

Review

Antibacterial Soaps and Other Cleaners May Actually Be Aiding in the Development of Super Bacteria

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ABSTRACT

The widespread use of antibiotics in the past 80-years has saved millions of lives, facilitated technological advances and killed unprecedented numbers of bacteria, pathogens, and pigs. Human-related bacteria perform a series of essential functions, and now we are beginning to understand how antibiotics have reshaped the ecology and the functional implications of these changes. Findings show that antibiotics affect the function of the immune system, our ability to resist pollution, and our ability to process food. Therefore, it is now more important than ever to examine how we use antibiotics. This article summarizes the current study on the short-term and long-term effects of antibiotic use on the human microbiota, from early life to adulthood, and its impact on diseases such as malnutrition, obesity, diabetes, and Clostridium difficile infection. Driven by the results of incorrect use of antibiotics, we are investigating the latest advances in the development of anti-virulent approaches to infection resistance while minimizing treatment resistance. We conclude the article by discussing probiotics and transplants in microbiota feces, which promise to return the microbiota after the damage of the microbial. Together, the results of studies in this area emphasize the importance of developing a mechanistic understanding of intestinal ecology to enable the development of new therapeutic strategies and to limit the rational use of antibiotics.

Keywords: Antibiotics Resistance; Bacteria Overuse; New Antimicrobial Agents.

FOREWORD

Over the past decade, our knowledge of the role of gut microbial in health and disease has increased dramatically, accompanied by an invisible hype surrounding its diagnostic and therapeutic potential. However, one area of application of the microbiome has so far remained distinct: its role as treatment instruction. Microbial research and improvements in high-output sequencing technologies revolutionized our current scientific point of view. The associated human microbiology is a prominent focus of clinical research. Extensive studies are often needed to study the composition of human microbial and the changes that have occurred in many human diseases.

The average longevity of a US citizen born in 1940 was expected to live to age 63. A baby born today should reach 78, partly because of antibiotics, but the assumption that safe antibiotics generally fostered overuse and led to increased bacterial resistance to treatment. Other, no less dangerous, of our love for antibiotics have received more attention. An antibiotic kills the bacteria we want as well as those we do not. Interior evidence from the laboratory and other deceptions, sometimes, our thick vegetation never recovers. This long-term changes in beneficial bacteria In people's bodies may even increase our susceptibility to infections and stress Overuse of antibiotics may fuel the dramatic increase in conditions such as obesity, diabetes, inflammatory bowel disease, allergies, and asthma, which have doubled more than many populations.

Diabetes type 2 and Obesity are considered by many to be behavioral diseases; "The patient eats too much" - eat less..... The more modern perception links this with our symbiotic partner in life: the microbiome. Alternation of the population of microbes that lives within us throughout our entire life. It is not clear how these changes occur and more importantly, how to harness the billions of organisms to avoid these terrifying series and save the agony that comes with them. The overuse of Antibiotic medicines can become a harming cause that facilitates the changes in the constitution of the microbiome.

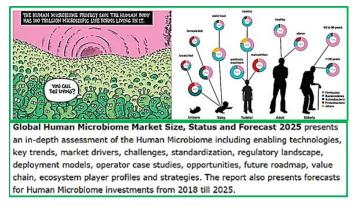
Global Human Microbiome Market: Venture Capitalists See Promise in Microbiome-based Technologies. Only to Increase Investments.¹ The following are general targets for microbiome R&D: Gastrointestinal Disorders, Metabolic Disorders, Women's Health, and Skin Disorders. Leading technologies applied are in the area of genome sequencing: 16s rRNA Sequencing and Metagenomics Sequencing.²

Over the past 15 years,³ The invisible microbial world is aided



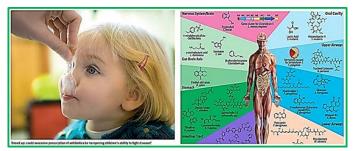
by the center of the stage thanks to DNA sequencing methods that allow researchers to identify bacteria and other organisms that cannot be cultured in culture, first of all, found large and diverse communities within our intestines, our skin, Later, studies involving mice without germs and other studies have revealed links between these bacteria, so-called microbiota, and health - with bacteria that play critical roles in immunity, obesity, and development, so much happened that both 2011 and 2013 Science called microbiome as one of its breakthroughs of the year in 2012 and 2016. Today, the meter the goal is to cover the progress that exposes the details of the ways in which the microbiota influences the physiology of the host, both healthy and ill, and how microbial, organically or molecularly, can be treated to improve host health. In addition, recognize that viruses have an impact, and understand how specific bacteria and their products contribute to healthy and sick countries.

Figure I. Health problems that are related to the microbiome of the humans, Are not curable with antimicrobial drugs



The microbiome⁴ is specialized to a specific gut habitat; species within the genus Helicobacter are remarkably specific for particular hosts.⁵ For example, H. pylori are associated with humans,⁶ and H. hepaticus is associated with mice. Gastric Helicobacter species are autochthonous: They have been (until the antibiotic age) nearly universally prevalent and usually not pathogenic to their natural host. Another example of a highly host-adapted gut microbe is Lactobacillus reuteri.⁷ Many "*small molecules*" and peptides are associated with the microbiome.⁸

Figure 2. Antimicrobial drugs that are overused



The microbiome, our symbiotic partner for life, seems to influence our physical situation in a healthy manner. Since the emergence of simple automatic gene sequencing technologies, the application of those for therapeutic targets are emerging rapidly. Those many illnesses like Rheumatism, Obesity, Diabetes, Neurodegeneration and mental disorders are targeted as subjects for this effort.

It seems that the microbiome constitution is altered by the application of therapeutic agents, mainly antibiotics that are so common in today's therapy. However beneficial, some of these agents are damaging. The future effort in antibacterial research shout considers microbiome sensitivity as well.

THE GUT MICROBIOTA: A STRUCTURAL OVER-VIEW

The microbial and viral communities found in human fecal samples are relatively stable over time and remarkably resistant to blooms of subpopulations, dietary changes, and antibiotics in moderate doses. These findings indicate that the microbial communities present in the large intestine (LI). Are to a significant degree dominated by an inhabitant of a place (autochthonous) microbes.

Human microbiota consists of 100 trillion bacteria belonging to several hundred different species. These fall into four main groups covering more than 90% of the bacterial population, namely pyramids, bacterias, actinobacteria, and proteobacteria, and include many other minor cornerstones such as Verrucomicrobia and Fusobacteria.[9] The representation of these groups varies throughout the gastrointestinal tract (GI)¹⁰ that is affected by certain microorganisms and nutrient feedings. The lawsuit is based on bony, aerobic, and verbal bacteria. Prominent members are Clostridia strains, whose activity ranges from beneficial shields (eg, C. scindens, IV-XIVA clusters) to pathogenic (eg, C. difficile, C. perfrigens). Streptococcus pathogens, enterococci, and staphylococci are also firms. Bacteroidetes are Gram-negative bacteria that are well adapted to the intestinal environment. Here they ferment carbs that are indigestible, producing SCFA, molecules that have been involved in a multitude of essential processes. Actinobacteria are grampositive and are generally considered beneficial, such as the Bifidobacterium genus, and which are included in many probiotic preparations. Proteobacteria Shelter contains Gram-negative bacteria, especially the family of Enterobacteriaceae, including E. coli and K. pneumoniae. These are not abundant under normal conditions but tend to expand on dysbiosis.¹¹ Most studies of microbiota have been performed in mice, although the microbiota of the individual and the mouse are different in the genotype. Some types of genes such as Prevotella, Pakli Bacteria, and Ruminococcus are abundant in humans, while others, namely lactobacillus, Aristippus and Turicibacter (is a genus in the Firmicutes phylum of bacteria that has most commonly found in the guts of animals), are widespread in mice.¹² However, it is possible to identify the core of a common task, and mice and human metagenomes look remarkably similar if analyzed from a functional point of view [ie, the representation of the encyclopedia of genes and the genome of Kyoto, describing the overall metabolic potential of a community.¹³ More importantly, the Growth Factor (GF)¹⁴ can be effectively restored with bacterial communities isolated from other species, including humans, salary effects that were observed in turn in the recipient's host. Reconstruction of GF mice with stool samples of oils or subjects is malnourished enough to phenocopy patient defects in energy harvesting or growth,¹⁵ demonstrating that despite interstellar differences, (the work with mouse models is a valuable tool to study the human microbiota).

Antibacterial agents are very effective in killing bacteria. However, there is considerably disputable surrounding their health benefits. Materials that do not produce residues (Table of Antibacterial) are used for a long time and continue to be active agents for controlling disease organisms in a wide range of local health services. When used under strict guidelines of application, residues in manufacturing agents have proven effective in controlling bacterial and fungal infections and clinical settings such as hospitals, nursing homes, nurseries and other health institutions where there may be a high risk of infection.

The microbial and viral communities found in human feces are relatively stable over time¹⁶ and are remarkably resistant to the growth of subpopulations, dietary changes,¹⁷ and antibiotics in moderate doses.¹⁸ These findings indicate that the microbial communities are located in the Large Intestine (LI). They are controlled mainly by the locus of the resident (autochthonous) bacteria.

Tuberculosis, food poisoning, cholera, pneumonia, sore throat, and meningitis: These are just a few of the diseases that are caused by bacteria. Maintaining hygiene both at home and in a clean body - is the best way to curb the spread of bacterial infections, but recently, consumers are getting the message that washing with regular soap is not enough. Antibacterial products have never been so popular. Soaps, household detergents, sponges, mattresses and lip-gloss, are now organizing components of bacteria, and scientists are asking themselves where, if any, the daily chemicals of healthy people.

The duration of antibiotic treatment in patients with sepsis, for example, may lead to overuse of antibiotics, which increases the risk of bacterial development. Proctonin (PCT) -based antibiotic use reduces exposure to antibiotics in community-acquired pneumonia. If it can also reduce, the exposure to antibiotics in severe oxygen is not known.

When a bacterial population is placed under pressure - such as an antibacterial chemical - a small sub-population armed with special defenses can develop. These dynasties survive and replicate as their weaker relatives. "What doesn't kill you makes you stronger" is the conventional rule here, as antibacterial chemicals opt for bacteria that tolerate their presence.

This article refers to current studies on the short-term and long-term effects of the use of antibiotics on human microbiomes, from early life to adulthood, and its impact on diseases such as malnutrition, obesity, diabetes, and clostridium inflammation.¹⁹

The production of healthy agricultural products may also suffer from the disadvantages of microbiome alterations. Antimicrobial agents are widely used in animal farms to prevent and treat disease in animals and promote growth. Antimicrobial agents may alter the bacterial community and improve animal fecal resistance.

Doctors usually prescribe antibiotics to treat infections. The choice of antibiotics is well specified in clinical guidelines for targeting specific pathogens, gram-positive bacteria or Gram-negative.²⁰ However, we know only little about the effects of antibiotics overall composition and load of gut microbiota immediately after treatment.

The gut microbiota contains many trillions of bacteria belonging to hundreds, thousands of species, and is essential for optimal preservation of physiological processes. The microbiota protects against other infections and pathologies by directly inhibiting invasive bacteria or by scheduling appropriate immune responses; In contrast, metabolites produced by some intestinal tract can promote a wide range of diseases such as atherosclerosis or cancer. Antibiotics alter the microbiota blending, resulting in an increased risk of disease, secondary infections, allergy, and obesity. In addition, they promote the spread of patho-resistant gens to drugs, doing the search for alternative clinical approaches mandatory. Innovative strategies are developed to replace or complement antibiotic treatments, in an attempt to divert the pathogens without disrupting micro bites and/or recreating the Commons communities along with the shield and under-seduction.

INTRODUCTION

The Human Digestive System (GI) includes hundreds of microbial species (microbiota) and thousands of species and is one of the most densely inhabited ecosystems on Earth.²¹ The claim that bacterial cells in the intestines exceed the number of human cells in the body by a ratio of 10: 1 was recently modified and suggested to be about 1: 1 ratio.²² However, the actual ratio and number of cells are not as important as the functional capacity of the gut microbiota, which has many positive benefits to host physiology health; including improved energy harvesting, vitamin synthesis, cell and immune cell modification of vaccine and development, and protection against infection.²³ The breakdown of the average "normal" colon composition has important implications for human health and disease, after being linked to conditions such as Inflammatory Bowel Disease (IBD), Irritable Bowel Syndrome (IBS), cancer and obesity.²⁴ In many cases, additional evidence is needed to fully link the microbiota and the disease, and it is not known whether a different microbiota is a cause or a consequence of the disease.²⁵ In the case of Clostridium-Difficile Infection (CDI), most cases are undoubtedly related to alteration of the colon composition, usually after administration of antibiotics to the host.[26] Here, we discuss how advances in microbial research revealed new opportunities for control of C. difficile.²⁷

In the past two decades, the microbiota has been shown in the intestines as a fundamental factor in host physiology and pathology. Trillions of bacteria inhabit the digestive system (GI) of complex metazoans (any multicellular animal), including humans, greatly expanding the host genetic repertoire. It translates the possibility of the host to perform functions that are encoded by its genome: Camps protect against pathogen invasion, extract extra energy from the food, and synthesize key molecules for tissue development in a manner that is highly specialized in their position relative to the digestive tract. Although the physiology of all organs is affected by microbiota, the mucous mucosa and its immune components are most affected by this symbiosis. We are reviewing for the first time recent findings that clarify the effect of microbiota on the immune system. Second, we discuss the involvement of intestinal interactions in the pathogenesis of the disease. Thirdly, we examine the role of antibiotics in disrupting or driving these processes. Finally, we discuss the mechanisms of antibiotic development and resistance, as well as the proposed approaches to overcome the drawbacks of antibiotic therapy.

Overuse of antibiotics may fuel the dramatic increase in conditions such as obesity, diabetes, inflammatory bowel disease, allergies, and asthma, which have multiplied more than many populations (see graph). We need to urgently explore this possibility. Even before we understand the full scope, action must be taken. Bacteria lived on animals - which constitute their microbial - because molecular life evolved about a billion years ago. The hosts derive many benefits from their bacteriological guests 2: the Bacteroides species living in our colon synthesize required vitamin K; the intestinal bacteria help us to resist invading organisms.

There is other evidence that antibiotics cause a change in the microbial composition that can lead to long-term physiological changes. For example, as farmers have discovered, ongoing, therapeutic under-dosages of many different antibacterial substances cause animals to gain weight with less food. Moreover, the longer the antibiotic starts, the more profound the effect. In the laboratory, we have preliminary evidence in a mouse model that changes in body fat and tissue composition



are associated with low-dose antibiotic therapy, which imitates farm use and high-dose therapy like those used to treat childhood infections. The changes in our microbiome may even fuel the transfer of deadly organisms such as Staphylococcus aureus, methicillin and Clostridium difficile.²⁸ This is not a surprise, because one of the essential roles of an intact microbial ecosystem is to resist intrusions by pathogenic organisms.

Antibiotic-related diarrhea due to Clostridium difficile (CDAD) is considered to reflect colonization of a poor microbial community by the pathogen. Scientists have created a profile of fecal microbiota of patients with CDAD (primary and recurrent episodes) by independent phylogenetic analysis in the culture of gene sequences in 16R RNA gene encoding. Compared to those in the control group, and patients with an initial episode, fecal communities in patients with recurrent CDAD were very variable in the bacterial composition and characterized by significantly reduced diversity. The preservation and restoration of microbial diversity may represent new strategies for the prevention and treatment of recurrent CDAD, which often suffers from existing therapies. Scientists have presented molecular-based ecological evidence for the role that reduced the diversity of bacteria in the case of CDAD. This finding may lead to new treatments and prevention against the newly contagious disease.

Recent discoveries of unexpected variations in the microbial composition of healthy individual's high- light the importance of identifying the processes that could possibly give rise to such variation. The ecological theory seeks to explain and predict observable phenomena, such as temporal and spatial patterns of diversity.²⁹

The ecological theory seeks to explain and predict observable phenomena, such as temporal and spatial patterns of diversity. The concept put forth in the late nineteenth and early twentieth centuries that 'everything is everywhere, but the environment selects' had a powerful impact on thinking about microbial community assembly, but a more recent appreciation of other ecological processes (such as diversification and dispersal limitation) suggests that this conceptualization was overly simplistic. Here, we explore how community assembly theory could be used to understand the human-associated microbiota and its role in health and disease. We focus on three scenarios relevant to the assembly of the human microbiome: assembly in previously unoccupied habitats (e.g., postnatal development), reassembly following disturbance (e.g., following antibiotic treatment), and assembly in the context of invasion (e.g., by a pathogen).

The higher the importance of identifying processes that can cause such a change.³⁰ The ecological theory seeks to explain and predict observable phenomena, such as temporal and spatial patterns of diversity. The concept presented at the end of the nineteenth century and the beginning of the twentieth century, "*Everything is everywhere, but the environment chooses*" has had a strong influence on thinking about microbiological community structure, but a newer assessment of other ecological processes (eg diversity and scattering) indicates that this concept Was too simplistic.³¹ Here, we explore how community theory can be used to understand microbiota associated with humans and its role in health and disease. We focus on three scenarios relevant to the human microbial assembly: assembly in previously unavailable habitats (eg postnatal development), re-assembly due to interference (such as antibiotic treatment) and its composition in the context of invasion (eg,).

ADAPTIVE MANAGEMENT OF THE HUMAN BODY

The transition from the clinical practice of the body - like a battlefield to the human response as a habitat - will necessitate rethinking how man

manages the human body. In the management of plant and animal communities, access to the system level known as "adaptive management" has become popular. This approach is a structured and iterative process of decision making that uses system monitoring to update management decisions on an ongoing basis.³² It has been successfully used to manage biodiversity in a variety of habitats, including communities in highly disturbed environments affected by overfishing by climate change. For the human body, we imagine that this approach will involve assessing microbiology during health, to create a healthy foundation, with more intensive monitoring during disease and treatment. This will require the development of new, accurate, and fast diagnostic tools to inform treatment decisions. Such diagnoses are not yet possible, but given the recent developments in our ability to review the human microbiology, this possibility is not far in the future, especially if we are able to identify certain microbiome components that contribute disproportionately to human health. An adaptive management approach to clinical medicine provides a beautiful example of personalized medicine, with treatments adapted to individuals based on diagnostic changes in the individual microbiome, and continually coordinated through constant monitoring. This intensive approach, guided by ecological theory, has the potential to revolutionize the treatment of the disease.³³

Interest in rebalancing human gut microbiota to treat disease is growing.³⁴ Diet, antibiotics, probiotics, prebiotics, and fecal microbiota transplants are treatments with reported potential.³⁵ For ASD - Autistic Spectrum Disorder, however, only temporary symptom improvements have been reported from vancomycin treatment,³⁶ and probiotics have had mixed clinical results with minimal microbiota analysis or long-term follow-up.³⁷ Contrasting to probiotics which contain a few bacterial species from milk cultures, fecal microbiota transplant (FMT fecal microbiota transplant) contains approximately a thousand-bacterial species native to the gut and has helped treat recurrent Clostridium difficile infection³⁸ and is promising for the treatment of chronic inflammatory diseases such as inflammatory bowel disease³⁹ and insulin sensitivity.[40] Therefore, ASD's GI and behavioral symptoms may derive, at least in part, from gut microbiota dysbiosis and FMT Fecal Microbiota Transplant may effectively rebalance the gut microbiota and alleviate some GI and ASD symptoms.

Antibiotic therapy with metronidazole, vancomycin or fidaxomicin is an initial treatment for C. difficile infection (CDI). However, CDI is unique because the use of antibiotics is also the leading risk factor for the acquisition of CDI or CDI due to repeated eradication of the "*normal*" gut microbiota. Therefore, there is an urgent need for alternative treatment, not an antibiotic treatment or prevent CDI. Here, we are reviewing a number of such potential treatments, which have emerged from advances in microbiome research.

CONFLICTS OF INTEREST

We have no conflicts of interest with nobody and have nothing to declare.

REFERENCES

1. Global Human Microbiome Market to Expand at a CAGR of 9.80% over 2018 to 2026 as Medical Research Improves, finds TMR.

2. Whole genome sequencing has largely been used as a research tool, but is currently being introduced to clinics. In the future of personalized medicine, whole genome sequence data will be an important tool to guide therapeutic intervention. The tool of gene sequencing at Single-Nucleotide Polymorphism (SNP) level is also used to pinpoint functional variants from association studies and improve the knowledge available to researchers interested in evolutionary biology, and hence may lay the foundation for predicting disease susceptibility and drug response.

3. a. microbiome.

b. Yaniv Erlich A vision for ubiquitous sequencing. New York, USA: Cold Spring Harbor Laboratory Press 25: 1411-1416

4. Human Microbiome Market Analysis and Research Report 2018 to 2025.

5. Solnick JV, Schauer DB. Emergence of diverse Helicobacter species in the pathogenesis of gastric and enterohepatic diseases. *Clin Microbiol Rev.* 2001; 14(1): 59-97. doi: 10.1128/CMR.14.1.59-97.2001

6. Linz B, Balloux F, Moodley Y, Manica A, LiuH An African origin for the intimate association between humans and Helicobacter pylori. *Nature*. 2007; 445(7130): 915-918. doi: 10.1038/nature05562

7. a. Frese SA, Benson AK, Tannock GW, Loach DM, Kim J The evolution of host specialization in the vertebrate gut symbiont Lactobacillus reuteri. *PLoS Genet.* 2011; 7(2): e1001314. doi: 10.1371/journal. pgen.1001314

b. Oh PL, Benson AK, Peterson DA, Patil PB, Moriyama EN. Diversification of the gut symbiont Lactobacillus reuteri as a result of host-driven evolution. *ISME J.* 2010; 4(3): 377-387. doi: 10.1038/ismej.2009.123

8. Microbial small molecules associated with human microbiome.

9. Rajilic-Stojanovic M, de Vos WM The first 1000 cultured species of the human gastrointestinal microbiota. *FEMS Microbiol Rev.* 2014; 38(5): 996-1047. doi: 10.1111/1574-6976.12075

10. Walter J, Ley R The human gut microbiome: ecology and recent evolutionary changes. *Annu Rev Microbiol.* 2011; 65: 411-429. doi: 10.1146/annurev-micro-090110-102830

11. Ley RE, Bäckhed F, Turnbaugh P, Lozupone CA, Knight RD, Gordon JI. Obesity alters gut microbial ecology. *Proc Natl Acad Sci U S A*. 2005; 102(31): 11070-11075. doi: 10.1073/pnas.0504978102

12. Nguyen TL How informative is the mouse for human gut microbiota research? *Dis Model Mech.* 2015; 8(1): 1-16. doi: 10.1242/dmm.017400

13. Xiao L A catalog of the mouse gut metagenome. Nat Biotechnol. 2015 Oct;33(10):1103-8. doi: 10.1038/nbt.3353

14. Henning Seedorf, Nicholas W Griffin, Vanessa K Ridaura, Alejandro Reyes, Jiye Cheng, et al. Bacteria from diverse habitats colonize and compete in the mouse gut. *Cell*. 2014; 159(2): 253-266. doi: 10.1016/j. cell.2014.09.008

15. a. Hsiao A Members of the human gut microbiota involved in recov-

ery from Vibrio cholerae infection. *Nature*. 2014; 515(7527): 423-426. doi: 10.1038/nature13738

b. Ridaura VK Gut microbiota from twins discordant for obesity modulate metabolism in mice. *Science*. 2013; 341(6150): 1241214. doi: 10.1126/science.1241214

c. Blanton LV. Gut bacteria that prevent growth impairments transmitted by microbiota from malnourished children. *Science*. 2016; 351(6275). pii: aad3311. doi: 10.1126/science.aad3311

d. Kau AL. Functional characterization of IgA-targeted bacterial taxa from undernourished Malawian children that pro-duce diet-dependent enteropathy. *Sci Transl Med.* 2015; 7(276): 276ra24. doi: 10.1126/sci-translmed.aaa4877

16. a. Costello EK, Lauber CL, Hamady M, Fierer N, Gordon JI, et al. Bacterial community variation in human body habitats across space and time. *Science*. 2009; 326(5960): 1694-1697. doi: 10.1126/science.1177486

b. Ley RE, Turnbaugh PJ, Klein S, Gordon JI Microbial ecology: human gut microbes associated with obesity. *Nature*. 2006; 444(7122): 1022-1023. doi: 10.1038/4441022a

c. Reyes A, Haynes M, Hanson N, Angly FE, Heath AC. Viruses in the faecal microbiota of monozygotic twins and their mothers. *Nature*. 2010; 466(7304): 334–338. doi: 10.1038/nature09199

17. Martinez I, Kim J, Duffy PR, Schlegel VL, Walter J Resistant starches types 2 and 4 have differential effects on the composition of the fecal microbiota in human subjects. *PLoS One*. 2010; 5(11): e15046. doi: 10.1371/journal.pone.0015046

18. Robinson CJ, Bohannan BJ, Young VB From structure to function: the ecology of host-associated microbial communities. *Microbiol Mol Biol Rev.* 2010; 74(3): 453–476. doi: 10.1128%2FMMBR.00014-10

19. Amy Langdon, Nathan Crook, Gautam Dantas The effects of antibiotics on the microbiome throughout development and alternative approaches for therapeutic modulation. *Genome Med.* 2016; 8: 39. doi: 10.1186/s13073-016-0294-z

20. McNulty CA European Antibiotic Awareness Day 2012 general practitioners encouraged to TARGET antibiotics through guidance, education and tools. *J Antimicrob Chemother*. 2012; 67(11): 2543-2546. doi: 10.1093/jac/dks358

21. Qin J, Li R, Raes J, Arumugam M, Burgdorf KS, et al. A human gut microbial gene catalogue established by metagenomic sequencing. *Nature*. 2010; 464(7285): 59–65. doi: 10.1038/nature08821

22. Sender R, Fuchs S, Milo R Are we really vastly outnumbered? Revisiting the ratio of bacterial to host cells in humans. *Cell*. 2016; 164(3): 337-340. doi: 10.1016/j.cell.2016.01.013

23. a. Backhed F, Ding H, Wang T, Hooper LV, Koh GY, et al. The gut microbiota as an environmental factor that regulates fat storage. *Proc Natl Acad Sci U S A*. 2004; 101(44): 15718-15723. doi: 10.1073/



pnas.0407076101

b. Backhed F, Ley RE, Sonnenburg JL, Peterson DA, Gordon JI Hostbacterial mutualism in the human intestine. *Science*. 2005; 307(5717): 1915-1920. doi: 10.1126/science.1104816

c. Hooper LV, Gordon JI. Commensal host-bacterial relationships in the gut. *Science*. 2001; 292(5519): 1115-1118. doi: 10.1126/science.1058709

d. Kurokawa K, Itoh T, Kuwahara T, Oshima K, Toh H, et al. Comparative metagenomics revealed commonly enriched gene sets in human gut microbiomes. *DNA Res.* 2007; 14(4): 169-181. doi: 10.1093/dnares/ dsm018

e. Rakoff-Nahoum S, Paglino J, Eslami-Varzaneh F, Edberg S, Medzhitov R Recognition of commensal microflora by toll-like receptors is required for intestinal homeostasis. *Cell.* 2004; 118(2): 229-241. doi: 10.1016/j.cell.2004.07.002

f. Samuel BS, Gordon JI. A humanized gnotobiotic mouse model of host-archaeal-bacterial mutualism. *Proc Natl Acad Sci U S A*. 2006; 103(26): 10011-10016. doi: 10.1073/pnas.0602187103

24. a. Frank DN, St Amand AL, Feldman RA, Boedeker EC, Harpaz N, et al. Molecular-phylogenetic characterization of microbial community imbalances in human inflammatory bowel diseases. *Proc Natl Acad Sci U S A*. 2007; 104(34): 13780–13785. doi: 10.1073%2Fpnas.0706625104

b. Kostic AD, Gevers D, Pedamallu CS, Michaud M, Duke F, et al. Genomic analysis identifies association of fusobacterium with colorectal carcinoma. *Genome Res.* 2012; 22(2): 292–298. doi: 10.1101/gr.126573.111

c. Turnbaugh PJ, Ley RE, Mahowald MA, Magrini V, Mardis ER, et al. An obesity-associated gut microbiome with increased capacity for energy harvest. *Nature*. 2006; 444(7122): 1027-1031. doi: 10.1038/na-ture05414

25. Scott, KP, Antoine JM, Midtvedt T, van Hemert S. Manipulating the gut microbiota to maintain health and treat disease. *Microb Ecol Health Dis.* 2015; 26: 25877. doi: 10.3402/mehd.v26.25877

26. Ananthakrishnan AN Clostridium difficile infection: Epidemiology, risk factors and management. *Nat Rev Gastroenterol Hepatol.* 2011; 8(1): 17-26. doi: 10.1038/nrgastro.2010

27. Eamonn P Culligan, Roy D Sleator. Advances in the Microbiome: Applications to Clostridium difficile Infection. *J Clin Med.* 2016; 5(9). pii: E83. doi: 10.3390/jcm5090083

28. Chang JY, Antonopoulos DA, Kalra A, Tonelli A, Khalife WT, et al. Decreased Diversity of the Fecal Microbiome in Recurrent Clostridium difficile-Associated Diarrhea. *J Infect Dis.* 2008; 197(3): 435-438. doi: 10.1086/525047

29. Costello EK, Stagaman K, Dethlefsen L, Bohannan BJ, Relman DA. The Application of Ecological Theory toward an Understanding of the Human Microbiome. *Science*. 2012; 336(6086): 1255-1262. doi: 10.1126/

science.1224203

30. a. Palmer C, Bik EM, DiGiulio DB, Relman DA, Brown PO. Development of the human infant intestinal microbiota. *PLoS Biol.* 2007; 5(7): e177. doi: 10.1371/journal.pbio.0050177

b. Ravel J, Gajer P, Abdo Z, Schneider GM, Koenig SS, et al. Vaginal microbiome of reproductive-age women. *Proc Natl Acad Sci U S A*. 2011; 108 Suppl 1: 4680-4687. doi: 10.1073/pnas.1002611107

c. Wu GD, Chen J, Hoffmann C, Bittinger K, Chen YY, Keilbaugh SA, et al. Linking long-term dietary patterns with gut microbial enterotypes. *Science*. 2011; 334(6052): 105-108. doi: 10.1126/science.1208344

31. O'Malley MA The nineteenth century roots of 'everything is everywhere. *Nat Rev Microbiol.* 2007; 5: 647.

32. Allan C, Stankey GH. Adaptive Environmental Management: A Practitioner's Guide. Heidelberg: Springer. 2009.

33. Gilbert JA, Krajmalnik-Brown R, Porazinska DL, Weiss SJ, Knight R. Toward effective probiotics for autism and other neurodevelopmental disorders. *Cell*. 2013; 155(7): 1446-1448. doi: 10.1016/j.cell.2013.11.035

34. a. Tillisch K, Labus J, Kilpatrick L, Jiang Z, Stains J, et al. Consumption of fermented milk product with probiotic modulates brain activity. *Gastroenterology*. 2013; 144(7): 1394-1401, 1401. e1-e4. doi: 10.1053/j.gastro.2013.02.043

b. Youngster I, Sauk J, Pindar C, Wilson RG, Kaplan JL, et al. Fecal microbiota transplant for relapsing Clostridium difficile infection using a frozen inoculum from unrelated donors: A randomized, open-label, controlled pilot study. *Clin Infect Dis.* 2014; 58(11): 1515-1522. doi: 10.1093/cid/ciu135

c. Prantera C, Lochs H, Grimaldi M, Danese S, Scribano ML, et al. Rifaximin-extended intestinal release induces remission in patients with moderately active Crohn's disease. *Gastroenterology*. 2012; 142(3): 473-481. e4. doi: 10.1053/j.gastro.2011.11.032

d. Brandt LJ, Aroniadis OC, Mellow M, Kanatzar A, Kelly C, et al. Longterm follow-up of colonoscopic fecal microbiota transplant for recurrent Clostridium difficile infection. *Am J Gastroenterol.* 2012; 107(7): 1079-1087. doi: 10.1038/ajg.2012.60

e. Moayyedi P, Quigley EMM, Lacy BE, Lembo AJ, Saito YA, et al. The effect of fiber supplementation on irritable bowel syndrome: a systematic review and meta-analysis. *Am J Gastroenterol.* 2014; 109(9): 1367-1374. doi: 10.1038/ajg.2014.195

35. Sandler RH, Finegold SM, Bolte ER, Buchanan CP, Maxwell AP, et al. Short-term benefit from oral vancomycin treatment of regressive-onset autism. *J Child Neurol.* 2000; 15(7): 429-435. doi: 10.1177/088307380001500701

36. Parracho HM, Gibson GR, Knott F, Bosscher D, Kleerebezem M, et al. A double blind, placebo-controlled, crossover-designed probiotic feeding study in children diagnosed with autistic spectrum disorders.



Int J Probiot Prebiot. 2010; 5(2): 69-74.

37. Bagdasarian N, Rao K, Malani PN. Diagnosis and treatment of Clostridium difficile in adults a systematic review. JAMA. 2015 Jan 27;313(4): 398-408. doi: 10.1001/jama.2014.17103

38. Moayyedi P, Surette MG, Kim PT, Libertucci J, Wolfe M, et al. Fecal microbiota transplantation induces remission in patients with active ul-

cerative colitis in a randomized controlled trial. *Gastroenterology*. 2015; 149(1): 102-109. e6. doi: 10.1053/j.gastro.2015.04.001

39. Vrieze A, Van Nood E, Holleman F, Salojarvi J, Kootte RS, et al. Transfer of intestinal microbiota from lean donors increases insulin sensitivity in individuals with metabolic syndrome. *Gastroenterology*. 2012; 143(4): 913-6. e7. doi: 10.1053/j.gastro.2012.06.031