

### **Online Course**

ROLE OF THE GUT MICROBIOTA IN HEALTH AND DISEASE

Release Date: Wednesday, February 19, 2020

End Date: Sunday, February 19, 2023

Estimated Time: 19.5 hours



#### Role of the Gut Microbiota in Health and Disease

#### **Description**

This enduringly interesting material is composed of five online modules which provide an evidence-based update on the role of the Gut Microbiota in health and disease.

Participants who complete the modules will be able to define what microbiota are and describe the general principles governing interactions between gut-resident microbes and humans. They will be able to identify the numerous facets of human biology that are influenced by the gut microbiota in health and disease. In addition, participants will learn about the effects of lifestyle/nutrition and antibiotic/probiotic use on shaping the gut microbiota composition.

Toward the end of the course, participants will be able to discuss the incorporation of the gut microbiota analysis into the daily practice of medicine and explain the principles behind the use of fecal transplants and the potential benefits and risks of this procedure.

#### **Learning Objectives**

At the end of this activity, participants will:

- Describe the general principles governing interactions between gut resident microbes and humans.
- Identify the numerous facets of human biology that are influenced by the gut microbiota in health and disease.
- Define the factors that can alter the microbiota in everyday life, including antibiotics and diet, which directly impact microbiota composition and function.
- Explain the principles behind the use of fecal transplants, the potential benefits and risks.
- Discuss the incorporation of the gut microbiota analysis into daily practice of medicine.

#### **Target Audience**

Physicians, Nurses, Dentists, Pharmacists, Allied Health Professionals, Students, Researchers, Educators Release Date: Wednesday, February 19, 2020

End Date: Sunday, February 19, 2023 Revision date: August 19, 2020 Estimated Time: 19.5 hours

#### **Note**

Participants **MUST** complete the course within 6 months from registration. They will receive an email with a link to access the course content along with necessary instructions.

#### **Identified Practice Gaps/Educational Needs**

The human gut microbiota contains trillions of microorganisms, primarily bacteria but also archaea, protists, viruses and fungi. Their number is about ten times more than human eukaryotic cells, and their genome extends to more than one fifty times more genes than human genes. In the last ten years, fundamental and experimental studies aiming to understand the role of gut microbiota in the onset of diseases have been proliferating around the world. We are currently living a tremendous paradigm shift in health sciences, where microbiota is being linked to diseases of 'modern civilization' such as cancer, diabetes, obesity, cardiovascular disease, autoimmune diseases etc. The role of the gut microbiota is becoming a central question in the study of diseases.

Indeed, the number of publications about the role of the gut microbiota has increased significantly during the past ten years (Figure 1, source: Pubmed). However, our search shows that the role of the gut microbiota is very little studied by scientists in Qatar (Figure 2, source: Pubmed).

Moreover, survey results from an ongoing study at WCM-Q show that among a group of 44 healthcare professionals 88.6% feel that healthcare professionals are not knowledgeable of the role of microbiota in inflammatory diseases such as IBD or in neuropsychiatric disorders such as Autism Spectrum Disorders and Attention Deficit Hyperactivity Disorders. Nevertheless, 100% of them believe there is a need for further investigations into the role of the gut microbiota in the gut-brain axis. Another online survey, of Qatar residents, shows that a large proportion of respondents are ready to participate in clinical trials involving modulation of the gut microbiota through either diet or fecal transplant (Figure 3) (source: UREP21-059-1-011- Qatar National research Funds).

In addition, new practice guidelines to help practitioners consider the gut microbiota have been described by various groups worldwide 1–5. The vagus nerve is described as a key modulator of the gut-brain axis in psychiatric and inflammatory disorders, revealing a wide range of clinical applications in the treatment of inflammatory diseases 6–8.

Neurosciences are experiencing a paradigm shift with the identification of the gut as the "second brain" and the existence of the gut-brain axis. It is, therefore, extremely difficult to hope for any change in practice before unraveling the mechanisms involved. This lecture will constitute one step forward in raising awareness among healthcare professionals of the importance of the microbiota-gut-brain axis by clarifying definitions and some of the mechanisms involved, such as the impact of diet on metabolites secretion by microorganisms, the role of the vagus nerve and other pathways to the organs, as well as potential clinical applications.

#### **Figures**

Figure 1: Publication counts using the MeSH Term "Microbiota". (source: Pubmed).

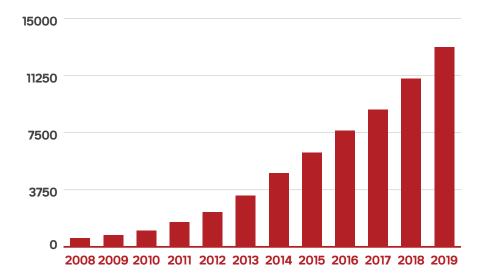


Figure 2: Publication counts using MeSH term: "microbiota AND Qatar". (source: Pubmed)

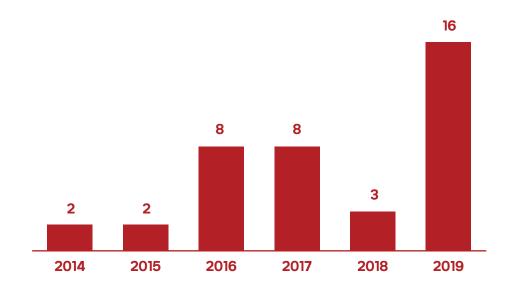
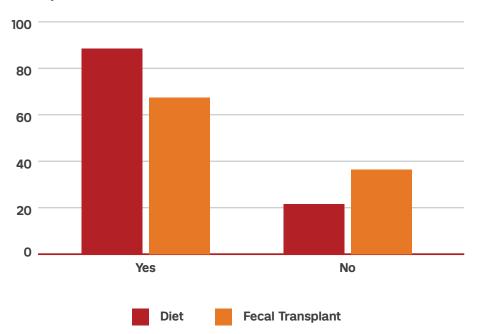


Figure 3: Readiness of respondents (%) who are resident in Qatar to participate in clinical trials involving diet or fecal transplants. (source: UREP21-059-1-011)



## Accreditation

#### **Disclosure of Relationships/Content Validity**

It is the policy of Weill Cornell Medicine-Qatar to adhere to Department of Healthcare Professions (DHP) and Accreditation Council for Continuing Medical Education (ACCME) Criteria, Policies, and Standards for Commercial Support and content validation in order to ensure fair balance, independence, objectivity, and scientific rigor in all its sponsored programs. All faculty participating in sponsored programs are expected to disclose relevant financial relationships pertaining to their contribution to the activity, and any discussions of off-label or investigational uses of approved commercial products or devices, or of any products or devices not yet approved in the United States and elsewhere. WCM-Q CME/CPD activities are intended to be evidence-based and free of commercial bias.

#### **Course Director**

Ghizlane Bendriss, PhD

#### **Course Faculty**

- Ghizlane Bendriss, PhD
- Ali Chaari, PhD
- Riham Shadid, PharmB

#### **Course Administrator**

Safia Rabia

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- Majda Sebah, BSC, PhD
- Riham Shadid, PharmB
- · Ali Sultan, MD, PhD
- Dana Ali, Medical Student

### The course Director, Scientific Planning Committee members and Faculty

- Have no relevant financial relationships to disclose.
- Will not be discussing unlabeled/unapproved use of drugs or products.

#### **Course Administrator**

Safia Rabia has disclosed the following financial relationship:

- Spouse employee of Al Wehda Medical Group.
- Will not be discussing unlabeled/unapproved use of drugs or products.

#### **ICR**

Ghizlane Bendriss, PhD

- Has no relevant financial relationships to disclose.
- Will not be discussing unlabeled/unapproved use of drugs or products.

#### **Evaluation**

An evaluation will be conducted online post activity. All participants are required to complete the Evaluation Form in order to qualify for a certificate. The evaluation allows us to assess the degree to which the activity met its objectives. It will also guide the planning of future activities and inform decisions about improving the educational program.

#### **Accreditation & Credit Designation Statements**



#### **ACCME**

The Weill Cornell Medicine-Qatar is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians.

The Weill Cornell Medicine-Qatar designates this enduring material for a maximum of 19.5 AMA PRA Category1 Credits™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.



Module	Topic
Module 1	Pre-evaluation
Module 2	Microbiota: definitions and general principles of interaction
Module 3	Evidence on the role of gut microbes in health and diseases
Module 4	Effect of nutrition on microbiota composition

Session Learning Objectives	Speaker
Identify knowledge gaps	Ghizlane Bendriss
<ul> <li>Define: microbiota, microbiome, metagenome, metabolome</li> <li>Identify, classify and localize microorganisms hosted by humans</li> <li>Define the terms symbiosis and Dysbiosis</li> <li>Identify and classify the</li> </ul>	Riham Shadid
mechanisms of microbiota/host interactions in humans	
<ul> <li>List all diseases/disorders where gut microbes have been shown to be involved</li> <li>Diagram for every disorder a current hypothesis on the role of gut microbesin pathogenesis</li> <li>Summarize most relevant evidence on the role of microbes in Health and Diseases</li> <li>Conclude on the role of lifestyle in microbiota composition and health and disease</li> </ul>	Ghizlane Bendriss
<ul> <li>Identify/classify microorganisms hosted by humans</li> <li>Define the terms symbiosis and dysbiosis</li> <li>Explain the importance of biodiversity of the gut in health and diseases</li> <li>Analyze populations' diets</li> <li>Explain biochemical interactions of gut microorganisms with food (carbohydrates, proteins, lipids, fibers) and how a diet can aggravate dysbiosis or reestablish a balanced biodiversity</li> </ul>	Ghizlane Bendriss





Module	Topic	Session Learning Objectives	Speaker
Module 5	Antibiotics, Probiotics and Microbiota	<ul> <li>Define the terms probiotic and antibiotic</li> <li>Classify antibiotics</li> <li>Explain what is resistance to antibiotic and its consequences</li> <li>Conclude on dangers of antibiotic overuse on microbiota diversity</li> <li>Identify the WHO requirements for the label "probiotic"</li> <li>Explain the role and importance of probiotics in health and diseases</li> <li>Summarize latest evidence on the clinical benefits of probiotics</li> <li>List methods and tools available to minimize the use of antibiotics</li> <li>Recognize cases that require use or not of antibiotic and/or probiotic using appropriate available tools</li> </ul>	Riham Shadid
Module 6	Fecal Transplants	<ul> <li>Explain the principle of fecal transplant</li> <li>Describe the diverse methods used up to date to perform fecal transplants</li> <li>List the evidence available on the benefits of fecal transplants</li> <li>Name the diseases/disorders which have shown positive responses to fecal transplants</li> <li>Evaluate the risks of fecal transplants</li> <li>State the current regulations on use of fecal transplants technique as a therapeutic treatment as per FDA</li> </ul>	Ghizlane Bendriss
Module 7	Latest technologies for study and analysis of microbiota, metagenome, and metabolome	<ul> <li>Lists and classify technologies used to study and analyze microbiota composition, metagenome and metabolome</li> <li>Compare costs of the technologies described</li> </ul>	Ali Chaari



Module	Topic
Module 8	Post-evaluation

Session Learning Objectives	Speaker
Conclude on the potential benefits of integrating routine analysis of microbiota in clinical settings	
<ul> <li>Describe the general principles governing interactions between gut resident microbes and humans</li> <li>Identify the numerous facets of human biology that are influenced by the gut microbiota in health and disease</li> <li>Define the factors that can alter the microbiota in everyday life, including antibiotics, diets, which directly impact microbiota composition and function</li> <li>Explain the principles behind the use of fecal transplants, the potential benefits and risks</li> <li>Discuss the incorporation of the gut microbiota analysis into daily practice of medicine</li> </ul>	Ghizlane Bendriss





**Ghizlane Bendriss, PhD** 

Lecturer in Biology and Neurosciences Weill Cornell Medicine-Qatar

Dr. Ghizlane Bendriss holds a PhD in neurobiology and neurophysiology as well as a master's in neurophysiology and cognitive neurosciences from the University of Aix-Marseille in France. She started her carrier in Research at the Center for Research in Oncobiology and Oncopharmacology in France, before joining Weill Cornell Medicine-Qatar in 2011. Dr. Ghizlane is a faculty lecturer and teaches Biological sciences and Neurophysiology to premedical students, in which she focuses on special senses and sensory nervous system. Driven by her interest in on the gut-brain axis, her studies on the gut microbiota lead her to become an advocate of lifestyle medicine. Her main research interest is about the effect of lifestyle on the development and physiology of the brain via the modulation of the gut microbiome. She developed and is currently leading several educational and research projects on the role of the gut microbiota in neurological and neuropsychiatric conditions such as autism spectrum disorders. She obtained a QNRF grant in 2017 to run a pilot study that aimed at assessing awareness and readiness of the population in enrolling in microbiome-targeting lifestyle interventions, as well as an internal grant as a co-investigator on a study that aims at charactering the probiotic content of dairy products in Qatar.

She developed and is the course director of two continued professional development courses that are serving her aims of raising awareness on the importance of lifestyle: 1/The Certificate in the Fundamentals of Music Therapy and 2/ The role of the Gut microbiota in Health and Disease.

She manages to merge her passion for teaching, her research interests and her passion for music while leading the first EEG-based exploration of the variables affecting cortical responses to Arab Music scales, through which she is teaching her students to run an EEG, ethics of human research, statistical analysis and scientific writing. This study also serves her vision of designing a clinical trial for children with Autism Spectrum Disorders.



Ali Chaari, PhD

Lecturer in Biochemistry
Weill Cornell Medicine-Qatar

Dr. Ali Chaari holds a PhD in Biochemistry and Biophysics. He is currently a lecturer in biochemistry at Weill Cornell Medicine-Qatar. Dr. Chaari is experienced in biochemistry, molecular biology, and biophysics. He has co-authored several original research articles, written two books and has presented his work at several conferences. In addition, he is active as a research mentor to WCM-Q's medical students.

Two active research areas of his are the study of amyloid proteins modulation in neurodegenerative diseases and diabetes, and the effect probiotics on health notably on neurodegenerative diseases and type 2 diabetes.



### Riham Nasereddin Shadid, PharmB, MSc

Dr. Riham Nasereddin Shadid is a pharmacist with a PhramB degree. She is also a professional post-graduate diabetes educator and a holistic health coach with more than 15 years of experience in Canada and the Middle East. She also has significant experience of designing and delivering continuing education programs for healthcare professionals. Dr. Riham is currently finishing her master's degree in biomedical and biological sciences at Hamad Bin Khalifa University, and her research is focused on the role of the gut microbiota in health and diseases.

### **References**

- Quigley EMM. Gut bacteria in health and disease. Gastroenterol Hepatol (N Y). 2013;9(9):560-569. http://www.ncbi.nlm.nih.gov/pubmed/24729765. Consulté le Octobre 26, 2018.
- O2. Kodukula K, Faller D V, Harpp DN, et al. Gut Microbiota and Salivary Diagnostics: The Mouth Is Salivating to Tell Us Something. Biores Open Access. 2017;6(1):123-132.doi:10.1089/biores.2017.0020.
- Pane M, Amoruso A, Deidda F, Graziano T, Allesina S, Mogna L. Gut Microbiota, Probiotics, and Sport. J Clin Gastroenterol. 2018;52:S46-S49. doi:10.1097/MCG.0000000000001058.
- 04. Clapp M, Aurora N, Herrera L, Bhatia M, Wilen E, Wakefield S. Gut microbiota's effect on mental health: The gut-brain axis. Clin Pract. 2017;7(4):987. doi:10.4081/cp.2017.987.
- Cammarota G, Ianiro G, Tilg H, et al. European consensus conference on faecal microbiota transplantation in clinical practice. Gut. 2017;66(4):569-580. doi:10.1136/gutjnl-2016-313017.
- Johnson RL, Wilson CG. A review of vagus nerve stimulation as a therapeutic intervention. J Inflamm Res. 2018;11:203-213. doi:10.2147/JIR. S163248.
- Breit S, Kupferberg A, Rogler G, Hasler G. Vagus Nerve as Modulator of the Brain-Gut Axis in Psychiatric and Inflammatory Disorders. Front psychiatry. 2018;9:44. doi:10.3389/fpsyt.2018.00044.
- Bonaz B, Bazin T, Pellissier S. The Vagus Nerve at the Interface of the Microbiota-Gut-Brain Axis. Front Neurosci. 2018;12:49. doi:10.3389/ fnins.2018.00049.
- 09. Gülden E, Wong FS, Wen L. The gut microbiota and Type 1 Diabetes. Clin Immunol. 2015;159(2):143-153. doi:10.1016/j.clim.2015.05.013.
- Diamant M, Blaak EE, de Vos WM. Do nutrient-gut-microbiota interactions play a role in human obesity, insulin resistance and type 2 diabetes? Obes Rev. 2011;12(4):272-281.doi:10.1111/j.1467-789X.2010.00797.x.
- 11. Sommer F, Bäckhed F. The gut microbiota--masters of host development and physiology. Nat Rev Microbiol. 2013;11(4):227-238. doi:10.1038/nrmicro2974.

- Phimister EG, Jess T. Microbiota, Antibiotics, and Obesity. N Engl J Med. 2014;371(26):2526-2528. doi:10.1056/NEJMcibr1409799.
- 13. Kootte RS, Vrieze A, Holleman F, et al. The therapeutic potential of manipulating gut microbiota in obesity and type 2 diabetes mellitus. Diabetes, Obes Metab. 2012;14(2):112-120. doi:10.1111/j.1463-1326.2011.01483.x.
- Meguid N, Anwar M, Zaki S, Kandeel W, Ahmed N, Tewfik I. Dietary Patterns of Children with Autism Spectrum Disorder: A Study Based in Egypt. Open access Maced J Med Sci. 2015;3(2):262-267.doi:10.3889/ oamims.2015.051.
- 15. Vuong HE, Hsiao EY. Emerging Roles for the Gut Microbiome in Autism Spectrum Disorder. Biol Psychiatry. 2017;81(5):411-423. doi:10.1016/j. biopsych.2016.08.024.
- Elder JH, Shankar M, Shuster J, Theriaque D, Burns S, Sherrill L. The gluten-free, casein-free diet in autism: Results of a preliminary doubleblind clinical trial. J Autism Dev Disord.2006;36(3):413-420. doi:10.1007/ s10803-006-0079-0.
- Colman RJ, Rubin DT. Fecal microbiota transplantation as therapy for inflammatory bowel disease: A systematic review and meta-analysis. J Crohn's Colitis. 2014;8(12):1569-1581. doi:10.1016/j.crohns.2014.08.006.
- 18. Kang D-W, Adams JB, Gregory AC, et al. Microbiota Transfer Therapy alters gut ecosystem and improves gastrointestinal and autism symptoms: an open-label study. Microbiome. 2017;5(1):10. doi:10.1186/s40168-016-0225-7.

- Quigley EMM. Gut bacteria in health and disease. Gastroenterol Hepatol (N Y) [Internet]. 2013 Sep [cited 2018 Oct 26];9(9):560–9.
- O2. Sun J, Chang EB. Exploring gut microbes in human health and disease: Pushing the envelope. Genes Dis [Internet]. 2014 Dec [cited 2017 Mar 13];1(2):132–9.
- Wang Y, Kasper LH. The role of microbiome in central nervous system disorders. Brain Behav Immun [Internet]. 2014 May [cited 2017 Mar 13];38:1–12.
- O4. Petersen C, Round JL. Defining dysbiosis and its influence on host immunity and Cell Microbiol. 2014 Jul;16(7):1024–33.
- 05. Zhang Y-J, Li S, Gan R-Y, Zhou T, Xu D-P, Li H-B. Impacts of gut bacteria on human health and diseases. Int J Mol Sci [Internet]. 2015 Apr 2 [cited 2017 Mar 13];16(4):7493–519.
- O6. Elisei C, de Castro AP. Insight into role of microbiota-gut-brain peptides as a target for biotechnology innovations. Front Biosci (Elite Ed) [Internet]. 2017 [cited 2019 Nov 12]:9:76–88.
- Jo J-H, Kennedy EA, Kong HH. Research Techniques Made Simple: Bacterial 16S Ribosomal RNA Gene Sequencing in Cutaneous Research. J Invest Dermatol [Internet]. 2016 Mar [cited 2019 Nov 12];136(3):e23–7.
- Finegold SM, Summanen PH, Downes J, Corbett K, Komoriya T. Detection of Clostridium perfringens toxin genes in the gut microbiota of autistic children. Anaerobe [Internet]. 2017 Feb 17 [cited 2017 Mar 13]:
- 09. Al-Asmakh M, Zadjali F. Use of Germ-Free Animal Models in Microbiota-Related Research. J Microbiol Biotechnol [Internet]. 2015 Oct 28 [cited 2017 Mar 13];25(10):1583–8. Available from: http://www.jmb.or.kr/journal/view.html?doi=10.4014/jmb.1501.01039
- Conlan S, Kong HH, Segre JA. Species-Level Analysis of DNA Sequence Data from the NIH Human Microbiome Project. Highlander SK, editor. PLoS One [Internet]. 2012 Oct 10 [cited 2019 Nov 14]:7(10):e47075.
- 11. Integrative HMP (iHMP) Research Network Consortium. The Integrative Human Microbiome Project: Dynamic Analysis of Microbiome-Host Omics Profiles during Periods of Human Health and Disease. Cell Host Microbe [Internet]. 2014 Sep 10 [cited 2019 Nov 14];16(3):276–89
- 12. Qin J, Li R, Raes J, Arumugam M, Burgdorf KS, Manichanh C, et al. A human gut microbial gene catalogue established by metagenomic sequencing. Nature [Internet]. 2010 Mar 4 [cited 2019 Nov 14];464(7285):59–65.
- 13. Costea PI, Hildebrand F, Arumugam M, Bäckhed F, Blaser MJ, Bushman FD, et al. Enterotypes in the landscape of gut microbial community composition. Nat Microbiol [Internet]. 2018 Jan [cited 2019 Nov 14];3(1):8–16.
- 14. Nash AK, Auchtung TA, Wong MC, Smith DP, Gesell JR, Ross MC, et al. The gut mycobiome of the Human Microbiome Project healthy cohort. Microbiome [Internet]. 2017 Dec 25 [cited 2019 Nov 14];5(1):153.
- 15. Palmer RJ, Jr. Composition and development of oral bacterial communities. Periodontol 2000 [Internet]. 2014 Feb [cited 2019 Nov 14];64(1):20–39.

- 16. Dang AT, Marsland BJ. Microbes, metabolites, and the gut-lung axis. Vol. 12, Mucosal Immunology. Nature Publishing Group; 2019. p. 843–50.
- 17. Anand S, Mande SS. Diet, microbiota and gut-lung connection. Front Microbiol. 2018 Sep 19;9(SEP).
- 18. Moffatt MF, Cookson WO. The lung microbiome in health and disease. Clin Med [Internet]. 2017 Dec [cited 2019 Nov 14];17(6):525-9.
- 19. Groer MW, Gregory KE, Louis-Jacques A, Thibeau S, Walker WA. The very low birth weight infant microbiome and childhood health. Birth Defects Res C Embryo Today [Internet]. 2015 Dec [cited 2017 Mar 13];105(4):252–64.
- Brotman RM. Vaginal microbiome and sexually transmitted infections: an epidemiologic perspective. J Clin Invest [Internet]. 2011 Dec [cited 2019 Nov 14];121(12):4610-7.
- 21. Staude B, Oehmke F, Lauer T, Behnke J, Göpel W, Schloter
- 22. M, et al. The Microbiome and Preterm Birth: A Change in Paradigm with Profound Implications for Pathophysiologic Concepts and Novel Therapeutic Strategies. Biomed Res Int [Internet]. 2018 [cited 2019 Nov 14];2018:7218187.
- 23. Popovic A, Parkinson J. Characterization of Eukaryotic Microbiome Using 18S Amplicon Sequencing. In: Methods in molecular biology (Clifton, NJ) [Internet]. 2018 [cited 2019 Nov 14]. p. 29–48.
- 24. Kong HH. Skin microbiome: genomics-based insights into the diversity and role of skin microbes. Trends Mol Med [Internet]. 2011 [cited 2019 Nov 14];17:320-8.
- 25. Byrd AL, Belkaid Y, Segre JA. The human skin microbiome. Nat Rev Microbiol [Internet]. 2018 Mar 15 [cited 2019 Nov 14];16(3):143–55.
- 26. Chow J, Lee SM, Shen Y, Khosravi A, Mazmanian SK. Host-bacterial symbiosis in health and disease. Adv Immunol [Internet]. 2010 [cited 2019 Nov 14]:107:243-
- 27. Skosnik PD, Cortes-Briones JA. Targeting the ecology within: The role of the gut- brain axis and human microbiota in drug addiction. Med Hypotheses [Internet]. 2016 Aug [cited 2017 Mar 13];93:77–80.
- Moos WH, Faller D V, Harpp DN, Kanara I, Pernokas J, Powers WR, et al. Microbiota and Neurological Disorders: A Gut Feeling. Biores Open Access [Internet]. 2016 [cited 2017 Mar 13];5(1):137–45
- 29. Mezzelani A, Raggi ME, Marabotti A, Milanesi L. Ochratoxin A as possible factor trigging autism and its male prevalence via epigenetic mechanism. Nutr Neurosci [Internet]. 2016 Jan 2 [cited 2017 Mar 13];19(1):43–6.
- 30. Kelly JR, Kennedy PJ, Cryan JF, Dinan TG, Clarke G, Hyland NP. Breaking down the barriers: the gut microbiome, intestinal permeability and stress-related psychiatric disorders. Front Cell Neurosci. 2015;9:392.
- 31. Thomas S, Izard J, Walsh E, Batich K, Chongsathidkiet P, Clarke G, et al. The Host Microbiome Regulates and Maintains Human Health: A Primer and Perspective for Non-Microbiologists HHS Public Access. Cancer Res [Internet]. 2017 [cited 2019 Sep 16];77(8):1783–812.

- 32. Kootte RS, Vrieze A, Holleman F, Dallinga-Thie GM, Zoetendal EG, de Vos WM, et al. The therapeutic potential of manipulating gut microbiota in obesity and type 2 diabetes mellitus. Vol. 14, Diabetes, Obesity and Metabolism. 2012. p. 112–20.
- Li Q, Zhou J-M. The microbiota-gut-brain axis and its potential therapeutic role in autism spectrum disorder. Neuroscience. 2016;324(March):131–9.
- Savage DS. Microbial ecology of the gastrointestinal tract. Annu Rev Microbiol. 1977;31(70):107–33.
- Hold GL. Gastrointestinal Microbiota and Colon Cancer. Dig Dis. 2016 Mar 30;34(3):244–50.
- 36. Gülden E, Wong FS, Wen L. The gut microbiota and Type 1 Diabetes. Clin Immunol. 2015 Aug;159(2):143–53.
- 37. Kootte RS, Vrieze A, Holleman F, Dallinga-Thie GM, Zoetendal EG, de Vos WM, et al. The therapeutic potential of manipulating gut microbiota in obesity and type 2 diabetes mellitus. Vol. 14, Diabetes, Obesity and Metabolism. 2012. p. 112–20.
- 38. Phimister EG, Jess T. Microbiota, Antibiotics, and Obesity. N Engl J Med. 2014;371(26):2526–8.
- 39. Diamant M, Blaak EE, de Vos WM. Do nutrient-gut-microbiota interactions play a role in human obesity, insulin resistance and type 2 diabetes? Obes Rev. 2011;12(4):272–81.
- 40. Tang WHW, Hazen SL. The contributory role of gut microbiota in cardiovascular disease. J Clin Invest. 2014 Oct;124(10):4204–11.
- 41. Hooper L V., Littman DR, Macpherson AJ. Interactions Between the Microbiota and the Immune System. Science (80-). 2012;336(6086):1268-73.
- 42. Ubeda C, Pamer EG. Antibiotics, microbiota, and immune defense. Vol. 33, Trends in Immunology. 2012. p. 459–66.
- 43. Umbrello G, Esposito S. Microbiota and neurologic diseases: potential effects of probiotics. J Transl Med. 2016 Dec 19;14(1):298.
- 44. Moos WH, Faller D V, Harpp DN, Kanara I, Pernokas J, Powers WR, et al. Microbiota and Neurological Disorders: A Gut Feeling. Biores Open Access. 2016;5(1):137–45.
- 45. Cryan JF, Dinan TG. Mind-altering microorganisms: the impact of the gut microbiota on brain and behaviour. Nat Rev Neurosci. 2012;13(10):701–12.
- Sommer F, Bäckhed F. The gut microbiota--masters of host development and physiology. Nat Rev Microbiol. 2013;11(4):227–38.
- 47. DeGruttola AK, Low D, Mizoguchi A, Mizoguchi E. Current Understanding of Dysbiosis in Disease in Human and Animal Models. Inflamm Bowel Dis. 2016 May;22(5):1137–50.
- 48. Wang Y, Kasper LH. The role of microbiome in central nervous system disorders. Brain Behav Immun. 2014 May;38:1–12.
- Hsiao EY, McBride SW, Hsien S, Sharon G, Hyde ER, McCue T, et al. Microbiota Modulate Behavioral and Physiological Abnormalities Associated with Neurodevelopmental Disorders. Cell. 2013 Dec;155(7):1451–63.

- 50. Sebastián Domingo JJ. Revisión del papel de los probióticos en la patología gastrointestinal del adulto. Gastroenterol Hepatol. 2017 Feb 6;
- 51. Martinez-Medina M, Denizot J, Dreux N, Robin F, Billard E, Bonnet R, et al. Western diet induces dysbiosis with increased E coli in CEABAC10 mice, alters host barrier function favouring AIEC colonisation. Gut. 2014 Jan;63(1):116–24.
- 52. Rose DR, Yang H, Serena G, Sturgeon C, Ma B, Careaga M, et al. Differential immune responses and microbiota profiles in children with autism spectrum disorders and co-morbid gastrointestinal symptoms. Brain Behav Immun. 2018 May;70:354–68.
- Shen J, Obin MS, Zhao L. The gut microbiota, obesity and insulin resistance. Vol. 34, Molecular Aspects of Medicine. 2013. p. 39–58.
- 54. Zhang Y-J, Li S, Gan R-Y, Zhou T, Xu D-P, Li H-B. Impacts of gut bacteria on human health and diseases. Int J Mol Sci. 2015 Apr 2;16(4):7493–519.
- 55. Sun J, Chang EB. Exploring gut microbes in human health and disease: Pushing the envelope. Genes Dis. 2014 Dec;1(2):132–9.
- Oliveira Magro D, Santos A, Guadagnini D, Moreira De Godoy F, Helena S, Silva M, et al. in the gut microbiota and mucins production.
- 57. Gaudier E, Jarry A, Blottière HM, de Coppet P, Buisine MP, Aubert JP, et al. Butyrate specifically modulates MUC gene expression in intestinal epithelial goblet cells deprived of glucose. Am J Physiol Liver Physiol. 2004 Dec;287(6):G1168–74.
- 58. Abell GCJ, Cooke CM, Bennett CN, Conlon MA, McOrist AL. Phylotypes related to Ruminococcus bromii are abundant in the large bowel of humans and increase in response to a diet high in resistant starch. FEMS Microbiol Ecol. 2008 Dec;66(3):505–15.
- Al-Asmakh M, Hedin L. Microbiota and the control of blood-tissue barriers. Tissue Barriers. 2015 Jul 3;3(3):e1039691.
- Petersen C, Round JL. Defining dysbiosis and its influence on host immunity and disease. Cell Microbiol. 2014 Jul;16(7):1024–33.
- Sabatino A, Regolisti G, Cosola C, Gesualdo L, Fiaccadori E. Intestinal Microbiota in Type 2 Diabetes and Chronic Kidney Disease. Curr Diab Rep. 2017 Mar 7;17(3):16.
- 62. Hold GL, Smith M, Grange C, Watt ER, El-Omar EM, Mukhopadhya I. Role of the gut microbiota in inflammatory bowel disease pathogenesis: what have we learnt in the past 10 years? World J Gastroenterol. 2014 Feb;20(5):1192–210.
- 63. Keeney KM, Yurist-Doutsch S, Arrieta M-C, Finlay BB. Effects of Antibiotics on Human Microbiota and Subsequent Disease. Annu Rev Microbiol. 2014;68(1):217–35.
- 64. Scott FI, Horton DB, Mamtani R, Haynes K, Goldberg DS, Lee DY, et al. Administration of Antibiotics to Children Before Age 2 Years Increases Risk for Childhood Obesity. Gastroenterology. 2016;151(1):120-129.e5.
- 65. Riley LW, Raphael E, Faerstein E. Obesity in the United States Dysbiosis from Exposure to Low-Dose Antibiotics? Front Public Heal. 2013;1:69.

- 66. Kushak RI, Winter HS, Buie TM, Cox SB, Phillips CD, Ward NL. Analysis of the Duodenal Microbiome in Autistic Individuals: Association with Carbohydrate Digestion. J Pediatr Gastroenterol Nutr. 2016 Nov 2;
- 67. Russo R, Cristiano C, Avagliano C, De Caro C, La Rana G, Raso GM, et al. Gut-brain axis: Role of lipids in the regulation of inflammation, pain and CNS diseases. Curr Med Chem. 2017 Feb 16;24(999):1–1.
- 68. Kho ZY, Lal SK. The Human Gut Microbiome A Potential Controller of Wellness and Disease. Front Microbiol. 2018 Aug 14;9:1835.
- 69. Fleming LL, Floch MH. Digestion and absorption of fiber carbohydrate in the colon. Am J Gastroenterol. 1986 Jul;81(7):507–11.
- 70. Morris G, Berk M, Carvalho A, Caso JR, Sanz Y, Walder K, et al. The Role of the Microbial Metabolites Including Tryptophan Catabolites and Short Chain Fatty Acids in the Pathophysiology of Immune-Inflammatory and Neuroimmune Disease. Mol Neurobiol. 2016 Jun 27;
- 71. Shen Q, Zhao L, Tuohy KM. High-level dietary fibre up-regulates colonic fermentation and relative abundance of saccharolytic bacteria within the human faecal microbiota in vitro. Eur J Nutr. 2012 Sep;51(6):693–705.
- 72. Tilg H, Moschen AR. Microbiota and diabetes: an evolving relationship. Gut. 2014;1–9.
- 73. Chiu CY, Cheng ML, Chiang MH, Kuo YL, Tsai MH, Chiu CC, et al. Gut microbial-derived butyrate is inversely associated with IgE responses to allergens in childhood asthma. Pediatr Allergy Immunol. 2019;
- 74. Jan G, Belzacq A-S, Haouzi D, Rouault A, Métivier D, Kroemer G, et al. Propionibacteria induce apoptosis of colorectal carcinoma cells via short-chain fatty acids acting on mitochondria. Cell Death Differ. 2002 Feb;9(2):179–88.
- 75. Wei W, Sun W, Yu S, Yang Y, Ai L. Butyrate production from high-fiber diet protects against lymphoma tumor. Leuk Lymphoma. 2016 Oct 2;57(10):2401–8.
- 76. Lenoir M, del Carmen S, Cortes-Perez NG, Lozano-Ojalvo D, Muñoz-Provencio D, Chain F, et al. Lactobacillus casei BL23 regulates Treg and Th17 T-cell populations and reduces DMH-associated colorectal cancer. J Gastroenterol. 2016 Sep 9;51(9):862–73.
- 77. Baldwin\* C, Millette\* M, Oth † D, Ruiz MT, Luquet F-M, Lacroix M. Probiotic Lactobacillus Acidophilus and L. Casei Mix Sensitize Colorectal Tumoral Cells to 5-Fluorouracil-Induced Apoptosis. Nutr Cancer. 2010 Apr 5;62(3):371–8.
- Takagi A, Ikemura H, Matsuzaki T, Sato M, Nomoto K, Morotomi M, et al. Relationship between the in vitro response of dendritic cells to Lactobacillus and prevention of tumorigenesis in the mouse. J Gastroenterol. 2008 Sep 20;43(9):661–9.
- 79. Vivarelli S, Salemi R, Candido S, Falzone L, Santagati M, Stefani S, et al. cancers Gut Microbiota and Cancer: From Pathogenesis to Therapy.
- 80. Filosa S, Di Meo F, Crispi S. Polyphenols-gut microbiota interplay and brain neuromodulation. Neural Regen Res. 2018 Dec;13(12):2055.

- 81. Zuo T, Ng SC. The Gut Microbiota in the Pathogenesis and Therapeutics of Inflammatory bowel disease. Vol. 9, Frontiers in Microbiology. Frontiers Media S.A.: 2018.
- 82. Anand S, Mande SS. Diet, microbiota and gut-lung connection. Front Microbiol. 2018 Sep 19;9(SEP).
- 83. Antonio J, Quaresma S, Poidinger M, Ohshima Y, Vitte J, Ghannoum MA, et al. The Gut Microbiome as a Major Regulator of the Gut-Skin Axis. 2018;
- 84. Muszer M, Noszczyńska M, Kasperkiewicz K, Skurnik M. Human Microbiome: When a Friend Becomes an Enemy. Arch Immunol Ther Exp (Warsz). 2015 Aug 15;63(4):287–98.
- 85. Arora SK, Dewan P, Gupta P. Microbiome: Paediatricians' perspective. Indian J Med Res. 2015 Nov;142(5):515–24.
- 86. Harris K, Kassis A, Major G, Chou CJ. Is the gut microbiota a new factor contributing to obesity and its metabolic disorders? Vol. 2012, Journal of Obesity. 2012.
- 87. Sircana A, Framarin L, Leone N, Berrutti M, Castellino F, Parente R, et al. Altered Gut Microbiota in Type 2 Diabetes: Just a Coincidence? Vol. 18, Current Diabetes Reports. Current Medicine Group LLC 1; 2018.
- 88. MacFabe DF. Enteric short-chain fatty acids: microbial messengers of metabolism, mitochondria, and mind: implications in autism spectrum disorders. Microb Ecol Health Dis. 2015;26:28177.
- 89. McLean MH, Dieguez D, Miller LM, Young HA. Does the microbiota play a role in the pathogenesis of autoimmune diseases? Gut. 2015 Feb;64(2):332–41.
- 90. Li B, Selmi C, Tang R, Gershwin ME, Ma X. The microbiome and autoimmunity: a paradigm from the gut-liver axis. Cell Mol Immunol. 2018 Jun 30;15(6):595–609.
- 91. Ettinger G, MacDonald K, Reid G, Burton JP. The influence of the human microbiome and probiotics on cardiovascular health. Gut Microbes. 2014 Nov 2;5(6):719–28.
- 92. Romano KA, Vivas EI, Amador-Noguez D, Rey FE. Intestinal Microbiota Composition Modulates Choline Bioavailability from Diet and Accumulation of the Proatherogenic Metabolite Trimethylamine-N-Oxide. Blaser MJ, editor. MBio. 2015 Mar 17;6(2):e02481.
- 93. Zhu W, Gregory JC, Org E, Buffa JA, Gupta N, Wang Z, et al. Gut Microbial Metabolite TMAO Enhances Platelet Hyperreactivity and Thrombosis Risk. Cell. 2016 Mar;165(1):111–24.
- 94. Brown JM, Hazen SL. Microbial modulation of cardiovascular disease. Nat Rev Microbiol. 2018 Mar 8;16(3):171–81.
- de Theije CGM, Bavelaar BM, Lopes da Silva S, Korte SM, Olivier B, Garssen J, et al. Food allergy and food-based therapies in neurodevelopmental disorders. Pediatr Allergy Immunol. 2014 May:25(3):218–26.
- 96. Umbrello G, Esposito S. Microbiota and neurologic diseases: potential effects of probiotics. J Transl Med. 2016 Oct 19;14(1):298.

- Berding K, Donovan SM. Microbiome and nutrition in autism spectrum disorder: current knowledge and research needs. Nutr Rev. 2016 Dec;74(12):723–36.
- Fung TC, Olson CA, Hsiao EY. Interactions between the microbiota, immune and nervous systems in health and disease. Nat Neurosci. 2017 Feb 16;20(2):145–55.
- 99. Breen DP, Halliday GM, Lang AE. Gut-brain axis and the spread of 8-synuclein pathology: Vagal highway or dead end? Mov Disord. 2019 Mar 17;34(3):307–16.
- 100. Collins SM, Surette M, Bercik P. The interplay between the intestinal microbiota and the brain. Nat Rev Microbiol. 2012 Nov 24;10(11):735–42.
- Hill JM, Lukiw WJ. Microbial-generated amyloids and Alzheimer's disease
   (AD). Front Aging Neurosci. 2015 Feb 10;7.
- 102. Friedland RP. Mechanisms of Molecular Mimicry Involving the Microbiota in Neurodegeneration. J Alzheimer's Dis. 2015 Mar 18;45(2):349–62.
- 103. Seguella L, Capuano R, Sarnelli G, Esposito G. Play in advance against neurodegeneration: exploring enteric glial cells in gut-brain axis during neurodegenerative diseases. Expert Rev Clin Pharmacol. 2019 Jun 3;12(6):555–64.
- 104. Kodukula K, Faller D V, Harpp DN, Kanara I, Pernokas J, Pernokas M, et al. Gut Microbiota and Salivary Diagnostics: The Mouth Is Salivating to Tell Us Something. Biores Open Access [Internet]. 2017 [cited 2018 Oct 261:6(1):123–32.
- 105. Antonio J, Quaresma S, Poidinger M, Ohshima Y, Vitte J, Ghannoum MA, et al. The Gut Microbiome as a Major Regulator of the Gut-Skin Axis. 2018 [cited 2019 Sep 16];
- 106. Dang AT, Marsland BJ. Microbes, metabolites, and the gut-lung axis. Vol.12, Mucosal Immunology. Nature Publishing Group; 2019. p. 843-50.
- 107. Martinez KA, Romano-Keeler J, Zackular JP, Moore DJ, Brucker RM, Hooper C, et al. Bacterial DNA is present in the fetal intestine and overlaps with that in the placenta in mice. PLoS One [Internet]. 2018 [cited 2019 May 26];13(5):e0197439.
- 108. Simrén M, Barbara G, Flint HJ, Spiegel BMR, Spiller RC, Vanner S, et al. Intestinal microbiota in functional bowel disorders: a Rome foundation report. Gut [Internet]. 2013 Jan 1 [cited 2019 Nov 26];62(1):159–76. Available from: https://gut.bmj.com/content/62/1/159
- 109. Sircana A, Framarin L, Leone N, Berrutti M, Castellino F, Parente R, et al. Altered Gut Microbiota in Type 2 Diabetes: Just a Coincidence? Vol. 18, Current Diabetes Reports. Current Medicine Group LLC 1;
- 110. Anand S, Mande SS. Diet, microbiota and gut-lung connection. Front Microbiol. 2018 Sep 19;9(SEP).
- 111. Sun J, Chang EB. Exploring gut microbes in human health and disease: Pushing the envelope. Genes Dis [Internet]. 2014 Dec [cited 2017 Mar 13];1(2):132–9.
- Galvez J, Rodríguez-Cabezas ME, Zarzuelo A. Effects of dietary fiber on inflammatory bowel disease. Mol Nutr Food Res. 2005 Jun;49(6):601–8.

- 113. Cockburn DW, Koropatkin NM. Polysaccharide Degradation by the Intestinal Microbiota and Its Influence on Human Health and Disease. J Mol Biol [Internet]. 2016 Aug 14 [cited 2019 Nov 26];428(16):3230–52.
- 114. El Kaoutari A, Armougom F, Gordon JI, Raoult D, Henrissat B. The abundance and variety of carbohydrate-active enzymes in the human gut microbiota. Nat Rev Microbiol [Internet]. 2013 Jul 10 [cited 2019 Nov 26];11(7):497–504.
- 115. Reichardt N, Vollmer M, Holtrop G, Farquharson FM, Wefers D, Bunzel M, et al. Specific substrate-driven changes in human faecal microbiota composition contrast with functional redundancy in short-chain fatty acid production. ISME J [Internet]. 2018 Feb 1 [cited 2019 Nov 26];12(2):610–22.
- 116. Duncan SH, Belenguer A, Holtrop G, Johnstone AM, Flint HJ, Lobley GE. Reduced dietary intake of carbohydrates by obese subjects results in decreased concentrations of butyrate and butyrate-producing bacteria in feces. Appl Environ Microbiol [Internet]. 2007 Feb [cited 2019 Nov 26];73(4):1073–8.
- 117. De Filippis F, Pellegrini N, Vannini L, Jeffery IB, La Storia A, Laghi L, et al. High-level adherence to a Mediterranean diet beneficially impacts the gut microbiota and associated metabolome. Gut [Internet]. 2016 Nov [cited 2019 Nov 26];65(11):1812–21.
- 118. Jie Z, Xia H, Zhong S-L, Feng Q, Li S, Liang S, et al. The gut microbiome in atherosclerotic cardiovascular disease. Nat Commun [Internet]. 2017 Dec 10 [cited 2019 Nov 26];8(1):845.
- 119. Ettinger G, MacDonald K, Reid G, Burton JP. The influence of the human microbiome and probiotics on cardiovascular health. Gut Microbes [Internet]. 2014 Nov 2 [cited 2017 Mar 13]:5(6):719–28
- 120. Tang WHW, Hazen SL. The contributory role of gut microbiota in cardiovascular disease. J Clin Invest [Internet]. 2014 Oct [cited 2017 Mar 13];124(10):4204–11.
- 121. Viguiliouk E, Stewart SE, Jayalath VH, Ng AP, Mirrahimi A, de Souza RJ, et al. Effect of Replacing Animal Protein with Plant Protein on Glycemic Control in Diabetes: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. Nutrients [Internet]. 2015 Dec 1 [cited 2019 Nov 26];7(12):9804–24.
- 122. Malik VS, Li Y, Tobias DK, Pan A, Hu FB. Dietary Protein Intake and Risk of Type 2 Diabetes in US Men and Women. Am J Epidemiol [Internet]. 2016 Apr 15 [cited 2019 Nov 26];183(8):715–28. Available from: https://academic.oup.com/aje/article-lookup/doi/10.1093/aje/kwv268
- 123. Holmes AJ, Chew YV, Colakoglu F, Cliff JB, Klaassens E, Read MN, et al. Diet-Microbiome Interactions in Health Are Controlled by Intestinal Nitrogen Source Constraints. Cell Metab [Internet]. 2017 Jan 10 [cited 2019 Nov 26];25(1):140–51. Available from: https://linkinghub.elsevier.com/retrieve/pii/S1550413116305538
- 124. Selma M V., Espín JC, Tomás-Barberán FA. Interaction between Phenolics and Gut Microbiota: Role in Human J Agric Food Chem [Internet]. 2009 Aug 12 [cited 2019 Nov 26];57(15):6485–501.

- 125. Sun H, Chen Y, Cheng M, Zhang X, Zheng X, Zhang Z. The modulatory effect of polyphenols from green tea, oolong tea and black tea on human intestinal microbiota in vitro. J Food Sci Technol [Internet]. 2018 Jan 2 [cited 2019 Nov 26];55(1):399–407.
- 126. Williams B, Grant L, Gidley M, Mikkelsen D. Gut Fermentation of Dietary Fibres: Physico-Chemistry of Plant Cell Walls and Implications for Health. Int J Mol Sci [Internet]. 2017 Oct 20 [cited 2019 Feb 14];18(10):2203.
- 127. Sheflin AM, Melby CL, Carbonero F, Weir TL. Linking dietary patterns with gut microbial composition and function. Gut Microbes [Internet]. 2017 Mar 4 [cited 2019 Jun 3];8(2):113–29.
- 128. Larrosa M, Yañéz-Gascón MJ, Selma MV, González-Sarrías A, Toti S, Cerón JJ, et al. Effect of a low dose of dietary resveratrol on colon microbiota, inflammation and tissue damage in a DSS-induced colitis rat model. J Agric Food Chem [Internet]. 2009 Mar 25 [cited 2019 Nov 26];57(6):2211–20.
- 129. De Filippo C, Cavalieri D, Di Paola M, Ramazzotti M, Poullet JB, Massart S, et al. Impact of diet in shaping gut microbiota revealed by a comparative study in children from Europe and rural Africa. Proc Natl Acad Sci [Internet]. 2010 Aug 17 [cited 2019 Nov 26];107(33):14691–6.
- 130. Willett W, Rockström J, Loken B, Springmann M, Lang T, Vermeulen S, et al. Food in the Anthropocene: the EAT-Lancet Commission on healthy diets from sustainable food systems. Lancet [Internet]. 2019 Feb [cited 2019 Nov 26];393(10170):447-92. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0140673618317884
- 131. de Vrese M, Schrezenmeir J. Probiotics, prebiotics, and synbiotics. Adv Biochem Eng Biotechnol 2008;111:1-66.
- 132. Antibiotics: Classification and mechanisms of action with emphasis on molecular perspectives.; 2016.
- 133. Blaser MJ. Antibiotic use and its consequences for the normal microbiome. Science 2016 -4-29;352(6285):544-545.
- 134. Bush K. CHAPTER 14 ß-Lactam antibiotics: penicillins. In: Finch RG, Greenwood D, Norrby SR, Whitley RJ, editors. Antibiotic and Chemotherapy (Ninth Edition) London: W.B. Saunders; 2010. p. 200-225.
- 135. Dinos GP. The macrolide antibiotic renaissance. British Journal of Pharmacology 2017 Sep;174(18):2967-2983.
- 136. Grossman TH. Tetracycline Antibiotics and Resistance. Cold Spring Harbor perspectives in medicine 2016 Apr 1,;6(4):a025387.
- 137. Batra P, Deo V, Mathur P, Gupta AK. Cotrimoxazole, a wonder drug in the era of multiresistance: Case report and review of literature. J Lab Physicians 2017;9(3):210-213.
- 138. Chaudhary AS. A review of global initiatives to fight antibiotic resistance and recent antibiotics' discovery. Acta pharmaceutica Sinica. B 2016 Nov 1,;6(6):552-556.
- 139. Li B, Webster TJ. Bacteria antibiotic resistance: New challenges and opportunities for implant-associated orthopedic infections. J Orthop Res 2018 01;36(1):22-32.

- 140. Hofer U. The cost of antimicrobial resistance. Nat Rev Microbiol 2019 01;17(1):3.
- 141. Ventola CL. The antibiotic resistance crisis: part 1: causes and threats. P & T : a peer-reviewed journal for formulary management 2015 Apr:40(4):277-283.
- 142. Goossens H, Ferech M, Vander Stichele R, Elseviers M. Outpatient antibiotic use in Europe and association with resistance: a cross-national database study. Lancet 2005 Feb 12-18;365(9459):579-587.
- 143. Yoon MY, Yoon SS. Disruption of the Gut Ecosystem by Antibiotics. Yonsei medical journal 2018 Jan;59(1):4-12.
- 144. Landers TF, Cohen B, Wittum TE, Larson EL. A Review of Antibiotic Use in Food Animals: Perspective, Policy, and Potential. Public Health Rep 2012 Jan 1,;127(1):4-22.
- 145. Langdon A, Crook N, Dantas G. The effects of antibiotics on the microbiome throughout development and alternative approaches for therapeutic modulation. Genome Med 2016 -4-13;8.
- 146. Sun L, Ma L, Ma Y, Zhang F, Zhao C, Nie Y. Insights into the role of gut microbiota in obesity: pathogenesis, mechanisms, and therapeutic perspectives. Protein Cell 2018 05:9(5):397-403.
- 147. Jackson C, Hsia Y, Bielicki JA, Ellis S, Stephens P, Wong ICK, et al. Estimating global trends in total and childhood antibiotic consumption, 2011-2015. BMJ Global Health 2019 Feb;4(1):e001241.
- 148. WHO | Rational use of medicines. Available at: http://www.who.int/medicines/areas/rational use/en/ (Links to an external site.).
- 149. McDonagh MS, Peterson K, Winthrop K, Cantor A, Lazur BH, Buckley DI. Interventions to reduce inappropriate prescribing of antibiotics for acute respiratory tract infections: summary and update of a systematic review. J Int Med Res 2018 Aug;46(8):3337-3357.
- Kutty N. Treating Children Without Antibiotics in Primary Healthcare.
   Oman Med J 2011 -9;26(5):303-305.
- 151. Easton G, Saxena S. Antibiotic prescribing for upper respiratory tract infections in children: how can we improve? London journal of primary care 2010 Jul;3(1):37-41.
- 152. Daliri EB, Lee BH. New perspectives on probiotics in health and disease. Food Science and Human Wellness 2015 Jun;4(2):56-65.
- 153. Ganguly NK, Bhattacharya SK, Sesikeran B, Nair GB, Ramakrishna BS, Sachdev HPS, et al. ICMR-DBT Guidelines for Evaluation of Probiotics in Food. Indian J Med Res 2011 -7;134(1):22-25.
- 154. Probiotics Market Size & Share | Industry Research Report, 2019-2025. Available at: https://www.grandviewresearch.com/industry-analysis/probiotics-market (Links to an external site.).
- 155. Rondanelli M, Faliva MA, Perna S, Giacosa A, Peroni G, Castellazzi AM. Using probiotics in clinical practice: Where are we now? A review of existing meta-analyses. Gut Microbes 2017 Nov 2,;8(6):521-543.

- 156. Suez J, Zmora N, Zilberman-Schapira G, Mor U, Dori-Bachash M, Bashiardes S, et al. Post-Antibiotic Gut Mucosal Microbiome Reconstitution Is Impaired by Probiotics and Improved by Autologous FMT. Cell 2018 09 06;;174(6):1406-1423.e16.
- 157. Zmora N, Zilberman-Schapira G, Suez J, Mor U, Dori-Bachash M, Bashiardes S, et al. Personalized Gut Mucosal Colonization Resistance to Empiric Probiotics Is Associated with Unique Host and Microbiome Features. Cell 2018 09 06,;174(6):1388-1405.e21.
- 158. Tao Y, Gu Y, Mao X, Zhang L, Pei Y. Effects of probiotics on type II diabetes mellitus: a meta-analysis. J Transl Med 2020 -1-17;18.
- 159. Khalesi S, Sun J, Buys N, Jayasinghe R. Effect of Probiotics on Blood Pressure: A Systematic Review and Meta-Analysis of Randomized, Controlled Trials. Hypertension 2014 July 21,;DOI:10.1161/ HYPERTENSIONAHA.114.03469.
- 160. Wilkins T, Sequoia J. Probiotics for Gastrointestinal Conditions: A Summary of the Evidence. American family physician 2017 Aug 1,:96(3):170.
- 161. Huang R, Hu J. Positive Effect of Probiotics on Constipation in Children: A Systematic Review and Meta-Analysis of Six Randomized Controlled Trials. Front Cell Infect Microbiol 2017;7.
- 162. Hayes SR, Vargas AJ. Probiotics for the prevention of pediatric antibiotic-associated diarrhea. Explore (NY) 2016;12(6):463-466.
- 163. Lau CS, Chamberlain RS. Probiotics are effective at preventing Clostridium difficile-associated diarrhea: a systematic review and meta-analysis. Int J Gen Med 2016 -2-22;9:27-37.
- 164. Wei D, Heus P, van de Wetering, Fleur T., van Tienhoven G, Verleye L, Scholten RJ. Probiotics for the prevention or treatment of chemotherapy- or radiotherapy-related diarrhoea in people with cancer. Cochrane Database Syst Rev 2018 08 31,:8:CD008831.
- 165. Hao Q, Dong BR, Wu T. Probiotics for preventing acute upper respiratory tract infections. Cochrane Database of Systematic Reviews 2015(2).
- 166. Felis GE. Effects of Probiotics on Cognitive Reactivity, Mood, and Sleep Quality. Frontiers in Psychiatry 2019 Mar 1,;10.
- 167. Wu D, Wu C, Zhang S, Zhong Y. Risk Factors of Ventilator-Associated Pneumonia in Critically III Patients. Front Pharmacol 2019 -5-09;10.
- 168. Luedtke SA, Yang JT, Wild HE. Probiotics and Necrotizing Enterocolitis: Finding the Missing Pieces of the Probiotic Puzzle. J Pediatr Pharmacol Ther 2012;17(4):308-328.
- 169. Sharland M, Kendall H, Yeates D, Randall A, Hughes G, Glasziou P, et al. Antibiotic prescribing in general practice and hospital admissions for peritonsillar abscess, mastoiditis, and rheumatic fever in children: time trend analysis. BMJ 2005 Aug 06,;331(7512):328-329.
- 170. Kenealy T, Arroll B. Antibiotics for the common cold and acute purulent rhinitis. Cochrane Database Syst Rev 2013 Jun 04,(6):CD000247.

- 171. Spinks A, Glasziou PP, Del Mar CB. Antibiotics for sore throat. Cochrane Database Syst Rev 2013 Nov 05,(11):CD000023.
- 172. Glasziou PP, Del Mar CB, Sanders SL, Hayem M. Antibiotics for acute otitis media in children. Cochrane Database Syst Rev 2004(1):CD000219.
- 173. Thompson PL, Gilbert RE, Long PF, Saxena S, Sharland M, Wong ICK. Effect of antibiotics for otitis media on mastoiditis in children: a retrospective cohort study using the United kingdom general practice research database. Pediatrics 2009 Feb;123(2):424-430.
- 174. Ma Y, Liu J, Rhodes C, Nie Y, Zhang Ethical Issues in Fecal Microbiota Transplantation in Practice. The American Journal of Bioethics [Internet]. 2017 [cited 26 November 2019];17(5):34-45.
- 175. Walker, A. W. & Parkhill, J. Fighting Obesity with Bacteria. Science (80-). 341, 1069–1070 (2013)
- 176. Wang A, Popov J, Pai N. Fecal microbial transplant for the treatment of pediatric inflammatory bowel disease. World Journal of Gastroenterology [Internet]. 2016 [cited 26 November 2019];22(47):10304.

