Post DDW Review: Functional GI Disorders

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Irritable Bowel Syndrome

- Affects 40 million people in the US. Nearly 1 billion worldwide.
- It is the most expensive disorder in GI
- Why is it so expensive?

IBS and Stress

Military study:

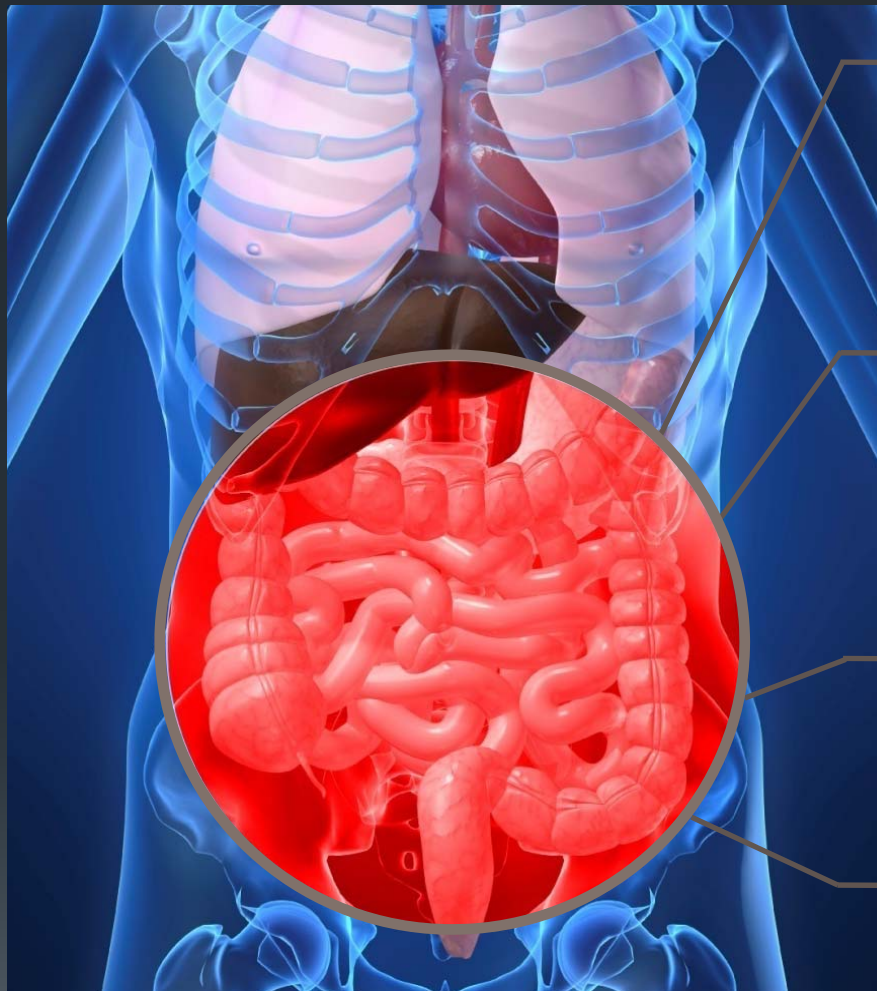Shooting gun in combat ❌

Shooting another human ❌

Active combat ❌

Injured in combat ❌

Only Food Poisoning was associated with IBS

Porter CK, et al. Dig Dis Sci 2013

Drug Therapy

Diarrhea
- **Loperamide**
- **Diphenoxylate**
- **Alosetron**
- **Cholestyramine**
- **Antibiotics**

Constipation
- **Fiber**
- **Osmotic and stimulant laxatives**
- **Lubiprostone**
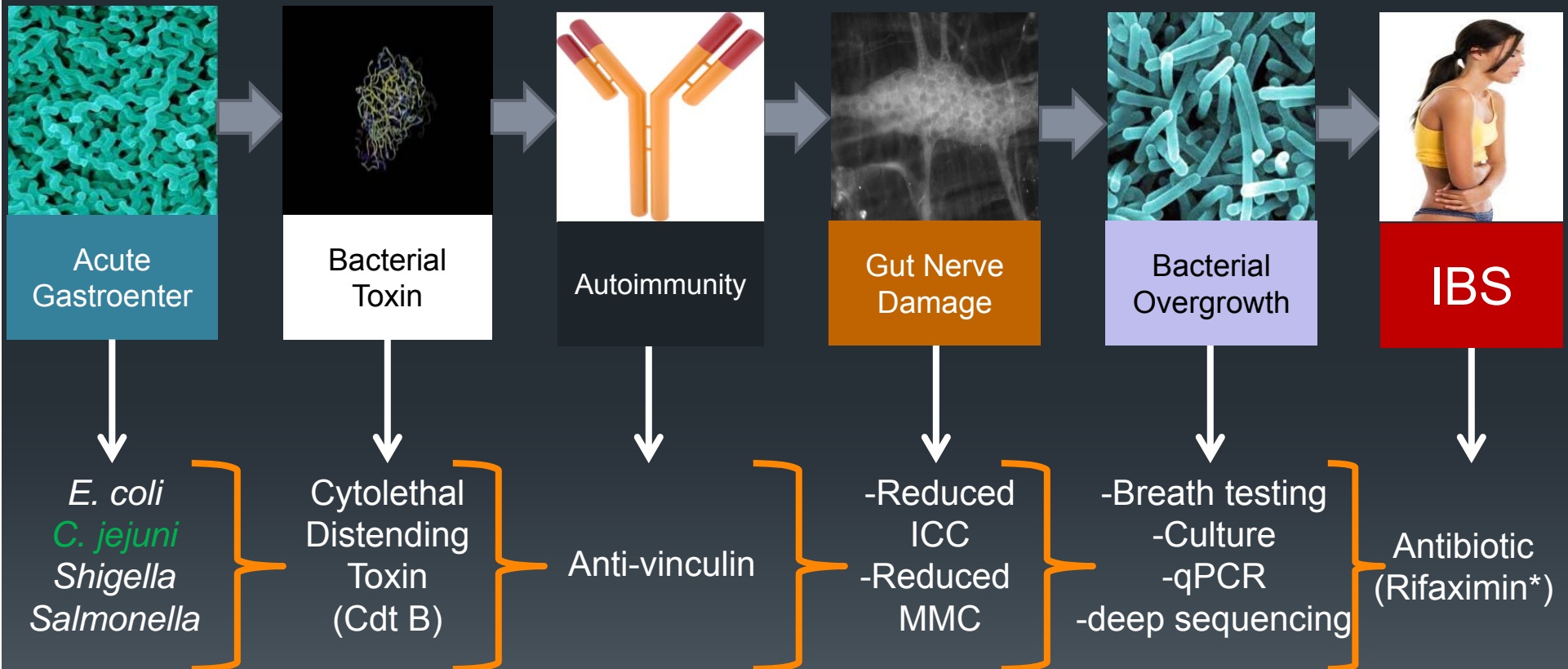
Abdominal pain/ discomfort
- **Antispasmodics**
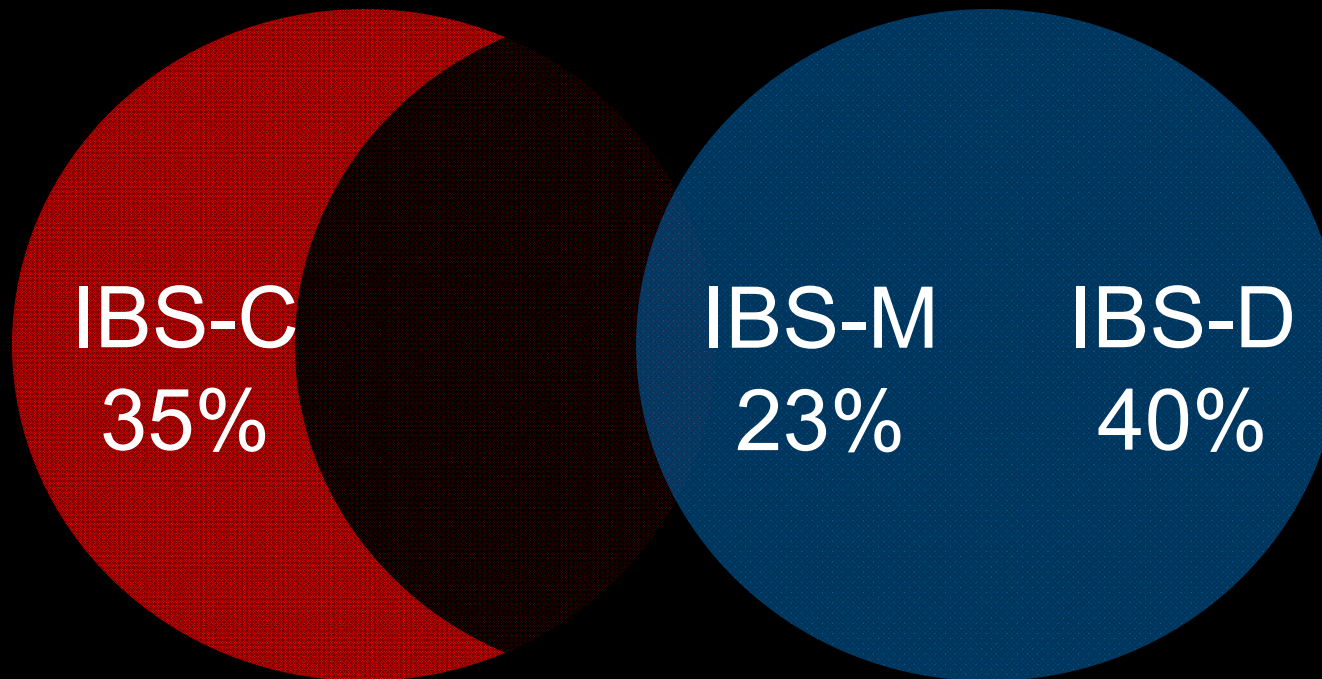- **Antidepressants**
- **Alosetron**

Bloating
- **Antibiotics**
- **Probiotics**

Camilleri M. *Gastroenterology*. 2001;120:652-668.
Drossman DA, et al. *Gastroenterology*. 2002;123:2108-2131.
ACG Task Force on IBS. *Am J Gastroenterol*. 2009;104(suppl 1):S1-S35.
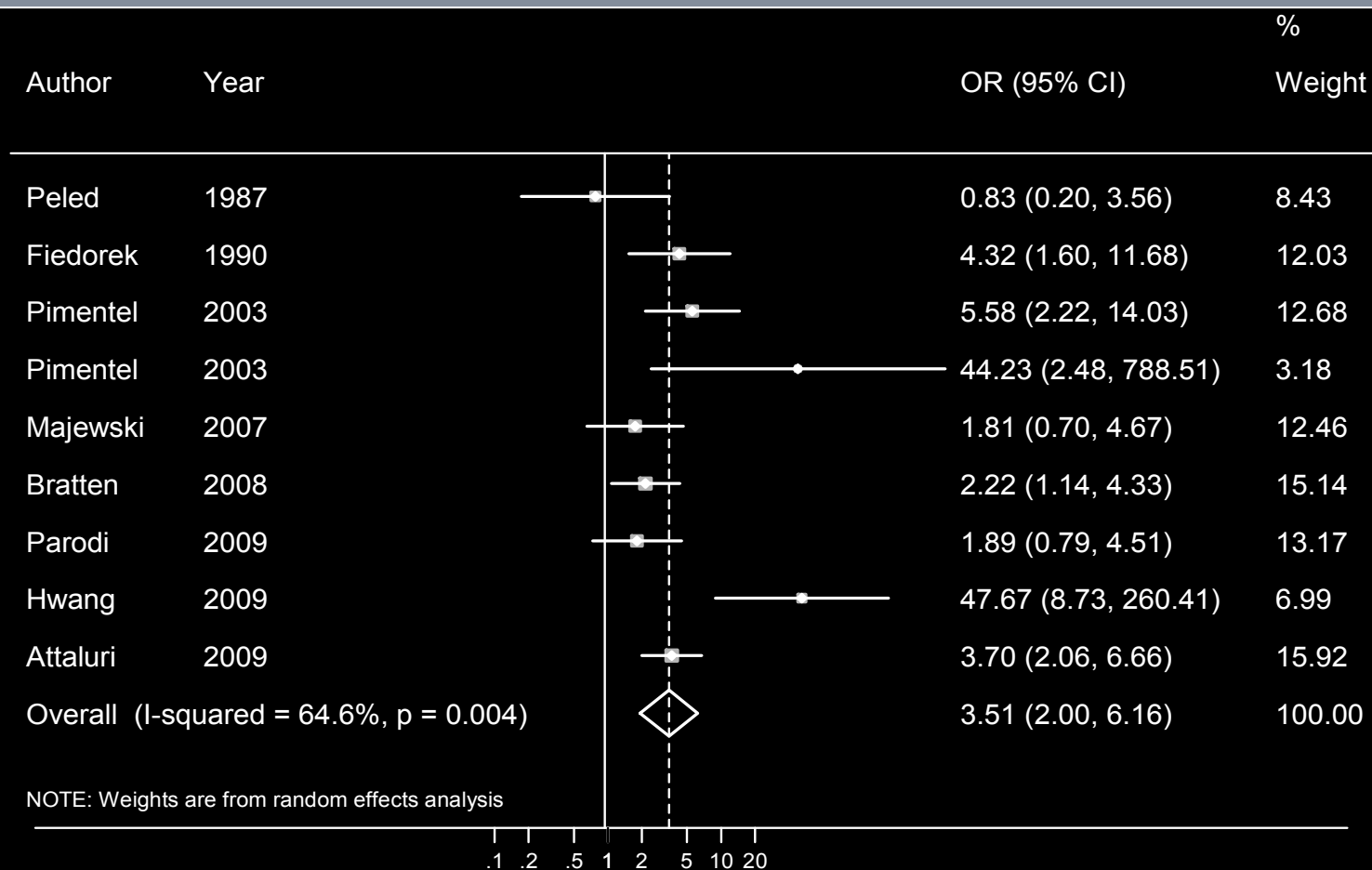
IBS Pathophysiologic Sequence

Acute Gastroenter	Bacterial Toxin	Autoimmunity	Gut Nerve Damage	Bacterial Overgrowth	IBS
E. coli *C. jejuni* *Shigella* *Salmonella*	Cytolethal Distending Toxin (Cdt B)	Anti-vinculin	-Reduced ICC -Reduced MMC	-Breath testing -Culture -qPCR -deep sequencing	Antibiotic (Rifaximin*)

Is IBS really two disease?

IBS-C
35%

IBS-M
23%

IBS-D
40%

Constipation IBS

Non-Constipation
IBS

Methane- Important in C-IBS

Meta-analysis of studies

Author	Year	OR (95% CI)	% Weight
Peled	1987	0.83 (0.20, 3.56)	8.43
Fiedorek	1990	4.32 (1.60, 11.68)	12.03
Pimentel	2003	5.58 (2.22, 14.03)	12.68
Pimentel	2003	44.23 (2.48, 788.51)	3.18
Majewski	2007	1.81 (0.70, 4.67)	12.46
Bratten	2008	2.22 (1.14, 4.33)	15.14
Parodi	2009	1.89 (0.79, 4.51)	13.17
Hwang	2009	47.67 (8.73, 260.41)	6.99
Attaluri	2009	3.70 (2.06, 6.66)	15.92
Overall (I-squared = 64.6%, p = 0.004)		3.51 (2.00, 6.16)	100.00

NOTE: Weights are from random effects analysis

.1 .2 .5 1 2 5 10 20

Kunkel, et al. Dig Dis Sci, 2011.

Competitive Gas Dynamics
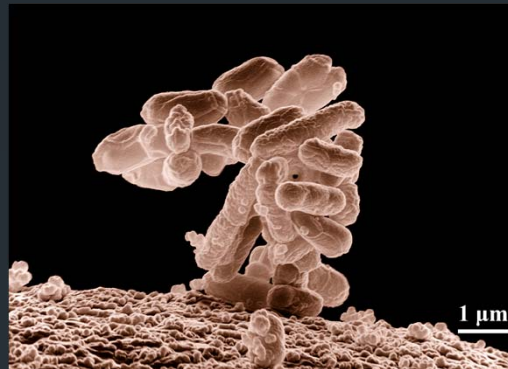
Hydrogen Producing Bacteria

Hydrogen

Methane Producers

$$4H_2 \longrightarrow 1CH_4$$

Hydrogen Sulfide Producers

$$5H_2 \longrightarrow 1H_2S$$
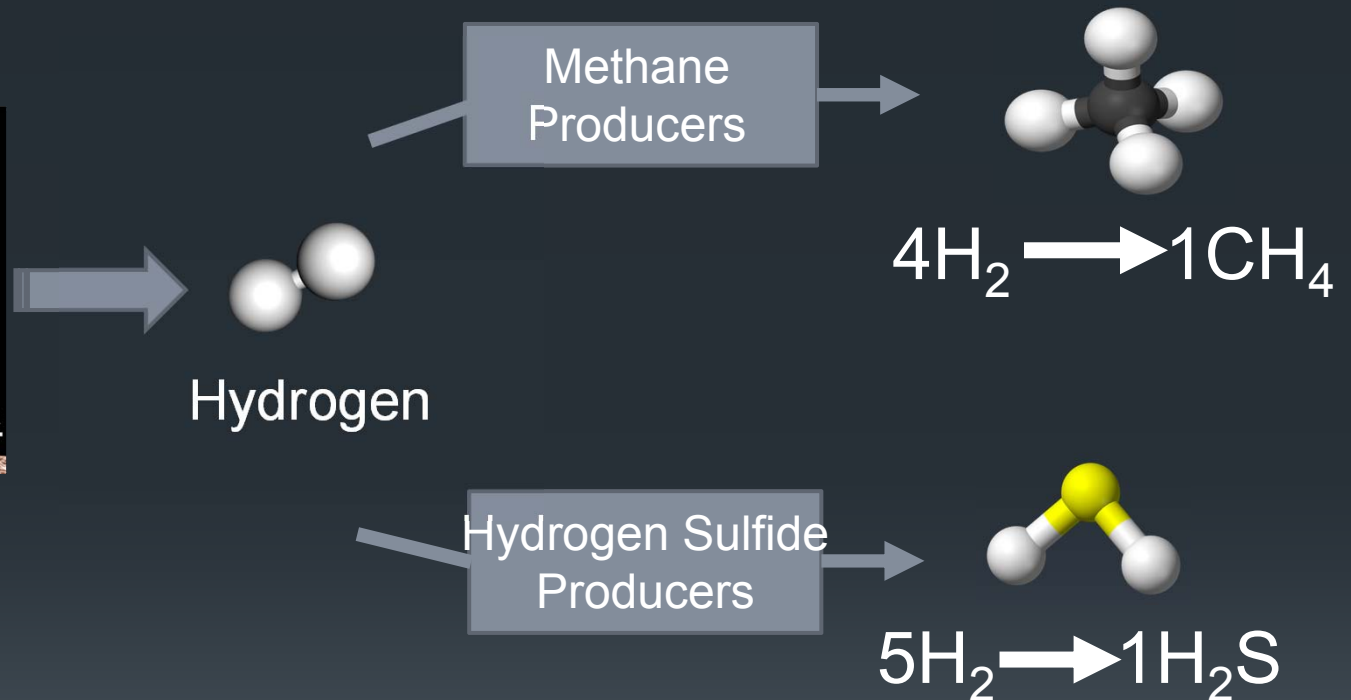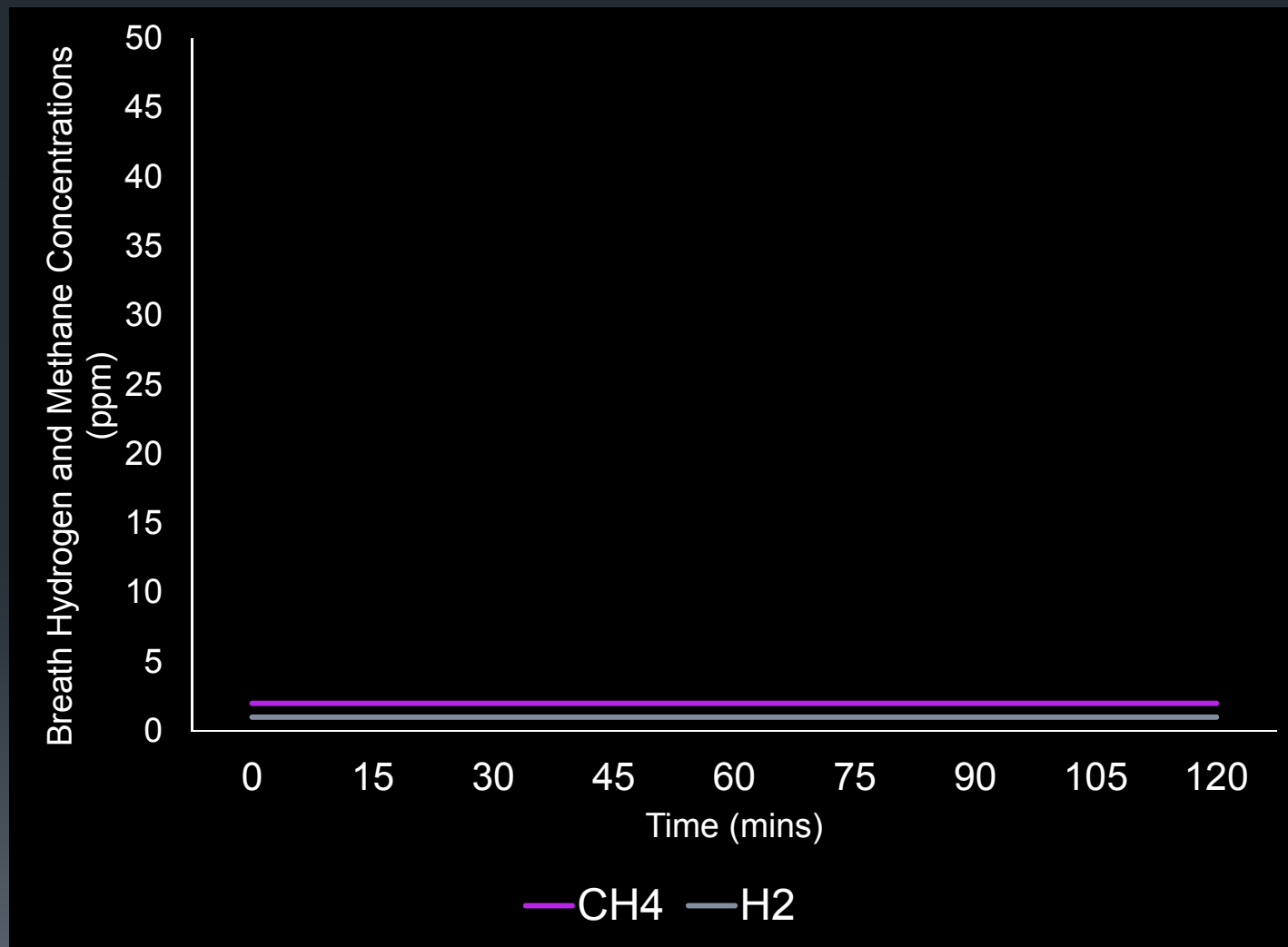
Gibson et al. Gut 1990.; Strocchi et al. Gut 1991.
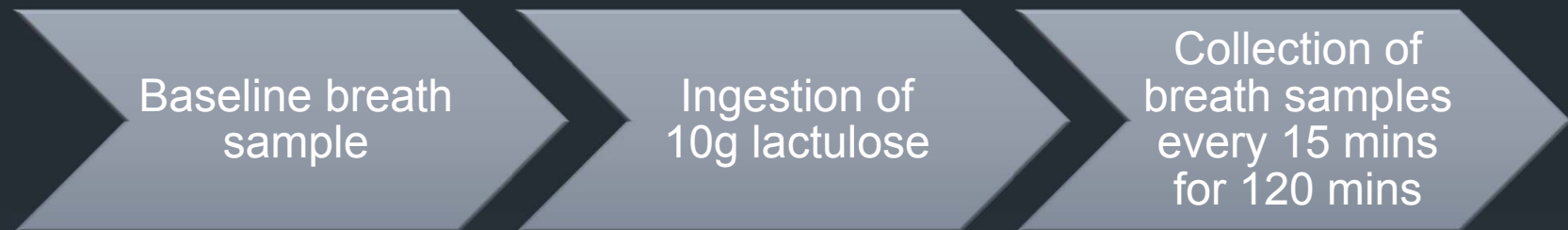
Flat-line breath test

Study Subjects

127 patients recruited from GI Motility Program of Cedars-Sinai Medical Center

Subjects ≥ 18 years undergoing lactulose breath testing were eligible to participate in this study

Subjects prepared with standard-of-care diet restriction and fast

Lin, et al. DDW 2017

Methods: Gas Collection

Baseline breath sample	Ingestion of 10g lactulose	Collection of breath samples every 15 mins for 120 mins

- Patients completed questionnaire during 120 minute breath test collection:
  - Gastrointestinal symptoms
  - Medical/surgical history
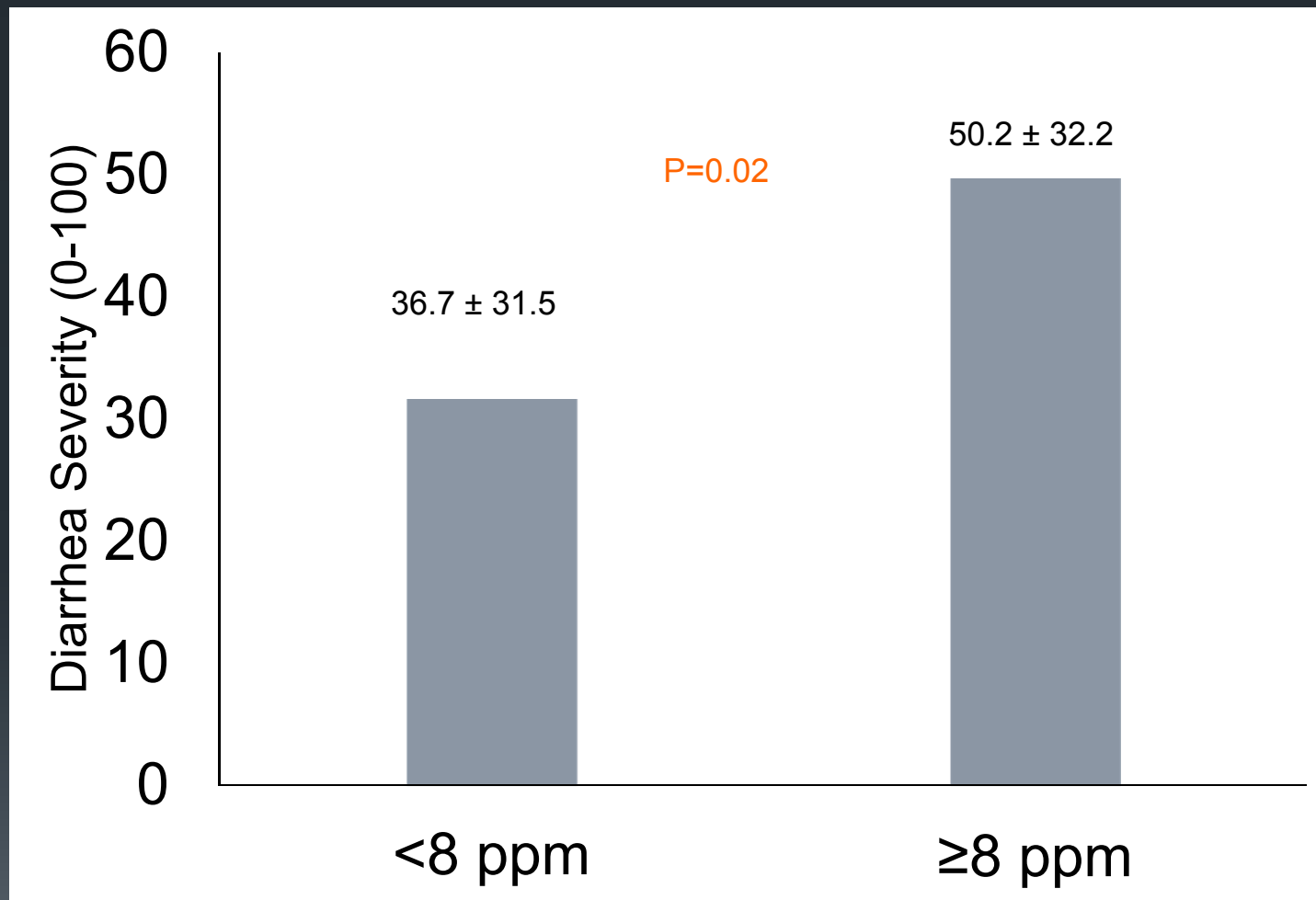 - Demographics
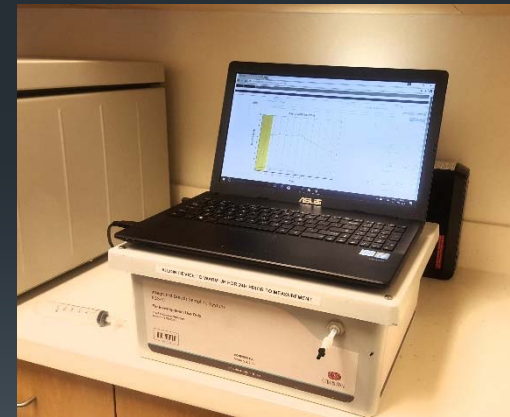
Lin, et al. DDW 2017

Results

Demographics

	H$_2$S Cutoff		
	<8 ppm (n=77)	**≥8 ppm (n=50)**	**P-value**
Age (years)	46.2 ± 16.8	53.6 ± 16.7	P=0.02
Gender (%female)	64.9	80.3	P=0.07

Lin, et al. DDW 2017

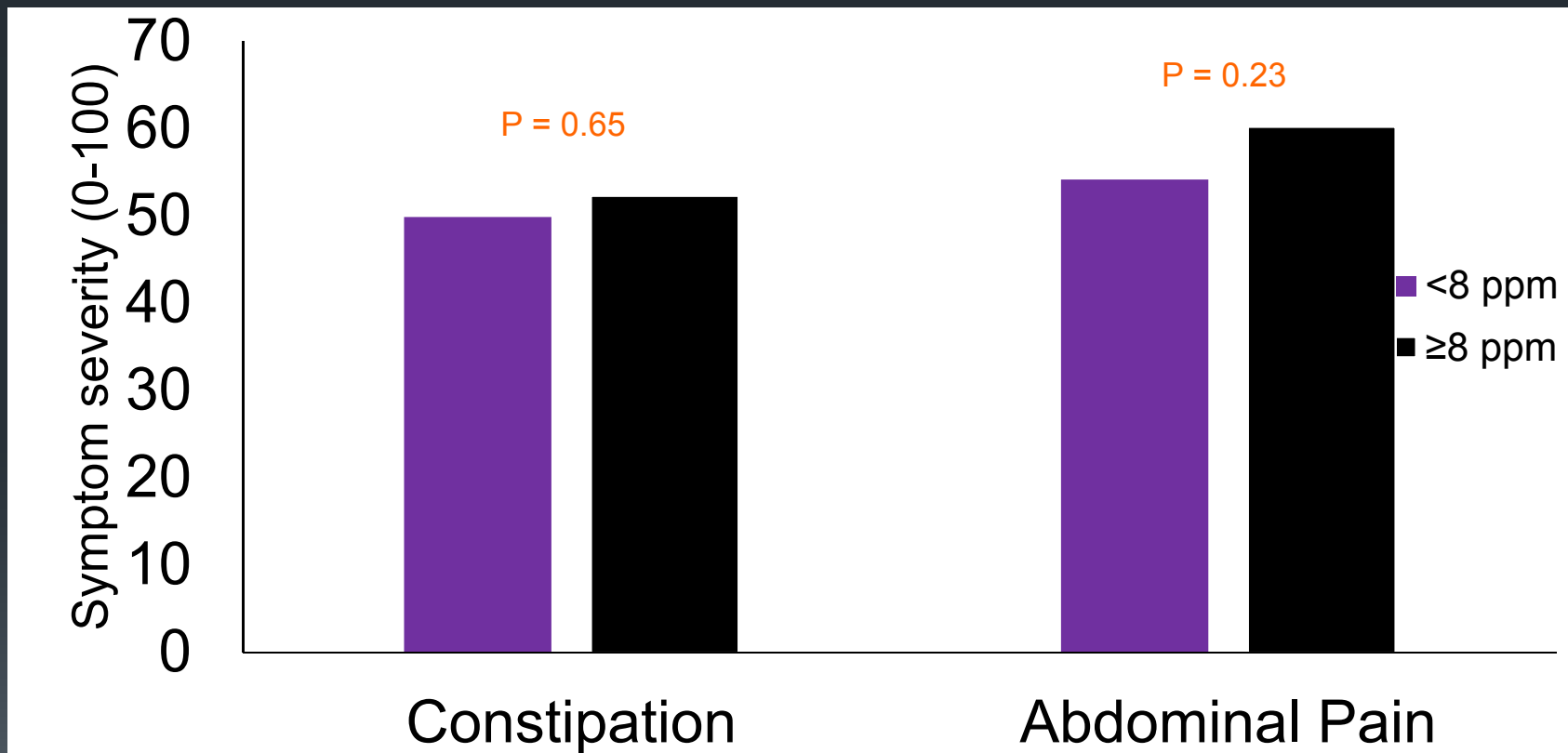# Diarrhea and Hydrogen Sulfide

Urgency and Hydrogen Sulfide
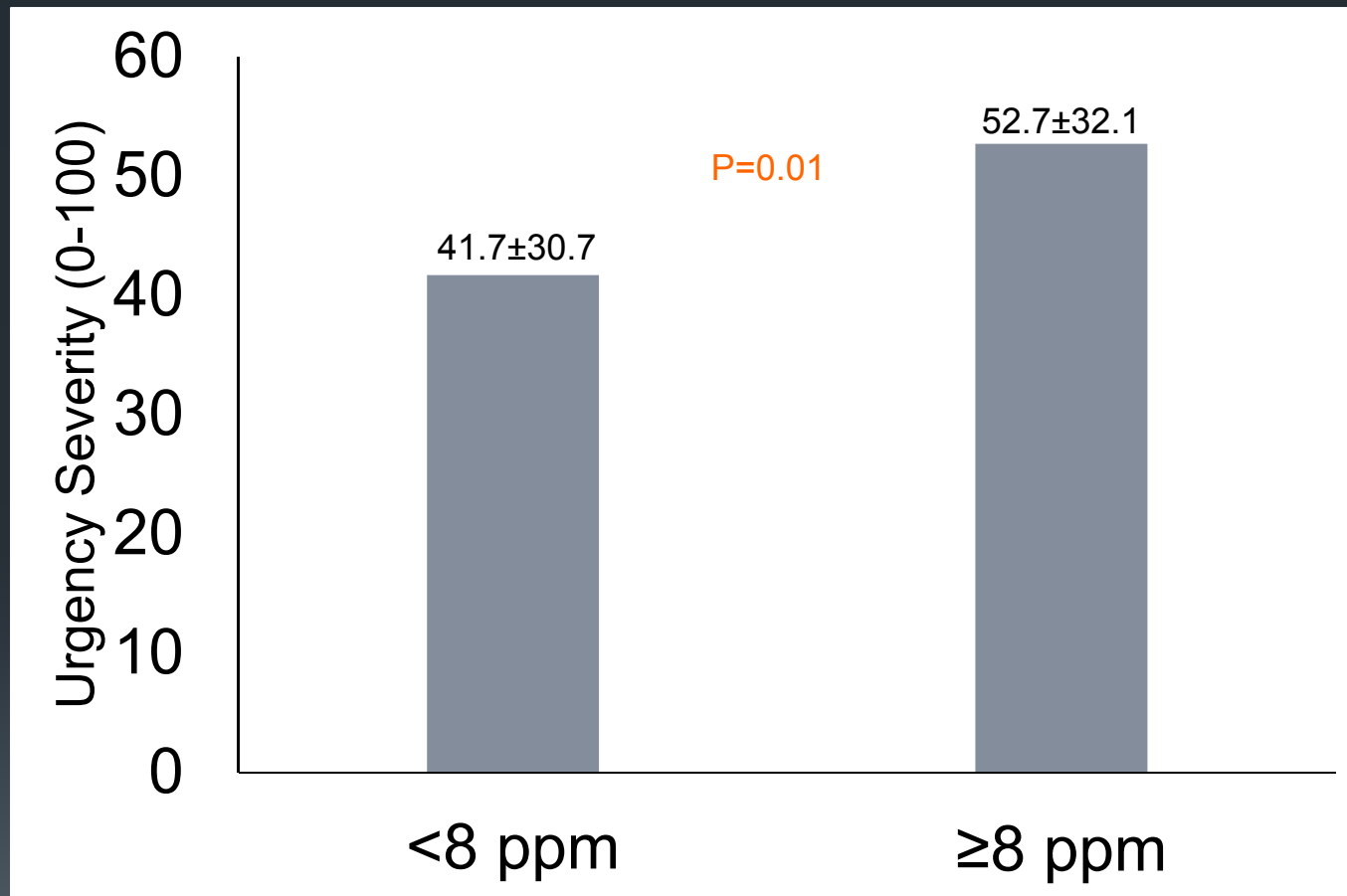
Mean ± Standard Deviation

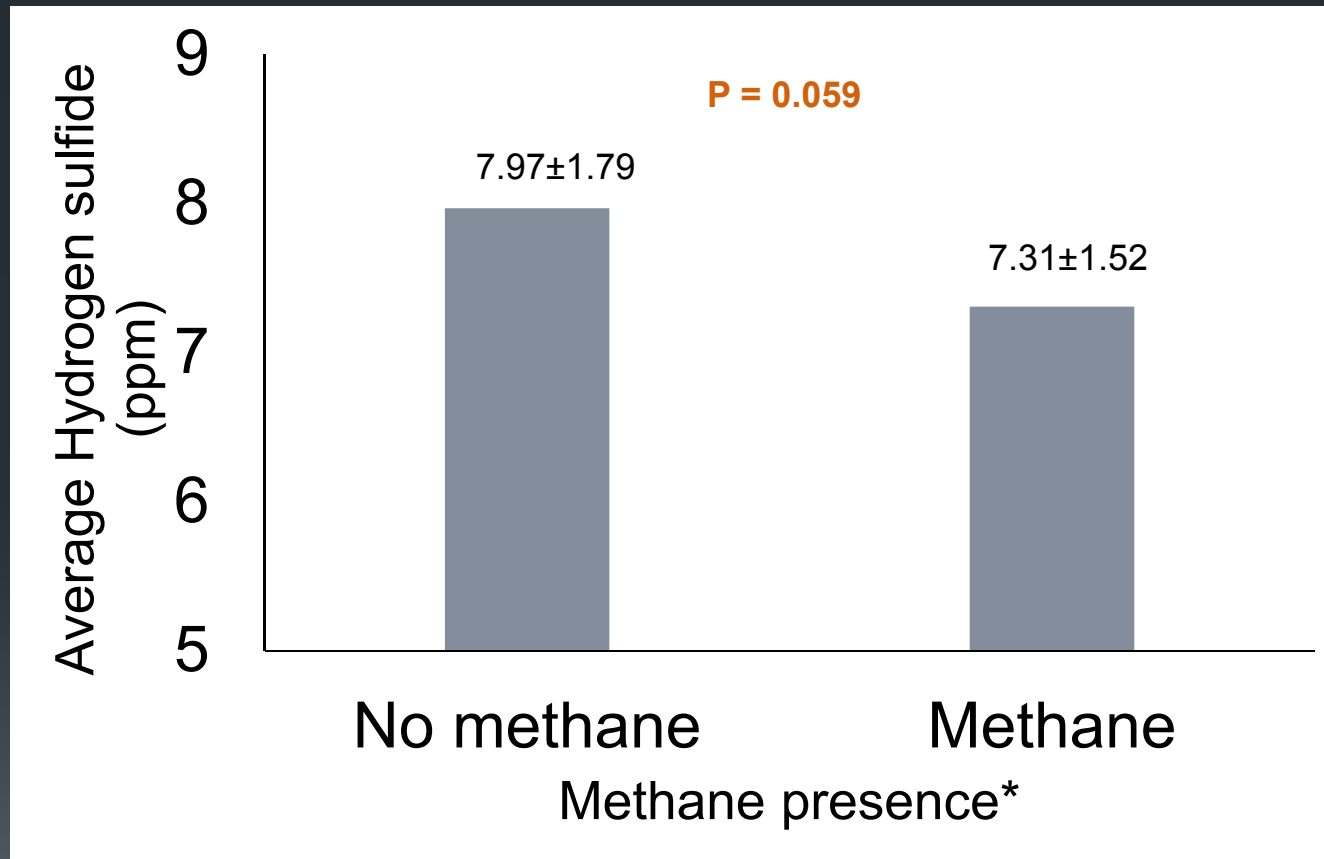Lin, et al. DDW 2017

Constipation, Abdominal Pain and Hydrogen Sulfide

Lin, et al. DDW 2017

Methane and Hydrogen Sulfide

P = 0.059

7.97±1.79

7.31±1.52

Average Hydrogen sulfide (ppm)

No methane   Methane

Methane presence*

*Methane presence defined by maximum methane on breath test (>5 ppm)

Mean ± Standard Deviation

Rezaie et al. Am J Gastroenterol 2017.

Diarrhea and Max ≥1.2 ppm Hydrogen Sulfide
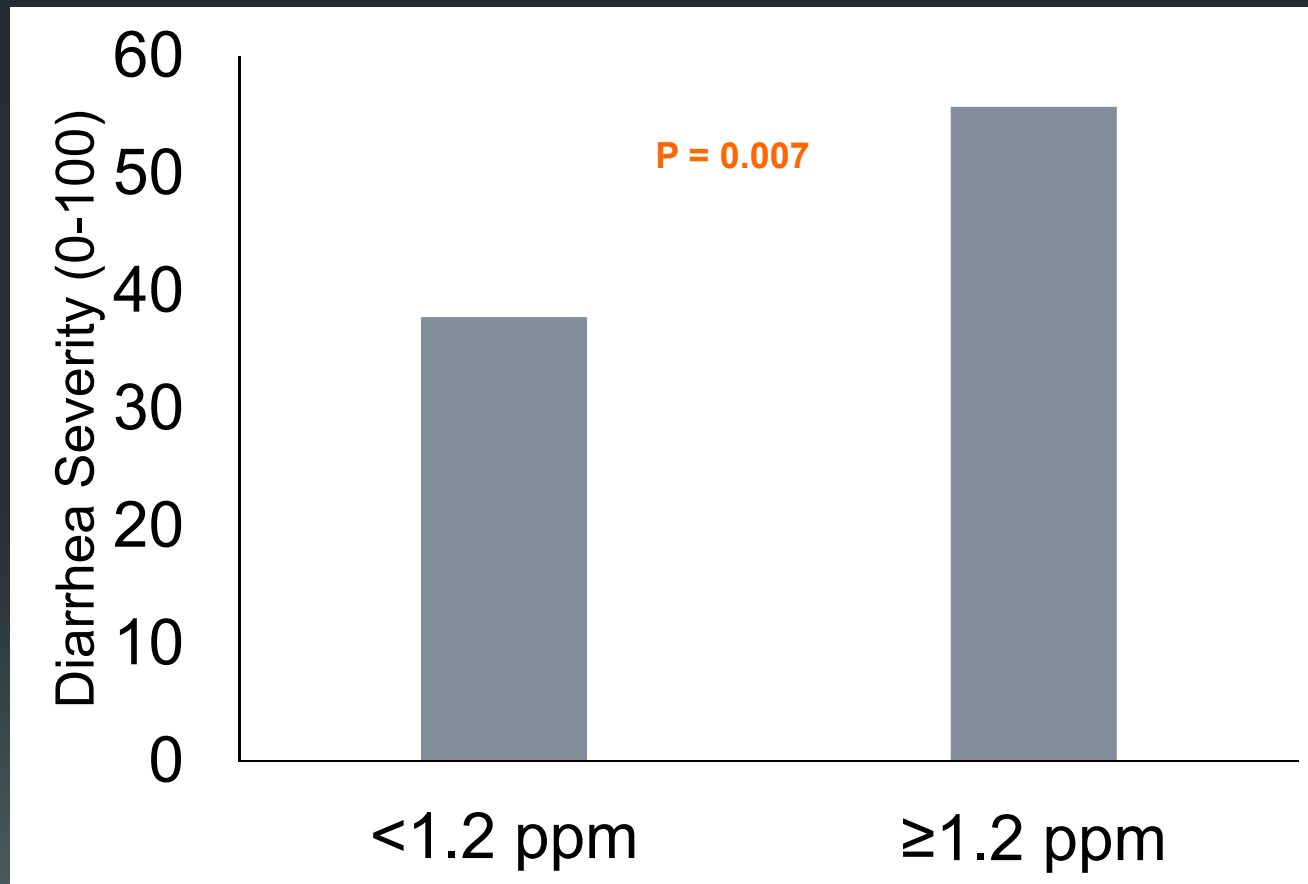
Lin, et al. DDW 2017

Urgency and Max ≥1.2 ppm Hydrogen Sulfide
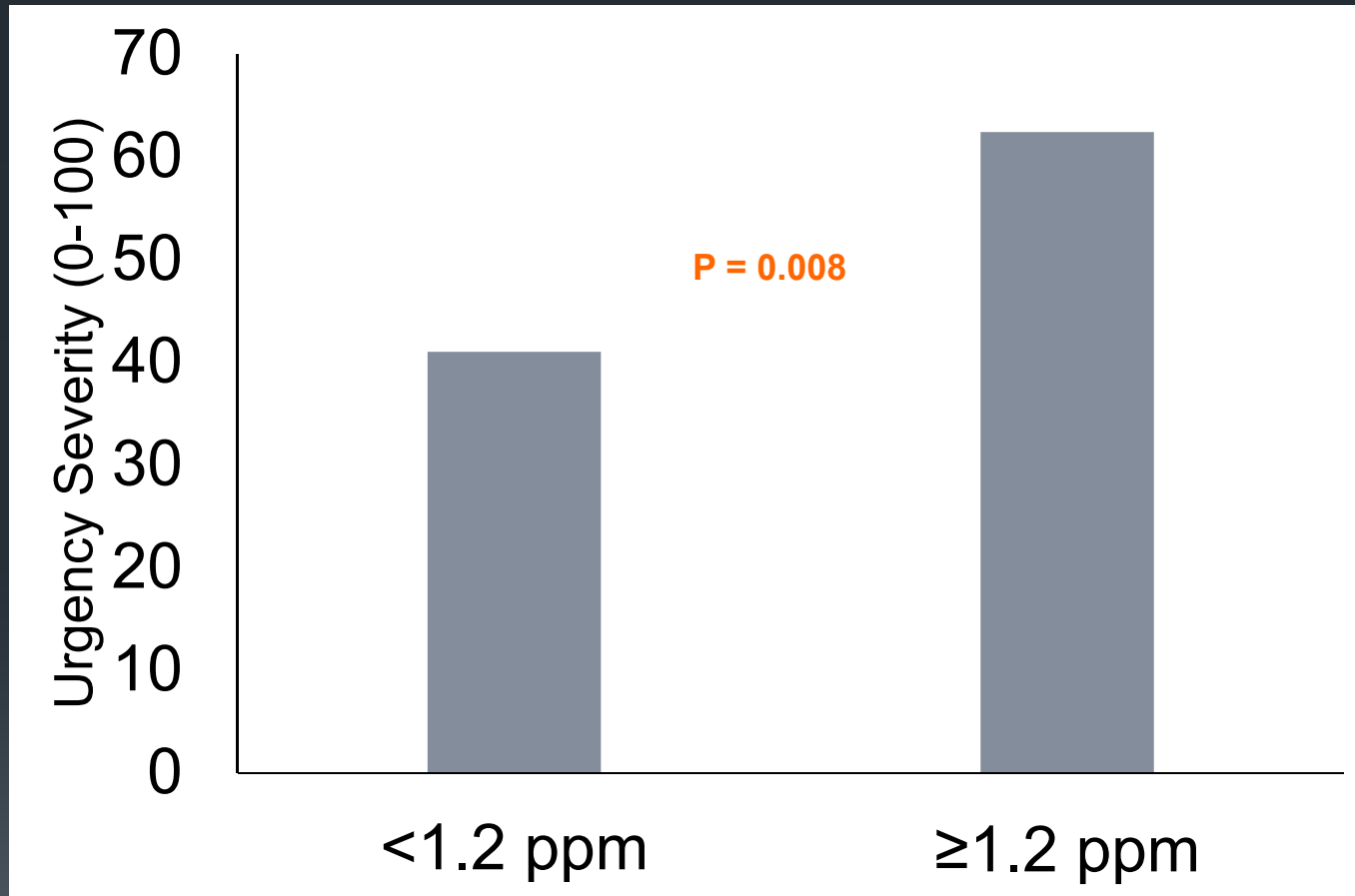
H_2S and H_2 Interaction in <u>non</u>-CH_4 Producers

Total n=109   (N=27)   (N=27)   (N=27)   (N=28)
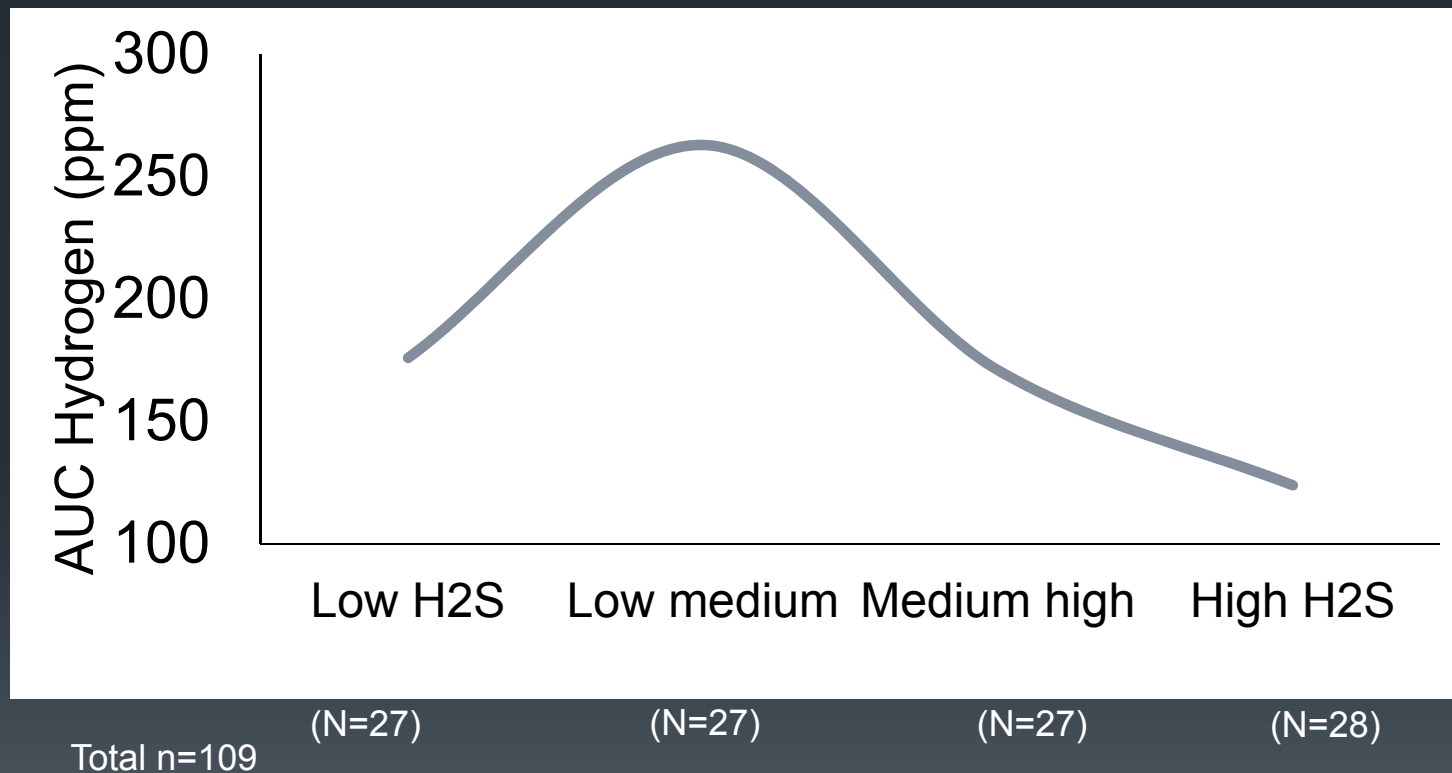
H2S and H2 Interaction and Diarrhea
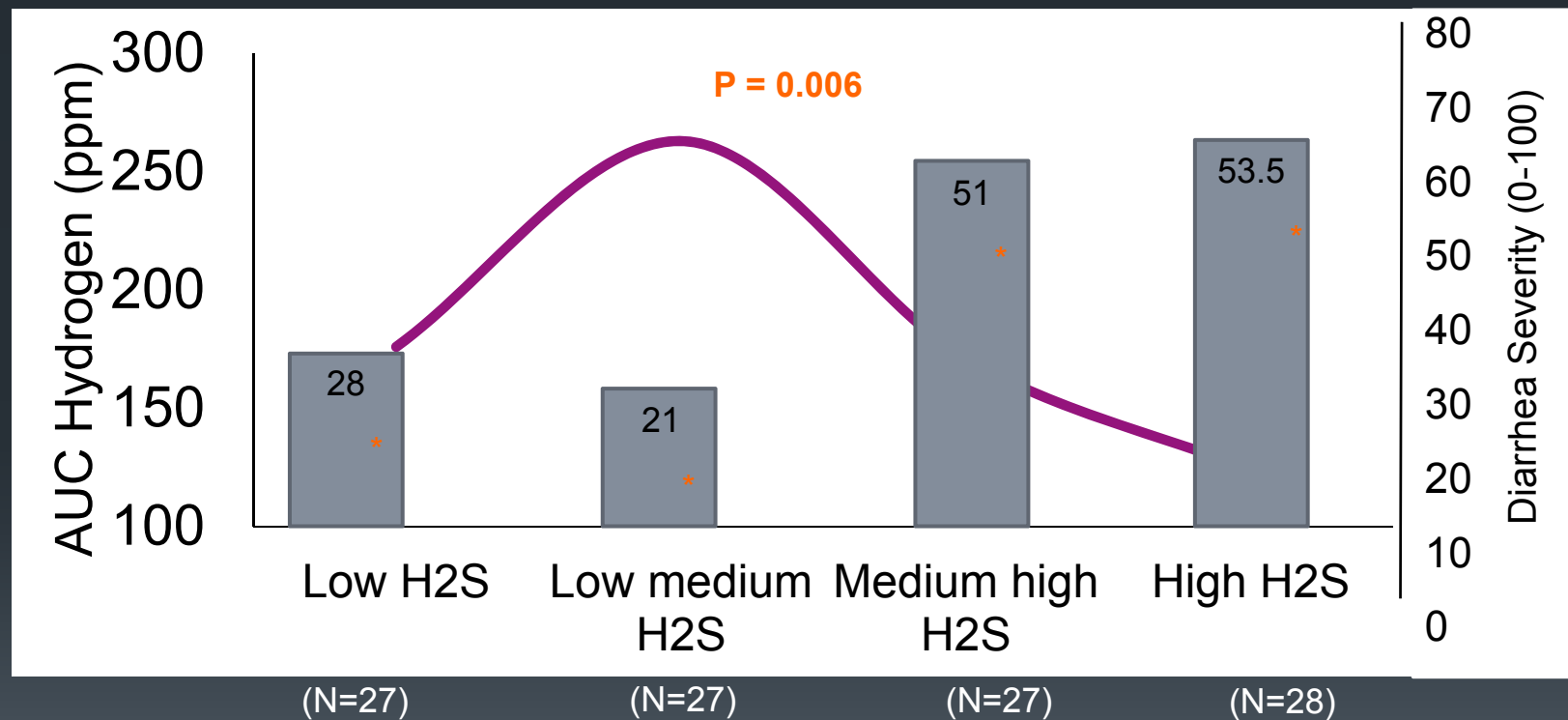
Total n=109

*Spearman's rank correlation = 0.25

IBS Microbial Hypothesis

Acute Gastroenteritis → CdtB Toxin → Autoimmunity to vinculin → Gut ICC/neuronal Changes → Bacterial Overgrowth → IBS

CEDARS-SINAI®

Risk of PI-IBS After Infectious Gastroenteritis*

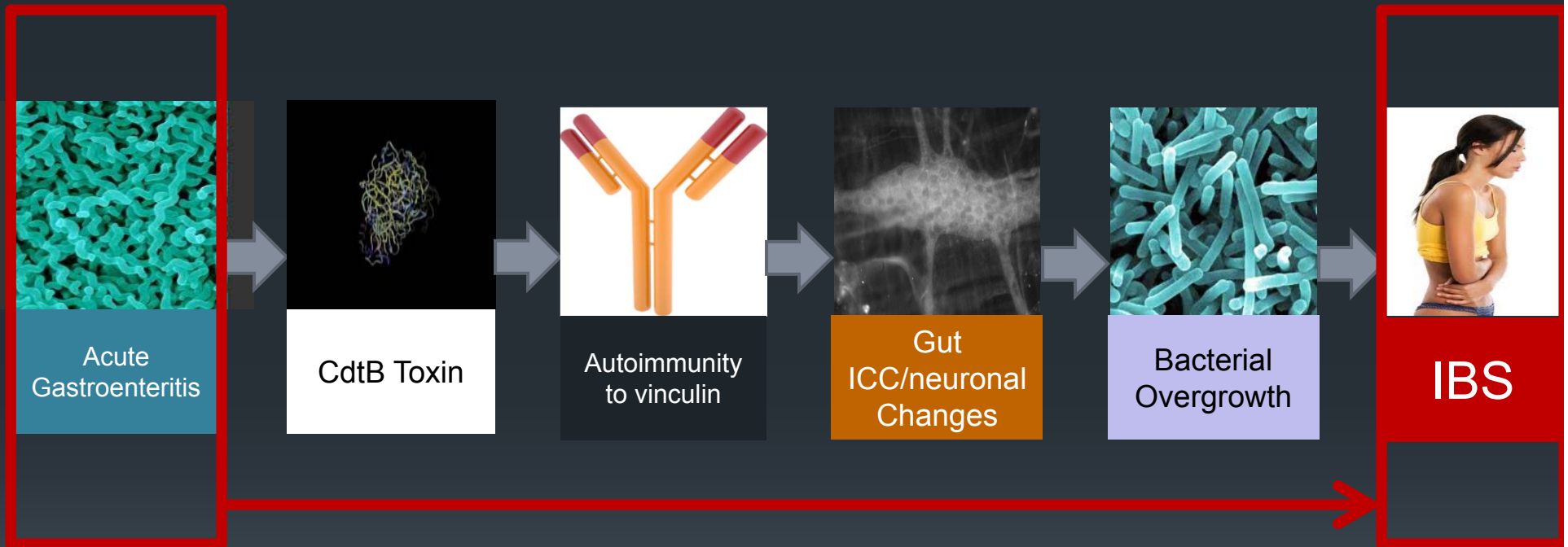| Author, Year	n/N	Event Rate (95% CI)
Bacterial		
Bettes, 2014	101/425	0.238 (0.200-0.280)
Cremon, 2014	33/204	0.162 (0.117-0.219)
Nielsen, 2014	56/268	0.209 (0.164-0.262)
Koh, 2012	6/65	0.092 (0.042-0.191)
Youn, 2012	17/124	0.137 (0.087-0.210)
Schwille-Kiuntke, 2011	22/48	0.458 (0.324-0.599)
Lim, 2010	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%

0.00   0.25   0.50

RR=4.23; 95% CI, 3.15−5.69

11% of people exposed

1 in 9 who experience food poisoning

FOOD POISONING CAUSES IBS!!

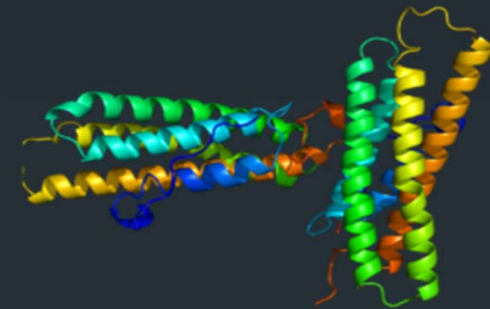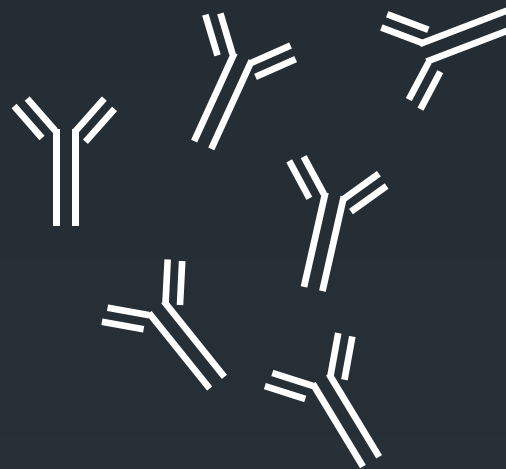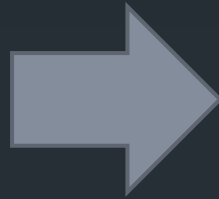A review of 45 studies

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

Molecular Mimicry/Autoimmunity

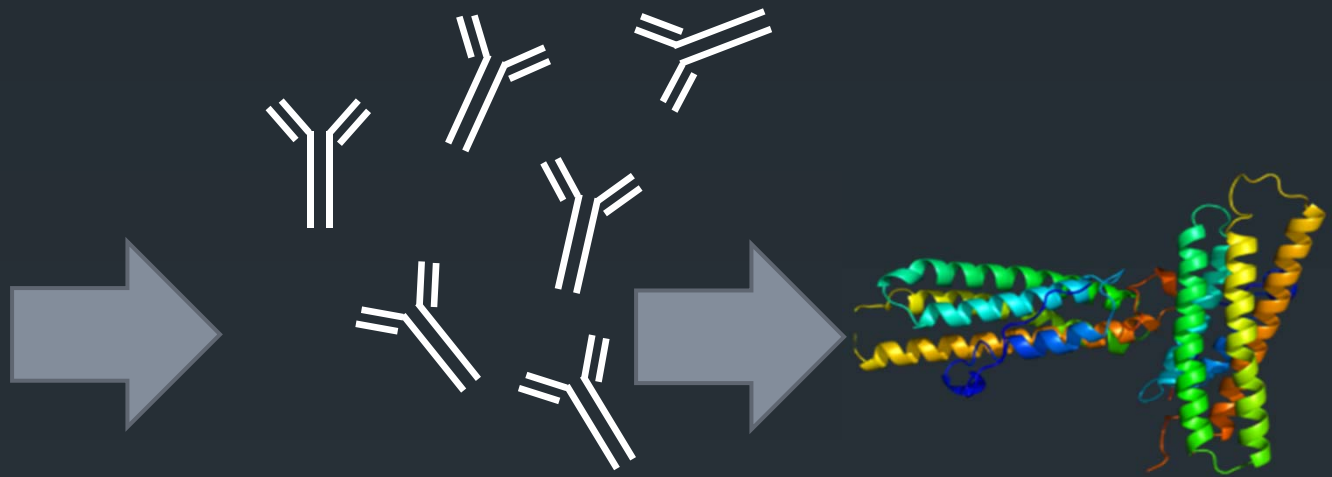Cytolethal
Distending
Toxin B

Human
Vinculin

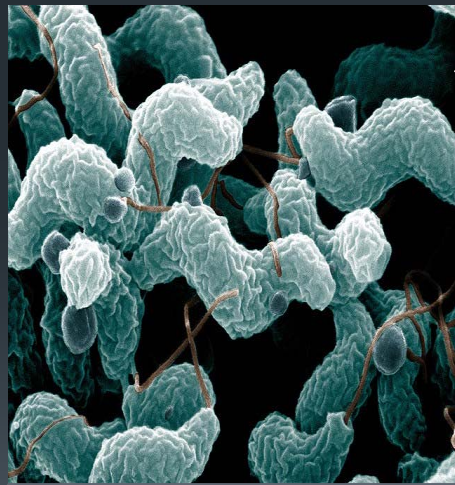# Molecular Mimicry/Autoimmunity
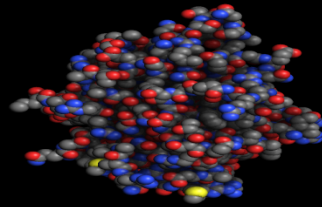
Cytolethal
Distending
Toxin B
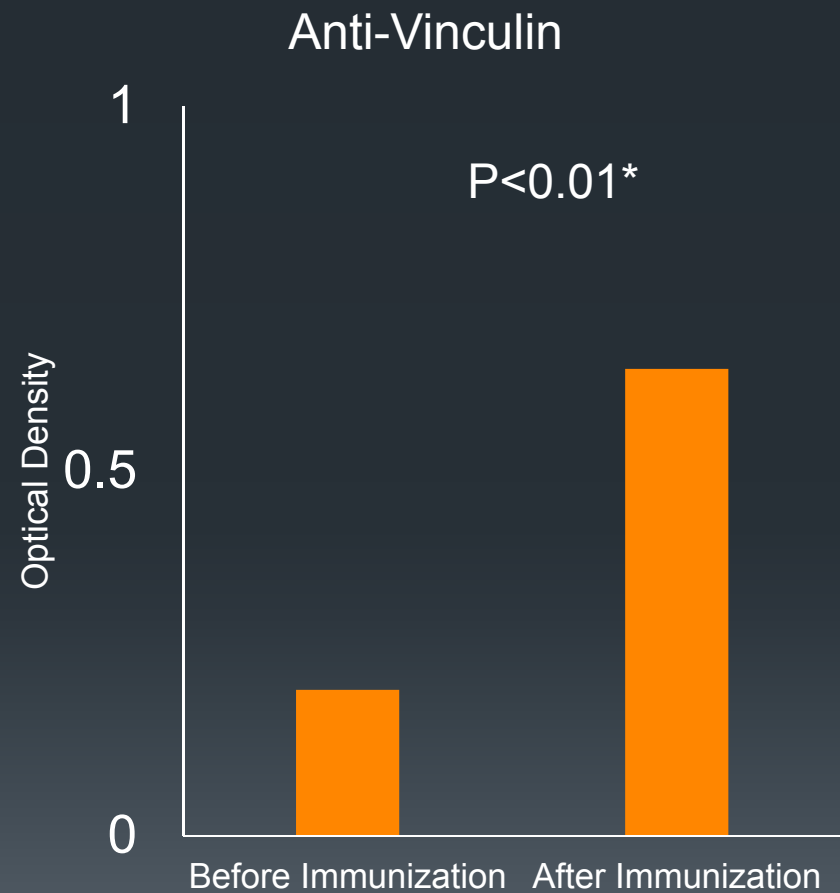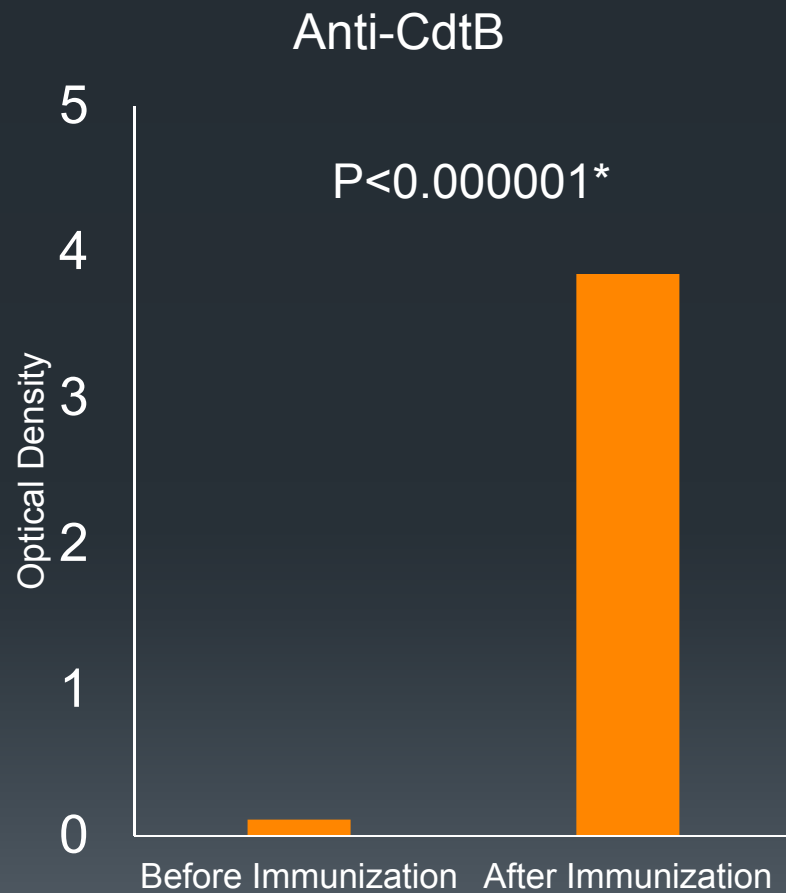
Human
Vinculin

Immunization Trial

Campylobacter

Recombinant
CdtB

Sprague-Dawley
Rats

Serum Antibody Response to CdtB

Anti-CdtB

P<0.000001*

Optical Density (y-axis: 0, 1, 2, 3, 4, 5)

Before Immunization   After Immunization

Anti-Vinculin

P<0.01*

Optical Density (y-axis: 0, 0.5, 1)

Before Immunization   After Immunization

*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

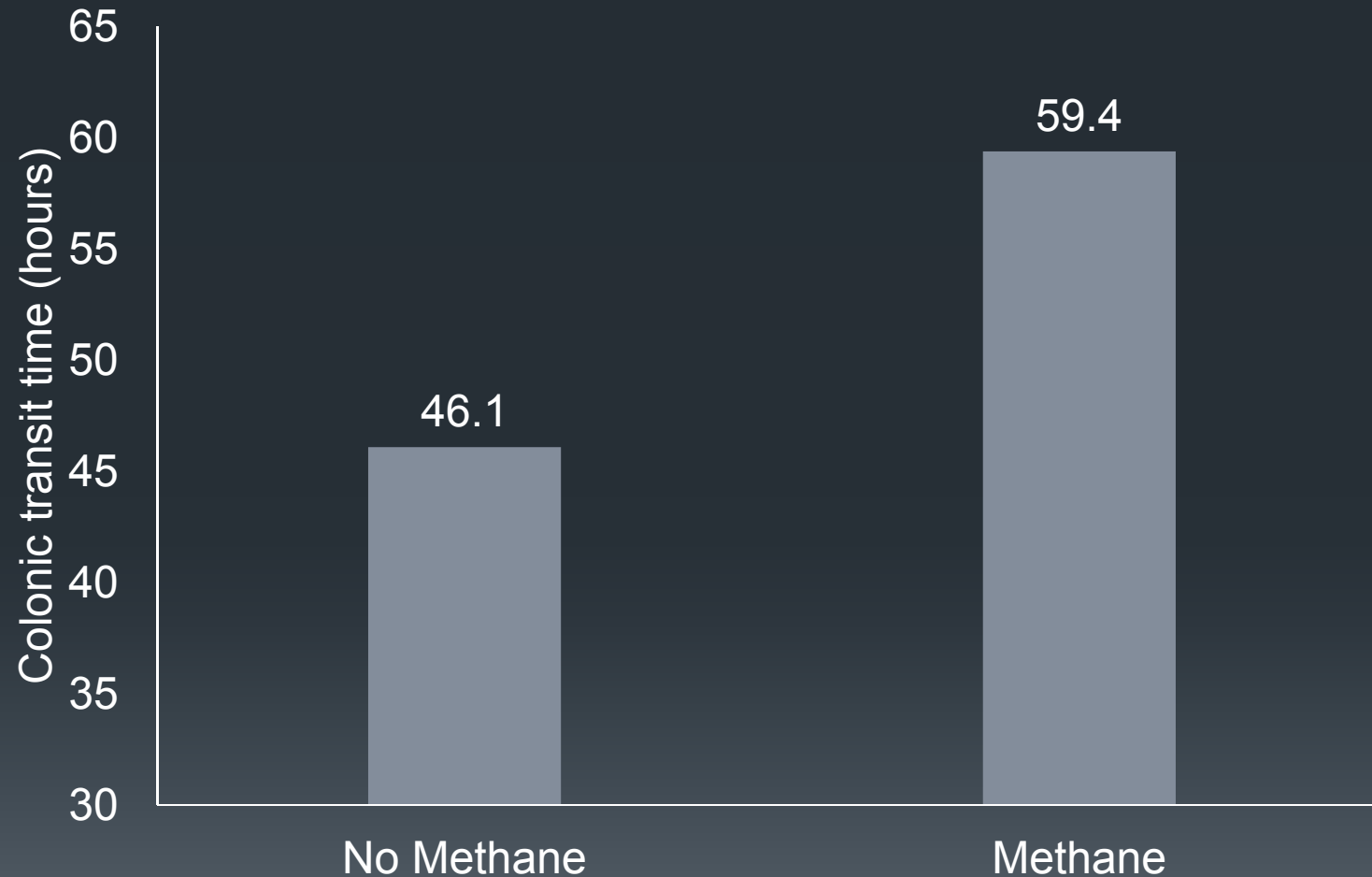# Transit is slower with methane
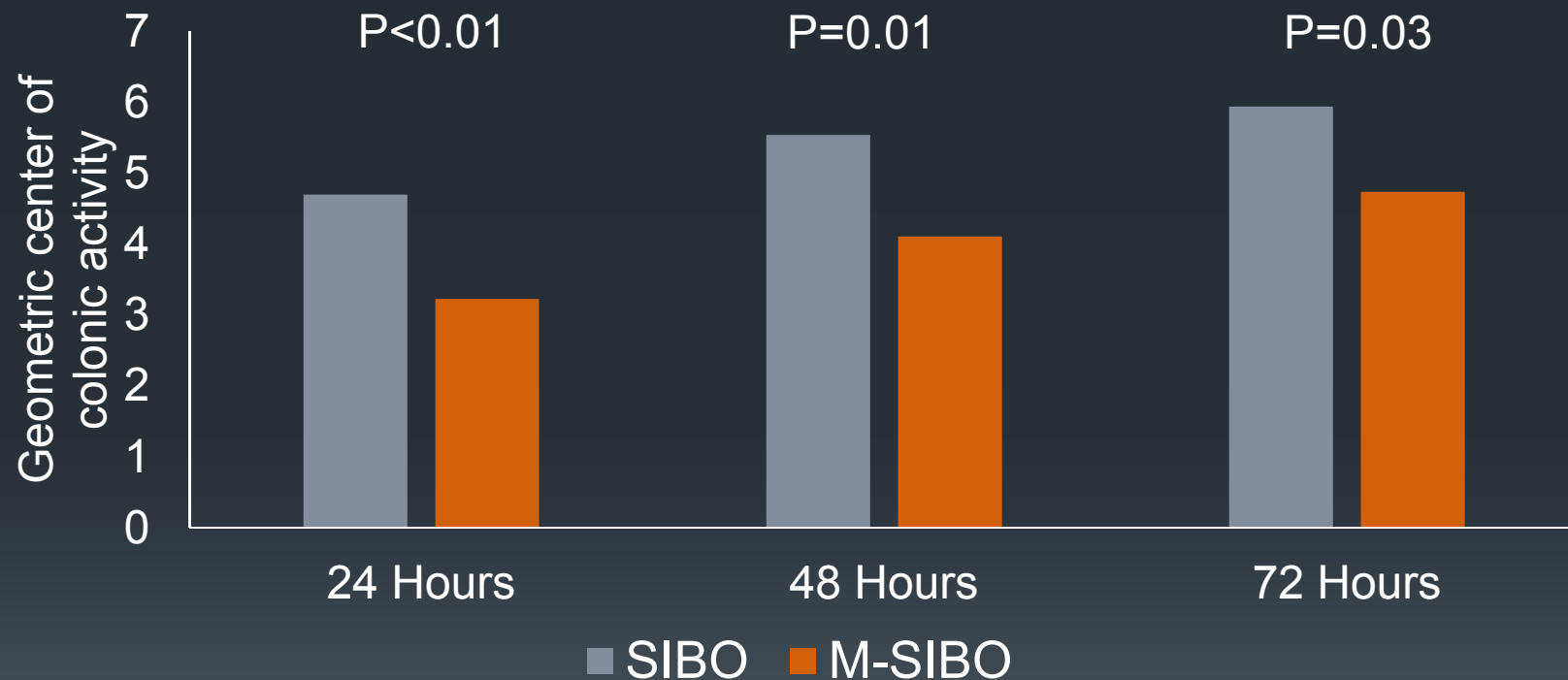
Transit is slower when methane is present.

Kataria, et al. DDW 2017

Colonic Transit Time and Methane

Colonic transit time (hours)

65
60 — 59.4
55
50
46.1
45
40
35
30

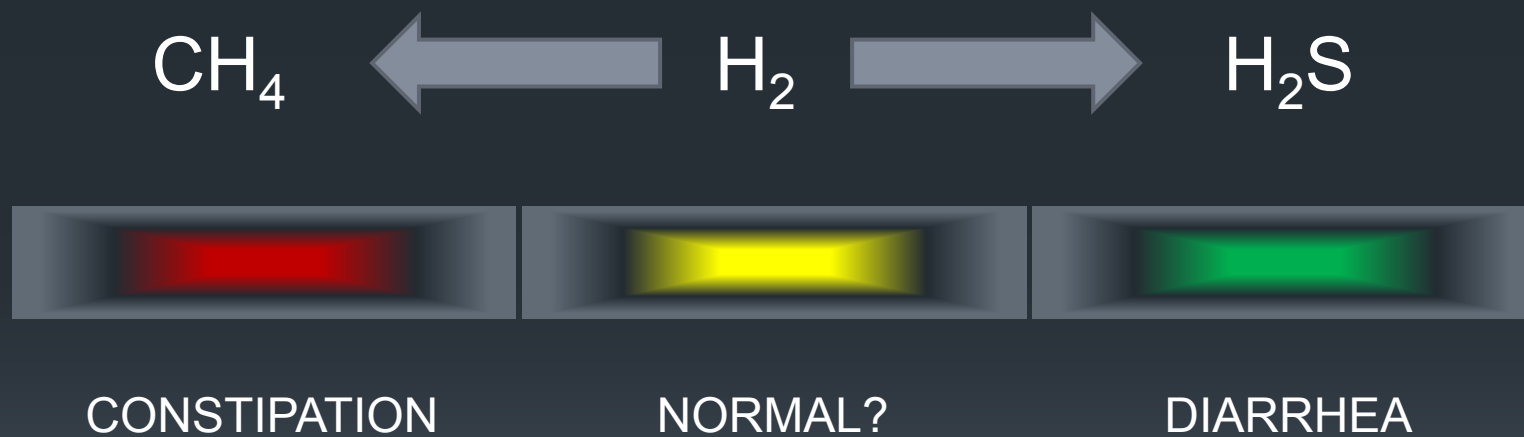No Methane   Methane

N=187 subjects, 70 with methane.
Transit based on wireless capsule.

Sharma, et al. DDW 2017

Methane – Friend of Foe

$$CH_4 \quad \longleftarrow \quad H_2 \quad \longrightarrow \quad H_2S$$

CONSTIPATION   NORMAL?   DIARRHEA

Fecal Transplant for IBS-D from Sweden

- DBRCT of 16 patients.
- Randomized to colonoscopy with no FMT (n=8) and one with FMT (n=8)
- Primary outcome = IBS-SSS in 4 week follow up

Outcome	Placebo	FMT	P-value
IBS-SSS	-61.6 ± 50.8	-63.3 ± 43.1	NS

- Equal benefit in both placebo and FMT group. The conclusion is that the bowel prep was the factor that improved patients but purging microbes

Holster, et al. DDW 2017

Oral α-galactosidase in IBS

- IBS patients are sensitive to FODMAPS such as beans which contain galacto-oligosaccharides (GOS)

Methods:

- First identified IBS patients sensitive to fructans based on breath testing
- All patients were fed diets high in GOS
- Randomized to full dose α-galactosidase, half dose or placebo
- Overall symptoms measured on a VAS (0-100mm) during the diet and then for a period after the enzyme/placebo

Tuck, et al. DDW 2017

Oral α-galactosidase in IBS

Results:

- n=31 patients (20 IBS-D, 4 IBS-C, 7 IBS-M)
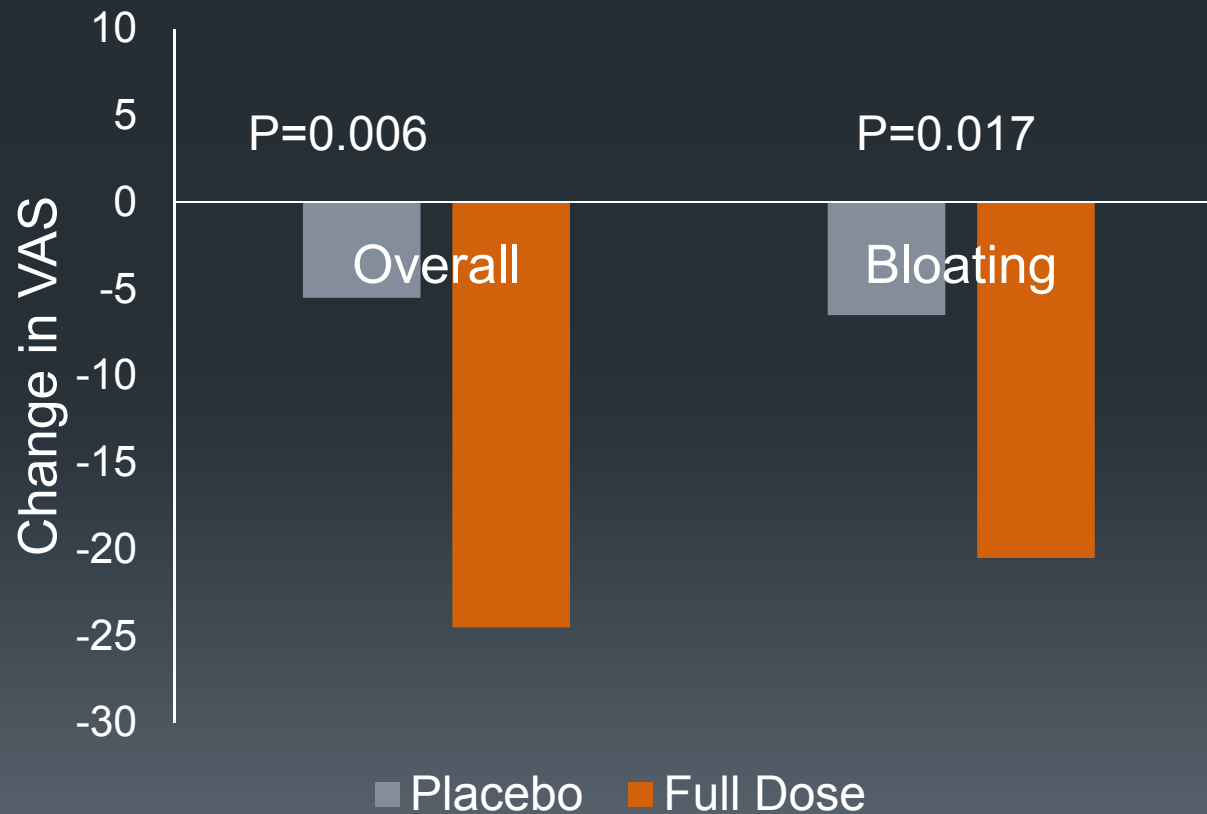
Tuck, et al. DDW 2017

Oral α-galactosidase in IBS

Interpretation:

1. Why not simply avoid beans
2. Using α-galactosidase helps deter symptoms in IBS patients who eat products containing GOS
3. Only the full dose of product was successful

Tuck, et al. DDW 2017

SIBO and conditions

- SIBO is increasing in awareness
- What is the distribution of positive SIBO among patients sent for breath testing

Methods

- Retrospective chart review of 432 patients who underwent breath testing at Thomas Jefferson University
- Goal to see among patients with positive breath test, what determines the positive test in what proportion

Results

- Out of 432 subjects 183 had a positive test

Kistler, et al. DDW 2017

SIBO and conditions

Risk Factor	Number	Percent
Abdominal Surgery	4	2.70
Celiac Disease	14	7.57
Chronic Pancreatitis	6	3.24
Chronic Steroids	1	0.54
CKD	5	2.70
Crohns	8	4.32
CVID	1	0.54
DM	17	9.19
Gastric Bypass	9	4.86
Gastric sleeve	3	1.63
Gunshot wound	1	0.54
HIV	1	0.54
IBS	93	50.27
Old Age	17	9.19
Small bowel divertic	1	0.54
Total	183	100

Kistler, et al. DDW 2017

Specific Bacteria and IBS

Background

- Suspect that after gastroenteritis there is a "dysbiosis" which leads to chronic symptoms

Methods

- Sigmoid biopsies were taken from unprepped IBS patients and 17 healthy controls
- Biopsies were mounted immediately in an ex vivo system with oxygen supply to allow continued production of mucous and cell survival.
- Mucus was then collected and mass spec assessed the contents and assess microbes by metabolic signature
- Any findings were then confirmed in a validation cohort of 40 IBS and 6 controls

Jabbar, et al. DDW 2017

Specific Bacteria and IBS

Results

- Identified *Brachyspira* (a spirochete) and Pseudomonas only in IBS and one or both in 43% of patients but not healthy.
- In validation study, only 10% of IBS and 0% of healthy subjects
- Correlation with surge in immune cells and anti-microbial proteins

Conclusions

- Suggest that these bacteria may have a role in IBS

Jabbar, et al. DDW 2017

Thanks