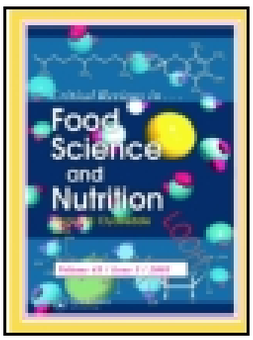

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REVIEW

Antibiotic-induced gut dysbiosis and barrier disruption and the potential protective strategies

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ABSTRACT

The oral antibiotic therapies administered widely to people and animals can cause gut dysbiosis and barrier disruption inevitably. Increasing attention has been directed toward antibiotic-induced gut dysbiosis, which involves a loss of diversity, changes in the abundances of certain taxa and consequent effects on their metabolic capacity, and the spread of antibiotic-resistant bacterial strains. Treatment with beta-lactam, glycopeptide, and macrolide antibiotics is associated with the depletion of beneficial commensal bacteria in the genera *Bifidobacterium* and *Lactobacillus*. The gut microbiota is a reservoir for antibiotic resistance genes, the prevalence of which increases sharply after antibiotic ingestion. The intestinal barrier, which comprises secretory, physical, and immunological barriers, is also a target of antibiotics. Antibiotic induced changes in the gut microbiota composition could induce weakening of the gut barrier through changes in mucin, cytokine, and antimicrobial peptide production by intestinal epithelial cells. Reports have indicated that dietary interventions involving prebiotics, probiotics, omega-3 fatty acids, and butyrate supplementation, as well as fecal microbiota transplantation, can alleviate antibiotic-induced gut dysbiosis and barrier injuries. This review summarizes the characteristics of antibiotic-associated gut dysbiosis and barrier disruption, as well as the strategies for alleviating this condition. This information is intended to provide a foundation for the exploration of safer, more efficient, and affordable strategies to prevent or relieve antibiotic-induced gut injuries.

KEYWORDS

Antibiotic; dietary supplementation; FMT; gut barrier disruption; gut dysbiosis; gut immunity; probiotics

Introduction

Antibiotics, which include beta-lactam, glycopeptide, macrolide, quinolone, and aminoglycoside drugs, are administered widely to both humans and animals, predicted that the total sales of antibiotics would increase from $27.1 billion in 2015 to $35.6 billion by 2022 (Morgun et al. 2015; Research and Markets 2017). The consequent rapid increase in antibiotic resistance has attracted global attention. More than 700,000 people die from drug-resistant bacterial infections each year (Review on Antimicrobial Resistance 2014). Projections suggest that by 2050, 10 million people will be at risk of such infections, and the lost global production will increase to $100 trillion (Malone and Gordon 2016). The gastrointestinal (GI) tract is the most susceptible organ to orally administered antibiotics, and increasing attention has been directed toward the effects of these drugs on gut ecology. The evidence supports a causal role for antibiotics to gut histopathological lesions, such as epithelial tissue destruction, cecal swelling and desquamation (Shi et al. 2017). Antibiotic therapies can induce antibiotic-associated diarrhea, which may attribute to unintended disruption of the gut microbiota, leading to opportunistic infection of *Clostridium difficile*, *C. perfringens*, *Staphylococcus aureus*, and *Klebsiella oxytoca*, thus causing mucosal immune disorders and diarrhoeal disease (Larcombe, Hutton, and Lyras 2016).

The gut microbiota is considered as a "superorganism" with important roles in human physiology and metabolism, as well as immune system development (Power et al. 2014; Rooks and Garrett 2016; Ivanov et al. 2008). For example, the presence of segmented filamentous bacteria and members of the phylum Cytophaga-Flavobacterium-Bacteroides were shown to correlate with the differentiation of Th17 cells (Ivanov et al. 2008; Ivanov et al. 2009), whereas several *Clostridium* and *Bacteroides* species induce the production and differentiation of regulatory T (Treg) cells (Atarashi et al. 2011). The mucin-utilizing species *Peptostreptococcus russellii* inhibits inflammation and enhances gut barrier function by producing the metabolite indole acrylic acid (Wlodarska et al. 2017). Some clinical trials have demonstrated that changes to the gut microbiota in early life may have lasting immune and metabolic consequences related to

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inflammatory bowel diseases, allergies, and obesity (Bailey et al. 2014; Russell et al. 2012). Moreover, antibiotic-induced perturbations of the gut microbiota can increase host susceptibility to enteric pathogens, such as *Salmonella enterica* serovar Typhimurium, leading to greater infectivity and more severe gut pathology (Sekirov et al. 2008). In addition, the effects of antibiotics on gut microbiota not only include changing their abundance and composition, but also include the evolution, optimization and transmission of antibiotic resistance genes (ARGs), collectively forming resistomes (Wright 2007). Therefore, the human gut microbiota is considered a reservoir for ARGs where members exchange these genes, thereby promoting the spread of resistance (van Schaik 2015).

The intestine comprises a physical barrier composed of intestinal epithelial cells (IECs) linked by inter-epithelial tight junctions (TJs), a secretory barrier that contains mucus and antimicrobial peptides (AMPs), and an immunological barrier that includes various immune cell populations and molecules. This barrier maintains homeostasis in the body by preventing the entry of xenobiotics from the GI lumen (Camara-Lemarroy et al. 2018). However, antibiotic treatment disrupts these three barriers in addition to affecting the gut microbiota (Table 1) (Morgun et al. 2015; Lange et al. 2016). For example, antibiotic-induced microbiota fluctuations can weaken IECs barrier via altering the production of mucin, cytokine, and AMPs (Wlodarska and Finlay 2010).

Notably, the diet also affects the intestinal barrier by inducing rapid and dramatic changes in the microbiota composition (Reimer 2019). Mouse model and clinical studies have demonstrated the broad ability of probiotics to prevent antibiotic-induced gut dysbiosis and injures (Leclercq et al. 2017; Evans et al. 2016). Moreover, fecal microbiota transplantation (FMT) can almost completely resolve serious intestinal adverse events caused by antibiotic therapy (Ekmekciu, von Klitzing, Fiebiger, Escher, et al. 2017) and is thus considered as a new and effective method for limiting multidrug-resistant pathogen infection and preventing further infection (Leung et al. 2018). Herein, we summarize the characteristics of antibiotic-associated gut dysbiosis and barrier disruption and the strategies used to alleviate these conditions. Our review demonstrates the importance of appropriate antibiotic use from the perspective of intestinal injury and lays a foundation for the exploration of safer and more efficient ways to prevent or relieve antibiotic-induced gut injuries.

Effects of antibiotics on the gut microbiota

The bacterial communities in the gut are in the ideal balanced state, so the elimination of one "keystone" species may exert great effects on other species, including increases in the proportions of some taxa with the similar roles to these "keystone," and the disappearance of several species depending on the "keystone" species for survival (Chung et al. 2012). Hence, the effects of antibiotics extend beyond the antibiotic-sensitive bacterial species (Ivanov et al. 2008). Antibiotics also pose another health risk associated with the spread of antibiotic-resistant bacteria and ARGs (Morgun et al. 2015). Here, we summarize the various characteristics of antibiotic-induced gut dysbiosis, which include a loss of microbial diversity, changes in the abundance of certain taxa and the effects on their metabolic capacities, and the potential spread of antibiotic-resistant bacteria and ARGs (Lange et al. 2016) (Table 1).

Loss of diversity and alteration in abundance of certain taxa

The effects of antibiotics on gut microbiota diversity and the recovery capability of the gut microbiota

In a previous study of fecal samples from three healthy adults, ciprofloxacin treatment was shown to affect the abundance of approximately a third of the bacterial taxa, consequently reducing the richness, diversity, and balance of the gut microbiota (Dethlefsen and Relman 2011). In that study, although most species recovered after 6 months of treatment, populations of some species were not fully restored, and the level of reconstitution varied between the individuals. Similarly, the authors of a recent study observed that the gut microbiota had largely been restored to its initial state at 8–31 months after treatment with a cocktail of oral antibiotics, but some differences in community composition still existing (Haak et al. 2019). The recovery capability of the gut microbiota was individualized and relate to individual ages, the amounts and times of antibiotic treatment, as well as the ability of an ecosystem to return to equilibrium after antibiotic exposure (Relman 2012; Yassour et al. 2016; Koo et al. 2019). The young healthy adults have stable microbial community functions in general (Buffie and Pamer 2013; Becattini, Taur, and Pamer 2016). Moreover, repeated perturbations to an ecosystem are considered especially harmful when they have not enough time to recover from the initial damage (Paine, Tegner, and Johnson 1998). It has been reported that the gut microbiota would recover from a single antibiotic exposure within about 2 weeks in adults, but repeated exposure can greatly expand the time frame (Relman 2012; Dethlefsen and Relman 2011).

Antibiotics-induced alteration in abundance of certain taxa

Palleja et al. investigated the changes in the gut microbiota of 12 healthy Caucasian men within 6 months after the oral ingestion of a cocktail of vancomycin, meropenem, and gentamicin. The results indicated the loss of some important strains, including *Bifidobacterium* species with anti-pathogenic bacteria and immunostimulatory functions and the butyrate-producing species *Coprococcus eutactus*, *Eubacterium ventriosum*, and *Methanobrevibacter smithii*, which are associated with highly efficient polysaccharide digestion (Palleja et al. 2018). Notably, in one subject, cephalosporin (ceftriaxone) caused a major alteration in the gut microbiota such that the proportion of the species *UBorkfalki ceftriaxensis* increased to 92% of the total

Table 1. Antibiotic-induced gut dysbiosis and barrier disruption.

Antibiotics	Experiment model	Administered way	The effects on gut microbiota and metabolites	The effects on gut barrier	Outcomes	Ref.
Beta-lactam antibiotic (main for G^+): The antibacterial mechanism involves interfere with cell wall synthesis.						
Ampicillin	4-wk-old male C57BL/6 mice	500 mg/kg/d by gavage for 14 d	Alpha-diversity↓; Firmicutes↓: *Dorea*↓, *Enterococcus*↑, Lachnospiraceae↓, *Coprobacillus*↓; Bacteroidetes↓; Proteobacteria↑: *Klebsiella*↑, Enterobacter↑; Verrucomicrobia↓: *Akkermansia*↓; SCFAs: succinate↑, butyrate↓	↑: Gut permeability, IFN-γ, NF-κB, MCP-1 and RegIIIγ in the colon. ↓: TJ proteins (ZO-1, occludin), IgA in the colon	Antibiotic caused structural and functional changes in gut microbiota, and affect barrier function and immune response in mice.	Shi, Kellingray, et al. (2018)
	4-wk-old male C57BL/6J mice	30 mg/kg/d via gavage or by tail vein injection for 5 d	Ampicillin resistance gene↑	—	Oral ampicillin increased resistance gene levels much more than the intravenous one.	Zhang et al. (2013)
Penicillin	Male and female BALB/c mice (breeding pairs)	31 mg/kg/d in drinking water from 1 wk before birth to postnatal day 21 and day 42	In offspring: Firmicutes↑: Lachnospiraceae↑, Erysipelotrichaceae↑, Lactobacillaceae↓; Bacteroidetes↓: S24-7↓, Prevotellaceae↓, Rikenellaceae↓; Proteobacteria↑; Tenericutes↑; Deferribacteres↓; Cyanobacteria↓	No effects on gut barrier or inflammation.	Early-life penicillin use induced long-term gut microbiota changes and neuropsychiatric disorders.	Leclercq et al. (2017)
	Male and female C57BL/6J mice	1 mg/kg/d in drinking water for 30 wk	Firmicutes: *Lactobacillus*↓, *Staphylococcus*↑, *Allobaculum*↓; Bacteroidetes: S24-7↑, Rikenellaceae↓; Proteobacteria: Stenotrophomonas↑, Burkholderia↑	↓: Th17, IL-17, IL-22, AMP in ileum	Low-dose exposure to penicillin in early-life led to metabolic alterations and affected of genes expression involved in immunity in ileum via changing gut microbiota.	Cox et al. (2014)
	Female C57BL/6J mice	1 mg/kg/d in drinking water for 7 wk (subtherapeutic antibiotic treatment)	Firmicutes↑: Lachnospiraceae↑; Bacteroidetes/Firmicutes↓; ↑: SCFAs level, adiposity metabolism	—	Early-life antibiotic treatment increased adiposity and hormones metabolism, changed key genes involved in the metabolism of carbohydrates to SCFAs.	Cho et al. (2012)
Ceftriaxone or Meropenem	Male BALB/c mice	216.3 or 216.3 mg/kg/d via subcutaneous injection for 4 d	Firmicutes↑: Papillibacter↓, *Clostridium*↑; Bacteroidetes↓: *Prevotella*↓, *Alistipes*↓; Proteobacteria↓	—	Antibiotic had adverse effects on gut microbiota.	Yin et al. (2015)
Cefoperazone/Sulbactam	Male BALB/c mice	288.3 mg/kg/d via subcutaneous injection for 4 d	Firmicutes↓; Proteobacteria↑	—	Antibiotic had adverse effects on gut microbiota.	Yin et al. (2015)
Cefixime	4-wk-old male C57BL/6J mice	150 mg/kg twice per day by gavage for 2 wk	diversity↓; Firmicutes↑: *Lactobacillus*↓, *Enterococcus*↑, *Butyricicoccus*↓; Bacteroidetes↓: *Parabacteroides*↓; Proteobacteria: *Pseudomonas*↑;	↑: Inflammatory responses in the gut (↑ C-reactive protein , Complement 3 and IgG)	Cefixime induced prominent inflammatory responses in the gut, and pathological changes in the cecum.	Shi et al. (2017)

(*continued*)

Table 1. Continued.

Antibiotics	Experiment model	Administered way	The effects on gut microbiota and metabolites	The effects on gut barrier	Outcomes	Ref.
			Actinobacteria: *Bifidobacterium*↓, *Asaccharobacter*↓; *Butyricimous*↓; SCFAs↓			
Amoxicillin	4-wk-old female C57BL/6J mice	Amoxicillin in drinking water for 12 h	Alpha diversity ↓, Bacteroidetes↑: *Bacteroides thetaiotaomicron*↑; Firmicutes↓: *Acidaminococcus fermentans*↓, *Selenomonas ruminantium*↓, *Enterococcus*↓, *Streptococcus*↓, *Lactobacillus*↓, *Paenibacillus*↓, *Lachnoclostridium*↓, *Butyrivibrio*↓, *Roseburia*↓, *Ruminococcus*↓, *Eubacterium*↓, *Clostridium*↓, Oscillibacter↓, *Heliobacterium*↓; Proteobacteria↓: Pseudomonas↓; Actinobacteria↓: *Bifidobacterium*↓, Eggerthella↓; Polysaccharide utilization ↑	—	Amoxicillin changed the metabolic environment in the gut and the microbiota at the whole-community and species-level.	Cabral et al. (2019)
	4-wk-old male and female C57BL/6J mice	Oral gavage with 25 mg/kg amoxicillin, three times per day for 1 wk	*Klebsiella*↑, *Escherichia-Shigella*↑; *Bifidobacterium*↓, *Lactobacillus*↓; β-lactam resistance genes↑, efflux resistance genes↑	—	Amoxicillin has prolonged impact on gut microbiota composition and structure, and increased the diversity and abundance of ARGs in gut microbiota	Lin et al. (2020)
Ceftriaxoneto	Patient HD.S1	2 g/d intravenous ceftriaxone for 4 d, after last injection 12–24 h to collect fecal sample.	↓ indicates permanent miss: Firmicutes: ^{U}*Borkfalki ceftriaxensis*↑, *Ruminococcus bromii*↓, *L. lactis*↓, *L. casei*↑, *S. thermophilus*↑, *Eubacterium rectale*↓, *Roseburia inulinivorans*↓, *Feacalibacterium prausnitizii*↓; Bacteroidetes: *Bacteroides* sp.↓, *B. vulgatus*↓, *B.sartorii*↓, *B. fragilis*↓, *Parabacteroides distasonis*↑; Actinobacteria: *Propionibacterium freudenreichi*↑	—	After antibiotic treatment, a low abundant species sharply bloomed and nine commensal bacteria permanently lost.	Hildebrand et al. (2019)
Penicillins (amoxicillin and penicillin V)	142 Finnish preschool children aged 2–7	Individual penicillins purchase records	Firmicutes↓: *Lactobacillus*↓	—	Penicillin had a less effect on gut microbiota than macrolides in preschool children.	Korpela et al. (2016)
Cocktail of ß-lactam Cephalosporins/ Ampicillin /Sulbactam (penicillins)	18 healthy and 5 hospitalized individuals receiving antibiotic therapy with or without *C. difficile* infection	Samples obtained from 3 mo after the antibiotic therapy	Alpha-diversity↓; Firmicutes↓: Lachnospiraceae↓; Proteobacteria↑: Enterobacteriaceae↑; Bacteroidete↑	—	Antibiotic-induced changes in some gut microbiota species, such as Lachnospiraceae, may be related to	Knecht et al. (2014)

					colonization resistance against *C. difficile*	
Glycopeptide antibiotics (main for G^+): The antibacterial mechanisms involve inhibition of cell wall or ribonucleic acid synthesis and change of cell membrane permeability.						
Vancomycin	C57BL/6 mice	100 mg/L in sterile water for 10 d	Tenericutes↑; Firmicutes↓: Lachnospiraceae↓, Ruminococcaceae↓; Bacteroidetes↓: Prophyromonadaceae↓, Rikenellaceae↓; Proteobacteria↑: Enterobacteriaceae↑	—	3-wk period of recovery resulted in an increase of diversity.	Robinson and Young (2010)
	7-wk-old female C57BL/6J mice and breeding pairs	200 mg/L in drinking water for 2 d	Alpha diversity↓; Firmicutes: Lachnospiraceae↓, Ruminococcaceae↓, *Lactobacillus*↑; Bacteroidetes↓: Alistipes↓, Bacteroidales↓; Actinobacteria: Adlercreutzia↓; Verrucomicrobia↑: *Akk. muciniphila* ↑; Tenericutes↓	↓: Colonic Treg cells	Early life of antibiotic exposure changed microbiota, thus enhancing susceptibility to allergic asthma.	Russell et al. (2012)
	C57BL/6 female mice	50, 100 mg/L in drinking water for 2 d	Firmicutes: Lactobacilli↓, Enterococci/D-Streptococci↓; Cytophaga-Flavobacterium-Bacteroides (CFB)↓; Proteobacteria: Enterobacteriaceae↑, Gammaproteobacteria↑	Vancomycin did not cause inflammatory in gut, but after *Salmonella* serovar Typhimurium infection, ↑: TNF-a, IL-6, MCP-1, keratinocyte chemoattractant.	Vancomycin increased susceptibility to *Salmonella* serovar Typhimurium infection.	Sekirov et al. (2008)
	C57BL/6 mice	1 or 0.5 g/L in drinking water on a weekly basis	CFB (loss); Proteobacteria: Gammaproteobacteria↑	↓: Th17 cells, IL-17, IgA producing cells and ↑: Treg cells among the CD4+ T cells in small intestine lamina propria (LP)	Microbiota composition regulated Th17: Treg balance in LP and may thereby affecting intestinal immunity.	Ivanov et al. (2008)
	Male BALB/c mice	283.8 mg/kg/d via subcutaneous injection for 4 d	Firmicutes↓: *Enterococcus*↓, Escherichia↑, Lactobacillaceae↑, *Lactobacillus*↓, *Clostridium*↓; Bacteroidetes: Bacteroides spp.↓, Parabacteroides↓; Proteobacteria: Enterococci↑, Enterobacteriaceae↑; Actinobacteria: Bifidobacteria↓, Eggerthella↓	—	Vancomycin has a much greater effect on gut microbiota than Azithromycin.	Yin et al. (2015)
	4-wk-old C57BL/6 mice	500 mg/L in drinking water for 4 wk	Firmicutes: Clostridia↓; Proteobacteria: Enterobacteriaceae↑	↓: Foxp3+ Tregs	Antibiotic reduced Foxp3+ Tregs, which due to a decrease in *Clostridium* species	Atarashi et al. (2011)
	NOD mice for diabetes	Adults: 500 mg/L in drinking water from 8 wk of age to onset of diabetes; Pups: 83 mg/kg/d from birth to weaning (day 28) by orally	Firmicutes↓: Ruminococcaceae↓, Lachnospiraceae↓; Proteobacteria↑: Proteus↑; Bacteroidetes↓: Porphyromonadaceae↓, *Barnesiella*↓, *Alistipes*↓; Verrucomicrobia↑: *Akk. muciniphila*↑	↑: Differentiation (CD)4+ T cells producing IFN-γ and TNF-α in the neonatally treated mice	Early life of vancomycin treatment increased *Akk. muciniphila* and reduced type 1 diabetes incidence.	Hansen et al. (2012)

(*continued*)

Table 1. Continued.

Antibiotics	Experiment model	Administered way	The effects on gut microbiota and metabolites	The effects on gut barrier	Outcomes	Ref.
	Rheumatoid arthritis patients	Orally (250 mg four times a day) for 2 wk	Firmicutes: Lachnospiraceae↓, *Faecalibacterium*↓, *Clostridium* XIVa↓, Dorea↓, Roseburia↓, Oscilibacter↓; Proteobacteria↑: Enterobacteriaceae↑, Escherichia/Shigella↑; Bacteroidetes↓: Prevotella↓; Fusobacteria↑	—	Vancomycin exerted long-term negative effects on gut microbiota, and increased pathogen colonization.	Isaac et al. (2017)
	20 male obese subjects with metabolic syndrome	500 mg vancomycin t.i.d. for 7 d	diversity↓; Firmicutes↓: *L. plantarum*↑; SCFA producing bacteria: *E.hallii*↓, *F. Prausznitzii*↓; Proteobacteria↑: *E. coli*↑, *Serratia*↑, *Haemophilus*↑; ↓: bile acid dehydroxylation, secondary bile acids in feces. Firmicutes contributed to bile acid and glucose metabolism.	—	Antibiotic reduced insulin sensitivity.	Vrieze et al. (2014)
Macrolide antibiotics (main for G^+): The antibacterial mechanism involves inhibition of protein synthesis.						
Azithromycin	Male BALB/c mice	72.1 mg/kg/d via subcutaneous injection for 4 d	Firmicutes: *Enterococcus*↑, *Lactobacillus*↓, Papillibacter↓	—	Azithromycin has a much lower effect on gut microbiota than vancomycin and beta-lactams.	Yin et al. (2015)
Cocktail of Macrolide (azithromycin and clarithromycin)	142 Finnish preschool children	individual antibiotic purchase records	Actinobacteria↓: *Bifidobacterium*↓, Collinsella↓, Coriobacteriaceae↓, Eggerthella↑; Firmicutes: *Lactobacillus*↓, *Streptococcus*↑, Christensenella↓, Anaerostipes↓; Bacteroidetes↑: Bacteroides↑, Parabacteroides↑; Proteobacteria↑: Enterobacteriaceae↑;	—	Macrolide use in early life is associated with increased risk of asthma and predisposes to antibiotic-associated weight gain.	Korpela et al. (2016)
Quinolone antibiotics (main for G^-): The antibacterial mechanism involves inhibition of DNA synthesis.						
Ciprofloxacin	3 healthy adults	The two of 5-d courses of 500 mg orally two times daily.	Alpha diversity↓; Firmicutes: Lachnospiraceae↑, Subdoligranulum↑, Moryella↑	—	Antibiotic-induced gut dysbiosis had individualized responses, and did not recovered completely, which may shift to an alternative stable state.	Dethlefsen and Relman (2011)
Fluoroquinolone	Healthy and hospitalized individuals	Samples obtained from 3 mo after the antibiotic therapy	Proteobacteria↑; Bacteroidete↑	—	—	Knecht et al. (2014)
Aminoglycoside antibiotics (main for aerobe): The antibacterial mechanism involves inhibition of protein synthesis.						
Streptomycin	C57BL/6 female mice	150, 300, 450 mg/L in drinking water for 2 d	Firmicutes: Lactobacilli↓; CFB↑, Proteobacteria↑	Streptomycin did not cause inflammatory in gut, but after *Salmonella* serovar Typhimurium	Streptomycin had a dose-dependent effect on gut microbiota and increased susceptibility	Sekirov et al. (2008)

				infection, ↑: TNF-a, IL-6, MCP-1, keratinocyte chemoattractant.	to *Salmonella* serovar Typhimurium infection	
Kanamycin	Infancy BALB/c mice (3 wk old)	Orally administered 600 μg/d for 7 d	The changed gut microbiota recovered after 10 wk.	↑: IgG1 and IgE levels in serum ↓: IgG2a level, the number of lymphocytes in Peyer patches.	Antibiotic-induced gut microbiota changes in infancy may induce Th1/Th2 balance toward Th2-dominant immunity	Oyama et al. (2001)
Lincosamides antibiotics (main for G^+ and anaerobes): The antibacterial mechanism involves inhibition of protein synthesis.						
Clindamycin	8 healthy subjects	150 mg clindamycin capsules four times a day for 7 d. Fecal samples were collected at 9 time points within 2 y.	Bacteroidetes: Bacteroides↓; ↑: resistance genes *erm*B, *erm*F and *erm*G, confer resistance to clindamycin and also to macrolides	—	Long after a short antibiotic exposure would exert long term effects on gut microbiota, keeping up to 2 y.	Jernberg et al. (2007)
Nitroimidazoles antibiotics (main for anaerobes): The antibacterial mechanism involves inhibition of DNA synthesis.						
Metronidazole	C57BL/6 female mice (10 wk old)	750 mg/L in drinking water for 4 d	Bacteroidetes: Porphyromonadaceae↓; Firmicutes: Lactobacilli ↑	↓: Muc2, mucus thickness and mucosal barrier; ↑: TNF-a, IFN-γ, MCP-1, inflammatory tone of the intestine	Antibiotics caused more serious *C. rodentium*-induced colitis.	Wlodarska et al. (2011)
Metronidazole	female Wistar Hannover rats (8 wk old)	a daily dosage of 0.5 mL of metronidazole solution with 8 mg/mL	—	↑: Intestinal permeability	Antibiotic-induced changes in microbiota may be related to changes in gut permeability.	Tulstrup et al. (2015)
Cocktail of different classes of antibiotics						
Ampicillin, metronidazole, neomycin, gentamicin, and vancomycin	C57BL/6 mice, GF mice	Amp., met., neo. and gen. (1 g/L each), and van. (0.5 g/L) in drinking water for 1 wk	Bacteroidetes/Firmicutes↑; Firmicutes: *Allobaculum*↓; SCFAs↓	↑: Th1 cell, TNF-a, IL-6, MCP-1, susceptibility to infections	Antibiotic caused a long-term of immune disruption and susceptibility to infections.	Scott et al. (2018)
Ampicillin, vancomycin, neomycin and metronidazole	C57BL/6 mice; BALB/c mice; GF mice	Amp., met. and neo. (1 g/L each), and van. (0.5 g/L) in drinking water for 4–5 wk	Proteobacteria: Enterobacterales↑, Pseudomonadales↑, Betaproteobacteria↑	↓: immune gene expression, T lymphocyte numbers, IgA-producing plasma cells, mitochondrial gene expression and mitochondrial functions	About 2/3 antibiotic-induced gene expression changes in the gut microbiota, 1/3 in the gut.	Morgun et al. (2015)
Vancomycin, neomycin and metronidazole	mice	Van. and met. (1 g/L each), neo. (0.5 g/L) in drinking water for at least 1 wk	Firmicutes: vancomycin-resistant *Enterococcus*↑	↓: RegIIIγ	Antibiotic-induced compromised mucosal innate immune defence, can be alleviated through stimulating TLR.	Brandl et al. (2008)
Ampicillin and neomycin	male BALB/c mice	Amp. 1.0 g/L and neo. 0.5 g/L in drinking water for 2 wk	Firmicutes:Bacteroidetes ratio ↑	↑: Intestinal permeability, TNF-a:IL-10 ratio	Antibiotic treatment reduced femoral trabecular bone volume (bone loss).	Schepper et al. (2019)
Kanamycin, gentamicin, colistin, metronidazole, and vancomycin	C3H/HeJ and C3HeB/FeJ female mice	To gavage with 200 μL mixture: kan., gen., met. and van.(4, 0.35, 2.15	Aerobic bacterial ↓, from 10^9 to 10^5 CFU/g; Anaerobic	The proportions of B and T cells were altered. ↑: Th2	Antibiotic can induce allergic response.	Bashir et al. (2004)

(*continued*)

Table 1. Continued.

Antibiotics	Experiment model	Administered way	The effects on gut microbiota and metabolites	The effects on gut barrier	Outcomes	Ref.
		and 0.45 g/L), and col. (8500 U/mL) for 7 d, then via drinking water until sacrifice (1:50)	bacteria↓, from 10^{10} to 10^{8} CFU/g	cytokine response, serum IgE levels; ↓: IFN-γ response		
Ciprofloxacin and metronidazole	male C57BL/6 mice (8 wk old)	Cip. (0.2 g/L) and met. (1 g/L) in drinking water for 2 wk	Firmicutes: Clostridiales↓, *Ruminococcus*↓, *Dehalobacterium*↓, Oscillospira↓, Dorea↓, Lachnospira↓; Bacteroidetes: Prevotella↓, S24-7↓, Proteobacteria: Desulfovibrio↓, Actinobacteria: Adlercreutzia↓,	—	Antibiotic changed mucosal microbiome and gut transcriptome.	Suez et al. (2018)
Vancomycin, meropenem and gentamicin	12 healthy Caucasian men, 18–40 y old	500 mg mer. and van., 40 mg gen. in apple juice and ingested orally once-daily for 4 d	↓ indicates permanent miss; Firmicutes: *Coprococcus* spp.↓, *Faecalibacterium prausnitzii*↓, *Roseburia hominis*↓, *Eubacterium* spp.↓, *Anaerostipes hadrus*↓, *Clostridium* spp.↑, *C. bolteae*↑, *Enterococcus faecalis*↑, Veillonella, spp.↑, Megasphaera micronuciformis↑; Proteobacteria: *E. coli*↑, Klebsiella spp.↑; Actinobacteria: *Bifidobacterium*↓; Euryarchaeota: *Methanobrevibacter smithii*↓; Fusobacteria: *Fusobacterium nucleatum*↑	—	After 6 mo of antibiotic treatment, a mild imprint still existed in gut microbiota, and ARG carriage modulated the recovery processes in healthy adults.	Palleja et al. (2018)
Ciprofloxacin and metronidazole	46 healthy volunteers	Oral cip. 500 mg bi-daily and met. 500 mg tri-daily for 7 d	Firmicutes: *Clostridium celatum*↓, *C. leptum*↓, C. HGF2↑, *Streptococcus infantarius*↑, Dorea formicigenerans↓, *Subdoligranulum*↓, *Ruminococcus flavefaciens*↓, *R. prausnitzii*↓, *Eubacterium biforme*↓, *E. hallii*↓; Bacteroidetes: *Odoribacter splanchnicus*↓; Proteobacteria: Escherichia↑; Actinobacteria: *Actinomyces odontolyticus*↑	—	Antibiotic changed mucosal microbiome and gut transcriptome.	Suez et al. (2018)

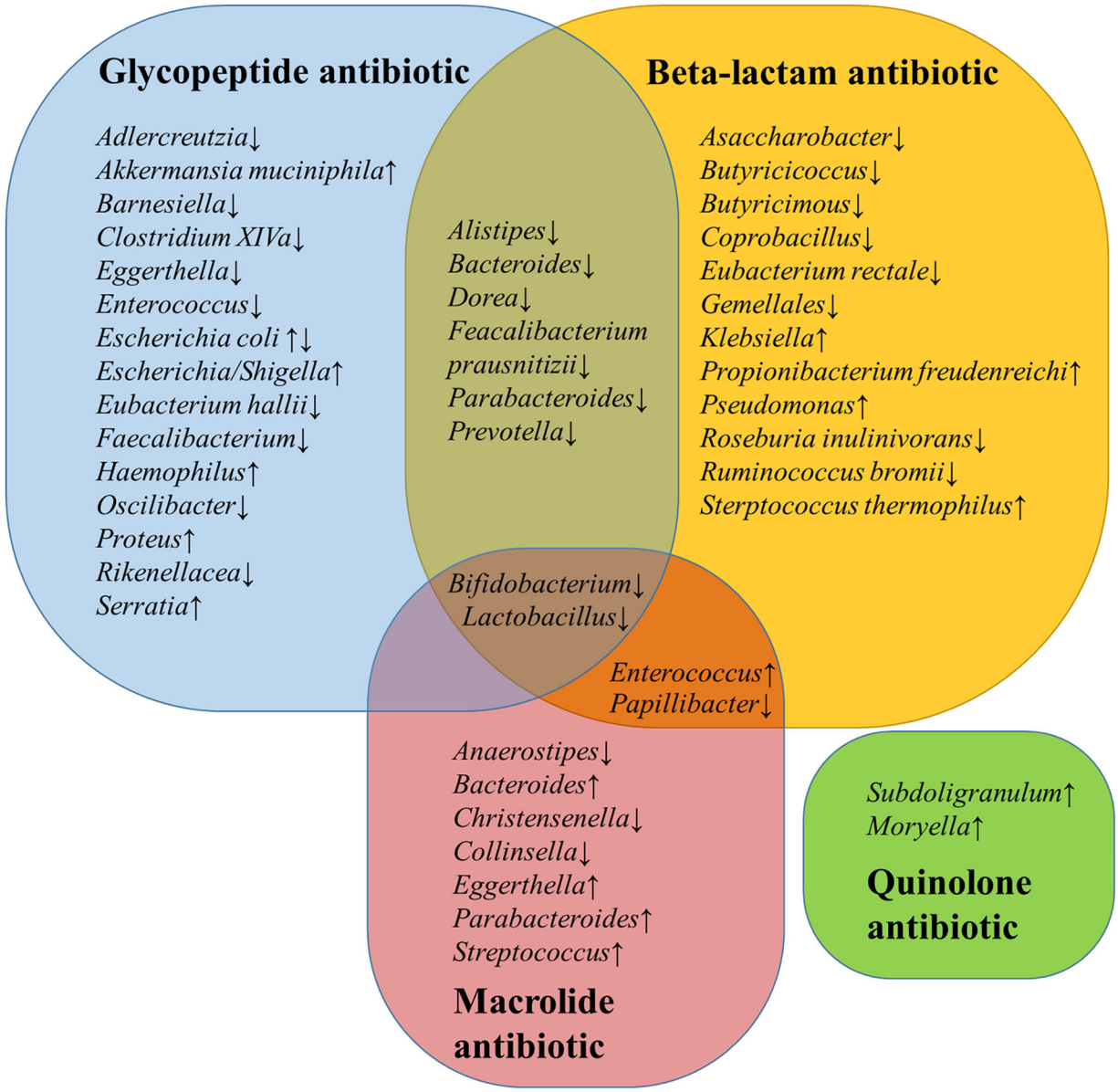

Figure 1. Effects of different antibiotic classes on the gut microbiota at the genus level.

abundance due to a 2000-fold increase in the absolute abundance (Hildebrand et al. 2019). Normally, *UBorkfalki ceftriaxensis* has a low abundance in at least a third of adults and exhibits a stable association with host health. This species was also the first colonizing organism after antibiotic treatment, which ultimately caused long-lasting changes in the gut microbiota and permanent losses of nine commensal strains, including *Ruminococcus bromii*, *L. lactis*, *Eubacterium rectale*, *Roseburia inulinivorans*, *Faecalibacterium prausnitzii*, *Bacteroides* spp., *B. vulgatus*, *B. sartorii*, and *B. fragilis* (Hildebrand et al. 2019). These strains play an important role in maintaining the host's health, for example, *B. fragilis* could modulate the Th1/Th2 cell balance (Mazmanian et al. 2005) For antibiotic-treated children, the diversity of gut microbiota was less at the level of both species and strains, and some species were even dominated by single strains (Yassour et al. 2016).

The influence factors of antibiotic-induced gut microbiota alteration

The changes in the gut microbiota induced by different classes of antibiotics are vary according to the drug spectrum, administration route, or host characteristic and state (Jernberg et al. 2010; Raymond et al. 2016; Yassour et al. 2016) (Table 1 and Figure 1). Tulstrup et al. compared the effects of four antibiotics belonging to three classes, namely beta-lactam antibiotic (amoxicillin, cefotaxime), glycopeptide antibiotic (vancomycin) and nitroimidazoles antibiotic (metronidazole), on gut microbiota, and observed varying effects according to class (Tulstrup et al. 2015). Cefotaxime increased the relative abundance of Bifidobacteriaceae, and vancomycin elevated those of Lactobacillaceae and Verrucomicrobiaceae. Particularly, metronidazole exerted no effects on the microbiota, likely because it was absorbed mainly in the small intestine and little of the drug reached

the ileum, cecum, and colon (Löfmark, Edlund, and Nord 2010). In contrast, neomycin was poorly absorbed in the gut and dramatically reduced gut microbiota density by up to 90% (Vijay-Kumar et al. 2010; Miller et al. 2019). Macrolides can inhibit protein synthesis and are excreted via the biliary system, and act mainly against gram-positive bacteria. Korpela et al. showed that in Finnish children (age: 2–7 years), macrolides reduced the relative abundances of Actinobacteria and Firmicutes and increased those of Bacteroidetes and Proteobacteria, whereas penicillin V and amoxicillin did not significantly alter the gut microbiota (Korpela et al. 2016). The effect on Proteobacteria might be attributable to the ability of the outer membranes of Proteobacteria species to block interactions between the antibiotic and its target, UDP-N-acetylmuramyl pentapeptide (Barna and Williams 1984). Furthermore, the baseline microbiota composition of the host also palys a vital role on the antibiotic-mediated gut microbiota changes (Lavelle et al. 2019). For instance, the two groups of mice had different gut microbiota composition, the microbiota in A group mice (mice A) dominated by Prevotella and Faecalibacterium, while those in B group mice (mice B) dominated by Bacteroides and Parabacteroides. After antibiotic treatment, mice B maintained a more stable profile than mice A (Lavelle et al. 2019). Also, after cefprozil exposure, the enrichment of the opportunistic pathogen *Enterobacter cloacae* was only observed in volunteers who initially had a Bacteroides enterotype with lower microbiota diversity (Raymond et al. 2016).

The effects of beta-lactam, glycopeptide, macrolide antibiotic on gut microbiota

The effects of the three common classes of antibiotics on gut microbiota at the genus level were summarized according to previous studies (Figure 1). Interestingly, all three classes of antibiotics decreased the relative abundances of *Bifidobacterium* and *Lactobacillus*. Moreover, glycopeptide and beta-lactam antibiotics had similar effects on the gut microbiota at the genus level, including the depletion of *Alistipes*, *Bacteroides*, *Dorea*, *Parabacteroides*, and *Prevotella*. These similar effects were partly attributable to similarities in the antibacterial mechanisms of these drugs, which interfere with cell wall synthesis and mainly target gram-positive bacteria.

Spread of antibiotic resistant bacteria and ARGs

The spread of antibiotic resistant bacteria

The intestinal microbiota provides resistance against colonization and invasion by pathogens not only via resource competition, (Baumgartner et al. 2020), but also via inducing the expression of AMPs, such as RegIIIγ, or via activating innate immunity in the mucosa via the TLR-MyD88 pathway (Brandl et al. 2008). However, antibiotic use can destroy the balance in the intestinal microbiota and increase susceptibility to infectious pathogens. The abuse of antibiotics has led to the proliferation of various antibiotic-resistant pathogens and even "superbugs," such as methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant *Enterococcus* (VRE). It has been reported that exposure to vancomycin (Morris et al. 1995), ciprofloxacin (Morris et al. 1995), aminoglycosides (Handwerger et al. 1993) and antibiotics that are active against anaerobes (Lucas et al. 1998) were related to the VRE's colonization and infection. Notably, antibiotic that promoted the expansion of antibiotic resistant microorganisms may not only be the one it is resistant, for example, vancomycin for VRE, but also antibiotic that kills several species that exert colonization resistance, such as Lachnospiraceae (Pamer 2016; Reeves et al. 2011). Besides, the spread of antibiotic resistant microorganisms may attribute to impairment of mucosal innate immune defenses caused by antibiotics (Brandl et al. 2008). It is worth mentioning that Donskey et al. investigated the effects of different antibiotics on the VRE colonization density in colonized patients (Donskey et al. 2000). The results showed that the antibiotics with high specificity for anaerobic bacteria, such as vancomycin and ciprofloxacin, promoted higher density VRE colonization than antibiotics with minimal anti-anaerobic activity, such as ciprofloxacin and cephalexin, suggesting that avoiding the use of these anti-anaerobic antibiotics in patients may decrease the spread of VRE (Donskey et al. 2000).

The evidences and characteristics of ARGs' spread

The spread of ARGs induced by antibiotic usage is also a serious public health issue (Yassour et al. 2016). A large cohort study showed that Chinese adults harbored more diverse and abundant ARGs than Danish and Spanish adults (Hu et al. 2013), and obese children harbored more ARG types than Chinese adults (Wu et al. 2016), which may be closely related to more frequent antibacterial treatment and the extensive antibiotics exposure in China (Wu et al. 2016; Barth et al. 2005). The abundances of specific ARGs, such as erythromycin resistance genes *erm*B, *erm*F, and *erm*G, were shown to increase after a short exposure to clindamycin (Jernberg et al. 2007). Similarly, florfenicol treatment increased the transfer of ARGs in the fish gut and enriched the abundance of ARGs by at least 4.5-fold (Saenz et al. 2019). In swine, even a short exposure to a low-dose antibiotic cocktail enriched the abundances of more than 20 ARGs (Looft et al. 2012). It is well-known that the gut microbiota is a reservoir for ARGs, thus enabling the exchange of these genes between different species and accelerating the evolution and spread of antibiotic resistance (van Schaik 2015; Stecher, Maier, and Hardt 2013). ARGs existed across multiple phyla, such as Firmicutes, Bacteroidetes and Proteobacteria (Wu et al. 2016). Bacteria belonging to Firmicutes carried the minimum load of ARGs, and most of them only carried one gene type, while the members of Enterobacteriaceae bacteria, especially *Klebsiella*, *Enterobacter* and *Escherichia* carried the heavy load of ARGs and these bacterial taxa were hubs connecting multiple ARGs types (Wu et al. 2016). Enterobacteriaceae are known for their propensity to transfer genes, especially in the presence of gut inflammation (Stecher et al. 2012). Moreover,

tetracycline resistance genes (*tetX*) in *Bifidobacterium* may initially be transferred from pathogenic bacteria in the intestine (Spigaglia, Barbanti, and Mastrantonio 2008) and that every kind of *tetX* may be apt to insert in the neighboring specific *Bifidobacterium* genes (Ammor et al. 2008).

The influence factors of ARGs' spread

The effects of antibiotics on ARGs are vary depending on the different antibiotic, administration route, and genomic context of host intestinal microbiota. According to a study by Willmann et al., treatment with ciprofloxacin or cotrimoxazole induced similar changes in the gut microbial diversity in hematological patients but had different effects on the gut resistome (Willmann et al. 2019). The increases in sulfonamide ARGs (148%) and ARG-carrying plasmids were only observed in the cotrimoxazole-treated group, indicating that cotrimoxazole is more likely than ciprofloxacin to promote ARGs' spread (Willmann et al. 2019). The higher impact on the plasmidome compared with ciprofloxacin might be due to the selection of sulfonamide ARGs which are often localized on integron cassettes, typically to be found on conjugative plasmids (Gillings 2014). In the same clinical study, higher intestinal plasmid diversity before treatment reflected a higher transmission potential, and thus a higher chance for positive ARG selection under antibiotic pressure. Besides, following the children exposed to the antibiotics, two alternative patterns for ARG abundance were observed depending on their genomic context: genes carried on microbial mobile elements would persist much longer after stopping antibiotic exposure, while genes on the chromosome tended to show a sharp decline after stopping antibiotic exposure (Yassour et al. 2016). The results suggested that the genomic context of the ARG may influence its spread and persistence upon exposure to antibiotics. Another interesting study demonstrated that an antibiotic-induced increase in the ARG levels among the gut microbiota may be affected by the drug administration route, e.g., the oral drugs may have more prominent effects than injected drugs (Zhang et al. 2013).

The mechanism of ARGs' spread

It is important to understand the underlying mechanisms of how resistance is acquired by bacteria and spreads within gut microbiota (Baumgartner et al. 2020; Berendonk et al. 2015). The ARGs predate our use of antibiotics and antibiotic resistance is an ancient natural phenomenon which exists widely in the environment (D'Costa et al. 2011). However, the large-scale production and use of antibiotics have accelerated the spread of antibiotic resistant microorganisms and ARGs, greatly increasing the frequency of antibiotic resistance (Knapp et al. 2010; Peak et al. 2010). Antibiotics in the environment have selective pressure on environmental microorganisms. Resistant microorganisms with ARGs can survive and gradually become dominant microorganisms (vertical evolution), and continuously transmit their ARGs to other microorganisms (horizontal evolution), thereby increasing the number of ARGs (Sommer et al. 2017). Furthermore, the common pathway acquiring ARGs for antibiotic-resistant bacteria in the gut microbiota is horizontal gene transfer (HGT) (McInnes et al. 2020; Stinear et al. 2001; Dehoux et al. 2016). It can occur via different mechanisms, including transformation (the bacteria absorb naked DNA from the environment), transduction (genetic material is transferred between donor and recipient bacteria via a phage intermediate), and conjugation (mobile genetic elements, such as plasmids, transfer via a pilus formed between donor and recipient cells) (McInnes et al. 2020). More recently, the role of membrane vesicles (MVs) in HGT has also been recognized (McInnes et al. 2020). There are several factors that may promote the occurrence of HGT in the gut, including the host's inflammation and the production of membrane-destabilizing agents by both the microbiota and the host (Sitaraman 2018).

Antibiotics-induced metabolic changes related to gut microbiota

The changes on SCFAs levels

The antibiotic treatment causes a loss of diversity and compositional changes in the gut microbiota, which inevitably lead to metabolic changes at the whole-community and single-species levels (Vangay et al. 2015). Short-chain fatty acids (SCFAs) are important metabolites of the gut microbiota that serve as the main energy source for IECs, exert anti-inflammatory effects, and improve epithelial barrier functions (Shi, Kellingray, et al. 2018). The abundances of SCFA-producing bacterial species, including *Eubacterium hallii*, *E. ventriosum*, *Faecalibacterium prausznitzii*, and *Coprococcus eutactus*, were shown to be reduced significantly after antibiotic administration, thereby causing decreases in the SCFA levels (Scott et al. 2018; Palleja et al. 2018; Vrieze et al. 2014).

The changes on energy metabolism

Although the gut microbiota returns to an almost-normal state after antibiotic treatment, the associated metabolic changes are long-lasting (Cox et al. 2014). In children, antibiotic therapy may be related to obesity-related dysbiosis during the first 2 years of life, and it may enhance the efficiency of energy harvesting of certain microbiota, thereby promoting metabolic diseases and obesity (Turnbaugh et al. 2006; Korpela et al. 2016). Moreover, sub-therapeutic antibiotic doses would increase body mass in both farm animals (Blaser and Falkow 2009) and laboratory mice (Cox et al. 2014; Cho et al. 2012). The mice administrated sub-therapeutic levels of penicillin had lower fecal caloric energy levels relative to control mice, despite received a similar dietary intake, suggesting that the intestinal microbiota of the treated mice had adapted to obtain sufficient energy from the indigestible components of the diet (Cho et al. 2012). Furthermore, germ-free mice that received fecal transplantation from antibiotic-treated obese model mice showed an increase in the fat mass compared with mice that received fecal transplantation from non-treated mice. These

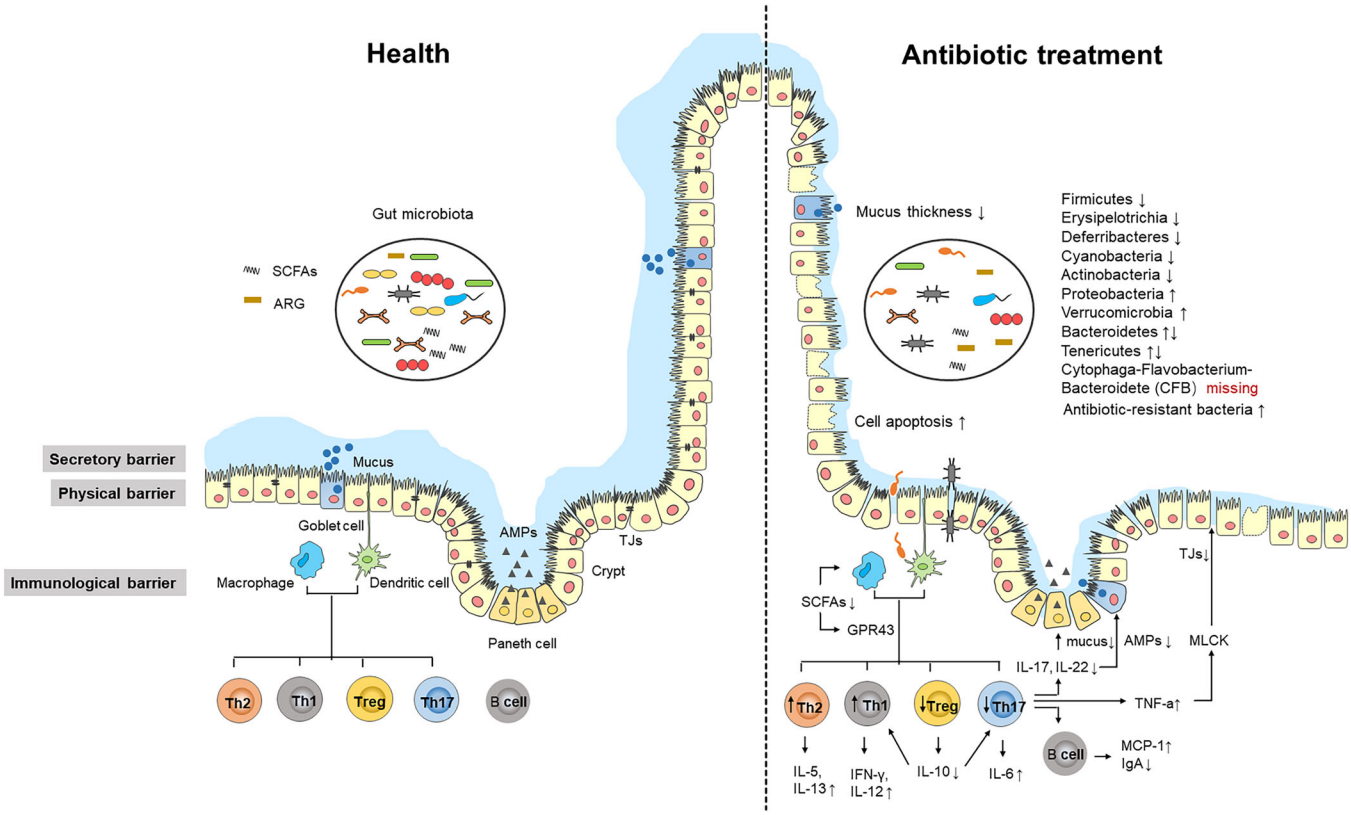

Figure 2. Antibiotic-induced gut dysbiosis and barrier disruption.

observations suggest that the gut microbiota plays a causal role in the development of obesity (Cox et al. 2014).

The changes on glucose, bile acid and oxalate metabolism

Antibiotic treatment can also affect glucose and lipid metabolism as the changes in the composition of gut microbiota. For example, the depletion of Firmicutes by vancomycin also altered bile acid and glucose metabolism in mice (Vrieze et al. 2014). Amoxicillin treatment led to a sharp increase in the abundance of *Bacteroides thetaiotaomicron* and a consequent increase in polysaccharide utilization, and the sensitivity of this species to amoxicillin was increased by glucose and decreased by polysaccharides *in vitro* (Cabral et al. 2019). In addition, vancomycin-induced overgrowth of *Lactobacillus murinus* impaired gut metabolic function, especially including a decrease of available biotin in the gut, finally causing the development of alopecia in mice (Hayashi et al. 2017). Oral cefazolin led to the loss of a specific function of the gut microbiota, oxalate metabolism, which is associated with urinary stone disease (Miller et al. 2019). Moreover, ampicillin was shown to induce gut microbiota dysbiosis, thereby reducing the levels of butyrate and 2-oxoisovalerate and increasing the levels of succinate, tauro-bile acid, lactate, and choline in mouse feces (Shi, Kellingray, et al. 2018).

Effects of antibiotics on the gut barrier

It is undoubted that antibiotics treatment can perturb the microbiota composition and cause gut dysbiosis, but their effects can be more complex (Morgun et al. 2015). Many studies have demonstrated that antibiotics could directly or indirectly disrupt the gut barrier (Shi, Kellingray, et al. 2018; Tulstrup et al. 2015; Shi, Zhao, et al. 2018), which comprises physical, secretory, and immunological components (Camara-Lemarroy et al. 2018) (Figure 2).

The disruption of the physical and secretory barriers

The direct disruption on physical and secretory barriers

Antibiotic can not only directly disrupt physical and secretory barrier, but also indirectly destroy them via perturbing intestinal microbiota. Antibiotics have been shown to induce the overproduction of reactive oxygen species (ROS) and suppress mitochondrial gene expression and function, especially in the crypts and villous epithelium, thereby leading to IECs apoptosis and damage of the physical barrier (Barnhill, Brewer, and Carlson 2012; Kalghatgi et al. 2013; Morgun et al. 2015). Moreover, antibiotic-treated germ-free mice exhibited suppression of gene expression related to both cellular and mitochondrial ribosomes (Morgun et al. 2015). The relative mechanisms might involve that the antibiotics inhibit RNA polymerase I that transcribes rRNA, or a deficit in ATP can lead to repression rRNA promoters (Murano et al. 2008). Tulstrup et al. also observed that metronidazole increased intestinal permeability but did not affect the gut microbiota composition, indicating that the effects of this antibiotic were independent of the gut microbiota (Tulstrup et al. 2015). Surprisingly, antibiotic-resistant bacteria have similar effects on intestinal tissue as do the antibiotics

themselves, such as affecting mitochondrial respiration and ribosomes. For example, *Pseudomonas* was the most prominent candidates for mitochondrial inhibition in the host cells. The pathways of antibiotic-induced IECs death *in vivo* may involve depletion of the majority of commensals, and decrease of intestinal immunity, providing an opportunity for *Pseudomonas* and other antibiotic-resistant bacteria to grow and increase in density. The increased antibiotic-resistant bacteria, in turn, allow for the activation of quorum-sensing-controlled virulence factors (Jimenez et al. 2012). These factors directly stimulate mitochondria-dependent apoptosis in the intestinal epithelial cells. In addition, the function of goblet cell can be estimated from the levels of goblet cell-specific proteins, such as Muc2, TFF3, and Relmβ. Treatment with metronidazole reduced intestinal integrity in mice, indicated by the expression of *Muc2*, *TFF3*, and *Relmβ* gene (Wlodarska et al. 2011).

The gut microbiota-mediated disruption on physical barrier

The changes in the gut microbiota composition induced by antibiotics can disrupt the physical barrier by altering the expression of TJ proteins and increasing the apoptosis of IECs, leading to microbiota and pro-inflammatory mediators leakage into the underlying lamina propria and causing inflammation (Wlodarska and Finlay 2010; Morgun et al. 2015). Shi et al. demonstrated that the expression of the TJ proteins ZO-1 and occludin reduced by approximately 50% in the colon after ampicillin treatment, and these changes were associated with antibiotic-induced decreases in the abundance of Lachnospiraceae and SCFA levels (Shi, Kellingray, et al. 2018).

The gut microbiota-mediated disruption on mucus barrier

The intestinal mucus layer is an important mediator of IECs commensal interactions, and its function is largely influenced by the gut microbiota. The effects of antibiotic on the colonic mucus layer are driven by their distinct impact on the gut microbiota (Wlodarska et al. 2011). The metronidazole-induced microbiota disruption caused the loss of intestinal integrity in mice by impairing goblet cell and reducing mucus thickness, thereby increasing attachment of enteric pathogen *Citrobacter rodentium* to the intestinal epithelium (Wlodarska et al. 2011). Moreover, vancomycin treatment increased the abundance of the mucin-degrading species *Akkermansia muciniphila*, which decreased the protective mucus layer and potentially increased the possibility of contact between other intestinal gram-negative bacteria (e.g., Proteobacteria) and intestinal immune cells. Such contact would stimulate receptors such as TLR-4 on immune cells to induce inflammation (Wang et al. 2009). Moreover, a recent study showed that *A. muciniphila* could directly alter the profiles of mucosal gene expression and modulate the expression of genes involved in immune regulation (Derrien et al. 2011).

The gut microbiota-mediated disruption on other secretory barrier

Microbiota-specific fluctuations caused by antibiotic may cause alteration in concentrations of microbe-associated molecular patterns (MAMPs) in the gut, including cell surface markers, such as lipopolysaccharide, polysaccharide A, lipoteichoic acid, and peptidoglycan (Wlodarska and Finlay 2010). A large change in MAMP concentrations could reduce IECs barrier function and affect mucin, cytokine, and AMPs production by IECs (Wlodarska and Finlay 2010). For example, administration of ampicillin and penicillin increased the abundance of Proteobacteria, a potential lipopolysaccharides source, promoting the endotoxin and D-lactate through the intestinal physical and secretory barrier, thus causing inflammation and increasing the levels of pro-inflammatory immunological factors, such as IFN-γ and MCP-1 (Shi, Kellingray, et al. 2018; Cani et al. 2008; Leclercq et al. 2017). RegIIIγ is a C-type lectin that can kill gram-positive bacteria and is secreted by IECs and Paneth cells (Cash et al. 2006). The expression of RegIIIγ is also induced by commensal microbes, such as *Bacteroides thetaiotaomicron* and depends on TLR-MyD88-mediated signals (Brandl et al. 2007; Cash et al. 2006; Sonnenburg, Chen, and Gordon 2006). After penicillin exposure, *RegIIIγ* and *Relmβ* genes expression involved in AMPs were downregulated (Cox et al. 2014). Exposure to a cocktail of vancomycin, neomycin, and metronidazole lead to notable downregulation of the intestinal expression of RegIIIγ (Brandl et al. 2008). In contrast, Shi et al. demonstrated that ampicillin treatment increased the level of RegIIIγ, which may be associated with the proliferation of intestinal macrophages (Shi, Kellingray, et al. 2018).

Disruption of the immunological barrier

The effect on innate immunity

Antibiotics can directly inhibit respiratory activity in immune cells, thereby impairing their phagocytic activity and immunological barrier function (Yang et al. 2017). Moreover, antibiotics can also indirectly disrupt the immunological barrier via disturbance of gut microbiota composition. It is well known that gut microbiota plays a proven and vital role in the modulation of gut immunity (Rooks and Garrett 2016; Ivanov et al. 2008). Antibiotic-induced changes in the gut microbiota composition in mucosal innate immunity may lead to differential regulation of the Th17/Treg balance affecting intestinal immune responses (Wlodarska and Finlay 2010). It is likely that a large portion of the microbiota have similar MAMPs, functioning as symbiosis factors (Mazmanian, Round, and Kasper 2008), to promote protective intestinal immune responses (Wlodarska and Finlay 2010). Furthermore, macrophages in the healthy gut are highly specialized and usually respond to the gut microbiota without triggering an inflammatory response. The gut microbiota is crucial for the maintenance of macrophage-dependent gut immune homeostasis to prevent inflammation, which is mediated by SCFA-dependent pathways (Scott et al. 2018). Macrophages usually

reduce responsiveness to bacteria stimulation to suppress their active immune response to gut microbiota (Bain et al. 2014; Scott et al. 2018). Antibiotic treatment caused that macrophages are hyperresponsive to bacteria stimulation, thus inducing these cells to produce more inflammatory cytokines and increasing the host susceptibility to pathogens infection (Scott et al. 2018). Even re-exposed to normal gut microbiota in antibiotic-treated mice, Th1 cell-mediated inflammation in the colon increased, which is a long-term and macrophage-dependent response. The production of IL-12 implicates macrophages as drivers of the Th1 cell response (Schreiber et al. 2013), and IL-10 has been identified as a key regulator of intestinal macrophages (Denning et al. 2007; Murai et al. 2009; Shouval et al. 2016). Thus, restoring macrophage homeostasis after antibiotic treatment may be a novel strategy for preventing persistent immune dysfunction (Scott et al. 2018).

The effect on adaptive immunity

The gut microbiota can also influence intestinal immunity via the regulation of different T cell populations (Rooks and Garrett 2016; Ivanov et al. 2008). In vancomycin-treated mice, a striking reduction in the colonic population of Treg cells led to a reduction in the IL-10 level. These changes may have been due to a reduction in *Clostridium* species (clusters IV and XIVa) that induce the production and differentiation of Treg cells (Russell et al. 2012; Atarashi et al. 2011). After exposure to vancomycin, cytophaga-flavobacter-bacteroidetes (CFB) phylum, correlated with Th17 cell differentiation, was eliminated from gut microbiota in mice (Ivanov et al. 2008). Similarly, low-dose penicillin reduced the expression of genes related to Th17 cells, as well as the abundances of *Lactobacillus* and *Allobaculum* (Ivanov et al. 2008; Ivanov et al. 2009). The abundances of these genera are positively correlated with RORγT and IL-17 expression, indicating their important roles in Th17 cell differentiation (Cox et al. 2014). Antibiotic treatment leads to intestinal inflammation not only by dysregulating T cell immunity, but also by enhancing susceptibility to infection. For example, antibiotic-mediated changes in the microbiota composition would increase susceptibility to enteric pathogens such as *Salmonella* Typhimurium, leading to more serious changes in the microbiota and ultimately intestinal inflammation and pathology (Sekirov et al. 2008).

Protective and alleviating strategies for antibiotic-induced gut injuries

The diet can rapidly and dramatically change the gut microbiota composition, with consequent effects on the intestinal barrier (Reimer 2019). The ability of probiotics to alleviate antibiotic-induced gut dysbiosis and injuries was widely demonstrated in both mouse model and clinical studies (Leclercq et al. 2017; Evans et al. 2016). Moreover, fecal microbiome transplantation (FMT) can almost completely improve serious antibiotic-related adverse effects in the gut, especially *C. difficile* infection (Ekmekciu, von Klitzing, Fiebiger, Escher, et al. 2017). Therefore, the main protective strategies against antibiotic-induced gut injuries can be classified into four types: dietary supplementation, probiotics supplementation, FMT, and others (Table 2 and Figure 3).

Dietary supplementation

The relationship between antibiotic, gut microbiota and diet in vitro

Several *in vitro* studies investigated the relationship between antibiotic, gut microbiota and diet. Marzorati et al. explored the effect of different diets (high-protein HP and high-fiber HF-diet) on gut microbiota and their functional stability when treated with an antibiotic cocktail using Simulator of the Human Intestinal Microbial Ecosystem (SHIME). The results showed that the HF diet group had a quicker recovery after antibiotic exposure, compared to the HP diet group, which probably as HF-diet led to a higher relative abundance of Clostridia XIVa (butyrate producers) and a higher SCFA production, thereby increasing the adaptation of the gut microbiota and decreasing the perturbation of antibiotic on its composition (Marzorati et al. 2017). Besides, the nutrient availability and utilization, especially carbohydrates, play an important role in the sensitivity of specific gut microbiota to the antibiotic. For example, in the presence of polysaccharides, *B. thetaiotaomicron* has more tolerance to amoxicillin (Cabral et al. 2019). Mao et al. revealed the protective effect of konjac glucomannan (KGM) on *Bifidobacteria* against several antibiotics, such as penicillin and streptomycin *in vitro*, suggesting that KGM has the potential to be used for protecting the human gut probiotic bacteria against the damage caused by specific antibiotics (Mao et al. 2018). The protective effect may be attributed to the adsorption of antibiotics and the formation of a viscous layer of polysaccharides surrounding the bacteria. However, further investigation should be carried out in mixed cultures of gut microbiota to evaluate the potential application in human gut microbiota.

The regulation of dietary on antibiotic-induced gut microbiota alteration

Plenty of *in vivo* researches also demonstrated that dietary factors can induce rapid and profound changes in the microbiota composition (Birchenough and Hansson 2017), even modulate the antibiotic-induced gut microbiota alteration. For example, the mixture of various plants and vegetables, a traditional Chinese herbal medicine Shen Ling Bai Zhu San, can modulate the structure of the gut microbiota during antibiotic treatment (AAD model), such as increasing the abundance of beneficial bacteria (e.g., *Bacteroides* spp.) and decreasing the abundance of harmful bacteria (e.g., *Sutterella* spp.) (Lv et al. 2017). After 1 day of amoxicillin treatment, glucose supplementation reduced the abundance of Bacteroides (Cabral et al. 2019). Shi et al. demonstrated that prebiotic fructo-oligosaccharides could reverse cefixime-induced changes in the gut microbiota, including an increase in the abundance of *Akkermansia* spp. (Shi et al. 2017).

Table 2. Strategies to alleviate gut injuries caused by antibiotics.

Strategy	Administered way	Antibiotic administration	Experiment model	Target sites	Outcomes and possible alleviate mechanisms	Ref.
Dietary supplementation: It is a safe and easy intervention approach against antibiotic-induced gut injuries for the general public, but dietary intervention studies have far greater challenges in terms of consistency, quality control, confounding, and interpretation.						
Inulin-type fructans	6 g/d	Antibiotic prescription	258 healthy children aged 3–6	Gut microbiota	Fructans regulated antibiotic-caused changes in microbiota composition, such as increasing abundance of *Bifidobacterium*.	Soldi et al. (2019)
Fructo-oligosaccharides (FOS)	0.5 g/kg/d by oral gavage	Oral gavage with 50 or 150 mg/kg cefixime, twice per day	Male C57BL/6J mice (4 wk old)	Gut microbiota	FOS restored cefixime-induced gut microbiota changes, such as a sharp increase in *Akkermansia*.	Shi et al. (2017)
Inulin	3.0 g/kg by oral gavage	Oral gavage with 25 mg/kg amoxicillin, three times per day for 7 d	Male and female C57BL/6J mice (4 wk old)	Gut microbiota	Inulin restored the gut microbiota via reconstituting microbial community and stimulating specific prebiotic respectively, as well as eliminated ARG abundance and diversity enrichment significantly.	Lin et al. (2020)
Omega-3 fatty acids	Omega-3 fatty acids-enriched fish oil (5%) diet for 2 mo	Azithromycin	Fat-1 mice (5 wk old)	Gut microbiota	Elevated tissue omega-3 fatty acids can attenuate the azithromycin-induced gut dysbiosis, chronic inflammation and obesity, and the possible mechanisms may involve in reducing harmful *E. coli* growth and increasing growth of beneficial bifidobacteria and lactobacilli, thus decreasing LPS level and inhibiting endotoxemia, inflammation, and metabolic syndrome.	Kaliannan et al. (2015, 2016)
Glucose supplementation	30% glucose added to normal chow	Amoxicillin for 5 wk	C57BL/6J mice	Gut microbiota	Glucose intake elevated sugar absorption in the upper digestive tract and reduced glucose level in cecum, which in turn decreasing its availability to the microbiota. Glucose increased alpha diversity and decreased Bacteroidetes expanded induced by amoxicillin.	Cabral et al. (2019)
Fiber supplementation	30% glucose added to normal chow	Amoxicillin for 5 wk	MIC assay	Gut microbiota	Fiber supplementation protects *B. thetaiotaomicron* from amoxicillin *in vitro*.	Cabral et al. (2019)
Traditional Chinese herba—Shen Ling Bai Zhu San (SLBZS)	Gastric gavage with SLBZS 2 mL (1.2 g) twice per day for 7 d after antibiotic treatment	Gastric gavage with lincomycin 2 mL (1.2 g) for 7 d to induce antibiotic-associated diarrhea (AAD)	Male Wistar rats	Gut microbiota	SLBZS increased beneficial bacteria, such as Bacteroides spp., and decreased harmful bacteria, such as *Sutterella* spp.	Lv et al. (2017)
Microbiota-targeted dietary intervention	Diet with whole grains, traditional Chinese medicinal foods and prebiotics	Antibiotic prescription	35 of obese children	Gut microbiota	The dietary reduced several ARGs in Klebsiella, Enterobacter and Escherichia, and changed the dominant fermentation of gut microbiota from protein to carbohydrate and reduced gut resistome.	Wu et al. (2016)
Konjac glucomannan (KGM)	5 g/L of KGM and KGM-US (ultrasound treated KGM)	1–2048 ug/mL of antibiotic solutions (enrofloxacin,	Minimum inhibitory concentration (MIC) and minimum	Gut microbiota (*Bifidobacteria*)	KGM have protective effects for the human gut probiotic bacteria against the damage caused by antibiotics,	Mao et al. (2018)

(*continued*)

Table 2. Continued.

Strategy	Administered way	Antibiotic administration	Experiment model	Target sites	Outcomes and possible alleviate mechanisms	Ref.
		penicillin, tetracycline or streptomycin).	bactericidal concentration (MBC)		which partly due to their adsorbance ability and biofilm formation effects.	
Traditional and next-generation probiotics supplementation: It is a safe and easy intervention approach against antibiotic-induced gut injuries for the general public. However, probiotics may have potential adverse effects, such as bacteremia, for some specific patients. Therefore, the benefits must be weighed against this risk when considering the continued use of probiotics in the patients, particularly for ICU patients.						
L. rhamnosus JB-1	10^9 CFU/d in drinking water during day until postnatal day 21	31 mg/kg of Penicillin V per day during night through the drinking water	BALB/c mice (breeding pairs, 6–8 wk old)	Gut microbiota	JB-1 reversed penicillin-induced gut dysbiosis, impaired anxiety-like and social behaviors, which may due to its ability to secret SCFAs, thereby affecting the luminal pH, and regulating gut microbiota.	Leclercq et al. (2017)
L. reuteri ATCC PTA6475	3.3×10^8 CFU/mL in drinking water for 4 wk	Cocktail of amppicillin (1.0 g/L) and neomycin (0.5 g/L) were given weekly for 2 wk in drinking water	Male BALB/c mice (11 wk old)	Gut microbiota and intestinal barrier	Its active metabolites and proteins exert benefit effects on gut microbiota, and permeability and inflammation.	Schepper et al. (2019)
L. plantarum CCFM602, *L. casei* CCFM 2710, *L. rhamnosus* CCFM492, and *L. helveticus* CCFM6	0.4×10^9 CFU via oral gavage twice per day for 4 wk	Oral gavage with cefixime (50 or 150 mg/kg), twice per day.	Male C57BL/6J mice (4 wk old)	Gut microbiota	The cocktail increased gut microbiota diversity and SCFAs-producing species, enhanced immunity and resistance to opportunistic pathogen.	Shi et al. (2017)
L. acidophilus CL1285 and *L. casei* LBC80R	One or two probiotic capsules (total 5×10^9 or 10^{10} CFU) per day for 5 d or 21 d after of the last antibiotic use	Antibiotic therapy with penicillin, cephalosporin, or clindamycin	255 of adult inpatients aged 50–70	Gut microbiota and immunological barrier	Probiotic reduced risk of antibiotic-associated diarrhea (AAD) and *C. difficile*-associated diarrhea (CDAD) via repopulating gut microbiota, enhancing immune response to inhibit pathogen.	Gao et al. (2010)
L.belveticus R0052 and *L. rbamnosus* R0011	Two probiotic capsules (total 8×10^9 CFU) per day for 14 d	Two capsules (total 1.75 g amocicillin and 0.25 g clavulanic acid) per day for 7 d	160 of healthy individuals aged 18–50	Gut microbiota and immunological barrier	The cocktail reduced duration of AAD and diarrhea-like defecation events due to their ability to adhere to human epithelial cells, enhance gut barrier, inhibit pathogen adhesion and reinforce anti-inflammatory response.	Evans et al. (2016)
L. acidophilus LA-5 and *Bifidobacterium* BB-12	Probiotic capsules	500 mg of amoxycillin or cefadroxil thrice or twice daily respectively for 7 d	45 of patients aged 18–70	Gut microbiota and immunological barrier	The cocktail reduced duration of AAD as they enhanced gut barrier and immunomodulation (increase of IgA and interferons).	Chatterjee et al. (2013)
L. acidophilus CL1285, *L. casei* LBR80R and *L. rhamnosus* CLR2	98 g BIO K + CL1285 lactobacilli fermented milk (5×10^{10} CFU) per day for 29–40 d	Metronidazole (alone or in combination) or vancomycin monotherapy for the treatment of an infection for 3–14 d	437 of adult patients	Gut microbiota and immunological barrier	Probiotic prevented and reduced the severity of AAD in patients receiving antibiotic therapy, and the possible pathways may involve in increase of gut barrier function, anti-inflammatory properties and antagonistic activity against pathogen.	Sampalis, Psaradellis, and Rampakakis (2010); Beausoleil et al. (2007)
L. casei DN-1,14,001 *L bulgaricus*, and	100 g yoghurt drink containing three	Intake clindamycin, cephalosporins,	135 hospital patients (mean	Gut microbiota		Hickson et al. (2007)

Streptococcus thermophilus	probiotics (total 4×10^{10} CFU) twice a day for 1 wk longer than duration of antibiotic treatment	aminopenicillins or other antibiotics in the past 4 wk	age 74) receiving antibiotics		Probiotic reduced the incidence of AAD and CDAD by regulating gut microbiota.	
E. coli, *L. johnsonii* or VSL#3	Recolonized with 10^9 CFU in 0.3 mL PBS	Quintuple antibiotic cocktail for 8 wk	C57BL/6J mice	Immunological barrier	Probiotics increased CD4+ and CD8+ cell numbers, frequencies of Treg cells and activated dendritic cells, and restored memory /effector T cell, thus restoring intestinal immunity functions.	Ekmekciu, von Klitzing, Neumann, et al. (2017); Ekmekciu, von Klitzing, Fiebiger, Neumann, et al. (2017)
L. acidophilus CL1285, *L. casei* LBR80R and *L. rhamnosus* CLR2	10^7 CFU/mL of three probiotics	256 mg/ L tobramycin	*In vitro* model (OD 4.0 of *S.s aureus* and OD 3.1 of *P.s aeruginosa*)	Methicillin-resistant *S. aureus* and *P. aeruginosa*	Tobramycin do not affect the growth and metabolic activity of encapsulated probiotics, thereby that the probiotic can eliminate methicillin-resistant strains *S. aureus* and *P. aeruginosa*, two main bacteria causing chronic wounds.	Li et al. (2018)
Gut commensal bacteria that contains *Blautia producta*, *Bacteroides sartorii*, *Parabacteroides distasonis*, and *Clostridium bolteae*	—	—	Female C57BL/ 6 mice	Gut microbiota	*B. producta* inhibited vancomycin-resistant Enterococcus (VRE) growth by producing a lantibiotic. *C. bolteae* enabled intestinal colonization with *B. producta* exerting indirect effects on VRE clearance. *B. sartorii* and *P. distasonis* produce β-lactamase that permit *C. bolteae* and *B. producta* to colonize and clear VRE.	Caballero et al. (2017)
Fecal microbiota transplantation (FMT): FMT is an effective and direct approach to reestablish the gut microbiota and prevent future infections for the patients whose intestines are colonized with multidrug-resistant pathogens, but various factors limit its clinical application, including a lack of standardized methods, ethical issues, and uncertainty regarding long-term safety.						
FMT	Fecal microbiota from control mice	Quintuple antibiotic cocktail for 8 wk	C57BL/6J mice (8–10 wk)	Immunological barrier	FMT may be the most efficient method in restoring antibiotics-induced injuries on the immune system.	Ekmekciu, von Klitzing, Neumann, et al. (2017); Ekmekciu, von Klitzing, Fiebiger, Escher, et al. (2017)
FMT	Fecal microbiota from family, household members or friends of patients	Antibiotic therapy	Patients who had multiply-recurrent CDI	Antibiotic-resistant bacteria	FMT changed the distribution of ARGs-carrying bacteria.	Leung et al. (2018)
Autologous FMT (aFMT)	Autologous fecal microbiota	Mice: ciprofloxacin (0.2 g/L) and metronidazole (1 g/L) in drinking water for 2 wk; Human: oral ciprofloxacin 500 mg bi-daily and metronidazole	Male C57BL/6 mice (8 wk old) and health adults	Gut microbiota	aFMT restored mucosal microbiota and gut transcriptome reconstitution.	Suez et al. (2018)

(*continued*)

Table 2. Continued.

Strategy	Administered way	Antibiotic administration	Experiment model	Target sites	Outcomes and possible alleviate mechanisms	Ref.
		500 mg tri-daily for 7 d				
aFMT	Autologous fecal microbiota	Oral gavage with 25 mg/kg amoxicillin, three times per day for 7 d	Male and female C57BL/6J mice (4 wk old)	Gut microbiota	aFMT restored the gut microbiota via reconstituting microbial community and stimulating specific prebiotic respectively, as well as eliminated ARGs abundance, such as *ndm-1 and blaPER*.	Lin et al. (2020)
aFMT	Autologous fecal microbiota	Antibiotic therapy	Adult allo-HSCT patients	Gut microbiota	aFMT increased microbiota diversity and re-build the gut microbiota.	Taur et al. (2018)
Others: The other strategies are divided into three categories, including 1) reduce the exposure of antibiotics to gut microbiota; 2) increase intestinal barrier function, such as mucosal barrier and immunological barrier; 3) supplement with beneficial substances that are reduced after antibiotic exposure.						
Adsorbent-based DAV132 product	7.5 g of DAV132 was administered orally thrice a day for 7 d	400 mg of moxifloxacin was administered orally once a day for 5 d	28 of human adult volunteers	Gut microbiota	DAV132 effectively protected gut microbiota in antibiotic-treated volunteers. The target of DAV132 was the ileo-cecal region and thus reducing antibiotic level and protecting intestine microbiota.	de Gunzburg et al. (2018)
TLR ligands-Lipopolysaccharide (LPS)	2–4 μg/μL LPS in drinking water for 1 wk	Cocktail of vancomycin (1 g/L), neomycin sulfate (500 mg/L,) and metronidazole (1 g/L) in drinking water for 1 wk	mice	Immunological barrier	Administration of TLR ligands to mucosal surfaces to enhance innate immune defenses may exert beneficial impacts.	Brandl et al. (2008)
High-molecular-weight polymer MDY	1.25% MDY in drinking water for 4 wk	Cocktail of ampicillin (1.0 g/L) and neomycin (0.5 g/L) in drinking water	BALB/c mice	Secretory barrier	MDY restored gut dysbiosis and barrier function, and prevented gut inflammation	Schepper et al. (2019)
Butyrate	200 mM butyrate in drinking water for 7 d	Cocktail of ampicillin, metronidazole, neomycin, gentamicin, vancomycin	C57BL/6 mice	Immunological barrier	Butyrate altered the metabolic behavior of macrophages and promoted alternative activation of macrophage, thus preventing antibiotic-induced dysregulation of T cell immunity in gut.	Scott et al. (2018)
Butyrate	300 mM butyrate or acetate in drinking water for 21 d	Cocktail of metronidazole, vancomycin, ampicillin and kanamycin	C57BL/6 mice	Secretory barrier	Butyrate increased antimicrobial peptide (AMP) expression in gut. GPR43 mediates microbiota metabolite SCFA, regulating AMP expression in IECs by activation of mTOR and STAT3.	Zhao et al. (2018)

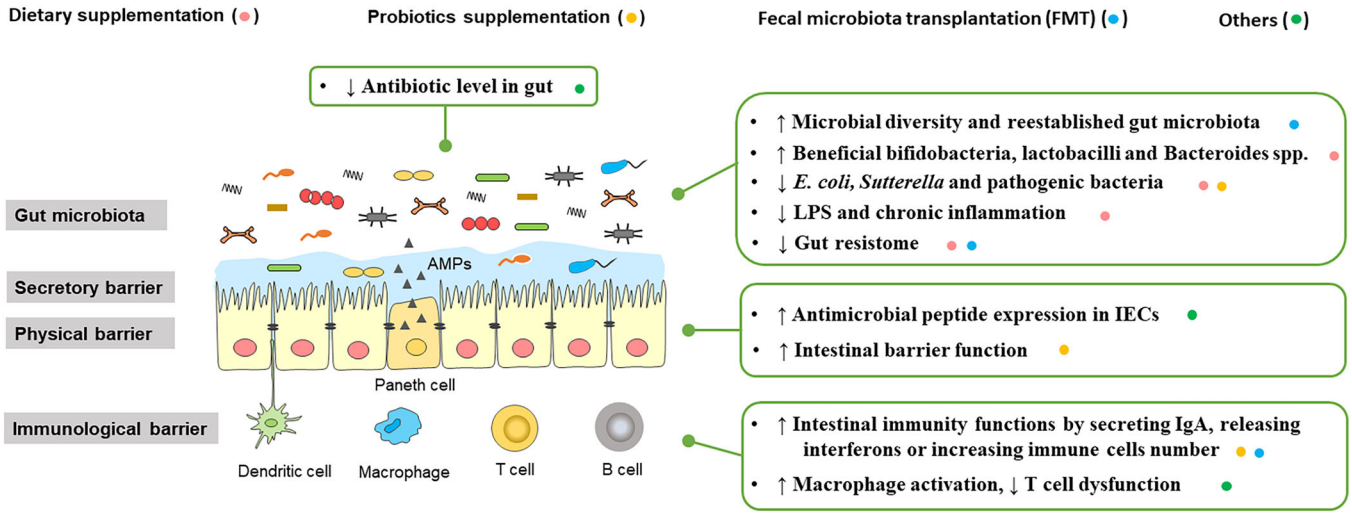

Figure 3. Protective and alleviating strategies for antibiotic-induced gut injuries.

Similarly, a daily 6-g prebiotic inulin-type fructan supplement regulated antibiotic-induced changes in the gut microbiota composition, such as an increased abundance of *Bifidobacterium* (Soldi et al. 2019). Another dietary study revealed that a diet composed of whole grains, traditional Chinese medicinal foods, and prebiotics reduced multidrug resistant bacteria and the richness and diversity of the whole gut resistome, especially for ARGs in the *Klebsiella*, *Enterobacter* and *Escherichia* in obese children (Wu et al. 2016).

Diet mitigated antibiotic-induced adverse effects on the host via modulating the gut microbiota

Diet modulated the antibiotic-induced microbiota alteration, thus mitigating its adverse effects on the host. Kaliannan et al. reported that the omega-3 fatty acids, rather than omega-6 fatty acids, could enhance the expression and secretion of intestinal alkaline phosphatase, which alters the gut microbiota composition to reduce the lipopolysaccharide level and gut permeability and ultimately alleviate inflammation (Kaliannan et al. 2015). Later, they found that omega-3 fatty acids could reverse azithromycin-induced gut dysbiosis and obesity in mice and suggested that oral administration of omega-3 may be a safe and effective way for preventing obesity in children who exposed to antibiotics (Kaliannan et al. 2015, 2016). In addition, antibiotic-induced gut dysbiosis (overgrowth of *Lactobacillus murinus*) and metabolic dysfunction (decrease of available biotin), thereby promoting alopecia in mice fed a biotin-deficient diet. While a normal diet with biotin supplementation can reverse the established alopecia symptoms in mice (Hayashi et al. 2017).

The challenges of dietary intervention

Diets are highly heterogeneous and the dietary intervention studies are facing huge challenges in terms of consistency, quality control, confounding, and interpretation (Ludwig, Ebbeling, and Heymsfield 2019). For example, many factors, including environment, psychology, and behavior can affect dietary behavior. Moreover, unlike drug can be evaluated its efficacy and effectiveness via phase one to four clinical trials, the lack of standardization in dietary study design is another challenge. Therefore, a more rigorous attitude, a healthy dose of humility and well-designed experimental design, such as randomized controlled trials, are necessary (Ramsden and Domenichiello 2017).

Probiotic supplementation

Traditional probiotics supplementation

Probiotics are considered safe and are widely used in both animals and humans to confer health benefits such as the regulation of gut microbiota and promotion of anti-inflammatory responses (Tankou et al. 2018). The concurrent ingestion of the probiotic strain *Lactobacillus rhamnosus* JB-1 (10^9 CFU/d) with penicillin can prevent the biological and behavioral changes induced by the latter. These effects are mediated by restoring gut dysbiosis, which includes the reversal of changes in the abundances of Enterobacteriaceae, S24-7, Lachnospiraceae, and Erysipelotrichaceae (Leclercq et al. 2017). The probiotic strain promoted the production of SCFA, which affects the luminal pH and creates an inhospitable environment for Enterobactericeae growth, thereby reducing their abundance in the gut (Veiga et al. 2010). In another study, *L. reuteri* 4675, but not *L. rhamnosus* GG and nonpathogenic *Escherichia coli*, reduced antibiotic-mediated (ampicillin and neomycin) increases in the Firmicutes/Bacteroidetes ratio, intestinal permeability, and the TNF-α/IL-10 ratio in mice (Schepper et al. 2019). Moreover, several clinical studies have demonstrated that oral ingestion of a cocktail of probiotics, such as *L. acidophilus*, *L. casei*, *L. rbamnosus* and *Bifidobacterium* could reduce the risk of antibiotic-associated diarrhea (AAD), possibly by regulating the gut microbiota, increasing the gut barrier function, and modulating immune responses (Gao et al. 2010; Evans et al. 2016; Chatterjee et al. 2013; Sampalis, Psaradellis, and Rampakakis 2010). Interestingly, Li et al. encapsulated probiotics in alginate, followed by co-administration with antibiotics, and determined that tobramycin did not affect the growth and metabolic activity of encapsulated probiotics.

Accordingly, these agents could exert a synergistic role to eradicate two methicillin-resistant pathogens (Li et al. 2018). Therefore, co-administration of probiotics and antibiotics via biofilm-inspired encapsulation offers a promising approach for treating complex infections and overcoming antimicrobial resistance.

Next-generation probiotics supplementation

Ongoing studies aim to identify commensal bacterial species that could be developed into next-generation probiotics intended to reestablish or enhance colonization resistance and eliminate potential pathogens from the gut. Such probiotics would reduce the incidence of antibiotic-resistant bacterial infections (Pamer 2016). A cocktail of commensal bacteria containing *Blautia producta*, *B. sartorii*, *Parabacteroides distasonis*, and *Clostridium bolteae* was shown to reverse antibiotic-induced susceptibility to VRE infection (Caballero et al. 2017). *Bl. producta* inhibits VRE growth by producing a lantibiotic similar to nisin A (Kim et al. 2019). *C. bolteae* and *Bl. producta* can co-colonize the intestine, thus enabling the former to exert indirect effects on VRE clearance. *B. sartorii* and *P. distasonis* produce β-lactamase, which enables *C. bolteae* and *Bl. producta* to colonize and clear VRE. Their results demonstrated that inter-species cooperativity is essential for colonization resistance against VRE (Caballero et al. 2017). Besides, gram-negative commensal microbes *Bacteroides thetaiotaomicron* can induce RegIIIγ in the mouse intestine (Sonnenburg, Chen, and Gordon 2006), thereby enhancing defence against VRE (Brandl et al. 2008). Thus, the species has the potential to mitigate the adverse effects of antibiotics on the intestine.

The necessary of personalized probiotic supplementation

Due to the strain-specific effects of probiotics, the current data of beneficial effects mainly focus on individual probiotic strains rather than general probiotics (Szajewska 2016). Moreover, the effects of probiotics on mucosal microbiota structure and gut transcriptome are transient and individualized. Current empiric probiotics supplementation may be inadequate in terms of universally and persistently impacts on the intestinal mucosa (Zmora et al. 2018). Therefore, it is necessary to develop new personalized probiotic supplementation approaches. The identified baseline microbiota composition and other host factors may potentially enable to predict the probiotics-permissive or -resistant state, which would achieve the goal that specific probiotic interventions can tailor to specific individuals in different clinical settings (Zmora et al. 2018).

The risks of probiotic supplementation

Probiotics are generally safe and exert health benefits, but may have potential adverse effects, such as bacteremia, for some specific patients (Szajewska 2016; Yelin et al. 2019; Salminen et al. 2004). Yelin et al. reported a dramatically higher risk of *Lactobacillus* bacteremia for intensive care unit (ICU) patients treated with probiotics LGG (1.1% incidence) compared to those not treated (only 0.009% incidence). The probiotic strains may direct clonal transmit to the bloodstream, thus directly causing bacteremia and adaptively evolving, including the acquisition of antibiotic resistance, in ICU patients (Yelin et al. 2019). Therefore, the benefits must be weighed against this risk when considering the continued use of probiotics in the patients, particularly for ICU patients.

Fecal microbiota transplantation

The effects of FMT on gut microbiota

FMT is considered a novel method for controlling multidrug-resistant pathogens (MRPs) and preventing potential or future infections, and is widely used to manage patients whose intestines are colonized with MRPs such as *C. difficile* or are considered at risk of infection after antibiotic treatment. The effects of FMT are mediated mainly via direct competition between the transplanted microbiota and *C. difficile*, the restoration of secondary bile acid metabolism in the intestine, and repair of the gut barrier via the stimulation of mucosal immunity (Khoruts and Sadowsky 2016). Moreover, FMT can alter the distribution of species carrying ARGs by changing the overall composition of the gut microbiota. In a study of eight FMT donor-recipient pairs, Leung et al. observed that 37 and 95 ARGs were acquired by or removed from FMT recipients, respectively, indicating a broad clearance of ARGs after FMT (Leung et al. 2018). Besides, antibiotic treatment was shown to reduce mesenteric lymph node and Treg cell populations, while FMT could increase the Treg cell population, activate dendritic cells, and fully restore memory/effector T cell populations in the intestines. These changes indicate the effective recovery of antibiotic-induced collateral damage to the immune system (Ekmekciu, von Klitzing, Fiebiger, Escher, et al. 2017). Finally, autologous FMT also enhances microbial diversity and re-builds the gut microbiota in healthy adults, patient and mice ingested antibiotic (Taur et al. 2018; Suez et al. 2018).

The challenges of FMT

However, various factors limit the clinical application of FMT, including a lack of standardized methods, ethical issues, and uncertainty regarding long-term safety (Zhang et al. 2018). A variety of methodology issues should be addressed for FMT. In addition to the requirement of antibiotic pretreatment, the route and frequency of administration are also different among trials; the characteristics of super-donors should be identified and will vary among diseases; the factors in stool samples that mediate its therapeutic effects must also be defined. Answering these questions will help refine and enhance FMT approach (D'Haens and Jobin 2019). Moreover, the risk factors of FMT include transmission of pathogenic bacteria or ARGs from the donor, and transmission or increase of susceptibility to diseases associated with gut microbiota (Hill 2020).

Others

There are several other ways to alleviate antibiotic-induced gut injuries, mainly via the following three pathways.

Reduce the exposure of antibiotics to gut microbiota

In a clinical trial involving 28 healthy adult volunteers, the co-administration of an adsorbent-based product, DAV132, and moxifloxacin reduced the exposure of the gut microbiota to the antibiotic by 99% and thus protected the richness and composition of the intestinal microbiota (de Gunzburg et al. 2018).

Increase intestinal barrier function

The stimulation of TLRs in the mucosal epithelium is related closely to the alleviation of antibiotic-induced damage to innate immune structures in the mucosa, suggesting a possible therapeutic mechanism that could be used to reduce ARB's colonization and infection (Brandl et al. 2008). In certain clinical situations, administration of TLR ligands (lipopolysaccharide or lipoteichoic acid) to mucosal surfaces to enhance innate immune defenses may exert the beneficial impacts. In addition, for patients receiving broad-spectrum antibiotic therapy, specific induction of antimicrobial molecules, for example, RegIIIγ by the oral LPS administration, could be a potential therapeutic method (Brandl et al. 2008). Moreover, MDY-1001, a high-molecular-weight polymer used as a mucus supplement, reduced the gut barrier disruption induced by ampicillin and neomycin via increases in the Firmicutes/Bacteroidetes ratio and the TNF-α/IL-10 ratio (Schepper et al. 2019).

Supplement with beneficial substances that are reduced after antibiotic exposure

Generally, the levels of SCFAs reduced during antibiotic therapy, so it is necessary to explore whether SCFA supplementation during antibiotic treatment can alleviate gut injury. Scott et al. reported that the oral administration of butyrate, but not acetate or propionate, during antibiotic treatment prevented antibiotic-associated gut immune dysfunction by promoting macrophage activation and preventing T cell dysfunction (Scott et al. 2018). Zhao et al. reported that oral supplementation with SCFAs can promote the production of RegIIIγ, a secreted C-type lectin that can kill VRE, and the expression of defensin in IECs via the receptor GPR43, which is mediated by mammalian target of rapamycin (mTOR) and signal transducers and activator of transcription 3 (STAT3) (Zhao et al. 2018).

Conclusions and future directions

Antibiotics can affect gut microbiota composition significantly, leading to a dysbiotic effect and disruption of the intestinal barrier, including the secretory, physical and immunological barrier. The adverse effects of antibiotics on gut health should be considered, particularly in infants and young children, when prescribing antibiotics without compromising clinical practice. Looking for better antibiotic substitutes (bacteriocins, probiotics or phage) and antibiotic adjuvants (β-lactamase inhibitors) may be good ways to minimize the usage of antibiotics and the emergence of resistance (Hols et al. 2019; Wright 2016; Kortright et al. 2019).

For unavoidable use of antibiotics, there are several protective strategies to mitigate antibiotic-induced gut dysbiosis. FMT (including aFMT) may be an effective and direct approach to reestablish the gut microbiota, eliminate MRPs from the gut, and prevent future infections, but the clinical application of FMT should be standardized and cautious. Moreover, as the gut microbiota is sensitive to dietary factors, including probiotic supplementation, so the dietary strategy represents a striking intervention approach to the healing of antibiotic-induced gut injuries. We recommend that people who are receiving antibiotic therapy consume sufficient amounts of probiotics (*Bifidobacterium* and *Lactobacillus*), prebiotics, whole grains, and omega-3 fatty acids. Dietary intervention may be an affordable and safe, and easy option for gut microbiota restoration after antibiotic exposure for billions of people worldwide.

As these protective strategies are not universally effective or one-size-fits-all, a new and exciting aspect of intervention research is focused on the precision or personalization. Different individuals, especially for children and infants, have highly individualized microbial profiles and the variable responses of the gut microbial communities to antibiotics and dietary (Christensen et al. 2018; Yassour et al. 2016). It is worth mentioning that the baseline characterization and enterotyping of the gut microbiota (e.g. Enterotype 1, Enterotype 2 and Enterotype 3) should be taken into account in the future study, which may enable us to better understand personalized nutrition and variable health responses to antibiotic and dietary. In other words, dietery-enterotype-antibiotic interactions should gain further insights. In addition, host genetic background also dramatically affected the antibiotic-induced changes in gut microbiota metabolism (Fujisaka et al. 2018). Therefore, in subsequent decades, the stratification of individuals according to the enterotype, genotypes and different antibiotic sensitivities may improve the therapeutic outcomes and effectiveness of the interventions.

Author contributions

Conceptualization: L.L.Y., Q.X.Z., and W.C. Funding acquisition: L.L.Y., F.W.T., L.P.F., and W.C. Investigation: H.D. Project administration: H.D. and L.L.Y. Supervision: L.P.F. and W.C. Writing—original draft: H.D. and L.L.Y. Writing—review and editing: H..D., L.L.Y., and Q.X.Z.

Competing interests

The authors declare that they have no competing interests.

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References

Ammor, M. S., A. B. Florez, P. Alvarez-Martin, A. Margolles, and B. Mayo. 2008. Analysis of tetracycline resistance tet(W) genes and their flanking sequences in intestinal Bifidobacterium species. *The Journal of Antimicrobial Chemotherapy* 62 (4):688–93. doi: 10.1093/jac/dkn280.

Atarashi, K., T. Tanoue, T. Shima, A. Imaoka, T. Kuwahara, Y. Momose, G. Cheng, S. Yamasaki, T. Saito, Y. Ohba, et al. 2011. Induction of colonic regulatory T cells by indigenous *Clostridium* species. *Science (New York, N.Y.)* 331 (6015):337–41. doi: 10.1126/science.1198469.

Bailey, L. C., C. B. Forrest, P. Zhang, T. M. Richards, A. Livshits, and P. A. DeRusso. 2014. Association of antibiotics in infancy with early childhood obesity. *JAMA Pediatrics* 168 (11):1063–9. doi: 10.1001/jamapediatrics.2014.1539.

Bain, C. C., A. Bravo-Blas, C. L. Scott, E. G. Perdiguero, F. Geissmann, S. Henri, B. Malissen, L. C. Osborne, D. Artis, and A. M. Mowat. 2014. Constant replenishment from circulating monocytes maintains the macrophage pool in the intestine of adult mice. *Nature Immunology* 15 (10):929–37. doi: 10.1038/ni.2967.

Barna, J. C., and D. H. Williams. 1984. The structure and mode of action of glycopeptide antibiotics of the vancomycin group. *Annual Review of Microbiology* 38:339–57. doi: 10.1146/annurev.mi.38.100184.002011.

Barnhill, A. E., M. T. Brewer, and S. A. Carlson. 2012. Adverse effects of antimicrobials via predictable or idiosyncratic inhibition of host mitochondrial components. *Antimicrobial Agents and Chemotherapy* 56 (8):4046–51. doi: 10.1128/AAC.00678-12.

Barth, J. H., C. A. Bray, J. Broom, F. Brown, and H. Ross. 2005. The impact of obesity on drug prescribing in primary care. *British Journal of General Practice* 55 (519):743–9.

Bashir, M. E. H., S. Louie, H. N. Shi, and C. Nagler Anderson. 2004. Toll-like receptor 4 signaling by intestinal microbes influences susceptibility to food allergy. *Journal of Immunology* 172 (11):6978–87. doi: 10.4049/jimmunol.172.11.6978.

Baumgartner, M., F. Bayer, K. R. Pfrunder-Cardozo, A. Buckling, and A. R. Hall. 2020. Resident microbial communities inhibit growth and antibiotic-resistance evolution of *Escherichia coli* in human gut microbiome samples. *PLoS Biology* 18 (4):e3000465. doi: 10.1371/journal.pbio.3000465.

Beausoleil, M., N. Fortier, S. Guenette, A. L'Ecuyer, M. Savoie, M. Franco, J. Lachaine, and K. Weiss. 2007. Effect of a fermented milk combining *Lactobacillus acidophilus* Cl1285 and *Lactobacillus casei* in the prevention of antibiotic-associated diarrhea: A randomized, double-blind, placebo-controlled trial. *Canadian Journal of Gastroenterology = Journal canadien de gastroenterologie* 21 (11):732–6. doi: 10.1155/2007/720205.

Becattini, S., Y. Taur, and E. G. Pamer. 2016. Antibiotic-induced changes in the intestinal microbiota and disease. *Trends in Molecular Medicine* 22 (6):458–78. doi: 10.1016/j.molmed.2016.04.003.

Berendonk, T. U., C. M. Manaia, C. Merlin, D. Fatta-Kassinos, E. Cytryn, F. Walsh, H. Burgmann, H. Sorum, M. Norstrom, M. N. Pons, et al. 2015. Tackling antibiotic resistance: The environmental framework. *Nature Reviews. Microbiology* 13 (5):310–7. doi: 10.1038/nrmicro3439.

Birchenough, G., and G. C. Hansson. 2017. Bacteria tell us how to protect our intestine. *Cell Host & Microbe* 22 (1):3–4. doi: 10.1016/j.chom.2017.06.011.

Blaser, M. J., and S. Falkow. 2009. What are the consequences of the disappearing human microbiota? *Nature Reviews. Microbiology* 7 (12):887–94. doi: 10.1038/nrmicro2245.

Brandl, K., G. Plitas, B. Schnabl, R. P. DeMatteo, and E. G. Pamer. 2007. MyD88-mediated signals induce the bactericidal lectin RegIII gamma and protect mice against intestinal Listeria monocytogenes infection. *The Journal of Experimental Medicine* 204 (8):1891–900. doi: 10.1084/jem.20070563.

Brandl, K., G. Plitas, C. N. Mihu, C. Ubeda, T. Jia, M. Fleisher, B. Schnabl, R. P. DeMatteo, and E. G. Pamer. 2008. Vancomycin-resistant enterococci exploit antibiotic-induced innate immune deficits. *Nature* 455 (7214):804–7. doi: 10.1038/nature07250.

Buffie, C. G., and E. G. Pamer. 2013. Microbiota-mediated colonization resistance against intestinal pathogens. *Nature Reviews. Immunology* 13 (11):790–801. doi: 10.1038/nri3535.

Caballero, S., S. Kim, R. A. Carter, I. M. Leiner, B. Susac, L. Miller, G. J. Kim, L. Ling, and E. G. Pamer. 2017. Cooperating commensals restore colonization resistance to vancomycin-resistant *Enterococcus faecium*. *Cell Host & Microbe* 21 (5):592–602.e4. doi: 10.1016/j.chom.2017.04.002.

Cabral, D. J., S. Penumutchu, E. M. Reinhart, C. Zhang, B. J. Korry, J. I. Wurster, R. Nilson, A. Guang, W. H. Sano, A. D. Rowan-Nash, et al. 2019. Microbial metabolism modulates antibiotic susceptibility within the murine gut microbiome. *Cell Metabolism* 30 (4):800–23.e7. doi: 10.1016/j.cmet.2019.08.020.

Camara-Lemarroy, C. R., L. Metz, J. B. Meddings, K. A. Sharkey, and V. W. Yong. 2018. The intestinal barrier in multiple sclerosis: Implications for pathophysiology and therapeutics. *Brain* 141 (7):1900–16. doi: 10.1093/brain/awy131.

Cani, P. D., R. Bibiloni, C. Knauf, A. Waget, A. M. Neyrinck, N. M. Delzenne, and R. Burcelin. 2008. Changes in gut microbiota control metabolic endotoxemia-induced inflammation in high-fat diet-induced obesity and diabetes in mice. *Diabetes* 57 (6):1470–81. doi: 10.2337/db07-1403.

Cash, H. L., C. V. Whitham, C. L. Behrendt, and L. V. Hooper. 2006. Symbiotic bacteria direct expression of an intestinal bactericidal lectin. *Science* 313 (5790):1126–30. doi: 10.1126/science.1127119.

Chatterjee, S., P. Kar, T. Das, S. Ray, S. Gangulyt, C. Rajendiran, and M. Mitra. 2013. Randomised placebo-controlled double blind multicentric trial on efficacy and safety of *Lactobacillus acidophilus* LA-5 and Bifidobacterium BB-12 for prevention of antibiotic-associated diarrhoea. *J Assoc Physicians India* 61 (10):708–12.

Cho, I., S. Yamanishi, L. Cox, B. A. Methé, J. Zavadil, K. Li, Z. Gao, D. Mahana, K. Raju, I. Teitler, et al. 2012. Antibiotics in early life alter the murine colonic microbiome and adiposity. *Nature* 488 (7413):621–6. doi: 10.1038/nature11400.

Christensen, L., H. M. Roager, A. Astrup, and M. F. Hjorth. 2018. Microbial enterotypes in personalized nutrition and obesity management. *The American Journal of Clinical Nutrition* 108 (4):645–51. doi: 10.1093/ajcn/nqy175.

Chung, H., S. J. Pamp, J. A. Hill, N. K. Surana, S. M. Edelman, E. B. Troy, N. C. Reading, E. J. Villablanca, S. Wang, J. R. Mora, et al. 2012. Gut immune maturation depends on colonization with a host-specific microbiota. *Cell* 149 (7):1578–93. doi: 10.1016/j.cell.2012.04.037.

Cox, L. M., S. Yamanishi, J. Sohn, A. V. Alekseyenko, J. M. Leung, I. Cho, S. G. Kim, H. Li, Z. Gao, D. Mahana, et al. 2014. Altering the intestinal microbiota during a critical developmental window has lasting metabolic consequences. *Cell* 158 (4):705–21. doi: 10.1016/j.cell.2014.05.052.

D'Haens, G. R., and C. Jobin. 2019. Fecal microbial transplantation for diseases beyond recurrent *Clostridium difficile* infection. *Gastroenterology* 157 (3):624–36. doi: 10.1053/j.gastro.2019.04.053.

D'Costa, V. M., C. E. King, L. Kalan, M. Morar, W. W. L. Sung, C. Schwarz, D. Froese, G. Zazula, F. Calmels, R. Debruyne, et al. 2011. Antibiotic resistance is ancient. *Nature* 477 (7365):457–61. doi: 10.1038/nature10388.

de Gunzburg, J., A. Ghozlane, A. Ducher, E. L. Chatelier, X. Duval, E. Ruppe, L. Armand-Lefevre, F. Sablier-Gallis, C. Burdet, L. Alavoine, et al. 2018. Protection of the human gut microbiome from

antibiotics. *The Journal of Infectious Diseases* 217 (4):628–36. doi: 10.1093/infdis/jix604.

Dehoux, P., J. C. Marvaud, A. Abouelleil, A. M. Earl, T. Lambert, and C. Dauga. 2016. Comparative genomics of *Clostridium bolteae* and *Clostridium clostridioforme* reveals species-specific genomic properties and numerous putative antibiotic resistance determinants. *BMC Genomics* 17 (1):819. doi: 10.1186/s12864-016-3152-x.

Denning, T. L., Y. C. Wang, S. R. Patel, I. R. Williams, and B. Pulendran. 2007. Lamina propria macrophages and dendritic cells differentially induce regulatory and interleukin 17-producing T cell responses. *Nature Immunology* 8 (10):1086–94. doi: 10.1038/ni1511.

Derrien, M., P. Van Baarlen, G. Hooiveld, E. Norin, M. Muller, and W. M. de Vos. 2011. Modulation of mucosal immune response, tolerance, and proliferation in mice colonized by the mucin-degrader *Akkermansia muciniphila*. *Frontiers in Microbiology* 2:166. doi: 10.3389/fmicb.2011.00166.

Dethlefsen, L., and D. A. Relman. 2011. Incomplete recovery and individualized responses of the human distal gut microbiota to repeated antibiotic perturbation. *Proceedings of the National Academy of Sciences of the United States of America* 108 (Supplement_1): 4554–61. doi: 10.1073/pnas.1000087107.

Donskey, C. J., T. K. Chowdhry, M. T. Hecker, C. K. Hoyen, J. A. Hanrahan, A. M. Hujer, R. A. Hutton-Thomas, C. C. Whalen, R. A. Bonomo, and L. B. Rice. 2000. Effect of antibiotic therapy on the density of vancomycin-resistant enterococci in the stool of colonized patients. *The New England Journal of Medicine* 343 (26):1925–32. doi: 10.1056/NEJM200012283432604.

Ekmekciu, I., E. von Klitzing, U. Fiebiger, U. Escher, C. Neumann, P. Bacher, A. Scheffold, A. A. Kuhl, S. Bereswill, and M. M. Heimesaat. 2017. Immune responses to broad-spectrum antibiotic treatment and fecal microbiota transplantation in mice. *Frontiers in Immunology* 8:397. doi: 10.3389/fimmu.2017.00397.

Ekmekciu, I., E. von Klitzing, U. Fiebiger, C. Neumann, P. Bacher, A. Scheffold, S. Bereswill, and M. M. Heimesaat. 2017. The probiotic compound VSL#3 modulates mucosal, peripheral, and systemic immunity following murine broad-spectrum antibiotic treatment. *Frontiers in Cellular and Infection Microbiology* 7:167. doi: 10.3389/fcimb.2017.00167.

Ekmekciu, I., E. von Klitzing, C. Neumann, P. Bacher, A. Scheffold, S. Bereswill, and M. M. Heimesaat. 2017. Fecal microbiota transplantation, commensal *Escherichia coli* and *Lactobacillus johnsonii* strains differentially restore intestinal and systemic adaptive immune cell populations following broad-spectrum antibiotic treatment. *Frontiers in Microbiology* 8:2430. doi: 10.3389/fmicb.2017.02430.

Evans, M., R. P. Salewski, M. C. Christman, S. A. Girard, and T. A. Tompkins. 2016. Effectiveness of *Lactobacillus helveticus* and *Lactobacillus rhamnosus* for the management of antibiotic-associated diarrhoea in healthy adults: A randomised, double-blind, placebo-controlled trial. *The British Journal of Nutrition* 116 (1):94–103. doi: 10.1017/S0007114516001665.

Fujisaka, S., J. Avila-Pacheco, M. Soto, A. Kostic, J. M. Dreyfuss, H. Pan, S. Ussar, E. Altindis, N. Li, L. Bry, et al. 2018. Diet, genetics, and the gut microbiome drive dynamic changes in plasma metabolites. *Cell Reports* 22 (11):3072–86. doi: 10.1016/j.celrep.2018.02.060.

Gao, X., Wang, M. Mubasher, C. Y. Fang, C. Reifer, and L. E. Miller. 2010. Dose-response efficacy of a proprietary probiotic formula of *Lactobacillus acidophilus* CL1285 and *Lactobacillus casei* LBC80R for antibiotic-associated diarrhea and *Clostridium difficile*-associated diarrhea prophylaxis in adult patients. *The American Journal of Gastroenterology* 105 (7):1636–41. doi: 10.1038/ajg.2010.11.

Gillings, M. R. 2014. Integrons: Past, present, and future. *Microbiology and Molecular Biology Reviews: MMBR* 78 (2):257–77. doi: 10.1128/MMBR.00056-13.

Haak, B. W., J. M. Lankelma, F. Hugenholtz, C. Belzer, W. M. de Vos, and W. J. Wiersinga. 2019. Long-term impact of oral vancomycin, ciprofloxacin and metronidazole on the gut microbiota in healthy humans. *The Journal of Antimicrobial Chemotherapy* 74 (3):782–6. doi: 10.1093/jac/dky471.

Handwerger, S., B. Raucher, D. Altarac, J. Monka, S. Marchione, K. V. Singh, B. E. Murray, J. Wolff, and B. Walters. 1993. Nosocomial outbreak due to *Enterococcus faecium* highly resistant to vancomycin, penicillin, and gentamicin. *Clinical Infectious Diseases* 16 (6): 750–5. doi: 10.1093/clind/16.6.750.

Hansen, C. H. F., L. Krych, D. S. Nielsen, F. K. Vogensen, L. H. Hansen, S. J. Sørensen, K. Buschard, and A. K. Hansen. 2012. Early life treatment with vancomycin propagates *Akkermansia muciniphila* and reduces diabetes incidence in the NOD mouse. *Diabetologia* 55 (8):2285–94. doi: 10.1007/s00125-012-2564-7.

Hayashi, A., Y. Mikami, K. Miyamoto, N. Kamada, T. Sato, S. Mizuno, M. Naganuma, T. Teratani, R. Aoki, S. Fukuda, et al. 2017. Intestinal dysbiosis and biotin deprivation induce alopecia through overgrowth of *Lactobacillus murinus* in mice. *Cell Reports* 20 (7): 1513–24. doi: 10.1016/j.celrep.2017.07.057.

Hickson, M., A. L. D'Souza, N. Muthu, T. R. Rogers, S. Want, C. Rajkumar, and C. J. Bulpitt. 2007. Use of probiotic Lactobacillus preparation to prevent diarrhoea associated with antibiotics: Randomised double blind placebo controlled trial. *BMJ (Clinical Research ed.)* 335 (7610):80. doi: 10.1136/bmj.39231.599815.55.

Hildebrand, F., L. Moitinho-Silva, S. Blasche, M. T. Jahn, T. I. Gossmann, J. Huerta-Cepas, R. Hercog, M. Luetge, M. Bahram, A. Pryszlak, et al. 2019. Antibiotics-induced monodominance of a novel gut bacterial order. *Gut* 68 (10):1781–90. doi: 10.1136/gutjnl-2018-317715.

Hill, C. 2020. Balancing the risks and rewards of live biotherapeutics. *Nature Reviews. Gastroenterology & Hepatology* 17 (3):133–4. doi: 10.1038/s41575-019-0254-3.

Hols, P., L. Ledesma-Garcia, P. Gabant, and J. Mignolet. 2019. Mobilization of microbiota commensals and their bacteriocins for therapeutics. *Trends in Microbiology* 27 (8):690–702. doi: 10.1016/j.tim.2019.03.007.

Hu, Y., X. Yang, J. Qin, N. Lu, G. Cheng, N. Wu, Y. Pan, J. Li, L. Zhu, X. Wang, et al. 2013. Metagenome-wide analysis of antibiotic resistance genes in a large cohort of human gut microbiota. *Nature Communications* 4:2151. doi: 10.1038/ncomms3151.

Isaac, S., J. U. Scher, A. Djukovic, N. Jiménez, D. R. Littman, S. B. Abramson, E. G. Pamer, and C. Ubeda. 2017. Short- and long-term effects of oral vancomycin on the human intestinal microbiota. *The Journal of Antimicrobial Chemotherapy* 72 (1):128–36. doi: 10.1093/jac/dkw383.

Ivanov, I. I., R. d L. Frutos, N. Manel, K. Yoshinaga, D. B. Rifkin, R. B. Sartor, B. B. Finlay, and D. R. Littman. 2008. Specific microbiota direct the differentiation of IL-17-producing T-helper cells in the mucosa of the small intestine. *Cell Host & Microbe* 4 (4):337–49. doi: 10.1016/j.chom.2008.09.009.

Ivanov, I. I., K. Atarashi, N. Manel, E. L. Brodie, T. Shima, U. Karaoz, D. Wei, K. C. Goldfarb, C. A. Santee, S. V. Lynch, et al. 2009. Induction of intestinal Th17 cells by segmented filamentous bacteria. *Cell* 139 (3):485–98. doi: 10.1016/j.cell.2009.09.033.

Jernberg, C., S. Lofmark, C. Edlund, and J. K. Jansson. 2010. Long-term impacts of antibiotic exposure on the human intestinal microbiota. *Microbiology (Reading, England)* 156 (Pt 11):3216–23. doi: 10.1099/mic.0.040618-0.

Jernberg, C., S. Löfmark, C. Edlund, and J. K. Jansson. 2007. Long-term ecological impacts of antibiotic administration on the human intestinal microbiota. *The ISME Journal* 1 (1):56–66. doi: 10.1038/ismej.2007.3.

Jimenez, P. N., G. Koch, J. A. Thompson, K. B. Xavier, R. H. Cool, and W. J. Quax. 2012. The multiple signaling systems regulating virulence in Pseudomonas aeruginosa. *Microbiology and Molecular Biology Reviews: MMBR* 76 (1):46–65. doi: 10.1128/MMBR.05007-11.

Kalghatgi, S., C. S. Spina, J. C. Costello, M. Liesa, J. R. Morones-Ramirez, S. Slomovic, A. Molina, O. S. Shirihai, and J. J. Collins. 2013. Bactericidal antibiotics induce mitochondrial dysfunction and oxidative damage in Mammalian cells. *Science Translational Medicine* 5 (192):192ra85. doi: 10.1126/scitranslmed.3006055.

Kaliannan, K., B. Wang, X. Y. Li, A. K. Bhan, and J. X. Kang. 2016. Omega-3 fatty acids prevent early-life antibiotic exposure-induced gut microbiota dysbiosis and later-life obesity. *International Journal of Obesity (2005)* 40 (6):1039–42. doi: 10.1038/ijo.2016.27.

Kaliannan, K., B. Wang, X. Y. Li, K. J. Kim, and J. X. Kang. 2015. A host-microbiome interaction mediates the opposing effects of omega-6 and omega-3 fatty acids on metabolic endotoxemia. *Scientific Reports* 5:11276. doi: 10.1038/srep11276.

Khoruts, A., and M. J. Sadowsky. 2016. Understanding the mechanisms of faecal microbiota transplantation. *Nature Reviews. Gastroenterology & Hepatology* 13 (9):508–16. doi: 10.1038/nrgastro.2016.98.

Kim, S. G., S. Becattini, T. U. Moody, P. V. Shliaha, E. R. Littmann, R. Seok, M. Gjonbalaj, V. Eaton, E. Fontana, L. Amoretti, et al. 2019. Microbiota-derived lantibiotic restores resistance against vancomycin-resistant Enterococcus. *Nature* 572 (7771):665–9. doi: 10.1038/s41586-019-1501-z.

Knapp, C. W., J. Dolfing, P. A. I. Ehlert, and D. W. Graham. 2010. Evidence of increasing antibiotic resistance gene abundances in archived soils since 1940. *Environmental Science & Technology* 44 (2):580–7. doi: 10.1021/es901221x.

Knecht, H., S. C. Neulinger, F. A. Heinsen, C. Knecht, A. Schilhabel, R. A. Schmitz, A. Zimmermann, V. M. dos Santos, M. Ferrer, P. C. Rosenstiel, et al. 2014. Effects of β-lactam antibiotics and fluoroquinolones on human gut microbiota in relation to *Clostridium difficile* associated diarrhea. *PLoS One* 9 (2):e89417. doi: 10.1371/journal.pone.0089417.

Koo, H., J. A. Hakim, D. K. Crossman, R. Kumar, E. J. Lefkowitz, and C. D. Morrow. 2019. Individualized recovery of gut microbial strains post antibiotics. *NPJ Biofilms Microbiomes* 5 (1):30. doi: 10.1038/s41522-019-0103-8.

Korpela, K., A. Salonen, L. J. Virta, R. A. Kekkonen, K. Forslund, P. Bork, and W. M. De Vos. 2016. Intestinal microbiome is related to lifetime antibiotic use in Finnish pre-school children. *Nature Communications* 7:10410. doi: 10.1038/ncomms10410.

Kortright, K. E., B. K. Chan, J. L. Koff, and P. E. Turner. 2019. Phage therapy: A renewed approach to combat antibiotic-resistant bacteria. *Cell Host Microbe* 25 (2):219–32. doi: 10.1016/j.chom.2019.01.014.

Lange, K., M. Buerger, A. Stallmach, and T. Bruns. 2016. Effects of antibiotics on gut microbiota. *Digestive Diseases (Basel, Switzerland)* 34 (3):260–8. doi: 10.1159/000443360.

Larcombe, S., M. L. Hutton, and D. Lyras. 2016. Involvement of bacteria other than *Clostridium difficile* in antibiotic-associated diarrhoea. *Trends in Microbiology* 24 (6):463–76. doi: 10.1016/j.tim.2016.02.001.

Lavelle, A., T. W. Hoffmann, H. P. Pham, P. Langella, E. Guedon, and H. Sokol. 2019. Baseline microbiota composition modulates antibiotic-mediated effects on the gut microbiota and host. *Microbiome* 7 (1):111. doi: 10.1186/s40168-019-0725-3.

Leclercq, S., F. M. Mian, A. M. Stanisz, L. B. Bindels, E. Cambier, H. Ben-Amram, O. Koren, P. Forsythe, and J. Bienenstock. 2017. Low-dose penicillin in early life induces long-term changes in murine gut microbiota, brain cytokines and behavior. *Nature Communications* 8 (1):15602. doi: 10.1038/ncomms15062.

Leung, V., C. Vincent, T. J. Edens, M. Miller, and A. R. Manges. 2018. Antimicrobial resistance gene acquisition and depletion following fecal microbiota transplantation for recurrent *Clostridium difficile* infection. *Clinical Infectious Diseases* 66 (3):456–7. doi: 10.1093/cid/cix821.

Li, Z., A. M. Behrens, N. Ginat, S. Y. Tzeng, X. Lu, S. Sivan, R. Langer, and A. Jaklenec. 2018. Biofilm-Inspired encapsulation of probiotics for the treatment of complex infections. *Advanced Materials (Deerfield Beach, Fla.)* 30 (51):e1803925. doi: 10.1002/adma.201803925.

Lin, H., Q. Wang, M. Yuan, L. Liu, Z. Chen, Y. Zhao, R. Das, Y. Duan, X. Xu, Y. Xue, et al. 2020. The prolonged disruption of a single-course amoxicillin on mice gut microbiota and resistome, and recovery by inulin, Bifidobacterium longum and fecal microbiota transplantation. *Environmental Pollution* 265 (Pt A):114651. doi: 10.1016/j.envpol.2020.114651.

Löfmark, S., C. Edlund, and C. E. Nord. 2010. Metronidazole is still the drug of choice for treatment of anaerobic infections. *Clinical Infectious Diseases* 50 (Suppl 1):S16–S23. doi: 10.1086/647939.

Looft, T., T. A. Johnson, H. K. Allen, D. O. Bayles, D. P. Alt, R. D. Stedtfeld, W. J. Sul, T. M. Stedtfeld, B. Chai, J. R. Cole, et al. 2012. In-feed antibiotic effects on the swine intestinal microbiome. *Proceedings of the National Academy of Sciences of the United States of America* 109 (5):1691–6. doi: 10.1073/pnas.1120238109.

Lucas, G. M., N. Lechtzin, D. W. Puryear, L. L. Yau, C. W. Flexner, and R. D. Moore. 1998. Vancomycin-resistant and vancomycin-susceptible enterococcal bacteremia: Comparison of clinical features and outcomes. *Clinical Infectious Diseases* 26 (5):1127–33. doi: 10.1086/520311.

Ludwig, D. S., C. B. Ebbeling, and S. B. Heymsfield. 2019. Improving the quality of dietary research. *JAMA* 322 (16):1549. doi: 10.1001/jama.2019.11169.

Lv, W., C. Liu, C. Ye, J. Sun, X. Tan, C. Zhang, Q. Qu, D. Shi, and S. Guo. 2017. Structural modulation of gut microbiota during alleviation of antibiotic-associated diarrhea with herbal formula. *International Journal of Biological Macromolecules* 105 (Pt 3):1622–9. doi: 10.1016/j.ijbiomac.2017.02.060.

Malone, K. M., and S. V. Gordon. 2016. Antibiotic methylation: A new mechanism of antimicrobial resistance. *Trends in Microbiology* 24 (10):771–2. doi: 10.1016/j.tim.2016.08.003.

Mao, Y. H., A. X. Song, Z. P. Yao, and J. Y. Wu. 2018. Protective effects of natural and partially degraded konjac glucomannan on Bifidobacteria against antibiotic damage. *Carbohydrate Polymers* 181:368–75. doi: 10.1016/j.carbpol.2017.10.083.

Marzorati, M., R. Vilchez-Vargas, J. V. Bussche, P. Truchado, R. Jauregui, R. A. El Hage, D. H. Pieper, L. Vanhaecke, and T. Van de Wiele. 2017. High-fiber and high-protein diets shape different gut microbial communities, which ecologically behave similarly under stress conditions, as shown in a gastrointestinal simulator. *Molecular Nutrition & Food Research* 61 (1). doi: 10.1002/mnfr.201600150.

Mazmanian, S. K., J. L. Round, and D. L. Kasper. 2008. A microbial symbiosis factor prevents intestinal inflammatory disease. *Nature* 453 (7195):620–5. doi: 10.1038/nature07008.

Mazmanian, S. K., C. H. Liu, A. O. Tzianabos, and D. L. Kasper. 2005. An immunomodulatory molecule of symbiotic bacteria directs maturation of the host immune system. *Cell* 122 (1):107–18. doi: 10.1016/j.cell.2005.05.007.

McInnes, R. S., G. E. McCallum, L. E. Lamberte, and W. van Schaik. 2020. Horizontal transfer of antibiotic resistance genes in the human gut microbiome. *Current Opinion in Microbiology* 53:35–43. doi: 10.1016/j.mib.2020.02.002.

Miller, A. W., T. Orr, D. Dearing, and M. Monga. 2019. Loss of function dysbiosis associated with antibiotics and high fat, high sugar diet. *The ISME Journal* 13 (6):1379–90. doi: 10.1038/s41396-019-0357-4.

Morgun, A., A. Dzutsev, X. Dong, R. L. Greer, D. J. Sexton, J. Ravel, M. Schuster, W. Hsiao, P. Matzinger, and N. Shulzhenko. 2015. Uncovering effects of antibiotics on the host and microbiota using transkingdom gene networks. *Gut* 64 (11):1732–43. doi: 10.1136/gutjnl-2014-308820.

Morris, J. G., Jr., D. K. Shay, J. N. Hebden, R. J. McCarter, Jr., B. E. Perdue, W. Jarvis, J. A. Johnson, T. C. Dowling, L. B. Polish, and R. S. Schwalbe. 1995. Enterococci resistant to multiple antimicrobial agents, including vancomycin. Establishment of endemicity in a university medical center. *Annals of Internal Medicine* 123 (4):250–9. doi: 10.7326/0003-4819-123-4-199508150-00002.

Murai, M., O. Turovskaya, G. Kim, R. Madan, C. L. Karp, H. Cheroutre, and M. Kronenberg. 2009. Interleukin 10 acts on regulatory T cells to maintain expression of the transcription factor Foxp3 and suppressive function in mice with colitis. *Nature Immunology* 10 (11):1178–84. doi: 10.1038/ni.1791.

Murano, K., M. Okuwaki, M. Hisaoka, and K. Nagata. 2008. Transcription regulation of the rRNA gene by a multifunctional nucleolar protein, B23/nucleophosmin, through its histone chaperone activity. *Molecular and Cellular Biology* 28 (10):3114–26. doi: 10.1128/MCB.02078-07.

Oyama, N., N. Sudo, H. Sogawa, and C. Kubo. 2001. Antibiotic use during infancy promotes a shift in the T(H)1/T(H)2 balance toward

T(H)2-dominant immunity in mice. *The Journal of Allergy and Clinical Immunology* 107 (1):153–9. doi: 10.1067/mai.2001.111142.

Paine, R. T., M. J. Tegner, and E. A. Johnson. 1998. Compounded perturbations yield ecological surprises. *Ecosystems* 1 (6):535–45. doi: 10.1007/s100219900049.

Palleja, A., K. H. Mikkelsen, S. K. Forslund, A. Kashani, K. H. Allin, T. Nielsen, T. H. Hansen, S. Liang, Q. Feng, C. Zhang, et al. 2018. Recovery of gut microbiota of healthy adults following antibiotic exposure. *Nature Microbiology* 3 (11):1255–65. doi: 10.1038/s41564-018-0257-9.

Pamer, E. G. 2016. Resurrecting the intestinal microbiota to combat antibiotic-resistant pathogens. *Science (New York, N.Y.)* 352 (6285): 535–8. doi: 10.1126/science.aad9382.

Peak, N., C. W. Knapp, R. K. Yang, M. M. Hanfelt, M. S. Smith, D. S. Aga, and D. W. Graham. 2010. Abundance of six tetracycline resistance genes in wastewater lagoons at cattle feedlots with different antibiotic use strategies. *Environmental Microbiology* 9 (1):143–51.

Power, S. E., P. W. O'Toole, C. Stanton, R. P. Ross, and G. F. Fitzgerald. 2014. Intestinal microbiota, diet and health. *The British Journal of Nutrition* 111 (3):387–402. doi: 10.1017/S0007114513002560.

Ramsden, C. E., and A. F. Domenichiello. 2017. PURE study challenges the definition of a healthy diet: But key questions remain. *Lancet* 390 (10107):2018–9. doi: 10.1016/S0140-6736(17)32241-9.

Raymond, F., A. A. Ouameur, M. Deraspe, N. Iqbal, H. Gingras, B. Dridi, P. Leprohon, P. L. Plante, R. Giroux, E. Berube, et al. 2016. The initial state of the human gut microbiome determines its reshaping by antibiotics. *The ISME Journal* 10 (3):707–20. doi: 10.1038/ismej.2015.148.

Reeves, A. E., C. M. Theriot, I. L. Bergin, G. B. Huffnagle, P. D. Schloss, and V. B. Young. 2011. The interplay between microbiome dynamics and pathogen dynamics in a murine model of *Clostridium difficile* Infection. *Gut Microbes* 2 (3):145–58. doi: 10.4161/gmic.2.3.16333.

Reimer, R. A. 2019. Establishing the role of diet in the microbiota-disease axis. *Nature Reviews. Gastroenterology & Hepatology* 16 (2): 86–7. doi: 10.1038/s41575-018-0093-7.

Relman, D. A. 2012. The human microbiome: Ecosystem resilience and health. *Nutrition Reviews* 70 Suppl 1:S2–S9. doi: 10.1111/j.1753-4887.2012.00489.x.

Research and Markets. 2017. Global antibacterial drugs market to 2022—Vaccines retain market prominence while pipeline offers innovative approaches to tackling antimicrobial resistance.

Review on Antimicrobial Resistance. 2014. *Antimicrobial resistance: Tackling a crisis for the health and wealth of nations*. Review on Antimicrobial Resistance.

Robinson, C. J., and V. B. Young. 2010. Antibiotic administration alters the community structure of the gastrointestinal micobiota. *Gut Microbes* 1 (4):279–84. doi: 10.4161/gmic.1.4.12614.

Rooks, M. G., and W. S. Garrett. 2016. Gut microbiota, metabolites and host immunity. *Nature Reviews. Immunology* 16 (6):341–52. doi: 10.1038/nri.2016.42.

Russell, S. L., M. J. Gold, M. Hartmann, B. P. Willing, L. Thorson, M. Wlodarska, N. Gill, M. R. Blanchet, W. W. Mohn, K. M. McNagny, et al. 2012. Early life antibiotic-driven changes in microbiota enhance susceptibility to allergic asthma. *EMBO Reports* 13 (5): 440–7. doi: 10.1038/embor.2012.32.

Saenz, J. S., T. V. Marques, R. S. C. Barone, J. E. P. Cyrino, S. Kublik, J. Nesme, M. Schloter, S. Rath, and G. Vestergaard. 2019. Oral administration of antibiotics increased the potential mobility of bacterial resistance genes in the gut of the fish Piaractus mesopotamicus. *Microbiome* 7 (1):24. doi: 10.1186/s40168-019-0632-7.

Salminen, M. K., H. Rautelin, S. Tynkkynen, T. Poussa, M. Saxelin, V. Valtonen, and A. Jarvinen. 2004. *Lactobacillus bacteremia*, clinical significance, and patient outcome, with special focus on probiotic L. rhamnosus GG. *Clinical Infectious Diseases* 38 (1):62–9. doi: 10.1086/380455.

Sampalis, J., E. Psaradellis, and E. Rampakakis. 2010. Efficacy of BIO K + CL1285 in the reduction of antibiotic-associated diarrhea—A placebo controlled double-blind randomized, multi-center study. *Archives of Medical Science: AMS* 6 (1):56–64. doi: 10.5114/aoms.2010.13508.

Schepper, J. D., F. L. Collins, N. D. Rios-Arce, S. Raehtz, L. Schaefer, J. D. Gardinier, R. A. Britton, N. Parameswaran, and L. R. McCabe. 2019. Probiotic *Lactobacillus reuteri* prevents postantibiotic bone loss by reducing intestinal dysbiosis and preventing barrier disruption. *Journal of Bone and Mineral Research* 34 (4):681–98. doi: 10.1002/jbmr.3635.

Schreiber, H. A., J. Loschko, R. A. Karssemeijer, A. Escolano, M. M. Meredith, D. Mucida, P. Guermonprez, and M. C. Nussenzweig. 2013. Intestinal monocytes and macrophages are required for T cell polarization in response to *Citrobacter rodentium*. *The Journal of Experimental Medicine* 210 (10):2025–39. doi: 10.1084/jem.20130903.

Scott, N. A., A. Andrusaite, P. Andersen, M. Lawson, C. Alcon-Giner, C. Leclaire, S. Caim, G. Le Gall, T. Shaw, J. P. R. Connolly, et al. 2018. Antibiotics induce sustained dysregulation of intestinal T cell immunity by perturbing macrophage homeostasis. *Science Translational Medicine* 10 (464):eaao4755. doi: 10.1126/scitranslmed.aao4755.

Sekirov, I., N. M. Tam, M. Jogova, M. L. Robertson, Y. Li, C. Lupp, and B. B. Finlay. 2008. Antibiotic-induced perturbations of the intestinal microbiota alter host susceptibility to enteric infection. *Infection and Immunity* 76 (10):4726–36. doi: 10.1128/IAI.00319-08.

Shi, Y., L. Kellingray, Q. Zhai, G. L. Gall, A. Narbad, J. Zhao, H. Zhang, and W. Chen. 2018. Structural and functional alterations in the microbial community and immunological consequences in a mouse model of antibiotic-induced dysbiosis. *Frontiers in Microbiology* 9:1948. doi: 10.3389/fmicb.2018.01948.

Shi, Y., Q. Zhai, D. Li, B. Mao, X. Liu, J. Zhao, H. Zhang, and W. Chen. 2017. Restoration of cefixime-induced gut microbiota changes by Lactobacillus cocktails and fructooligosaccharides in a mouse model. *Microbiological Research* 200:14–24. doi: 10.1016/j.micres.2017.04.001.

Shi, Y., X. Zhao, J. Zhao, H. Zhang, Q. Zhai, A. Narbad, and W. Chen. 2018. A mixture of *Lactobacillus* species isolated from traditional fermented foods promote recovery from antibiotic-induced intestinal disruption in mice. *Journal of Applied Microbiology* 124 (3):842–54. doi: 10.1111/jam.13687.

Shouval, D. S., A. Biswas, Y. H. Kang, A. E. Griffith, L. Konnikova, I. D. Mascanfroni, N. S. Redhu, S. M. Frei, M. Field, A. L. Doty, et al. 2016. Interleukin 1β mediates intestinal inflammation in mice and patients with interleukin 10 receptor deficiency. *Gastroenterology* 151 (6):1100–4. doi: 10.1053/j.gastro.2016.08.055.

Sitaraman, R. 2018. Prokaryotic horizontal gene transfer within the human holobiont: Ecological-evolutionary inferences, implications and possibilities. *Microbiome* 6 (1):163. doi: 10.1186/s40168-018-0551-z.

Soldi, S., S. Vasileiadis, S. Lohner, F. Uggeri, E. Puglisi, P. Molinari, E. Donner, C. Sieland, T. Decsi, M. Sailer, et al. 2019. Prebiotic supplementation over a cold season and during antibiotic treatment specifically modulates the gut microbiota composition of 3-6 year-old children. *Beneficial Microbes* 10 (3):253–63. doi: 10.3920/BM2018.0116.

Sommer, M. O. A., C. Munck, R. V. Toft-Kehler, and D. I. Andersson. 2017. Prediction of antibiotic resistance: Time for a new preclinical paradigm? *Nature Reviews. Microbiology* 15 (11):689–96. doi: 10.1038/nrmicro.2017.75.

Sonnenburg, J. L., C. T. Chen, and J. I. Gordon. 2006. Genomic and metabolic studies of the impact of probiotics on a model gut symbiont and host. *PLoS Biology* 4 (12):e413. doi: 10.1371/journal.pbio.0040413.

Spigaglia, P., F. Barbanti, and P. Mastrantonio. 2008. Tetracycline resistance gene tet(W) in the pathogenic bacterium *Clostridium difficile*. *Antimicrobial Agents and Chemotherapy* 52 (2):770–3. doi: 10.1128/AAC.00957-07.

Stecher, B., R. Denzler, L. Maier, F. Bernet, M. J. Sanders, D. J. Pickard, M. Barthel, A. M. Westendorf, K. A. Krogfelt, A. W. Walker, et al. 2012. Gut inflammation can boost horizontal gene transfer between pathogenic and commensal Enterobacteriaceae.

Proceedings of the National Academy of Sciences of the United States of America 109 (4):1269–74. doi: 10.1073/pnas.1113246109.
Stecher, B., L. Maier, and W.-D. Hardt. 2013. "Blooming" in the gut: How dysbiosis might contribute to pathogen evolution. *Nature Reviews. Microbiology* 11 (4):277–84. doi: 10.1038/nrmicro2989.
Stinear, T. P., D. C. Olden, P. D. Johnson, J. K. Davies, and M. L. Grayson. 2001. Enterococcal vanB resistance locus in anaerobic bacteria in human faeces. *Lancet (London, England)* 357 (9259):855–6. doi: 10.1016/S0140-6736(00)04206-9.
Suez, J., N. Zmora, G. Zilberman-Schapira, U. Mor, M. Dori-Bachash, S. Bashiardes, M. Zur, D. Regev-Lehavi, R. Ben-Zeev Brik, S. Federici, et al. 2018. Post-antibiotic gut mucosal microbiome reconstitution is impaired by probiotics and improved by autologous FMT. *Cell* 174 (6):1406–23.e16. doi: 10.1016/j.cell.2018.08.047.
Szajewska, H. 2016. What are the indications for using probiotics in children? *Archives of Disease in Childhood* 101 (4):398–403. doi: 10.1136/archdischild-2015-308656.
Tankou, S. K., K. Regev, B. C. Healy, E. Tjon, L. Laghi, L. M. Cox, P. Kivisakk, I. V. Pierre, L. Hrishikesh, R. Gandhi, et al. 2018. A probiotic modulates the microbiome and immunity in multiple sclerosis. *Annals of Neurology* 83 (6):1147–61. doi: 10.1002/ana.25244.
Taur, Y., K. Coyte, J. Schluter, E. Robilotti, C. Figueroa, M. Gjonbalaj, E. R. Littmann, L. Ling, L. Miller, Y. Gyaltshen, et al. 2018. Reconstitution of the gut microbiota of antibiotic-treated patients by autologous fecal microbiota transplant. *Science Translational Medicine* 10:460. doi: 10.1126/scitranslmed.aap9489.
Tulstrup, M. V., E. G. Christensen, V. Carvalho, C. Linninge, S. Ahrne, O. Hojberg, T. R. Licht, and M. I. Bahl. 2015. Antibiotic treatment affects intestinal permeability and gut microbial composition in wistar rats dependent on antibiotic class. *PLoS One* 10 (12):e0144854. doi: 10.1371/journal.pone.0144854.
Turnbaugh, P. J., R. E. Ley, M. A. Mahowald, V. Magrini, E. R. Mardis, and J. I. Gordon. 2006. An obesity-associated gut microbiome with increased capacity for energy harvest. *Nature* 444 (7122):1027–31. doi: 10.1038/nature05414.
van Schaik, W. 2015. The human gut resistome. *Philosophical Transactions of the Royal Society of London. Series B, Biological Sciences* 370 (1670):20140087. doi: 10.1098/rstb.2014.0087.
Vangay, P., T. Ward, J. S. Gerber, and D. Knights. 2015. Antibiotics, pediatric dysbiosis, and disease. *Cell Host Microbe* 17 (5):553–64. doi: 10.1016/j.chom.2015.04.006.
Veiga, P., Gallini, C. A. C. Beal, M. Michaud, M. L. Delaney, A. Dubois, A. Khlebnikov, Van Hylckama Vlieg Je, S. Punit, and J. N. Glickman. 2010. Bifidobacterium animalis subsp. lactis fermented milk product reduces inflammation by altering a niche for colitogenic microbes. *Proceedings of the National Academy of Sciences of the United States of America* 107 (50):21943.
Vijay-Kumar, M., J. D. Aitken, F. A. Carvalho, T. C. Cullender, S. Mwangi, S. Srinivasan, S. V. Sitaraman, R. Knight, R. E. Ley, and A. T. Gewirtz. 2010. Metabolic syndrome and altered gut microbiota in mice lacking Toll-like receptor 5. *Science* 328 (5975):228–31. doi: 10.1126/science.1179721.
Vrieze, A., C. Out, S. Fuentes, L. Jonker, I. Reuling, R. S. Kootte, E. van Nood, F. Holleman, M. Knaapen, J. A. Romijn, et al. 2014. Impact of oral vancomycin on gut microbiota, bile acid metabolism, and insulin sensitivity. *Journal of Hepatology* 60 (4):824–31. doi: 10.1016/j.jhep.2013.11.034.
Wang, Z-j, Fu, -m Zhang, L-s Wang, Y-w Yao, Q. Zhao, and X. Gao. 2009. Lipopolysaccharides can protect mesenchymal stem cells (MSCs) from oxidative stress-induced apoptosis and enhance proliferation of MSCs via Toll-like receptor(TLR)-4 and PI3K/Akt. *Cell Biology International* 33 (6):665–74. doi: 10.1016/j.cellbi.2009.03.006.
Willmann, M., M. J. G. T. Vehreschild, L. M. Biehl, W. Vogel, D. Dörfel, A. Hamprecht, H. Seifert, I. B. Autenrieth, and S. Peter. 2019. Distinct impact of antibiotics on the gut microbiome and resistome: A longitudinal multicenter cohort study. *BMC Biology* 17 (1):76. doi: 10.1186/s12915-019-0692-y.
Wlodarska, M., and B. B. Finlay. 2010. Host immune response to antibiotic perturbation of the microbiota. *Mucosal Immunology* 3 (2):100–3. doi: 10.103.8/mi.2009.135.
Wlodarska, M., B. Willing, K. M. Keeney, A. Menendez, K. S. Bergstrom, N. Gill, S. L. Russell, B. A. Vallance, and B. B. Finlay. 2011. Antibiotic treatment alters the colonic mucus layer and predisposes the host to exacerbated *Citrobacter rodentium*-induced colitis. *Infection and Immunity* 79 (4):1536–45. doi: 10.1128/IAI.01104-10.
Wlodarska, M., C. Luo, R. Kolde, E. d'Hennezel, J. W. Annand, C. E. Heim, P. Krastel, E. K. Schmitt, A. S. Omar, E. A. Creasey, et al. 2017. Indoleacrylic acid produced by commensal Peptostreptococcus species suppresses inflammation. *Cell Host Microbe* 22 (1):25–37. doi: 10.1016/j.chom.2017.06.007.
Wright, G. D. 2007. The antibiotic resistome: The nexus of chemical and genetic diversity. *Nature Reviews. Microbiology* 5 (3):175–86. doi: 10.1038/nrmicro1614.
Wright, G. D. 2016. Antibiotic adjuvants: Rescuing antibiotics from resistance. *Trends in Microbiology* 24 (11):862–71. doi: 10.1016/j.tim.2016.06.009.
Wu, G., C. Zhang, J. Wang, F. Zhang, R. Wang, J. Shen, L. Wang, X. Pang, X. Zhang, L. Zhao, et al. 2016. Diminution of the gut resistome after a gut microbiota-targeted dietary intervention in obese children. *Scientific Reports* 6:24030. doi: 10.1038/srep24030.
Yang, J. H., P. Bhargava, D. McCloskey, N. Mao, B. O. Palsson, and J. J. Collins. 2017. Antibiotic-induced changes to the host metabolic environment inhibit drug efficacy and alter immune function. *Cell Host Microbe* 22 (6):757–65.e3. doi: 10.1016/j.chom.2017.10.020.
Yassour, M., T. Vatanen, H. Siljander, A. M. Hamalainen, T. Harkonen, S. J. Ryhanen, E. A. Franzosa, H. Vlamakis, C. Huttenhower, D. Gevers, et al. 2016. Natural history of the infant gut microbiome and impact of antibiotic treatment on bacterial strain diversity and stability. *Science Translational Medicine* 8 (343):343ra81. doi: 10.1126/scitranslmed.aad0917.
Yelin, I., K. B. Flett, C. Merakou, P. Mehrotra, J. Stam, E. Snesrud, M. Hinkle, E. Lesho, P. McGann, A. J. McAdam, et al. 2019. Genomic and epidemiological evidence of bacterial transmission from probiotic capsule to blood in ICU patients. *Nature Medicine* 25 (11):1728–32. doi: 10.1038/s41591-019-0626-9.
Yin, J., P. M. Wang, S. S. X. Liao, X. Peng, Y. He, Y. R. Chen, H. F. Shen, J. Su, Y. Chen, Y. X. Jiang, et al. 2015. Different dynamic patterns of β-lactams, quinolones, glycopeptides and macrolides on mouse gut microbial diversity. *PLoS One* 10 (5):e0126712. doi: 10.1371/journal.pone.0126712.
Zhang, F., B. Cui, X. He, Y. Nie, K. Wu, D. Fan, and FMT-standardization Study Group. 2018. Microbiota transplantation: Concept, methodology and strategy for its modernization. *Protein Cell* 9 (5):462–73. doi: 10.1007/s13238-018-0541-8.
Zhang, L., Y. Huang, Y. Zhou, T. Buckley, and H. H. Wang. 2013. Antibiotic administration routes significantly influence the levels of antibiotic resistance in gut microbiota. *Antimicrobial Agents and Chemotherapy* 57 (8):3659–66. doi: 10.1128/AAC.00670-13.
Zhao, Y., F. Chen, W. Wu, M. Sun, A. J. Bilotta, S. Yao, Y. Xiao, X. Huang, T. D. Eaves-Pyles, G. Golovko, et al. 2018. GPR43 mediates microbiota metabolite SCFA regulation of antimicrobial peptide expression in intestinal epithelial cells via activation of mTOR and STAT3. *Mucosal Immunology* 11 (3):752–62. doi: 10.1038/mi.2017.118.
Zmora, N., G. Zilberman-Schapira, J. Suez, U. Mor, M. Dori-Bachash, S. Bashiardes, E. Kotler, M. Zur, D. Regev-Lehavi, R. B. Brik, et al. 2018. Personalized gut mucosal colonization resistance to empiric probiotics is associated with unique host and microbiome features. *Cell* 174 (6):1388–405. doi: 10.1016/j.cell.2018.08.041.