Decoding PI: Unraveling the gastrointestinal health (GI) connection

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Peter J. Mannon, M.D.
Director, Paustian IBD Center
Ruth and Bill Scott Endowed Presidential Chair
of Internal Medicine
University of Nebraska Medical Center, Omaha

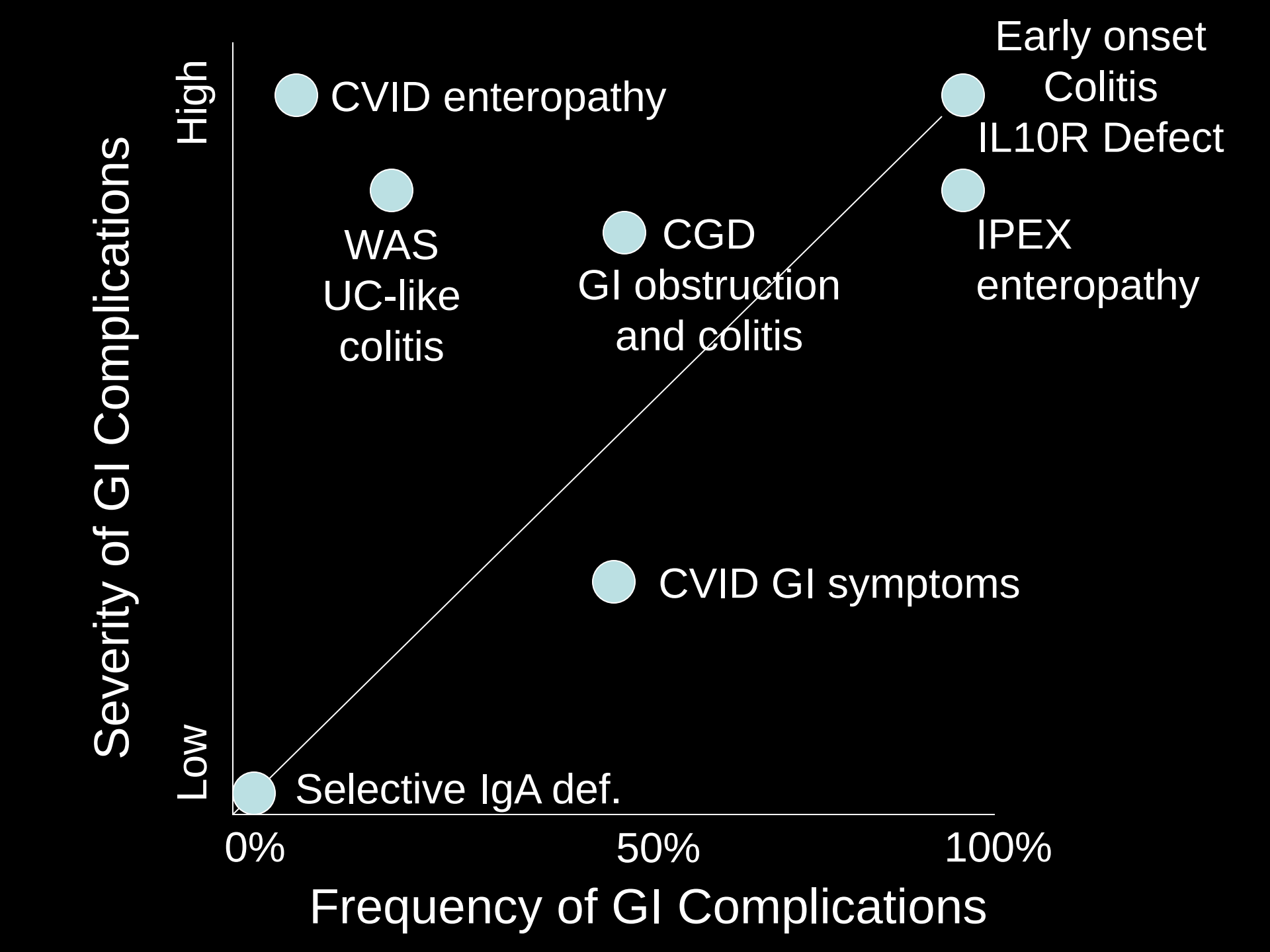
GI Complications of PID

- Why do they happen?
- How often do they happen and who is at risk?
- What are the GI complications of PID?
- How can we manage and treat them?
- What's happening to the "good" bacteria in my gut (after so many antibiotics)? (Dysbiosis in PID)

Why Can PID Affect the Gut?

- The gut has the highest concentration of immune cells of any organ
- The gut is a first line of defense against organisms and antigens/allergens
- The gut is exposed to large amounts of microbes,

  > 100 trillion (up to 4-5 lbs)
- The gut has devised immune mechanisms to balance its daily responses (mucus and cell lining barrier, antibody production, anti-bacterial proteins)
- Possible changes in the gut microbiome related to the immunodeficiency and prior antibiotic treatment


Severity of GI Complications
High
Low
CVID enteropathy
Early onset
Colitis
IL10R Defect
WAS
UC-like
colitis
CGD
GI obstruction
and colitis
IPEX
enteropathy
CVID GI symptoms
Selective IgA def.
0%
50%
100%
Frequency of GI Complications

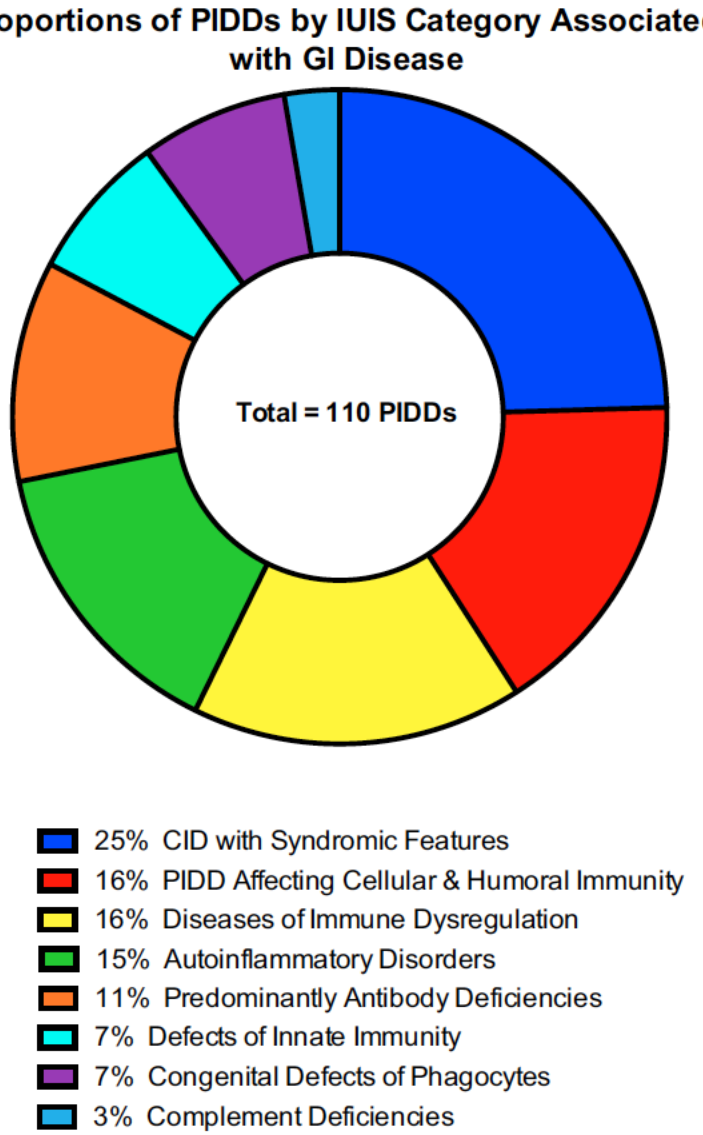
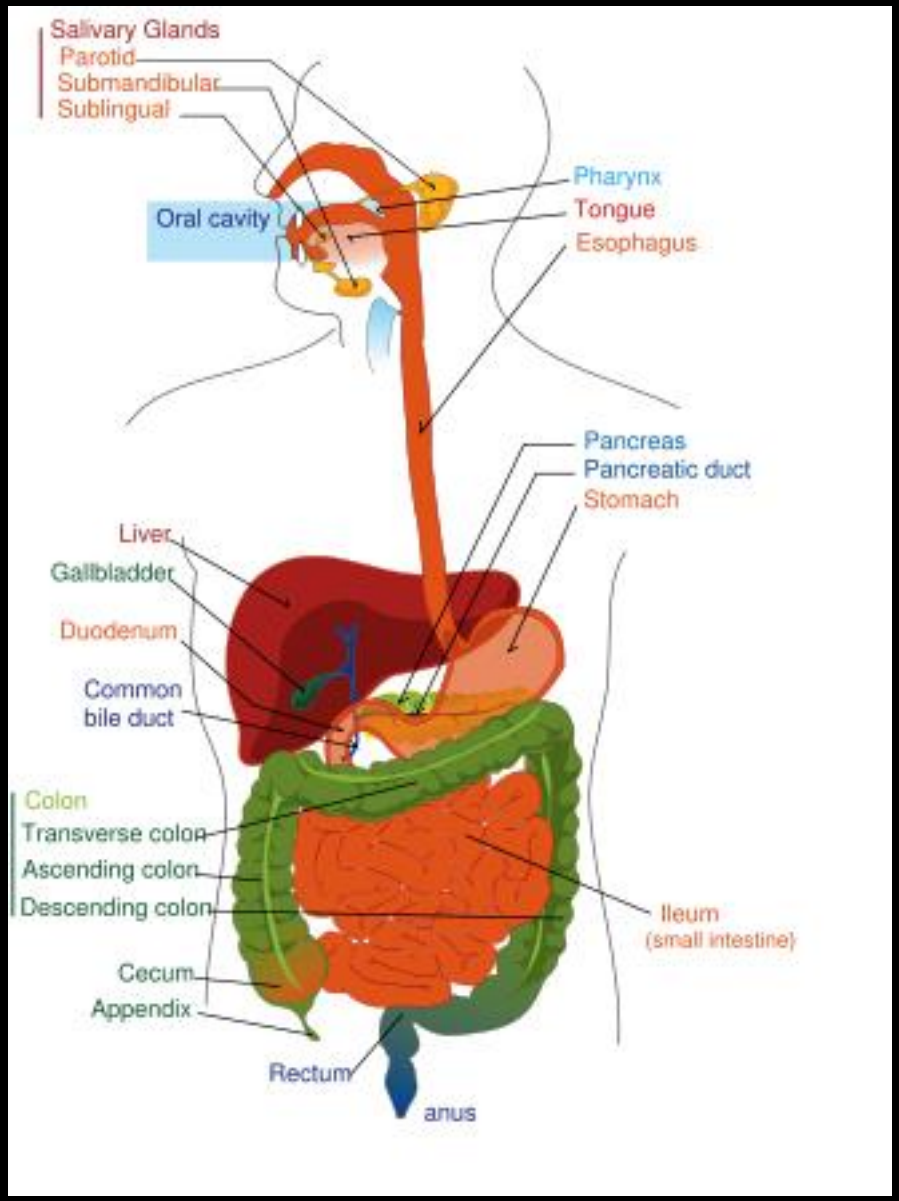


Fig. 1 Proportions of PIDDs by IUIS category associated with GI disease

Gut Complications of PID: What are They?

- Infections
- Inflammation/Autoimmunity
- Cancer

Anatomy and Function of the Gastrointestinal Tract



GI Complications of PID: Symptoms

Esophagus: Pain with swallowing, food/liquids get stuck, heartburn

Stomach: Pain in upper abdomen, feeling “full”, vomiting

Small Intestine: Bloating/pain/vomiting after meals, large volume watery diarrhea, excess gas, weight loss

Colon: Diarrhea, blood in stool, feelings of urgency and incomplete evacuation

Gut Complications: Who is at Risk?

PID	Features	Treatment	GI Effects	Management
Selective IgA Deficiency	IgA def	None	Little to none	Treat gut infections
CVID	IgG, IgA, IgM def	Ig Replacement	Inf. diarrhea, SIBO, wt loss/malab., cirrhosis	Abx, steroids, immunomodulators
CGD	Def. Phagocytic cell killing	Abx for infections, IFNγ, G-CSF/GM-CSF	Diarrhea inf/non, obstruction,liver absc.,colitis	Abx, drain absc.,G/M-CSF, CyA, IFX
SCID	Low to absent T, B, NK cells	Ig Rx, PCP Prophylx, HSCT	Recur. Inf. Diarrhea, wt loss, thrush; GVHD	Abx for bacteria, fungi (oroesoph/perianal)
Wiskott-Aldrich syndrome	Impaired T/B cells, eczema, low platelets	HSCT, anti-CD20 for autoim. cytopenias	Non-infectious colitis	5ASA, steroids, immunomodulators
Hyper-IgM syndrome, type 1	Low IgA, IgG, def. T, NK function	Ig Rx, HSCT ± liver Transplant	Crypto. Diarrhea, cholangitis, cirrhosis, bil. Ca	Avoid Cryptospor. exposure
IPEX syndrome	Autoimmune endocrine and gut effects	HSCT	Weight loss, malabsorption, diarrhea	Temp. use steroids,immunomodulators

Symptom Frequency: Italian Survey to Date on GI Symptoms and Disease in PID (CVID 86.5%, hypogamm 12.1%, XLA 1.4%)

72/141 (51%) pts→GI questionnaire→

- Bloating/Diarrhea 37%
- Bleeding 1.4%
- Dyspepsia 12.2%

141 colonoscopy→15 (11%) had chronic inflammation appearance and 17 (12%) had biopsy of acute and chronic inflammation, 24 with NLH (17%)

Nicola et al. Biomedicines 2023

Symptom Frequency: Best Survey to Date on GI Symptoms and Disease in CVID

103 pts→GI questionnaire→

- Bloating 34%
- Diarrhea 26%
- Constipation 13%
- Pain 30%

53/103 endoscopy→45% had chronic inflammation (mostly inc. intraepithelial lymphocytyes)

Loss of gut plasma cells assoc. with signs of body-wide inflammation/leaky gut

Take home: The most common biopsy findings were NOT assoc. with any symptoms

Jorgensen et al. AJG 2016

Gastrointestinal Complications of Common Variable Immunodeficiency

- Heightened susceptibility to protozoan and bacterial pathogens
  - *Giardia lamblia*
  - *Salmonella* (non-typhoidal)
  - *Shigella*
  - *Campylobacter* sp.
  - *H. pylori*
  - Norovirus
  - SMALL BOWEL OVERGROWTH
- Chronic IVIG therapy may decrease incidence of infectious diarrhea, esp. *Giardia* (controversial)

Gastrointestinal Complications of Common Variable Immunodeficiency

- Autoimmune activity can lead to parotitis, atrophic gastritis, pernicious anemia, chronic active hepatitis
- Nodular Lymphoid Hyperplasia
- 5-10% of CVID patients develop a chronic diarrhea/weight loss/malabsorption syndrome, unrelated to GI pathogens and despite ongoing IVIG therapy

CVID Enteropathy

- Insidious onset unexplained weight loss
- Chronic diarrhea, usually without stool WBC (evaluation may reveal excess fat, abnormal mucosal absorption, less often protein-losing enteropathy)
- Malnutrition effects (hypocalcemia, coagulopathy, megaloblastic anemia, hypoalbuminemia, dermatitis)

Gut Complications of CVID: Pitfalls in Diagnosis

- Celiac sprue-like? villus blunting and malabsorption
  - but unlike celiac disease:
    - lacks LP plasma cells and crypt hyperplasia
    - preserved brush border and Goblet cells
    - normal enterocyte maturation
    - gluten-free diet of little help
- Confirm susceptibility with HLA typing of DQA1 and DQB1 alleles

DQ2: DQA1*05/DQB1*02

DQ8: DQA1*03/DQB1*0302

Gut Complications of CVID:
Current Management Strategies for Enteropathy

- Eliminate treatable causes (bacterial overgrowth, enteric pathogens, chronic norovirus)
- Corticosteroids
- Hydroxychloroquine
- Cyclosporine, azathioprine
- Total parenteral nutrition
- Biologics (e.g. Remicade, Humira, Entyvio, Stelara)
-Clinicaltrials.gov Anti-p-40

Gastrointestinal Complications of CGD

- Infection
  - Liver abscess
  - Perianal Abscess with Sepsis
  - Dental Abscess
- Inflammatory
  - Esophageal dysmotility
  - Oral ulcers/granulomatous stomatitis
  - Gastric outlet obstruction
  - Small bowel obstruction
  - Colitis

Management Strategies in GI Complications of CGD

- Conventional IBD therapies: mesalamine, corticosteroids; antibiotics and steroids for gastric outlet obstruction
- G-CSF/GM-CSF
- HLA-identical cord-blood stem cell transplant
- Surgery: perianal, ischiorectal abscess drainage, diverting ostomies; skilled surgeon in for liver abscess
- Infliximab (anti-TNFα antibody) but caution for exacerbating infections, abscesses post fistula closure
- Anakinra (anti-IL-1β)

Complications of PID: Gastrointestinal Cancers

- Though ↑ rate compared to normal population

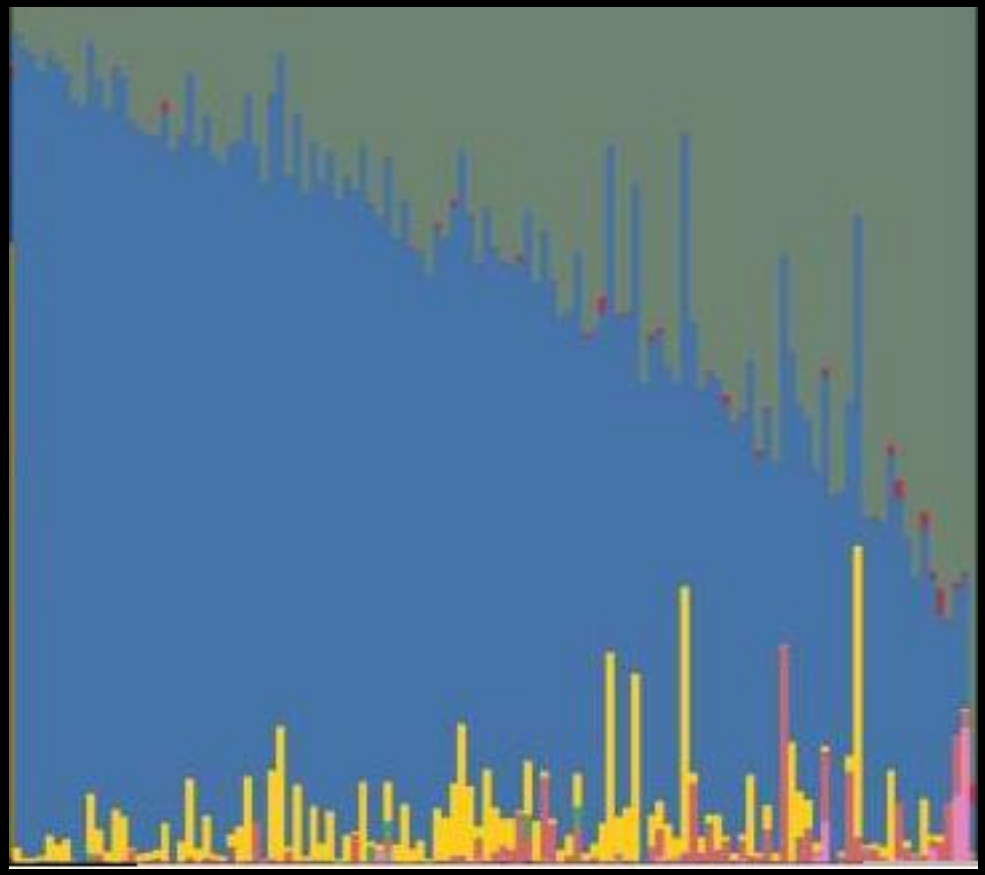
  Rates are generally < 5%

- Pernicious anemia and gastric cancer
- Non-Hodgkins lymphoma and MALT
- Nodular lymphoid hyperplasia (benign)
- Colorectal cancer

The Gut Microbiome

- Est. 10^{14} bacteria in the gut (human body is made up of 10^{13} cells)
- Est. 10^{11} bacteria flow from the pharynx to the stomach each day
- The gut microbiome is subject to
  - Environmental factors
    - antibiotics, diet composition
  - Host genetic factors
    - twin studies
    - Immune gene knockout animal models (colitogenic microbiota, pathobiont outgrowth)

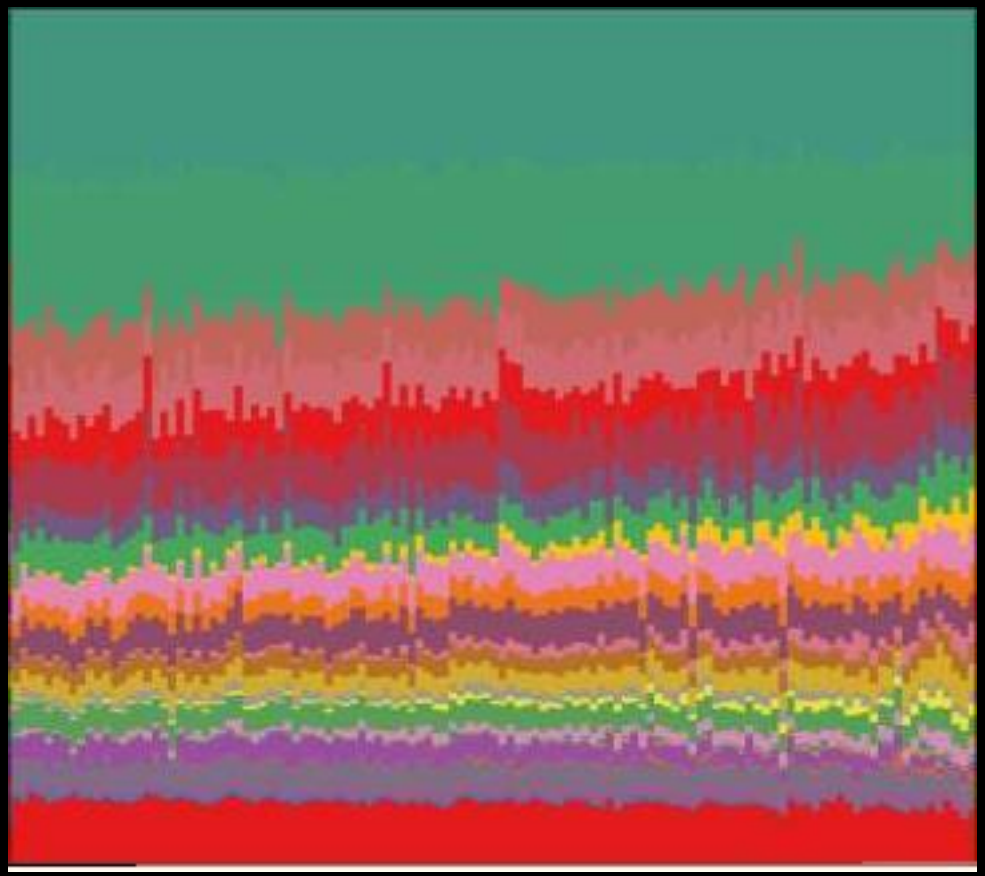
Distribution of Stool Bacteria by Phyla in Healthy Adults



- Firmicutes
- Actinobacteria
- Bacteroidetes
- Proteobacteria
- Fusobacteria
- Tenericutes
- Spirochaetes
- Cyanobacteria
- Verrucomicrobia
- TM7

HMP, *Nature*, 2012

Distribution of Stool Bacteria by Metabolic Pathways Imputed from the Metagenome



HMP, *Nature*, 2012

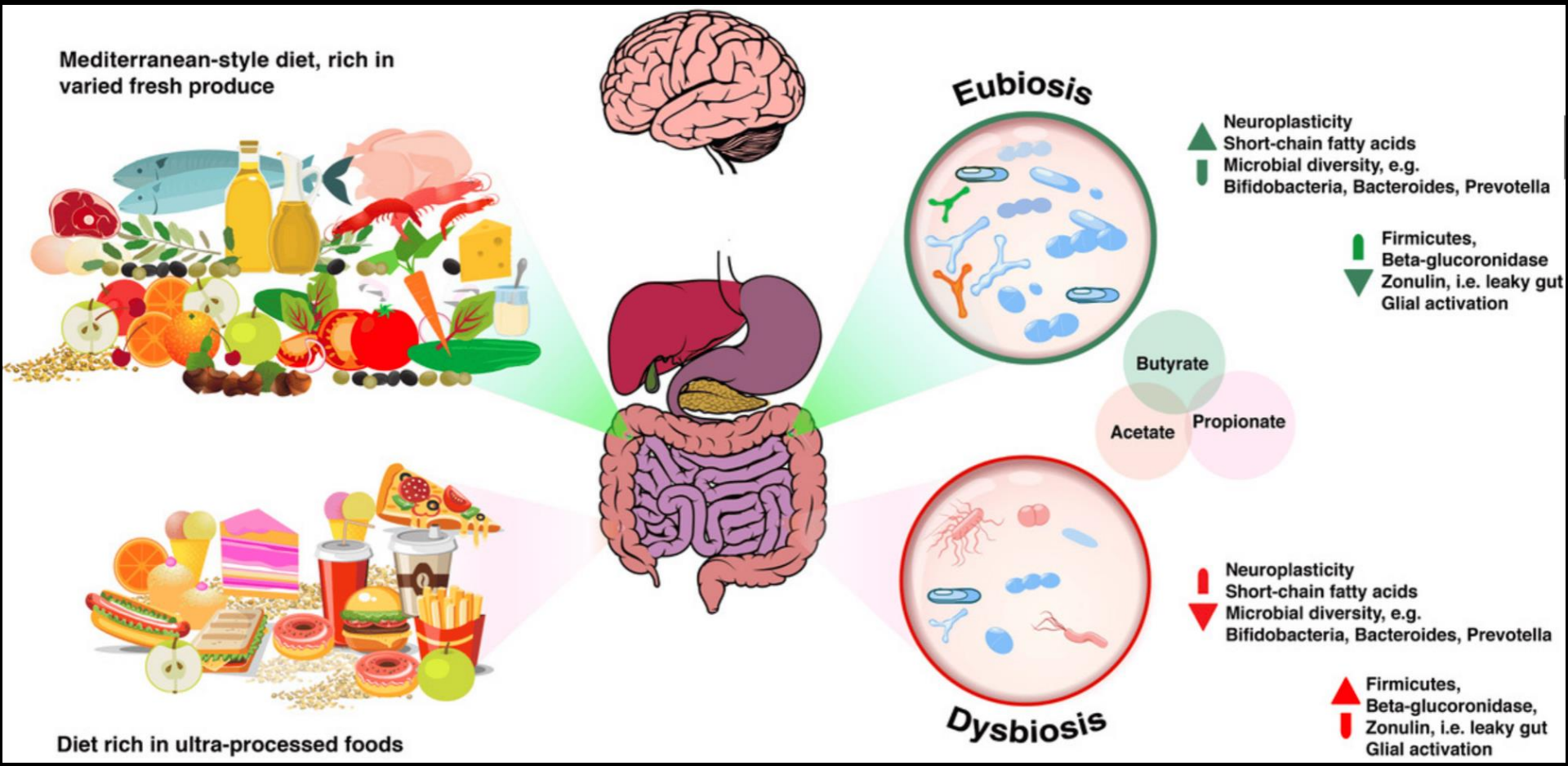
The Gut Microbiome: Influences to Consider

- Diet
- Drug exposure
- Disease state
- Genetic background

The Gut Microbiome: Effects At and Beyond the Gut

- Obesity/Metabolic Syndrome
- Allergic asthma/Autoimmune disease ("missing microbiota hypothesis")
- Mood/Central nervous system diseases
- "Leaky gut"
- Post-infectious irritable bowel syndrome

Diet, Gut Microbiome, Metabolites, Body Effects



Dallmeier 2018 straightfromascientist.com

The Gut Microbiome:
Approaches to Maintain or Restore Order

- Probiotics
- Prebiotics
- Synbiotics
- Fecal Transplant
- More highly targeted antibiotics for *C. difficile* e.g.

The Probiotic Landscape

- Not regulated by the FDA
- Cautionary tales (contamination, human pathogens); likely best avoided in the critically ill and in the immunocompromised
- No robust data for medical indications; ileal pouch and VSL#3
- *Lactobacillus*, *Bifidobacterium*, and *Saccharomyces boulardii*

Clostridium difficile infection (CDI)

- “antibiotic associated colitis”
- Severe watery diarrhea and colitis
- Diagnosed by PCR of stool for toxin DNA
- Flagyl/vancomycin treatment; fidaxomicin and narrow-spectrum antibiotics for CDI
- Prolonged antibiotics for recurrent/persistent infection
- Fecal microbiota transplant (FMT)
- Refractory/severe CDI: IVIG, colectomy
- Prevention: avoid antibiotics (!); possibly probiotics but only *L. casei/L. acidophilus*
- Future: antibodies to toxin B (Bezlotoxumab), vaccines (limited help in PIDs), luminal Abs (oral bovine colostrum)

GI Complications of PID: Conclusions

- Maintain awareness of risk and possible PID-specific complications
- NOT ALL GI SYMPTOMS ARE DUE TO THE PID SO ROUTINE, THOROUGH WORK-UP IS ALWAYS VALUABLE
- Opportunities exist to study the effect of the gut microbiome in PID (genetic, immuune, antibiotic effects) as to its relation to GI and non-GI symptoms