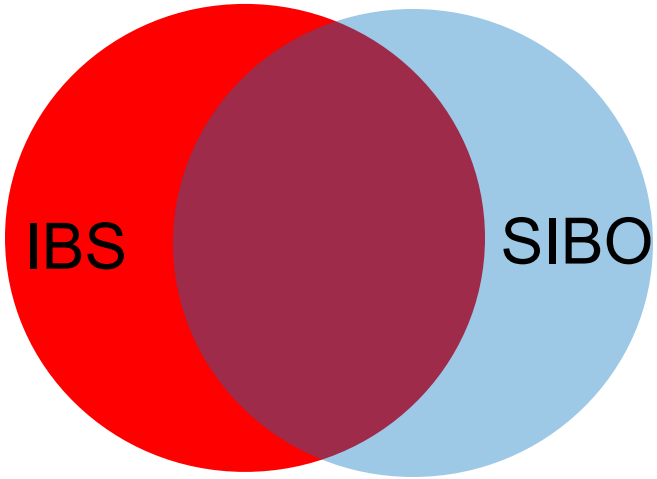


What is SIBO



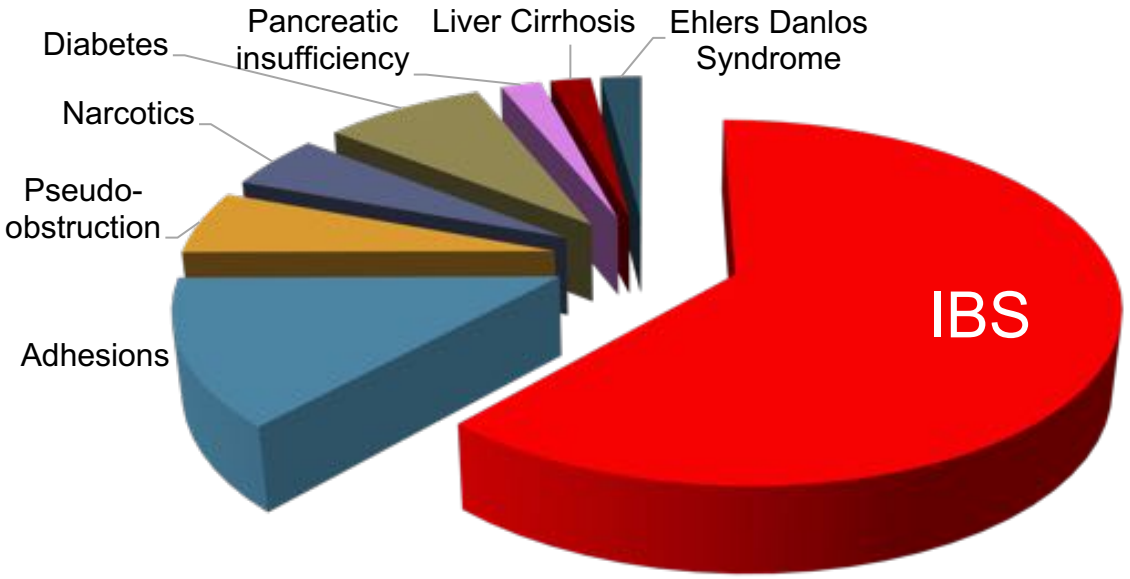
Rezaie, et al. Am J Gastreonterol 2017

SIBO and IBS are Intertwined

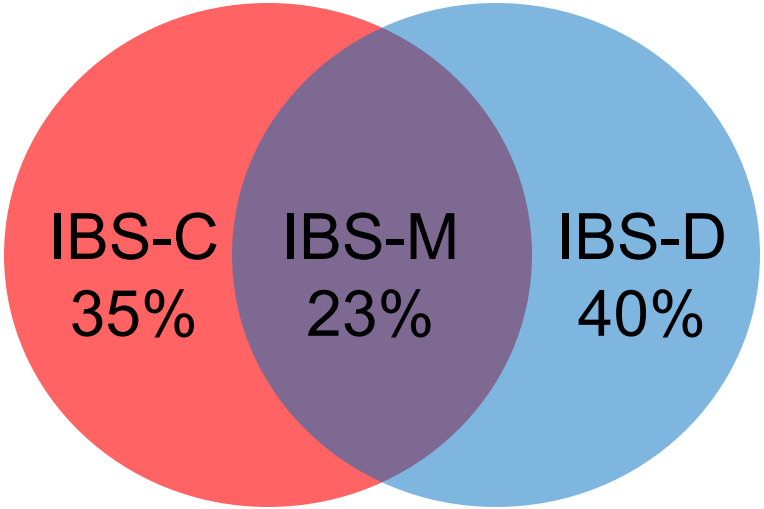


-Not all IBS is SIBO
-Not all SIBO is IBS

Conditions Associated with SIBO

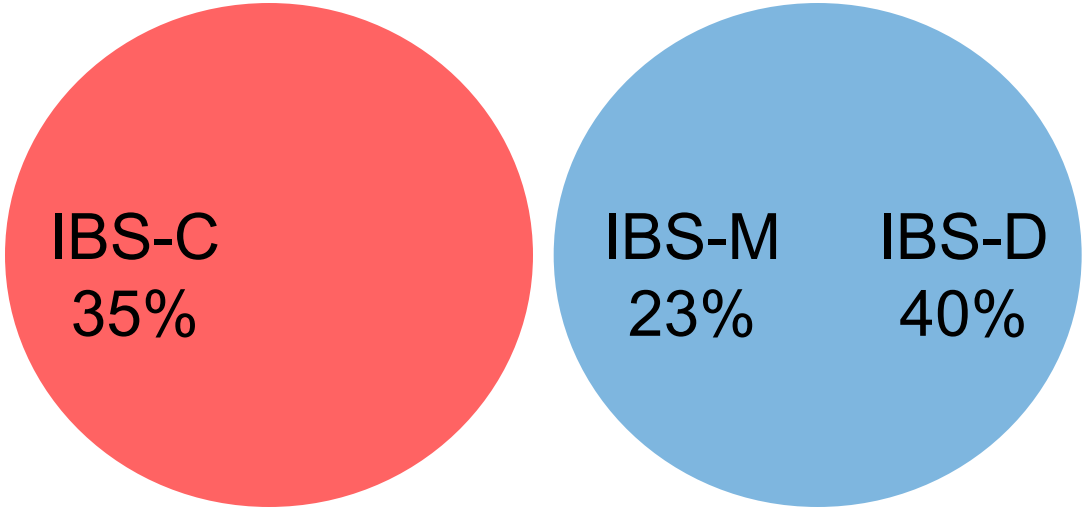


Types of IBS



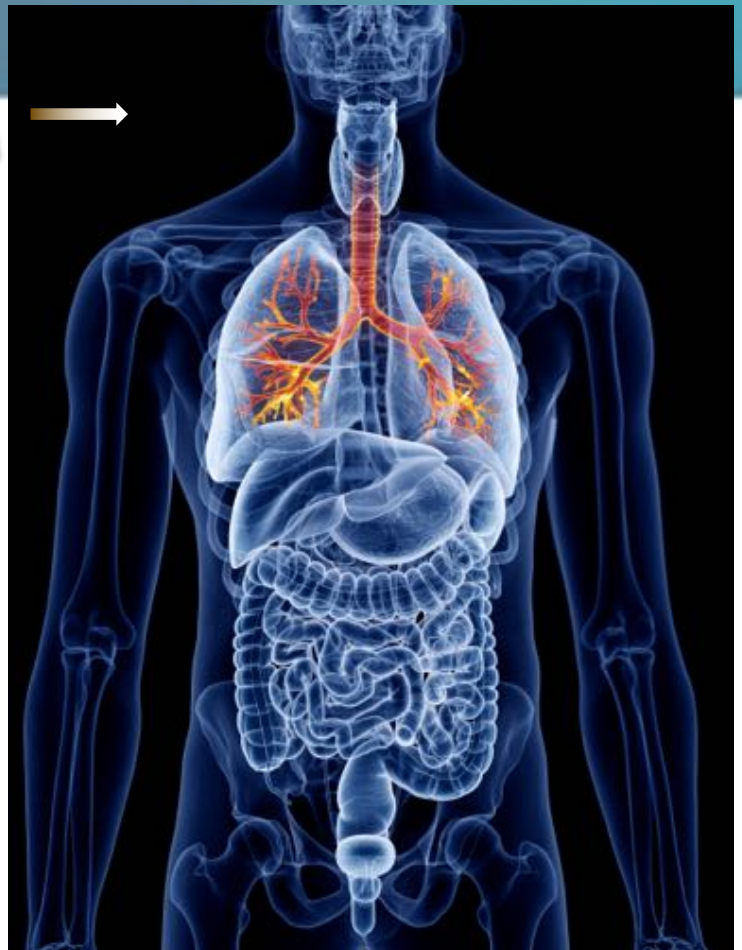
Lovell RM et al. *Clin Gastroenterol Hepatol*. 2012;(10):712-721.

Is IBS really two diseases?

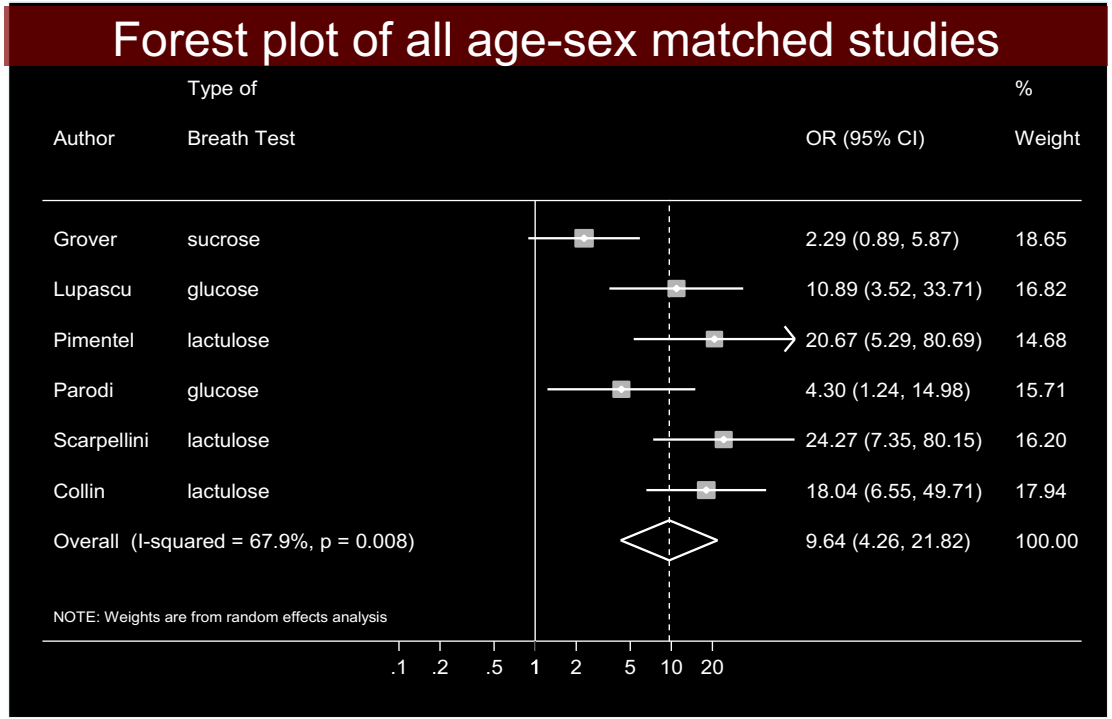


Constipation IBS

Non-Constipation IBS



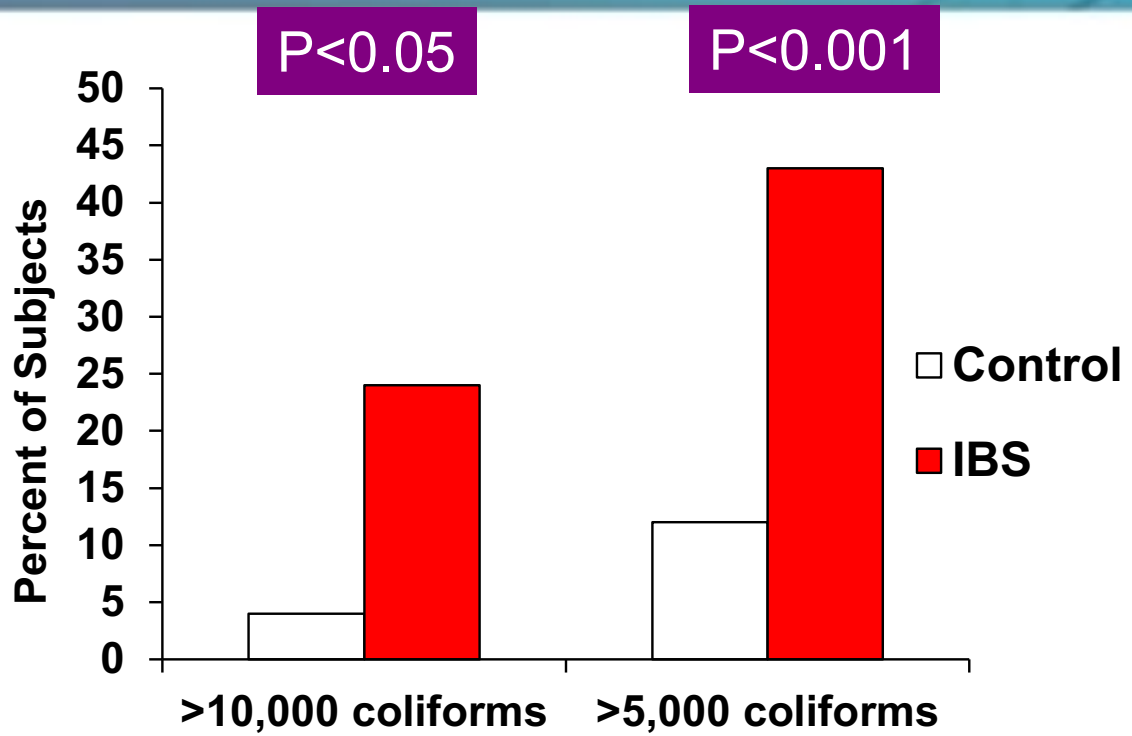
Breath Testing is abnormal in IBS



CEDARS-SINAI

Shah, et al Dig Dis Sci, 2010

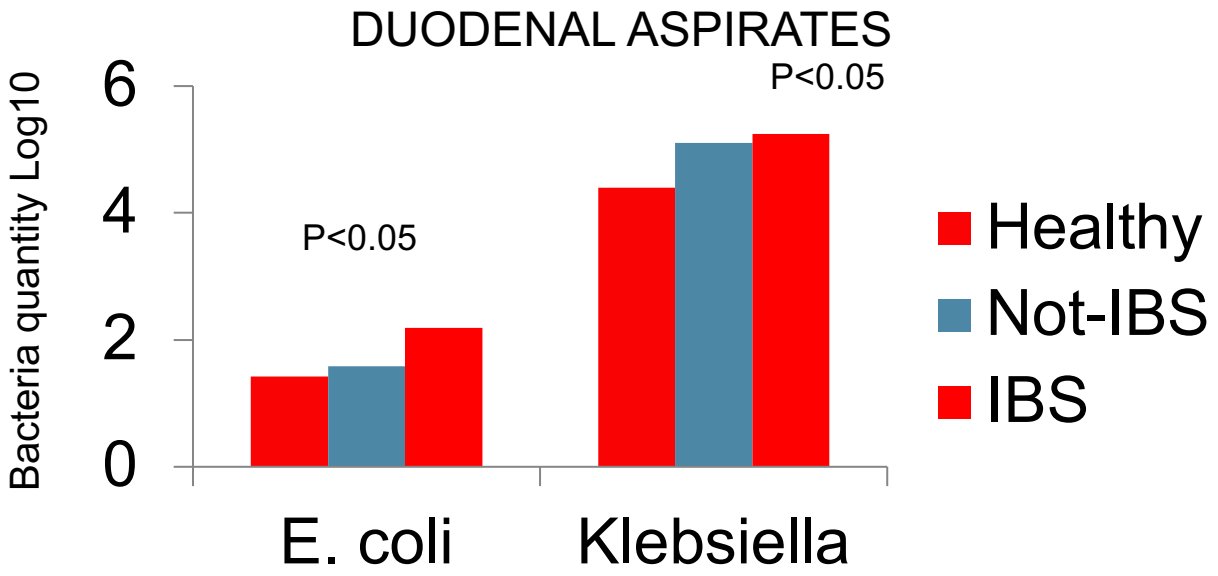
Small Bowel Culture in IBS



N=165 IBS, 26 controls

Posserud, et al, Gut, 2007;56:802-8.

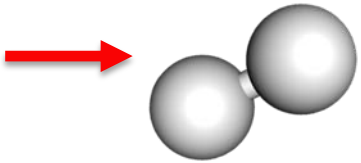
Single Organism PCR in IBS



Pyleris, et al. Scand J Gastroenterol, 2015

Fermentation Byproduct: Hydrogen

Hydrogen-Producing Bacteria



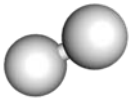
H_2

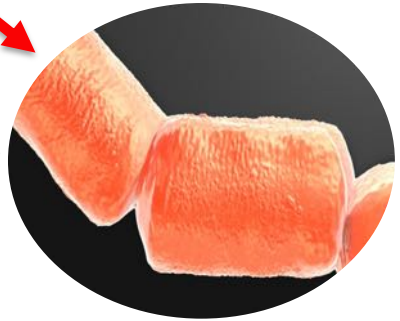
BUT:

- Not correlated to symptoms
- Used as fuel by other microbes

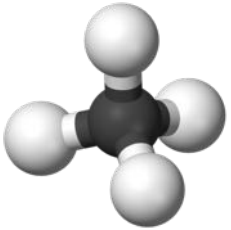
Fermentation Byproducts: Hydrogen and Methane

Hydrogen-Producing Bacteria





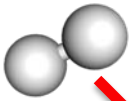
Methane-Producing Archaea

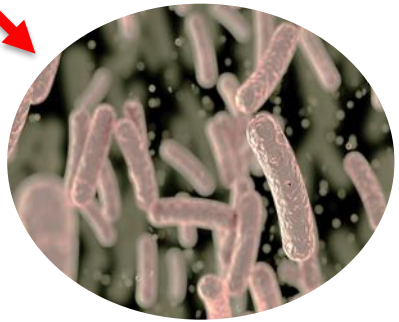


$4\ H_2 \rightarrow 1\ CH_4$

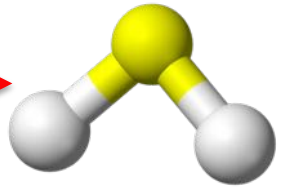
Fermentation Byproducts: Hydrogen and Hydrogen Sulfide

Hydrogen-Producing Bacteria





Sulfate-Reducing Bacteria

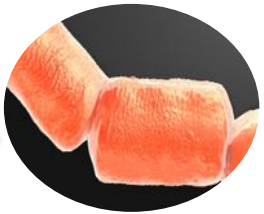


$5\ H_2 \rightarrow 1\ H_2S$

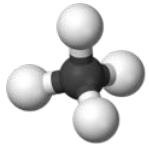
Fermentation Byproducts: Hydrogen and Methane and Hydrogen Sulfide

Hydrogen-Producing Bacteria

H_2

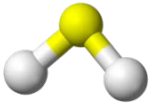


Methane-Producing Archaea



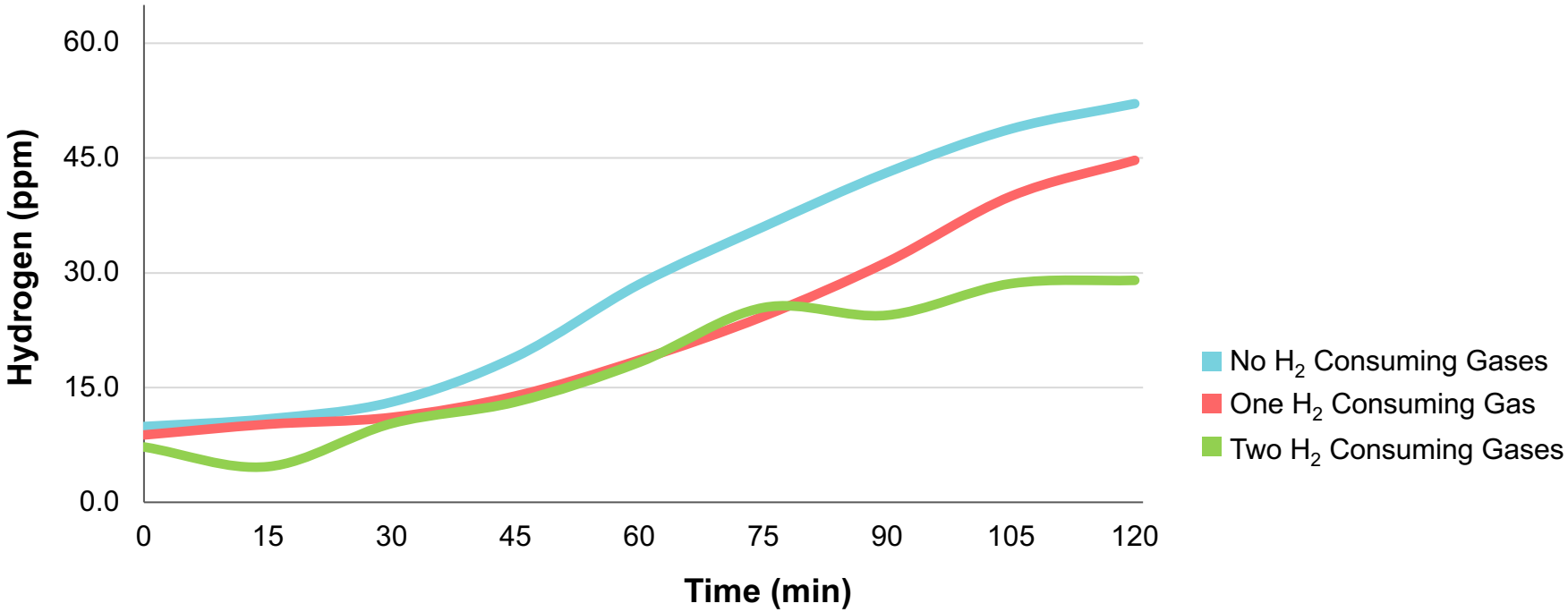
$4\ H_2 \rightarrow 1\ CH_4$

Sulfate-Reducing Bacteria

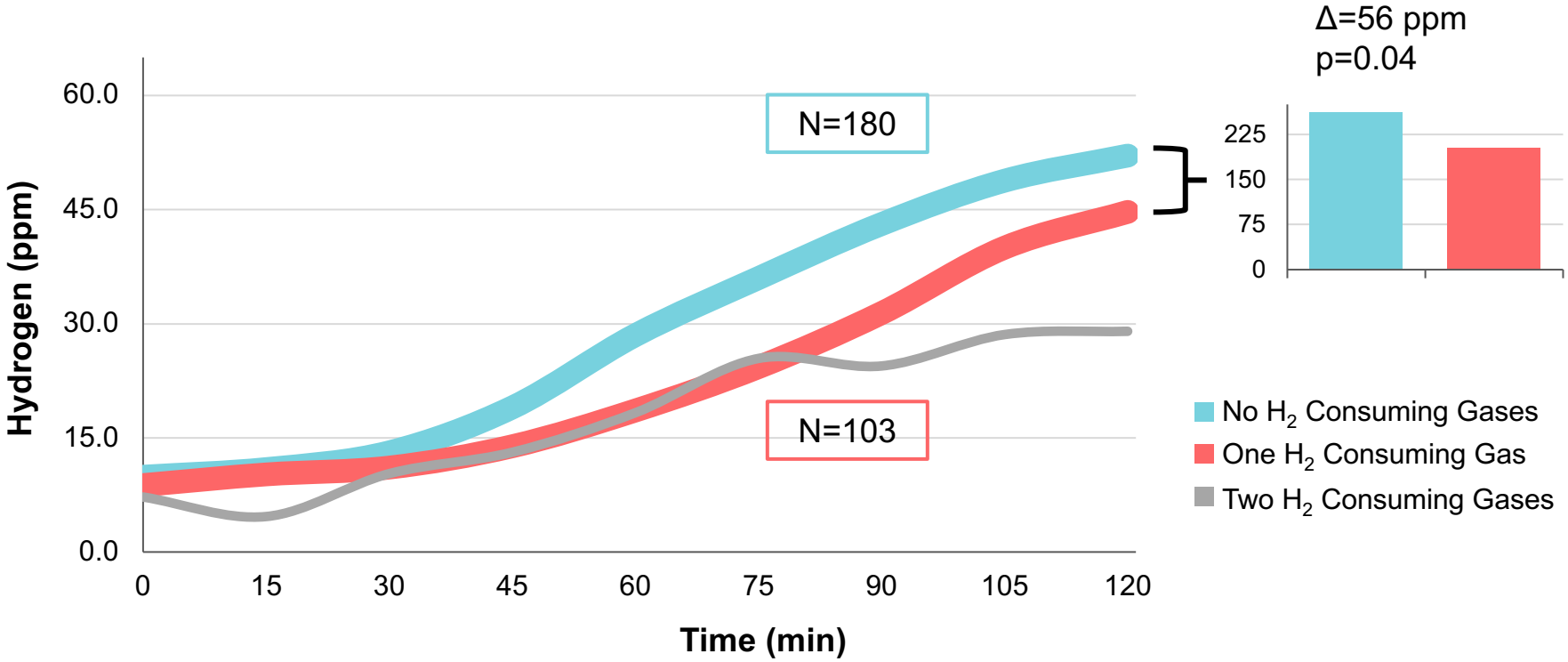


$5\ H_2 \rightarrow 1\ H_2S$

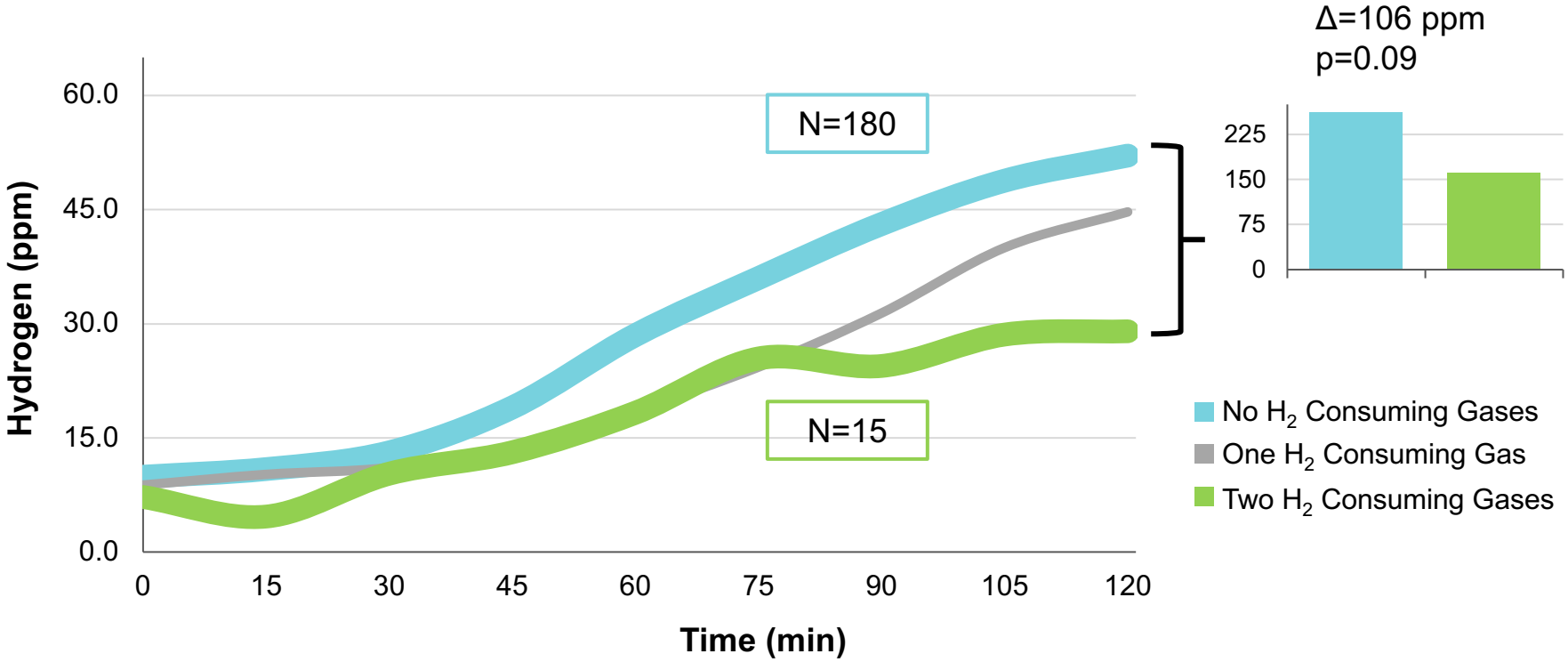
Gas Interactions



Gas Interactions



Gas Interactions

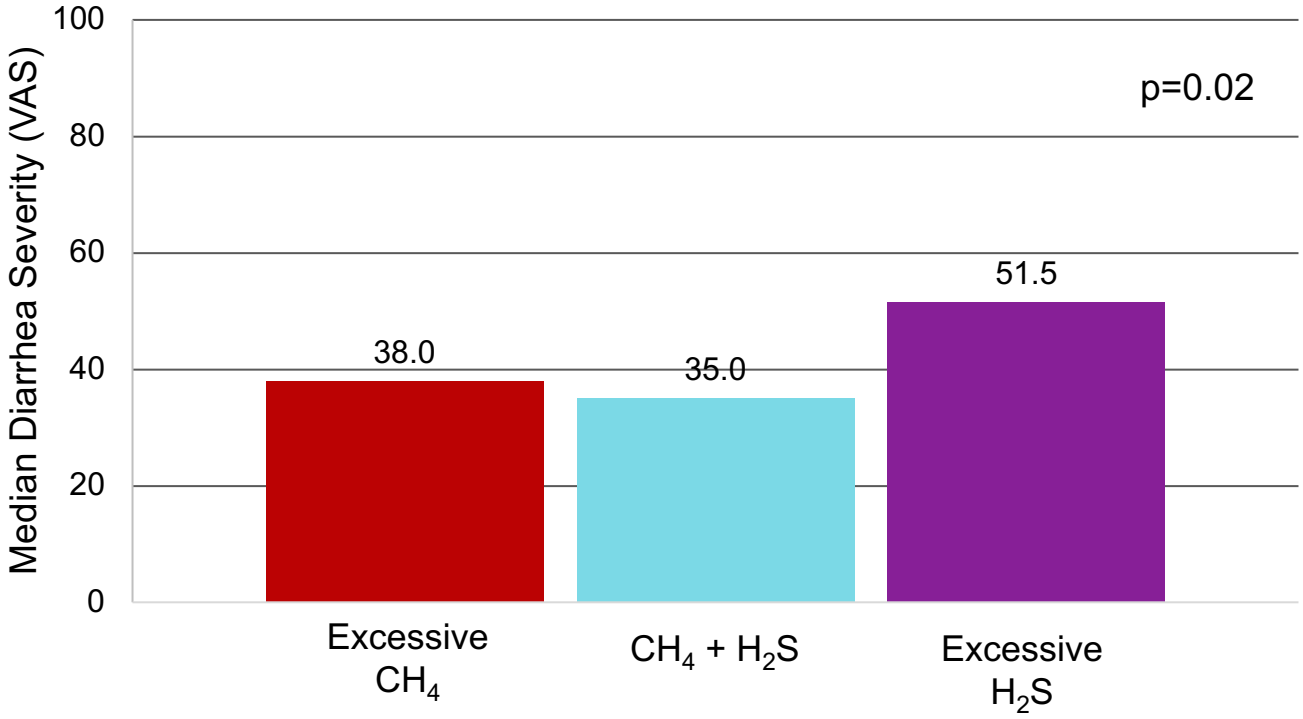


IBS-D Symptoms Stratified by Presence of H_2S

Symptom	H_2S Positive (≥1.2 ppm) mean ± SD	H_2S Negative (<1.2 ppm) mean ± SD	p value
Abdominal pain	59.1 ± 30.7	54.4 ± 28.3	0.10
Bloating	65.2 ± 26.2	66.6 ± 26.8	0.63
Diarrhea	52.1 ± 32.4	41.2 ± 31.8	0.01
Discharge of Mucus	25.9 ± 28.2	26.5 ± 29.3	0.83
Excess Gas	60.8 ± 26.6	63.1 ± 26.7	0.55
Urgency	51.4 ± 32.4	42.3 ± 31.7	0.04

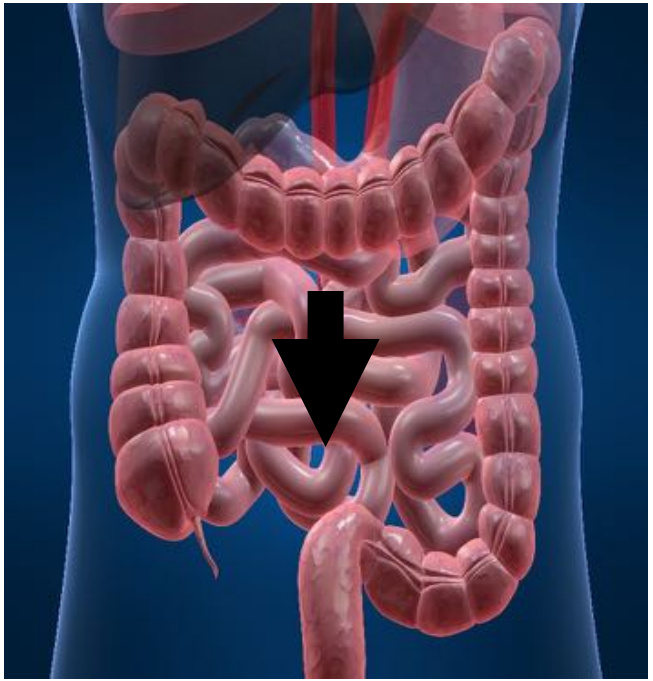
Singer-Englar, et al. DDW 2018 1089

Median Diarrhea Severity by Consuming Gas



Singer-Englar, et al. DDW 2018 1089

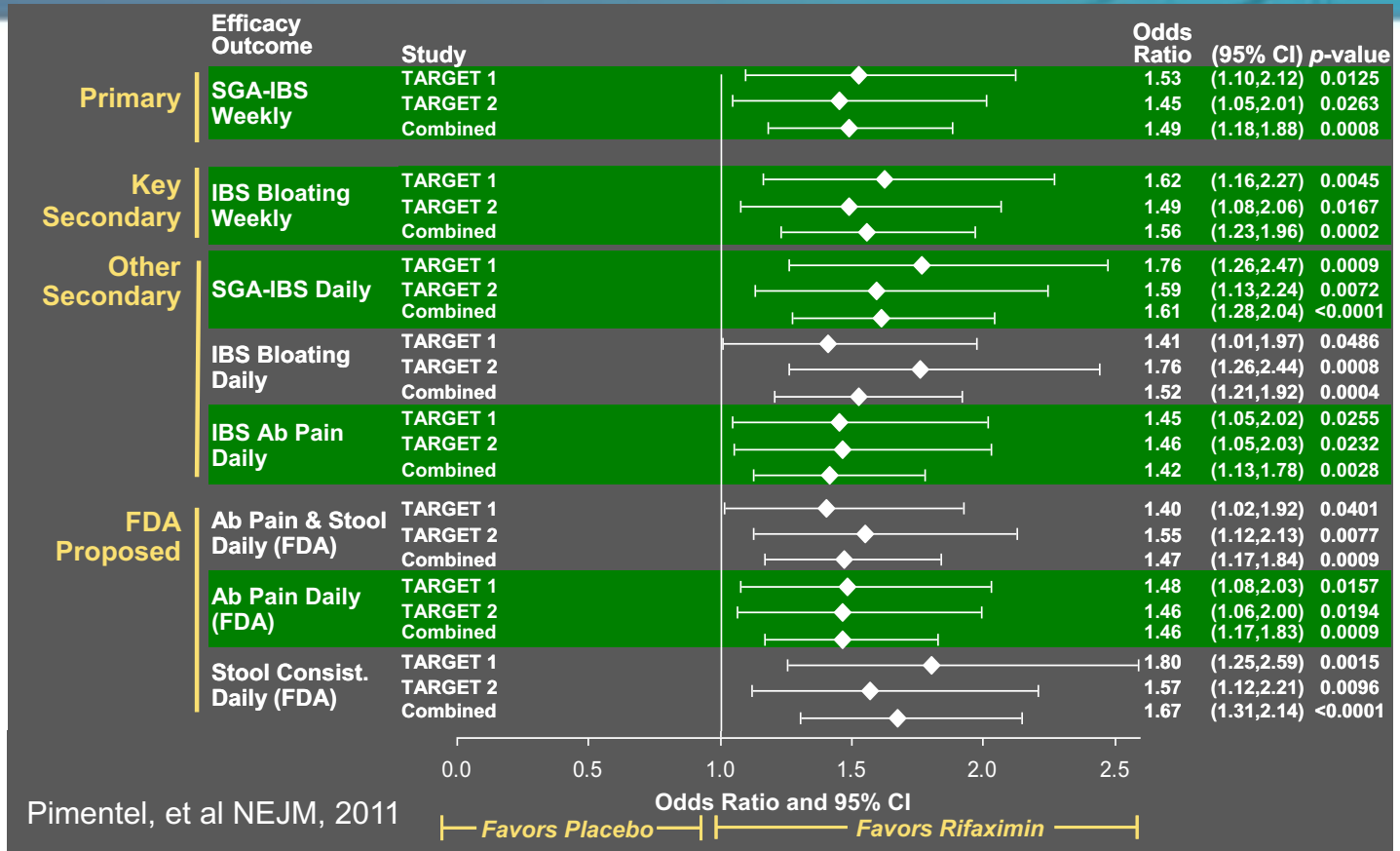
Rifaximin



- Non-absorbed rifamycin derivative
- Few side effects
- Preferentially reduces bacteria in the small bowel and not the colon

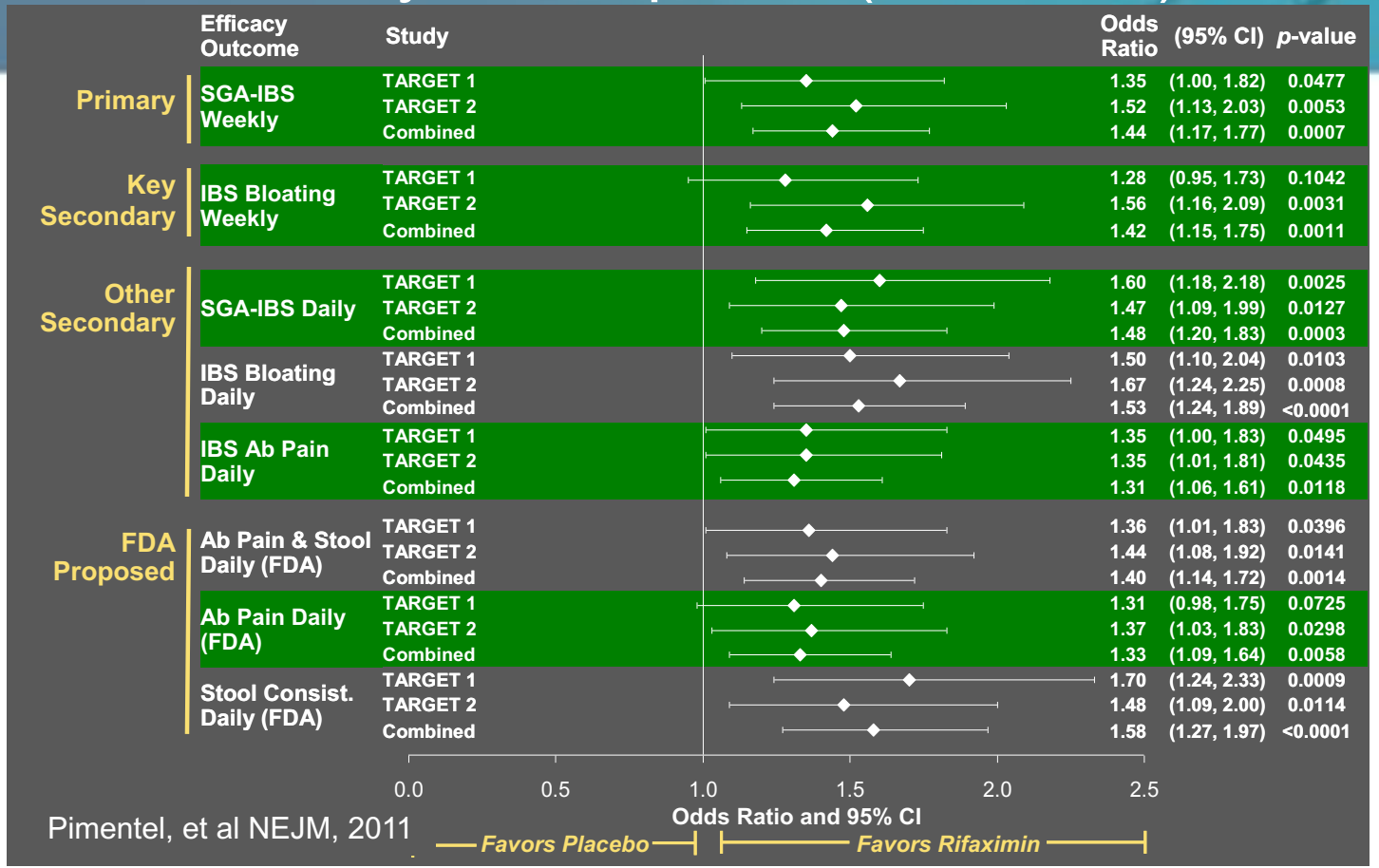
Kim, et al. Dig Dis Sci, 2013

Primary Outcome (4 weeks after Tx)



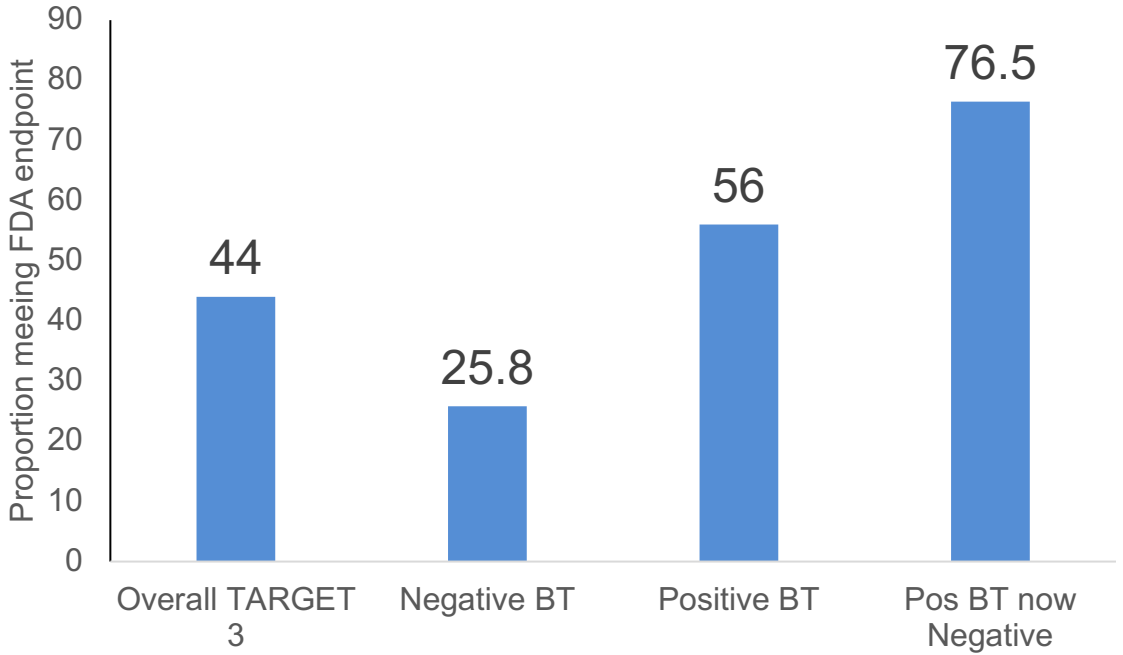
Pimentel, et al NEJM, 2011

Durability of Response (3 months)



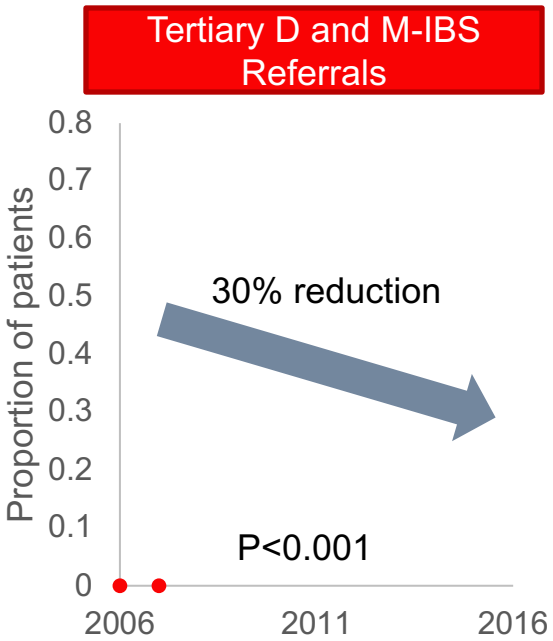
Pimentel, et al NEJM, 2011

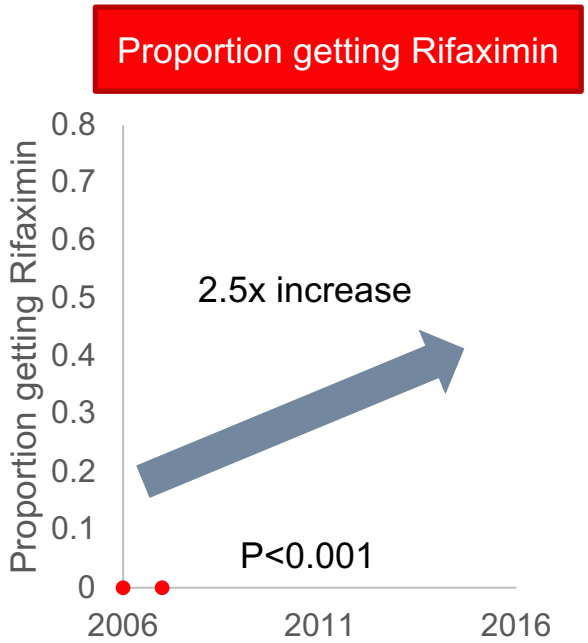
Breath testing and Rifaximin Response



Rezaie, et al. ACG Meeting, 2017

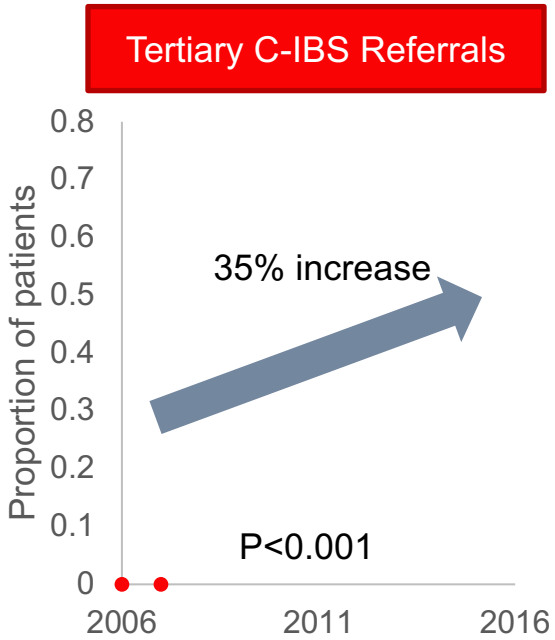
Impact of Rifaximin on D-IBS





Oh, et al. ACG Meeting, 2017

Impact of Rifaximin on D-IBS



Despite many C-IBS drugs

Oh, et al. ACG Meeting, 2017

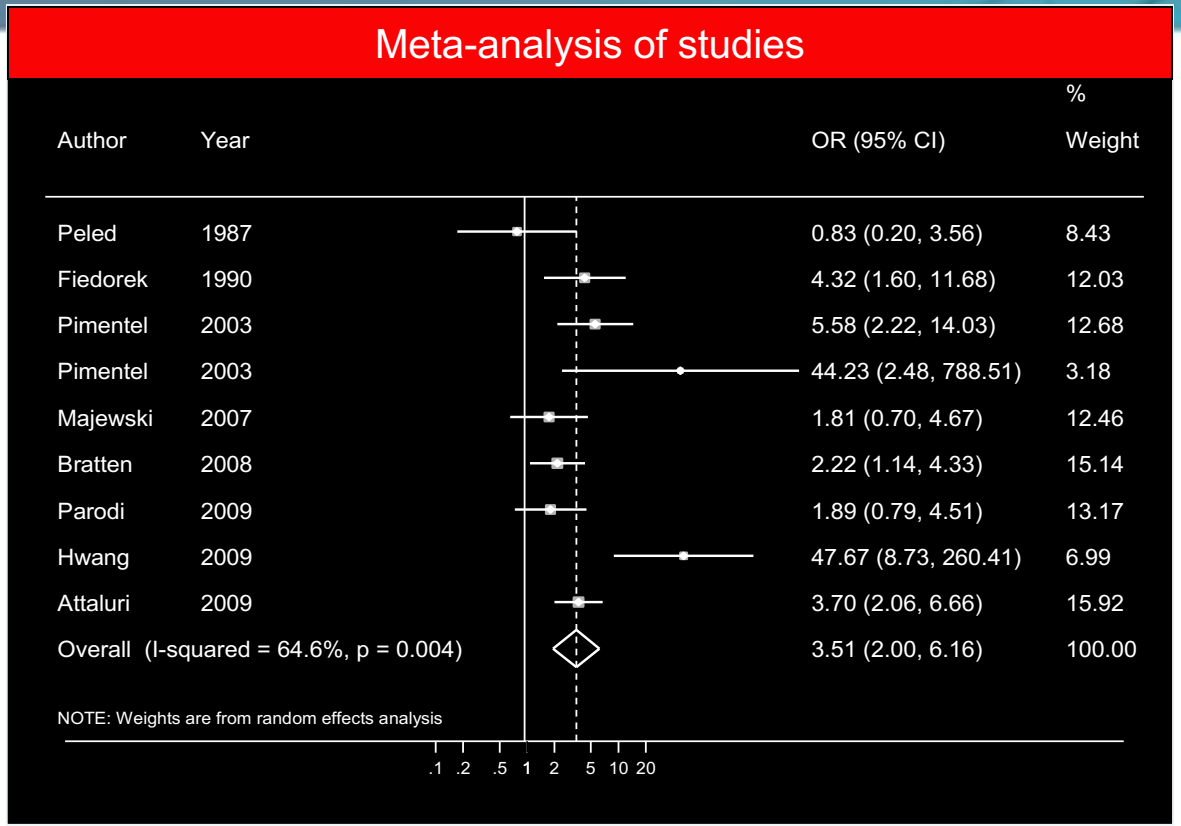
Diet and Small Bowel Microbiome

- 15 volunteers
- Small bowel microbiome analysis before and after high fiber diet.
- SIBO increased to 80% on high fiber diet with consequent digestive symptoms
- Inverse correlation between microbial alpha diversity and intestinal permeability
- Resolved with resumption of normal diet.

- CONCLUSION: Diet is also important

Saffouri, et al. DDW 2018 Su1941

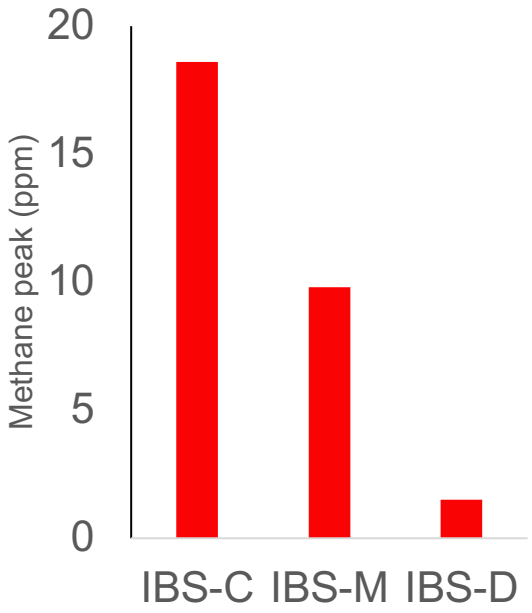
Methane- Important in C-IBS



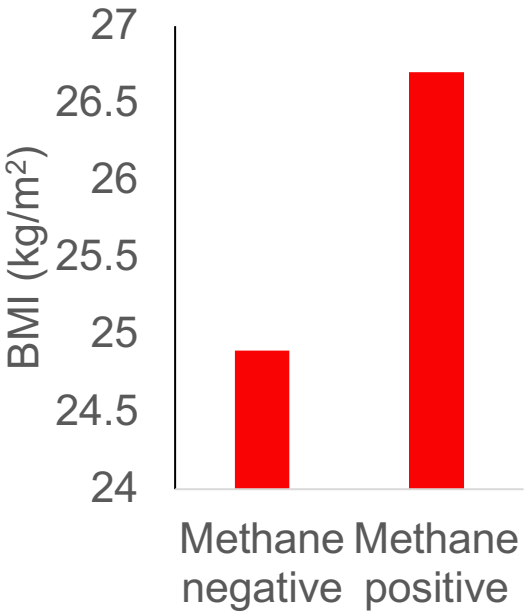
Kunkel, et al. Dig Dis Sci, 2011.

Methane and Constipation- Mexican Study

P=0.008



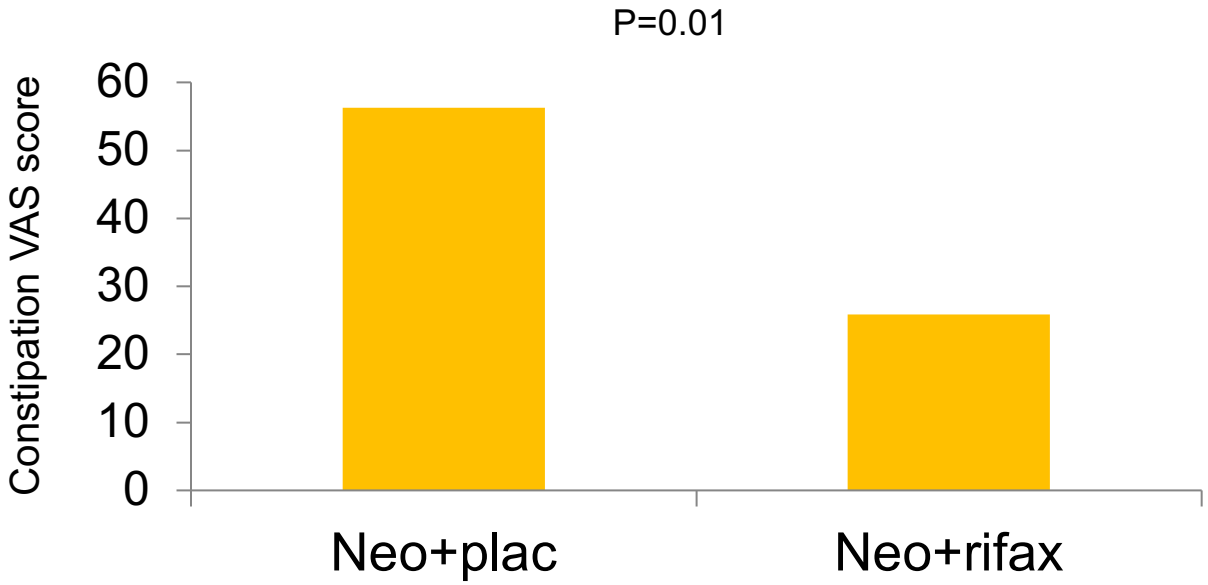
P=0.023



N=67 IBS and n=132 healthy

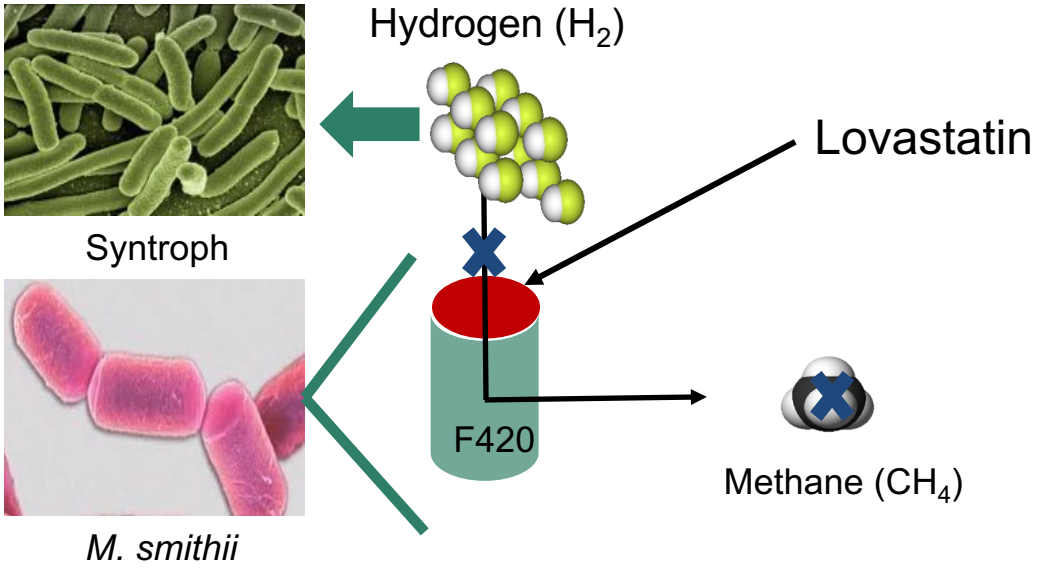
Troche, et al. DDW 2018 Tu1636

Methane Positive C-IBS
Double Blind Placebo Controlled Trial



Pimentel, et al. Dig Dis Sci, 2014.

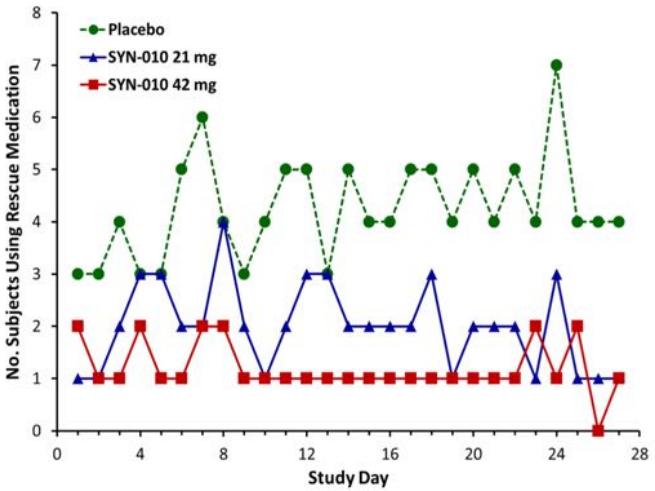
How Lovastatin would help



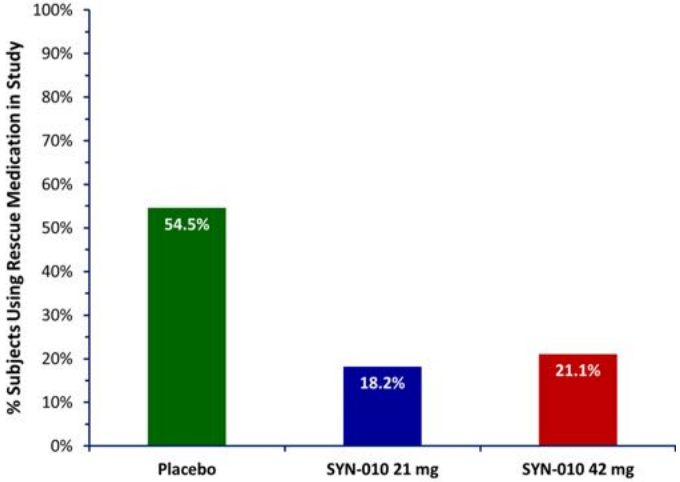
F420 is the key enzyme in path that makes methane in *M. smithii*

Lovastatin affect on laxative use

Daily use of RLax® (bisacodyl; 5 mg) in Study 1

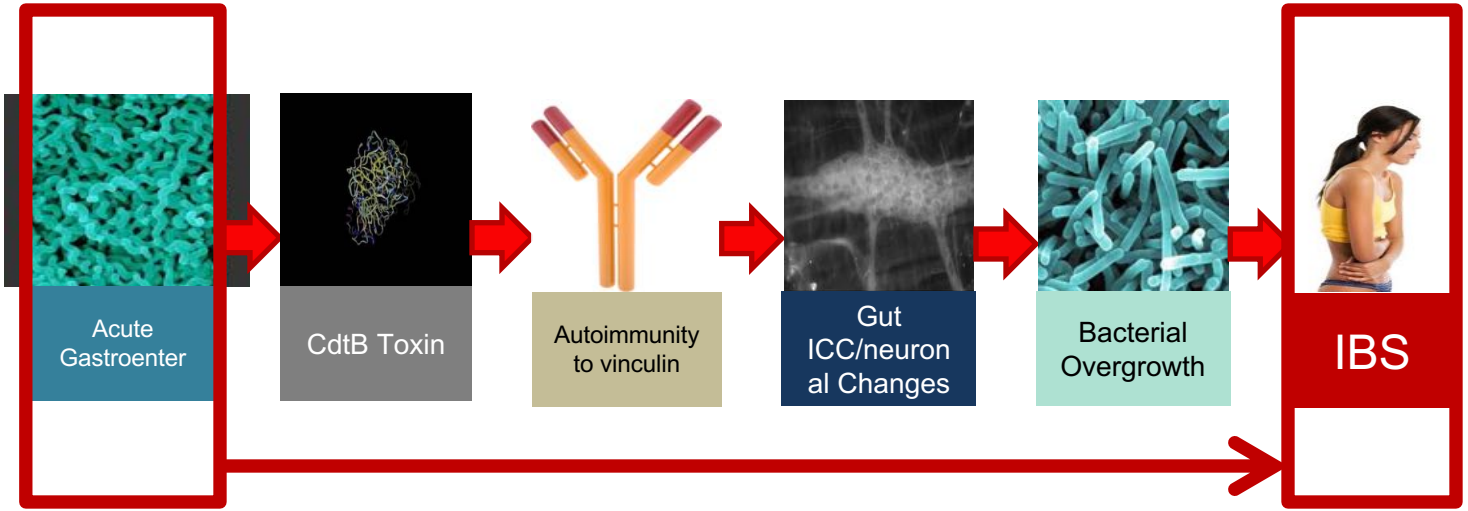


% Subjects using RLax® (bisacodyl; 5 mg) in Study 1

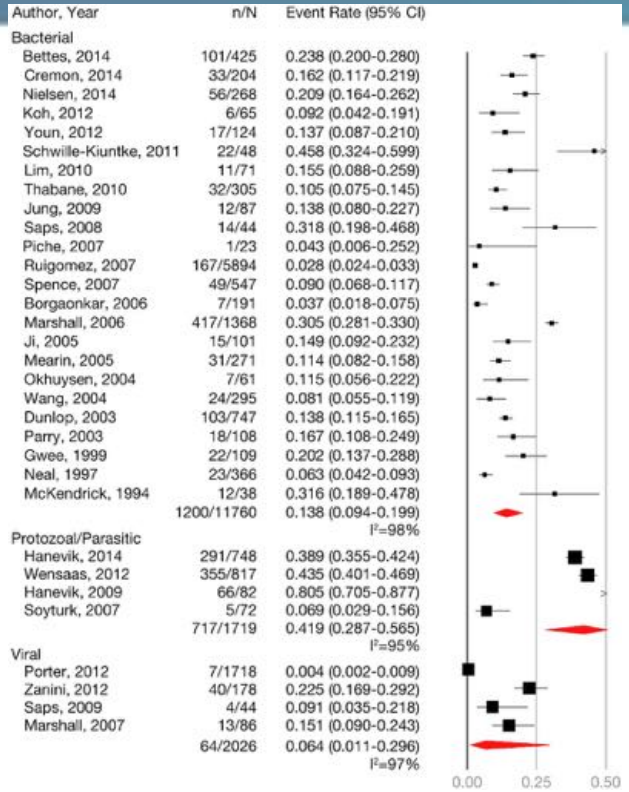


Gottlieb, et al. DDW, 2016

IBS Microbial Hypothesis



Risk of PI-IBS After Infectious Gastroenteritis*



Author, Year	n/N	Event Rate (95% CI)
Bacterial		
Bettes, 2014	101/425	0.238 (0.200-0.280)
Cremon, 2014	33/204	0.162 (0.117-0.219)
Nielsen, 2014	56/268	0.209 (0.164-0.262)
Koh, 2012	6/65	0.092 (0.042-0.191)
Youn, 2012	17/124	0.137 (0.087-0.210)
Schwille-Kiuntke, 2011	22/48	0.458 (0.324-0.599)
Lim, 2010	11/71	0.155 (0.088-0.259)
Thabane, 2010	32/305	0.105 (0.075-0.145)
Jung, 2009	12/87	0.138 (0.080-0.227)
Saps, 2008	14/44	0.318 (0.198-0.468)
Piche, 2007	1/23	0.043 (0.006-0.252)
Ruigomez, 2007	167/5894	0.028 (0.024-0.033)
Spence, 2007	49/547	0.090 (0.068-0.117)
Borgaonkar, 2006	7/191	0.037 (0.018-0.075)
Marshall, 2006	417/1368	0.305 (0.281-0.330)
Ji, 2005	15/101	0.149 (0.092-0.232)
Mearin, 2005	31/271	0.114 (0.082-0.158)
Okhuysen, 2004	7/61	0.115 (0.056-0.222)
Wang, 2004	24/295	0.081 (0.055-0.119)
Dunlop, 2003	103/747	0.138 (0.115-0.165)
Parry, 2003	18/108	0.167 (0.108-0.249)
Gwee, 1999	22/109	0.202 (0.137-0.288)
Neal, 1997	23/366	0.063 (0.042-0.093)
McKendrick, 1994	12/38	0.316 (0.189-0.478)
	1200/11760	0.138 (0.094-0.199)
		I^2=98%
Protozoal/Parasitic		
Hanevik, 2014	291/748	0.389 (0.355-0.424)
Wensaas, 2012	355/817	0.435 (0.401-0.469)
Hanevik, 2009	66/82	0.805 (0.705-0.877)
Soyturk, 2007	5/72	0.069 (0.029-0.156)
	717/1719	0.419 (0.287-0.565)
		I^2=95%
Viral		
Porter, 2012	7/1718	0.004 (0.002-0.009)
Zanini, 2012	40/178	0.225 (0.169-0.292)
Saps, 2009	4/44	0.091 (0.035-0.218)
Marshall, 2007	13/86	0.151 (0.090-0.243)
	64/2026	0.064 (0.011-0.296)
		I^2=97%

RR=4.23; 95% CI, 3.15−5.69

11% of people exposed

1 in 9 who experience food poisoning

FOOD POISONING CAUSES IBS!!

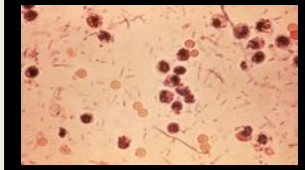
A review of 45 studies

Klem, et al. Gastroenterol 2017

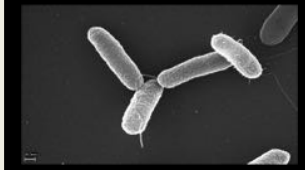
Risk Factors

- Severity of Food poisoning
- Female
- Blood in stool
- Antibiotics needed
- More than 7 days of illness
- Psychological factors

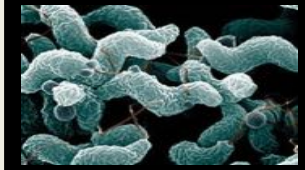
Klem, et al. Gastroenterol 2017



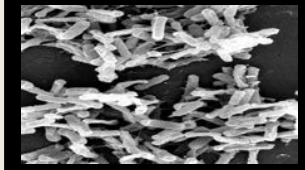
Shigella



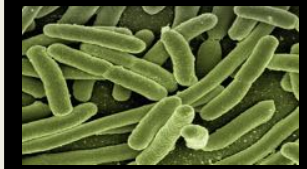
Salmonella



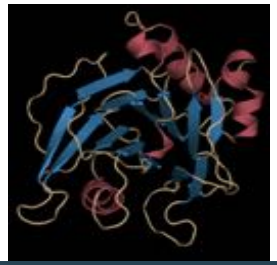
Campylobacter



C. difficile

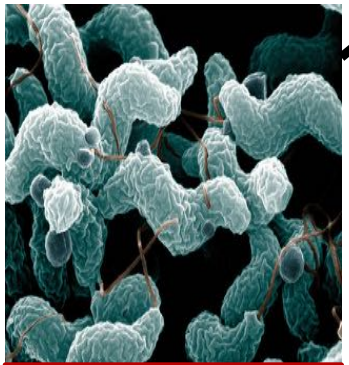


E. coli

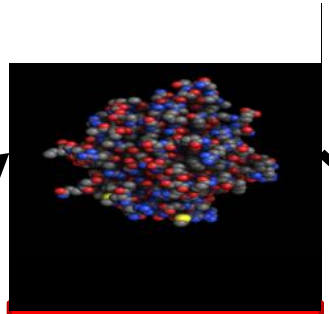


CYTOLETHAL DISTENDING TOXIN B

Immunization Trial



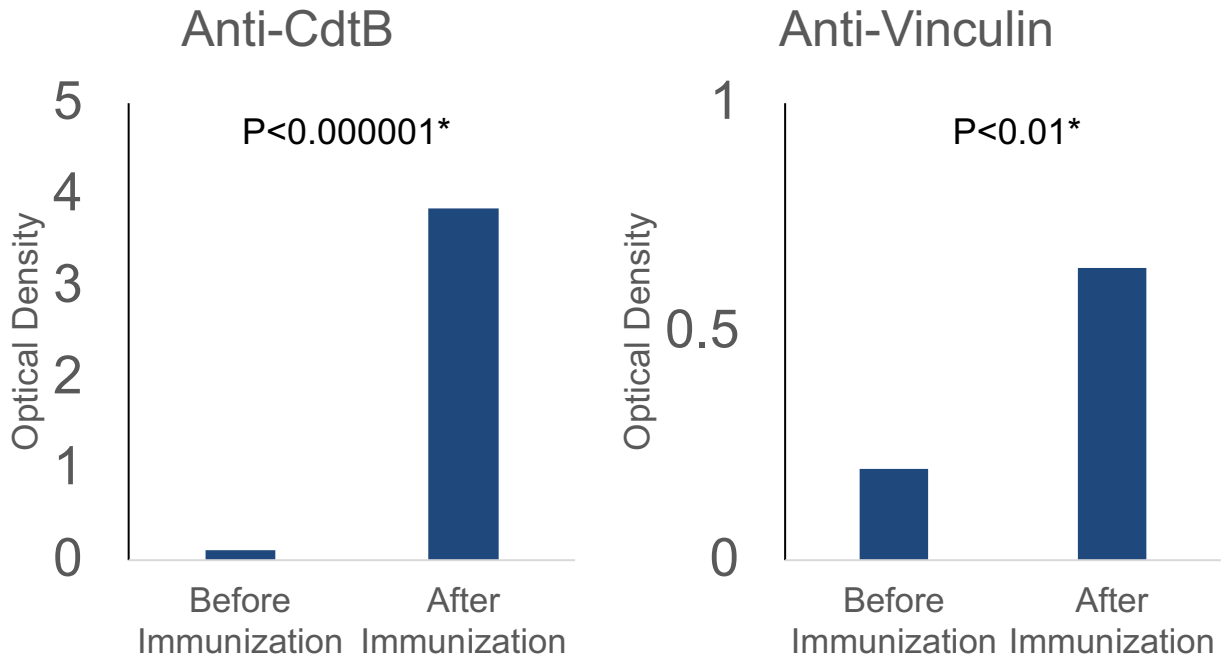
Campylobacter



Recombinant CdtB

Sprague-Dawley Rats

Serum Antibody Response to CdtB

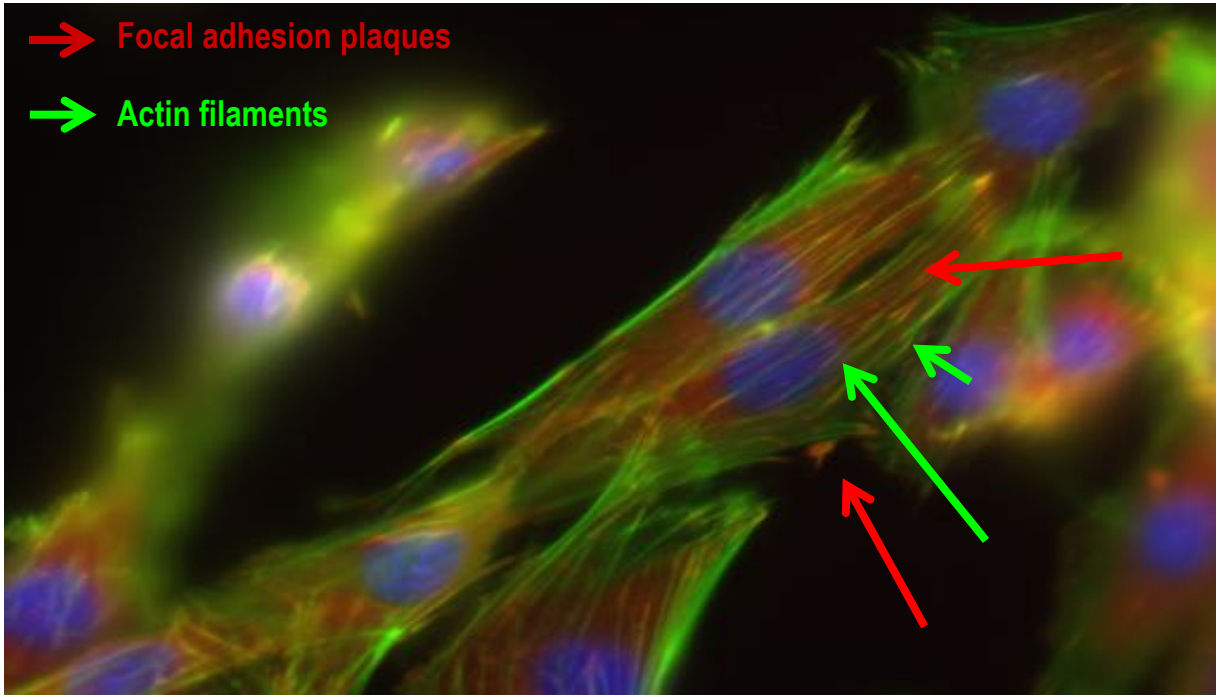


*Paired t-Test

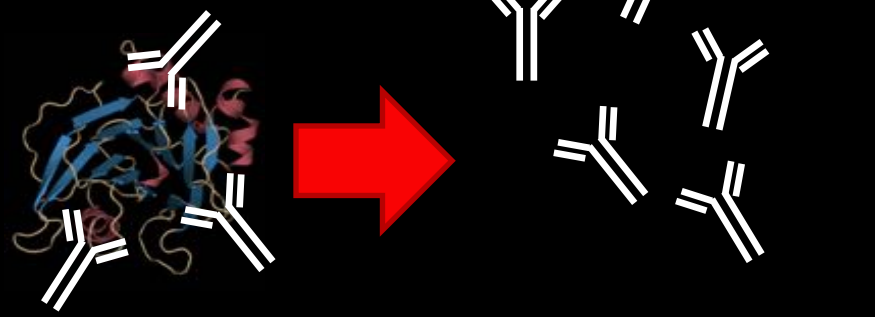
Anti-CdtB Implications

Factor	R_s	P-value
Duodenal Microbial Counts	0.32	0.01
Ileal Microbial Counts	0.33	0.01
Vinculin expression	-0.28	0.03
Stool wet weight	0.26	0.04
TNF-α expression	-0.32	0.01
IL-1β expression	-0.66	<0.0001
IL-8 expression	0.06	0.64
β-defensin expression	-0.03	0.77

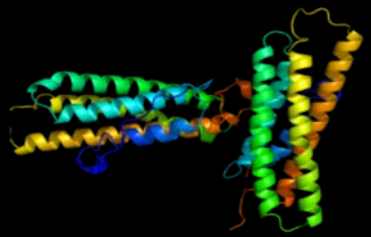
Vinculin



Molecular Mimicry/Autoimmunity



Cytolethal Distending Toxin B



Human Vinculin

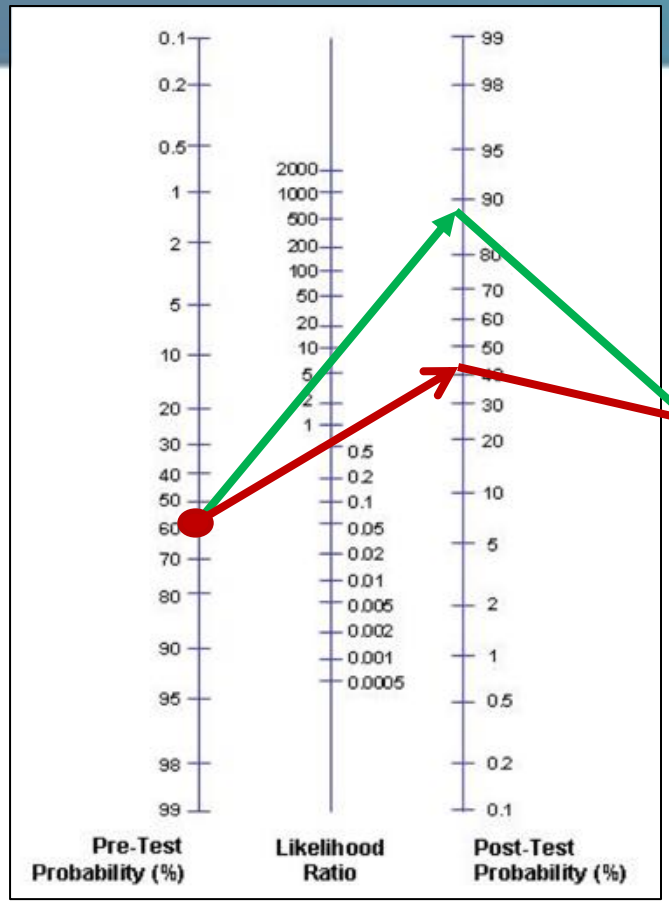
Blood Test For IBS

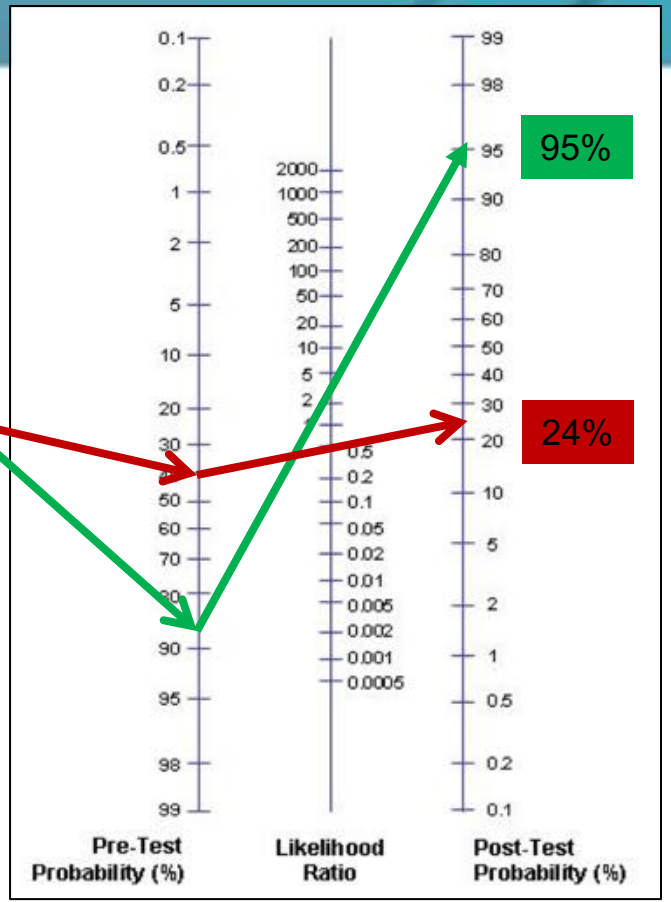
- D-IBS subjects (N=2375)
- Subjects with IBD (N=142) which included Crohn's disease (N=73) and ulcerative colitis (N=69)
- Subjects with celiac disease (N=121)
- Healthy subjects (N=43)

Pimentel, et al. Plos One, 2015

Anti-CdtB

Anti-CdtB and Anti-vinculin





2018 NCSCG 15TH ANNUAL POST-DDW SYMPOSIUM

PIMENTEL

Anti-CdtB and Anti-vinculin Are Specific For The Diagnosis of IBS-D and IBS-M and Are Predictors of Rifaximin Response in Mexican Patients

Miguel A. Valdovinos[1], Max J. Schmulson Wasserman[3], Jose Maria Remes Troche[2], Luis R. Valdovinos-Garcia[1], Ana Teresa Abreu[4], Genaro Vazquez[5], Ricardo Raña[6]

[1]Gastroenterology, Instituto Nacional de Ciencias Medicas y Nutricion, Mexico, DF, Mexico; [2]Universidad Veracruzana, Veracruz, Veracruz , Mexico; [3]Universidad Nacional Autonoma de Mexico, Mexico, Mexico; [4]Hospital Angeles Pedregal, Mexico, Mexico; 5Hospital Universitario, Monterrey, Nuevo Leon, Mexico;
[6]Hospital Español, Mexico, Mexico

Aim/Methods

Aim

- To investigate the diagnostig yield and predictive value for rifaximin response of anti-CdtB and anti-vinculin antibodies in Mexican IBS patients without constipation

Methods

- Observational and transversal study involving IBS-D and IBS-M patients, according to Rome IV criteria, attending several private GI clinics in Mexico
- Demographic data, duration of symptoms, history of gastroenteritis, comorbidities, recent use of antibiotics and PPIs, anti-CdtB and anti-vinculin antibodies titers and response to rifaximin treatment were evaluated
  - Titers of anti-CdtB ≥2.80 and anti-vinculin ≥1.68, were considered positive
  - A response to rifaximin was defined as a >50% improvement in global and individual IBS symptoms after 10 days of therapy

Valdovinso MA et al. Presented at DDW 2018. Washington, DC: June 2, 2018; Abstract 1650.

Results:
Baseline Demographics and Disease Characteristics

Baseline Demographics and Disease Characteristics

	n (%)[a]
Patients, n (%)	140
Women	90 (64%)
Mean age, y (range)	45.6 (16-82)
Mean symptom duration, mos (range)	44.3 (0.7-504)
IBS Subtype	
IBS-D	85 (60.7)
IBS-M	35 (39.3)
History of gastroenteritis	65 (46.4)
Antibody positivity	
Anti-CdtB	38 (27)
Anti-vinculin	40 (28)
One or both	78 (55.7)

[a]Unless otherwise noted.
Valdovinso MA et al. Presented at DDW 2018. Washington, DC: June 2, 2018; Abstract 1650.

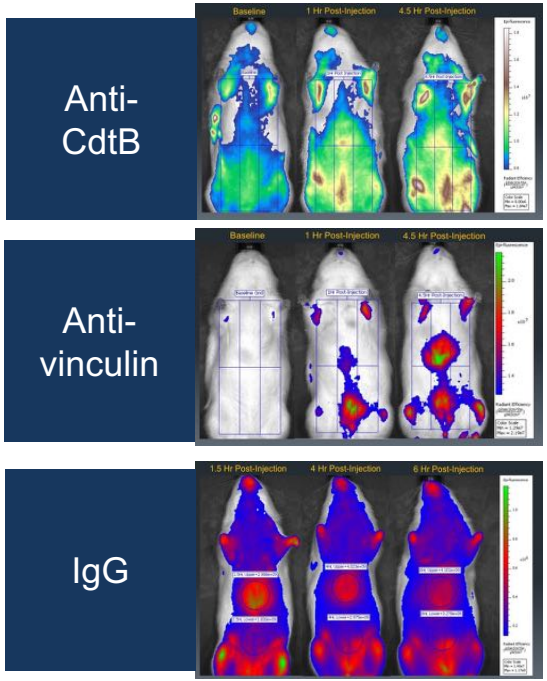
Results:
Diagnostic Performance

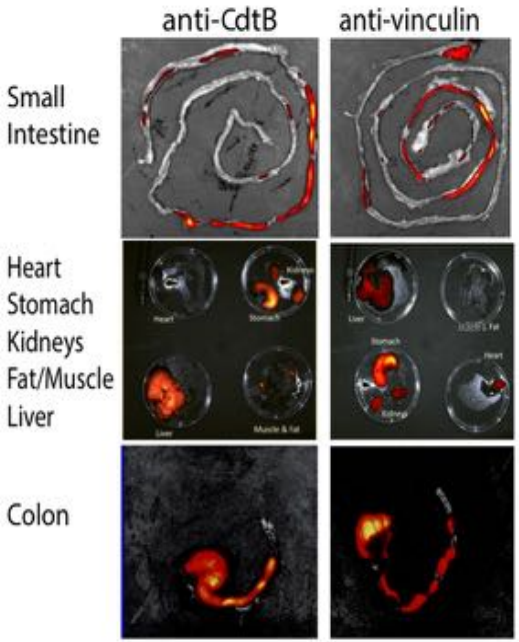
	Anti-CdtB	Anti-vinculin	Both
IBS-D and IBS-M			
Sensitivity	30.4	31.3	46.9
Specificity	88.0	84.0	72.0
PPV	92.1	90.0	88.5
NPV	21.6	21.0	22.8
IBS-D			
Sensitivity	68.4	67.5	67.2
Specificity	47.0	47.0	50.0
PPV	32.5	33.7	51.2
NPV	80.0	78.3	66.7
IBS-M			
Sensitivity	23.7	22.5	21.3
Specificity	74.5	74.0	72.1
PPV	25.7	25.7	37.1
NPV	72.4	70.5	54.3

Valdovinso MA et al. Presented at DDW 2018. Washington, DC: June 2, 2018; Abstract 1650.

- Favorable response to rifaximin associated with
  - Presence of both antibodies (RM: 11.7, CI 95%: 4.7-29, *P* <0.001)
  - Anti-CdtB (RM: 12.3, CI 95%: 3.5-42.8, *P* <0.001)
  - Anti-vinculin (RM: 5.2, CI 95%: 2.0 -13.7; *P*<0.001)
- A previous gastroenteritis, use of PPIs or antibiotics were not associated to a positive anti-CdtB or anti-vinculin

Antibodies localize to gut





Weitsman, et al. DDW 2018 Tu1251

2018 NCSCG 15TH ANNUAL POST-DDW SYMPOSIUM

A Double-Blind, Randomized, Placebo-Controlled Trial of Fecal Microbiota Transplantation Capsules (FMTC) For the Treatment of IBS-D

Olga Christina Aroniadis[1,2], Lawrence J Brandt1,2, Caterina Oneto[3], Paul Feuerstadt4,5, Alex Sherman[3], Allan W. Wolkoff[1,2], Ian Andrew Downs[2], Alana Zanetti-Yabur1, Yolanda Ramos3, Candace L. Cotto4, Zain Kassam6, Ryan J. Elliott6, Robert Rosenbaum[6], Shrish Budree[6], Rotem Gura Sadovsky[7], Sonia Timberlake7, Paige Swanson[7], Mimi Kim[8], Marla J. Keller[2]

1Gastroenterology and Liver Diseases, Montefiore Medical Center, Bronx, New York, United States; 2Medicine, Albert Einstein College of Medicine, Bronx, New York, United States; 3Concorde Medical Center, Manhattan, New York, United States; 4Medical Research Center of Connecticut, Hamden, Connecticut, United States; 5Gastroenterology, Yale University School of Medicine, New Haven, Connecticut, United States; 6OpenBiome, Somerville, Massachusetts, United States; 7Finch Therapeutics, Somerville, Massachusetts, United States; [8]Biostatistics and Epidemiology, Albert Einstein College of Medicine, Bronx, New York, United States

Aim/Methods

Introduction/Aims

- To investigate the safety and efficacy of FMT capsules in a randomized, placebo-controlled trial

Methods

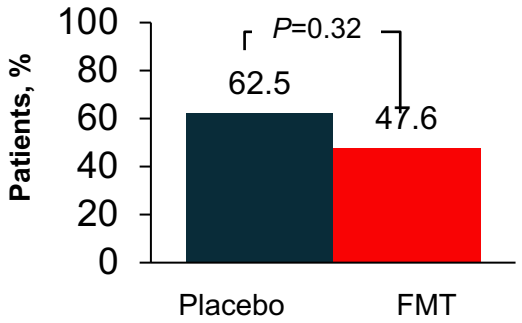
- Multicenter, double-blind, randomized, placebo-controlled trial enrolled 18-65 year old subjects with moderate-severe IBS-D (IBS-Symptom Severity Score [IBS-SSS] ≥175)
- Subjects were randomized 1:1 to FMTc followed by placebo capsules (Pc) or Pc followed by FMTc
- At randomization, subjects received 3 consecutive days of either 25 FMTc (50 gms of stool from a healthy donor) or 25 Pc and were followed for 12 weeks
  - All subjects crossed over into the alternate arm at 12 weeks and were followed for another 12 weeks
- The primary outcome was clinical response defined by a decrease in IBS-SSS by ≥50 points at 12 weeks compared between groups using a Chi-square analysis
- Pre- and post-intervention stool samples were collected in all subjects for 16s microbiome analysis

Aroniadis OC et al. Presented at DDW 2018. Washington, DC: June 3, 2018; Abstract 742.

Results

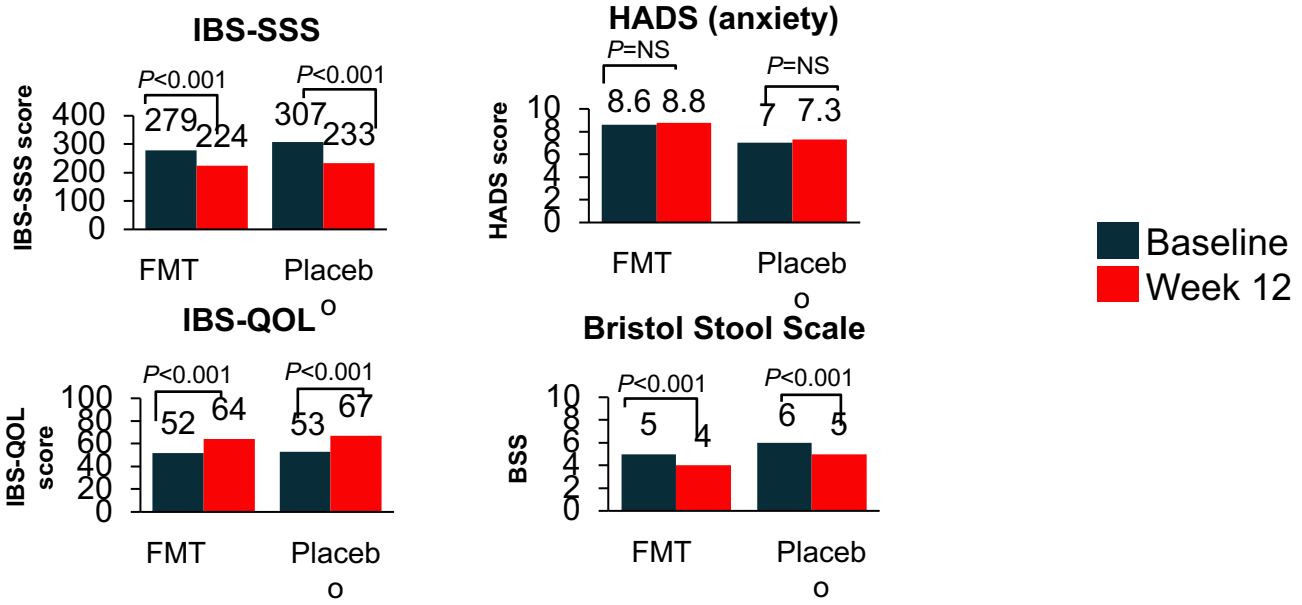
- Subjects in each group had significant improvement in IBS-SSS, IBS-QOL, and BSS scores between baseline and 12 weeks
- However, clinical response rates did not differ significantly between FMT and placebo groups at 12 weeks (48% vs 63%, p=0.32), nor did IBS-SSS, IBS-QOL, HADS and BSS scores after adjustment for baseline scores

Primary Endpoint
Clinical Response Rate[a]



Aroniadis OC et al. DDW 2018. Abstract 742.

Results: Secondary Endpoints



Aroniadis OC et al. DDW 2018. Abstract 742.

Conclusions

- FMT did not induce significant symptom relief at 12 weeks compared with placebo
- Subgroup analysis suggested that FMT may be more effective in patients with PI-IBS

Holvoet T al. DDW 2018. Abstract 617.

2018 NCSCG 15TH ANNUAL POST-DDW SYMPOSIUM

Fecal Microbiota Transplantation in IBS with Predominant Abdominal Bloating: Results from a Double-Blind, Placebo-Controlled Clinical Trial

Tom Holvoet[1], Marie Joossens[2,3], Boelens Jerina[4], Evelien Christiaens[1], Lander Heyerick[1], Bruno Verhasselt[4], Martine De Vos[1], Pieter Hindryckx[1], Jeroen Raes[2,3], Danny De Looze[1]

[1]Gastroenterology, Ghent University Hospital, Ghent, Belgium; [2]Microbiology and Immunology, KU Leuven, Leuven, Belgium; [3]Center for the Biology of Disease, VIB, Leuven, Belgium; [4]Microbiology, Ghent University Hospital, Ghent, Belgium

Aim/Methods

Introduction/Aims

- To examine the effects of FMT in IBS patients with severe abdominal bloating

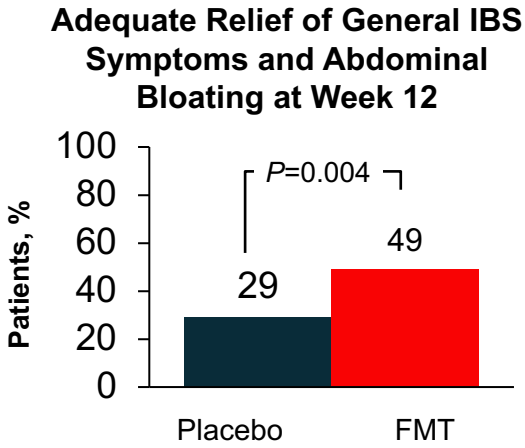
Methods

- Randomized, double-blind, single-center placebo-controlled trial in patients with refractory IBS symptoms and predominant abdominal bloating defined by Rome III criteria, aged 18-75 years, without constipation
- Patients were randomly assigned (2:1) to transplantation with fresh donor stool or with placebo (patient's own frozen stool)
  - Donors (N=2) were selected based on both having a high microbial richness and yielding good clinical results in a preliminary pilot trial and screened for infectious diseases on a regular basis
  - Transplants were prepared as previously described and administered through a nasojejunal tube which was placed electromagnetically guided (Cortrak)
- Primary endpoint was self-reported improvement of overall IBS symptoms and abdominal bloating in particular, 12 weeks after transplantation
- 16S rRNA amplicon sequencing was performed to follow the dynamics of the gut microbiota

Holvoet T al. DDW 2018. Abstract 617.

Results

- 64 IBS patients were randomized to active donor treatment (n= 42) or placebo (n=22)
- Statistically significant reduction was seen in discomfort (mean reduction of 19% p=0.001), the number of stools (-13%, *P*=0.02), urgency (-38%, p=0.01), abdominal pain -26%, *P* =0.001) and flatulence (-10%, *P* =0.04) in the donor group but not in the placebo group, while IBS-related quality of life improved as well in the donor group (+16%, *P* =0.03)
- There were no significant differences in the efficacy of individual donors
- Microbiota analysis are currently ongoing



Holvoet T al. DDW 2018. Abstract 617.

Conclusions

- In this double-blind, placebo-controlled clinical trial, FMT with healthy donor stools significantly improved symptoms of IBS patients with predominant abdominal bloating

Holvoet T al. DDW 2018. Abstract 617.

2018 NCSCG 15TH ANNUAL POST-DDW SYMPOSIUM

Fecal Microtiota Transplantation Alters Gut Microbiota in Patients with IBS: Results From A Randomized, Double-Blind, Placebo-Controlled Trial

Sofie Halkjær[1], Alice Christensen[2], Bobby Lo[1], Patrick Browne[3], Stig Günther[2], Lars Hestbjerg Hansen[3], Andreas Munk Petersen[1]

[1] Hvidovre University Hospital, Hvidovre, Denmark; [2]Aleris-Hamlet Hospitals Søborg, 2860 Copenhagen, Denmark; [3]Aarhus University, Roskilde, Denmark

Aim/Methods

Introduction

- To investigate if FMT resulted in an altered gut microbiota and improvement in clinical outcome in patients with IBS

Methods

- 52 adult patients with Rome III-defined, moderate to severe IBS based on a symptom score of at least 175 in the IBS-SSS were included
  - Clinical history and symptoms were assessed and fecal samples were collected at screening
  - Patients were randomized to FMT or placebo capsules for 12 days and followed for 6 months
- Study visits were performed at baseline, 1 month, 3 months and 6 months, where patients were asked to register their symptoms using the IBS-SSS and IBS specific quality of life (IBS-QoL)
  - Prior to each visit fecal samples were collected, inclusive of a sample 3 days after treatment was completed (day 15)

Halkjær S et al. DDW 2018. Abstract 914.

Results

- Patients receiving FMT capsules had an increase in biodiversity to the extent that they were not statistically distinguishable from the donors
  - Placebo patients remained statistically indistinguishable from their pre-treatment state (Mann-Whitney U-test, $P < 0.05$)
- No significant difference in improvement in IBS-SSS score was observed 3 months after treatment
- IBS-QoL improved significantly ($P=0.003$) at 3 months in placebo patients compared with FMT-treated patients

Halkjær S et al. DDW 2018. Abstract 914.

Conclusions

- In a randomized double-blinded placebo controlled study, we found that FMT changed gut microbiota in IBS patients
- However, patients in the placebo-group experienced greater symptom relief compared to the FMT-group
- Altering the gut microbiota is not enough to obtain clinical improvement in IBS
- Different study designs and larger studies are required to examine the role of FMT in IBS

Halkjær S et al. DDW 2018. Abstract 914.