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Intestinal Microbiome

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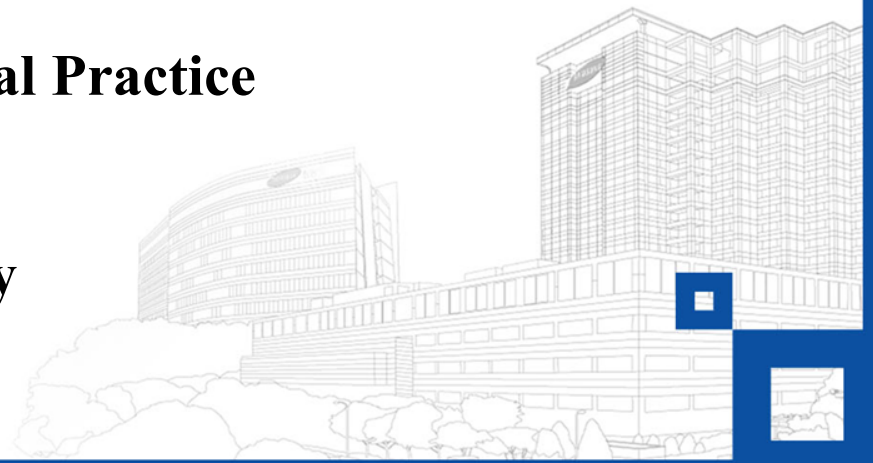
Contents



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I

The Human Intestinal Microbiome in Health and Disease

The Human Intestinal Microbiome in Health and Disease

Biomarker sequencing: The process of cataloguing microbes in a mixed-species community through analysis of sequence variation in a single ubiquitous gene.

Holobiont: The totality of organisms in a given ecosystem (e.g., the shared human and microbial ecosystem); also called a superorganism.

Metabolome: The complete set of small-molecule chemicals found in a biologic sample.

Metagenome: All the genetic material present in an environmental sample, consisting of the genomes of many individual organisms.

Methanogenic archaea: Methane-producing microbes of the ancient Archaea kingdom.

Microbiome: The collection of all genomes of microbes in an ecosystem.

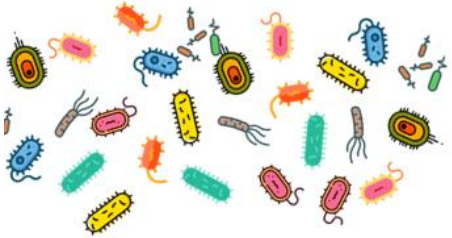
Microbiota: The microbes that collectively inhabit a given ecosystem.

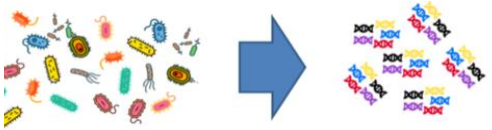
Pathobionts: Typically benign endogenous microbes with the capacity, under altered ecosystem conditions, to elicit pathogenesis.

Prebiotics: Nutritional substrates that promote the growth of microbes that confer health benefits in the host.

Probiotics: Live microbes that confer health benefits when administered in adequate amounts in the host.

Synbiotics: Formulations consisting of a combination of prebiotics and probiotics.





Analyzing Microbiota

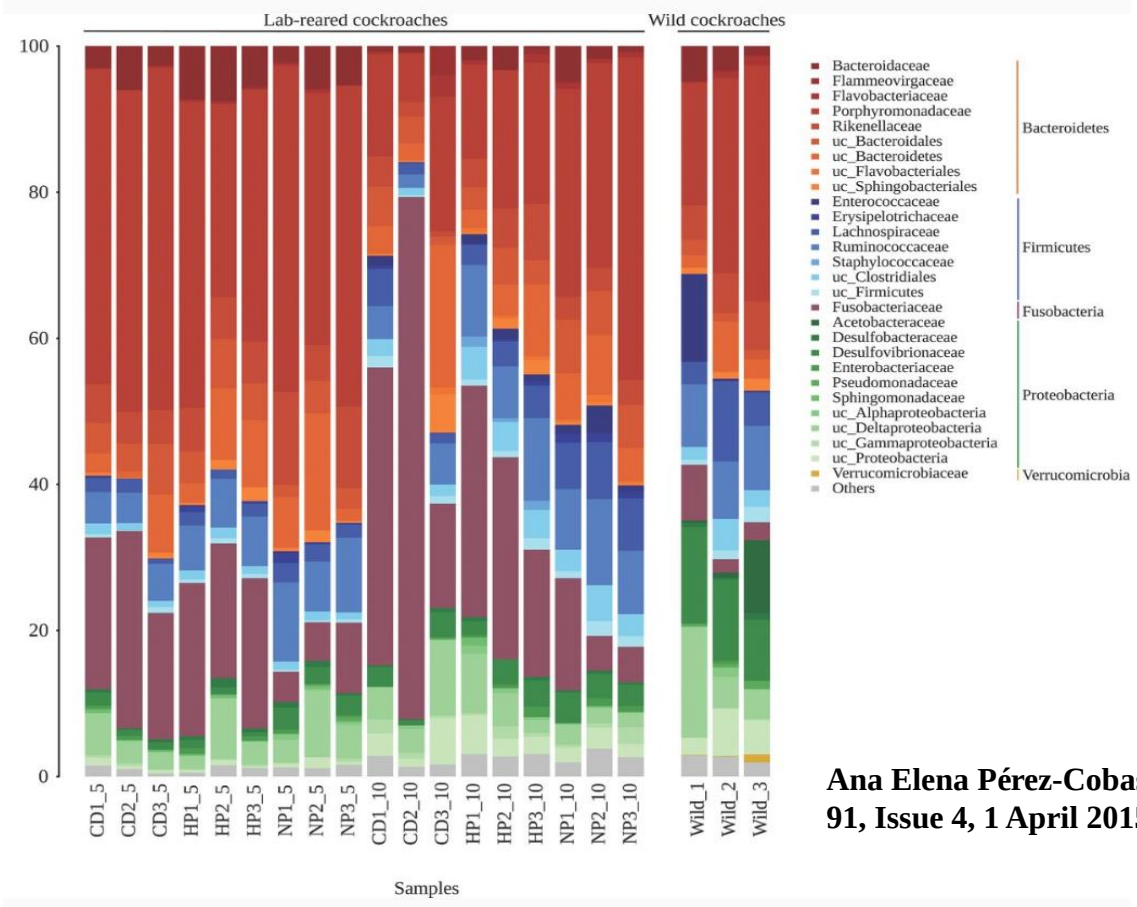
Table 1. Tools for Analyzing Microbiota.

Approach	Data	Platform	Pros and Cons
Biomarker sequencing (e.g., 16S rRNA gene or internal transcribed spacer region)*	Community composition	Next-generation sequencing	Is cost-effective, is semiquantitative, permits resolution of genus level and in some cases species level; shorts reads may make accurate classification difficult
Metagenomics	Generation of draft genomes, functional capacity, growth dynamics	Next-generation sequencing	Has capacity for strain-level reconstruction, is quantitative, allows for functional annotation with pathway predictions; is currently very costly, has community coverage that may be relatively shallow in more complex assemblages
Metatranscriptomics (RNA sequencing)	Gene expression	Next-generation sequencing	Highly expressed genes are more likely than others to be detected, depletion of human transcripts is possible, requires immediate preservation or processing of fresh or snap-frozen intestinal specimens
Metaproteomics	Protein expression	Liquid or gas chromatography–mass spectrometry	Primarily detects dominant proteins; makes removal of host-derived proteins impossible
Metabolomics	Metabolic productivity	Liquid or gas chromatography–mass spectrometry or magnetic resonance spectroscopy	Is semiquantitative; can be targeted or untargeted; detects metabolites that are platform- and database-dependent; detects metabolites that may originate from microbes, diet, or host

* The term rRNA denotes ribosomal RNA.

Susan V. Lynch et al. N Engl J Med 2016;375:2369-79

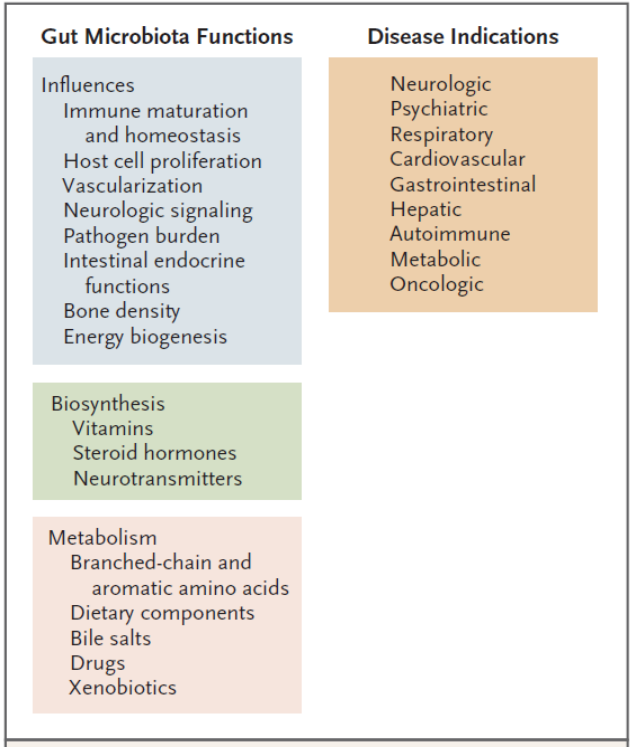
The Human Intestinal Microbiome in Health and Disease



Ana Elena Pérez-Cobas et al. FEMS Microbiology Ecology, Volume 91, Issue 4, 1 April 2015, fiv022

Intestinal Microbiota Play a Critical Role in…

- **Maturation & education** (host immune response)
- **Protection pathogen overgrowth**
- **Host-cell proliferation & vascularization**
- **Intestinal endocrine functions, neurologic signaling & bone density**
- **Energy biogenesis** (5 to 10% of daily energy requirements)
- **Biosynthesize vitamins, neurotransmitters & multiple other compounds**
- **Metabolize bile salts**
- **React or modify specific drugs**
- **Eliminate exogenous toxin**



Susan V. Lynch et al. N Engl J Med 2016;375:2369-79

Gut Microbiota across the Ages

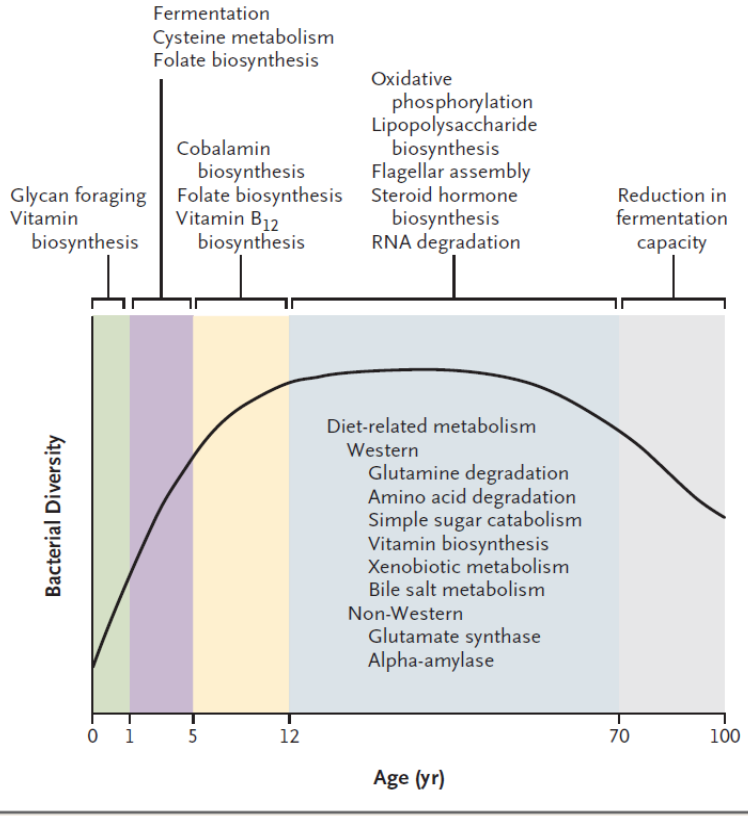


Figure 2. Temporal Development of the Gut Microbiota in Humans.

- **DNA based microbiota studies**
  - **Placenta of healthy mother**
  - **Amniotic fluid of preterm infants**
  - **Meconium**
- **During the first postnatal years**
- **Early childhood (between 1 and 5 years of age)**
- **Preadolescence (7 to 12 years of age)**
- **Elderly**

Susan V. Lynch et al. N Engl J Med 2016;375:2369-79

Gut Microbiota across the Ages

- **Swedish infant–mother dyads**

  - gut microbiota of vaginally delivered neonates similar to maternal gut & vaginal microbiota
  - composition of the gut microbiota in infants changes to resemble adult microbiota (association with the cessation of breast-feeding (Bäckhed F et al. Cell Host Microbe 2015; 17: 852.)

- **Healthy adult gut microbiota**

  - Bacteroidetes, Firmicutes, Actinobacteria, Proteobacteria, Verrucomicrobia, methanogenic archaea (primarily Methanobrevibacter smithii), Eucarya (predominantly yeasts), phages (Reyes A et al. Nature 2010; 466: 334-8)
  - Despite this taxonomic interindividual variation, the functional capacity of the adult gut microbiota is relatively consistent across healthy persons (Qin J, Li R et al. Nature 2010;464: 59-65) (Human Microbiome Project Consortium. Nature 2012; 486: 207-14)

Influences on the Gut Microbiota

- **Endogenous and exogenous factors influence the gut microbiota**

  - Mode of delivery of a neonate

  - Host genetic features

  - Host immune response

  - Diet (including dietary supplements, breast-feeding, and formula- feeding)

  - Xenobiotics (including antibiotics) and other drugs

  - Infections

  - Diurnal rhythm

  - Environmental microbial exposures

  - Childhood diseases such obesity and allergy

Susan V. Lynch et al. N Engl J Med 2016;375:2369-79

Influences on the Gut Microbiota

- **Immunity**

- Sensing of microbes by regulatory T (T reg) cells (Studies of mice)
promotes mucosal tolerance
prevents overgrowth of segmented filamentous bacteria
(by triggering intestinal development, synthesis of T reg cells & secretion of antimicrobial IgA)

- Recently, significantly higher relative risk of allergy in 2-year-old children, asthma in 4-year-old children.
In ex vivo assays, associated products
→ increase CD4+ cells (interleukin-4 , increased interleukin-4 production)
→ reduced the number of CD4+CD25+FOXP3+ cells,
→ contribute to subclinical inflammation that precedes childhood disease development

Fujimura KE et al. Nat Med 2016; 22: 1187-91

Influences on the Gut Microbiota

- **Diet and Other Environmental Influences**

  - Healthy adults restricted to meat or vegetable intake

  rapid and reproducible gut microbiota responses, with meat consumption selectively enriching for bile metabolizing microbiota

  → Associated with inflammatory bowel disease

  - Persons have very different metabolic responses to identical meals

  - Pathogenic nfection

  Vibrio cholerae

  Human immunodeficiency virus (HIV)

Dysbiosis of Gut Microbiota

- **"Common ground" hypothesis**

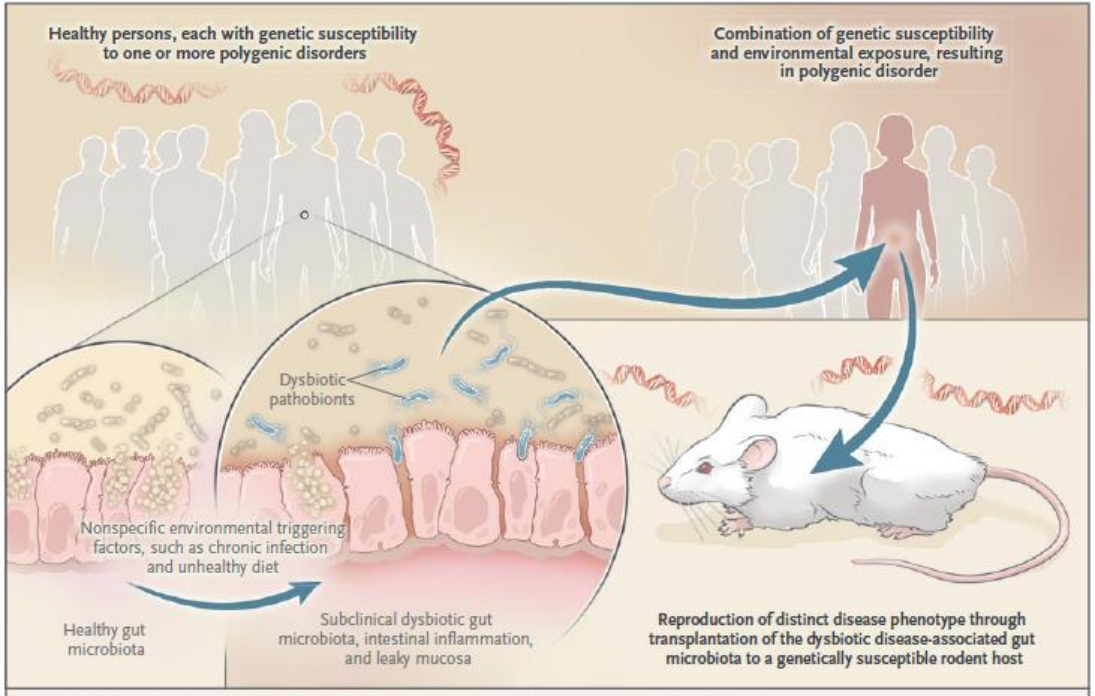


Figure 3. "Common Ground" Hypothesis of Pathogenesis Caused by Dysbiotic Gut Microbiota.

Hansen TH et al. Genome Med 2015; 7: 33.

Dysbiosis of Gut Microbiota

- **Association studies in humans and rodents disease-related dysbioses wide spectrum of common chronic disorders**
  - **atherosclerosis**
  - **metabolic disorders**
  - **asthma**
  - **autism spectrum disorder**

- **Although many novel insights have been gained from these explorations, the study of the gut microbiome in human health and disease remains fraught with challenges**
  - **Intraindividual variability of the microbiome with changes in lifestyle**
  - **reproducibility issues,**
  - **statistically underpowered case–control studies**
  - **phenotypically, etiologically, and microbiologically heterogeneous**

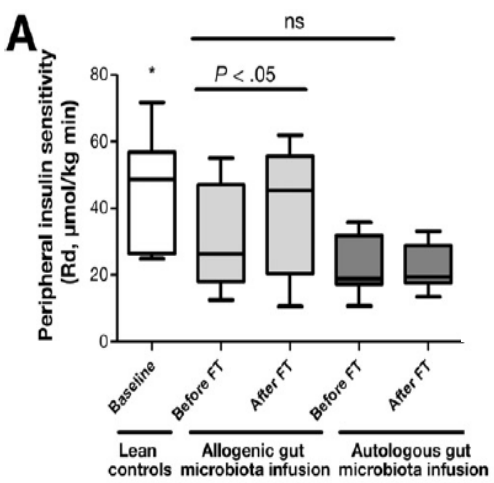
Dysbiosis of Gut Microbiota

- **Human obesity, kwashiorkor, childhood asthma, massive weight loss after bariatric surgery and the insulin-resistant state of third-trimester pregnancy**

- **Transplantation of fecal microbiota from healthy lean human donors to obese patients with insulin resistance is associated with improvement in whole-body insulin sensitivity in the recipients**

Vrieze A et al. Gastroenterology 2012; 143(4): 913-6.e7.

Dysbiosis of Gut Microbiota



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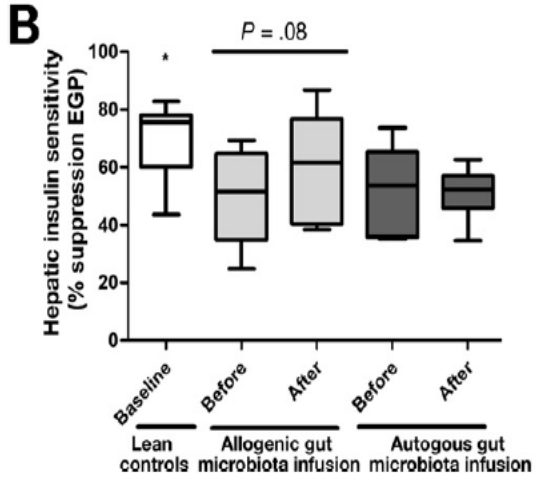

(n = 9)
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GASTROENTEROLOGY 2012;143:913–916

Therapeutic and Preventive Opportunities

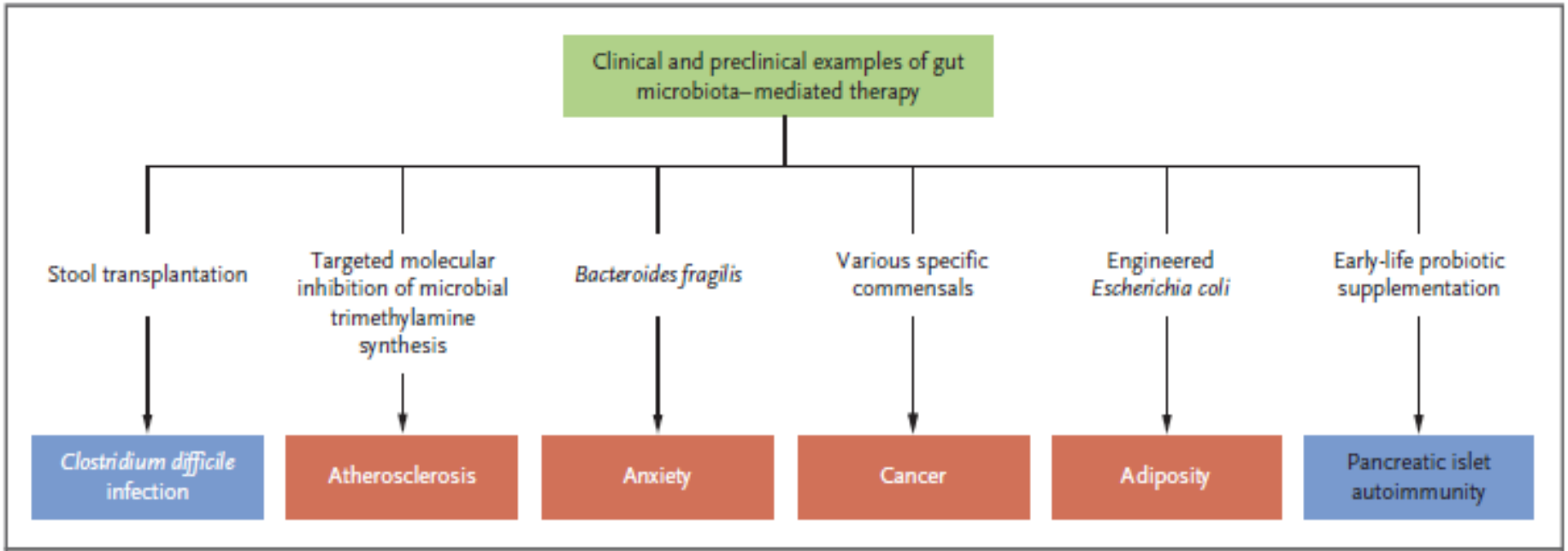

Figure 4. Gut Microbiota and Specific Commensals as Potential Preventive or Therapeutic Agents.

Clinical studies are indicated in blue, and preclinical (mouse) studies in red.

Susan V. Lynch et al. N Engl J Med 2016;375:2369-79

Dietary Interventions Targeting Gut Microbiota

- **On the basis of studies in both animals and humans, dietary intake appears to be a major short-term and long-term regulator of the structure and function of gut microbiota.**

  Macfarlane S et al. Aliment Pharmacol Ther 2013; 38: 804-16

- **Still, only a relatively small number of randomized, clinicall controlled dietary interventions targeting the gut microbiota have been reported in humans**

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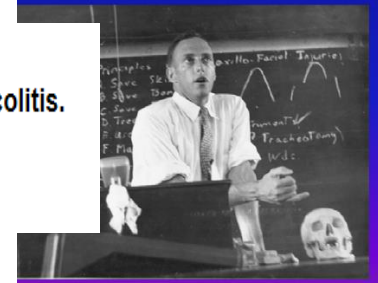
Fecal Microbiota Transplantation (FMT)

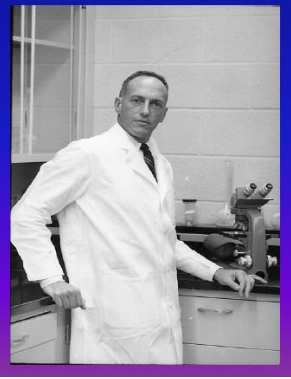
Fecal Microbiota Transplantation (FMT)

Scientific Ingenuity

• Postoperative talc powder granulomas	Ann Surg 1947
• Tuberculostatis chemotherapy	J Exp Med 1948
• Pedicle grafts for the upper esophagus	J Thor Surg 1949
• Intravenous coconut water	Arch Surg 1954
• Human adrenal cortical autografts	Ann Surg 1955
• Ammonia metabolism in hepatic coma	Am J Med 1956
• Islet cell adenoma and peptic ulceration	Gastroenterology 1956
• Hypothermia in pneumococcal peritonitis	J Clin Invest 1956



- Extracorporeal Hepatic Support
- Gortex Graft
- Multiple Organ Failure



Surgery. 1958 Nov;44(5):854-9.

Fecal enema as an adjunct in the treatment of pseudomembranous enterocolitis.

EISEMAN B, SILEN W, BASCOM GS, KAUVAR AJ.

PMID: 13592638

http://www.ucdenver.edu/academics/colleges/medicalschool

Fecal Microbiota Transplantation (FMT)

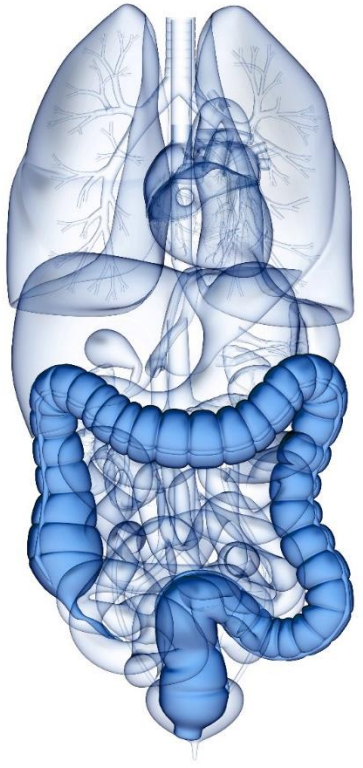
Gut Online First, published on January 13, 2017 as 10.1136/gutjnl-2016-313017

OPEN ACCESS

European consensus conference on faecal microbiota transplantation in clinical practice

Giovanni Cammarota,[1] Gianluca Ianiro,[1] Herbert Tilg,[2] Mirjana Rajilić-Stojanović,[3] Patrizia Kump,[4] Reetta Satokari,[5] Harry Sokol,[6] Perttu Arkkila,[7] Cristina Pintus,[8] Ailsa Hart,[9] Jonathan Segal,[9] Marina Aloi,[10] Luca Masucci,[11] Antonio Molinaro,[12] Franco Scaldaferri,[1] Giovanni Gasbarrini,[1] Antonio Lopez-Sanroman,[13] Alexander Link,[14] Pieter de Groot,[15] Willem M de Vos,[5,16] Christoph Högenauer,[4] Peter Malfertheiner,[14] Eero Mattila,[17] Tomica Milosavljević,[18] Max Nieuwdorp,[12,15,19] Maurizio Sanguinetti,[11] Magnus Simren,[20] Antonio Gasbarrini,[1] The European FMT Working Group

Gastroenterology 2015;1



AGA SECTION

Update on Fecal Microbiota Transplantation 2015: Indications, Methodologies, Mechanisms, and Outlook

Colleen R. Kelly,[1] Stacy Kahn,[2] Purna Kashyap,[3] Loren Laine,[4,5] David Rubin,[2] Ashish Thomas Moore,[7] and Gary Wu[8]

[1]Lifespan Women's Medicine Collaborative, The Miriam Hospital, Alpert Medical School of Brown University, Prov Rhode Island; [2]Inflammatory Bowel Disease Center, Section of Pediatric Gastroenterology, Hepatology, & Nutrition, of Chicago, Chicago, Illinois; [3]Department of Gastroenterology and Hepatology, Mayo Clinic, Rochester, Minnesot of Digestive Diseases, Yale School of Medicine, New Haven, Connecticut; [5]Veterans Affairs Connecticut Healthca West Haven, Connecticut; [6]Sinai AppLab, Division of Gastroenterology, Department of Medicine, Icahn School of M Mount Sinai, New York, New York; [7]Infectious Disease Consultants of Kansas, Wichita, Kansas; and [8]Division of Gastroenterology, Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania

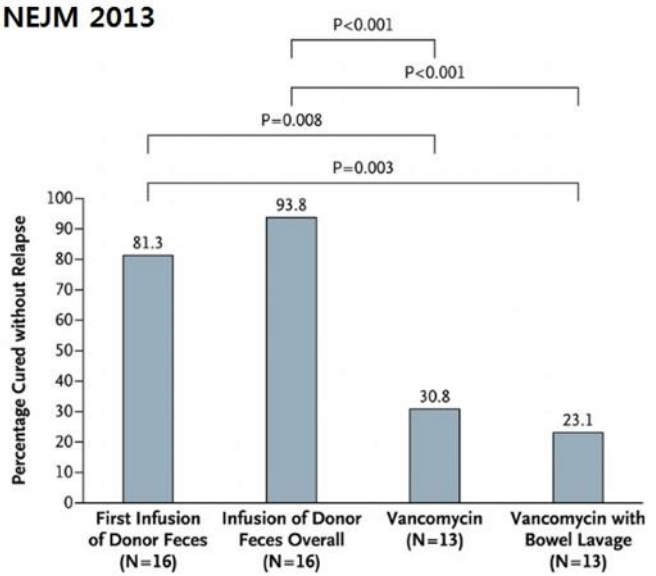
Indications

- **FMT for rCDI**

  Statement: FMT is recommended as treatment option for both mild and severe rCDI. Its implementation in clinical practice is recommended.

  Quality of evidence: high

  Strength of recommendation: strong



Van Nood E et al. N Engl J Med 2013;368:407–15.
Cammarota G et al. Aliment Pharmacol Ther 2015;41:835–43

Indications

- **FMT for refractory CDI**

  Statement: FMT can be considered as a treatment option for refractory CDI.

  Quality of evidence: low

  Strength of recommendation: strong

- **FMT for the first episode of CDI**

  Statement: There is insufficient evidence to recommend FMT as a treatment for the first episode of CDI.

  Quality of evidence: low

  Strength of recommendation: weak

Indications

- **Other indications**

  The experts panel took into account other clinical indications for a possible use of FMT in the clinical practice, such as IBD, IBS, metabolic disorders, paediatrics, but for none of them emerged an evidence-based recommendation to use FMT except that in a context of research.

Donor selection

- **General recommendations**

  Statement: Potential donors for FMT have to undergo, at the beginning of the selection process, a medical interview to exclude history and risk factors.

  Quality of evidence: low

  Strength of recommendation: strong

  Statement: Screened donors have to undergo a further interview on the same day of the donation, in order to check any recently onset potentially harmful issue.

  Quality of evidence: low

  Strength of recommendation: strong

Donor selection

Box 1 Key issues to select potential donors at the preliminary interview

INFECTIOUS DISEASES

- History of, or known exposure to, HIV, HBV or HCV, syphilis, human T-lymphotropic virus I and II, malaria, trypanosomiasis, tuberculosis
- Known systemic infection not controlled at the time of donation
- Use of illegal drugs
- Risky sexual behaviour (anonymous sexual contacts; sexual contacts with prostitutes, drug addicts, individuals with HIV, viral hepatitis, syphilis; work as prostitute; history of sexually transmittable disease)
- Previous reception of tissue/organ transplant
- Previous (<12 months) reception of blood products
- Recent (<6 months) needle stick accident
- Recent (<6 months) body tattoo, piercing, earring, acupuncture
- Recent medical treatment in poorly hygienic conditions
- Risk of transmission of diseases caused by prions
- Recent parasitosis or infection from rotavirus, *Giardia lamblia* and other microbes with GI involvement
- Recent (<6 months) travel in tropical countries, countries at high risk of communicable diseases or traveller's diarrhoea
- Recent (<6 months) history of vaccination with a live attenuated virus, if there is a possible risk of transmission
- Healthcare workers (to exclude the risk of transmission of multidrug-resistant organisms)
- Individual working with animals (to exclude the risk of transmission of zoonotic infections)

GI, METABOLIC AND NEUROLOGICAL DISORDERS

- History of IBS, IBD, functional chronic constipation, coeliac disease, other chronic GI disorders
- History of chronic, systemic autoimmune disorders with GI involvement
- History of, or high risk for, GI cancer or polyposis
- Recent appearance of diarrhoea, hematochezia
- History of neurological/neurodegenerative disorders
- History of psychiatric conditions
- Overweight and obesity (body mass index >25)

DRUGS THAT CAN IMPAIR GUT MICROBIOTA COMPOSITION

- Recent (<3 months) exposure to antibiotics, immunosuppressants, chemotherapy
- Chronic therapy with proton pump inhibitors

Box 2 Issues to address on the same day of donation to check any recently onset of harmful events

- Newly appeared GI signs and symptoms, for example, diarrhoea, nausea, vomiting, abdominal pain, jaundice
- Newly appeared illness or general signs as fever, throat pain, swollen lymph nodes
- Use of antibiotics or other drugs that may impair gut microbiota, new sexual partners or travels abroad since the last screening
- Recent ingestion of a substance that may result harmful for the recipients
- Travel in tropical areas—contact with human blood (sting, wound, showing, piercings, tattoos)—sexual high-risk behaviour
- Diarrhoea (more than three loose or liquid stools per day) among members of the entourage (including children) within 4 weeks of donation

Donor selection

- **General recommendations**

  Statement: Suitable donors for FMT should undergo both blood and stool testing at most 4 weeks before donation. If there are no changes in donor's health and specific circumstances, testing may be repeated up to 8 weeks.

  Quality of evidence: low

  Strength of recommendation: strong

  Statement: Related or unrelated donors can be selected when FMT is performed to treat CDI. For other indications, the choice may be driven by specific needs.

  Quality of evidence: moderate

  Strength of recommendation: strong

Donor selection

Box 3 Blood and stool testing to check donors for any potentially transmittable disease

GENERAL BLOOD TESTING

- Cytomegalovirus
- Epstein-Barr virus
- Hepatitis A
- HBV
- HCV
- Hepatitis E virus
- Syphilis
- HIV-1 and HIV-2
- *Entamoeba histolytica*
- Complete blood cell count with differential
- C-reactive protein and erythrocyte sedimentation rate
- Albumin
- Creatinine and electrolytes
- Aminotransferases, bilirubin, gamma-glutamyltransferase, alkaline phosphatase

BLOOD TESTING IN SPECIFIC SITUATIONS

- Human T-lymphotropic virus types I and II antibodies
- *Strongyloides stercoralis*

GENERAL STOOL TESTING

- Detection of *Clostridium difficile*
- Detection of enteric pathogens, including *Salmonella*, *Shigella*
- *Campylobacter*, *Escherichia coli O157 H7*, *Yersinia*, vancomycin-resistant enterococci, methicillin-resistant *Staphylococcus aureus*, Gram-negative multidrug-resistant bacteria
- Norovirus
- Antigens and/or acid fast staining for *Giardia lamblia* and *Criptosporidium parvum*
- Protozoa (including *Blastocystis hominis*) and helminths
- Faecal occult blood testing

STOOL TESTING IN SPECIFIC SITUATIONS

- Detection of *Vibrio cholera* and *Listeria monocytogenes*
- Antigens and/or acid fast staining for *Isospora* and *Microsporidia*
- Calprotectin
- *Helicobacter pylori* faecal antigen
- Rotavirus

Preparation of faecal material

- **Preparation of faecal material**

  Statement: A minimum set of general steps has to be followed for the preparation of fresh faeces.

  Quality of evidence: moderate

  Strength of recommendation: strong

Statement: Frozen faecal material can be used for FMT. A minimum set of general steps has to be followed for the preparation of frozen material.

Quality of evidence: moderate

Strength of recommendation: strong

Preparation of faecal material

Box 4 Minimum general steps to follow for the preparation of fresh and frozen faecal material

FRESH FAECAL MATERIAL

- Fresh stool should be used within 6 hours after defecation
- To protect anaerobic bacteria, the storage and preparation should be as brief as possible
- Until further processing, the stool sample can be stored at ambient temperature (20°C–30°C)
- Anaerobic storage and processing should be applied if possible
- A minimum amount of 30 g of faeces should be used
- Faecal material should be suspended in saline using a blender or manual effort and sieved in order to avoid the clogging of infusion syringes and tubes
- A dedicated space, disinfected using measures that are effective against sporulating bacteria, should be used
- Protective gloves and facial masks should be used during preparation

FROZEN FAECAL MATERIAL

- At least 30 g of donor faeces and 150 mL of saline solution should be used
- Before freezing, glycerol should be added up to a final concentration of 10%
- The final suspension should be clearly labelled and traceable, and stored at −80°C
- On the day of faecal infusion, faecal suspension should be thawed in a warm (37°C) water bath and infused within 6 hours from thawing
- After thawing, saline solution can be added to obtain a desired suspension volume
- Repetitive thawing and freezing should be avoided

Clinical Management and Feacal Delivery

- **Antibiotics**

  Statement: Patients with rCDI should be treated with vancomycin or fidaxomicin at least for 3 days before FMT. Antibiotics should be stopped 12–48 hours before faecal infusion.

  Quality of evidence: moderate

  Strength of recommendation: strong

- **Bowel lavage**

  Statement: Recipients should be prepared with bowel lavage by polyethylene glycol before procedure when FMT is performed by upper route or by colonoscopy.

  Quality of evidence: low

  Strength of recommendation: weak

Clinical Management and Feacal Delivery

- **FMT via colonoscopy**

  Statement: When possible, donor stools should be infused into the right colon via the working channel of the colonoscope. In cases of severe colitis, faecal suspension can be disposed in the left colon for safety reasons.

  Quality of evidence: high

  Strength of recommendation: strong

- **FMT via enema**

  Statement: FMT can be applied by enema. Patients should be instructed to hold the infused material for at least 30 min and to remain supine to minimise the urge to defecate. The procedure could be repeated.

  Quality of evidence: low

  Strength of recommendation: strong

Clinical Management and Feacal Delivery

- **FMT via upper GI tract**

  Statement: FMT can be performed via upper GI tract. The faecal suspension can be delivered through the working channel of a gastroscope, or through nasogastric, nasojejunal or gastrostomy tube. Patients must be kept in a 45° upright position for 4 hours after infusion in order to prevent aspiration.

  Quality of evidence: high

  Strength of recommendation: strong

  Statement: FMT appears to be safe even in immunocompromised and critically ill patients regardless the route of delivery. In case of critically ill patients, faecal infusion by enema(s) should be preferred.

  Quality of evidence: low

  Strength of recommendation: strong

Clinical Management and Feacal Delivery

Statement: Faecal infusion can be repeated in case of treatment failure or clinical recurrence of CDI.

Quality of evidence: high

Strength of recommendation: strong

- **Short-term monitoring of patients for adverse events**

  Statement: Recipients should be monitored for the occurrence of possible acute complications related to the procedure.

  Quality of evidence: low.

  Strength of recommendation: weak.

Clinical Management and Feacal Delivery

- **Long-term monitoring of patients for adverse events**

  Statement: Periodicity and length of follow-up for long-term adverse events are not determined. Follow-up should include clinical and analytical data.

  Quality of evidence: low

  Strength of recommendation: weak

- **Monitoring of patients for efficacy outcomes**

  Statement: Patients receiving FMT for CDI should be followed up for at least 8 weeks.

  Quality of evidence: low

  Strength of recommendation: strong

Basic requirements for implementing FMT centre

- **Basic requirements for implementing an FMT centre**

  Statement: Development of referral FMTcentres for the treatment of CDI in clinical practice is encouraged. Centres should be implemented in hospitals with appropriate expertise and facilities.

  Quality of evidence: moderate

  Strength of recommendation: strong

  Statement: FMT centres need to have an access or be part of the facility that allows safe processing of human samples (biosafety level 2) including aliquoting, storage and preparation of faeces. Stool banking is encouraged.

  Quality of evidence: low

  Strength of recommendation: strong

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III

In Clinical Practice

In Clinical Practice

- 우선 donor 를 배우자(또는 가족)로 결정 screening (HAV IgM, HBsAg, HCV Ab, RPR, HIV Ab, Stool exams & culture, C difficile toxin assay) 실시함.

- 시술 당일 donor stool 100g을 냉장상태로 받아서 300cc 생수와 섞어 잘 저어줌. 대변은 락앤락에 담아 오도록 함.

- 거즈를 댄 통에 섞은 내용물을 조금씩 부으면 부유물이 없는 emulsion 이 나오는데 약 100cc 정도 획득함.

In Clinical Practice

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- 내용물 주입은 colyte로 prep 한 뒤 cecum 혹은 병변보다 proximal part에 시행함.

- 본원 donor 선정 및 screening 은 감염내과
  stool prep은 임상병리
  delivery 소화기내과

- Emulsion 만들 때,
  N95 마스크 쓰시길 추천함.

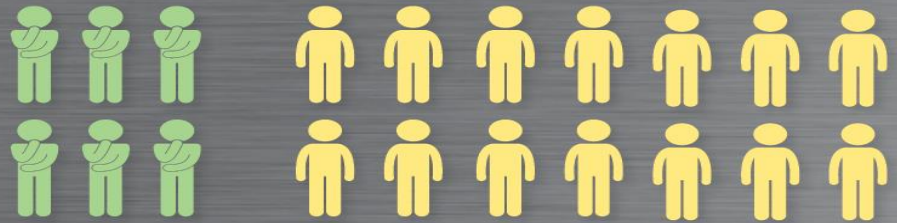
Poop in a Pill

It's no joke. *Clostridium difficile*, or C-diff, causes debilitating diarrhea and is linked to 14,000 deaths in the U.S. every year.

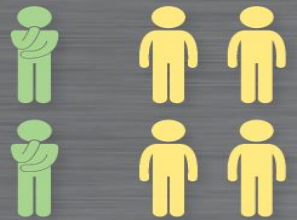
Fecal transplantation—the delivery of pre-screened, healthy donor stool to a patient by colonoscopy or nasogastric tube—is typically prescribed as an effective alternative to long-term antibiotic use in treating this infectious disease. But new research co-authored by Boston Children's Pediatric Gastroenterologist Dr. George Russell, says there is a third, less invasive, less expensive option to treat C-diff: poop in a pill.

A group of physicians from Boston Children's, Massachusetts General Hospital, Harvard Medical School and Tel Aviv University conducted a clinical trial with 20 patients and found:

Initial treatment
Symptoms resolved in 14 of the 20 patients.



Second try
This time symptoms cleared up in 4 of the 6 patients who did not respond at first.



= **90% success**

Boston Children's Hospital
Until every child is well™

Learn more at **bostonchildrens.org/fecaltransplant**

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Summary

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- **Association studies have shown disease-related dysbioses across a wide spectrum of common chronic disorders, including atherosclerosis, metabolic disorders, asthma, and autism spectrum disorder.**

- **Although many novel insights have been gained from these explorations, the study of the gut microbiome in human health and disease remains fraught with challenges.**

- **A “common ground” hypothesis, whichhas yet to be rigorously examined, has been proposed to explore the question of whether imbalances of gut microbial communities are a consequence or a cause of chronic polygenic diseases.**

Summary

- **Only clinical indication with sufficient evidence of benefit from the implementation of FMT in clinical practice is CDI.**

  The consensus panel strongly recommends the implementation of FMTcentres for the treatment of CDI in adults.

- **Moreover, there is no strong evidence-based recommendation for the use of FMT in other clinical conditions, although interesting findings come from the application of FMT for the treatment of UC, MS, IBS and, more recently, graft-versus-host disease.**

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Thank you

Intestinal Microbiome