Diet and the Gut Microbiota

Tamara Duker Freuman, MS, RD, CDN

NYCNEN
January 27, 2017

EAST RIVER
GASTROENTEROLOGY & NUTRITION

Objectives

1. Describe key dietary influencers of the gut microbiota at different stages of the human life cycle

    - Infancy/early childhood
    - Adulthood

2. Explain the effect of dietary patterns on the composition of the gut microbiota

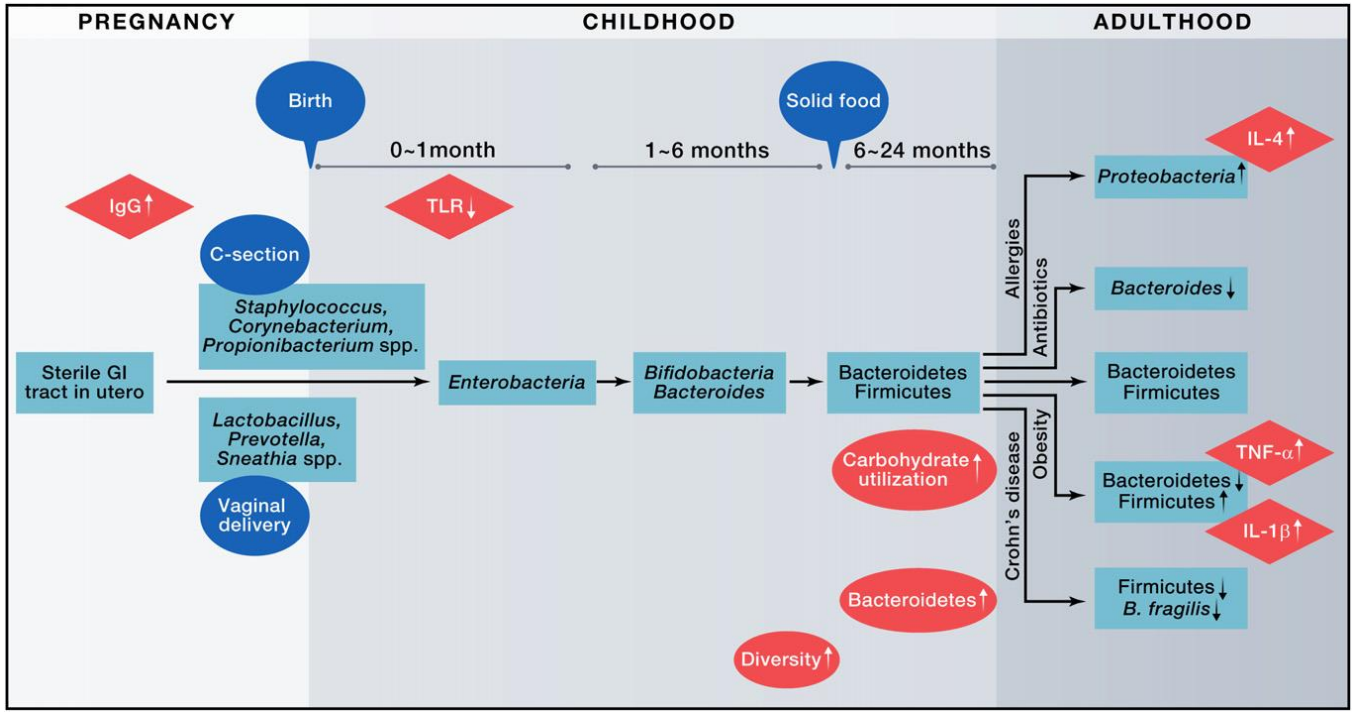
3. Understand benefits vs. risks of probiotic supplementation

The gut microbiota is made, not born

Gut presumed sterile at birth (but some evidence of early microbial colonization)

By age 3, gut microbiota is considered mature, will contain 100 trillion microbes from >1,000 different species

Numerous influences in first three years of life play a role in shaping the microbial 'footprint'



Source: Clemente JC, Ursell LK, Parfrey LW, Knight R. The impact of the gut microbiota on human health: an integrative view. Cell. 2012 Mar 16;148(6):1258-70.

Key influencers of early childhood gut microbiota

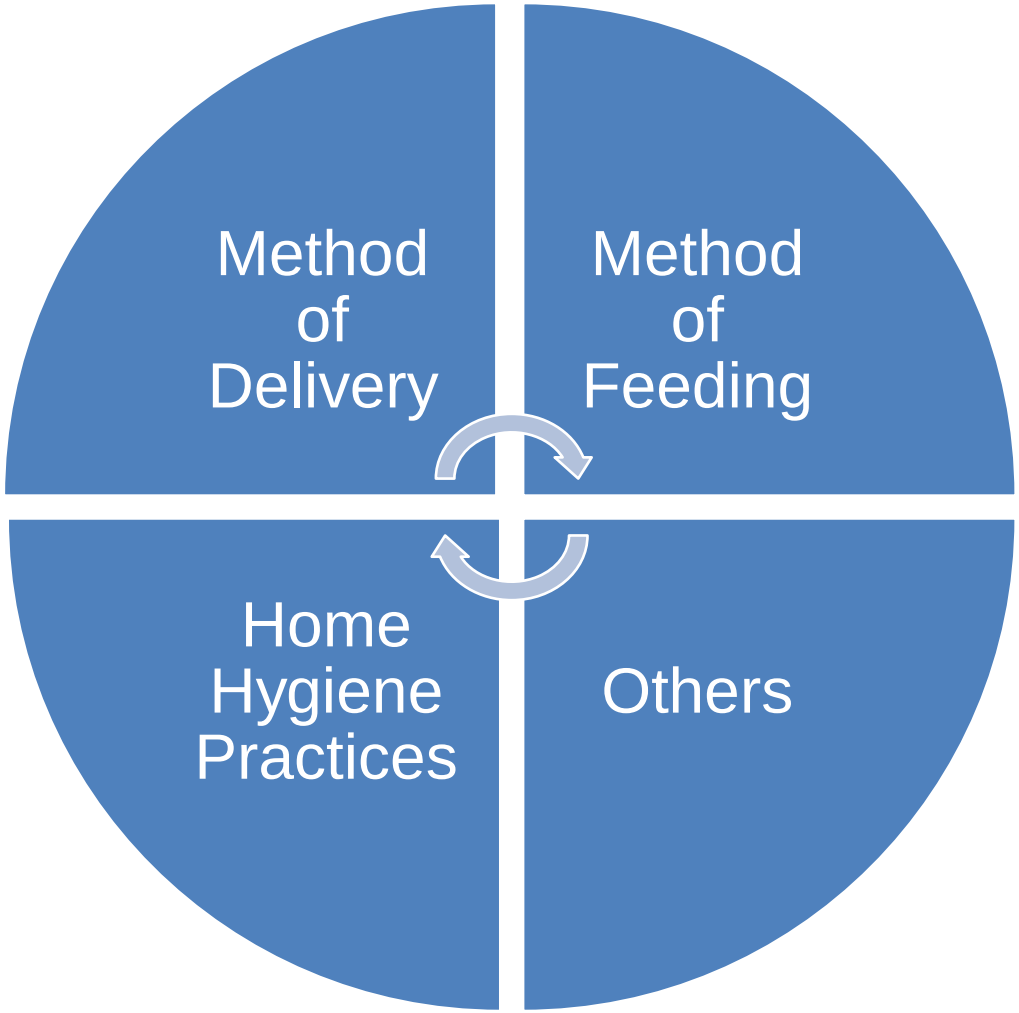
Vaginal birth vs. C-section

Siblings/ daycare

Pets/animals

Urban vs. rural

Sterilizing dishes, pacifiers



Breastfeeding vs formula

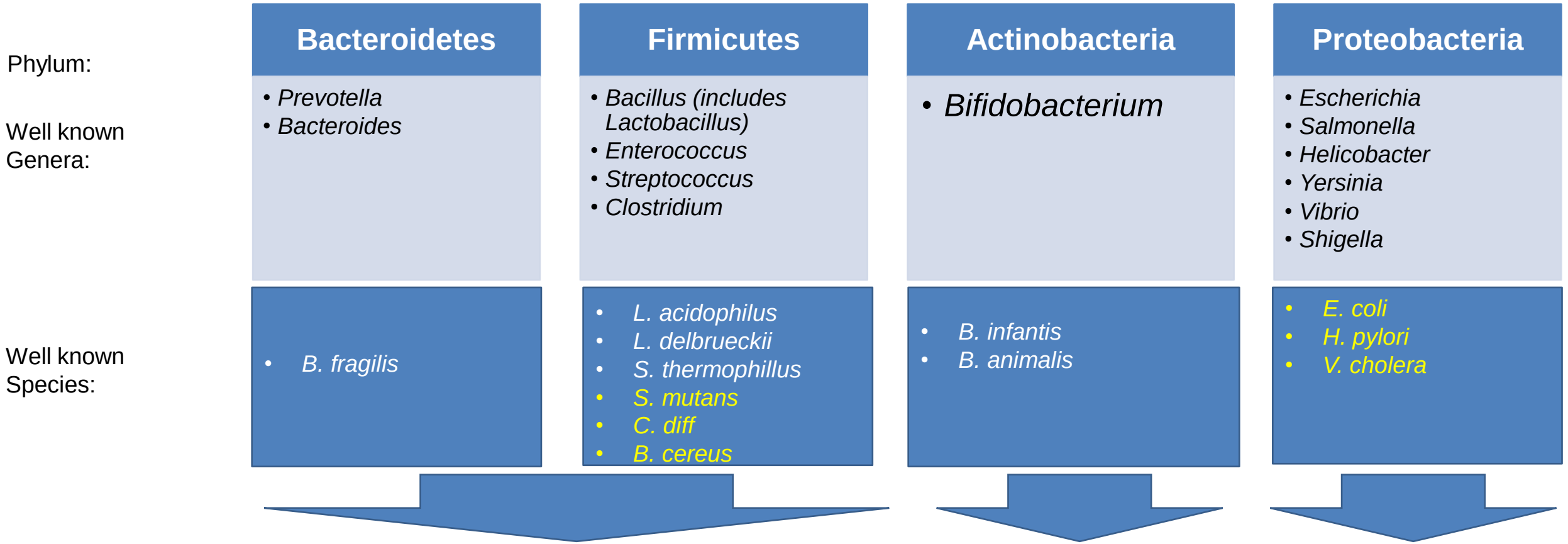
Weaning method?

Dietary pattern on weaning

Antibiotic use:
Type, duration, frequency

Genetics: gut microbial ecology may be inherited to some degree

(Cheat Sheet: Key Characters in the Human Gut Microbiota)



Long term macrnutrient intake patterns influence ‘Enterotype’

Named for genera of predominant microbes

Type 1: Bacteroides (Phylum: Bacteroidetes)

Associated with diets high in animal protein and saturated/animal fats, lower in fiber

Western Diet

Type 2: Prevotella (Phylum: Bacteroidetes)

Associated with diets high in fiber from plants and starchy carbohydrates, and sugars

Agrarian society diet, possibly/presumably Vegans as well)

Type 3?: Ruminococcus (Phylum: Firmicutes)

Also associated with Western-style diets;

Some consider this to be variation of Type 1 with higher ratio of Firmicutes: Bacteriodetes

Higher ratio of Firmicutes: Bacteroidetes is associated with obesity

Method of infant feeding

Breastfeeding associated with more beneficial "enterotype" vs. formula feeding

- Breastfed: Predominantly *Bifidobacteria*, also *Lactobacilli* & *Prevotella*
- Role of oligosaccharides→ prebiotic effect that may nourish *Bifidobacteria*
- Skin to mouth→ introduces maternal skin flora (promotes species diversity)

Formula feeding associated with reduced colonization with *Bifidobacteria*

- *Bifidobacteria* are less dominant, equally balanced with Bacteroidetes species
- More likely to be colonized with potentially pathogenic species like *E. coli* and *C. diff*

Unclear whether pre-mastication plays a meaningful role in development of infant gut microbiota

- Historically, pre-mastication was commonly practiced at weaning, but prevalence in Western societies now rare
- When studied in non Western societies, emphasis only on salivary microbiota (and limited studies suggest influence may be minimal)
- Saliva hypothesized to contribute to early childhood virome in particular at an immunologically optimal time (EBV)

Early childhood

Period of weaning associated with significant change, diversification in gut microbiome

- Year 1-2: microbiome undergoes “second shift” as complementary foods introduced
    - Prolonged breastfeeding into toddlerhood has strong effect on shaping adult microbiome profile
- Method of early infant feeding ceases to impact direction of microbiome development (but not future health risks)
- Developing microbial profile appears heavily influenced by diet
    - *Bacteroides plebeius* in Japanese gut microbiota, *Xylanibacter* in rural African microbiota → absent from North American/Western European microbiota

Gut microbiota stabilizes by ~age 3, more closely resembles adult

Antibiotic use is the factor most likely to provoke significant disturbances in development trajectory of gut microbiome in early childhood

- Frequency of antibiotic use also associated with increased risk of various allergic/autoimmune diseases in later life
- Presumably mediated by effect on microbiome

Impact of diet in shaping gut microbiota revealed by a comparative study in children from Europe and rural Africa

Carlotta De Filippo[a], Duccio Cavalieri[a], Monica Di Paola[b], Matteo Ramazzotti[c], Jean Baptiste Poullet[d], Sebastien Massart[d], Silvia Collini[b], Giuseppe Pieraccini[e], and Paolo Lionetti[b,1]

- **Children aged 1-6 from Burkina Faso and Florence, Italy**
- **African kids ate ~2x more fiber and 60-70% less fat compared to European kids**
- **BF: 73% Bacteroidetes, 12% Firmicutes**
- **EU: 51% Firmicutes, 27% Bacteroidetes**
- **More SCFA in Burkina Faso kids’ stool**
- **BF children had significantly richer (more species) and more biodiverse microbiota vs IT children**

High fiber intake promotes healthier, leaner enterotype

Fiber a primary energy substrate for colonic bacteria, so intake impacts composition of microbiota

- Higher fiber diets associated with increased microbial diversity and increased SCFA production
- Increased SCFA content in stool associated with leaner enterotypes (lower ratio Firmicutes: Bacteroidetes)
- High fiber diet→ ↑ SCFAs→ protects gut mucosal barrier from damage by the microbiota

High fiber, lower calorie diets associated with greater microbial diversity (taxonomic, functional) vs. Western style diets

- Small, short term feeding studies suggest a variety of whole, plant based foods have a prebiotic effect on gut microbiota: whole grain cereals, apples, fruits/veg…
- Available research limited as to specific effects of other high fiber food groups or types of fiber (e.g., soluble vs. insoluble)

Prebiotic fiber intake (inulin) has narrow but notable impact on *Bifidobacteria* and *Lactobacilli* species

- *Bifidobacteria* typically minority genus in adult human gut microbiota but may have protective role vs. IBD, metabolic diseases

Other dietary factors with observed effect on gut microbiota

Dairy intake?

- Eliminating dietary intake of dairy correlated with reduced *Lactobacillus* levels (is this good or bad?)

Iron supplementation?

- Iron fortification/supplementation to cereal in 6 month old Kenyan children resulted in increased pathogen abundance and inflammatory diarrhea compared to infants fed unfortified cereal

Malnutrition and assorted micronutrient deficiencies?

- Increased prevalence of microbes in the P*roteobacteria* phylum (pathogens) in context of malnutrition, RYGB surgery, choline deficiency
- Iron depletion associated with increased *Lactobacilli* and *Enterobacteriaceae* (pathogenic family in the Proteobacteria phylum), decreased *Roseburia spp*. (SCFA producing microbes in phylum Firmicutes).

Researchers are just beginning to scratch the surface as to complex relationship between dietary factors and the gut microbiota!

Limited Role of Supplemental Probiotics in Shaping Gut Microbiota

Commercialized probiotic supplements problematic on many levels

- **Strain selection:**
  - Based on convenience/ “culturability,” not necessarily efficacy→ vast majority of microbes in human gut are not able to be cultured!
  - Single strain vs. multi-strain

- **Evidence basis**: Limited testing to verify efficacy and beneficial “probiotic” effect for most products on market
  - E.g., *Lactobacillus*: helpful or harmful?

- **Lax regulation**: numerous studies have shown mislabeling of commercial probiotic supplements is rampant

Supplemental probiotics have not shown to have significant or lasting impact on microbiota

- When studies have shown benefits, they’re typically “small & transient” → benefits typically cease when supplementation ceases

Benefits vs Risks of Supplemental Probiotics

Any demonstrated benefits of probiotic supplements are product and symptom specific

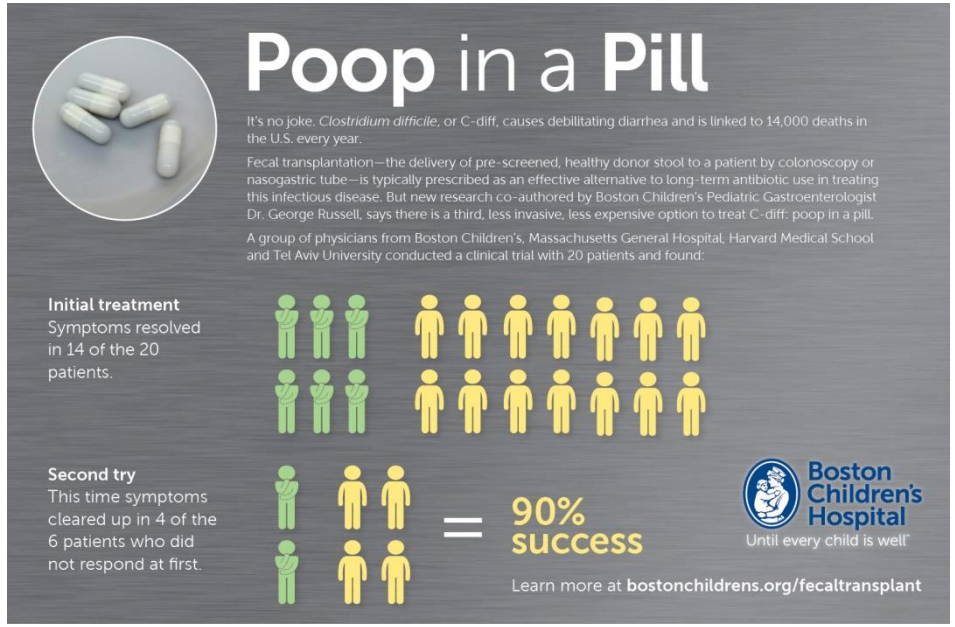
- Best evidence available supports role of various species/strains in managing pediatric gastroenteritis/AAD
- Align (*B. infantis*)→ constipation
- VSL #3 (*Bifidobacterium spp., Lactobacillus spp., S. thermophilus*) → UC, Pouchitis
- Florastor (*S. boulardii lyo* CNCM I-745)→ preventing AAD/*C. diff*
- Cardioviva (*L. reuteri* NCIMB 30242)→ lowers LDL and TC by ~10%

Supplemental probiotics not without risk

- SIBO in predisposed individuals→ PPI use/hypochlorhydria; slow transit
- Populations at risk of sepsis: immunocompromised infants/children, those with IVs/central line

Future of supplemental probiotics likely to be:

- Personalized, customized (not mass market)
- Symbiotic cocktails vs. single strains
- FMT



Adult gut microbiota both stable and dynamic

Mature gut microbiota remarkably stable, trends back to baseline enterotype even after disruptions

- Assuming relatively stable dietary patterns, health status, environment
- Baseline enterotype rebounds after course of antibiotics within ~4 weeks, and may be faster after repeated exposure to same drug
  - Exception: Ciprofloxacin (6 months or more)

Major change in dietary patterns can alter gut microbiome within days…

- Plant based→ high sugar Western diet changes microbiota within a single day in terms of relative proportion of species/strains, but enterotype remains stable in the short run

…But longer-term dietary practices are what dictate enterotype

- Longer term dietary patterns *could* produce more profound, significant changes at the enterotype level…
- …but responsiveness to significant dietary change may be hampered by baseline enterotype
- (Need lots more research!)

Care & Feeding of Your Gut Microbiota

Consume the highest fiber, "highest FODMAP" diet you can comfortably tolerate

- Aim for variety of sources from whole foods: vegetables, whole grains, fruits, nuts, seeds, beans/legumes, tubers…
- Seek out naturally rich prebiotic foods, such as artichokes, sunchokes, jicama, alliums, chicory, rye

Cook/store grains/starches to maximize resistant starch content

- Rice/potatoes: cook→ cool→ reheat (do so safely to avoid "fried rice syndrome" from *B. cereus*!)

Include cultured/fermented foods in your regular diet

- Cultured beverages (kombucha, kvass, e.g.,), fermented vegetables, fermented soy/beans…
- Cultured dairy (?)

Limit exposure to antibacterial personal care products and unnecessary antibiotic medication

Acknowledgements

Thank you:

Jessica Caricato, Dietetic Intern, Teacher's College, Columbia University, for research support

Eric Goldstein, MD, Gastroenterologist, for content review (and giving me the morning off work to present!)

References (I)

1. Ferranti E, Dunbar SB, Dunlop AL, Corwin EJ. 20 Things you Didn't Know About the Human gut Microbiome. The Journal of cardiovascular nursing. 2014 Nov;29(6):479.
2. Clemente JC, Ursell LK, Parfrey LW, Knight R. The impact of the gut microbiota on human health: an integrative view. Cell. 2012 Mar 16;148(6):1258-70.
3. Voreades N, Kozil A, Weir TL. Diet and the development of the human intestinal microbiome. Recent Discoveries in Evolutionary and Genomic Microbiology. 2015 Aug 4:40.
4. Dominguez-Bello MG, Costello EK, Contreras M, Magris M, Hidalgo G, Fierer N, Knight R. Delivery mode shapes the acquisition and structure of the initial microbiota across multiple body habitats in newborns. Proceedings of the National Academy of Sciences. 2010 Jun 29;107(26):11971-5.
5. Penders J, Thijs C, Vink C, Stelma FF, Snijders B, Kummeling I, van den Brandt PA, Stobberingh EE. Factors influencing the composition of the intestinal microbiota in early infancy. Pediatrics. 2006 Aug 1;118(2):511-21.
6. Dunn RR, Fierer N, Henley JB, Leff JW, Menninger HL. Home life: factors structuring the bacterial diversity found within and between homes. PLoS One. 2013 May 22;8(5):e64133.
7. Hesselmar B, Sjöberg F, Saalman R, Åberg N, Adlerberth I, Wold AE. Pacifier cleaning practices and risk of allergy development. Pediatrics. 2013 Jun 1;131(6):e1829-37.
8. Hesselmar B, Hicke-Roberts A, Wennergren G. Allergy in children in hand versus machine dishwashing. Pediatrics. 2015 Mar 1;135(3):e590-7.
9. Ley R, Backhed F, Turnbaugh P, Lozupone C, Knight R, Gordon J. Obesity alters gut microbial ecology. Proc Natl Acad Sci U S A. 2005 Aug 2; 102(31): 11070–11075.
10. Mueller NT, Bakacs E, Combellick J, Grigoryan Z, Dominguez-Bello MG. The infant microbiome development: mom matters. Trends in molecular medicine. 2015 Feb 28;21(2):109-17.
11. Dogra S, Sakwinska O, Soh SE, Ngom-Bru C, Brück WM, Berger B, Brüssow H, Karnani N, Lee YS, Yap F, Chong YS. Rate of establishing the gut microbiota in infancy has consequences for future health. Gut microbes. 2015 Sep 3;6(5):321-5.
12. Harmsen HJ, Wildeboer–Veloo AC, Raangs GC, Wagendorp AA, Klijn N, Bindels JG, Welling GW. Analysis of intestinal flora development in breast-fed and formula-fed infants by using molecular identification and detection methods. Journal of pediatric gastroenterology and nutrition. 2000 Jan 1;30(1):61-7.
13. Koenig JE, Spor A, Scalfone N, Fricker AD, Stombaugh J, Knight R, Angenent LT, Ley RE. Succession of microbial consortia in the developing infant gut microbiome. Proceedings of the National Academy of Sciences. 2011 Mar 15;108(Supplement 1):4578-85.
14. Quercia S, Candela M, Giuliani C, Turroni S, Luiselli D, Rampelli S, Pirazzini C. From lifetime to evolution: timescales of human gut microbiota adaptation. Recent Discoveries in Evolutionary and Genomic Microbiology. 2015 Aug 4:31.
15. Bode L. Human milk oligosaccharides: every baby needs a sugar mama. Glycobiology. 2012 Sep 1;22(9):1147-62.

References (II)

16. LaTuga MS, Stuebe A, Seed PC. A review of the source and function of microbiota in breast milk. InSeminars in reproductive medicine 2014 Jan (Vol. 32, No. 01, pp. 068-073). Thieme Medical Publishers.
17. Han CS, Martin MA, Dichosa AE, Daughton AR, Frietze S, Kaplan H, Gurven MD, Alcock J. Salivary microbiomes of indigenous Tsimane mothers and infants are distinct despite frequent premastication. PeerJ. 2016 Nov 3;4:e2660.
18. Velasquez-Manoff, M. (2012). *An epidemic of absence: a new way of understanding allergies and autoimmune diseases*. New York, NY: Scribner.
19. De Filippo C, Cavalieri D, Di Paola M, Ramazzotti M, Poullet JB, Massart S, Collini S, Pieraccini G, Lionetti P. Impact of diet in shaping gut microbiota revealed by a comparative study in children from Europe and rural Africa. Proc Natl Acad Sci U S A. 2010 Aug 17;107(33):14691-6.
20. Lozupone CA, Stombaugh JI, Gordon JI, Jansson JK, Knight R. Diversity, stability and resilience of the human gut microbiota. Nature. 2012 Sep 13;489(7415):220-30.
21. Dave M, Higgins PD, Middha S, Rioux KP. The human gut microbiome: current knowledge, challenges, and future directions. Translational Research. 2012 Oct 31;160(4):246-57.
22. Marra F, Lynd L, Coombes M, Richardson K, Legal M, Fitzgerald JM, Marra CA. Does antibiotic exposure during infancy lead to development of asthma?: a systematic review and metaanalysis. Chest. 2006 Mar;129(3):610-8.
23. David LA, Maurice CF, Carmody RN, Gootenberg DB, Button JE, Wolfe BE, Ling AV, Devlin AS, Varma Y, Fischbach MA, Biddinger SB. Diet rapidly and reproducibly alters the human gut microbiome. Nature. 2014 Jan 23;505(7484):559-63.
24. Wu GD, Chen J, Hoffmann C, Bittinger K, Chen YY, Keilbaugh SA, Bewtra M, Knights D, Walters WA, Knight R, Sinha R, Gilroy E, Gupta K, Baldassano R, Nessel L, Li H, Bushman FD, Lewis JD. Linking long-term dietary patterns with gut microbial enterotypes. Science. 2011 Oct 7;334(6052):105-8
25. Holmes E, Li JV, Marchesi JR, Nicholson JK. Gut microbiota composition and activity in relation to host metabolic phenotype and disease risk. Cell metabolism. 2012 Nov 7;16(5):559-64.
26. Tuohy KM[1], Conterno L, Gasperotti M, Viola R. Up-regulating the human intestinal microbiome using whole plant foods, polyphenols, and/or fiber. J Agric Food Chem. 2012 Sep 12;60(36):8776-82
27. Arumugam M[1], Raes J, Pelletier E, Le Paslier D, Yamada T, Mende DR, Fernandes GR, Tap J, Bruls T, Batto JM, Bertalan M, Borruel N, Casellas F, Fernandez L, Gautier L, Hansen T, Hattori M, Hayashi T, Kleerebezem M, Kurokawa K, Leclerc M, Levenez F, Manichanh C, Nielsen HB, Nielsen T, Pons N, Poulain J, Qin J, Sicheritz-Ponten T, Tims S, Torrents D, Ugarte E, Zoetendal EG, Wang J, Guarner F, Pedersen O, de Vos WM, Brunak S, Doré J; MetaHIT Consortium, Antolín M, Artiguenave F, Blottiere HM, Almeida M, Brechot C, Cara C, Chervaux C, Cultrone A, Delorme C, Denariaz G, Dervyn R, Foerstner KU, Friss C, van de Guchte M, Guedon E, Haimet F, Huber W, van Hylckama-Vlieg J, Jamet A, Juste C, Kaci G, Knol J, Lakhdari O, Layec S, Le Roux K, Maguin E, Mérieux A, Melo Minardi R, M'rini C, Muller J, Oozeer R, Parkhill J, Renault P, Rescigno M, Sanchez N, Sunagawa S, Torrejon A, Turner K, Vandemeulebrouck G, Varela E, Winogradsky Y, Zeller G, Weissenbach J, Ehrlich SD, Bork P. Enterotypes of the human gut microbiome. Nature. 2011 May 12;473(7346):174-80.
28. Holscher HD, Bauer LL, Gourineni V, Pelkman CL, Fahey GC Jr, Swanson KS. Agave Inulin Supplementation Affects the Fecal Microbiota of Healthy Adults Participating in a Randomized, Double-Blind, Placebo-Controlled, Crossover Trial. J Nutr. 2015 Sep;145(9):2025-32
29. Hooda S[1], Boler BM, Serao MC, Brulc JM, Staeger MA, Boileau TW, Dowd SE, Fahey GC Jr, Swanson KS. 454 pyrosequencing reveals a shift in fecal microbiota of healthy adult men consuming polydextrose or soluble corn fiber. J Nutr. 2012 Jul;142(7):1259-65.
30. Armougom F, Henry M, Vialettes B, Raccah D, Raoult D. Monitoring bacterial community of human gut microbiota reveals an increase in Lactobacillus in obese patients and Methanogens in anorexic patients. PloS one. 2009 Sep 23;4(9):e7125.
31. Jaeggi T, Kortman GA, Moretti D, Chassard C, Holding P, Dostal A, Boekhorst J, Timmerman HM, Swinkels DW, Tjalsma H, Njenga J. Iron fortification adversely affects the gut microbiome, increases pathogen abundance and induces intestinal inflammation in Kenyan infants. Gut. 2015 May 1;64(5):731-42.

References (III)

32. Huys G, Vancanneyt M, D'Haene K, Vankerckhoven V, Goossens H, Swings J. Accuracy of species identity of commercial bacterial cultures intended for probiotic or nutritional use Res Microbiol. 2006 Nov;157(9):803-10.
33. Barengolts E. GUT MICROBIOTA, PREBIOTICS, PROBIOTICS, AND SYNBIOTICS IN MANAGEMENT OF OBESITY AND PREDIABETES: REVIEW OF RANDOMIZED CONTROLLED TRIALS. Endocrine Practice. 2016 Jul 13;22(10):1224-34.
34. Goldenberg JZ, Lytvyn L, Steurich J, Parkin P, Mahant S, Johnston BC. Probiotics for the prevention of pediatric antibiotic-associated diarrhea. Cochrane Database Syst Rev. 2015 Dec 22;(12):CD004827. doi: 10.1002/14651858.CD004827.pub4.
35. Turnbaugh PJ, Ridaura VK, Faith JJ, Rey FE, Knight R, Gordon JI. The effect of diet on the human gut microbiome: a metagenomic analysis in humanized gnotobiotic mice. Science translational medicine. 2009 Nov 11;1(6):6ra14-.
36. Hehemann J, Correc G, Barbeyron T, Helbert W, Czjzek M, Gurvan M.. Transfer of carbohydrate-active enzymes from marine bacteria to Japanese gut microbiota. *Nature.* 2010 *April 8;* 464: 908-912.
37. Griffin N, Ahern P, Cheng J, Heath A, Ilkayeva O, Newgard C, Fontana L, Gordon J. Prior Dietary Practices and Connections to a Human Gut Microbial Metacommunity Alter Responses to Diet Interventions. Cell Host and Microbe. 2016 Dec.