Microbiome ▶▶ GI Disorders

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Key Points

• Our gut microbiota
• Were to find them?
• Symbiosis or Why do we need them?
• Dysbiosis or when things go wrong
• How to modulate microbiota?
• Does it help?
• The future
Who Are Them

- 100 Trillions of microbial organisms
- Microbiota: Bacteria, viruses, fungi, and protozoa
- Bacteria: Main 4 phyla (99% of total)

Firmicutes
Bacteroidetes
Stomach and Duodenum
$10^1 - 10^2$ CFU/mL
- Lactobacilli
- Streptococci
- Yeasts

Colon
$10^{10} - 10^{12}$ CFU/mL
- Bacteroides
- Bifidobacteria
- Streptococci
- Eubacteria
- Fusobacteria
- Clostridia
- Veillonella
- Coliform bacteria
- Lactobacilli
- Proteus
- Staphylococci
- Pseudomonades
- Yeasts
- Protozoa

Jejunum and Ileum
$10^4 - 10^8$ CFU/mL
- Lactobacilli
- Coliform bacteria
- Streptococci
- Bacteroides
- Bifidobacteria
- Fusobacteria
Where to Find Them

INTESTINAL LUMEN

Microbiota

MUCOSA
Mucosa vs. Lumen

- **Firmicutes**
- **Bacteroidetes**
- **Actinobacteria**
- **Proteobacteria**
- **Fusobacteria**
- **Verrucomicrobia**
- **Cyanobacteria**
- **Elusimicrobia**
- **Others**
High throughput sequencing reveals distinct microbial populations within the mucosal and luminal niches in healthy individuals

Yehuda Ringel¹,⁎,†, Nitsan Maharshak¹,²,†, Tamar Ringel-Kulka³, Elizabeth Ashley Wolber¹, R Balfour Sartor¹, and Ian M Carroll¹

Summary: Microbiota Along the GI Tract

• Mapping is improved
• Limited information due to:
  – Culturing anaerobic bacteria
  – Limited accessibility (…small intestine)
  – Stool samples vs. Mucosal biopsies
  – Regional differences and similarities
  – Bowel preparation for colonoscopy

• Psychosomatic Medicine, 2017, 857-867
• Aliment Pharmacol Ther 2015;42:1211–21.
Why Do We Need Microbiota?

- **Nutrient & Energy**
  - Bifidobacterium ➤ Vitamin K & B
  - Bacteroidetes and Firmicutes ➤ Butyrate

- **Immune training & control**
  - IgA production
  - T helper (Th1/Th2) balance
  - Regulatory T cells ➤ Suppress inflammation
  - Barrier function

- **Defense**
  - Colonization resistance
  - Production of antimicrobial factors

Gut 2016;65(2):330–9
What Can Go Wrong

• Eubiosis vs. Dysbiosis
• High vs. Reduced Stability & Diversity

Gut 2013; 62:159-176
Who Affects Stability and Diversity

Extrinsic
- Diet
- Medications
  - PPI
  - Opioids
  - NSAID’s
  - Antibiotics
- Delivery
- Feeding

Intrinsic
- Acid secretion
- O₂ production
- Genetics
- Immune system
- Motility
- Stress
Why Dysbiosis Is important?

• Association with GI diseases?
  – Inflammatory Bowel Disease (IBD)
  – Irritable Bowel Syndrome (IBS)
  – Obesity

• Alteration of gut microbiota were identified!

• Questions:
  – What is the relevance?
  – Manipulating microbiota = Therapy for IBS and IBD?

• Cell Host Microbe 2014;15:382–92
• Inflamm Bowel Dis 2009;15:1183–9
  Am J Gastroenterol 2015;110:921–30
• Cell 2015;160:447–60
  Gut 2012;61:997–1006
• Aliment Pharmacol Ther 51–41:342;2015
Inflammatory Bowel Diseases (IBD)

- Ulcerative Colitis (UC) & Crhon’s Disease (CD)
- Chronic, Remitting, and Relapsing
- Prevalence approaches 1%
- Diagnosis: Before the age of 40 years
- Poor quality of life and social functioning
- Genetic and environmental factors

Gastroenterology 2012;142:46–54
Pathophysiology - IBD

Etiology?

Immune response + Genetics + Environment

Crohn's disease

Ulcerative colitis
Genetically susceptible individuals develop intolerance to dysregulated gut microflora (dysbiosis) and chronic inflammation develops ...
Gut Microbiota in IBD

• Fecal samples:
  ↓ – Less: Firmicutes and Bacteroides
     Bacterial Diversity
  ↑ – More: Proteobacteria and Actinobacteria

• Mucosal biopsies
  ↓ – Less: Firmicutes
     Bacterial Diversity
  ↑ – More: Proteobacteria Bacteroides
Characterization of Gut Microbiota in IBD

- Observational studies
- Children and adults with IBD:
  - Abundance of
    - Erysipelotrichales (order)
    - Clostridiales (order)
    - **Butyrate producers**
    - Gram-negative Clostridia
  - Fecal bacterial diversity and fungal diversity
  - Mucosal Firmicutes
  - Fecal Candida
  - Bacteriophages and Eukaryotic viruses
Disease-Specific Alterations in the Enteric Virome in Inflammatory Bowel Disease

Graphical Abstract

Authors
Jason M. Norman, Scott A. Handley, ..., Miles Parkes, Herbert W. Virgin

Correspondence
virgin@wustl.edu

In Brief
The enteric virome is abnormal in multiple cohorts of inflammatory bowel disease patients, exhibiting disease-specific features that are not explained by changes in bacterial diversity and richness.
Clinical Evidence

• What is the link?
  – Abnormal immune response to a normal microbiota?
  – Normal immune response to an abnormal microbiota?

• Trigger Flare or Complications:
  – Pediatric: Lower diversity and abundance of Rothia Mucilaginosa
  – Adults: lower Firmicutes/Bacteroidetes ratio

• Maintain Active Inflammation ► Complications
  – Pediatric: Lower diversity

• Maintain Remission and Block Flares:
  – High abundance of Faecalibacterium Prausnitzii

• Good Response to Therapy
  – High abundance of Faecalibacterium Prausnitzii

• Psychosomatic Medicine, 2017, 857-867
• Cell Host Microbe 2014;15:382–92
Links: Gut Microbiota - IBD

• Conclusions:
  – Evidence is growing
  – Links are still… too weak!
  – More studies are needed on
    • Composition
    • Association with natural course

• Psychosomatic Medicine, 2017, 857-867
• Aliment Pharmacol Ther 2015;42:1211–21.
Irritable Bowel Syndrome (IBS)

- Chronic, Recurrent condition
- Abdominal pain + Altered bowel movements
- Normal clinical investigations
- Young age
- Prevalence approaches 11%
- Low QOL and Work productivity
- Low Social functioning
- Rome IV Criteria

IBS Subtypes

- Diarrhea-predominant IBS (IBS-D)
- Constipation-predominant (IBS-C)
- Mixed IBS (IBS-M)
- Post Infectious IBS (10%)
Pathophysiology of IBS

- Etiology?
  - Abnormal Brain-Gut Interactions
  - Visceral Hypersensitivity
  - Gut Dysmotility and Secretion
  - Psychosocial Factors
  - Gut Microbiota Composition
  - Gut Permeability
  - Low Grade Immune Activity
Brain-Gut Axis
Biopsychosocial Model

- Bio
- Psycho
- Social
Pathophysiology of IBS
The Role of Microbiota

• Bacterial Gastroenteritis ► Post-Infection IBS
• Small Intestinal Bacterial Overgrowth (SIBO)
• Microbiota in IBS is different?
• Efficacy of Antibiotics and Probiotics
Post Infectious IBS

• 10% of all IBS cases
• Infection ► 7-10 times risk ► IBS
• Risk factors
  – Females
  – Children
  – Mood disorders
  – Antibiotics
Small Intestinal Bacterial Overgrowth (SIBO)

- Biopsies are impractical
- Breath tests = Practical alternative
- Metaanalysis:
  - IBS patients have more SIBO
  - Symptoms overlap
  - Antibiotics are effective

![SIBO Test Results](image)

- 1st Peak
- 2nd Peak

Collection Time
1. Baseline
2. 20 min
3. 40 min
4. 60 min
5. 80 min
6. 100 min
7. 120 min**
8. 140 min
9. 160 min
10. 180 min

Hydrogen

H₂

SIBO Test Results
Gut Microbiota in IBS

- Different Microbiota Compositions:
  - Increased **Firmicutes**/Bacteroidetes Ratio
  - More Fecal **Ruminococcus Torques**
  - Reduced Fecal **Lactobacilli**
  - Reduced Fecal and Mucosal **Diversity**

Gut 2012;61:997–1006
Fecal and Mucosa-Associated Intestinal Microbiota in Patients with Diarrhea-Predominant Irritable Bowel Syndrome
Clinical Evidence

- Symptoms ↔ microbiota?
- IBS+Constipation: More Bifidobacteria?
- Overlap with Controls
- **Non**-Microbiota factors count!
- Evidence is growing

Psychosomatic Medicine, 2017, 857-867
Gut 2012;61:997–1006
Very Few Clear Targets ▶ Therapy?
Therapeutic Approaches for Dysbiosis

- Diet & Prebiotics
- Probiotics
- FMT
- Antibiotics

DYSBIOSIS
Very few targets ► Empirical treatment

- Diet
- Prebiotics
- Probiotics
- Fecal Microbial Transplantation (FMT)
- Antibiotics
  - Rifaximin, Metronidazole
On What Diet Are You?
Trends in Diet Interventions in IBS

Dimidi E et al., Curr Opin Clin Nutr Metab Care 2017
No. 1 Empirical Diet Intervention

• Low FODMAP Diet
  – Fermentable…
  – Oligosaccharides
  – Disaccharides
  – Monosaccharides
  – And Polyols
Diet Interventions in IBS

• Common practice
• The Low FODMAP Diet reduces symptoms
• Effect on gut microbiota?
• Side effect - May reduce microbiota diversity!

The Role of FIBER

Desai MS et al., Cell 2016;167:1339-1353
**Probiotics**

**CONSENSUS STATEMENTS**

**EXPERT CONSENSUS DOCUMENT**

The International Scientific Association for Probiotics and Prebiotics consensus statement on the scope and appropriate use of the term probiotic

Colin Hill, Francisco Guarner, Gregor Reid, Glenn R. Gibson, Daniel J. Morenstein, Bruno Pot, Lorenzo Morelli, Roberto Berni Canani, Harry J. Flint, Seppo Salminen, Philip C. Caulder and Mary Ellen Sanders

<table>
<thead>
<tr>
<th>Probiotic</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \Pi \rho \omega = \text{for} )</td>
</tr>
<tr>
<td>( \beta \iota \sigma = \text{life} )</td>
</tr>
</tbody>
</table>

*Live organisms, which when administered in adequate amounts, confer a health benefit on the host*

Hill C et al., Nat Rev Gastroenterol Hepatol 2014;11:506-14
Probiotics in Health

- Systemic review
- 7 Randomized control trials
- Healthy adults
- No effect on microbiota parameters

Kristensen NB et al., Genome Med 2016;8:52
## Probiotics in Disease

### A Meta-Analysis of Probiotic Efficacy for Gastrointestinal Diseases

Marina L. Ritchie*, Tamara N. Romanuk

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Positive Effect</th>
<th>Risk reduction</th>
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<tbody>
<tr>
<td>Infectious Diarrhea</td>
<td>Yes</td>
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<tr>
<td>Antibiotic ▶ Diarrhea</td>
<td>Yes</td>
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<tr>
<td>Traveler Diarrhea</td>
<td>No</td>
<td></td>
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<tr>
<td>IBS</td>
<td>Yes</td>
<td>0.5</td>
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<tr>
<td>IBD - Paucities</td>
<td>Yes</td>
<td>0.5</td>
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<tr>
<td>Helicobacter pylori</td>
<td>Yes</td>
<td>0.5</td>
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<tr>
<td>Clostridium Colitis</td>
<td>Yes</td>
<td>0.5</td>
</tr>
<tr>
<td>Necrotizing Ent. Colitis</td>
<td>No</td>
<td></td>
</tr>
</tbody>
</table>

- 74 studies
- 84 trials
- 10,351 patients
Probiotics - Recommendations

American College of Gastroenterology Monograph on Management of Irritable Bowel Syndrome

INTERVENTIONS THAT MODIFY THE MICROBIOTA: PROBIOTICS

- 53 RCTs involving 5'545 patients
- Probiotics superior to placebo (RR of IBS not improving = 0.81)
- NNT: 7
- Adverse events not higher with probiotics (RR 1.09)
- Significant heterogeneity between studies (I2 = 71%, P < 0.001)

We suggest probiotics, taken as a group, to improve global symptoms, as well as bloating and flatulence in IBS patients

Recommendation: weak; Quality of evidence: low

Ford AC et al., Am J Gastroenterol 2018;113:1-18
Effect of Green Kiwifruit in Functional Constipation and IBS-C
Primary Outcome: CSBM

Barbara G et al. DDW 2018
Fecal Microbial Transplantation (FMT)

Clinical Practice
- *C. Difficile* Infection
  - Relapsing/Recurrent
  - Resistant

Research
- IBD
- IBS
- Obesity/Metabolic Synd.
- Diabetes Mellitus Type 2
- Fatty Liver
- Hepatic Encephalopathy
- Pediatric Allergy Synd.

Following FMT ►
**Increased** Microbial Diversity!

Fecal Microbial Transplantation: Preparation and Delivery Modalities

**Preparation**
- Fresh
- Frozen
- Dry Capsule

**Delivery**
- Nasogastric tube
- Enema
- Colonoscopy
Trials of FMT in IBS
## Trials of FMT in IBS

<table>
<thead>
<tr>
<th>Trial</th>
<th>No. of Patients</th>
<th>Symptoms</th>
<th>Side effects</th>
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<tr>
<td>Johnsen 2018</td>
<td>90</td>
<td>Improved</td>
<td>No Serious</td>
</tr>
</tbody>
</table>

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Johnsen PH et al., Lancet Gastroenterol Hepatol 2018;3:17-24
FMT in IBS: STUDY 1

FMT for IBS Primary endpoint
Symptom relief of more than 75 points on the IBS-SSS

(p=0.049)

- No serious adverse events

Johnsen PH et al., Lancet Gastroenterol Hepatol 2018;3:17-24
FMT in IBS: STUDY 2

IBS (n=52) → FMT Capsules (n=26) → Placebo (n=30)

10 days Treatment period → 6 months Follow up

Halkjær SI, et al. Gut 2018
FMT in IBS: STUDY 2

- FMT increased biodiversity (First study)
- Symptoms and quality of life improved with placebo

Change in Symptom Severity

Change in Quality of Life

Halkjær SI, Christensen AH, Lo BZS, et al. Gut 2018
Oral FMT for Recurrent CDI

Overall cure rate 94%

- 83.6% Cured w/ 1 dose
- 8.6% Cured w/ 2 doses
- 2% Cured w/ 3 doses
- 2% Failed 2 or more
- 4% Failed. No re-tx.

Youngster et al. BMC Medicine (2016) 14:134
Randomized FMT Trials in Adult UC Patients

Fecal Microbiota Transplantation Induces Remission in Patients With Active Ulcerative Colitis in a Randomized Controlled Trial

Paul Moayyedi,¹ Michael G. Surette,¹ Peter T. Kim,²,³ Josie Libertucci,¹ Melanie Wolfe,¹ Catherine Onischi,³ David Armstrong,¹ John K. Marshall,¹ Zain Kassam,⁴ Walter Reinisch,¹ and Christine H. Lee³

Findings From a Randomized Controlled Trial of Fecal Transplantation for Patients With Ulcerative Colitis

Noortje G. Rossen,¹ Susana Fuentes,² Mirjam J. van der Spek,¹ Jan G. Tijssen,³ Jorn H. A. Hartman,² Ann Duflou,¹ Mark Löwenberg,¹ Gijs R. van den Brink,¹ Elisabeth M. H. Mathus-Vliegen,¹ Willem M. de Vos,²,⁴ Erwin G. Zoetendal,² Geert R. D’Haens,¹ and Cyriel Y. Ponsioen¹

Moayyedi P; Gastro 2015
Rossen NG; Gastro 2015
Multi-Donor FMT for Active Ulcerative Colitis

- Multicenter, double-blind, randomized, placebo-controlled trial
- Mild-moderate active UC to either FMT or placebo colonoscopic infusion, followed by enemas 5 days per week for 8 weeks
- FMT enemas were from between 3-7 unrelated donors
- **Primary outcome:** steroid-free clinical remission with endoscopic remission or response at week 8
- Performed 16S rRNA stool analysis to assess associated microbial changes

Paramsothy S; Lancet 2017
Antibiotics in IBS: Rifaximin

- Poorly absorbed, broad spectrum antibiotic
- Structural analogue of rifampin
- Inhibits bacterial RNA synthesis by binding to the β-subunit of bacterial DNA-dependent RNA polymerase
- Five polymorphic forms of rifaximin have been identified so far, i.e. rifaximin-α, −β, −γ, −δ, −ε
- Rifaximin-α has negligible absorption: <1%
Effect of Rifaximin on Gut Microbiota

5-days Rifaximin (800 mg / day) in 10 healthy volunteers

Bacterial count / 105 per gram of faeces

Weeks

0 1 2 4 8 12

1 10 100 1000 10000

E. Coli

Other enterobacteriaceae

Enterococci

Clostridium spp.

Anaerobic cocci

Gillis Drugs 1995; DeLeo Drug Exptl Clin Res 1986
The Eubiotic Effect of Rifaximin

Xu D et al., Gastroenterology 2014;146:484-96
Multi-Donor FMT for Active Ulcerative Colitis

OPENBIOME

LEARN MORE

Processed over 4000 pounds of stool
that’s 2 tons of stool!

3% passed only
of prospective donors through our rigorous screening process.
Primary Outcomes

- 6-month UC related hospitalizations
- 6-month cumulative incidence of infection
- UC Remission at week 12
Study: Fecal Microbiota in Small Intestinal Bacterial Overgrowth (SIBO)

- **Breath tests:**
  - 60 patients with SIBO
  - 20 patients without SIBO
  - 20 Healthy controls

- **Results**
Conclusions & The future

• GI symptom generation is linked to gut microbiome
• In some patients with IBS gut microbiota is different
• Treatment options:
  – Restriction diets ➤ Reduce biodiversity
  – Probiotics, Antibiotics ➤ Beneficial but limited
  – FMT ➤ Conflicting results
• Future: More studies:
  – Diet-Microbiota interactions-GI symptoms
  – Host-Microbiota interactions
  – Treatment studies-Symptom generation
Thank you!