Human Microbiome Journal 9 (2018) 11–15

Contents lists available at ScienceDirect

Human Microbiome Journal

journal homepage: www.elsevier.com/locate/humic

Intestinal microbiota and antibiotic resistance: Perspectives and solutions

Climent Casals-Pascual[a,b], Andrea Vergara[a], Jordi Vila[a,b,*]

[a] Department of Clinical Microbiology, Center of Biomedical Diagnosis, Hospital Clinic, Barcelona, Spain
[b] ISGlobal, Hospital Clínic – Universitat de Barcelona, Barcelona, Spain

ARTICLE INFO

Keywords:
Gut
Intestinal microbiota
Antibiotic resistance
Perspectives
Solutions

ABSTRACT

The intestinal commensal microbiota provides a myriad of benefits to the healthy host, including colonisation resistance against pathogens. Perturbations of the intestinal microbiota (dysbiosis) may adversely affect the health status of an individual and prevent protection against colonisation. The whole range of antibiotic resistance genes (resistome) in a specific microbiota is found in pathogenic and non-pathogenic bacteria. The administration of antibiotics may cause dysbiosis, contributing to the loss of colonisation resistance followed by an increment of the resistome in the intestinal microbiota. Treatments to control the current increase of multi drug-resistant (MDR) bacteria are extremely limited. In this context, the administration of healthy faecal microbiota to restore colonisation resistance and displace MDR bacteria emerges as a promising therapeutic alternative.

This brief review describes the role of the intestinal microbiota as a reservoir of MDR bacteria, the impact of different groups of antibiotics in the selection of MDR bacteria and crucially, the potential use of faecal microbiota transplantation using “healthy” or “MDR-free microbiota” to displace MDR bacteria and restore colonisation resistance.

Introduction

The intestinal microbiota constitutes a diverse ecosystem that contains thousands of different microbial species [1]. Most of these species belong to the *Bacteroidetes*, *Firmicutes*, *Actinobacteria*, and to a lesser extent *Proteobacteria* phyla. However, the relative proportions of each taxa vary dramatically between individuals and even within individuals over their lifetime. The composition of an individual’s microbiota is influenced by many factors [2,3], namely age, geographical provenance and environment, dietary habits, co-morbidities and use of probiotics, prebiotics and antibiotics. Human immune homeostasis [4], modulation of gastrointestinal development [5] and metabolism of nutrients [6] all benefit from the intestinal commensal microbiota. Moreover, the host is endowed by the intestinal microbiota with resistance against a wide range of pathogens, a mechanism known as colonisation resistance. Colonisation resistance results from (1) indirect mechanisms, i.e., the activation of innate immune defences in the mucosa and the production of protective metabolites such as secondary biliary acids, antimicrobial peptides and short-chain fatty acids; and (2) direct mechanisms, through direct competition, secretion of bacteriocins, and nutrient depletion [7,8]. In essence, the perturbation of the normally stable gut microbiota, known as dysbiosis, may adversely affect the health status of an individual and, critically, cause the loss of protection against colonisation. Indeed, changes in the taxonomic composition of an individual’s microbiome either through loss of diversity or loss of specific taxonomic groups has been associated with enhanced susceptibility to different conditions [9–11], namely gastrointestinal infections, diabetes, obesity, liver disease, colon cancer and inflammatory bowel disease. Nevertheless, a healthy microbiota has the ability to reverse dysbiotic changes to their original state. The ability of the microbiota to restore a healthy microbiome ecosystem, also known as “resilience”, depends on (i) external factors such as diet or class of antibiotic received by the individual and (ii) internal factors, like age and presence of co-morbidities.

This short review describes the role of the intestinal microbiota as a reservoir of multi drug-resistant (MDR) bacteria, the potential impact of antibiotics in the selection of MDR bacteria and, finally, the emerging use of faecal microbiota transplant (FMT) using “healthy” or “MDR-free microbiota” to displace MDR bacteria and restore colonisation resistance. The outline of this review is summarised in Fig. 1.

Intestinal microbiota resistome

Antibiotic resistance is a significant global public health threat [12]. Reservoirs of MDR bacteria are ubiquitous, and they can merge with the gut microbiome via two mechanisms: firstly, exogenous MDR bacteria

* Corresponding author at: Department of Clinical Microbiology, Hospital Clinic, 08036 Barcelona, Spain.
E-mail address: jvila@clinic.cat (J. Vila).

https://doi.org/10.1016/j.humic.2018.05.002
Received 20 March 2018; Received in revised form 4 May 2018; Accepted 18 May 2018
Available online 31 May 2018

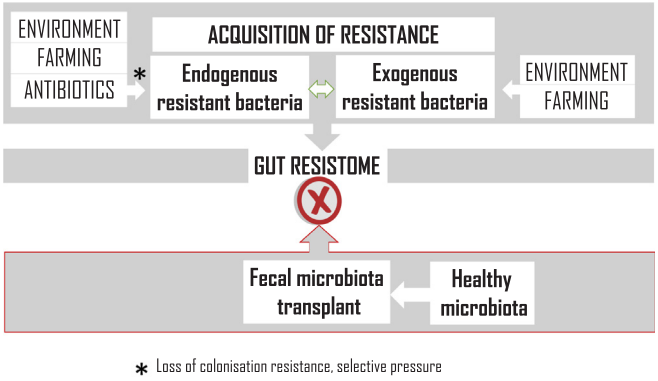

Fig. 1. Intestinal microbiota as a reservoir of multi drug-resistant (MDR) bacteria. The intestine resistome refers to the antibiotic resistance genes found in the intestinal microbiota. Exogenous MDR bacteria can be acquired by the host from the environment and previously susceptible bacteria may become resistant through selection of antibiotic-resistant mutants mediated mainly by the presence of antibiotics. Faecal microbiota transplant using "healthy" or "MDR-free microbiota" can displace MDR bacteria and restore colonisation resistance.

can be acquired by the host and colonise the intestinal epithelium; secondly, previously susceptible bacteria may become resistant through selection or induction of antibiotic-resistant mutants mediated by the presence of antibiotics or by gene transfer events.

The concept of "antibiotic resistome" was first coined [13] to describe the collection of antibiotic resistance genes found in the environment. The whole range of antibiotic resistance genes can be found in both pathogenic and non-pathogenic bacteria. However, the antibiotic resistance genes found in pathogenic bacteria represent just the tip of the iceberg of the resistome. A large reservoir of AR genes exists in various ecosystems, such as the human body, including in commensal bacteria [14]. In this sense, AR genes known from available databases to date, are likely to represent just a small fraction of the "true" population of AR genes, with plenty of new AR genes that will be discovered as new sequenced bacterial genomes become available [15]. In addition, resistome can be defined at multiple levels. Globally, the resistome refers to a large reservoir of antibiotic-resistance genes found in the environment. Locally, the intestinal resistome refers to the antibiotic resistance genes found in the intestinal microbiota and finally, at the bacterial level, it refers to the resistant genes carried by a specific bacterial species.

The resistome is established in the first few months of life or perhaps during birth. Moore and colleagues [16] reported the presence of antibiotic resistant genes in 14 out of 18 antibiotics from 8 drugs classes tested in a sample of 22 healthy infants and children without prior exposure to antibiotics. Another study characterising the intestinal microbiome of 6 month-old infants without prior exposure to antibiotics found diverse antibiotic resistance genes against aminoglycosides and beta-lactam antibiotics [17]. This research supports the view that infants acquire resistant bacteria either directly from their mothers or through contact with external non-human sources of resistant bacteria. A metagenomic analysis of the microbiome established that the microorganisms found in the early phase of colonisation of the gastrointestinal tract of premature infants were also detected in the environment of the neonatal intensive care unit, probably indicating the existence of a cycle between the environment and the infant's intestine [18].

Interestingly, Forslund and colleagues [19] reported geographical differences in the analysis of the resistome (including 68 classes and subclasses of antibiotics) of faecal samples from different countries. They concluded that the resistome of individuals from Spain, France and Italy was higher than those from Denmark, Japan and the United States. These changes correlated with a higher consumption of antibiotics in the former group, and suggested a potential link between the use of antibiotics in both human and animals and the resistant determinants in the human intestinal microbiome. In a similar study, the number and abundance of resistance genes was higher in the faecal samples of 162 Chinese individuals than in the Spanish and Danish groups studied [20].

Antibiotics are administered to animals therapeutically but also as growth promoters in the farming industry. Consequently, the consumption of meat from these animals represents an additional exposure to antibiotics for the human microbiome and thus, it may increase antimicrobial resistance through selective pressure. The intestinal microbiota of farming animals play an important role in the mechanisms for the antibiotic growth effect [21]: reduction of growth-depressing microbial metabolites, reduction of microbes competing for host nutrients, inhibition of subclinical infections, and enhanced uptake of nutrients through thinning of the intestinal walls. Although therapeutic doses of antibiotics are designed to achieve concentrations that are inhibitory to bacterial targets, it is plausible that antibiotic sub-inhibitory concentrations for some bacteria can be found in some organs/tissues. Also, antibiotic-resistant bacteria exist in the environment, including animal intestinal ecosystems. The selection and persistence of resistance driven by antibiotics on commensal bacteria creates a reservoir of resistance acquisition for both bacterial pathogens and human foodborne pathogens.

The impact of the use of some specific antibiotics in the diversity of gut microbiota and in the resistome of gut microbiota have extensively been shown [11,22,23]. Overall, different features of the antibiotic such as class, potency, spectrum and regimen can affect in different ways the intestinal microbiota and hence antibiotic resistant mutants can be selected, for instance, by over-expression of an efflux pump and producing resistance to multiples pathogens.

Impact of antibiotics in human intestinal microbiota

The administration of antibiotics may contribute to or cause dysbiosis by directly eliminating the bacterial populations that confer colonisation resistance to the intestinal microbiome. Most research published on colonisation resistance has followed the 1956 original observation by Miller and colleagues [24], which demonstrated that the dose of *Salmonella enterica* serovar Typhimurium required to cause an infection was 100 000-fold lower in mice who had previously received antibiotics. Furthermore, the extensive use of antibiotics has led to the expansion of antibiotic-resistant bacterial species and an increased abundance of antibiotic resistance genes within commensal bacteria that can be transferred to invading pathogens. The following factors might influence the impact of antibiotics on the intestinal microbiota [2,25,26]: class of antibiotic, pharmacokinetics, pharmacodynamics, range of action, dosage, duration, and administration route.

One of the dominant phyla of the healthy intestinal microbiota, the *Bacteroidetes* phylum, includes a number of bacterial species that protect the host against pathogens. For example, *Bacteroides thetaiotaomicron* [27] confers protection against viral infections by increasing the expression of type I IFN-induced GTPases and against Gram-positive bacteria through the expression of the C-type lectins REGIIIγ and REGIIIβ. This microorganism also produces a soluble factor that represses toxin production by enterohaemorrhagic *Escherichia coli* [28]. Lipopolysaccharide and flagellin stimulate Toll-like receptor 4 positive stromal cells and Toll-like receptor 5 plus CD103 positive dendritic cells to enhance expression of REGIIIγ, and avoid colonisation by vancomycin-resistant *Enterococcus* spp. (VRE) [27]. In the *Firmicutes* phylum, *Lactobacillus* spp. maintains intestinal colonisation by expressing mucus-binding pili. Interestingly, a clinical trial conducted in 2003 reported that the administration of vancomycin in combination with *Lactobacillus plantarum* decreased the number of recurrences of *Clostridium difficile* infection when compared with the administration of vancomycin alone [29]. In another study, a 7-day course of vancomycin given to people with obesity decreased bacterial diversity in these patients

and reduced the proportion of *Firmicutes* [30]. This phylum has been involved in the production of short-chain fatty acids (SCFAs) and bile acid metabolism, and in this study they found an increased adipose tissue gene expression of oxidative pathways and decreased immune-related pathways after vancomycin treatment [30]. SCFAs, like acetates, propionate and butyrate, are produced by the microbiota as a result of the fermentation and decomposition of resistant starches and dietary fiber [31]. Different receptors for SCFAs with an important role in immune regulation and metabolism have been identified in intestinal epithelial cells, immune cells, and adipocytes. Moreover, the production of SCFAs is one of the protective mechanisms used by the endogenous microbiota to prevent attachment and invasion of enteric pathogens to the intestinal epithelium. Specifically, the protection results from inducing the production of LL-37, a cathelicidin with antimicrobial properties [32]. Maintaining an appropriate concentration of SCFAs is critical to preserve intestinal homeostasis and the mechanisms that underlie colonisation resistance. Since the phyla *Firmicutes* and *Bacteroidetes* include species that predominantly contribute to the production of SCFAs [31], the loss of these phyla commonly found after antibiotic treatment is likely to have a major impact in the normal functions of the intestinal microbiota.

Several reviews attempt to unify all the literature regarding the effect of the different groups of antibiotics in the intestinal microbiota [2,25,29,33]. However, it is difficult to obtain conclusive evidence from these studies due to the small sample sizes and heterogeneity of the data, namely co-administration of other antibiotics or other drugs, previous antibiotic exposure or hospitalization, age groups, dosing regimens and method of microbiome analysis (culture, Denaturing Gradient Gel Electrophoresis, Terminal Restriction Fragment Length Polymorphism, cloning and sequencing, and Next Generation Sequencing). Although advances in metagenomic sequencing have improved our understanding of the intestinal microbiome, the diversity of protocols implemented (DNA extraction, 16S rRNA analysis versus shotgun, bioinformatics pipeline, databases and statistical analysis) have failed to consistently identify those antibiotics with the highest or lowest impact on the intestinal microbiome. It is possible that by designing studies that compare the impact of specific antibiotic for specific indications on the intestinal microbiota, we will be able to ascertain the degree of dysbiosis associated with a particular antibiotic class. In this context, describing the dysbiotic potential could become a new parameter to consider when developing new antibiotics [34].

To date, the best clinical example to illustrate the potential impact of antibiotics on the intestinal microbiome is the infection by *Clostridium difficile*. This microorganism primarily causes infections in hospitalised patients and residents of long-term health care facilities following the use of broad-spectrum antibiotics. *C. difficile* is the most common cause of nosocomial diarrhoea, with a clinical presentation that ranges from mild diarrhoea to potentially fatal pseudomembranous colitis and toxic megacolon. Although most antibiotics increase the risk of developing *C. difficile* colitis, this condition is generally associated with the use of fluoroquinolones, cephalosporins and primarily, clindamycin [35], which has a broad-spectrum activity against Gram-positive and obligate anaerobic bacteria. Clindamycin is excreted in bile and thus reaches high concentration in faeces. In experimental models, a single dose of clindamycin markedly reduces the diversity of the intestinal microbiota [36].

Also, another source of antimicrobial activity in the human gut are non-ribosomal peptides and polyketides. These secondary metabolites have widespread effect as antimicrobials, antifungal, antiparasitic agents [37].

Can we control the resistome? Current strategies to eliminate MDR bacteria

The increasing proportion of infections caused by MDR bacteria that infect patients has triggered, in many hospitals, the screening of MDR carriage, in particularly in patients admitted to critical care units. The treatments available to control the surge in prevalence of MDR bacteria is very limited. To control the spread of antimicrobial resistance within the health services, the strategies put in place are early identification of MDR bacteria in rectal swabs of patients at high risk of being colonised, i.e., patients with prior hospital admissions, critical care patients and patients who have recently received broad-spectrum antibiotics, followed by patient isolation in case of positive results, which has major logistic and economic implications.

The screening strategies rely on the identification of particular microorganisms on selective media, namely carbapenem-resistant *Enterobacteriaceae* (CRE) and extended-spectrum beta-lactamases-producing *Enterobacteriaceae* (ESBL-E).

However, the current evidence indicates that our ability to control the spread of AR genes is far from effective, as evidenced by the recent emergence of MCR-1. This plasmid-mediated resistance against polymyxins, heralds the loss of effective tools against the last resource available against multi-drug resistant bacteria [38].

Faecal microbiota transplant as a solution

The administration of healthy faecal microbiota to restore colonisation resistance and displace MDR bacteria is becoming widely accepted as a therapeutic alternative. Indeed, FMT is already the recommended treatment for recurrent *C. difficile* infection (CDI) [7,27]. Indirect evidence from studies evaluating the clinical efficacy of FMT in CDI has shown that the mean number of antibiotic-resistance genes of 34.5 (± 6.7) prior to FMT significantly decreased to 12.2 (± 7.0), 1 to 3 weeks after FMT. This observation together with evidence from animal models suggesting that VRE and CRE can be eliminated following FMT supports the clinical potential for this procedure to control the resistome.

So how does FMT work?

The increasing number of successful reports of FMT to treat CDI, in addition to the experimental models, has shed some light on the mechanism underlying the beneficial effects of FMT. Indeed, the restoration of colon microbiota in patients with CDI can effectively displace the infective pathogen by restoring the activity of antimicrobial peptides, inhibiting spore germination and vegetative growth mediated by bile acids, and activating immune-mediated colonisation resistance [39]. All these mechanisms are inhibited or absent in the dysbiotic intestine. Intuitively, the residual flora (microbiota) remaining in the colon of CDI dysbiotic patients should not be difficult to displace with a sudden influx of approximately 10^{12} “healthy” bacteria with optimal reproductive fitness. The question remains if these mechanisms play a role in patients colonised by MDR bacteria, since the degree of dysbiosis is possibly minor than in CDI patients.

Successful reports of MDR-bacteria elimination with FMT to date

Since 2014, 21 studies with a total of 111 patients have been published to address the potential use of FMT to eliminate antibiotic-resistant microorganisms, mainly CRE, ESBL-E and VRE (Table 1). The majority of these reports are observational studies resulting from patients treated for recurrent CDI who were known to be colonised with MDR bacteria which disappear after FMT was conducted. The proportion of successful decolonisation ranged from 79% for CREs, 83% for VREs to 93% for ESBL-E. Follow-up times ranged from 2 weeks to 8 months. Although the success rate is remarkably high, 9 of these studies were single-patient reports. However, the two studies with the higher sample size (N = 20) unequivocally showed a decrease in colonisation or a reduction in the number of antibiotic resistance genes [40].

Table 1
Use of FMT for patients with intestinal tract colonization with resistant bacteria.

Study design	N° Patients	VRE	ESBL-E	CRE	Others	Intervention for FMT	Results	Ref.
Case report	1			X		Naso-duodenal tube	Decolonized for at least 8 months	[41]
Case report	1		X			Naso-duodenal tube	Decolonized after 2 weeks and for at least 12 weeks	[42]
Case report	1	X				Enema	Colonized at 3 months	[43]
Case report	1			X	X	Colonoscopy	Decolonized for at least 2 years	[44]
Case report	1	X				Naso-duodenal tube	VRE relative abundance: 84% before FMT, 24% after 3 weeks, 0.2% after 7 months	[45]
Case report	1			X		Naso-duodenal tube	Decolonized after 7 days and for at least 14 days	[46]
Prospective single-centre study	8	X				Oral	8/8 titers decreased > 2-fold at 4 weeks	[47]
Prospective single-centre study	5				X	Naso-jejunal tube	5/5 decolonized of MRSA for 3 months	[48]
Case report	1		X	X		Naso-duodenal tube	Decolonized at 10 days	[49]
Case report	1			X		Colonoscopy	Decolonized after 6 weeks and for at least 6 months	[50]
Prospective multicentre study	9	X				NA	9/9 decolonized at first time point post-FMT	[51]
Prospective single-centre study	11	X				Enema	72.7% (8/11) decolonized after 6 months	[52]
Prospective single-centre study	20		X	X	X	Colonoscopy	20/20 reduction in number and diversity of antibiotic resistance genes	[53]
Prospective single-centre study	8	X	X	X	X	Colonoscopy	8/8 reduction in number and diversity of antibiotic resistance genes	[54]
Case series	3	X				Enema	3/3 Colonized for 3 months	[55]
Case report	1		X			Naso-duodenal tube	Colonized after 1 week and 3 months	[56]
Case report	1			X		Upper gastrointestinal endoscopy	Decolonized at 15, 45, and 100 days	[57]
Pilot prospective multicentre study	8	X		X		Naso-duodenal tube	25% (2/8) decolonized after 1 month and 37.5% (3/8) after 3 months	[58]
Prospective single-centre study	20	X	X	X	X	Naso-duodenal tube	75% (15/20) decolonized after 1 month and 93% (13/14) after 6 months	[59]
Prospective single-centre study	8	X	X		X	Enema	37 and 95 antimicrobial resistance genes were acquired by or removed respectively	[60]
Case series	1		X			Colonoscopy	Decolonized at 6 weeks	[61]

Abbreviations: VRE, Vancomycin Resistant Enterococcus; CRE, Carbapenem Resistant Enterobacteriaceae; ESBL-E, Extended Spectrum Beta Lactamase Producing-Enterobacteriaceae; FMT, faecal microbiota transplant.

Limitations and challenges ahead

Although the number of antibiotic-resistance (ABR) genes has been reported to be higher in patients with CDI, the amount of ABRs in the healthy population is not negligible. In the Human Microbiome Project, the estimated mean number of ABR genes in healthy controls was 6, with a range from 0 to 39 genes. The translation of research results from microbiome studies to patient care requires carefully designed clinical trials and safe manufacturing and delivery strategies. It is essential to conduct trials to elucidate the benefits that can be expected from FMT. It is biologically plausible that a combination of a minimal set of species may account for the majority of beneficial effects of FMT. However, the ecological impact on the microbiome of this strategy in conditions other than CDI has not been studied in detail.

Conclusions

The increasing number of hospital-acquired infections caused by MDR bacteria indicates a large and uncontrolled reservoir of these microorganisms, which seamlessly transit between hosts and the immediate environment. The value of FMT in the elimination of MDR bacteria has become more evident in recent years with an increasing number of reports showing that FMT can re-establish colonisation resistance as well as other functions associated with a normal intestinal microbiota. However, most studies published to date are of limited sample size and few have been designed to address this specific question. Nonetheless, the promising results on the potential use of FMT to control the resistome warrant novel and specifically designed large scale studies to gauge the impact of this intervention. Once conclusive evidence is available to support its use, FMT may change the way we manage patients infected or colonised by MDR bacteria and the control of MDR bacteria in the community.

Conflict of interest

The authors report no conflict of interest.

References

[1] Lloyd-Price J, Abu-Ali G, Huttenhower C. The healthy human microbiome. Genome Med 2016;8:51.
[2] Lagier J-C, Million M, Hugon P, Armougom F, Raoult D. Human gut microbiota: repertoire and variations. Front Cell Infect Microbiol 2012;2:136.
[3] Davenport ER, Sanders JG, Song SJ, Amato KR, Clark AG, Knight R. The human microbiome in evolution. BMC Biol 2017;15:127.
[4] Kelly D, Conway S, Aminov R. Commensal gut bacteria: mechanisms of immune modulation. Trends Immunol 2005;26:326–33.
[5] Stappenbeck TS, Hooper LV, Gordon JI. Developmental regulation of intestinal angiogenesis by indigenous microbes via Paneth cells. Proc Natl Acad Sci U S A 2002;99:15451–5.
[6] Hooper LV, Midtvedt T, Gordon JI. How host-microbial interactions shape the nutrient environment of the mammalian intestine. Annu Rev Nutr 2002;22:283–307.
[7] Pamer EG. Resurrecting the intestinal microbiota to combat antibiotic-resistant pathogens. Science 2016;352:535–8.
[8] Lawley TD, Walker AW. Intestinal colonization resistance. Immunology 2013;138:1–11.
[9] Marchesi JR, Adams DH, Fava F, Hermes GDA, Hirschfield GM, Hold G, et al. The gut microbiota and host health: a new clinical frontier. Gut 2016;65:330–9.
[10] Becattini S, Taur Y, Pamer EG. Antibiotic-induced changes in the intestinal microbiota and disease. Trends Mol Med 2016;22:458–78.
[11] Francino MP. Antibiotics and the human gut microbiome: dysbioses and accumulation of resistances. Front Microbiol 2015;6:1543.
[12] Roca I, Akova M, Baquero F, et al. The global threat of antimicrobial resistance: science for intervention. New Microb New Infect 2015;6:22–9.
[13] D'Costa VM, McGrann KM, Hughes DW, Wright GD. Sampling the antibiotic resistome. Science 2006;311:374–7.
[14] Aarts H, Margolles A. Antibiotic resistance genes in food and gut (non-pathogenic) bacteria Bad genes in good bugs. Front Microbiol 2014;5:754.
[15] Xavier BB, Das AJ, Cochrane G, De Ganck S, Kumar-Singh S, Aarestrup FM, et al. Consolidating and exploring antibiotic resistance gene data resources. J Clin Microbiol 2016 Apr;54(4):851–9.
[16] Moore AM, Patel S, Forsberg KJ, Wang B, Bentley G, Razia Y, et al. Pediatric fecal microbiota harbor diverse and novel antibiotic resistance genes. PLoS ONE 2013;8:e78822.
[17] Fouhy F, Ogilvie LA, Jones BV, Ross RP, Ryan AC, Dempsey EM, et al. Identification of aminoglycoside and β-lactam resistance genes from within an infant gut functional metagenomic library. PLoS ONE 2014;9:e108016.

[18] Brooks B, Firek BA, Miller CS, Sharon I, Thomas BC, Baker R, et al. Microbes in the neonatal intensive care unit resemble those found in the gut of premature infants. Microbiome 2014;2:1.
[19] Forslund K, Sunagawa S, Kultima JR, Mende DR, Arumugam M, Typas A, et al. Country-specific antibiotic use practices impact the human gut resistome. Genome Res 2013;23:1163–9.
[20] Hu Y, Yang X, Qin J, Lu N, Cheng G, Wu N, et al. Metagenome-wide analysis of antibiotic resistance genes in a large cohort of human gut microbiota. Nat Commun 2013;4:2151.
[21] Allen HK, Stanton TB. Altered egos: antibiotic effects on food animal microbiomes. Annu Rev Microbiol 2014;2014(68):297–315.
[22] Perez-Cobas AE, Artacho A, Knecht H, Ferrus ML, Friedrichs A, Ott SJ, et al. Differential effects of antibiotic therapy on the structure and function of human gut microbiota. PLoS ONE 2013;8:e80201.
[23] Jernberg C, Löfmark S, Edlund C, Jansson JK. Long-term impacts of antibiotic exposure on the human intestinal microbiota. Microbiology 2010;156:3216–23.
[24] Miller CP, Bohnhoff M, Rifkind D. The effect of an antibiotic on the susceptibility of the mouse's intestinal tract to Salmonella infection. Trans Am Clin Climatol Assoc 1957;68:51–8.
[25] Ianiro G, Tilg H, Gasbarrini A. Antibiotics as deep modulators of gut microbiota: between good and evil. Gut 2016;65:1906–15.
[26] Lange K, Buerger M, Stallmach A, Bruns T. Effects of antibiotics on gut microbiota. Dig Dis 2016;34:260–8.
[27] Buffie CG, Pamer EG. Microbiota-mediated colonization resistance against intestinal pathogens. Nat Rev Immunol 2013;13:790–801.
[28] de Sablet T, Chassard C, Bernalier-Donadille A, Vareille M, Gobert AP, Martin C. Human microbiota-secreted factors inhibit shiga toxin synthesis by enterohemorrhagic Escherichia coli O157:H7. Infect Immun 2009;77:783–90.
[29] Wullt M, Hagslätt MJ, Odenholt I. Lactobacillus plantarum 299v for the treatment of recurrent clostridium difficile-associated diarrhoea: a double-blind, placebo-controlled trial. Scand J Infect Dis 2003;35:365–7.
[30] Reijnders D, Goossens GH, Hermes GDA, Neis EPJG, van der Beek CM, Most J, et al. Effects of gut microbiota manipulation by antibiotics on host metabolism in obese humans: a randomized double-blind placebo-controlled trial. Cell Metab 2016;24:63–74.
[31] Ohira H, Tsutsui W, Fujioka Y. Are short chain fatty acids in gut microbiota defensive players for inflammation and atherosclerosis? J Atheroscler Thromb 2017;24:660–72.
[32] Sun Y, O'Riordan MXD. Regulation of bacterial pathogenesis by intestinal short-chain Fatty acids. Adv Appl Microbiol 2013;85:93–118.
[33] Sullivan. Effect of antimicrobial agents on the ecological balance of human microflora. LANCET Infect Dis Lancet Infect Dis 2001;1:101–14.
[34] Ruppé E, Burdet C, Grall N, De Lastours V, Lescure F-X, Andremont A, et al. Impact of antibiotics on the intestinal microbiota needs to be re-defined to optimize antibiotic usage. Clin Microbiol Infect 2018;24:3–5.
[35] Brown KA, Khanafer N, Daneman N, Fisman DN. Meta-analysis of antibiotics and the risk of community-associated Clostridium difficile infection. Antimicrob Agents Chemother 2013;57:2326–32.
[36] Buffie CG, Jarchum I, Equinda M, Lipuma L, Gobourne A, Viale A, et al. Profound alterations of intestinal microbiota following a single dose of clindamycin results in sustained susceptibility to Clostridium difficile-induced colitis. Infect Immun 2012;80:62–73.
[37] Ansari MZ, Yadav G, Gokhale RS, Mohanty D. NRPS-PKS: a knowledge-based resource for analysis of NRPS/PKS megasynthases. Nucleic Acids Res 2004;32:405–13.
[38] Skov R, Monnet D. Plasmid-mediated colistin resistance (mcr-1 gene): three months later the story unfolds. Euro Surveill 2016;21(9).
[39] Khoruts A, Sadowsky MJ. Understanding the mechanisms of faecal microbiota transplantation. Nat Rev Gastroenterol Hepatol 2016;13:508–16.
[40] Wong WF, Santiago M. Microbial approaches for targeting antibiotic-resistant bacteria. Microb Biotechnol 2017;10:1047–53.
[41] Freedman A, Eppes S. Use of stool transplant to clear fecal colonization with carbapenem-resistant enterobacteraciae (CRE): proof of concept. Open Forum Infect Dis 2014;1(suppl.1). S65-S65.
[42] Singh R, van Nood E, Nieuwdorp M, van Dam B, ten Berge IJM, Geerlings SE, et al. Donor feces infusion for eradication of Extended Spectrum beta-Lactamase producing Escherichia coli in a patient with end stage renal disease. Clin Microbiol Infect 2014;20:O977–8.
[43] Jang M-O, An JH, Jung S-I, Park K-H. Refractory clostridium difficile infection cured with fecal microbiota transplantation in vancomycin-resistant enterococcus colonized patient. Intest Res 2015;13:80–4.
[44] Crum-Cianflone NF, Sullivan E, Ballon-Landa G. Fecal microbiota transplantation and successful resolution of multidrug-resistant-organism colonization. J Clin Microbiol 2015;53:1986–9.
[45] Stripling J, Kumar R, Baddley JW, Nellore A, Dixon P, Howard D, et al. Loss of vancomycin-resistant enterococcus fecal dominance in an organ transplant patient with clostridium difficile colitis after fecal microbiota transplant. Open Forum Infect Dis 2015;2. ofv078.
[46] Lagier J-C, Million M, Fournier P-E, Brouqui P, Raoult D. Faecal microbiota transplantation for stool decolonization of OXA-48 carbapenemase-producing Klebsiella pneumoniae. J Hosp Infect 2015;90:173–4.
[47] Lombardo M-J. Vancomycin-resistant enterococcal (VRE) titers diminish among patients with recurrent Clostridium difficile infection after administration of SER-109, a novel microbiome agent. IDSA; 2015.
[48] Wei Y, Gong J, Zhu W, Guo D, Gu L, Li N, et al. Fecal microbiota transplantation restores dysbiosis in patients with methicillin resistant Staphylococcus aureus enterocolitis. BMC Infect Dis 2015;15:265.
[49] Biliński J, Grzesiowski P, Muszyński J, Wróblewska M, Mądry K, Robak K, et al. Fecal microbiota transplantation inhibits multidrug-resistant gut pathogens: preliminary report performed in an immunocompromised host. Arch Immunol Ther Exp (Warsz) 2016;64:255–8.
[50] García-Fernández S, Morosini MI, Cobo M, Foruny JR, López-Sanromán A, Cobo J, et al. Gut eradication of VIM-1 producing ST9 Klebsiella oxytoca after fecal microbiota transplantation for diarrhea caused by a Clostridium difficile hypervirulent R027 strain. Diagn Microbiol Infect Dis 2016;86:470–1.
[51] Eysenbach L, Allegretti JR, Aroniadis O, Brandt L, Donovan D, Fischer M. Clearance of vancomycin-resistant enterococcus colonization with fecal microbiota transplantation among patients with recurrent clostridium difficile infection. IDSA; 2016.
[52] Dubberke ER, Mullane KM, Gerding DN, Lee CH, Louie TJ, Guthertz H, et al. Clearance of vancomycin-resistant enterococcus concomitant with administration of a microbiota-based drug targeted at recurrent clostridium difficile infection. Open forum Infect Dis 2016;3. ofw133.
[53] Millan B, Park H, Hotte N, Mathieu O, Burguiere P, Tompkins TA, et al. Fecal microbial transplants reduce antibiotic-resistant genes in patients with recurrent clostridium difficile infection. Clin Infect Dis 2016;62:1479–86.
[54] Jouhten H, Mattila E, Arkkila P, Satokari R. Reduction of antibiotic resistance genes in intestinal microbiota of patients with recurrent clostridium difficile infection after fecal microbiota transplantation. Clin Infect Dis 2016;63:710–1.
[55] Sohn KM, Cheon S, Kim Y-S. Can Fecal microbiota transplantation (FMT) eradicate fecal colonization with vancomycin-resistant enterococci (VRE)? Infect Control Hosp Epidemiol 2016;37:1519–21.
[56] Stalenhoef JE, Terveer EM, Knetsch CW, Van't Hof PJ, Vlasveld IN, Keller JJ, et al. Fecal microbiota transfer for multidrug-resistant gram-negatives: a clinical success combined with microbiological failure. Open Forum Infect Dis 2017;4. ofx047.
[57] Ponte A, Pinho R, Mota M. Fecal microbiota transplantation: is there a role in the eradication of carbapenem-resistant Klebsiella pneumoniae intestinal carriage? Rev Española Enfermedades Dig 2017;109:392.
[58] Davido B, Batista R, Michelon H, Lepainteur M, Bouchand F, Lepeule R, et al. Is faecal microbiota transplantation an option to eradicate highly drug-resistant enteric bacteria carriage? J Hosp Infect 2017;95:433–7.
[59] Bilinski J, Grzesiowski P, Sorensen N, Madry K, Muszynski J, Robak K, et al. Fecal microbiota transplantation in patients with blood disorders inhibits gut colonization with antibiotic-resistant bacteria: results of a prospective, single-center study. Clin Infect Dis 2017;65:364–70.
[60] Leung V, Vincent C, Edens TJ, Miller M, Manges AR. Antimicrobial resistance gene acquisition and depletion following fecal microbiota transplantation for recurrent clostridium difficile infection. Clin Infect Dis 2018;66:456–7.
[61] Lahtinen P, Mattila E, Anttila V-J, Tillonen J, Teittinen M, Nevalainen P, et al. Faecal microbiota transplantation in patients with Clostridium difficile and significant comorbidities as well as in patients with new indications: a case series. World J Gastroenterol 2017;23:7174–84.