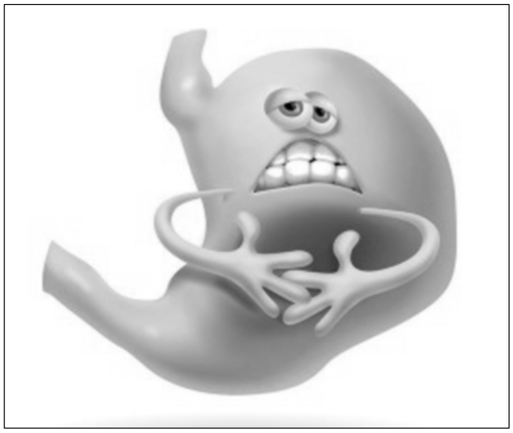
Gut Check: Understanding the Microbiome



Tieraona Low Dog, MD

Founder: Medicine Lodge Ranch

National Geographic's: *"Life Is Your Best Medicine," "Healthy At Home,"* *and "Fortify Your Life"*

www.DrLowDog.com

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Objectives

1. Identify examples of how diet, lifestyle, and the environment influence the human microbiome.
2. Discuss the relationship between the microbiota and disease.
3. Identify how certain medications, such as proton pump inhibitors and antibiotics, impact oral and gut microbiota.
4. Describe the role of diet, dietary fiber, prebiotics and probiotics in optimizing the microbiota.

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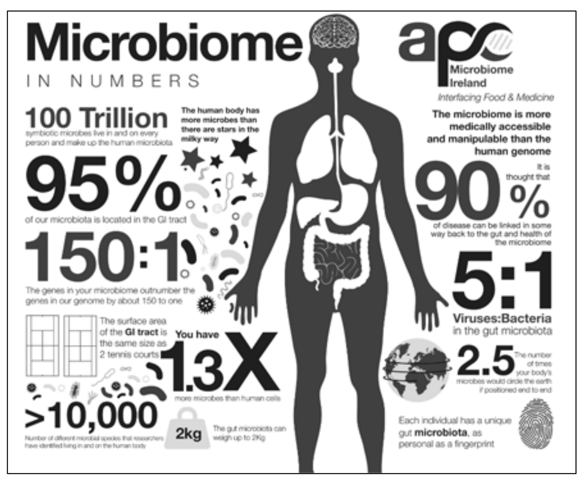
Definitions

- ***Microbiome*—collective genomes** of microbes in particular environment
- *M**icrobiota***—community of **microorganisms** themselves.
- **Core microbiome** similar for all individuals **Variable microbiome** different between individuals.
- **Lower diversity** marker of ***dysbiosis*:** associated with autoimmune disease, obesity, and metabolic conditions.



Valdes AM, et al. *BMJ 2018;361:k2179*

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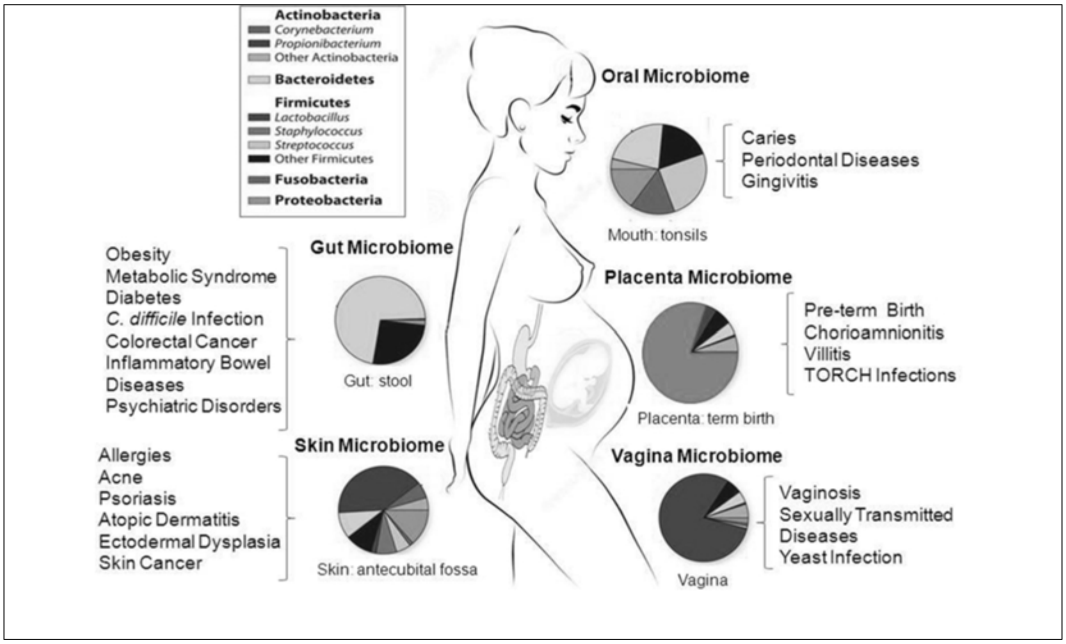

Graphic from: Belizario, JE, et al. *Front Microbiol* 2015; October 6

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Birth

- Babies **born vaginally** covered in microbial film as they pass through birth canal.
- Babies born **by C-section** are **colonized by skin microbes**—very different species.
- Babies **acquire microbes from everyone and everything they touch.**
- **Where** the baby is born, what type of **delivery, if breastfed or bottle fed** – all these impact the microbiome for **months or years after birth.**

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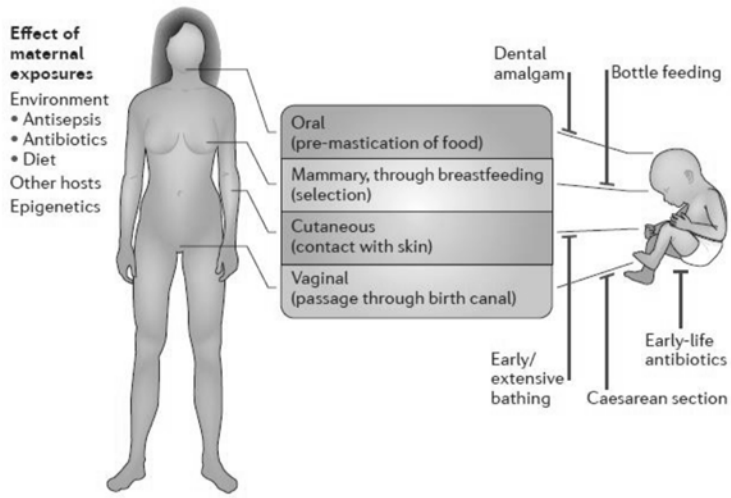
Mother→ Child Transfer of Microbes (Modern)



Breast milk contains numerous genera of microbes and **prebiotic human milk oligosaccharides**, which support growth of ***Bifidobacterium* spp**; important for **inhibiting pathogenic** organisms, **modulating mucosal barrier function**, and **promoting immunological and inflammatory responses**.

Nature Reviews Genetics 2012;13:260-70

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Neonatal Microbiome

- Greatest insults to natural assembly of neonatal microbiome: **C-section delivery, antibiotic use, and formula feeding.**
- **Differences** in specific microbial species observed between **C-section- and vaginally delivered babies up to 7 years after birth.**
- **Intrapartum antibiotic use** associated with **lower abundance of *Lactobacilli* and *Bifidobacteria* in neonatal gut.**
- **Formula feeding** associated with increased prevalence of ***C. difficile*, *Bacteroides fragilis*, and *E. coli* and decreased prevalence of *Bifidobacteria*.**

Salminen S, et al. *Gut.* 2004;53:1388–1389; Aloisio I, et al. *Appl Microbiol Biotechnol.* 2014;98:6051–6060.
Mueller NT, et al. *Trends Mol Med* 2015; 21(2): 109-17

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Probiotics and Birth Mode

- Mothers given probiotic (*Bifidobacterium breve*, *Propionibacterium freundenreichii subsp. shermanii* JS, *Lactobacillus rhamnosus Lc705*, and *L. rhamnosus GG*.
- **Probiotic group** (N = 168 breastfed and 31 formula-fed), or **placebo supplement** (N = 201 breastfed and 22 formula-fed)given during **pregnancy, infants received same**.
- **Placebo group:** both **birth mode and antibiotic use**, significantly associated with altered microbiota composition/function, **particularly reduced *Bifidobacterium*.**
- **Probiotic group:** effects of **antibiotics/birth mode** either completely **eliminated or reduced.**

Korpela K, et al. Probiotic Supplementation Restores Normal Microbiota Composition and Function in Antibiotic-Treated and in Caesarean-Born Infants. *Microbiome* 2018; 6(1): 182

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Birth to 3 Years

- Within weeks, **microbial specialization** occurs. Different populations in mouth, gut, skin, etc.
- Microbial populations in infant **similar to people they live with.** Microbiota dramatically altered by **new foods, antibiotics, proton-pump inhibitor us**e, etc. These shifts can last many, many years.
- **Number and types of species increase and change with age**. Example: babies have more folate *producing* microbes – adults have more folate *harvesting* microbes.

Azad MB, et al. Gut microbiota of healthy Canadian infants: profiles by mode of delivery and infant diet at 4 months. *Can Medical Association Journal*, 2013; 185(5), 385-394.

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Age 3 to Old Age

- **Microbiome becomes stable**. Even with disruptions (medications, disease, dietary changes) – **usually returns to baseline.**
- **Large shifts** occur with onset of **puberty** (skin changes), **pregnancy** (vaginal microbiome), **menopause,** etc.
- **After age 65, *microbe populations and diversity decrease.***
- **Climate, geography, diet, hygiene, medication use, etc. all impact microbiome.**

Yatsunenko T, et al. Human gut microbiome viewed across age and geography. *Nature* 2012; 486:222-228.
The Human Microbiome Project Consortium (2012). Structure, function and diversity of the healthy human microbiome. *Nature* 2012; 86, 207-214.

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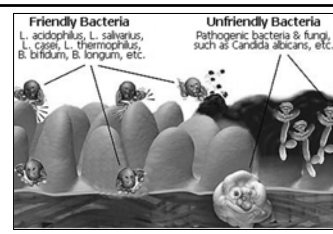
Microbiota……..



- **Train and modulate immune system (e.g., skin, gut)**
- **Convert skin oils** to compounds that keep **skin supple and lower pH**
- **Block adhesion and suppress growth of pathogenic bacteria**
- Provide nutrients for intestinal cells, maintaining **tight junctions**, **reducing permeability**.
- Make **ARA and DHA,** signal brain cells to divide (infants). **Gut and brain neurons communicate. Gut microbes make serotonin, melatonin, GABA, and others.**
- **Produce vitamins** and assist in building **amino acids.**
- Help maintain **blood pressure** (complex carbs → formate → impact salt processing)

Wilkins T, et al. Probiotics for Gastrointestinal Conditions: A Summary of the Evidence. *Am Fam Physician* 2017 Aug 1;96(3):170-178.

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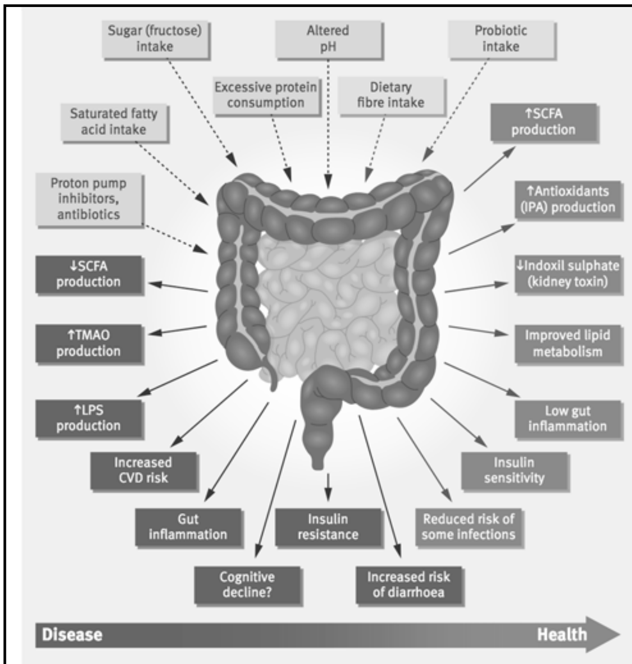

- **Many dietary, lifestyle and medications** can dramatically impact the microbiome and ultimately impact human health.

From: Valdes AM, et al. Role of gut microbiota in nutrition and health. *British Medical Journal* 2018;361:j2179

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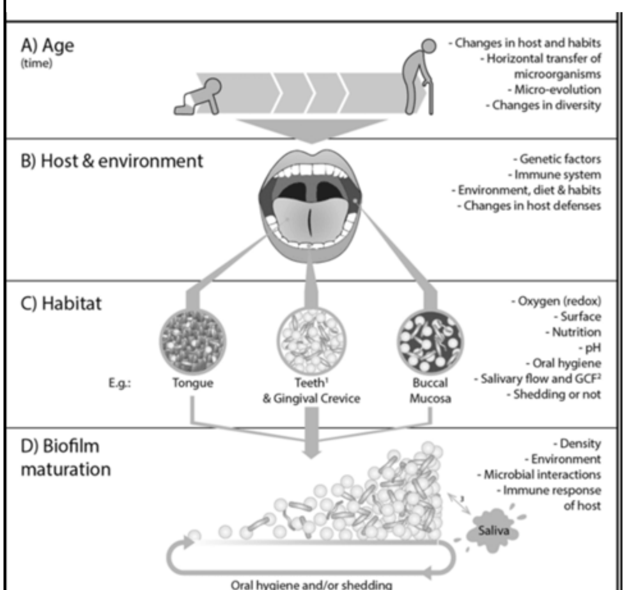

Oral Microbiome

- Extensively studied as part of the **Human Microbiome Project.**
- **700 microbial species**: bacteria, fungi, viruses, archaea and protozoa form complex ecological community. **Oral microbiota generally exist as biofilm.**
- ***Actinobacteria*, *Bacteroidetes*, *Firmicutes*, *Proteobacteria*** most significant for oral health.

Graphic from: Rosler BT, et al. *Journal of Dental Research* 2018; 97(4): 371-80

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Oral Microbiota Among Most Diverse

- Despite different etiologies, **periodontitis and caries** driven by feedforward loop between **microbiota and host** that favors **emergence and dysbiosis.**
- Disturbance in oral microbiota may impact **diabetes, CVD and certain cancers.**

Zhang Y, et al, Human oral microbiota and its modulation for oral health, *Biomedicie & Pharmacotherapy* 2018; 99:883-93

Lamont RJ, et al. The oral microbiota: dynamic communities and host interactions. *Nature Reviews Microbiology* 2018; 16: 745-59

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Table 1 Distribution of dominant microorganisms in oral cavity

From: The oral microbiota – a mechanistic role for systemic diseases

Section	Dominant microorganism
Hard palate	*Streptococcus, Uncl.Pasteurellaceae, Veillonella, Prevotella, Uncl.Lactobacillales*
Tongue dorsum	*Streptococcus, Veillonella, Prevotella, Uncl. Pasteurellaceae, Actinomyces*
Saliva	*Prevotella, Streptococcus, Veillonella, Uncl. Pasteurellaceae*
Palatine tonsils	*Streptococcus, Veillonella, Prevotella, Uncl. Pasteurellaceae, Fusobacterium*
Throat	*Streptococcus, Veillonella, Prevotella, Uncl. Pasteurellaceae, Actinomyces, Fusobacterium, Uncl. Lactobacillales*
Buccal mucosa	*Streptococcus, Uncl. Pasteurellaceae, Gemella*
Keratinised ginguva	*Streptococcus, Uncl. Pasteurellaceae*
Supragingvial plaque	*Streptococcus, Capnocytophaga, Corynebacterium, Uncl. Pasteurellaceae, Uncl. Neisseriaceae*
Subgingival plaque	*Streptococcus, Fusobacterium, Capnocytophaga, Prevotella, Corynebacterium*
Dentures	*Staphylococcus epidermidis, Streptococcus*
Lips	*Streptococcus, Candida albicans*

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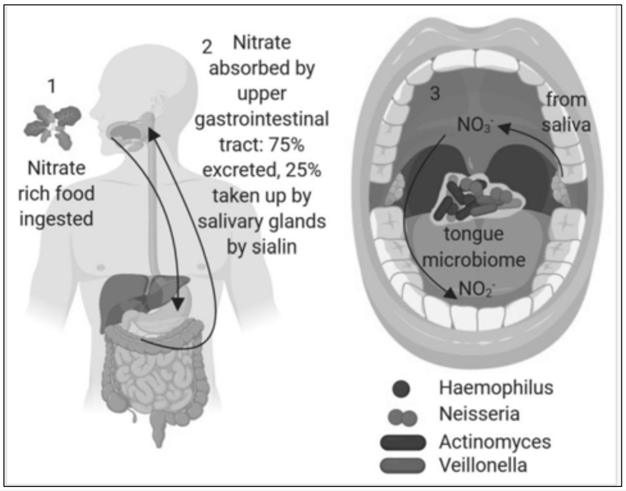
Oral Microbiota and Blood Pressure



- Upon interaction with **oral bacteria**, **nitrate is reduced to nitrite**, swallowed and **absorbed, raising plasma nitrite levels.**
- Endogenous nitrite reductases in circulation reduce **plasma nitrite further to bioactive NO**, which then acts as **vasodilator.**

Gee LC, et al. *Curr Hypertens Rep* 2016; 18: 17.

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Mouthwash, Tongue Cleaning and BP

- In healthy volunteers, **chlorhexidine increased systolic BP ~ 5 mm/Hg**, equivalent to manipulation of dietary salt intake
- Those who **cleaned tongue** twice daily, had **greatest increase in systolic BP after using chlorhexidine.**

Grant MM, et al. *J Clin Med* 2019; 8(8): 1110

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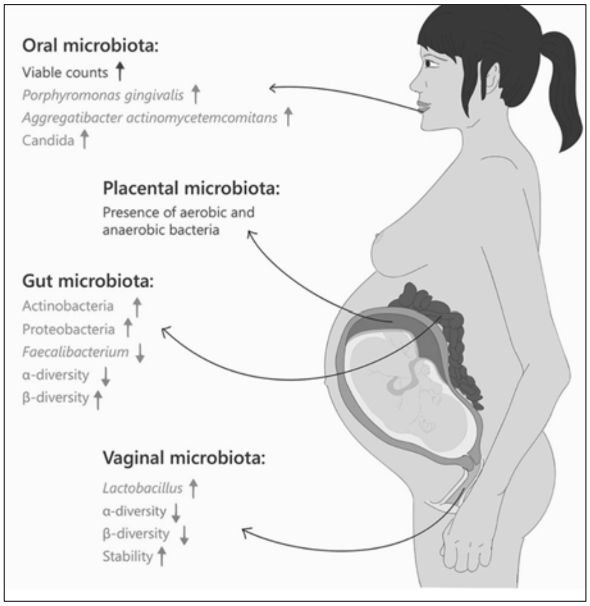

Pregnancy

- Early stages of pregnancy, total number of **microbes increase significantly**.
- *P. gingivalis*, *A. actinomycetemcomitans* in gingival sulcus **significantly higher** than that non-pregnant women.
- During late pregnancy, ***Candida* is more frequently detected.**

Fujiwara N, et al. *J Investig Clin Dent* 2015; 8: e12189–e12197.

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Periodontitis and Preterm Birth

- **Pre-term birth (PB)**: delivery taking place before 259 days gestation.
- PB accounts for **75-80% perinatal mortality** and for **most neurological and respiratory complications in neonates.**
- **Periodontitis** associated with **PB, low birth weight, pre-eclampsia**.
- ***P. gingivalis*** associated with **shorter gestations** and **C-section** delivery.
- **Periodontal treatment associated with fewer PB.**

Vanterpool SF, et al. *Porphyromonas gingivalis* within placental villous mesenchyme and umbilical cord stroma is associated with adverse pregnancy outcome. *PLoS One*. 2016;11(1):1–16; López NJ, et al. Effect of periodontal treatment on preterm birth rate: A systematic review of meta-analyses. *Periodontol 2000*; 2015;67(1):87–130.

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Microbes: Energy and Inflammation

- **Microbiota** can **increase energy** production from diet and participate in regulation of **fatty acid tissue composition.**
- **Increase in *Firmicutes*** in **relation to *Bacteroidetes,*** increases absorption **of calories from food**, increasing **weight and fat mass.**
- **Dysbiosis** with antibiotic use, especially **during first 3 years life.**
- ***Firmicutes*** significantly increase **plasma LPS**; activating **TLR4** and upregulating expression of **pro-inflammatory cytokines**

Duranti S, et al. Obesity and microbiota: an example of an intricate relationship. *Science* 2017; 12:18.
Fessler MB, et al. *Curr Opin Lipidol* 2009; DOI: 10.1097/MOL.0b013e32832fa5c4

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Child Weight Gain Trajectories Linked To Oral Microbiota Composition

- Gut and oral microbiota **of 226 two-year-olds analyzed with gene sequencing**.
- Weight/length measured 7 time points to identify children with **rapid weight gain** (strong risk factor for childhood obesity)
- Rapid weight gain associated with ***less*** diversity and **higher ratio of *Firmicutes* to *Bacteroidetes*** in oral microbiota.

Craig SJC, et al. *Sci Rep* 2018; 8(1): 14030

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Title of the study	Year	Subjects of the study	Final result(s) gathered	Reference
Childhood overweight after establishment of the gut microbiota: the role of delivery mode, pre-pregnancy weight and early administration of antibiotics.	2011	28354 mother-child	Antibiotics in infancy influences the risk of overweight in later childhood	Ajslev et al., 2011
Infant antibiotic exposures and early-life body mass.	2013	11532 children	Exposure to antibiotics during the first 6 months of life was associated with increases in body mass.	Trasande et al., 2013
Antibiotic treatment during infancy and increased body mass index in boys: an international cross-sectional study.	2014	74946 children	Exposure to antibiotics during the first 12 months of life is associated with a small increase in BMI in boys aged 5–8 years	Murphy et al., 2014
Infant antibiotic exposure and the development of childhood overweight and central adiposity	2014	1047 children	Antibiotic use in the first year of life was associated with overweight	Azad et al., 2014
Association of antibiotics in infancy with early childhood obesity.	2014	64580 children	Repeated exposure to broad-spectrum antibiotics was associated with early childhood obesity	Bailey et al., 2014
Prenatal exposure to antibiotics, cesarean section and risk of childhood obesity.	2015	436 mother-child dyads	Exposure to antibiotics in the second or third trimester of pregnancy were associated with higher risk of childhood obesity.	Mueller et al., 2015
Prenatal exposure to systemic antibacterials and overweight and obesity in Danish schoolchildren: a prevalence study.	2015	9886 children	Prenatal exposure to systemic antibacterials was associated with an increased risk of overweight and obesity at school age	Mor et al., 2015
Antibiotic exposure in infancy and risk of being overweight in the first 24 months of life.	2015	6114 boys and 5948 girls	Antibiotic exposure before 6 months was associated with increased body mass	Saari et al., 2015
Early Life Antibiotic Exposure and Weight Development in Children.	2016	979 children	Repeated exposure to antibiotics early in life, especially β-lactam agents, is associated with increased weight and height.	Mbakwa et al., 2016
Antibiotic Use and Childhood Body Mass Index Trajectory.	2016	142824 children	Body Mass Index increase	Schwartz et al., 2016
Administration of Antibiotics to Children Before Age 2 Years Increases Risk for Childhood Obesity.	2016	21714 children	Administration of 3 or more courses of antibiotics before age of 2 years was associated with an increased risk of early childhood obesity	Scott et al., 2016

Del Fiol FS, et al. Obesity: A new adverse effect of antibiotics? *Front Pharmacol* 2018; https://doi.org/10.3389/fphar.2018.01408

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Antibiotics and Obesity

American children on average:

- **By 2 years age: 3 full doses of antibiotics**
- **By 10 years age: 10 full doses of antibiotics**
- **By 20 years age: 17 full doses antibiotic**
- **Four or more courses** of antibiotics given before 3 years age independently **associated with obesity at age 5**. (OR: 1.6).

Cox LM. Antibiotics in early life and obesity. *Nat. Rev. Endocrinol 2015;* 11, 182–190.

Kelly D, et al. Antibiotic use in early childhood and risk of obesity: longitudinal analysis of a national cohort. World J Pediatrics 2019;15(4):390-397.

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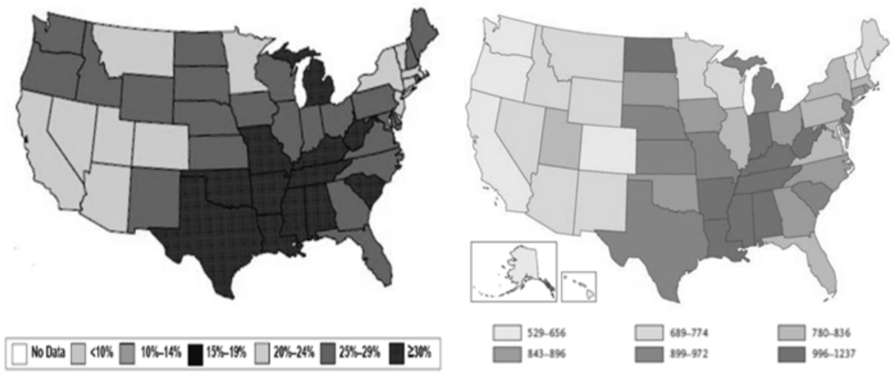
Comparisons between the geography of obesity and antibiotic use, 2010



Antibiotic prescriptions per 1000 persons, 2010

L Segal & MJ Blaser, *Ann Am Thor Soc* 2014

Observational data

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Antibiotics and Microbes

- **Disrupt existing microbiota**; linked to **antibiotic-associated diarrhea**, **pseudomembranous colitis**, and increased **susceptibility** to another infection.
- Extent of change depends on **antibiotic type, duration and dose.**
- **Azithromycin, amoxicillin, clindamycin, and ciprofloxacin** decrease oral microbiota diversity.

Abeles SR, et al. Microbial diversity in individuals and their household contacts following typical antibiotic courses. *Microbiome* 2016; 4: 39–51.

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Antibiotic Prophylaxis

- UIC study: **80% of antibiotics** prescribed by **dentists for prophylaxis unnecessary.**
- **Amoxicillin 69% of scripts**
- **Clindamycin** next most prescribed **(dentists are highest frequency prescribers)** – strongly associated with *C. difficile*.

Suda KJ, et al. *JAMA Network Open* 2019;2(5):e193909.

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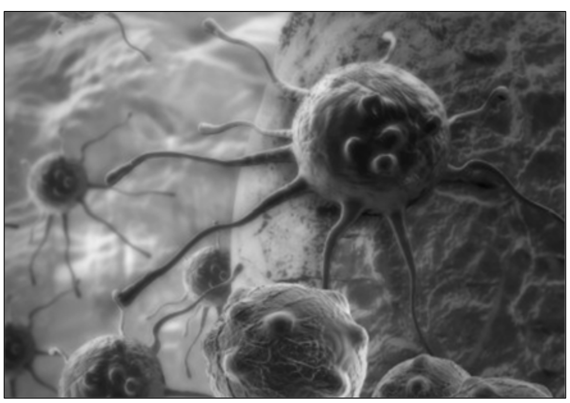
Esophageal Cancer



- **Sixth leading** cause cancer **death**
- ***P. gingivalis*** detected in **61% of cancerous tissues**, 12% adjacent tissues, and **0% of normal esophageal mucosa.**
- **Eradication of common oral pathogen** *might* help **reduce the burden of esophageal cancer**

Gao, S, et al. *Infect Agent Cancer* 2016; **11**: 3–12.

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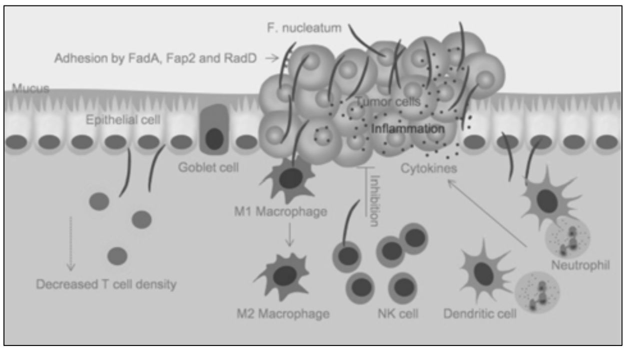
Colorectal Cancer



- ***Fusobacteria*** cause excessive immune responses/**turn on cancer growth genes**. **Linked with colorectal cancer.**
- Have **specific surface molecules that allow them to invade cells.**
- *F. nucleatum* associated with **periodontitis,** abundant in oral cavity, thought to **originate there**.

Nosho K, et al. Association of *Fusobacterium nucleatum* with immunity and molecular alterations in colorectal cancer. *World J Gastroenterol* 2016; 22: 557–566

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Pancreatic Cancer and Gum Disease

- **10-year study:** bacterial contents in mouthwash samples from **361 Americans who later developed pancreatic CA + 371 matched controls** were analyzed.
- *P. gingivalis and Aggregatibacter actinomycetemcomitans* associated with **> 50% increased risk of pancreatic cancer.**
- Screening tool? Prevention?

Fan X, et al. *Gut* 2018; 67(1): 120-7   Graphic from Getty Images

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Oral Inflammation = Systemic Inflammation

- **Severe periodontitis 6th most prevalent disease** worldwide with an overall **prevalence 11.2% and ~ 743 million people affected**.
- **Oral pathogenic bacteria** including *F. nucleatum, P. gingivalis*, and *A. actinomycetemcomitans* have been detected in a multitude of **extra-oral tissue sites, including the lung, heart, gut, placenta, and inflamed joints.**
- **Oral *Treponema*** spirochetes found in brains of those with **Alzheimer's** dementia and in **branches of the trigeminal nerves.**

From: Konkel JE, et al. Distal Consequences of Oral Inflammation *Front. Immunol* 2019; https://doi.org/10.3389/fimmu.2019.01403

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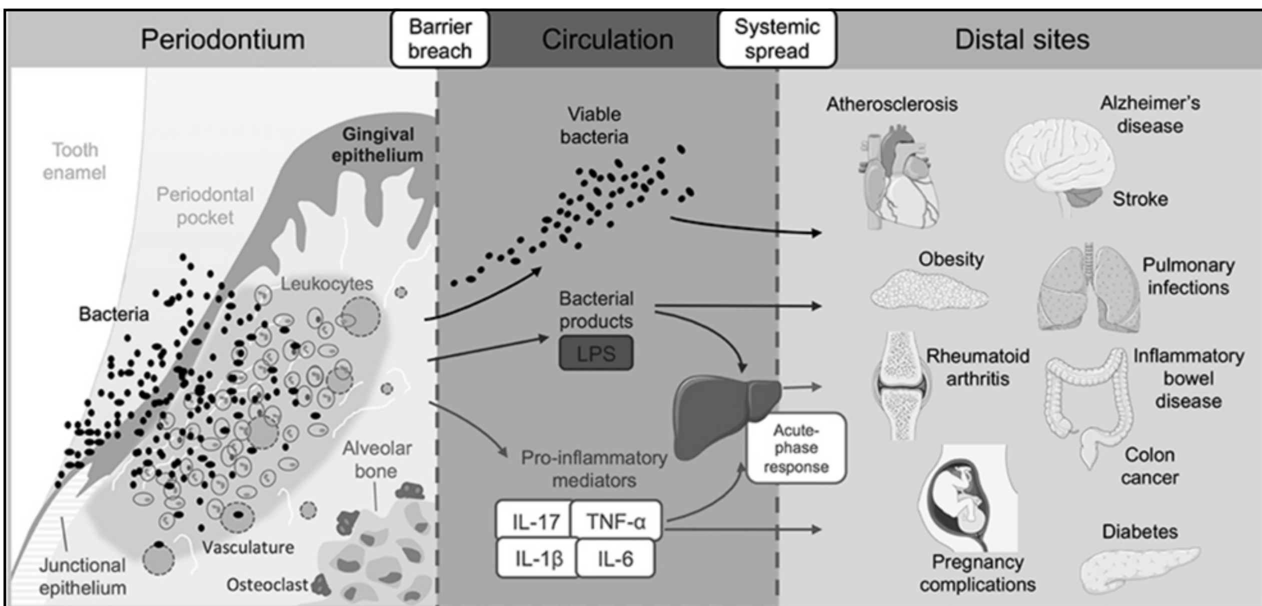

From: Konkel JE, et al. Distal Consequences of Oral Inflammation *Front. Immunol* 2019; https://doi.org/10.3389/fimmu.2019.01403

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LPS and Neuroinflammation

- **LPS enter circulation due to decreased barrier function**
- Highly immunogenic, **bind TLR-4,** trigger **systemic inflammation** and **degrade BOTH intestinal and blood brain barriers.**
- **TLR-4** expressed on microglia and neurons: **once activated, produce pro-inflammatory cytokines (TNF-α, IL-1β, NO).**
- LPS induces **cognitive impairment, anxiety, depression in animal models.**
- ***Systemic* inflammation/infection** can **change microglial phenotype** and **disrupt BBB integrity** in absence of precipitating neuronal damage/infection

Zhao J, et al. *Sci Rep* 2019; 9:5790 doi:10.1038/s41598-019-42286-8

Kure C, et al. *Front Pharmacol* 2017; doi.org/10.3389/fphar.2017.00117

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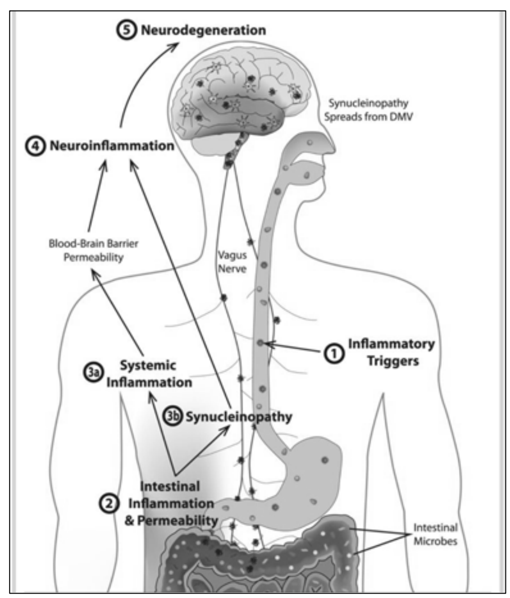
Brain-Gut Axis

- Human studies/animal models of **depression show increased inflammatory mediators in both periphery and CNS.**
- ***Healthy oral and gut microbiota plus adequate dietary fiber*** help prevent disruption of intestinal lining and blood-brain barrier.

Carlessi AS, et al. *Eur J Neurosci 2019*; doi: 10.1111/ejn.14631.



Houser MC, et al. *Parkinson's Disease* 2017; doi:10.1038/s41531-016-0002-0

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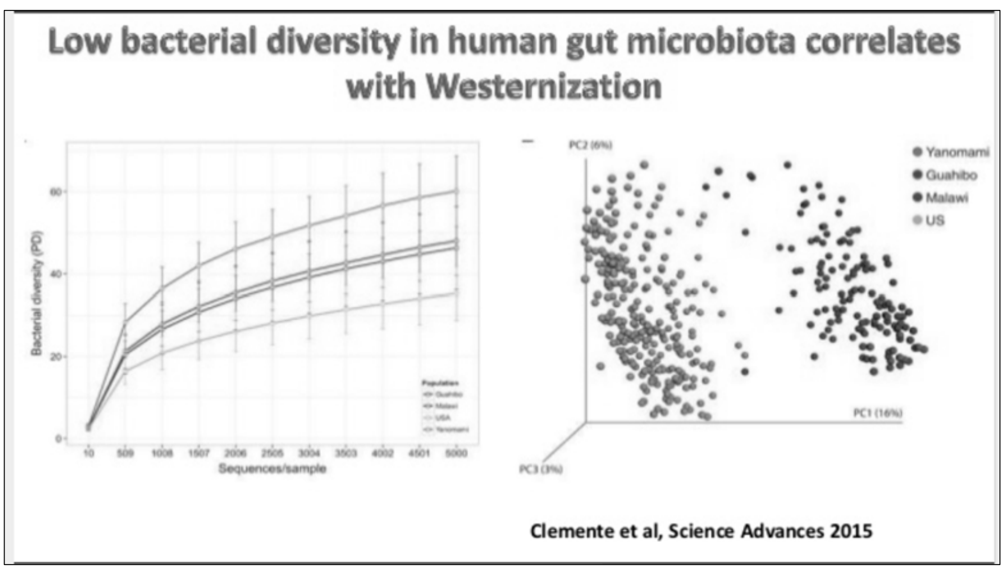

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It's the Fiber Folks!

- Diets **high in fiber, low in sugar increase *Bifidobacteria,* decreasing intestinal permeability.**
- Prebiotics: **un-digestible plant fiber** acts as food for microbiota.
- **Bananas, onions, garlic, leeks, Jerusalem artichoke, apple skin, chicory root, dandelion greens, beans, wheat flour all** prebiotics.

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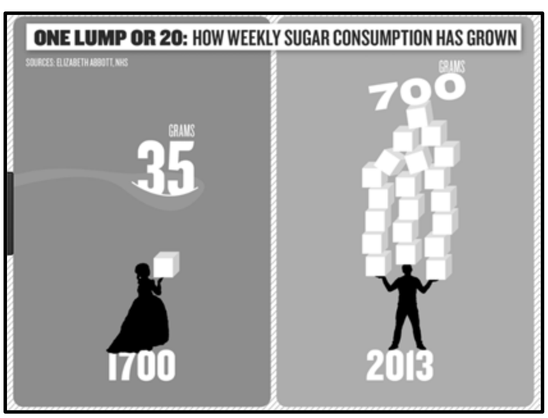
Too Little Fiber, Too Much Sugar



Canadians average daily sugar intake:

- **101 grams (24 tsp) children 1-8 years**
- **115 grams (27 tsp) children 9-18 years**
- **85 grams (20 tsp) for adults - lower due to increase intake "diet" sodas.**

Langlois K, et al. Change in total sugars consumption among Canadian children and adults. *Health Rep* 2019 Jan 16;30(1):10-19.

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Obesity and Microbiota?

- **Early disruption** of gut microbiota = **too few *Bifidobacteria,*** can lead to **obesity.**
- **Diet high in sugar, simple carbs, and saturated fat** encourages microbes better at ***extracting*** energy from food, **signaling body to store energy as fat.**
- Bacteria transplanted from overweight mice to thin mice make the thin mice gain weight.

Federico A, et al. Gut microbiota, obesity and metabolic disorders. *Minerva Gastroenterol Dietol* 2017;63(4):337-344.

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Sugar Substitutes

- Sugar substitutes frequently ***1000 times sweeter*** than sucrose.
- Despite GRAS status by regulatory agencies, sugar substitutes **can have negative effects** on gut microbiota.
- **Sucralose, saccharin and stevia all shown to disrupt** balance and **diversity** of gut microbiota.

Nettleton JE, et al. Reshaping the gut microbiota: Impact of low calorie sweeteners and the link to insulin resistance? *Physiol Behav* 2016;164(Pt B):488-93.

Ruiz-Ojeda FJ, et al. Effects of Sweeteners on the Gut Microbiota: A Review of Experimental Studies and Clinical Trials, *Adv Nutr* 2019; 10(1): S31-48

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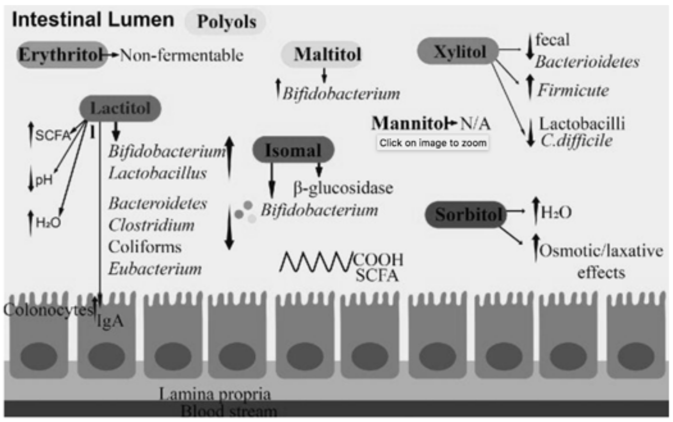
The Polyols (Sugar Alcohols)



- **Erythritol, mannitol and sorbitol** have **no effect** on gut microbiota.
- **Isomaltose and maltitol,** increase *bifidobacteria* and may have **prebiotic actions.**

Ruiz-Ojeda F, et al. Effects of sweeteners on the gut microbiota: a review of experimental studies and clinical trials. *Adv Nutr* 2019; 10(S1): PMC6363527

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https://irishhealthstores.com/news-events/fermented-foods/

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Table 1 | Examples of foods, nutrients, and dietary patterns that influence human health linked to their effe

Dietary element	Effect on gut microbiome	Effect on health outcomes mediated by gut microbiome
Low FODMAP diet	Low FODMAP diet increased Actinobacteria; high FODMAP diet decreased abundance of bacteria involved in gas consumption[58]	Reduced symptoms of irritable bowel syndrome[56]
Cheese	Increased *Bifidobacteria*,[97 98] which are known for their positive health benefits to their host through their metabolic activities.[99] Decrease in *Bacteroides* and *Clostridia*, some strains of which are associated with intestinal infections[98]	Potential protection against pathogens.[100] Increased production of SCFA and reduced production of TMAO[99]
Fibre and prebiotics	Increased microbiota diversity and SCFA production[22 101 102]	Reduced type 2 diabetes[22] and cardiovascular disease[103]
Artificial sweeteners	Overgrowth of Proteobacteria and *Escherichia coli*.[104] *Bacteroides*, *Clostridia*, and total aerobic bacteria were significantly lower, and faecal pH was significantly higher[47]	Induced glucose intolerance[105]
Polyphenols (eg, from tea, coffee, berries, and vegetables such as artichokes, olives, and asparagus)	Increased intestinal barrier protectors (*Bifidobacteria* and *Lactobacillus*), butyrate producing bacteria (*Faecalibacterium prausnitzii* and *Roseburia*) and *Bacteroides vulgatus* and *Akkermansia muciniphila*.[107] Decreased lipopolysaccharide producers (*E coli* and *Enterobacter cloacae*)[106]	Gut micro-organisms alter polyphenol bioavailability resulting in reduction of metabolic syndrome markers and cardiovascular risk markers[108]
Vegan	Very modest differences in composition and diversity in humans and strong differences in metabolomic profile compared with omnivore diet in humans[50]	Some studies show benefit of vegetarian over omnivore diet,[109] others fail to find a difference[110]

Valdes AM, et al. Role of gut microbiota in nutrition and health. *British Medical Journal* 2018;361:j2179

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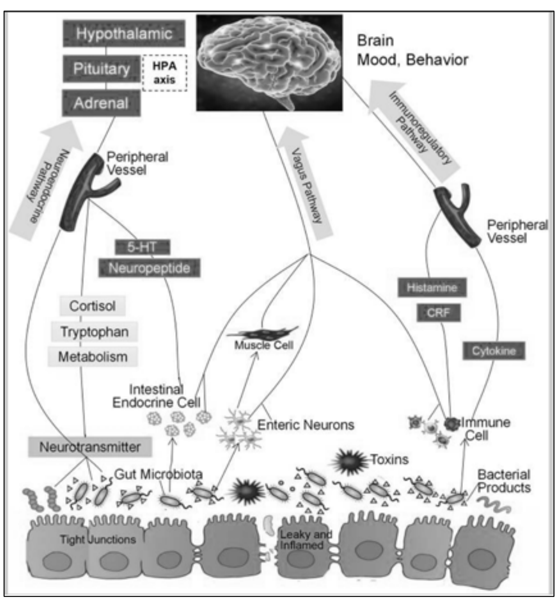

Sleep and Stress

- Disruption of **circadian rhythm** alters gut microbiome equilibrium. ***Microbes and humans share circadian clock.***
- Emotional and physiological **stress affect gut** microorganisms; impacting immune and nervous systems.
- ***Lactobacillus, Bifidobacterium*, and *Enterococcus* supplementation *may* improve stress response**.

Farre N, et al. Sleep and circadian alterations and the gut microbiome: associations or causality. *Current Sleep Med Reports* 2018; 4(1):50-57

Li, Y, et al. The role of microbiome in insomnia, circadian disturbance and depression. *Front Psychiatr* 2018; doi: 10.3389/fpsyt.2018.00669

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Early exposure to microbes has important health effects, leading many researchers to examine the "hygiene hypothesis"

Megan Scudellari PNAS 2017;114:7:1433-1436

PNAS

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Allergies and Asthma: Hygiene Hypothesis

Charles Schultz, Peanuts. (Pig-Pen)

- **Allergies are rare** in developing countries **but rates of asthma and seasonal allergies tripled in high income nations since 1980s.**
- *Our genes haven't changed.*
- Early exposure to **environmental microbes** train immune system.
- Hand sanitizers, antibacterial soaps, air filters**, "clean living"** may **negatively impact this training.**

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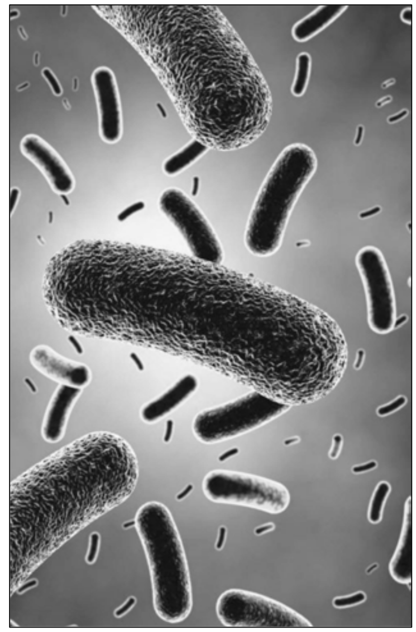
- Randomized placebo-controlled trial of ***L. rhamnosus*** **HN001** given from **35 weeks gestation to 6 months postpartum** to women who were breastfeeding and **2 years for all infants.**
- At **2 years and 11 years**: **54% reduction in eczema**, **27% reduction hay fever, and 29% reduction in atopic sensitization to food and aeroallergens.**

Wickens K, et al. *Pediatr Allergy Immunol* 2018; 29(8): 808-14



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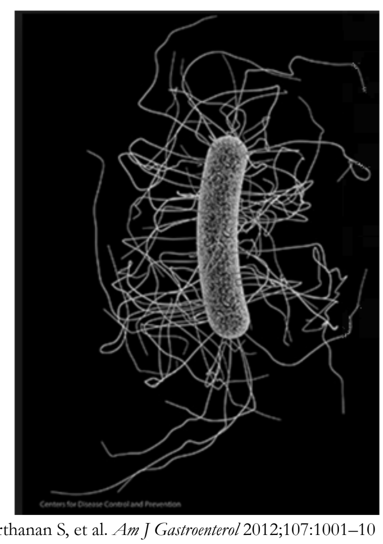
Medications: Proton Pump Inhibitors

- Millions take PPIs for heartburn when not indicated or for too long. ***PPIs dramatically disrupt gut microbiota.***
- Meta-analysis 23 studies (n=300,000): ***65% increase risk C. difficile associated diarrhea amongst those taking PPI.***
- PPI users have ***5 times the risk*** **of developing GI infections** compared to non-users.



Janarthanan S, et al. *Am J Gastroenterol* 2012;107:1001–10
Hafiz RA, et al. *Ann Pharmacother.* 2018 Jul;52(7):613-622.
https://choosingwiselycanada.org/heartburn-gerd-ppi/

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Role for Probiotics

- 2017 Cochrane systematic review/meta-analysis **31 RCTs: moderate certainty evidence that probiotics are effective for preventing *C. difficile* associated diarrhea in both adults and children.**
- ***Why are they not recommended?***

Goldenberg JZ, et al. *Cochrane Database Syst Rev.* 2017 Dec 19;12:CD006095.

L. Casei image: Power and Syred/Science Photo Library

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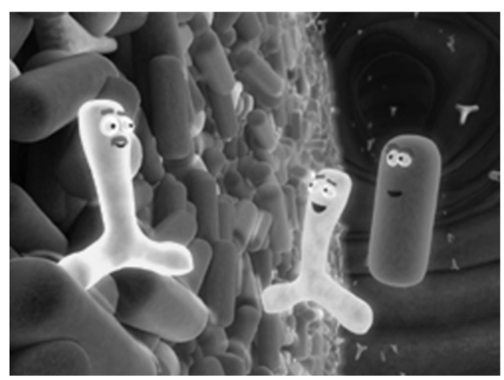
Acute Infectious Diarrhea

- **Strong evidence** for probiotics in **acute infectious diarrhea**, which is common for those **traveling,** kids going to **daycare,** etc.
- Meta-analysis **17 RCTs** (2,102 children): significant **reduction in duration** of diarrhea with probiotic use (20 fewer hours).
- Meta-analysis **8 RCTs** (1,229 children): *L. reuteri* reduced duration of diarrhea (25 fewer hours), increased cure rate days 1 and 2.



Urbańska M, et al. Systematic review with meta-analysis: *Lactobacillus reuteri* DSM 17938 for diarrhoeal diseases in children. *Aliment Pharmacol Ther.* 2016;43(10):1025–1034.
Feizizadeh S, et al. Efficacy and safety of *Saccharomyces boulardii* for acute diarrhea. *Pediatrics.* 2014;134(1):e176–e191.

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Summary of Systematic Review Analyzing the Role of Probiotics on Clinical Outcomes

Outcome	Reference	No of studies/ participants	Evidence of benefit?
Clostridium difficile associated diarrhoea in adults and children	Goldenberg et al (2017)[111]	39/9955	Yes
Necrotising enterocolitis	Al Faleh et al (2014)[112] Rees et al (2017)[113]	17/5338	Yes
Antibiotic associated diarrhoea in children	Goldenberg et al (2015)[114]	26/3898	Yes
Probiotics for preventing acute upper respiratory tract infections	Hao et al (2015)[115]	12/3720	Yes
Urinary tract infections	Schwenger et al (2015)[116]	9/735	No
Prevention of asthma and wheeze in infants	Azad et al (2013)[117]	6/1364	No
Prevention of eczema in infants and children	Mansfield et al (2014)	16/2797	Yes
Prevention of invasive fungal infections in preterm neonates	Agrawal et al (2015)[119]	19/4912	Unclear
Prevention of nosocomial infections	Manzanares et al (2015)[120]	30/2972	Yes
Treatment of rotavirus diarrhoea in infants and children	Ahmadi et al (2015)[121]	14/1149	Yes
Prevention and treatment of Crohn's disease and ulcerative colitis	Saez Lara et al (2015)[122]	14/821 ulcerative colitis 8/374 Crohn's disease	Yes
Pulmonary exacerbations in children with cystic fibrosis	Ananathan et al (2016)[123]	9/275	Yes
Type 2 diabetes (fasting glucose, glycated haemoglobin test)	Akbari et al (2016)[124]	13/805	Yes
Type 2 diabetes (insulin resistance, insulin levels)	Zhang et al (2016)[125]	7/425	Yes
Necrotising enterocolitis in pre-term neonates with focus on *Lactobacillus reuteri*	Athalye-Jape et al (2016)[126]	6/1778	Yes
Reduction of serum concentration of C reactive protein	Mazidi et al (2017)[127]	19/935	Yes
Cardiovascular risk factors in patients with type 2 diabetes	Hendijani et al (2017)[128]	11/641	Yes
Reduction of total cholesterol and low density lipoprotein cholesterol	Wu et al (2017)[129]	15/976	Yes
Depressive symptoms	Wallace and Milev (2017)[79,130]	6/1080	Yes
Vulvovaginal candidiasis in non-pregnant women	Xie et al (2018)[131]	10/1656	Yes

From: Valdes AM, et al. Role of gut microbiota in nutrition and health. *BMJ* 2018;361:j2179

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Clinical Resource Tool: www.usprobioticguide.com

AEProbio

Clinical Guide to Probiotic Products Available in USA

Indications, Dosage Forms and Clinical Evidence to Date - 2019 Edition

Introduction Adult Health Womens Health Pediatric Health Functional Foods References About

INDICATIONS FOR PEDIATRIC HEALTH

Show 10 entries

Brand Name	Probiotic Strain	Dosage Form	CFU/Dose	No of Doses/Day	Indications (Level of Evidence)
Bio-Kult® Infantis	L. casei PXN® 37™ L. rhamnosus PXN® 54™ Streptococcus thermophilus PXN® 66™ L. acidophilus PXN® 35™ B. breve PXN® 25™ L. delbrueckii ssp. bulgaricus PXN® 39™ B. infantis PXN® 27™	Sachet	1B/sachet	½ -1 sachet	CE/AD - Childhood eczema/ Atopic dermatitis (III) Colic - Colic (II) HP - Helicobacter pylori - Adjunct to standard eradication therapy (III)
BioGaia® ProTectis® Baby Drops with Vitamin D	L. reuteri DSM 17938	Drops	100M/5drops	5 drops	AAD - Antibiotic associated diarrhea - Prevention (I) C - Constipation (I) CE/AD - Childhood eczema/ Atopic dermatitis (III) CID - Common infectious disease - community acquired (I) Colic - Colic (I) IBS/FAP - Irritable bowel syndrome/Functional abdominal pain (I) ID - Infectious diarrhea (I) Regurg/ GI Mot - Reduces regurgitation/ Improves gastrointestinal motility (I)
BioGaia® ProTectis®	L. reuteri DSM 17938	Chew. tabs Drops	100M/tab 100M/5drops	1 tab 5 drops	AAD - Antibiotic associated diarrhea - Prevention (I) C - Constipation (I) CE/AD - Childhood eczema/ Atopic dermatitis (III) CID - Common infectious disease - community acquired (I) Colic - Colic (I) IBS/FAP - Irritable bowel syndrome/Functional abdominal pain (I) ID - Infectious diarrhea (I) Regurg/ GI Mot - Reduces regurgitation/ Improves gastrointestinal motility (I)
Gerber® Good Start® Soothe Powder Infant Formula	L. reuteri DSM 17938	Powder	1M/gram	Routine feeding if alternative to breast milk is required	AAD - Antibiotic associated diarrhea - Prevention (I) Colic - Colic (I) ID - Infectious diarrhea (I) Regurg/ GI Mot - Reduces regurgitation/ Improves gastrointestinal motility (I)
Gerber® Soothe Probiotic Colic Drops	L. reuteri DSM 17938	Drops	100M/5 drops	5 drops	AAD - Antibiotic associated diarrhea - Prevention (I) C - Constipation (I) CE/AD - Childhood eczema/ Atopic dermatitis (III) CID - Common infectious disease - community acquired (I) Colic - Colic (I) IBS/FAP - Irritable bowel syndrome/Functional abdominal pain (I) ID - Infectious diarrhea (I) Regurg/ GI Mot - Reduces regurgitation/ Improves gastrointestinal motility (I)

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Click next to brand name to see evidence……

Colic - Colic	I	82. Savino, F., E. Pelle, E. Palumeri, R. Oggero, and R. Miniero. "Lactobacillus reuteri (American Type Culture Collection Strain 55730) versus simethicone in the treatment of infantile colic: a prospective randomized study." Pediatrics 119.1 (2007): e124-e130. 85. Chau, K., E. Lau, S. Greenberg, S. Jacobson, P. Yazdani-Brojeni, N. Verma, and G. Koren. "Probiotics for infantile colic: a randomized, double-blind, placebo-controlled trial investigating Lactobacillus reuteri DSM 17938." The Journal of pediatrics 166.1 (2015): 74-78. 84. Sung, V., H. Hiscock, M.L.K. Tang, F.K. Mensah, M.L. Nation, C. Satzke, R.G. Heine, A. Stock, R.G. Barr, and M. Wake. "Treating infant colic with the probiotic Lactobacillus reuteri: double blind, placebo controlled randomised trial." BMJ 348 (2014): g2107. 83. Savino, F., L. Cordisco, V. Tarasco, E. Palumeri, R. Calabrese, R. Oggero, S. Roos, and D. Matteuzzi. "Lactobacillus reuteri DSM 17938 in infantile colic: a randomized, double-blind, placebo-controlled trial." Pediatrics 126.3 (2010): e526-e533.

Evidence is ranked using grading system of I, II, III. You can then see the references for your review.

http://www.usprobioticguide.com/PBCPediatricHealth.html?utm_source=pediatric_ind&utm_medium=civ&utm_campaign=USA_CHART Accessed January 17, 2019

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- **IT IS ALL CONNECTED….**
- Eat a diet rich in **whole plant foods, prebiotics, and fiber.**
- **Limit sugar intake and use of sugar substitutes.**
- Include **fermented foods/drinks.**
- Consider probiotics – be **species and strain specific.**
- Find healthy ways to manage your **stress and get adequate sleep**.
- Good **dental hygiene and regular dental visits.**

"When we try to pick out anything by itself, we find it hitched to everything else in the universe."
John Muir

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