

The Human Gut Microbiome and the Dissemination of Antibiotic Resistant Microbes

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ABSTRACT

As the impending danger of antibiotic resistance continues to rise, research into the largest reservoir of resistance genes is just starting to gain traction. The human gut microbiome represents a fundamental step in better understanding how antibiotic resistance develops, why it develops, and how it can be mitigated. Changing healthcare procedures and antibiotic prescriptions in pursuit of slowing down or outright preventing the arrival of a post-antibiotic era begins from infant's care and that of their mothers, and extends long into their (hopefully healthy) lifetimes.

It is not only healthcare procedures and prescriptions that require adjustment. The pharmaceutical industry's response to resistant bacteria was to simply make more powerful, broad-spectrum antibiotics. While this strategy was effective in the short term, it is beginning to show two fatal flaws. The first is that it damages the gut microbiome, and encourages antibiotic resistance. The second is that it is beginning to become economically unviable to research new broad-spectrum antibiotics. Narrow-spectrum antibiotics seek to solve both of these issues simultaneously, by providing a targeted attack against pathogens while sparing other microbiota, and allowing for economic incentive.

Finally, it is crucial to enhance education and outreach about the microbiome and antibiotic resistance. Since the topic is often excluded from school curriculums, not covered on exams, and lacks engaging learning material, many people lack understanding of basic concepts such as resistance and the roles of the microbiome. It is seen as a distant issue, one that does not directly affect the individual, and one the individual cannot affect. This cannot be further from the truth; by simply maintaining good gut health and using antibiotics responsibly, one is already contributing towards the solution.

Keywords

Bacteria, Human gut microbiome, Antibiotic Resistance, Livestock.

Introduction

The Human Gut Microbiome

The human gut microbiome is a new focus of research that has received much attention in recent years. Frustratingly, however, there remain many hurdles to fully understanding it. In general, the gut microbiome is a community of bacteria that inhabit the intestines. They can be categorized by diversity, stability

and resilience, relative prevalence of certain species, among other metrics, but these metrics often do not provide a way to precisely and reliably inform or guide health recommendations. Nevertheless, the microbiome collectively conducts a plethora of roles, both in the gut and in the body at large. In fact, the gut microbiome is not a passive entity within one's body; it plays essential roles in antibiotic and brain functions, among other things. Just as diverse as its roles are the things that affect the composition of the microbiome: age, genetics, birthing method, exercise, body weight, age, diet, disease, and of course, antibiotics [1].

Since the gut microbiome is often directly affected by broad-spectrum antibiotics, it harbors more antibiotic resistant bacteria than any other known environment. Beneficial bacteria may also play a role in passing resistance to pathogenic bacteria, further disseminating harmful antibacterial resistance. Once passed on, this resistance can persist for years, even in the absence of selective pressures encouraging it.

Antibiotic Resistance

Antimicrobial resistance (a broad term that encompasses antibiotic and antifungal resistance) is defined by the CDC as a microbe's development of the ability to neutralize the effects of drugs designed to kill them, enabling them to persist in their host [2]. Infection by such microbes is difficult to treat, not in the least due to the emergence of multi-drug resistant bacteria. Many such bacteria have enhanced transmissibility and morbidity due to resistance to classes of antibiotics specifically developed to combat them, especially in hospital-linked (nosocomial) infections. Resistance generally develops due to selective pressures imposed by the use of antibiotics, though the specific pathways generally take on two separate paths: intrinsic resistance and gene juggling [3].

Intrinsic resistance is a microbe's pre-existing ability to neutralize a drug, or at least a genetic aptitude to do so. A notable example was the discovery of bacterial penicillinases prior to the introduction of penicillin as a therapeutic. However, a pre-existing defense is not always discovered. In many cases, resistance develops because of gene amplification, or as a result of hypersensitivity to antibiotics in bacteria with mutated genomes. Additionally, bacteria that produce antibiotics often have resistance to the compounds they produce, and have been linked to clinical cases of resistance. Intrinsic resistance is an important area of research, as it can allow antibiotics to remain viable for longer thanks to reliable predictions of potential resistance pathways and appropriate mitigations [3].

Gene juggling is simply the random mutation of pre-existing enzyme genes, in a way that broadens their resistance spectra. Since resistance is nearly always biochemically possible, some combination of mutations will eventually arise, allowing a subset of microbes resistance. This resistance is not always fully transmissible, but it is possible for a fully resistant bacterium to impart partial resistance upon another, which may then go on to develop full resistance on its own [3].

Public Perceptions of Antibiotic Resistance and the Human Microbiome

Understanding one's own microbiome and the effects of antibiotics have become essential in administering a healthy lifestyle in the modern age, but there seems to be a severe lack of deep understanding among most, barring individuals who have studied these topics in grade school or college [4].

In a study done in the United Kingdom among adolescents aged 14-18, students who did not take advanced biology courses could say little about antibiotics and resistance beyond the importance of completing the full course of medication and following a

doctor's orders. Some even confused antibiotic resistance with drug dependence, while others thought the issue was irrelevant to their lives. When asked about the human microbiome, many of the participants demonstrated knowledge they received primarily through advertising and general media channels, such as high-fiber foods and yogurts containing live cultures being beneficial to gut health. They also noted that the microbiome contained "good bacteria" that helped the body digest foods it could not and fight "bad bacteria," and some reported they would seek alternatives to antibiotics if available in an effort to avoid harming their "good bacteria" [4].

On the other hand, students who took advanced biology courses demonstrated a better understanding of antibiotic resistance, linking it to antibiotic consumption in general and neglecting to complete a full course of antibiotics in particular. Additionally, they showed a genuine concern regarding antibiotic resistance [4].

Educators surveyed on the microbiome and antibiotic resistance fell into two categories: some were not comfortable teaching the material and felt a need to learn more about it themselves, while others were ready to teach material related to the topics. However, neither topic was covered in traditional trainings. Although the educators were motivated to cover the material overall, the fact that the topics were left out of school curriculums and tight school schedules meant that it would be impossible to incorporate into the classroom. Not only that, many educators were concerned about student engagement, citing a lack of worksheets, interactive activities, and educational animations and videos [4].

The Microbiome and Antimicrobial Resistance

Early Years: Antimicrobial Resistance in Infants

The metrics of every individual's microbiome are initially dictated very early on, even before birth. Mothers who take antibiotics during pregnancy or immediately prior to giving birth pass on lower amounts of bifidobacteria to their children, and the same is true of infants born by cesarean section. In addition, mothers who breastfeed their children while taking antibiotics also reduce the amount of bifidobacteria passed on. Bifidobacteria play an essential role in the infant microbiome, keeping bacterial strains that quickly develop resistance in check and encouraging diversity. With a decreased amount of bifidobacteria, the infants carry larger amounts of the bacteria that act as primary reservoirs of resistance genes [5]. It should be noted that the effects of a mother taking antibiotics are comparable to the infant taking the antibiotics directly, and that breastmilk is an essential source of bifidobacteria for infants [6].

Effect of Antibiotic Treatment on the Microbiome

It is well-known that non-discriminatory, broad-spectrum antibiotics affect the gut microbiome, but quantifying the exact effect is difficult. In a study conducted on mice, the intake of antibiotics (Ampicillin, Ciprofloxacin, and Fosfomycin across the three experimental groups) not only decreased the number of detectable species of bacteria by as much as 20 times, it also massively increased the relative prevalence of opportunistic

bacteria commonly associated with nosocomial infections. These opportunistic bacteria did exist in the gut microbiome prior to administration of antibiotics, but they had a lesser relative prevalence and had less resistance genes than the larger population of bacteria post-antibacterial exposure [7].

The mechanism by which the larger population acquired a greater antibacterial resistance may have been explored in another study, this time in healthy human participants. After administration of Moxifloxacin, a large decrease in gut microbiome diversity was noted. The maximal loss was recorded roughly seven days after administration, indicating that the antibiotic's concentration in the gut decreased very slowly. This slow decrease created replication spaces for resistant bacteria, with a constant selection pressure encouraging the development of resistance [8].

Effect of Non-Antibiotic Drugs on the Microbiome

Not only antibiotic drugs impact the gut microbiome. Proton-pump inhibitors (PPI) and laxatives are both associated with changes to microbiome diversity, both by directly inhibiting certain bacterial species and by indirectly affecting bacterial growth by changing the host's gut environment (PPIs change the gut pH, for example). These changes are significant enough that a consistent increase in resistance gene markers was observed in participants who took PPIs as compared to those who took no drugs at all. As for drugs that had no direct effect on the host's gut, some changes in diversity were observed, but no consistent increases in resistance markers. The use of multiple drugs, however, did result in a large decrease in diversity. This may be due to increased stress in the gut environment due to the presence of multiple drugs, or due to the underlying health condition that required the prescription of multiple drugs [9].

Spread of Antibiotic Resistance via Other Means: Travel and Livestock

Food consumption is linked to the dissemination of antibiotic resistant genes. At least, this is hypothesized in a study conducted on Swedish international exchange students, some of whom went to Central Africa and the remainder went to the Indian subcontinent. There was no statistical difference between the students based on destination, but both groups experienced an increase in resistance genes. However, the increase was seen in resistance genes that had occurred in low abundance prior to travel; the prevalence of resistance genes that were already abundant prior to travel remained essentially unchanged. Since only a small number of students required medication during their stay, drinking contaminated water and eating contaminated foods is the most likely vector for the increased resistance [10].

Livestock also play a role in disseminating antibiotic resistance. Since livestock are given consistent low doses of antibiotics to promote growth and reduce the risk of disease rather than large therapeutic doses, they represent the perfect opportunity for the development of antibacterial resistance. These genes can then be transferred to humans via contaminated food, water contaminated by livestock manure, food and surfaces contaminated by flies,

and so on. Migratory birds and other wildlife that may come into contact with livestock contaminants also facilitate the spread of resistance genes, which eventually make their way into human feces. At this point, mismanagement of human wastes by sewage companies or airlines can cause further dissemination of antibiotic resistance, again through contamination of drinking water [11].

Conclusions

Importance of Limiting Spread of Antibiotic Resistance

Antibiotic resistance represents an existential threat to the current lifestyle and access to healthcare many people across the world take for granted. Many scientists warn of a "post-antibiotic world," but the dangers of antibiotic resistance need not wait until then to manifest [12]. In 2019, antimicrobial resistance was associated with five million deaths worldwide. In the United States alone, nearly three million infections occur annually. The treatment for these patients require second or third-line treatments, which have severe side effects (such as organ failure) and sometimes require months of care [2]. Many antibiotics have already been retired due to bacterial populations developing high resistance to them, and the number of retired antibiotics will only increase; resistance is inevitable [3]. Reducing the rate at which antibiotic resistance occurs and limiting its spread is not only a matter of preserving medicine for future generations (as is the common perception), but a matter of preserving lives today.

Importance of Narrow-Spectrum Antibiotics

Broad-spectrum antibiotics are well-loved by the pharmaceuticals industry due to their versatility and ability to combat multi-drug resistant bacteria. However, they are a short-term solution that only make the problem worse by encouraging further, broader resistance in target bacterial populations, as well as in the bacteria of the microbiome. Additionally, broad-spectrum antibiotic sales are in decline, leading to a decrease in the willingness of pharmaceuticals companies to pursue new research [12].

Promoting narrow-spectrum antibiotics targeted for a particular class of pathogen solves several issues at once. Firstly, it provides pharmaceuticals companies with the necessary incentive to pursue research. Secondly, it relegates broad-spectrum antibiotics for last-resort cases, while positioning narrow-spectrum antibiotics as the primary course of action. By acting specifically against the pathogen and not other bacteria in the microbiome, the development of new resistance genes is reduced. Additionally, promoting narrow-spectrum antibiotics would automatically promote with it better and more accurate diagnosis techniques to ensure the right prescriptions are given, rather than the present situation where broad-spectrum antibiotics are used to treat conditions that are not caused by bacteria in the first place [12].

Importance of Education and Outreach

The importance of integrating educational material about the gut microbiome and antibacterial resistance into classrooms cannot be overstated. As noted before, many students found antibiotic resistance to be an issue that was irrelevant to them, even as they likely carried some resistant strain in their gut while saying so.

Advertisements being the primary source of information about the gut microbiome is also an issue that must be addressed, as many of the surveyed students felt no motivation to adjust their diets or lifestyle to better the health of their microbiome in spite of its essential roles in a variety of bodily functions beyond digestion. Finally, outreach programs that target social media platforms and encourage peer education were suggested as potential immediate solutions to the issue, considering the present lack of material and exclusion from school curriculums and examinations [4].

Future Trends

Future trends in microbiome research focus on determining what exactly a healthy gut is. The astonishing diversity contained within and the uniqueness of every individual's microbiome makes it difficult to establish what is and is not healthy, and whether or not a medical intervention beyond dietary advice is needed. Additionally, there is a possibility that the microbiome itself may be the solution to the problem of antibiotic resistance, and may be a therapeutic target to cure other illnesses. To be certain, however, more research is needed [1].

In terms of antibiotic resistance, it is clear that the present course of action chosen by us as a species is not a sustainable one. Eventually, decisive actions must be taken. Among these is restricting and auditing prescriptions to ensure they are justified and necessary, reducing the amount of antibiotics administered to livestock, and restricting the use of over-the-counter antibiotics. Of particular importance is aiding developing nations in building a system of control, as the present uncontrolled nature of antibiotics distribution in these nations contributes to the global rise in antibiotic resistance [3]. Finally, it is important to seek answers as to what other sources of antibiotic resistance exist besides the classical answers of antibiotic use in humans and livestock, such as mismanaged sewage and aircraft waste water [11].

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