Medicines, Our Gut Microbiota and Us

Your grandmother and my grandmother were both treated with the same medicine. Why is your grandmother recovering faster than mine?

Photo by Efrem Efre : https://www.pexels.com/photo/women-sitting-on-bench-with-a-dog-12794999/

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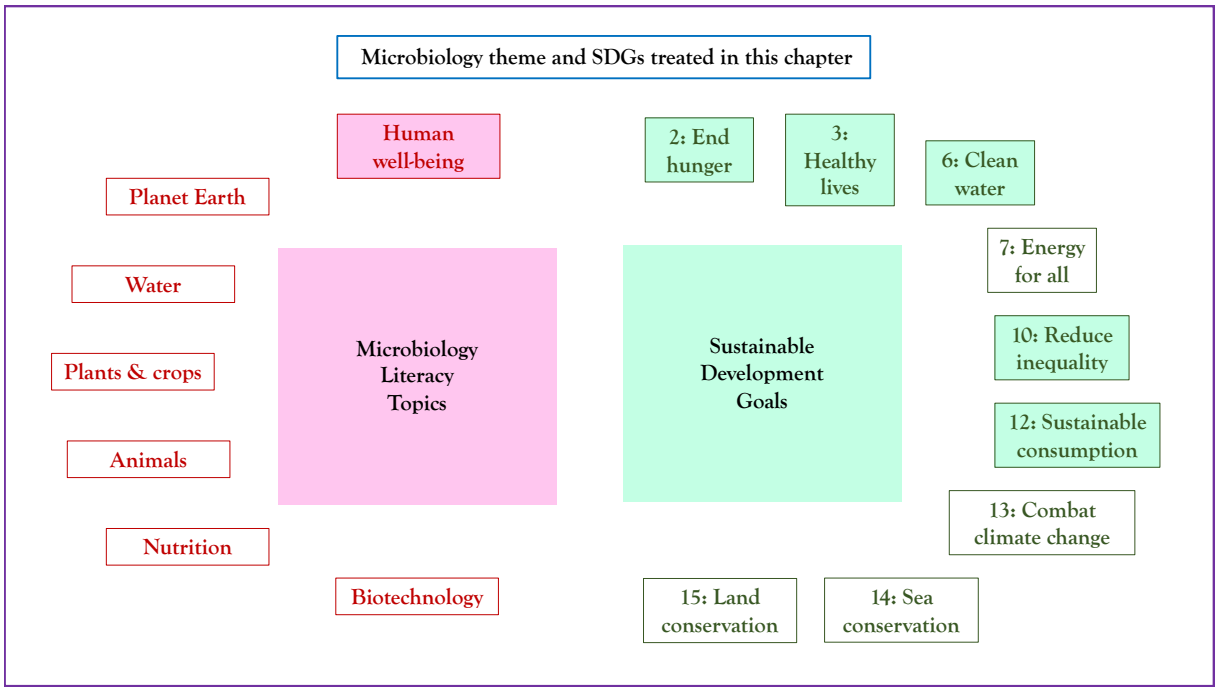
Medicines and the microbiome

Storyline

Millions of microorganisms, known collectively as our 'human microbiota', are living in our body and working side-by-side with our cells to keep us healthy. About 90% of these microbes are bacteria, of which the vast majority reside in the gut. Every person harbors a unique gut microbial community which helps to digest food, produces vitamins, and protects us from infections. However, the bacteria in our intestine have also been shown to break down medical drugs and thereby change the effect of the drugs on us. Furthermore, gut bacteria can be affected not only by antibiotics but also by other medicines we take. In this lesson, we describe what we currently know about the fascinating interaction between medical drugs and our microbiota, and how this knowledge can be used to change the efficacy of medical treatments.

The Microbiology and Societal Context

The microbiology: gut microbiome; influence of medicines on gut microbiota composition and activities; degradation of medicines by gut microbiota; production of new metabolites that affect us; *Sustainability issues:* end hunger; healthy lives; clean water; reduce inequality; sustainable consumption.



Medicines and the microbiome: the Microbiology

1. ***Our microbiomes.*** For a long time, microbes were only considered as a threat for human health, which resulted in a research focus on pathogenic bacteria. As we learned more and more about pathogens and how they make us sick, our fear of microbes increased. Meanwhile, we have however learned that most of the microorganisms living in and on the human body, collectively known as the human microbiota, are not harmful, and many of them are in fact beneficial. This microbial community consists of 10-100 trillion cells and contains an enormous diversity of bacteria, archaea, viruses and fungi. They colonize internal and external body surfaces including the gut, skin, oral mucosa, and conjunctiva.

2. ***DNA sequencing is the enabler of microbiome research.*** DNA sequencing is the technology that allows us to 'read' genomes – their sequences of A, T, G and C – and decipher what each gene codes for. Thanks to the recent developments in DNA sequencing technologies, our understanding of the role of the human microbiota in our health has hugely improved. For example, it is now possible to analyze the genetic material present in human-derived stool samples ('poo') and identify the thousands of microbial species that are present in the intestine. This type of analysis allows us to describe how many different types of microbes are present (microbial diversity) and their abundance. Furthermore, it is also possible to look for the presence of microbial genes of interest (*e.g.*, genes that confer antibiotic resistance). Using these approaches, scientists found that about 90% of the human microbiota are bacteria and most of them live in the intestinal tract.

The gut microbiota, the use of medication and antimicrobial resistance genes development

The development of antimicrobial resistance (AMR) is a global concern that threatens our future ability to fight infectious diseases. This encouraged the World Health Organization (WHO) to propose the "Global action plan on antimicrobial resistance". In this context, the gut microbiota of humans and animals represent an important reservoir of AMR genes. Pathogens could acquire AMR genes from gut bacteria through horizontal gene transfer (movement of genetic material from one organism to another that is not its offspring).

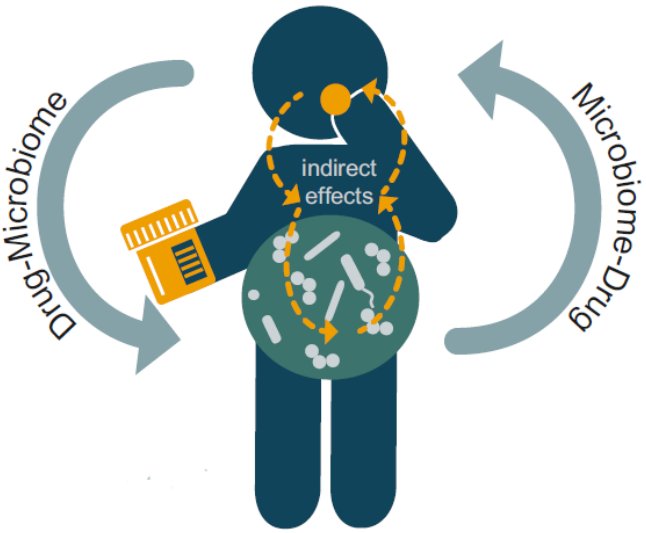
One of the most common causes of AMR development is the improper and extensive use of antimicrobial drugs. However, the impact of non-antibiotic drugs on AMR development is currently researched. Recent DNA sequencing analysis of human fecal samples revealed that commonly used medicinal drugs increase the abundance of some AMR genes. We expect that future investigations will shed light into the relationship between non-antibiotic drugs and the development of AMR and that they should potentially be considered as part of the Global action plan on fighting antimicrobial resistance (*see Potential Implications for Decisions section in this article*).

3. ***Microbiomes differ between individuals: yours is different from mine!*** The estimated number of bacterial cells in our bodies is at least as high as the number of human cells, which requires regulated interactions between our body and the gut bacteria. Indeed, gut bacteria can interact with human cells to directly influence their functioning. For example, bacteria can digest the food that we eat or synthesize vitamins. They can also protect us from infections by preventing

pathogen colonization, and by training our immune system. Due to the finely-tuned interactions between the microbiota and its human host, perturbations of the microbiota can strongly impact human health.

Interestingly, there is an enormous interpersonal variation in the gut bacteria composition among humans and every person harbors a unique microbial community. What we eat or drink, which medical drugs we take, but also factors such as our health status, lifestyle and genetics, seem to influence the composition of our microbiome. Here, we analyze the impact of this diversity in the context of medical drug treatments.

Scheme of the reciprocal interactions between the host, medical drugs and the gut microbiota.



Left: The intake of drugs can have a direct influence on individual members of the gut microbiota but can also change the composition and functionality of the microbiome through indirect, host-mediated ways (e.g., changes in the gut environment, such as pH, due to the use of medical drugs). Right: Intestinal bacteria can modify and breakdown drugs. These complex interactions could cause interpersonal differences in treatment outcomes. Scheme adapted from Zimmermann et al, 2021

4. ***What is the relationship between the gut microbiota and medical drugs?*** Most commonly used drugs are administered orally and travel through the gastrointestinal tract to be absorbed, typically in the small intestine. Once in the bloodstream, they are distributed throughout the body and hence to their target tissue(s), where they do their job to make us better. Eventually, drugs are transported to the liver where they can be broken down and then be eliminated via the urine or secreted back to the intestine.

During their passage through the intestine, drugs are exposed to the huge diversity of gut microbes. There, medical drugs, including antibiotics but also non-antibiotic drugs, can directly affect these gut bacteria by inhibiting their growth. Indeed, the use of medication seems to be an important driver of the pronounced interpersonal variation in the composition of human gut microbiome. On the other hand, like the liver, gut bacteria are also able to break down medical drugs and, when they do so, they modify their activities on our body. This bidirectional drug-microbe interaction can have important implications in medical treatments.

5. ***Medication shapes our gut microbiome composition.*** It is not unexpected that antimicrobials like antibiotics, antifungals, or antivirals, can impact our microbiota, as they are specifically designed to inhibit microorganisms. As a consequence of antibiotic treatments, the gut microbiome composition often changes. Surprisingly, a broad range of non-antibiotic drugs that target human cells, such as antidiabetics, antipsychotics, anti-inflammatory drugs, and laxatives, can also alter the gut microbiome composition following administration. These observations made with patients was also confirmed by experiments in the laboratory using isolated bacterial species exposed to medical drugs. In these experiments, scientists showed that many non-antibiotic drugs can inhibit growth of certain gut bacteria, whereas other bacterial strains are not affected.

6. ***Why do non-antibiotic drugs affect microbial cells?*** We do not know yet, but initial evidence suggests that these drugs may be functionally perceived in the same way that antibiotics are, and treated similarly. For example, some bacterial species develop resistance to antibiotics through the expression of efflux pumps which transport the antibiotic out of the bacteria, i.e. immediately expel any drug taken into the cell. Such pumps may also be activated as a result of exposure to non-antibiotic drugs, rendering microbe's resistant to non-antibiotics as well. Future research will deepen our understanding of the mode of action of non-antibiotic drugs on bacterial cells, their impact at community level, and how to avoid undesired shifts in the gut microbiota due to their usage.

7. ***Our gut microbiota can break down medical drugs.*** Recent research suggests that microbial drug metabolism, which is the chemical transformation of a drug that takes place in microbial cells, is a common phenomenon. When medical drugs reach the gut, they can be activated, inactivated or converted to other compounds (*e.g.*, toxic products) by the activity of gut microbes. This occurs because gut microbial cells contain molecular machines (enzymes) which modify a wide range of molecules, including complex carbohydrates and fibers commonly present in our food. Using the same machineries, the microbes can also break down a diverse range of medical drugs. As a consequence, microbial drug metabolism can impact intestinal drug concentrations and their breakdown products, altering both drug responses and adverse effects.

8. ***Microbiome differences between individuals may produce different responses to medicines.*** The microbiome and its pronounced interpersonal variation in composition are considered one of the possible reasons for the observed variation in the response to the same medication. That is why the issue of host-drug-microbiota interactions are gaining more attention in pharmaceutical research. While previous efforts mainly focused on human drug metabolism, increasing attention is given to microbial drug metabolism. One of the goals in the field is to elucidate the molecular mechanisms involved in this drug metabolism. The aim is to better understand how interpersonal differences in microbiome composition contribute to the interpersonal variation in both desired and adverse drug effects. Eventually, this will enable us to find new strategies for medical treatments in the future, and in particular to personalize clinical treatments to take into account patient differences.

9. ***Microbiota as a primary therapeutic target.*** In the previous sections, we discussed that while medication can change the microbiome composition, microbes are also able to metabolize

the drugs. Although we are only starting to understand how the host-drug-microbiota triad works, the perspectives are promising. These insights could be harnessed in a broad range of applications to improve drug efficacy and reduce adverse effects.

Currently, decisions about which drug and dose are most suitable for a given patient takes into account only human factors such as weight, blood parameters, and liver metabolism. With the increasing amount of research in the microbiome field, it will be possible to link the presence of certain gut bacteria and/or their enzymes with the efficacy of a medical treatment. For instance, the gut bacterium *Eggerthella lenta* metabolises and therefore is capable of reducing the concentration of digoxin, a drug used to treat heart failure and arrhythmias. Scientists identified the enzymes involved in digoxin metabolism and could demonstrate that their presence predicts digoxin treatment success.

As an alternative to the adaptation of the medical treatment to a specific microbiota, a patient's microbiota could also be modulated in order to improve the efficacy of a given therapy. The gut microbiota could be modified by different strategies including abiotic or biotic factors. Examples of abiotic approaches are the consumption of certain types of food, prebiotics (compounds that promote the growth of beneficial bacterial species) or postbiotics (the functional component extract of beneficial microbes). In the example of digoxin, researchers observed that increased protein consumption decreases the production of digoxin-reducing enzymes of *E. lenta*. This means that more protein in the diet results in less digoxin degradation by *E. lenta*, thus increased digoxin in the body leading to better therapeutic effect. This example illustrates how an abiotic factor (the proteins) can substantially change the efficacy of a medical treatment (digoxin).

Biotic approaches for microbiota modulation are based on biological agents, such as probiotic strains/communities (beneficial bacterial strains), engineered strains (bacterial species genetically modified to have a desired therapeutic effect for the patient) or phages (viruses that infect bacteria). In all these cases, the idea is to increase the abundance of the beneficial bacteria (for example, those which help to activate a drug) and/or decrease the amount of non-desired species (*e.g.* the strains that make a drug more toxic). These simple interventions hold the promise to increase the efficacy of existing and future medical drug treatments.

In some cases, it is not possible to adapt the medical treatment to the patient's microbiota and/or to modulate the microbiota to maximize the therapeutic effect. For example, antibiotics are indispensable to fight infections. These antibiotic treatments will however cause collateral damage on the microbiome composition. To restore the microbiota, fecal microbiota transplantation (FMT) has been successfully applied. In an FMT, gut microbiota is transferred from one person to another. FMT could be the microbiota collected from a healthy person or the person's own microbiota before the medical treatment (known as autologous FMT). Finally, the use of the previously mentioned microbiota abiotic and biotic modulating factors is also valid to contribute in the recovering of a healthy microbiota.

There are still many challenges to overcome in order to translate microbiome research to the clinics, including identifying the most efficient method in each situation or condition, understanding if the changes are transient or permanent, and evaluation of the costs and benefits of the intervention, and possible undesired secondary consequences. However, scientists are working to find the answers to these questions and start considering the microbiota as a factor in future therapeutic approaches.

Relevance for Sustainable Development Goals

The host-drug-microbiota interaction can be considered in the context of the following Sustainable Development Goals:

- **Goal 2. End hunger, achieve food security and improved nutrition and promote sustainable agriculture.** As in humans, the gut microbiota is essential for animal health. Medication (mainly antibiotics) is frequently administered to farm animals, also altering their gut microbiota. Apart from the global consequences in animal health, the use of medical drugs could also promote antimicrobial resistance (AMR) development in the gut microbiota of these animals. As gut bacteria can act as a reservoir of the AMR genes, farm animals are a potential source of new types of AMR. In line with this, the WHO recommends to only administer antibiotics to animals under veterinary supervision and to not use antibiotics for growth promotion or to prevent diseases in healthy animals. Although the impact of non-antibiotic drugs is still under research, we could extend these recommendations to all types of veterinary drugs. Together, these actions agree with the sustainable and conscious perspective in food production.
- **Goal 3. Ensure healthy lives and promote well-being for all at all ages.** The promising strategies mentioned in this article, which position the microbiota as a primary therapeutic target, will help to improve drug treatment efficacy. By modulating the gut microbiota, we could increase desired and decrease adverse treatment effects. Moreover, actions to maintain a healthy microbiota, for example, by simple changes in food, could have a positive impact on human health thus reducing the need for drugs. This is especially relevant in elderly people, as their consumption in medical drugs is typically higher compared to the rest of the population.
- **Goal 6. Clean water.** A significant proportion of medication taken by patients, and the metabolites produced from them through the activities of microbes and the liver, end up in urine and feces and are excreted into our wastewater. Some of these are long-lived and pass through wastewater treatment plants into surface waters and ultimately into groundwater, both of which may serve as drinking water supplies. Thus, drugs targeted to specific patients, and the metabolites from the microbiota of these patients, may after a journey, be taken up by a non-target community. Fortunately, the concentrations of these chemicals is very low at this stage, but it is believed that long term chronic exposure to such chemicals is not without risk. It is therefore crucial that we (a) determine which drugs and metabolites in drinking water are the most dangerous for us, (b) monitor their levels in discharged wastewater and drinking water, and (c) find effective new ways to remove them from drinking water.
- **Goal 10. Reduce inequality within and among countries.** The microbiota as a therapeutic target could represent an alternative to expensive therapies, making them more accessible to people independently of their economic status. For example, by changing food or taking specific supplements to modulate the microbiota, a medical treatment could significantly improve its efficacy at affordable costs.
- **Goal 12. Sustainable consumption and production**. Sustainability requires circularity, i.e. no release of substances into the environment after use. This is obviously not the case with medication which go from pharmacy to patient to wastewater. In addition, unused medication is often thrown into the trashcan and end up in a landfill, where they can leach out into the environment, or into the toilet, where they end up in wastewater. It is absolutely essential that unused medication is returned to the pharmacy for safe disposal. And, as indicated above, it is equally important that medication in wastewater are specifically targeted for destruction.

Potential Implications for Decisions

1. ***Individual***
    a. How can I modulate my microbiota to keep myself healthy?
    b. In case I need it, how can I modulate my diet/lifestyle to make medical drug treatment more efficient?
    c. Now that we are aware about the host-drug-microbiota interaction, it is important to avoid medication without any medical prescription. The medical drug consumption should be always under doctor indication who will control and evaluate the cost/benefit of the treatment.
    d. Medication in animals: always under prescription of a veterinarian.
    e. What do I do with that bottle of unused drug?

2. ***National policies***
    a. Incorporate the human microbiota in the discussion about the healthcare system and future research in the field.
    b. Guarantee the access to medical drugs which had more beneficial effect on the patients and on their microbiome as well.
    c. Promote campaigns for the rational use of medical drugs in humans but also in animals.

Pupil Participation

1. ***Class discussion of the issues associated with medication and microbiome.***

2. ***Pupil stakeholder awareness***
    a. Create a concept map to show the relationship between the environment/human, microbiome and medication.
    b. Explain how microbiota can impact the efficacy of drugs.
    c. Identify and highlight the mechanism through which non-antimicrobial drugs can contribute to the development of AMR.
    d. List possible ways of avoiding negative effects of medical drugs on the microbiome.
    e. Read through the sustainable development goals in the context of microbiota and medications. Identify the goal that you find the most important and provide a reasoning.

The Evidence Base, Further Reading and Teaching Aids

General articles about this topic:

- Common medications accumulate in gut bacteria. EMBL Communications (2021)
- 'When gut bacteria spoil drug treatment'. The science breaker. Sep 18, 2019. https://doi.org/10.25250/thescbr.brk262
- Commonly used drugs affect our gut bacteria. EMBL Communications (2018)
- Hannah Voak (2017) Manipulating the gut microbiome: the potential of poo. Science in school. 40
- Poo transplants better understood. EMBL Communications (2016)

- Global plan action on antimicrobial resistance. World Health Organization: https://www.who.int/publications/i/item/9789241509763
- The Sustainable Development Goals, United Nations (2015). https://sdgs.un.org/goals

Resources

- Video 'Non-Antibiotic Drugs Affect our Gut Bacteria': https://www.youtube.com/watch?v=4NQAmYvBfRc
- Video 'Do Gut Bacteria Contribute To Drug Metabolism?': https://www.youtube.com/watch?v=LyjiVRRhIzM
- Podcast: Microbes modifying medicine and kick starting plate tectonics. https://www.nature.com/articles/d41586-019-01775-6

Scientific publications

- Falony G, Joossens M, Vieira-Silva S, Wang J, Darzi Y, Faust K, Kurilshikov A, Bonder MJ, Valles-Colomer M, Vandeputte D et al (2016) Population-level analysis of gut microbiome variation. Science 352: 560 – 564
- Haiser HJ, Gootenberg DB, Chatman K, Sirasani G, Balskus EP, Turnbaugh PJ (2013) Predicting and manipulating cardiac drug inactivation by the human gut bacterium *Eggerthella lenta*. Science 341: 295 – 298
- Maier L, Pruteanu M, Kuhn M, Zeller G, Telzerow A, Anderson EE, Brochado AR, Fernandez KC, Dose H, Mori H et al (2018) Extensive impact of nonantibiotic drugs on human gut bacteria. Nature 555: 623 – 628
- Maier L, Typas A (2017) Systematically investigating the impact of medication on the gut microbiome. Curr Opin Microbiol 39: 128 – 135
- Zimmermann M, Zimmermann-Kogadeeva M, Wegmann R, Goodman AL (2019) Separating host and microbiome contributions to drug pharmacokinetics and toxicity. Science 363: eaat9931
- Zimmermann M, Zimmermann-Kogadeeva M, Wegmann R, Goodman AL (2019) Mapping human microbiome drug metabolism by gut bacteria and their genes. Nature 570: 462 – 467
- Zimmermann-Kogadeeva M, Zimmermann M, Goodman AL (2020) Insights from pharmacokinetic models of host-microbiome drug metabolism. Gut Microbes 11: 587 – 596
- Zimmermann, M. Patil, KR, Typas A, Maier L, Towards a mechanistic understanding of reciprocal drug microbiome interactions. Mol Syst Biol. (2021) 17: e10116
- Vich Vila, A., Collij, V., Sanna, S. et al. Impact of commonly used drugs on the composition and metabolic function of the gut microbiota. Nat Commun 11, 362 (2020). https://doi.org/10.1038/s41467-019-14177-z

Glossary

Efflux pump: transport proteins present in the cell membrane that have the function of exporting chemical compounds from inside the cell to the environment.

Engineered strains: bacterial species genetically modified to express specific therapeutic properties.

Enzyme: a protein that catalyzes (accelerates) chemical reactions.

Fecal microbiota transplantation (FMT): transfer the entire microbial gut community from one person to another. *Autologous* FMT refers to the transplantation of the microbial gut community of a person to the same person after a medical intervention.
Horizontal gene transfer: movement of genetic material from one organism to another that are not the offspring.
Human gut microbiota: the microbiota that lives in the human gastrointestinal tract.
Microbiota: the ecological community of microorganisms (bacteria, virus, fungi, archaea).
Metabolism: is the set of chemical reactions that occurs in every organism.
Metagenomics: is the study of the entire collection of DNA coming from a complex sample with several species, usually, microbes.
Pathogen: it is an organism (in this case microorganism) that can cause a disease.
Phages: specific type of virus that infects and replicates within bacterial cells.
Postbiotics: the functional output of beneficial microbes.
Prebiotic: specific compounds, such as certain sugars, that are preferred by microbiome subpopulation leading to their increase in abundance.
Probiotic: specific bacterial strains intended for therapeutic purposes. They are GRAS-certified (generally regarded as safe) by the Food and Drug Administration and include microbes from different phyla.

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