A 2016 Update in Gastroenterology and Inflammatory Bowel Disease

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Outline

- Proton pump inhibitors and adverse events
- Fecal transplant indications
- Inflammatory bowel disease update

PPIs: What we know…..

- Block secretion by irreversible binding H^+-K^+-ATPase pump on parietal cells
- Indicated for use in GERD, erosive/nonerosive esophagitis, NSAID-induced peptic ulcers, dyspepsia
- Increasing prevalence of long-term users
  - >15 million people had Rx for PPI in 2013
- Up to 70% of patients on chronic acid suppression lack an endoscopically verified indication for long-term use

Forgacs I, et al. *BMJ* 2008.

Known Adverse Effects

Potential Risk	Evidence
C diff	Multiple studies suggest >2-fold risk in community and hospital acquired infections
Community-acquired pneumonia	Minimal increased risk, not substantiated after controlling for confounders
Bone fracture	Conflicting results, long-term use may increase fracture risk esp in elderly
B12 deficiency	Most patients with a normal diet will not have deficiency; elderly, malnourished, post-gastric bypass may be at higher risk
Hypomagnesemia	Rare esp after controlling for confounders
Clopidogrel interaction	Possible increased risk but more prospective RCTs needed

Heidelbaugh JJ, et al. *Therap Adv Gastroenterol* 2012.

PPIs and increased risk of kidney disease?

	Atherosclerosis Risk in Communities Study (n = 10 482)		Geisinger Health System Replication Cohort (n = 248 751)	
Variable	**No. of Events**	**No. of Participants**	**No. of Events**	**No. of Participants**
PPI users	56	322	1921	16 900
H_2 receptor antagonist users	158	956	1022	6640
Nonusers	1224	9204	27 204	225 221
Association Between PPI Use and Incident CKD	**Hazard Ratio (95% CI)**	***P* Value**	**Hazard Ratio (95% CI)**	***P* Value**
Unadjusted baseline PPI use vs no PPI use	1.45 (1.11-1.90)	.006	1.20 (1.15-1.26)	<.001
Baseline PPI use vs no PPI use	1.50 (1.14-1.96)	.003	1.17 (1.12-1.23)	<.001
Time-varying PPI ever use vs never PPI use	1.35 (1.17-1.55)	<.001	1.22 (1.19-1.25)	<.001
Baseline PPI use vs baseline H_2 receptor antagonist use	1.39 (1.01-1.91)	.05	1.29 (1.19-1.40)	<.001
Baseline PPI use vs propensity score-matched no PPI use	1.76 (1.13-2.74)	.01	1.16 (1.09-1.24)	<.001
Time-varying PPI ever use vs never PPI use, after excluding baseline PPI users	NA	NA	1.24 (1.20-1.28)	<.001
Negative Control				
Baseline H_2 receptor antagonist use vs no H_2 receptor antagonist use	1.15 (0.98-1.36)	.10	0.93 (0.88-0.99)	.03

Lazarus B, et al. *JAMA Intern Med* 2016.

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PPIs and dementia?

Variable	Any dementia		Alzheimer's disease	
	Hazard ratio (95 % CI)	*p* value	Hazard ratio (95 % CI)	*p* value
PPI use[a,b]	1.38 (1.04–1.83)	0.02	1.44 (1.01–2.06)	0.04
Age[c]	1.12 (1.10–1.15)	<0.001	1.15 (1.11–1.19)	<0.001
Sex[d]	1.00 (0.81–1.24)	1.00	0.77 (0.57–1.03)	0.08
Education				
Low	Reference		Reference	
Middle	0.80 (0.64–1.00)	0.05	0.72 (0.53–0.97)	0.03
High	0.78 (0.55–1.10)	0.15	0.81 (0.52–1.28)	0.37
ApoE4	1.87 (1.52–2.31)	<0.001	2.25 (1.73–2.93)	<0.001
Depression[e]	2.28 (1.80–2.88)	<0.001	2.05 (1.50–2.81)	<0.001
Diabetes	1.30 (1.05–1.62)	0.02	1.21 (0.91–1.60)	0.20
Stroke	1.92 (1.38–2.67)	<0.001	0.99 (0.56–1.75)	0.98
Ischemic heart disease	1.10 (0.90–1.35)	0.35	1.06 (0.81–1.38)	0.66
Polypharmacy[f]	1.14 (0.92–1.42)	0.22	1.08 (0.82–1.42)	0.59
PPI use[a,g]	1.44 (1.10–1.90)	0.008	1.45 (1.03–2.05)	0.03

****Risk of incidence dementia and Alzheimer's disease in 3,300 community people >74 y/o**

Haenisch B, et al. *Eur Arch Psychiatry Clin Neurosci* 2015.

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ApoE4	1.87 (1.52–2.31)	<0.001	2.25 (1.73–2.93)	<0.001
Depression[e]	2.28 (1.80–2.88)	<0.001	2.05 (1.50–2.81)	<0.001
Diabetes	1.30 (1.05–1.62)	0.02	1.21 (0.91–1.60)	0.20
Stroke	1.92 (1.38–2.67)	<0.001	0.99 (0.56–1.75)	0.98
Ischemic heart disease	1.10 (0.90–1.35)	0.35	1.06 (0.81–1.38)	0.66
Polypharmacy[f]	1.14 (0.92–1.42)	0.22	1.08 (0.82–1.42)	0.59
PPI use[a,g]	1.44 (1.10–1.90)	0.008	1.45 (1.03–2.05)	0.03

****Risk of incidence dementia and Alzheimer's disease in 3,300 community people >74 y/o**

	Risk of Incident Dementia					
	75-79 y		80-84 y		≥85 y	
Risk Factor	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
PPI use calulated[a]						
With potential confounding factors	1.69 (1.49-1.92)	<.001	1.49 (1.35-1.66)	<.001	1.32 (1.22-1.43)	<.001
Without potential confounding factors	2.01 (1.78-2.28)	<.001	1.68 (1.51-1.86)	<.001	1.35 (1.25-1.46)	<.001
Age[b]	1.128 (1.109-1.148)	<.001	1.092 (1.076-1.107)	<.001	1.045 (1.040-1.051)	<.001
Sex[c]	1.10 (1.04-1.16)	<.001	1.15 (1.09-1.21)	<.001	1.16 (1.11-1.22)	<.001
Depression	1.44 (1.34-1.54)	<.001	1.35 (1.27-1.43)	<.001	1.15 (1.09-1.21)	<.001
Diabetes	1.16 (1.10-1.22)	<.001	1.04 (0.99-1.08)	.15	0.99 (0.95-1.03)	.45
Stroke	1.78 (1.59-2.00)	<.001	1.37 (1.23-1.54)	<.001	1.15 (1.04-1.27)	.01
Ischemic heart disease	0.94 (0.89-0.99)	.02	0.96 (0.92-1.00)	.07	0.90 (0.87-0.93)	<.001
Polypharmacy[d]	1.27 (1.21-1.34)	<.001	1.21 (1.15-1.26)	<.001	1.05 (1.02-1.09)	.003

****Risk of incident dementia in 74,000 people >74 y/o**

Haenisch B, et al. *Eur Arch Psychiatry Clin Neurosci* 2015.
Gomm W, et al. *JAMA Neurol* 2016.

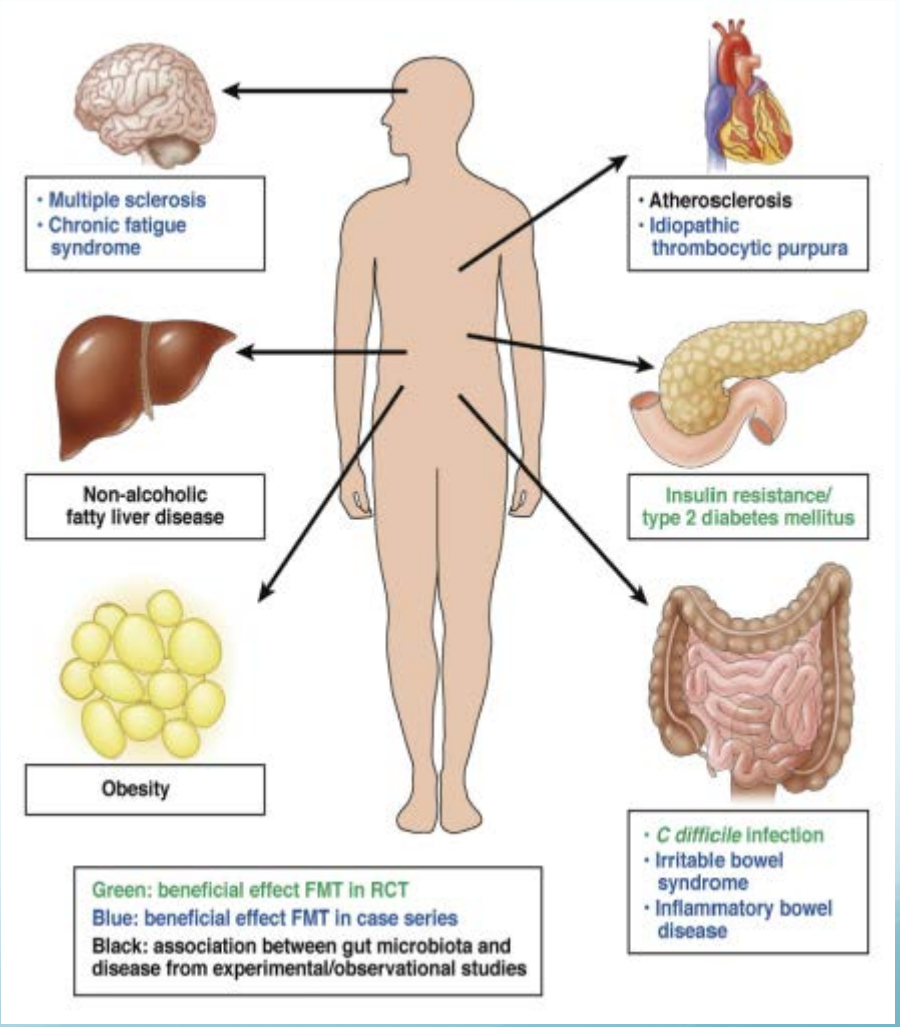
Potential Risk	Evidence	Recommendation
C diff	Multiple studies suggest >2-fold risk in community and hospital acquired infections	Weigh benefits and risks among inpatients; discontinue if no urgent need
Community-acquired pneumonia	Minimal increased risk, not substantiated after controlling for confounders	Probably OK to use when necessary
Bone fracture	Conflicting results, long-term use may increase fracture risk esp in elderly	Guidelines for bone mineral density screening do not change; consider risks/benefits esp in elderly
B12 deficiency	Most patients with a normal diet will not have deficiency; elderly, malnourished, post-gastric bypass may be at higher risk	Routine screening not recommended; screen high risk patients esp if anemic
Hypomagnesemia	Rare esp after controlling for confounders	Routine screening not recommended; consider screening high risk patients esp those on Mg depleting meds, arrythmias, seizure hx
Clopidogrel interaction	Possible increased risk but more prospective RCTs needed	Consider risks/benefits on an individual basis
Kidney disease	Possible association with increased new kidney disease	Use in short periods if necessary
Dementia	Possible association with new onset dementia and Alzheimer's	Use in short periods if necessary; consider lifestyle modifications, H2 blockers/antacids

Heidelbaugh JJ, et al. *Therap Adv Gastroenterol* 2012.

Fecal Transplant Indications

Fecal Transplant: the basics

- Gut microbiome responsible for multiple physiological functions
- Composed of bacteria, archaea, fungi, viruses
- Microbiome may play a role in some disease processes



Smits LP, et al. *Gastroenterology* 2013.

Clostridium difficile infection (CDI)

- CDI before fecal transplant….
  - 1st occurrence: metronidazole (or vancomycin)
  - 2nd occurrence: vancomycin +/- metrondiazole
  - 3rd occurrence: vancomycin with long taper vs. fidaxomycin
  - 4th occurrence: consider IVIG vs. longer vancomycin taper vs. rifaximin
- CDI post fecal transplant….
  - ≥3 episodes and failure to respond to 6-8 week vanco taper
  - 2 episodes of CDI resulting in hospitalization
  - CDI unresponsive to standard therapy for 1 wk

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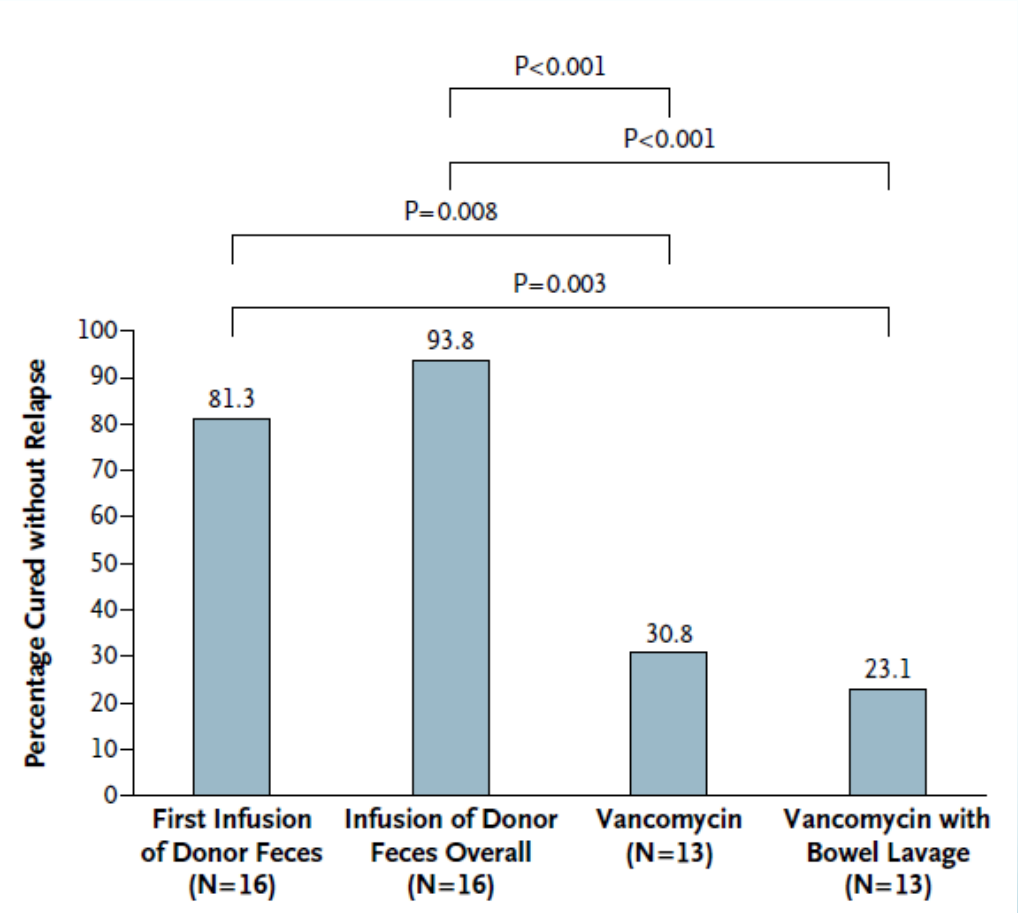
Duodenal Infusion of Donor Feces for Recurrent *Clostridium difficile*

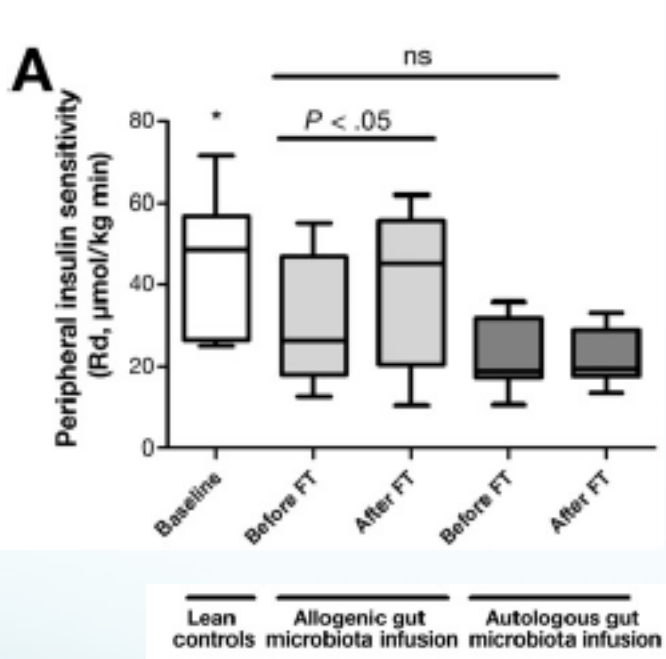
Els van Nood, M.D., Anne Vrieze, M.D., Max Nieuwdorp, M.D., Ph.D., Susana Fuentes, Ph.D., Erwin G. Zoetendal, Ph.D., Willem M. de Vos, Ph.D., Caroline E. Visser, M.D., Ph.D., Ed J. Kuijper, M.D., Ph.D., Joep F.W.M. Bartelsman, M.D., Jan G.P. Tijssen, Ph.D., Peter Speelman, M.D., Ph.D., Marcel G.W. Dijkgraaf, Ph.D., and Josbert J. Keller, M.D., Ph.D.

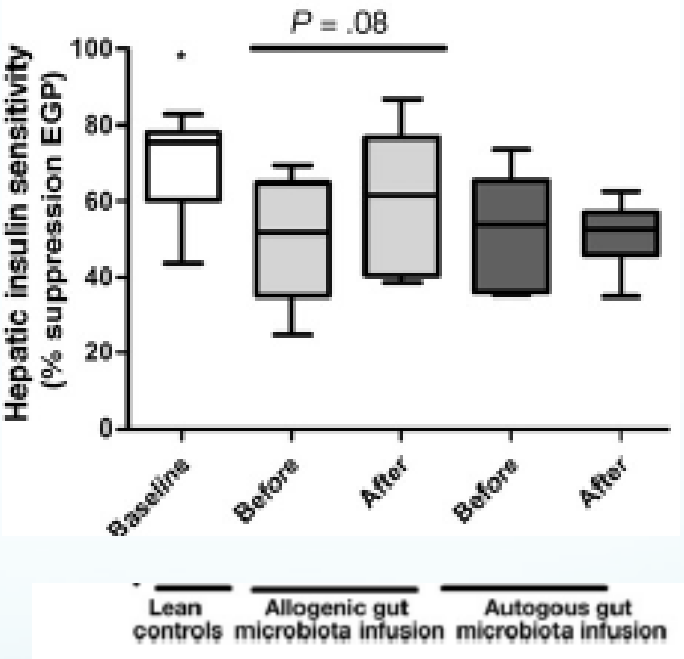
ABSTRACT

Fecal transplant is effective in CDI



Effective in obesity and insulin resistance?





Vrieze A, et al. *Gastroenterology* 2012.

Role in irritable bowel syndrome?

- Study of 45 patients with chronic constipation
  - 90% relief in defecation ease, bloating, and abdominal pain
  - 60% showed long-term benefit after 9-19 months
  - Issues: abstract form, no control patients

Andrews P, et al. *Gastroenterology* 1995.

Any role in inflammatory bowel disease?

Outcome	Placebo (n = 37)	FMT (n = 38)	*P* value
Clinical remission,[a] n (%)	2 (5)	9 (24)	.03
Clinical response,[b] n (%)	9 (24)	15 (39)	.16
Full Mayo score	6.34	6.09	.42
IBDQ score	149.38	152.13	.44
EQ-5D score	70.07	68.52	.99
CRP, *mg/L* (n = 17 placebo, n = 15 FMT)	3.3 ± 3.4	4.9 ± 5.9	.38
ESR, *mm/h* (n = 17 placebo, n = 15 FMT)	13.1 ± 11.2	15.9 ± 17.0	.59
Proportion with high ESR, n (%)	4 (24)	3 (20)	1.0
Proportion with high CRP, n (%)	5 (29)	2 (13)	.40
Patients with serious adverse events n (%)	2[c] (5)	3[d] (8)	1.0

Moayyedi P, et al. *Gastroenterology* 2015.

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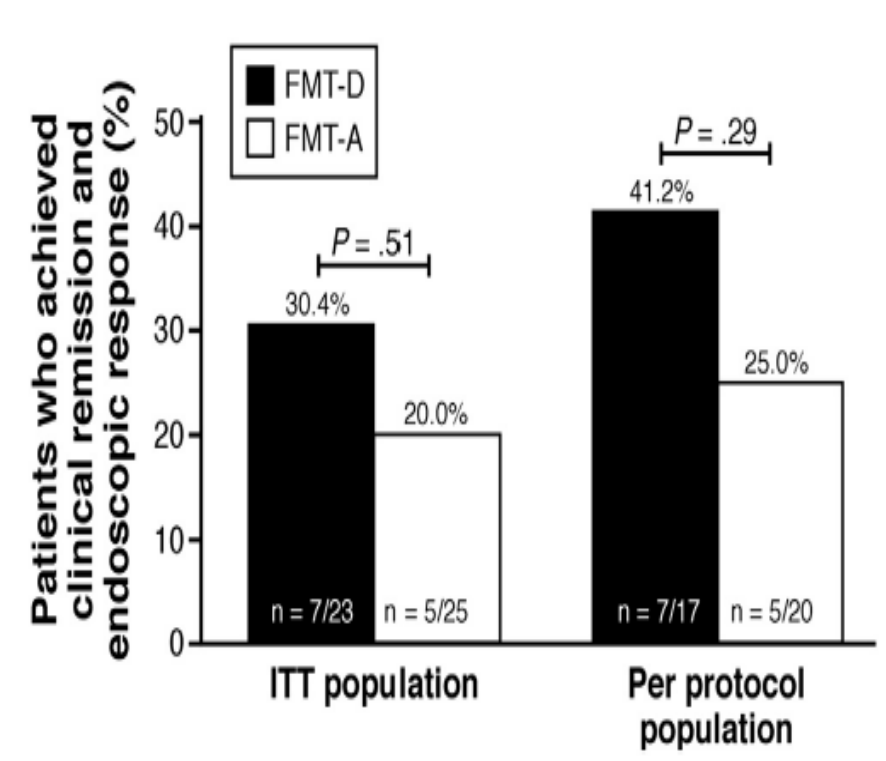

Moayyedi P, et al. *Gastroenterology* 2015.
Rossen NG, et al. *Gastroenterology* 2015.

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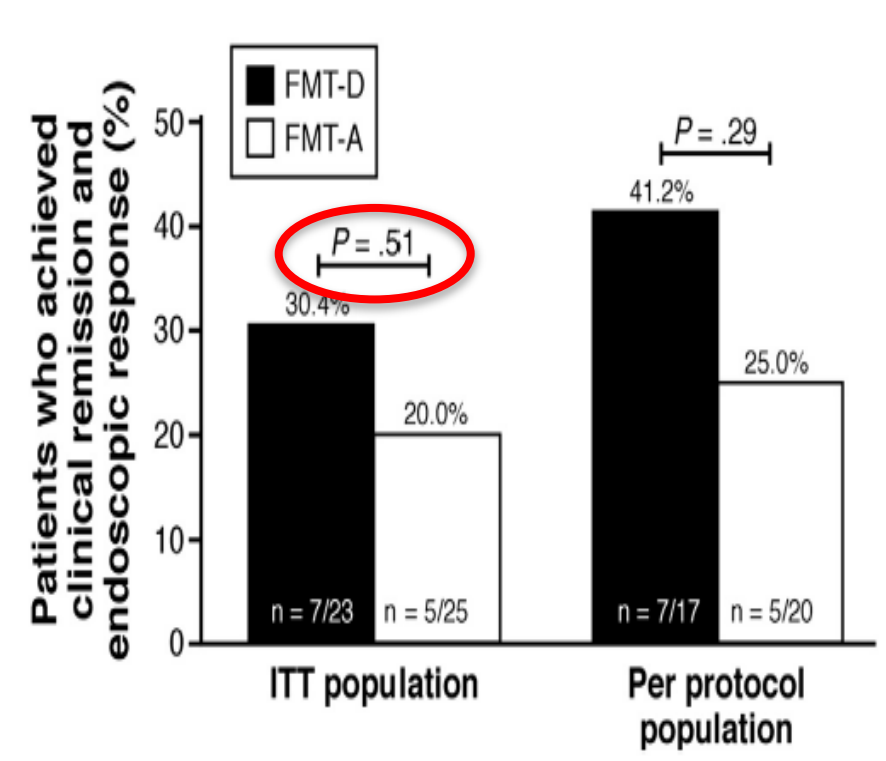


Moayyedi P, et al. *Gastroenterology* 2015.
Rossen NG, et al. *Gastroenterology* 2015.

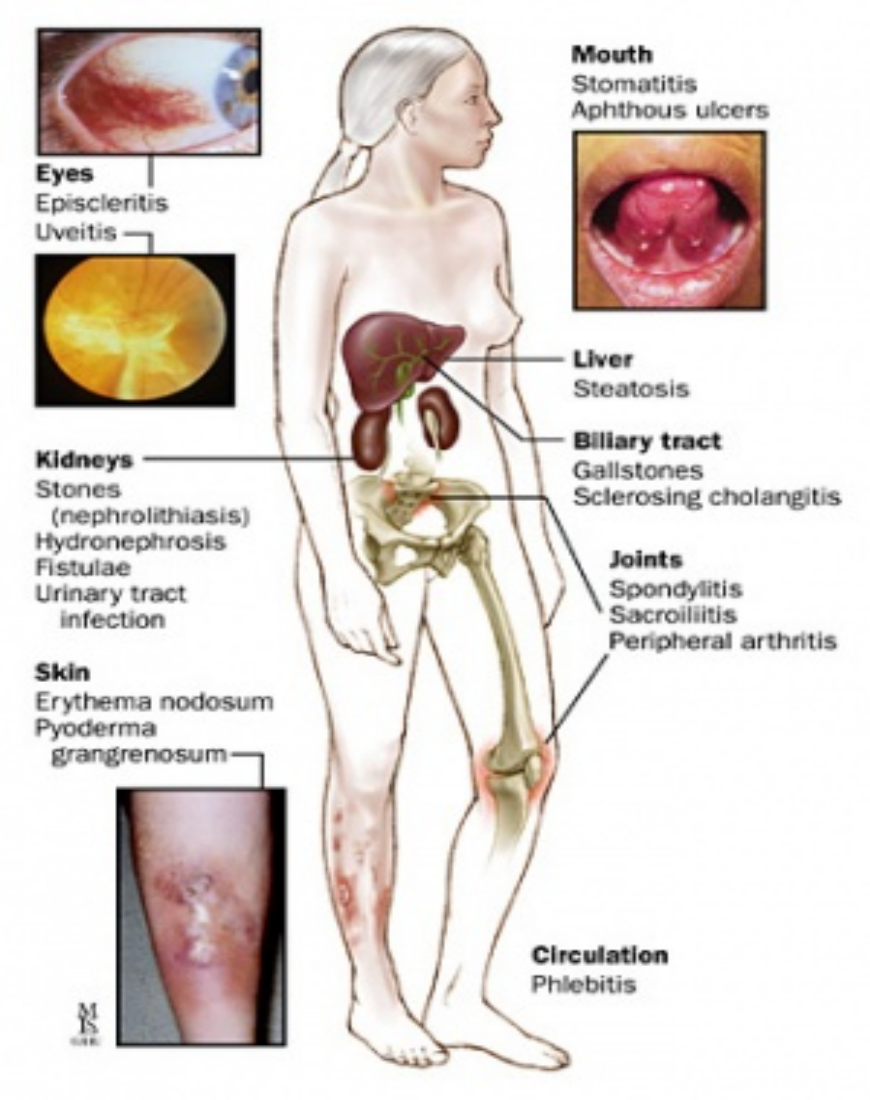
Disease Process	Evidence
C diff	Very effective; review of studies have reported cure rate of 85-93%
Obesity and insulin resistance	One pilot study in humans; clinical trails getting started
Irritable bowel syndrome	Small older human studies; clinical trials under way
Fatty liver disease	Clinical trials are under way
Hepatic encephalopathy	Clinical trials are under way
Inflammatory bowel disease	Mixed results thus far in Crohn's disease and ulcerative colitis; clinical trials under way

Inflammatory Bowel Disease

Inflammatory bowel disease: background

- Affects 1.5 million people in the US
  - Peak age of onset is in the teens and 20s
- Crohn’s disease and ulcerative colitis probably evolve from a combination of genetic, immune, microbiota, and environmental factors
- Systemic disorder

Crohn's and ulcerative colitis are systemic diseases



IBD medical therapy in 1996

Antibiotics	**Ciprofloxacin Metronidazole**	**Immunomodulators**	**6-Mercaptopurine Azathioprine Methotrexate**
Mesalamine	**Pentasa Sulfasalazine Osalazine Rowasa**	**Anti-TNF**	
		Anti-integrin	
Steroids	**Prednisone Hydrocortisone enemas**	**Surgery**	**Ileal pouch-anal anastomosis Small bowel resection Stricturoplasty**

IBD medical therapy in 2016

Antibiotics

Ciprofloxacin
Metronidazole

Mesalamine

Apriso
Pentasa
Delzicol
Sulfasalazine
Osalazine
Lialda
Colazal
Rowasa
Canasa

Steroids

Entocort
Prednisone
Hydrocortisone enemas
Cortifoam

Immunomodulators

6-Mercaptopurine
Azathioprine
Methotrexate

Anti-TNF

Infliximab
Adalimumab
Certolizumab
Golilmumab

Anti-integrin

Natalizumab
Vedolizumab

Surgery

Ileal pouch-anal anastomosis
Small bowel resection
Stricturoplasty

Emerging Medical Therapies

Drug	Mechanism of Action
Ustekinumab	Interleukin inhibitor
Tofacitinib	JAK inhibitor
Etrolizumab	Integrin inhibitor
Mongersen	SMAD7 inhibitor
?Stem Cell Therapy	

“What’s the best diet for my IBD?”

- Goal of treatment is two-fold:
  - 1) Induce remission of intestinal inflammation
  - 2) Eliminate symptoms
- Symptoms
  - Low residue or low fiber diet
  - Perhaps eliminate dairy products, caffeine
- Intestinal inflammation
  - Various diets have been tried: Paleolithic diet, Specific Carbohydrate Diet (SCD), Brat diet, fermentable oligo-, di-, and mono- saccharides diet (FODMAP)
  - No diet has been shown in studies to improve inflammation

What do you tell patients about diet and IBD?

- Patients have a strong interest in dietary modification as part of a holistic approach to their disease
- Along with other appropriate medical therapy, diet can be an important part of patients regaining some control over their symptoms
- My approach….
  - Creating a food diary with symptoms and determining individual potential triggers for symptoms
    - Essentially an elimination diet over time

Colorectal cancer rates in IBD are decreasing

	Crohn's disease (n=13,756) Absolute risk percent (95%CI)	Ulcerative colitis (n=35,152) Absolute risk percent (95%CI)
Any invasive cancer	5.6 (5.1–6.1)	6.3 (6.0–6.6)
Any gastrointestinal cancer	1.2 ((1.0–1.4)	1.4 (1.2–1.6)
Colorectal cancer	0.6 (0.4–0.8)	0.8 (0.7–0.9)
Small intestine cancer	0.07 (0.03–0.15)	0.03 (0.01–0.06)
Other GI cancers	0.5 (0.4–0.7)	0.6 (0.5–0.7)
Any extra-intestinal cancer	4.4 (4.0–4.9)	5.0 (4.7–5.3)
Hematological malignancies	0.7 (0.5–0.9)	0.4 (0.3–0.5)
Smoking related cancers	1.3 (1.1–1.5)	1.3 (1.2–1.5)
Female reproductive cancers	0.9 (0.7–1.1)	1 2 (1.1–1.3)
Other common cancer sites		
Prostate	0.4 (0.3–0.5)	0.7 (0.6–0.8)
Lung	0.9 (0.7–1.1)	0.8 (0.7–1.0)
Bladder	0.2 (0.1–0.3)	0.4 (0.3–0.4)
Melanoma	0.3 (0.2–0.5)	0.3 (0.2–0.4)
Breast	0.8 (0.6–1.0)	1.0 (0.8–1.1)
Uterus	0.07 (0.03–0.14)	0.1 (0.1–0.2)
Non-melanoma skin cancer	2.2 (1.9–2.5)	3.1 (2.9–3.3)

Kappelman MD, et al. *Clin Gastroenterol Hepatol* 2014.

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Inflammatory bowel disease take-aways

- IBD is a systemic illness
- Significant advances in medical therapy have and continue to emerge
- No specific diet has been shown to decrease intestinal inflammation
- Risk of colorectal cancer tied to IBD appears to be decreasing in some populations

Thank You

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