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Antibiotic-induced dysbiosis effects on the murine gastrointestinal tract and their systemic repercussions

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ABSTRACT

The gastrointestinal tract has become a focus of study recently. The crosstalk between microbiota, especially bacteria, and the intestinal mucosa has to be accurately balanced in order to maintain physiological homeostasis in the human body. This dynamic interaction results in different levels of short-chain fatty acids (SCFAs), IgA, and T cell lymphocyte subsets, which could lead the human body towards health or disease. The disruption of this microbiome characterises gut dysbiosis. Antibiotics are usually prescribed to fight against bacterial infection. They can also modulate the human microbiome, since it acts directly over organisational taxonomic units (OTUs) when taken orally. As a result, these pharmaceuticals enable gut dysbiosis and its systemic effects due to microbiome disturbance. Here, current data have been gathered from mice model experiments and epidemiological studies in an antibiotic-centred perspective. The presented data suggest the importance of translational studies in a murine model focusing on GIT homeostasis with bacterial groups since any changes to the GIT-microbiota have systemic repercussions in human health and disease.

1. Introduction

The human gut microbiota is composed of about 10^{13} bacteria dwelling in different sites in the body [1]. The gastrointestinal tract (GIT), as a result, is the most cellular organ inside human body, with an estimated 500 to 1000 different species of bacteria belonging to Firmicutes or Bacteroidetes, which dominate the gut; also, Proteobacteria, Verrucomicrobia, Actinobacteria, Fusobacteria and Cyanobacteria phyla live in the organ [2]. Therefore, human gut and bacteria crosstalk is important, not only for physiological balance, but also with regard to health-disease status [3]. In spite of the physiological balance between the GIT and the bacterial species that colonise the organ, many events can disturb this steady immunopathophysiological interplay.

Gut microbiota disturbance, known as gut dysbiosis, happens qualitatively and quantitatively [3]. Dysbiosis is characterised by an alternative microbiota state in which T cell subsets, Th1, Th2, Treg, and γδ T, and metabolites such as short-chain fatty acids (SCFA), antibodies (especially IgA) and cytokines are altered. This confirms that the microbiota has an influence over human immunological homeostasis, which expresses itself differently depending on the trigger event [1]. All of these host mediators promote communication between the GIT and extraintestinal organs. This means that any changes to the GIT-microbiota interplay have systemic repercussions [1,4].

The effects of antibiotics on gut microbiota are quite well described. Furthermore, any change in the gut microbiota also influences homeostasis of the human body. One of the influences of microbiota is related to antibiotic use. These pharmaceuticals, usually prescribed for infections, can also target commensal microbiota, enabling gut dysbiosis [5,6]. Importantly, their action is dependent not only on dose, timing and administration route [6], but also on the target of different bacterial species content and diversity present in the GIT, causing gut dysbiosis to have an influence on host perturbation directed towards health or, in the great majority of cases, disease.

Current evidence suggests that gut dysbiosis may have a causal role on small intestine bowel overgrowth (SIBO) [7], asthma [8], type 1 diabetes [9], gastroenteritis [6], sclerosing cholangitis [10], parental nutrition-associated liver disease [10], liver cancer [11], psychiatric disorders [12], obesity [13], *Clostridium difficile* disease [14], antibiotic-associated colitis [1], colorectal cancer [15], ischaemic stroke [16], necrotising enterocolitis [17], allergy [18,19], multiple sclerosis [20], autism [21], allogeneic stem cell transplantation [22], sepsis [23] and inflammatory bowel disease (IBD) [6]. Although research has mainly highlighted poor outcomes among mouse models and epidemiological studies, there is new evidence on shaping microbiota for treatment

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purposes, such as in Parkinson's disease [24], antibiotic-associated diarrhoea (AAD) [25] and SIBO [26].

This review aims to gather new evidence from epidemiological studies and experiments using murine models about antibiotic-induced dysbiosis and its consequences on the whole organism. Noteworthy, data will be identified through an antibiotic-centred perspective. For that, the PubMed and ScienceDirect platforms were used to select original articles with “gut dysbiosis” and “antibiotics” being used as key words. From the returned results, the abstracts were evaluated and a new selection was made. The selection criteria included being relevant and related to the theme, being written in English and being original or review articles published between 2012 and 2018. Beyond this, pharmaceutical descriptions were searched separately and some references from selected articles were also consulted. A total of 114 articles were selected using these criteria; the results are presented below according to antibiotic structure following their mechanism of action, their usage and their influence on disease and/or health status.

2. Effects of antibiotics on mouse models and human health

2.1. Glycopeptides

Glycopeptide antibiotics were originally isolated from plant and soil bacteria. These compounds contain minor structural variations, usually with regard to their glycosylation state. All glycopeptides share a common heptapeptide backbone containing either a glycosylated cyclic or polycyclic non-ribosomal peptide with three characteristic ring systems in the aromatic side chains [27].

Both vancomycin and teicoplanin inhibit bacterial cellular wall synthesis, regardless of their concentration. Specifically, they bind to D-alanil-alanine, which prevents the action of peptideoglycan polymerase. Hence, peptideoglycan cannot get straightened, precluding synthesis of the outer structure of the bacterium. Vancomycin can also disrupt protoplasm homeostasis, since it alters membrane permeability and inhibits RNA synthesis [28,29]. This drug displays a dose-dependent effect, and also has a long-lasting residual action in vitro [30]. Vancomycin is mainly a Gram-positive bactericidal, despite it only having a bacteriostatic effect on enterococcus species [31].

2.1.1. Vancomycin

Vancomycin use in murine models has shown a myriad of host homeostasis changes. Wistar rats exposed to vancomycin had a heavier caecum than controls and the caecum pH was higher. There was a change in the bacterial community in the caecum, ileum and faeces. Remarkably, the anaerobic bacterial load was increased, with lower α and β diversities, characterised by a decrease in *Firmicutes* phylum and an increase in *Proteobacteria* and *Verrucomicrobiaceae*. In addition, intestinal permeability was diminished along SCFA levels, although succinate was higher than in controls [32].

One study, however, diverged from current data [33]. Mice under the same vancomycin regimen displayed no changes in total bacterial load. There was a decrease in the amount of *Firmicutes* and *Proteobacteria*. Moreover, morphological villi changes occurred in the GIT [33].

This antibiotic-induced dysbiosis is also related to hepatic inflammation in mice, depending on the type of diet used. It was associated with altered inflammatory gene expression in the ileum and liver, but a decrease in secondary bile acid levels [34], to which an antimicrobial action is attributed [10].

2.1.1.1. Type 1 diabetes (T1D). Studies on NOD mice have linked gut dysbiosis to type 1 diabetes [9,35,36]. Vancomycin-treated mice have shown increased Treg cell levels on the ileum and colon lamina propria, as well as a depletion of γδ and CD4+ T cells in the same GIT regions. This last change was responsible for the decrease in interleukin 17 synthesis. All of this was observed only for male animals [35]. It also highlighted an increase in the *Akkermansia* population in this dysbiosis model [35,36]. Moreover, Brown et al. [9] showed an increased incidence of T1D among NOD mice under the same treatment. This was related to lower levels of SCFA microbiota products, predisposing to a leaky gut barrier [37,38]. These last findings are supported by epidemiological evidence which demonstrated a positive statistical relation between prior antibiotic use and diabetes incidence [39].

In another study, vancomycin was given a protective role in diabetes development in NOD mice [36]. These divergent results might be due to the different antibiotic usage and treatment timing [40].

2.1.1.2. Glucose intolerance. To determine a relationship between and causal role for antibiotic-induced gut dysbiosis in glucose intolerance, non-caloric artificial sweetener-treated mice received vancomycin, as did the control animals. After a 4-week treatment, glucose intolerance was abolished in both groups [41]. The mechanisms associated with these findings suggest that glucose intolerance may be mediated by microbiota composition.

2.1.1.3. Clostridium difficile infection (CDI). Vancomycin is one therapeutic strategy against colitis, as its spectrum targets Gram-positive anaerobic bacteria [42]. However, a mouse model approach showed that, despite vancomycin treatment, CDI mice had a poor outcome and great microbiota changes due to the increase in Proteobacteria species, especially in the early stages after treatment [43]. As an option, fidaxomicin, a recently approved drug with a narrower spectrum, is related to a lower disease recurrence rate [42,44] and a higher cure percentage [45], since this antibiotic preserves the original microbiota better than vancomycin. Furthermore, it has ameliorated symptoms among autistic subjects, as they present a higher *C. difficile* gut content than healthy individuals [46].

2.1.1.4. Visceral pain. In contrast with the previous study [47], early life rat exposure to vancomycin decreased the visceral pain threshold among rats without an impact on immune cells, cytokines and corticosterone levels in serum [48], which shows that vancomycin-induced gut dysbiosis may have a causative role in pain sensitivity.

2.1.1.5. Alopecia. New evidence points towards vancomycin-gut dysbiosis having an influence over alopecia. Mice under this antibiotic treatment, and whose diet lacked biotin, presented a meaningful alopecia level. This event was positively correlated to *Lactobacillus murinus* overgrowth due to the action of vancomycin, as this species has a cluster that does not present biotin pathway genes in its genome [49].

2.1.1.6. Myocardial infarction. 48-hour vancomycin treatment on mice decreased ischaemic infarction injury in myocardium. This was directly related to the effect of the drug on microbiota, as it lowered leptin serum levels, and is known as a cardioprotective factor [50].

2.1.2. Teicoplanin

Teicoplanin, another glycopeptide antibiotic, also targets Gram-positive bacteria. Its usage is currently related to preoperative preparation of patients, e.g. before gastrointestinal, vascular, cardiac and plastic surgeries [51].

2.1.2.1. Neutropenic colitis. Reyna-figueroa et al. [52] showed that teicoplanin is a protective element against the development of neutropenic colitis in children with leukaemia undergoing chemotherapy. The authors hypothesised that this might happen due to the action of teicoplanin against Gram-positive bacteria, since colitis develops through *Clostridia* overgrowth in the gut [52].

2.2. β-Lactams

β-Lactams share an essential structure: the skeleton backbone shared by the widely employed family of natural and unnatural antimicrobial agents. The most widely used antibiotics, such as penicillin, aztreonam, cephalosporins, monobactams and carbapenem, all contain the azetidine-2-one heterocyclic organic compound, which is the core structural feature in a number of broad spectrum β-lactam derivatives [53].

The β-lactam mechanism of action is directly associated to the biosynthesis of bacterial cell wall enzymes, known as penicillin binding proteins (PBPs), which prevents them from building this molecular structure [54]. β-Lactams prevent peptideoglycan linkage to PBPs, as they react with the PBPs' serine amino acid by acylation [55]. Hence, bacteria are killed, since they cannot build this indispensable molecular component [56].

2.2.1. Penicillins

Penicillin was the first antibiotic discovered and its usage remains quite popular. It has been linked to augmented bone mass, probably due to the influence of the gut microbiota metabolic over bone tissue [57].

2.2.1.1. Obesity. Antibiotics are the most prevalent medicine prescribed by paediatricians [58]. Not only have experimental studies provided evidence of a link between antibiotics and obesity [59], they have also provided epidemiological observations [58]. Recently, some studies have linked prescription and repeated exposure to weight gain in children under 1 year of age. This effect continued into late childhood and adolescence, despite treatment withdrawal [58]. In a mouse model, penicillin-induced dysbiosis was also related to increased weight, supporting the influence of gut dysbiosis over obesity [60].

Epidemiological studies tend to corroborate these findings. A study conducted in the first 24 months of life of Finnish children revealed that penicillin exposure is a risk factor for becoming overweight after 24 months of age in male subjects. This was also related to early exposure to antibiotics and the frequency of recurrent use [61].

However, a recent epidemiological study states that, rather than antibiotics, infections during infancy are a risk for later obesity [62].

2.2.1.2. Coeliac disease. A case-control study in Sweden found that repeated antibiotic use before diagnosis is related to coeliac disease. Penicillin V and other pharmaceuticals from the same class showed a positive relationship [63]. According to the authors, antibiotic use was linked to small bowel inflammation, which may occur due to microbiota dysbiosis as a result of antibiotic treatment [63].

2.2.1.3. Gastroenteritis. The influence of penicillin over mice gut microbiota before and along with infection with *Campylobacter jejuni* or *Acinetobacter baumannii* has been assessed. Mice which received penicillin displayed low α diversity after pathogen challenge. Mice with dysbiosis who were previously treated were characterised by higher *Proteobacteria* and *Verrucomicrobia* counts and lower *Bacteroides* and *Firmicutes* levels. Those animals challenged with *C. jejuni* showed an increase in *Proteobacteria* and a decrease in *Firmicutes* bacteria just after infection, while those inoculated with *A. baumannii* displayed increased *Proteobacteria* and *Verrucomicrobia* populations [4].

2.2.1.4. Colorectal cancer (CRC). Epidemiological evidence demonstrated a positive statistical relationship between antibiotic use and colorectal cancer. This risk factor is changeable by time of exposure and number of incidences, as well as antibiotic type [15]. Penicillin has been strongly linked to this cancer [15]. It is hypothesised that this drug action against Gram-positive bacteria enables the overgrowth of anaerobic Bacteroides in microbiota, making people susceptible to CRC. Quinolones, cephalosporins and nitroimidazoles had a positive link as well [64], although macrolides and tetracycline did not [15].

Of note, oesophageal, gastric, pancreatic, lung and urinary tract cancers displayed prior use of antibiotics as a risk factor. Accordingly, Boursi et al. hypothesised that antibiotic-induced dysbiosis may predispose some genetically prone individuals to cancer development [65].

2.2.2. Amoxicillin

Amoxicillin belongs to the penicillin drug group. In Wistar rats, amoxicillin induced weight gain in the caecum and altered bacterial microbiota, as evidenced by lower α and β diversities. In particular, there was a decrease in *Firmicutes* phylum and an increase in *Proteobacteria*. Amoxicillin also caused lower SCFA production, although succinate was higher than in the controls [32]. Antibiotic-gut imbalance would last for three months after withdrawal [66].

2.2.2.1. Ischaemic stroke. Since a huge amount of Treg cells and γδ T cells are matured in the intestinal lamina propria, Benakis et al. assessed the role of the gut in ischaemic stroke [16]. Amoxicillin/clavulanate-treated mice showed the expansion of *Proteobacteria* and a diminished number of *Clostridiales* and *Bacteroidetes*. This dysbiosis was linked to higher amounts of Treg cells and lower numbers of IL-17 γδ T cells, preventing a greater infarct volume than in control animals. When faecal transplant was performed, despite a different taxonomic distribution, the protective role of microbiota in stroke remained [16].

2.2.3. Cephalosporins

2.2.3.1. Cefotaxime. In Wistar rats, cefotaxime treatment induced changes to the gut microbiota, featured by a lower α diversity. There was a bacterial increase among *Bifidobacteriaceae* and *Enterococcaceae*. Furthermore, a lower level of valerate - an SCFA - was found, although succinate was higher than in controls, leading to a disruption of gut homeostasis [32].

2.2.3.2. Ceftriaxone and cefoxitin. Another experiment using a murine model proposed investigating the mucosal barrier dysfunction when *Enterococcus faecium* is inoculated in cephalosporin-induced gut dysbiosed animals. The authors analysed Mucin-2, E-cadherin, sIgA and pIgR levels, molecules which are responsible for the physiological balance of the gut barrier. Overall, mucin-2 levels were low in the outlayer mucous gut layer and the pathogen had agglutinated with sIgA, pIgR and E-cadherin as it overgrew [67].

2.2.3.3. Cefradine. The influence of antibiotic-treated mice on influenza virus immune response was also assessed. Mice treated with cefradine displayed an increased number of *Escherichia coli* and anaerobes, while a decreased number of *Bifidobacterium* and *Enterococcus* in the gut. After being challenged with influenza, there was a greater virus content in antibiotic-treated mice than in those which were not on a pharmaceutical regimen. This permissive virus growth would have occurred by a decrease in Th1 and Th2 cells [68].

When gavaged with ceftriaxone, mice revealed a decreased number of *Lactobacilli*, *Enterococcus* and *Fusobacterium* and an increase in fungi compared to the controls [69]. Another study corroborated the decreased bacterial microbiota diversity and also highlighted morphological changes to GIT villi [33]. Moreover, SFCA and intestinal IgA levels were lower. Regarding lymphocytes, there were fewer activated T and B cells in Peyer's patches, mesenteric lymph nodes and the spleen, although there was a higher proportion of T cells and lower level of B cells [69].

2.2.3.4. Ceftriaxone. In another ceftriaxone study, the authors analysed the small intestine dendritic cells (DCs) of mice and found that, despite there being a higher DC amount than in controls, these cells were less matured and had a lower expression of immunological synapse proteins [70].

Furthermore, ceftriaxone-treated mice displayed long-lasting different effects depending on dose and temporal assessment [71].

Regarding gut dysbiosis, there was a dominancy succession: in the first 30 days of the experiment, the microbiota was dominated by *Enterococcus*; on the 60th day, by *Robinsoniella*; and after 2 months, by *Anaeroplasma* bacteria. Furthermore, especially in the beginning, there was increase in IFN-γ/IL4 and CD4/CD8 ratios, as well as low IgA levels detected in the gut mucosa. This profile proved to be dose- and time-dependent [71].

2.2.3.4.1. Neutropenic colitis. Chemotherapy promotes oedema in GIT, which prevents commensal bacteria from resisting pathobionts and pathogens, as well as altering metabolic pathways [52]. In this way, children under treatment for leukaemia are prone to developing neutropenic colitis. Reyna-figueroa et al. [52] assessed the antibiotic effect when used prior to leukaemia therapy in infants. They found ceftriaxone to be a risk factor for developing this type of colitis. It was hypothesised that, since neutropenic colitis happens due to Gram-positive *Clostridia* overgrowth, this antibiotic does not act efficiently against these bacteria [52].

2.2.3.5. Cefoperazone. Cefoperazone was administered to IL-10 knockout mice to analyse maternal exposure to antibiotics and its effect on offspring. It was found that pups born to mothers exposed to antibiotics had a decreased microbiota diversity, which made them more susceptible to colitis. In addition, higher levels of pro-inflammatory cytokines were found in these animals. Moreover, gut dysbiosis was present among mice offspring whose germ-free mothers received faecal transplants from the aforementioned mice [72].

2.3. Tetracyclines

Tetracyclines are antibiotics containing four rings, thus forming a rigid ring skeleton with groups on the upper and lower sides of the molecule. An active tetracycline (antibacterial activity) must possess a linearly arranged naphthacene ring system. All tetracyclines which act as inhibitors of protein synthesis in bacteria need the amino group and keto-enolic tautomers. The amino group is pivotal for the antibacterial activity. The inhibition of bacterial protein synthesis is related to the association between the host aminoacyl-RNA and bacterial ribosomes being prevented [73,74]. In Gram-negative bacteria, tetracycline-cation complexes pass through OmpF and OmpC, both of which are external membrane channels; the complexes become dissociated by Donnan potential inside the periplasm, which enables neutral tetracyclines to diffuse through the cytoplasmic membrane and interacts with bacterial ribosomes reversibly [73–75]. In Gram-positive bacteria, neutral tetracyclines pass through the enlarged cellular membrane and form a complex with ribosomes, as do Gram-negative species [73–75].

2.3.1. Minocycline

Minocycline seems to ameliorate schizophrenia and depression, and appears to be related to gut modifications by this pharmaceutical [46]. It has been studied as a Parkinson's disease drug. Since it reduces the *Firmicutes/Bacteroidetes* ratio, gut microbiota reconstitution has been hypothesised as part of the Parkinson's disease pathogenesis [24].

The effects of minocycline in a rat hypertension model have been assessed. Minocycline was able to reduce blood pressure and increase the levels of two SCFAs, butyrate and acetate. According to the authors, it was associated with a new gut microbiota composition, in which there was a higher level of *Firmicutes* and *Bacteroidetes*, though there was increased microbiota diversity when compared to controls [76].

Moreover, minocycline exerts anti-inflammatory effects over a colitogenic mice model. The authors revealed that this antibiotic regimen was able to restore a good commensal bacteria ratio. It improved colitis prognosis, by diminishing the immune response in the intestinal wall and TNF-α and IL-1β levels. Also, antibiotic treatment resulted in lower pathophysiological damage to the gut wall when the same mice were exposed again to colitic substances [21,77].

2.3.2. Doxycycline

Doxycycline effects were explored in both rats and mice. In a colitis model, both animal groups presented lower histological and pro-inflammatory cytokine markers when given this drug [78].

2.4. Quinolones

Quinolones are broad-spectrum pharmaceuticals [79]. These drugs display a range of pharmacodynamic effects over bacteria, depending on the inhibitor translational effect, efficacy level and requirement for aerobic metabolism in bacteria. They target two DNA topoisomerases: DNA gyrase and topoisomerase IV. While the first is the main Gram-negative bacteria target, the latter is specially aimed at Gram-positive bacteria [80].

2.4.1. Enrofloxacin

Enrofloxacin was used in a collagen-induced arthritis study, in order to assess gut dysbiosis effects over animal joints. Intestinal bacterial imbalance aggravated a disease-like state through higher levels of IFN-γ and IL-17A [81].

2.5. Metronidazole

Metronidazole and nitroimidazoles appear to exert bactericidal actions through four steps: bacterial entry into host cells; nitro-radical reduction; the cytotoxic effect of intermediate metabolites; and the synthesis of inactive final products [82]. This drug effect depends on a redox intermediate metabolite, which may interact with bacterial DNA, RNA or intracellular proteins. However, it mostly breaks DNA strands, inhibits their repair and disrupts transcription, leading to cellular death [83].

In a Wistar rat model, metronidazole did not change bacterial composition, nor α diversity, although there was increase in intestinal permeability. It was also characterised by higher amounts of *Bifidobacterium* and *Escherichia*, whereas there was a decrease in Lactobacillus amounts in the gut microbiota [32]. When infected with the influenza virus, dysbacteriosis in those animals promoted an increase in viral genetic material, alongside a decrease in Th1, Th2 and Treg cells [68].

2.5.1. Coeliac disease

It was found that the use of metronidazole a year prior to coeliac disease diagnosis has statistical relevance for this diagnosis, suggesting that this antibiotic-induced gut dysbiosis could be linked to the posterior development of this disease [63].

2.5.2. Clostridium difficile infection (CDI)

Metronidazole was the first drug approved to treat CDI, because of its mechanism, preventing the overgrowth of *Clostridium difficile*, a pathobiont inhabitant of the human gut microbiota [2].

2.5.3. Gastroenteritis

A *Citrobacter rodentium* gastroenteritis mice model has been well described for the study of attached pathogens [84]. Metronidazole exacerbates this pathogen infection in pre-treated mice through lower SFCA production and disruption of the mucous layer [64,84].

2.5.4. Site wound infection

Krezalek et al. [85] found an increased susceptibility to a methicillin-resistant *Staphylococcus aureus* (MRSA) strain inoculated in the microbiota wound infection after abdominal incision in a murine model. Rats were gavaged with oral metronidazole and given ampicillin intramuscularly. This group postulated a “Trojan Horse” mechanism, in which MRSA translocates from the intestine via neutrophils to infect the skin [85].

2.6. Aminoglycosides

Aminoglycosides inhibit translational processes by binding to the 30S ribosomal subunit [86]. First, they must go towards the cytoplasm environment, which happens via a three-step process: as these drugs are cationic or hydrophilic, they pass through the outer membrane porin channels from Gram-negative bacteria; after that, ionic binding drives their entry, firstly by a slow diffusional process and, second, by rapid drug absorption, which is related to antibiotic-bacterial ribosome complexation [87,88]. The aminoglycoside spectrum is aimed at facultative anaerobic and aerobic Gram-negative bacteria [89].

2.6.1. Streptomycin

This antibiotic was used in a cystic fibrosis mouse model. The treated group displayed less airway responsiveness, which appears to be related to lower amounts of *Lactobacillus* in the gut. Also, increased levels of Th17 cells were detected in the lungs and mesenteric lymph nodes [90].

Streptomycin has also been used to study *Salmonella typhimurium* in a mouse model. Streptomycin-exposed mice exhibited a microbiota with a high amount of *Enterococcaceae* and *Ruminococcaceae* bacteria, although *Bacteroidales* and *Clostridiales* levels were decreased. Dysbacteriosis facilitates pathogen infection and *Salmonella typhimurium* enabled *Enterobacteriaceae* intestinal overgrowth [91], sustained by RegIIIβ antimicrobials [92]. This occurred because streptomycin treatment on the gut microbiota allows higher electron acceptor levels in the mucosa, enabling facultative anaerobic overgrowth, e.g. *S. typhimurium* and enterobacteria [93].

2.6.1.1. Systemic sclerosis. In order to assess systemic sclerosis, immunised dendritic cell mice were subjected to streptomycin from gestation to the weaning period, late life or only during adult life. The full life exposure to antibiotics increased the *Bacteroidetes/Firmicutes* ratio and showed the strongest fibrosis in the lungs and skin. This was achieved through the higher expression of extracellular matrix-related genes, especially collagen genes. Noteworthy, a bias towards Th1 cells over Th2 cells was seen inside the lungs [94].

2.6.1.2. Liver metabolism. Streptomycin was also used in a mouse model to study the impact of gut dysbiosis on liver metabolism. The authors found that, in a temporal and dose-dependent manner, treated animals showed a slight increase in *Firmicutes* amounts and a significant decrease of *Bacteroidetes*. Higher levels of serum LPS were found, which augmented inflammatory pathways in liver. Moreover, the expression of oxidation enzymes in the liver was lower than in controls, whereas the translocation of enzymes towards the liver and triglyceride-targeted enzyme levels were increased, resulting in higher hepatic lipid content and liver weight [60].

2.6.2. Neomycin

Mice treated with neomycin featured a dysbiosis with higher levels of *Bifidobacterium, Enterococcus* and anaerobes, but lower *Lactobacillus* levels. When infected with influenza virus, neomycin-treated mice did not show any remarkable changes in Th1, Th2 and Treg profiles, despite viruses having proliferated the most under this model [68].

Furthermore, neomycin seems to have a protective role in the development of liver disease due to antibiotic-induced microbiota modifications [95].

2.6.2.1. T1 diabetes. A neomycin-induced gut dysbiosis and higher incidence of autoimmune diabetes has been determined in a NOD mice model [9]. This seems to be related to the lower production of SCFAs by the establishment of posterior antibiotic microbiota, as shown by the decreased content of *Desulfovibrio*, *Prevotella* and *Enterobacteriaceae*, yet an increase in *Rikenellaceae* [9].

2.7. Rifaximin

Rifaximin is a rifamycin-derived drug with bactericidal activity, which is responsible for the impairment of bacterial transcription, since it irreversibly binds to bacterial RNA polymerase. It is not greatly absorbed through oral intake [96], and targets intestinal Gram-positive and -negative bacteria, regardless of whether their metabolism is aerobic or anaerobic, such as *Escherichia coli*, *Salmonella*, *Shigella*, *Campylobacter*, *Plesiomonas* and *Aeromonas* [97].

2.7.1. Liver diseases

Rifaximin has been used in patients with cirrhosis, hepatic encephalopathy and spontaneous bacterial peritonitis, in the context of liver disease [26]. Hence, altered biliary acids are formed, inducing intestinal dysbiosis [98]. As illustrated by some clinical trials [99], the action of rifaximin consists of increasing the anti-inflammatory response by modulating cytokine release, although it does not seem to modify the microbiota load of subjects [98,99]. This may be linked to a compositional change induced by this drug, in which some beneficial *Enterobacteriaceae* had grown [99].

2.7.2. Irritable bowel syndrome (IBS)

Irritable bowel syndrome is a GIT symptom syndrome with no morphological changes to the intestinal tract, but is related to gut dysbiosis, even though no causal role has been attributed to this imbalance [47]. A clinical trial demonstrated that, despite rifaximin not changing the *Bacteroidetes/Firmicutes* ratio, gut microbiota species' richness increased, and was related to good IBS patient outcomes [100].

2.8. Colistin

Colistin, also known as polymyxin E, not only has a similar chemical structure to polymyxin B, but also seems to act in a similar way [101]. It targets Gram-negative lipopolysaccharide (LPS) [102,103]. Polymyxins display a strong positive charge, and a hydrophobic acyl chain, which are responsible for the bactericidal effect. This chemical structure allows polymyxins to interact with the external membrane and remove divalent cations [104]. Cellular permeability increases, as shown by intracytoplasmatic leakage, resulting in cell death [105,106]. Also, these antibiotics can bind to the LPS fat portion (lipid A), preventing its endotoxic effects [107].

In the colistin mouse model, decreased *Enterobacteriaceae* and increased *Lactobacillus*, *Bacteroides* and *Enterococcus* have been found in the caecal mucosa. Antibiotic-treated mice also showed higher levels of bacterial translocation, having been found in the spleen, liver, kidney and mesenteric lymph nodes. Moreover, the distal ileum displayed inflammatory signs, such as lower tight junction protein expression and altered morphology from these structures [108].

All of these antibiotic-induced dysbiosis effects on the murine gastrointestinal tract and their systemic repercussions are listed in Table 1.

3. Antibiotic cocktails used in anti-bacterial treatment and dysbiosis

Antibiotic cocktails are used not only in mice models, but also as a therapeutic regimen, especially on Intensive Care Units (ICUs). A case report of patients under corticoid therapy and antibiotics stated that they presented low intestinal microbiota diversity, with an increase in *Proteobacteria* and a decrease in *Firmicutes* and *Bacteroidetes* [109]. This evidence supports the pathophysiological mechanism of antibiotic-associated colitis.

3.1. Vancomycin, neomycin, ampicillin and metronidazole

This cocktail dysbiosis is related to the influence of hepatic inflammation levels in mice, depending on dietary exposure [34].

Table 1
Antibiotic-induced dysbiosis effects on the murine gastrointestinal tract and their systemic repercussions.

Antibiotic group	Antibiotic	Condition related to dysbiosis	Outcomes	References
Glycopeptides	Vancomycin	Type 1 diabetes (T1D) mice	↑Treg (ileum and colon) Depletion of γδ and TCD4+ (ileum and colon) ↓Interleukin-17 synthesis ↑*Akkermansia* sp. population	[9,35,36]
		Glucose intolerance	↓SCFA Abolished intolerance	[41]
		Clostridium difficile infection (CDI)	Microbiota change	[43]
		Alopecia	↑*Lactobacillus murinus*	[49]
		Myocardial infarction	↓Ischaemic infarction injury in myocardium ↓Leptin levels	[50]
	Teicoplanin	Neutropenic colitis	*Clostridia* overgrowth in the gut	[52,57]
β-Lactams	Penicillins		↑Bone mass	
		Obesity	↑Weight gain	[58,59,60,61]
		Coeliac disease	Bowel inflammation	[63]
		Gastroenteritis by *Campylobacter jejuni* and *Acinetobacter baumannii*	↓α diversity > Counts of *Proteobacterias* and *Verrucomicrobia* < *Bacteroides* and *Firmicutes* levels	[4]
		Colorectal cancer (CRC)	Excessive anaerobic *Bacteroides* growth	[64]
	Amoxicillin		↑Weight ↓α and β diversities ↓*Firmicutes* and ↑*Proteobacteria*	[32]
	Cephalosporins: Cefotaxime		Group with potential for CDI acquisition < α diversity ↑*Bifidobacteriaceae* and *Enterococcaceae* < SCFA	[32,132,134]
	Cephalosporins: Ceftriaxone and cefoxitin		↓Mucin-2 Pathogen had agglutinated with sIga, plgR and cadherin	[67]
	Cephalosporins: Cefradine	Influenza virus	↑Increased *Escherichia coli* and anaerobic bacteria amounts ↓*Bifidobacterium* and *Enterococcus* > Virus amount ↓Th1 and Th2	[68]
	Cephalosporins: Ceftriaxone		> Higher dendritic cell (DC) amounts Dendritic cells were less mature < Expression of immunological synapse proteins	[70]
		Dysbiosis (dosage and time)	30th day - microbiota was dominated by *Enterococcus* 60th day, by *Robinsoniella* After 2 months, by *Anaeroplasma* bacteria ↑IFN-γ/IL4 and CD4/CD8 ↓IgA	[71]
		Neutropenic colitis	GIT oedema Excessive Clostridia and Gram-positive bacteria growth	[52]
	Cephalosporins: Cefoperazone	Colitis	↓Diversity of the microbiota Higher levels of pro-inflammatory cytokines	[72]
Tetracyclines	Minocycline	Arterial hypertension	↓Blood pressure ↑Butyrate and acetate ↑*Firmicutes* and *Bacteroidetes*	[76]
		Colitis	Anti-inflammatory effects Restored good commensal bacteria ratio ↓Immune response on intestinal wall and ↓TNF-α and IL-1β levels	[21,77]
	Doxycycline	Colitis	↓Histological and pro-inflammatory cytokines Group with potential for CDI acquisition	[78,133,134]
Quinolones	Enrofloxacin	Arthritis	↑IFN-γ and IL-17A levels No change on bacterial composition, nor α diversity	[81]
Metronidazole	Metronidazole		↑Intestinal permeability ↑*Bifidobacterium* and *Escherichia* ↓*Lactobacillus*	[32]
		Influenza virus	↑Virus genetic material ↓Th1, Th2 and Treg cells	[68]
		Coeliac disease	Relevance to this disease diagnosis	[63]
		Clostridium difficile infection (CDI)	Prevented *Clostridium difficile* overgrowth	[2]
		Citrobacter rodentium gastroenteritis	Exacerbated this pathogen infection in pre-treated mice Lower SFCA production Disruption of mucous layer	[84,64]
Aminoglycosides	Streptomycin	Cystic fibrosis	< Airway responsiveness < *Lactobacillus* amounts ↑Levels of Th17 cells in lungs and mesenteric lymph nodes	[90]

(*continued on next page*)

Table 1 (*continued*)

Antibiotic group	Antibiotic	Condition related to dysbiosis	Outcomes	References
		Salmonella typhimurium	> *Enterococcaceae* and *Ruminococcaceae* < *Bacteroidales* and *Clostridiales* Increased *Enterococcaceae* and *Ruminococcaceae*	[91]
		Systemic sclerosis	↑*Bacteroidetes/Firmicutes* > Fibrosis in lung and skin > Expression of extracellular matrix-related genes > Th1 cells over Th2 cells were seen inside lungs	[94]
		Liver metabolism	↑*Firmicutes* and ↓*Bacteroidetes* Higher levels of LPS in serum < Oxidation liver enzymes expression > Higher hepatic lipid content and liver weight	[59]
	Neomycin	Influenza virus	> Levels of *Bifidobacterium*, *Enterococcus* and anaerobes ↓*Lactobacillus* There were not remarkable changes on Th1, Th2 and Treg profiles	[68]
		Liver disease	Protective role	[95]
		Type 1 diabetes (T1D)	< SCFA production	[94]
Rifaximin	Rifaximin	Liver diseases	Induction of biliary acids formation Modulation of cytokines release Beneficial *Enterobacteriaceae* growth	[98,99]
		Irritable bowel syndrome (IBS)	No change on *Bacteroidetes/Firmicutes* ratio ↑Gut microbiota species richness	[100]
Colistin (polymyxin E)			↓*Enterobacteriaceae* ↑*Lactobacillus, Bacteroides* and *Enterococcus* Higher levels of bacterial translocation Distal ileum displayed inflammatory signs	[108]

In a previous study, mice were subjected to a 14-day broad-spectrum antibiotic regimen, composed of vancomycin, neomycin, ampicillin and metronidazole. Beyond the huge changes to gut microbiota diversity, the authors found changes to T lymphocytes and their subsets until 6 weeks after the withdrawal of treatment. Interestingly, the new microbiota protected colitogenic mice from colitis, as evidenced by faecal transplant in the study [110].

Caputi et al. [111] focused on gut dysbiosis outcomes in the enteric nervous system. Mice treated with this antibiotic cocktail showed an increase in the caecum and spleen, altered glial arrangement and the up-regulation of TLR2 on GIT muscular and nervous layers. This evidence highlights the role of TLR2 on GIT dysmotility, since GIT transit was slower in dysbiotic mice [111].

Regarding constipation, two mice groups treated with this cocktail a priori received a faecal transplant from healthy humans and from humans with constipation respectively. After the 15th day, the group who received faeces from constipated patients showed lower evacuation parameters and, after analyses, serotonin transporter (SERT) mRNA had increased expression in faeces [112]. This enables a link to be established between gut dysbiosis and higher SERT levels and constipation.

It has also been reported, under this antibiotic treatment, that mice showed higher levels of bacteria inside colonocytes, but did not display any difference in the expression of tight junction proteins when compared to controls. It seems that dysbiosis increases transcytosis rather than paracellular translocation. Also, after inoculation with a virulent *E. coli* strain, there was an augmentation in some pro-inflammatory pathways [113].

3.2. Metronidazole, neomycin and polymyxin

Non-obese diabetic (NOD) female mice were subjected to an antibiotic regimen. Afterwards, their offspring were compared to control pups. Analysis revealed altered microbiota, an increase in CD8+ lymphocytes in mesenteric lymph nodes and a decrease of T cells in the gut Peyer's patches among medicated mother offspring. Also, there was increased lymphocyte infiltration inside the pancreas, although no statistical difference was found in diabetes incidence [114].

3.3. Bacitracin, neomycin and amphotericin B

Although amphotericin B does not have an antibacterial effect, it is important to describe a study conducted by Aguilera et al. [47]. Mice which received this cocktail presented a gut dysbiosis characterised by an increase in *Bacteroides* spp., *Clostridium*, *Coccoides*, *Lactobacillus-Enterococcus* spp. and a decreased number of *Bifidobacterium* spp. It might also explain the up-regulation of Toll-like receptor 4 (TLR4) in the gut. In addition, colonic cannabinoid receptors 1 and 2 showed different expression levels and an increased visceral pain threshold in antibiotic-treated mice [47]. Furthermore, when NO-synthase was inhibited in dysbiotic mice, GIT contractility diminished, which could explain the motility changes found in patients with irritable bowel syndrome [47].

3.4. Ampicillin, streptomycin, clindamycin

Mice undergoing this treatment presented depressive-like behaviour. Intestinal dysbiosis was featured by increasing the counts of *Proteobacteria* and *Actinobacteria*, composed of Gram-negative bacteria. Animals' behaviour changed towards immobility, although no neural or muscular impairments were found; also, curiosity for social novelty increased. These parameters were restored after treatment withdrawal [115]. Intestinal levels of endocannabinoidome members were low [115], alongside an increase in pro-inflammatory proteins, such as TNF-α and iNOS, in the duodenum and jejunum, as well as low levels of brain derived-neurotrophic factor (BDNF) and high levels of TrkB receptor found in the hippocampus [115]. The hippocampus features as an important target in the brain-gut axis, since the CA3 pyramidal neuron firing rate is also decreased. Moreover, hypertrophic glial cells were found in the medial prefrontal cortex in this mouse model [115]. These substances might link intestinal microbiome changes to depressive disorders in humans [116].

Brand new evidence suggests the modulation of gut dysbiosis, even under gestation [117]. Mouse mothers submitted to this cocktail, only during gestation, could influence the microbiota of their offspring. Pups displayed a lower bacterial load and richness compared to controls, with *Enterococcus* being the dominant group. Noteworthy, *Enterococcus*

dominancy was depicted among early broad-spectrum antibiotic regimen animals and infants as well [118]. These mice infants could not resist viral infection, which may be linked to the CD8+ T cell dysfunction found in the same mouse model [117]. This T cell subset impairment was further investigated by the same authors. They verified that some signalling components, such as Erk2, were not expressed properly, which led to TCR activation dysfunction and low IFN-γ expression. Of particular note, the presence of LPS restored CD8+ T cell function [119].

3.5. Streptomycin, colistin and ampicillin

It is reported in NOD mice that almost complete microbiota depletion increases the incidence of T1D in male animals. This seems to occur due to γδ and CD4+ T cells being able to synthesise interleukin-17 (IL-17) in the ileum and caecum [35].

3.6. Ampicillin, vancomycin and neomycin

This treatment was administered to mice in order to assess the relationship between the gut microbiome and tumours. Fourteen days after medicinal treatment, animals were challenged with B16F10 cells to induce tumours. It was found that the tumour growth and weight were higher among treated mice compared to controls. This is probably justified by the decreased infiltration of dendritic cells and macrophages inside the tumour and lower levels of Th1 cells systemically. It is important to highlight that it was not observed when animals received antibiotics after the injection of tumour cells. Then, animals treated a priori with pharmaceuticals were injected with lipopolysaccharide (LPS), a Gram-negative bacterium surface membrane component. This restored the immunological balance to combat tumours, showing that a decrease in *Proteobacteria* and *Bacteroidetes* due to antibiotic exposure made mice unable to fight against neoplasms [120].

3.7. Colistin, gentamicin, kanamycin, metronidazole, vancomycin and clindamycin

The link between autophagy and GIT dysbiosis has been assessed. Throughout antibiotic administration, there was an increase in *Desulfovibrio* spp. and *Bacteroidetes*, and a decrease in *Firmicutes* counts. Also, higher levels of autophagy genes as well as antimicrobial peptides were found in the distal small bowel. This reveals how autophagy may be linked to the gut microbiota [121].

3.8. Amoxicillin, phosphomycin and metronidazole

In order to ascertain the outcomes of ulcerative colitis treatment, a clinical trial was designed. Two different treatment groups were compared, one which received only the amoxicillin, phosphomycin and metronidazole therapy and another one pre-treated with this cocktail before receiving a faecal transplant. The combination of pharmaceuticals and faecal transplant showed the better results, because it altered *Bacteroidetes* and *Firmicutes* lesser than only antibiotic therapy [122].

3.9. Ampicillin, bacitracin, meropenem, neomycin and vancomycin

The crosstalk between the central nervous system and gut dysbiosis gets tighter over time. Mice submitted to this antibiotic cocktail presented, along with a significant disruption in commensal gut taxonomic groups, lower levels of SCFA, higher concentrations of corticosterone and phosphatidyl derivatives and no interleukin differences compared to controls. Moreover, novel memory acquisition was disrupted in antibiotic-treated mice. Within the four brain regions studied (amygdala, hippocampus, hypothalamus and medial prefrontal cortex), lower tight junction proteins and BDNF levels were found in the hippocampus, whereas some tight junction proteins had higher expression in the amygdala. Also, low levels of BDNF were found in the hypothalamus and medial prefrontal cortex. Thus, mice given this cocktail treatment displayed decreased bacterial load, altered microbiota diversity profile and cognitive impairment, concerning memory, was related to dysbiosis. It may be linked to altered cognitive-related protein expression in the hippocampus and amygdala [123]. This reinforces the fact that those changes in the gut microbiota lead to nervous system alterations [123].

3.10. Polymyxin and neomycin

In a renal injury mouse model, the authors administered these antibiotics to mice, which were receiving high salt concentrations through the water. Of note, after the almost complete depletion of the microbiota, antibiotic-treated mice showed the restoration of albumin serum levels, ileum IFN-γ, serum endotoxin levels and urine albumin/creatinine ratio, which means that renal function was restored. This highlights at least a partial role for high-salt induced dysbiosis in renal dysfunction [124].

3.11. Streptomycin, gentamicin, ciprofloxacin and bacitracin

To assess the influence of gut dysbiosis over spinal cord injury, mice were treated with a previously mentioned antibiotic cocktail. When submitted to this regimen before spinal injury, gut dysbiosis was linked to greater injury as well as to increased innate and adaptive immune responses, although the blood brain barrier permeability was not changed. Motion recovery was also delayed [125].

3.12. Clindamycin and Cefoperazone

In mice submitted to these antibiotics, papain was inhaled to induce allergic-like inflammation. Gut dysbiosis seems to influence lung inflammation, since it enhanced anatomical regional inflammation inside the lung, along with the increased expression of Th2 cytokines. Finally, it was observed that M2 macrophages were, in part, responsible for the lung immunological response [126].

3.13. Ampicillin and gentamicin

These antibiotics were used to treat diarrhoea associated with starvation, and its effects on the GIT were assessed. There was a decrease in *Prevotella*, *Blautia*, *Ruminococcus*, *Bifidobacterium*, *Megamonas* and *Faecalibacterium* and an increase in the *Enterobacteriaceae* family after cocktail exposure, along with the growth of antibiotic-resistant bacteria [127].

3.14. Ampicillin, vancomycin, ciprofloxacin, imipenem and metronidazole

In a neurogenesis model, the researchers have assessed this cocktail-induced dysbiosis over hippocampal neurogenesis. It was found that dysbiosis down-regulated neurogenesis, apparently, by the lack of a specific monocyte subset in antibiotic-treated mice [128].

3.15. Streptomycin, bacitracin, gentamicin and ciprofloxacin

Nod 2 knockout and wild type mice exposed to this cocktail got caused impaired tumourigenesis. It is suggested that some gut commensal bacteria diminish inflammation, like that enhanced by IL-6 [129].

All of these antibiotic cocktail-induced dysbiosis effects on the murine gastrointestinal tract and their systemic repercussions are listed in Table 2.

Table 2
Antibiotic cocktail-induced dysbiosis effects on the murine gastrointestinal tract and their systemic repercussions.

Antibiotic cocktail	Outcomes over organism	References
Vancomycin, neomycin, ampicillin and metronidazole	Influence on liver metabolism Altered T lymphocyte subsets Protection against colitis TLR2 up-regulation and dysmotility Higher SERT expression Promotion of constipation Increased on colonocytes transcytosis	[34,110,111,11,113]
Metronidazole, neomycin and polymyxin	↑T CD8+ lymphocytes in mesenteric lymph nodes ↓T cells in Peyer's patches	[114]
Bacitracin, neomycin and amphotericin B	Altered cannabinoid receptors expression Increased visceral pain threshold Dysmotility	[47]
Ampicillin, streptomycin, clindamycin	Depression-like behaviour ↑Pro-inflammatory cytokines in gut ↓BDNF levels in hippocampus	[115]
	T CD8+ dysfunction and impaired antiviral response	[117,119]
Streptomycin, colistin and ampicillin	↑IL-17 synthesis in colon ↑T1D susceptibility	[35]
Ampicillin, vancomycin and neomycin	↑Tumour growth	[120]
Colistin, gentamicin, kanamycin, metronidazole, vancomycin and clindamycin	↑Autophagy genes expression	[121]
Amoxicillin, phosphomycin and metronidazole	Ulcerative colitis treatment	[122]
Ampicillin, bacitracin, meropenem, neomycin and vancomycin	↓SCFA ↑Corticosterone levels ↓BDNF and tight junction proteins levels in hippocampus ↓Gut bacterial diversity Cognitive impairment	[123]
Polymyxin and neomycin	Restored renal function	[124]
Streptomycin, gentamicin, ciprofloxacin and bacitracin	Greater spinal cord injury Delayed motion recovery	[125]
Clindamycin and Cefoperazone	Influence on lung inflammation	[126]
Ampicillin and gentamicin	↑*Enterobacteriaceae* ↑Antibiotic resistant bacteria growth	[127]
Ampicillin, vancomycin, ciprofloxacin, imipenem and metronidazole	↓Neurogenesis	[128]
Streptomycin, bacitracin, gentamicin and ciprofloxacin	Impaired colonic tumourigenesis	[129]

4. Antibiotic-associated diseases with dysbiosis

4.1. *Clostridium difficile* infection (CDI)

CDI is a form of post-treatment antibiotic-associated colitis [2,130]. This antibiotic regimen is responsible for the decrease in anaerobic, *Bifidobacterium*, *Clostridium* and *Bacteroides* bacteria [131]. Its pathophysiological mechanism comprises the overgrowth of pathobiont species after gut dysbiosis due to bacteriotherapy for other diseases [37] and the secretion of *Clostridiales* toxins TcdA and TcdB [42]. Moreover, being 65-years old or more has been found to be a risk factor for developing this disease [132].

According to a recent meta-analysis, clindamycin features as the main antibiotic risk factor for acquiring CDI, followed by quinolones and cephalosporins [133], which is corroborated by other studies [134].

4.2. *Helicobacter pylori* treatment with metronidazole, amoxicillin and clarithromycin

There is evidence highlighting a minor inflammatory response, prior to *H. pylori* challenge, due to antibiotic-induced gastric microbiota dysbiosis [135].

Moreover, researchers have assessed patients whose *H. pylori* were eradicated one year after their treatment. It was observed that this bacteria vacancy improved bradykinesia in Parkinson's disease patients. This could have occurred through a lack of bacterial neurotoxins or due to improvements in PD drug absorption [136].

4.3. Tuberculosis treatment

A study conducted in Haitians demonstrated that antibiotics used in tuberculosis treatment, i.e. isoniazid, rifampin, pyrazinamide and ethambutol, induced gut dysbiosis, especially of the *genus* microbiota taxa, despite not altering the overall microbiota composition. The authors claimed that this was due to the narrower target spectrum of these pharmaceuticals [137].

5. Conclusion

This study shows how unique the crosstalk between microbiota and the human GIT is, especially by means of T cell subsets, pro- and anti-inflammatory cytokines and SCFA within itself and with other systems. It communicates with the entire organism, making its microbiome useful for further investigations. Furthermore, it is important to highlight that antibiotic misuse can induce not only dysbiosis but also the antibiotic resistance threat which leads to the search for another class of antibacterial drugs causing serious risk to human health. Here, the importance of translational studies in a murine model focusing on GIT homeostasis with bacterial groups was reviewed since any changes to the GIT-microbiota have systemic repercussions on human health or disease.

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