Broad-spectrum antimicrobials—considering 'holobiont' welfare

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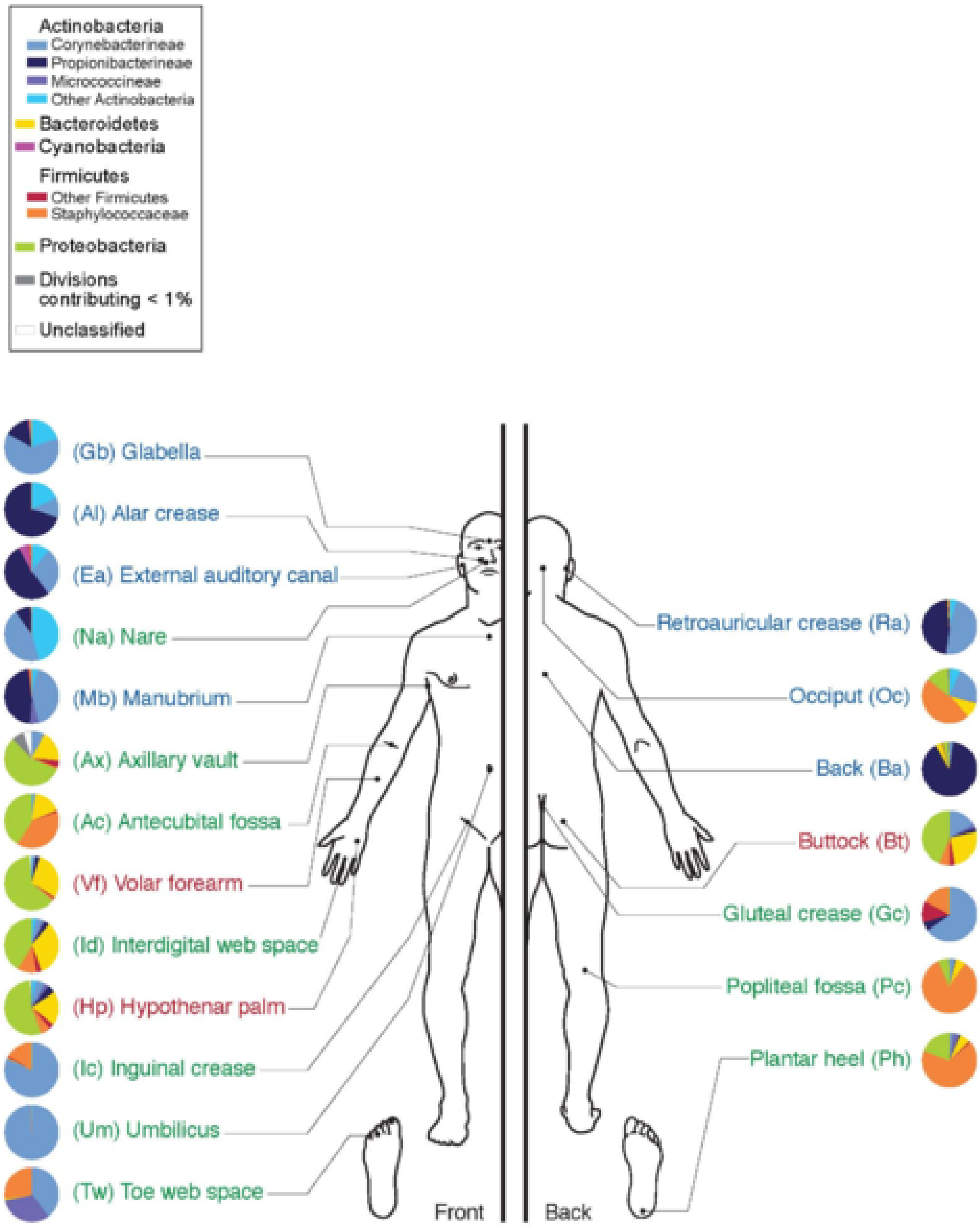

Distribution of the common bacterial phyla in each of the different body sites. Credit: Wikimedia Commons

The discovery of antibiotics (also referred to as antimicrobials) is perhaps the most revolutionary outcome in the medical sciences during the twentieth century, and has allowed medical practitioners to treat a wide range of bacterial infections; and therefore, antimicrobials are the most commonly prescribed drug in many types of illness all over the world. However, antibiotics may cause some adverse effects in the host body, yet it is often difficult to determine the long-term health effects of antimicrobials. However, different types of abnormalities that are common manifestations after antimicrobial therapy include: pathogen-induced colitis, cholera, atopic dermatitis, asthma, eczema, allergic sensitization, candidiasis, autoimmune encephalitis, and diabetes. A recent study out of the Center for Diabetes Research in Denmark showed that antibiotics exposure increases risk of developing Type 2 Diabetes.

Generally, antibiotics are used to kill or inhibit microbes in host body, but people rarely consider its effects on other cohabiting microorganisms. Human and animal bodies are home to diverse types of commensal microorganisms, and there is a symbiotic relationship between the host and these cohabiting microbes, which perhaps start from birth and continues throughout the life cycle. These commensal flora play a key role in the development, progression, and evolution of the host.

In an August 2015 essay published in *PLOS Biology*, scientists describe the relationship between host and microbes, and extended existing theory of ecology and evolutionary biology. Researchers have already shown that humans or other animals are not a single entity but rather a complex network of eukaryotic and prokaryotic cells. Therefore, when we take antimicrobial chemotherapy, we are not only trying to destroy pathogens but also our natural homeostasis with microbes.

Usefulness of antimicrobials

Humans rely on antimicrobials to treat ordinary bacterial infections, and the inevitable infections that come with minor or major surgery, cancer chemotherapy, and organ transplants. Beside therapeutics, antimicrobials are also used in food-producing animals to promote growth and as a metaphylaxis agent. There are different types and classes of antimicrobials. Antimicrobials are divided into two types based on the range of resistance and susceptibility: broad-spectrum and narrow-spectrum. Broad-spectrum antimicrobials are active against a wide range of bacterial species both in Gram-negative and Gram-positive organisms, such as tetracyclines, phenicols, fluoroquinolones, cephalosporin among others. Narrow-spectrum antimicrobials are only useful against particular species of microorganisms, such as glycopeptides and bacitracin (Gram-positive bacteria), polymixins (Gram-negative bacteria), aminoglycosides and sulfonamides (aerobic organisms), and nitroimidazoles (anaerobes) among others.

Considering host-microbes interactions

Based on the germ theory of disease, microorganisms are the source of many diseases, and scientific studies continue to investigate the role of microbes in infectious disease. Beyond the harmful groups of microorganisms, countless commensal flora are inhibiting with hosts as an inseparable partner. This natural host-microbes ecosystem evolved by integration mechanism, which shape the phenotypic and genomic landscape of a host. This integrated evolutionary perspective corroborates Lamarck's 'Milieu' theory and Darwin's pangenesis theory, where they indicated that life evolves and exists as a complex network that interplays with the environment. Advanced biological research has shown that human, animals, and plants are not a single entity but rather a 'bio molecular network' that consist of macrobe (host) and millions of unseen microbes, all of which have a noteworthy effect on host development, disease progression, immunity, psychology, behavior, and social interaction.

Collectively, all of these microbial communities that live inside the host body are known as 'microbiota', a word coined by Joshua Lederberg. The term 'microbiome' is commonly applied in this regard, which means the collection of all genomes of microorganisms living in association with the individual host body. In their 2015 *PLOS Biology* paper, authors Bordenstein and Theis explain the concept of host-microbe ecosystem more holistically, and break them down into underlying ten principles, outlined below.

The 10 principles of holobionts and their hologenomes
(proposed by Bordenstein and Kevin, 2015)

1. Holobionts and hologenomes are units of biological organization
2. Holobionts and hologenomes are not organ systems, superorganisms, or metagenomes
3. The hologenome is a comprehensive gene system
4. The hologenome concept reboots elements of Lamarckian evolution
5. Hologenomic variation integrates all mechanisms of mutation
6. Hologenomic evolution is most easily understood by equating a gene in the nuclear genome to a microbe in the microbiome
7. The hologenome concept fits squarely into genetics and accommodates multilevel selection theory
8. The hologenome is shaped by selection and neutrality
9. Hologenomic speciation blends genetics and symbiosis
10. Holobionts and their hologenomes do not change the rules of evolutionary biology

These ecosystems consist of microorganisms that include eukaryotes, archaea, bacteria and viruses. In the human body, the total number of bacterium is about 10 times more than the number of human cells, and about 1000 more genes than are present in the human genome. They are generally commensal to humans and are crucial for maintaining good health, for instance, bacterium produces rare vitamins and aid with digestion, and they help to shape the host's immune system.

In the *PLOS Biology* essay, Bordenstein says: "Today, there is an unmistakable transformation happening in the way that life is comprehended and it is as significant for many biologists as the modern synthesis. Animals and plants are no longer viewed as autonomous entities, but rather as 'holobionts' composed of the host plus all of its symbiotic microbes".

A holobiont refers to a unit of biological organization composed of a host and its microbiota, and similarly a hologenome is the complete genetic content of the host genome, including its organelles' genomes, and its microbiome. The term is now used to describe the host and its associated microbes, and it importantly fills the gap in what to call such assemblages. This holistic view of hologenomic concept defines plants and animals as polygenomic entities.

Therefore, changes in hologenome can lead to changes in overall phenotypes. Scientific studies have revealed that changes in the structure of the host microbiome correlates with numerous illness, for example, the loss of microbiome from host body could increase the incidence of immune and inflammatory related diseases.

Host-microbe ecosystem and broad-spectrum antimicrobials

Broad-spectrum antimicrobials are now routine medical treatment in many countries, and often the first choice of drug for common infections, which results in collateral damages to the host-microbe ecosystem associated with killing the pathogen. Broad-spectrum antimicrobials are convenient because of their wide range of coverage when treating complex and ambiguous infections disease conditions. Even in cases where the etiology of disease is confirmed, narrow-spectrum antimicrobials are used less often than broad-spectrum, often because narrow-spectrum alternatives are less available. This disruption in the holobiont relationship due to broad-spectrum antimicrobial therapy might have long-term phenotypic changes in the host, according to the concept proposed by Bordenstein. The authors said hologenomic variation integrates all mechanisms of mutation, since every hologenome is a multiple mutant. This means that there is variation across many individual genomes spanning the nucleus, organelles, and microbiome as well as base pair mutation, horizontal gene transfer, recombination, gene loss and duplication, and microbial loss and amplification are all sources of variation; which in long term could cause many severe health complications in humans and animals.

Conclusion

There is no ambiguity in the importance of antimicrobials for human and animal health. Antimicrobials are indispensable to reducing the morbidity and mortality associated with serious and life-threatening infections, and to keep the harmful microbes away from the host body during major or minor surgery, cancer chemotherapy, or other conditions that lead to immunosuppression. However, it is noteworthy that numerous harmless commensal microorganisms inhabit in the host body alongside the harmful pathogens, which perhaps play a key role in maintaining good health. Hence, the antibiotics do not merely affect the pathogens; they are also challenging for the natural microbial ecosystem inside the host body. The condition may become exaggerated during broad-spectrum antimicrobial chemotherapy because of the wide range of antimicrobial activities, which could greatly distress the natural flora. Therefore, new approaches and novel antibacterial therapeutics are required to combat pathogenic microorganism conserving holobiont ecosystem.

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