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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].

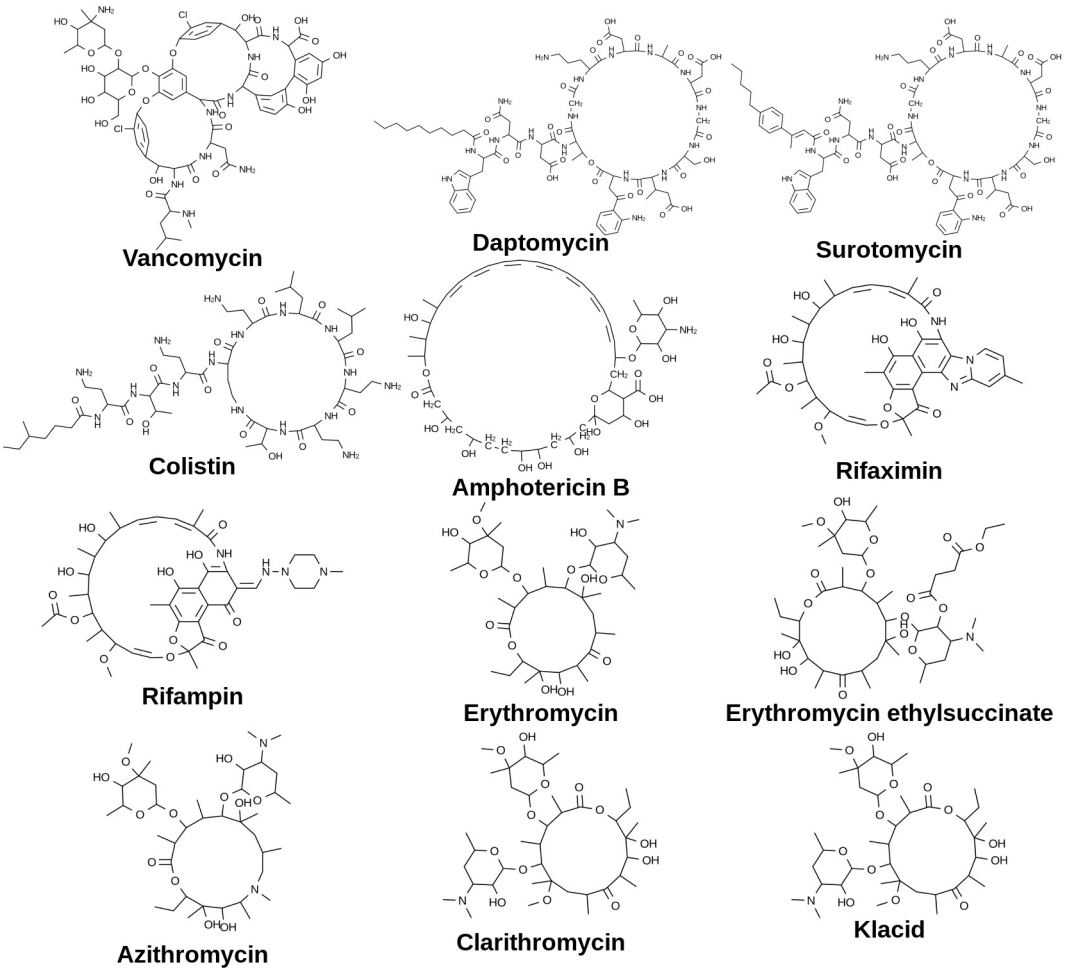

Fig. 1. Representative chemical structure of antibiotics (glycopeptides, cyclic lipopeptides, polymyxins, polyenes, rifamycins and macrolides) being used worldwide and whose use has been linked to changes in the composition of the human microbiota, particularly, in the microbiota inhabiting the gastrointestinal tract.

Among all human-prescribed antibiotics, the effect of approx. 68 (alone or in the form of cocktails or combinations) has been described to date in terms of the collateral changes produced in our microbial community composition. Figs. 1–3 summarize their representative chemical structures. Culturomics and next generation sequencing have demonstrated that post-antibiotic dysbiosis induces a reduction in the amount of bacteria and in microbiota diversity, as well as a loss of functional diversity combined with reduced colonization resistance against invading pathogens, implying the danger of antimicrobial resistance [35–40]. Such changes may exert future consequences on our health [41–43].

It is well documented, despite methodological differences, that different antibiotic treatments have not only markedly diverse effects on the composition of the total microbiota [36] but also on particular microbial taxons. Such collateral effects of antibiotic treatment on particular microbial clades may not be a direct consequence of the antibiotic itself alone, but of multiple factors that include the different type of administration and different pharmacokinetics of the original compounds [44,45] and the different resistance and degradation mechanisms that each microbe develops against each antibiotic [46–48]. Indeed, drugs and phytochemicals are transformed into bioactive (sulfasalazine, lovastatin, and ginsenoside Rb1), bioinactive (chloramphenicol, ranitidine, and metronidazole), and toxic metabolites (nitrazepam), which can also influence the microbial communities [45]. Additionally, meta llo-β-lactamase-producing bacteroides can shield other members of the microbiota from antibiotics [49].

Sixty-eight antibiotics, distributed among 22 groups, have been tested and their effects on our microbiota evaluated, as summarized in Figs. 1–3. Changes associated to all these antibiotics have mainly been reported to occur in the gut microbiota, although they have also been reported in the colorectal-associated tissue microbiota, nasal microbiota, oral microbiota (including salivary and subgingival biofilm microbiota), respiratory microbiota (including nasal microbiota), skin microbiota, and vaginal microbiota [50–104]. Changes were identified by analyzing 16S ribosomal RNA gene sequences and shotgun sequence datasets [105]. Fig. 4 summarizes all bacterial genera and phyla (right panel) in our microbiota whose abundance is influenced by all these different antibiotic treatments (external grey circle). It also depicts whether different antibiotics have similar effects or different bacterial groups (see links in inner circle).

Observation of Fig. 4 reveals that bacteria belonging to a restricted set of phyla and genera are strongly and statistically affected by antibiotics. Indeed, Fig. 4 (right panel) summarizes the list of 42 major microbial genera whose abundance is altered after treatment with any one of 68 antibiotics. This agrees with the fact that antibiotics can exert important eubiotic effects regardless of the original disease for which they were prescribed, causing perturbations without changing overall composition and diversity but rather affecting a specific set of bacteria [50]. For example, the abundance of only one bacterial clade was found to be significantly altered after treatment with mesalamine, tobramycin, gentamicin, flavomycin, amphotericin B, colistin sulfate, col-

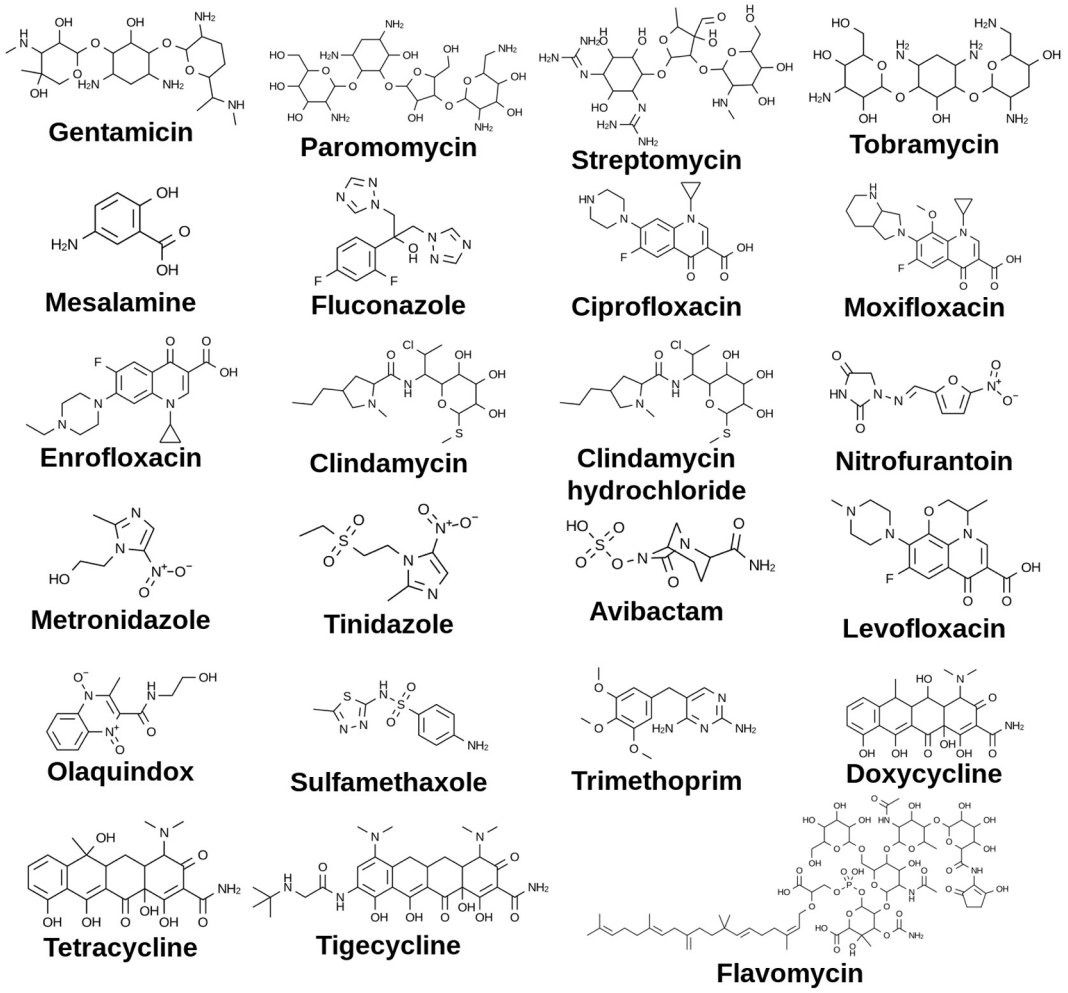

Fig. 2. Representative chemical structures of antibiotics (aminoglycosides, aminosalicylates, azoles, fluoroquinolones, lincosamides, nitrofurantoins, nitroimidazoles, non-β-lactam inhibitor, quinolones, quinoxalines, sulfonamides, tetracyclines and phosphoglycolipids) being used worldwide and whose use has been linked to changes in the composition of the human microbiota, particularly, in the microbiota inhabiting the gastrointestinal tract.

istin, olaquindox or ticarcillin [33,57,66,80]. By contrast, interventions with the fluoroquinolone enrofloxacin were associated with changes in 32 microbial groups [74,75]. Fluoroquinolones are among the most widely prescribed antibiotics and there is a major increase in resistance worldwide [106]. They constitute the second-line agents for use when narrow-spectrum antibiotics have failed [47], so it is anticipated that they may influence our microbiota to a greater extent. A second observation regarding Fig. 4 (see links in the inner circle) is that many bacterial genera become vulnerable to antibiotics, which differ in nature and clinical consequences. These will be discussed in detail later.

2.2. Bacterial groups most affected by antibiotics at the level of total microbiota

As shown in Fig. 4, of the bacterial genera influenced by the antibiotic treatments reviewed [50–104], the main phyla influenced are Actinobacteria, Bacteroidetes, Firmicutes, and Proteobacteria. The main genera within each group correspond to *Bifidobacterium*, *Bacteroides*, *Faecalibacterium*, and *Escherichia*, respectively. Other affected phyla include Fusobacteria (genus *Fusobacterium*), Planctomycetes (*Gemmata*), and Verrucomicrobia (*Akkermansia*). We made the following observations of the bacterial phyla influenced by the 22 groups (one being the group covering cocktails) of antibiotics considered:

(i) Of the 4 main affected phyla, cyclic lipopeptides (nr. 7 in Fig. 4) [103], nitroimidazoles (nr. 8) [60,81,82,104] and rifamycins (nr. 10) [50,100–102] have not been reported to statistically affect Proteobacteria.
(ii) Aminosalicylates (nr. 9) [80] and azolidines (nr. 18) [65] have been reported to mostly influence only members of Firmicutes.
(iii) Aminoglycosides (nr. 5) [33,57,99] and tetracyclines (nr. 11) [33,56] have not been observed to affect Actinobacteria.
(iv) Phosphoglycolipids (nr. 14) [66] have not been reported to affect Bacteroidetes.
(v) Polymyxins (nr. 13) [57,66], polyenes (nr. 15) [57], and sulfonamides (nr. 21) [60] seem to affect only Bacteroidetes and Firmicutes.
(vi) Nitrofurantoins (nr. 12), azoles (nr. 17), and a novel class of respiratory tract infection antibiotics (nr. 20), referred to as J01CAxx, J01EBxx, J01XExx, J01CFxx, D06BXxx, J01AAxx, and P01ABxx [60,82], have been reported to influence Actinobacteria and Firmicutes.
(vii) Quinolones (nr. 19) [51] have been reported to affect only Firmicutes and Proteobacteria.
(viii) Beta-lactams (amoxicillin) (nr. 1, AMO) [51–56], lincosamides (clindamycin) (nr. 3, CLI) [56,64,68–71,73] and phosphoglycolipids (flavomycin) (nr. 14, FLA) [66] are reported to affect Fusobacteria (*Fusobacterium*).

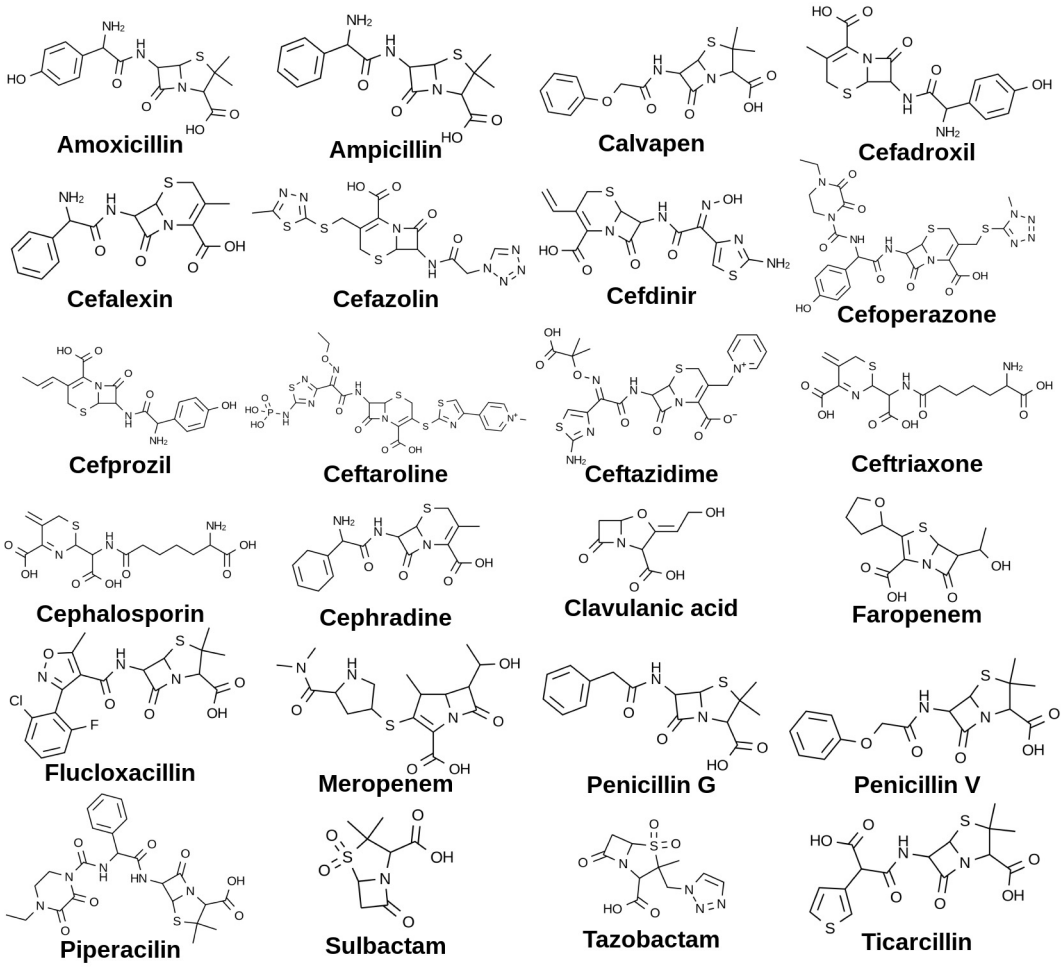

Fig. 3. Representative chemical structures of β-lactam antibiotics used worldwide and whose use has been linked to changes in the composition of the human microbiota, particularly, in the microbiota inhabiting the gastrointestinal tract.

(ix) Beta-lactams (cefprozil, and cephalosporin) (nr. 1, CEFP; CEP) affect Planctomycetes (*Gemmata*) [62,63].
(x) Beta-lactams (ceftriaxone and cephalosporin) (nr. 1, CEFP; CEFT) [51,62] and lincosamides (nr. 3) [74,75] affect Verrucomicrobia (*Akkermansia*).

The genera *Prevotella* (Bacteroidetes), *Clostridium*, *Enterococcus*, *Lactobacillus*, *Ruminococcus*, *Streptococcus*, *Eubacterium* (Firmicutes), and *Enterobacter* (Proteobacteria) figure among the most influenced by the antibiotics considered. Specifically, according to research, fluoroquinolones (nr. 2 in Fig. 4) do not affect *Prevotella* [48,51,52,56,60,65–69,74,75,77,90], beta lactams (nr. 1) do not influence *Lactobacillus* [33,36,44,51–63,77,83–85,87,88,134], and lincosamides (nr. 3) seem to have no effect on *Streptococcus* [56,68,70–73,90]. According to reports, a number of antibiotics affect only a few genera, e.g., nitrofurantoins (nr. 12) and azoles (nr. 17) [60] affect *Bifidobacterium* and *Faecalibacterium*; azolidines (nr. 18) [65] affect *Clostridium* and *Faecalibacterium*; quinolones (nr. 19) [51] affect *Staphylococcus* and *Escherichia*; respiratory tract infection antibiotics (nr. 20) [82] affect *Lactobacillus* and *Bifidobacterium*; and sulfonamides (nr. 21) [60] affect *Bacteroides* and *Faecalibacterium*.

As summarized in Fig. 4, antibiotic treatments comprising a cocktail of gentamicin and ampicillin are associated to alterations in a higher number of bacterial genera (nr. 22, F in Fig. 4) (32 genera), enrofloxacin (nr. 2, ENR) (32), ciprofloxacin (nr. 2, CIPF) (27) and clindamycin (nr. 3, CLI) (23), and to lower extent those with cefprozil (nr. 1, CEFP) (16), a cocktail of azithromycin and clarithromycin (nr. 22, H) (15), amoxicillin (nr. 1, AMO) (15), paromomycin (nr. 5, PAR) (12), cephalosporin (nr. 1, CEP) (12), fluoroquinolones (nr. 2) (10), moxifloxacin (nr. 2, MOX) (9), clavulanic acid (nr. 1, CLA) (9), ceftriaxone (nr. 1, CEFT) (9), ampicillin (nr. 1, AMP) (8), GSK1322322 (nr. 6, GSK) (7), a cocktail of ciprofloxacin and metronidazole (nr. 22, G) (7), surotomycin (nr. 7, SUR) (6), a cocktail of ceftaroline and avibactam (nr. 22, C) (6), clarithromycin (nr. 4, CLA) (6), tigecycline (nr. 11, TIG) (5), rifaximin (nr. 10, RIF) (5), a cocktail of ampicillin, sulbactam and cefazolin (nr. 22, M) (5), mesalamine (nr. 9, MES) (5), erythromycin (nr. 4, ERY) (5), truoxinc (nr. 1, TRU) (4), tazocin (nr. 1, TAZ) (4), nitrofurantoin (nr. 12, NIT) (4), cocktail of amoxicillin and clavulanic acid (nr. 22, K) (4), flucloxacillin (nr. 1, FLU) (4), faropenem (nr. 1, FAR) (4), colistinsulfate (nr. 13, COL) (4) and co-amoxicillin (nr. 1, CO-AMO) (4). All other antibiotics influenced less than 3 genera in our microbiota.

A comparison between the effects of treatments with a single antibiotic (nr. 1–21 in Fig. 4) or cocktails of antibiotics (nr. 22, F in Fig. 4) provides interesting results. For example, treatment with gentamicin and ampicillin (nr. 22, F) [92–96] is associated to effects on a greater number of genera (32 in total) compared to ampicillin (nr. 1, AMP) (8) and gentamicin (nr. 5, GEN) (1) alone [33,58,134]. Indeed, bacteria belonging to the *Enterobacter* genus were the only ones (out of 36 non-redundant genera

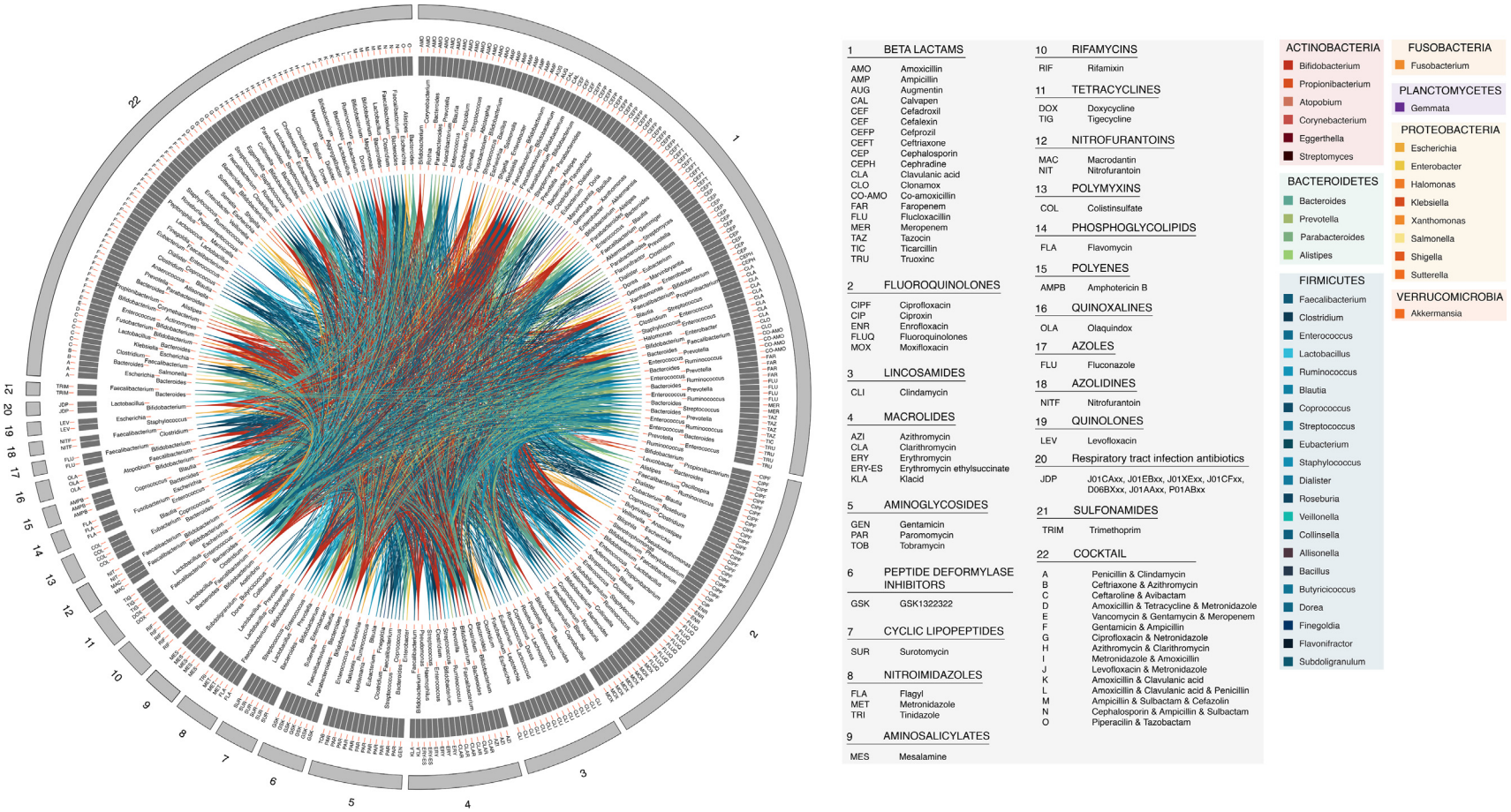

Fig. 4. Summarized graphic visualization of bacterial genera influenced by all main reviewed antibiotic treatments shown to influence our microbes. Antibiotic treatments included 21 antibiotics that have been used individually (numbers 1–21; legend, left panel) and 15 distinct cocktails of antibiotics (number 22; legend, left panel). Numbers in the outer light grey circle (1–22) represent the different antibiotic treatments reviewed. Next darker grey circle represents subcategories within each antibiotic intervention, identifiable by a three letter code included in the legend. Inner circle shows links among bacterial genera influenced by the diverse antibiotics (see legend for colors). This circle illustrates all possible connections among taxa affected by the different antibiotics, depicting the existence of a similar effect. For example, when a specific bacterial genus is influenced by two or more different antibiotics, then, a link is drawn. Each color is associated to different bacterial phyla and genera. Thus, the main affected phyla (and the genera associated to them), by all reviewed antibiotics appear in different hues of the same color: Actinobacteria are represented in hues of red; Bacteroidetes in green; Firmicutes in blue; Fusobacteria in light orange; Planctomycetes in purple; Proteobacteria in hues of yellow; and Verrucomicrobia in dark orange (legend, right panel). To produce the figure the following steps were undertaken: *i*) we reviewed the state of the art, as it stands in June 2016, of antibiotics interventions whose use in humans has been linked to changes in the composition of our microbial communities, as identified by monitoring the 16S rRNA amplicons generated from DNA; *ii*) information on the bacteria influenced by the different antibiotics was retrieved from the reviewed material; *iii*) a graphical tool was used to show the links among bacterial genera and corresponding phyla influenced by the diverse antibiotics within the main classes (determined by chemical nature and mode of action).

affected by any of the treatments) to be affected by all three treatments. Bacteria from the genera *Bacillus*, *Klebsiella*, *Salmonella* and *Streptococcus* were only altered by treatment with ampicillin (nr. 1, AMP) alone [58,134]. Similarly, treatment with a cocktail of azithromycin and clarithromycin (nr. 22, H) altered the abundance of 15 genera [83], whereas the treatment with azithromycin (nr. 4, AZI) [56] and clarithromycin (nr. 4, CLA) [60,61] alone altered 3 and 6 genera, respectively. Bacteria from the *Bacteroides* and *Bifidobacterium* genera were the only ones (out of 18 unique genera affected by any of the treatments) to be affected by all three treatments. By contrast a cocktail of ciprofloxacin and metronidazole (nr. 22, G) [91,97] was shown to alter a much lower number of genera (7) than in individuals treated with ciprofloxacin (nr. 2, CIPF) alone (27 in total) [48,51,56,60,64–68]. Only 5 out of 35 non-redundant genera were found to be affected by both treatments (*Bacteroides*, *Bifidobacterium*, *Clostridium*, *Faecalibacterium* and *Roseburia*). Also, treatment with a cocktail of ampicillin, sulbactam and cefazolin (nr. 22, M) resulted in changes in 5 genera [87], which is lower than those affected by interventions with ampicillin (nr. 1, AMP) (8 genera) [58,134]. Only the genus *Bifidobacterium* (out of 12 affected genera) was common to both treatments. Finally, treatment with amoxicillin and clavulanic acid (nr. 22, K) [85] mostly affects bacteria belonging to 4 genera, whereas amoxicillin (nr. 1, AMO) alone affects bacteria from 15 genera [36,51,53–56,131]. Only the genus *Bacteroides* (out of 18 affected genera) was common to both treatments. Finally, the cocktail of antibiotics comprising azithromycin and clarithromycin (nr. 22, H) has been found to affect *Christensenella*, which is reported to be the most heritable gut bacterium [107]. This bacterial genus was not affected when azithromycin and clarithromycin were prescribed individually [56,60,61].

Taken together, this comparative analysis at the genus level revealed that in some cases there is a synergetic negative effect on our microbes during treatments based on combining different antibiotics, which is not evident in other combined treatments. This was also observed at the phylum level. Thus, interventions with cocktails of gentamicin-ampicillin (nr. 22, F in Fig. 4) [92–96] and ciprofloxacin-metronidazole (nr. 22, G) [91,97] affect bacteria distributed within four different phyla (Actinobacteria, Bacteroidetes, Firmicutes, and Proteobacteria). By contrast, a combination of piperacillin and tazobactam (nr. 22, O in Fig. 4) [51] has been found to influence only Bacteroidetes.

The accumulated comparative data summarized in Fig. 4 also reveal that most sensitive bacteria are those associated to the following genera: *Bifidobacterium* (by 40 antibiotic treatments), *Bacteroides* (36) and *Faecalibacterium* (30), and to lower extend *Enterococcus* (20), *Clostridium* (17), *Prevotella* (14), *Blautia* (13), *Escherichia* (13), *Lactobacillus* (13), *Ruminococcus* (13), *Streptococcus* (11), *Eubacterium* (10), *Coprococcus* (8), *Parabacteroides* (8), *Dorea* (7), *Enterobacter* (7), *Alistipes* (6), *Dialister* (6), *Roseburia* (6), *Staphylococcus* (5), *Collinsella* (4), *Fusobacterium* (4), *Propionibacterium* (4), *Subdoligranulum* (4), *Veillonella* (3), *Akkermansia* (3), *Anaerostipes* (3), *Sutterella* (3), and *Allisonella*, *Atopobium*, *Bacillus*, *Butyricicoccus*, *Corynebacterium*, *Eggerthella*, *Finegoldia*, *Flavonifractor*, *Gemmata*, *Halomonas*, *Klebsiella*, *Lactococcus*, *Marvinbryantia*, *Megamonas*, *Salmonella*, *Shigella*, *Streptomyces* and *Xanthomonas* (2 each). Finally, bacteria belonging to the genera *Abiotrophia*, *Acetivibrio*, *Anaerococcus*, *Butyrivibrio*, *Christensenella*, *Coprobacillus*, *Gemella*, *Holdemania*, *Lachnospira*, *Oscillospira*, *Peptoniphilus*, *Peptostreptococcus*, *Solobacterium* (all from Firmicutes phylum), *Actinomyces*, *Adlercreutzia*, *Gardnerella*, *Leucobacter*, *Olsenella*, *Rothia* (from Actinobacteria), *Aggregatibacter*, *Aquabacterium*, *Asticcacaulis*, *Bilophila*, *Gemmiger*, *Haemophilus*, *Marinicella*, *Parasutterella*, *Phenylobacterium*, *Pseudomonas*, *Pseudoxanthomonas*, *Ralstonia*, *Serratia*, *Stenotrophomonas* (from Proteobacteria), *Leptotrichia* (Fusobacteria) and *Paraprevotella* (Bacteroidetes), were less susceptible to alterations, as their abundance was found to be altered by only one of the tested antibiotics.

Certain antibiotics have been shown to reduce the abundance of bacteria known to be beneficial for human health, such as bacteria of the genus *Faecalibacterium* (by 30 antibiotic treatments), *Bifidobacterium* (by 40 antibiotic treatments), and *Blautia* (by 13 antibiotic treatments), to cite some (Fig. 4). Noticeably, of the 68 antibiotic treatments reviewed, only two, namely fluoroquinolone enrofloxacin (nr 2, ENR in Fig. 4) [74] and a combination of three β-lactams (ampicillin, sulbactam and cefazolin) (nr. 22, M) [52,87,88] had a negative effect on all these three genera, which are known to be strongly involved in short chain fatty acid production and amelioration of inflammation. Thus, *Faecalibacterium* is a bacterium which is depleted during inflammatory conditions [108], and *Faecalibacterium* plays an important role in inducing regulatory T-cells [109] and decreasing intestinal permeability [110]. Bacteria of the genus *Bifidobacterium* are powerful bacteria that can protect the gut, boost the immune system and control inflammatory responses [111]. The abundance of *Blautia* increases following fecal microbiota transplantation from healthy donors to individuals with recurrent *Clostridium difficile* infections; the latter represent a subgroup of individuals with extremely impaired gut bacterial composition [112].

These studies highlight the fact that there is a call for preventive measures to define antibiotic-based treatment strategies that do not harm or unbalance our resident microbiota, especially those bacteria with an active role in health. One option is to use selective antibiotics that inhibit pathogens but have a neutral impact on beneficial bacteria, such as some of those previously mentioned. This is of special significance as when antibiotics are prescribed to treat infections in different organs they not only affect the susceptible pathogen but also untargeted beneficial bacteria. Also, the counts of susceptible bacteria decrease, so resistant bacteria may proliferate. These resistant bacteria may be opportunistic pathogens, such as *C. difficile*, causing *C. difficile*-associated diarrhea [113]. Accordingly, the selective inhibitory effect of 8-hydroxyquinoline on pathogenic (*C. difficile)* and beneficial (*Bifidobacterium longum*) strains has recently been studied using flow cytometry [114]. Briefly, both species were co-cultured and their growth in media with the natural antibiotic compound 8-hydroxyquinoline (8HQ) was monitored by flow cytometry, hybridizing cells with fluorescent probes. This study has shown that 8HQ exerts selective inhibitory activity against *C. difficile*, while it does not affect the growth of *B. longum.*

2.3. Other components of the total microbiota affected by antibiotics

Antibiotic treatment may also influence the interactions between phage and bacterial species, leading to a highly connected phage-bacteria network for horizontal gene transfer [115]. Antibiotic treatments, such as those with cocktails of *i*) β-lactams and sulfonamides (cefazolin, trimethoprim and sulfamethoxazole), *ii*) glycopeptides, cyclic lipopeptides and β-lactams (vancomycin, daptomycin and ceftazidime), *iii*) lycopeptides and rifamycins (vancomycin and rifampin), and *iv*) glycopeptides and β-lactams (vancomycin and meropenem) have been also been shown to influence the composition of virus, particularly siphoviruses (Caudovirus, Myoviridae, Podoviridae, Siphoviridae), herpes viruses, phycodnaviruses, poxviruses, mimiviruses, baculoviruses, and papillomaviruses both in the gut and oral microbiota [89]. Since different antibiotic cocktails affect similar types of viruses, and all cocktails contain vancomycin as a common component, it is plausible that this glycopeptide is most likely responsible for the observed effect. Notwithstanding, experimental evidence is required to support this hypothesis. Within fungi, the treatment

with a cocktail of ceftaroline and avibactam is associated to changes in the abundance of Candida [90]. Archaea are also a component of our microbiota, particularly that in the gut [116]. Among all the antibiotics tested, clindamycin was shown to influence the archaeal community structure, particularly the presence of a specific intestinal population of Crenarchaeota [73,116]. Methanobacteria were also affected by cefprozil and cephalosporin [62,63].

3. The fraction of the microbiota actively responding to antibiotics

Antibiotics perturb the original microbiome composition [8], particularly affecting at least 42 microbial genera, as shown by examining the effect of 68 different antibiotics on our total microbes (as reviewed here, see Fig. 4 and above). The altered bacterial community may be more vulnerable to the overgrowth of opportunistic pathogens and infections [117]. However, conventional studies based on the amounts of the 16S rRNA genes generated from DNA, commonly used to estimate such alterations, cannot determine the taxonomic diversity of the bacteria that most react, or not, to antibiotics (so-called active bacteria). This is because such methods also take into account dormant, dead and quiescent bacteria as they are also present in samples [118–121]. Bacteria which become highly transcriptionally active during treatments with antibiotics may be those that develop degradation mechanisms against antibiotics, or produce molecules promoting or inhibiting growth of pathogens in the presence of the antibiotics [122]. Information about the metabolically active species in individuals due to antibiotic therapy can be estimated by monitoring the 16S rRNA amplicons generated from cDNA, which is different to the total (inactive and active) species present in the microbiota (indicated by the amounts of the 16S rRNA genes generated from DNA). A recent example, in which authors examined individuals receiving antibiotic therapy based on three different antibiotic classes revealed differences between both approaches and the potential of analyzing 16S rRNA amplicons from cDNA [77]. Bacteria affiliated to *Shewanella*, *Enhydrobacter*, *Halomonas*, *Ralstonia*, *Staphylococcus* (Proteobacteria), *Streptococcus*, *Clostridium*, *Enterococcus* (Firmicutes), *Eggerthella*, *Propionibacterium*, and *Granulicatella* (Actinobacteria) were found to become highly transcriptionally active during treatment with β-lactam antibiotics and fluoroquinolones, but not with cephalosporins [77]. Abundances of those bacteria were not altered when changes in the total bacterial composition were investigated, which demonstrates that at least these bacterial groups are among those microbes that actively react to antibiotics.

Although there are well-established methods to isolate cDNA from our microbiota, its isolation is still challenging compared to the isolation and sequencing of DNA. This is why limited information is available in the literature regarding additional active microbial groups reacting to antibiotics besides β-lactam antibiotics and fluoroquinolones [77]. However, limited this information may be, the previous example demonstrates the potential of cDNA analysis to clearly study the effect of antibiotics, particularly if one wishes to decipher which bacteria become metabolically active during and after an antibiotic intervention.

Some techniques have recently been developed to help decipher which bacteria react to different antibiotics, but avoid the problem of producing cDNA. The first one involves flow cytometry (FC) [123]. The cell membrane structures of bacteria from our microbiota can be stained with fluorescent dyes and analyzed by FC to determine viable cells and thus distinguish between damaged and integer cells during an antibiotic treatment. These can be identified by analyzing 16S rRNA amplicons generated from DNA [124]. The second one is based on sequencing 16S rRNA amplicons generated from the DNA of secretory immunoglobulin A (SIgA)-coated, or uncoated, cells selected by fluorescence-activated cell sorting (FACS) [125]. FACS physically separates the cells that are fluorescently labeled for specific selected features. Note that non-coated SIgA cells are those with the ability to cover their cell surface by molecules whose presence avoids SIgA-opsonization [126]. These cells are expected to be antibiotic-resistant species that become abundant and active during antibiotic treatment. Recently, by analyzing fecal samples from 12 patients with *C. difficile* infection (CDI) under treatment with multiple antibiotics and 12 CDI^- individuals by FACS, researchers found that the proportion of active bacteria differs greatly from the SIgA-coated bacteria between individuals with and without antibiotic treatment, and is variable during the different antibiotic treatments [127]. In general, during antibiotic interventions the proportion of the bacteria opsonized by SIgA was lower than the proportion of active bacteria, suggesting that not all recently formed bacterial cells can be coated by SIgA immediately and, thus, are not antibiotic resistant species.

4. Consequences of antibiotics on microbiome function

As described above, a great deal of attention has been paid to the analysis of antibiotic-induced dysbiosis at the level of taxonomic composition, as exemplified by the relative abundance of total and active species. By contrast, there are fewer studies into alterations in molecular agents such as genes, proteins and metabolites [128], although they may be even more relevant to understanding the effects of antibiotics on microbiome and host function than the mere differential abundance of microbes. For example, metabolites absorbed and/or produced by the action of the microbiota, and released to our body organs, are the downstream products of gene and protein expression, whose quantification is the most reliable snapshot of changes in microbial activity [11]. For this reason, in recent years we have begun to appreciate the importance of quantifying microbial activity, and the diversity, expression and/or production level of genes, proteins and metabolites of our microbes, regardless of the bacterial community composition [129]. There are very few studies reporting such datasets in the context of investigating the influence of antibiotics on our microbes, and all of them are restricted to the gut microbiota. Below we summarize the major results.

4.1. Effects of antibiotics on microbial activity

The effect of the antibiotics may also be reflected in the damage and/or destruction of bacterial cells and consequently their decreased enzymatic activity. This can be observed as the loss of membrane integrity, membrane polarity and a decrease in nucleic acid content [130]. At the same time, during antibiotic interventions, antibiotic-susceptible bacteria are replaced by resistant bacteria, which maintain the metabolic functions of the entire microbiota [88,127,130]. This reflects so-called redundancy, meaning that functions conferred by multiple bacteria can be shared across related and unrelated bacterial species before and after an antibiotic intervention [11]. Although the overall microbiota function is thought to be maintained during antibiotic treatment, alterations in specific enzymatic activities have been observed, such as the hydrolysis of dietary polysaccharides. Particularly, treatments with a cocktail of cefazolin, ampicillin and sulbactam are associated to alterations in the activity level of so-called glycoside hydrolases, favoring the rapid and unbalanced assimilation of carbohydrates, related to obesity and diabetes type 2 [131]. It is plausible that after antibiotic treatment, a novel composition of the bacterial community is established, whose metabolic functions may be similar to those in the original microbiome [88,127,130].

However, the resistant bacteria that replace the susceptible ones may have similar classes of enzymes, but each with different enzymatic performance [131].

4.2. Effects of antibiotics on microbial gene expression and protein synthesis

To avoid inferring function from taxonomic data while avoiding functional redundancy of bacterial groups [11], investigations have started to apply high-throughput DNA and cDNA sequencing and protein expression analyses, mostly to reveal the extent of antibiotic-mediated dysbiosis. This is done by identifying presumptive functionally altered profiles, reflected by the level of gene content, gene expression and protein synthesis. The most obvious reaction of the microbiota is, firstly, an increase in the acquisition and expression of a small number of genes conferring antibiotic resistance [132]. A number of authors have published comprehensive and relevant reviews and studies on antibiotic resistance genes [29], thus it is not reviewed here. The scope of our review focuses rather on how antibiotics impact the expression level of other metabolically important microbial genes and proteins.

Recently, a multi-omic approach demonstrated that antibiotics affect the community composition from the initial stages of treatment, most likely after just 3 days of treatment with a cocktail of cefazolin, ampicillin and sulbactam [88]. Such changes were reversed when treatment finished. Thus, during antibiotic therapy, gut microbiota biodiversity reached the minimum 11 days after initiating therapy. However, when the therapy finished, the alpha diversity index of the bacterial population returns to that before initiating the intervention. However, some changes remain in the relative abundance of a sub-set of bacterial groups such as Ruminococcus, Barnesiella, and Clostridiale families. Thus, it is crucial to clarify whether gut communities with similar alpha diversity and small differences in beta diversity before and after the treatment, have or do not have a similar metabolic status. This was evaluated by analyzing the gene (meta-transcriptomics) and protein (meta-proteomics) expression profiles [88]. It was found that when antibiotic treatment was discontinued, the number and abundance level of genes and proteins being expressed and synthesized were significantly lower compared to those before initiating the treatment [88]. This implies important changes in the fluxes of gene and proteins when treatment was abandoned. It also suggests that the antibiotic-induced alterations of a few bacterial groups can cause major changes in gene and protein fluxes, whatever similarities exist in alpha diversity index. In another recent study, the number and expression of genes encoding dietary polysaccharide-degrading enzymes changed significantly in patients receiving β-lactam therapy of a cocktail of cefazolin, ampicillin and sulbactam [52,88]. This suggests that the antibiotic interventions drastically changed the microbial community and the species responsible for degrading dietary components, each having a different metabolic performance as shown by enzymatic activity tests [131]. Such alterations were also found as a consequence of ampicillin (β-lactam) treatment [33].

The utilization of amoxicillin (β-lactam), ciprofloxacin (fluoroquinolone), vancomycin (glycopeptide), chloramphenicol, and erythromycin have also been linked to the differential expression level of genes involved in tRNA biosynthesis, translation, vitamin transport, phosphate transport, stress response, and proton motive force [33]. Studies analyzing the diversity and production level of proteins in gut microbiota also reported that both clindamycin (lincosamide) and streptomycin (aminoglycoside) increased the synthesis of immunoglobulin proteins, transthyretin and chymotrypsin-like elastase family proteins, proteins involved in T-cell activation, chymotrypsinogen B, phospholipase A2, myosin-1a and cytochrome C [33].

The fact that different antibiotics cause similar alterations in microbial products (genes and proteins) suggests that it is possible to identify a set of core functions associated to antibiotic treatments, as we have done in this review on the bacterial genera that are influenced. This information may become available in the future, because at present there are limited data available for all 68 antibiotics reported to influence our microbes.

4.3. Alterations in microbial metabolite content during antibiotic treatment

From the available data on large cohorts, we can conclude that antibiotics are among the only drugs associated with significant alterations in our microbiota [8], and also that only a restricted set of bacterial genera are significantly affected by antibiotics (see Fig. 4). Antibiotics also cause important changes in the fluxes of gene and proteins and the activity they mediate. The next logical question to answer is to what extent antibiotics also alter the metabolite fluxes in the microbiota. This can be achieved by performing so-called metabolite profiling. This technique offers the opportunity to measure metabolites that are the final result of the action of the microbiota independently of its community composition, gene expression and protein synthesis, growth characteristics, gene mutations and protein structures [11]. Metabolite profiling thus constitutes the next logical step beyond descriptive studies of community composition, gene composition (metagenomics), gene expression (meta-transcriptomics) and protein expression (meta-proteomics), as it may provide greater insights into the metabolic changes in the active fraction of the microbiota under any conditions.

As mentioned above, one of the questions raised by the multiple observations of antibiotic-induced shifts in our microbiota composition is to what extent antibiotics also alter the metabolic fluxes in the microbiota. This was first reported in a study showing that treatment with the aminoglycoside streptomycin affected the abundance level of over 87% of all fecal metabolites detected [133]. However, treatment with clindamycin, piperacillin or tazobactam caused changes in 30% of all fecal metabolites detected [133]. Another recent study found that this percentage was significantly lower when examining the effect of combined intravenous therapy of ampicillin, sulbactam and cefazolin. Indeed, only 4.4% of all fecal metabolites detected were altered compared to controls [88]. This suggests that each antibiotic impacts the metabolite fluxes to a different extent, which may be linked to the extent of alterations caused by each antibiotic in microbiota species composition and gene and protein fluxes.

A second question regards the nature of the metabolic alterations caused by antibiotics. A comparative *omic* investigation of microbial communities in fecal samples taken at multiple time points from an individual (with a bacterial infection) subjected to β-lactam therapy of ampicillin, sulbactam and cefazolin has revealed antibiotic-associated imbalances in long linear and branched, saturated and unsaturated fatty acids, branched chain amino acids, cholesterol derivatives, vitamins, polyols, sugars, short peptides and polyamines [88]. Studies examining the impact of perinatal antibiotics on premature babies found that antibiotic intervention mostly caused differential abundance of short-chain fatty acids, particularly, acetate, propionate and butyrate [134]. Finally, an influence on acetate production was also associated to the treatment of healthy individuals with the aminoglycoside gentamicin and the β-lactam ampicillin [95]. Differential abundance of bacteria belonging to the genera *Bacteroides*, *Bifidobacterium*, *Faecalibacterium*, *Ruminococcus*, *Alistipes*, *Roseburia*, *Parabacteroides*, *Shigella-Escherichia*, and *Allisonella*, was unambiguously linked to

the differential production of short chain fatty acids during the antibiotics interventions [88,95,134].

4.4. Bacterial translocation during antibiotic treatment

Besides the alterations mentioned above, we should also highlight that antibiotics, such as oral antibiotics, are reported to induce the translocation of live native commensal bacteria across the colonic epithelium, thereby promoting inflammatory responses, and predisposing individuals to disease in response to coincident injury [135] or to anxiety-like behavior [136].

5. Conclusions and future directions

The densest and most complex bacterial community in the human body inhabits the large intestine and forms an ecosystem with interdependence and mutualism among the species forming it. This community is known as the gut microbiota and is essential for homeostasis and host health. The gut microbiota performs functions of nutrition, metabolism (the result of biochemical activity), and protection (preventing the invasion of infectious agents or the overgrowth of resident species with pathogenic potential). It also has trophic functions for the proliferation and differentiation of the intestinal epithelium, and plays a role in the development and modulation of the immune system. However, our skin, respiratory system, oral cavity, and vaginal/urinary cavity are also equally populated by microbial communities that are as diverse and important as that of the gastrointestinal tract. An alteration in the microbiota balance (or dysbiosis) is extensively associated to antibiotic use. Alterations have not only been found in the gut microbiota, but also in oral, respiratory tract and vaginal microbiota. When faced with antibiotic treatment, the microbiota has been found not to remain unaltered (resistant), but rather changes in microbial composition and function during and after the intervention. OMICS research has become attractive to fully define the compositional changes and the metabolic status of the microbiota when confronted with antibiotics. It is well documented that antibiotics reduce the amount and diversity of our microbes and cause losses in functional diversity and colonization resistance against invading pathogens; however, the comparative effect of antibiotics on the abundance of specific microbial clades in humans has not been reported before. This review fills this gap, discussing the effects of some 68 different antibiotics on human microbiota composition and microbiome function. Data are presented revealing that antibiotics produce changes in a specific set of bacteria, fungi, archaea and viruses. Microbes are identified that are most vulnerable to antibiotics, which are similar or different in nature and clinical consequences. The reported data also demonstrate that the microbe metabolic activity is also drastically changed as a direct consequence of antibiotic treatments. Indeed, the information provided in the review also points to specific metabolic alterations during antibiotic interventions, the understanding of which may provide future research lines in the post-antibiotic era. This, together with new technologies, such as flow cytometry, may help not only to understand which antibiotics produce major health benefits and minor collateral effects in our microbiota, but also to define nutritional supplements to improve the health of antibiotic-treated patients in cases where important nutritional or metabolic deficits may occur. Finally, the data reviewed here show that the establishment of new drug-based therapeutic strategies would require multi-variable analysis, in which a comprehensive analysis should be made of the effect of the type of drug, type of administration, pharmacokinetics of the original compound, and resistance mechanisms of the microbiota, to cite some. This information will help us to understand changes in the overall microbiome function.

Conflicts of interest

All authors declare no conflicts of interest.

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