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Review

Antibiotic use and microbiome function

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ABSTRACT

Our microbiome should be understood as one of the most complex components of the human body. The use of β-lactam antibiotics is one of the microbiome covariates that influence its composition. The extent to which our microbiota changes after an antibiotic intervention depends not only on the chemical nature of the antibiotic or cocktail of antibiotics used to treat specific infections, but also on the type of administration, duration and dose, as well as the level of resistance that each microbiota develops. We have begun to appreciate that not all bacteria within our microbiota are vulnerable or reactive to different antibiotic interventions, and that their influence on both microbial composition and metabolism may differ. Antibiotics are being used worldwide on a huge scale and the prescription of antibiotics is continuing to rise; however, their effects on our microbiota have been reported for only a limited number of them. This article presents a critical review of the antibiotics or antibiotic cocktails whose use in humans has been linked to changes in the composition of our microbial communities, with a particular focus on the gut, oral, respiratory, skin and vaginal microbiota, and on their molecular agents (genes, proteins and metabolites). We review the state of the art as of June 2016, and cover a total of circa 68 different antibiotics. The data herein are the first to compile information about the bacteria, fungi, archaea and viruses most influenced by the main antibiotic treatments prescribed nowadays.

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1. Introduction

The end of the twentieth century has witnessed a revolution in the life sciences and, specifically, in human health. In this respect, how we regard our relationship with our microbiota is currently under profound transformation due to the *–omics* paradigm, with the subsequent appearance of genomics (1986), proteomics (1995) and, most recently, metabol[n]omics (1999/2001) [1,2]. In the words of Martin J. Blaser, we are in the microbiome revolution [3]. Our skin, gastrointestinal tract, respiratory system, oral cavity, and vaginal/urinary cavity, with surface areas of up to approx. 1.8 m^2, 300–400 m^2, 160 m^2, 215 cm^2, and 90 cm^2 (for adults), respectively, harbor at least 5000 bacterial phylotypes in the adult body [4–7]. Inter-variability is a characteristic of the human body, as each body site houses from 2 to 7 community types with different relative abundances of at least 63 bacterial genera [7]. In the near future we should have a real estimation of the total biodiversity with the sampling of at least 41,000 individuals [8]. However, accumulated knowledge provides evidence for about 55 bacterial divisions in our body, including mainly Bacteroidetes (48%) and Firmicutes (51%), with the remaining 1% of phylotypes comprising Proteobacteria, Verrucomicrobia, Fusobacteria, Cyanobacteria, Actinobacteria and Spirochaetes, and then various species of archaea, fungi, protozoa, virus and other microorganisms [9].

According to R. Goodacre, this extremely complex pool of microbes and viruses can be regarded as a superorganism [10] that exists in a more intimate symbiotic relationship with its host than other microbial populations. Thus, its health status can be an indicator of human health [7,11]. We should not forget, however, that the human microbiota is continuously being exposed to factors that influence it dynamically [12,13]. The degree of changes in our microbiota depends not only on the nature, strength and duration of the perturbing factor itself, but also on the stability of each microbiota, assuming that each individual's microbiota is unique [11,14]. On some occasions, the nature of the disturbance or environmental stress in our body sites, particularly the gut environment, is so strong that the microbiota undergoes changes, acquiring a dysbiotic state [15]. The term dysbiosis is used in a broad sense to refer to an imbalance in the taxonomic composition of the microbiota.

Antibiotics influence bacterial growth curves and this is why they are used to kill pathogens. Bactericidal antibiotics directly kill the bacteria, while bacteriostatic antibiotics inhibit their growth. According their production mode and origin, antibiotics may be classified into natural, semisynthetic and synthetic. Natural antibiotics are a product of secondary metabolism of organisms, so they actually serve to enhance their survival in the nature. According to Berdy [16], there are about 17,000 bioactive natural products with antibiotic properties found in *Bacteria*, 8700 natural antibiotics in *Actinomycetales* and 4900 in *Fungi*. Most modern antibacterials are semisynthetic modifications of various natural compounds [17]. For example, penicillins produced by fungi of the genus *Penicillium* are the base for the current beta-lactam antibiotics.

In antibiotic treatment, the dose of the antibiotic must be considered. In microbiology, a frequently measured parameter is the minimal inhibitory concentration (MIC), defined as the lowest concentration of a drug that will inhibit the visible growth of an organism after overnight incubation (this period is extended for organisms such as anaerobes, which require prolonged incubation for growth). The range of antibiotic concentrations used for determining MICs is generally set by doubling dilution steps up and down from 1 mg/l [18]. However, at such concentrations, antibiotics are not specific for the pathogen they are prescribed to eliminate but also produce co-lateral effects in our microbiota. It is of great interest to identify the degree of such changes and the specific microbial and viral groups affected by each antibiotic used to date as we know that early gut [19], skin [20], respiratory [21], vaginal [22] and urinary [23] microbiota composition determines bacterial succession patterns and gut, skin, respiratory, vaginal and urinary health in children and adults [24].

Following on from the above considerations, this review gathers information on our current knowledge of the effect that multiple antibiotics, tested and commonly used in humans, have on our microbiota (gut, oral, respiratory, skin and vaginal microbiota). We review the state of the art as it stands in June 2016, with the scope encompassing only research related to the analysis of human microbiota.

2. Antibiotic usage as a factor influencing human total microbiota composition

In a recent study analyzing in-depth sequencing of the gut microbiomes of 1135 participants, the use of antibiotics was found to be significantly associated with alterations in microbiome composition [25]. Indeed, the only drugs significantly associated with the differential abundance of specific genera in phenotype-matched case-control analyses were β-lactam antibiotics [8]. Both studies reported that the abundance of two species from the genus *Bifidobacterium* (Actinobacteria phylum), out of a total of 1649 taxonomic clades detected, were strongly associated with the use of β-lactam antibiotics.

However, many antibiotics other than β-lactam antibiotics have been shown to influence the composition of our microbiota. Obtaining a clear picture of the influences of distinct antibiotic therapies is of special interest as broad-spectrum antibiotic therapy decimates the microbiome and thus impacts health negatively. This information may be essential to design pathogen-selective antibiotics in order to minimize disturbance to the microbiome, as short-term antibiotic treatments are able to shift the microbiota to long-term alternative dysbiotic states, which may promote the development and aggravation of diseases [26]. Furthermore, understanding the effect of different antibiotics is of practical importance because, for example, microbiota modulation by antibiotics (i.e., rifaximin) is a therapeutic option in patients with irritable bowel syndrome [27] and, in general, to potentially modulate intestinal homeostasis [28]. Accordingly, below we summarize bacterial genera and other components of our total microbiota influenced by all main antibiotic treatments reviewed to date.

2.1. Antibiotics associated with alterations in the total microbiota composition

Antibiotics are being used worldwide on a huge scale and are one of the pillars of medicine [29]. Indeed, the prescription of antibiotics is continuing to rise and the levels of antibiotic resistance are also escalating [29–33]. However, the number of new antibiotics appearing on the market continues to drop [34].

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