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Role of Microbiome and Antibiotics in Autoimmune Diseases

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Abstract

The global rise in the incidence of autoimmune diseases has paralleled the widespread use of antibiotics. Recently, the gut microbiome has been shown to be key in the development and maturation of a normal immune system, and a range of microbial disturbances have been associated with the development and activity of several autoimmune diseases. Here, we aim to provide an overview of the mechanistic crosstalk between the human microbiome, the immune system, and antibiotics. The disease-associated microbial gut dysbiosis, the potential role of antibiotics in the development and treatment of autoimmune diseases, and the manipulation of the gut microbiome with prebiotics and probiotics is discussed using 2 key autoimmune diseases as an example: inflammatory bowel disease and type 1 diabetes. Although some data suggest that widespread use of antibiotics may facilitate autoimmunity through gut dysbiosis, there are also data to suggest antibiotics may hold the potential to improve disease activity. Currently, the effect of fecal microbiota transplantation on several autoimmune diseases is being studied in clinical trials, and several preclinical studies are revealing promising results with probiotic and prebiotic therapies. (*Nutr Clin Pract.* 2020;00:1–11)

Keywords

antibacterial agents; antibiotics; autoimmune diseases; dysbiosis; gastrointestinal microbiome; microbiota; prebiotics; probiotics

Introduction

The human microbiome consists of bacteria, fungi, yeasts, viruses, and phages plus their genetic material. Each strain of bacteria has its own genome made up of thousands of genes, so that an individual's bacterial genome pool outnumbers the human genome by a factor of 100.[1] The gut microbiome comprises the largest microbial compartment in the human body, but the skin, mouth, vagina, and lungs also have a specific microbiome. Although there is clear microbial clustering within families and by geographic location, each individual possesses a unique microbiome that can change over time.[1]

The notion that the microbiome is involved in certain disease states dates back hundreds of years, for instance, with reports on "yellow soup" to treat cases of severe food poisoning and diarrhea in ancient China.[2] With the arrival of next-generation sequencing tools, knowledge regarding the human microbiome has expanded immensely in the last decade,[3] and an increasing number of illnesses are associated with shifts in the microbiome and its metabolome.[1]

An interesting observation is that the rising incidence of autoimmune diseases, such as inflammatory bowel diseases (IBDs), type 1 diabetes (T1D), multiple sclerosis (MS), and systemic lupus erythematosus has paralleled the widespread use of antibiotics.[4] Although necessary to treat and contain infectious diseases, antibiotics may have caused collateral damage to the commensal microorganisms by depleting the abundance of the natural flora and causing long-lasting changes in the diversity and function of microbiota, thus leaving the host more vulnerable to other disease states.[5]

Here, we aim to provide an overview of the mechanistic crosstalk between the human microbiome, the immune system, antibiotic usage, and microbiome-related therapeutic strategies for key autoimmune diseases. As the list of autoimmune disease contains >100 diseases,[6] it is impossible to review them all in a single manuscript. Therefore, this

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Table 1. Twenty Most Prevalent Autoimmune Diseases in the United States.

Disease	US prevalence	US population
Inflammatory bowel disease	1.3%	3,100,000
Rheumatoid arthritis	0.81%	2,580,000
Hashimoto's autoimmune thyroiditis	0.74%	2,375,100
Celiac disease	0.70%	2,250,000
Grave's disease	0.59%	1,887,000
Diabetes mellitus, type 1	0.45%	1,440,000
Vitiligo	0.38%	1,200,600
Rheumatic fever	0.23%	750,000
Pernicious anemia/atrophic gastritis	0.14%	452,700
Alopecia areata	0.14%	450,000
Immune thrombocytopenic purpura	0.07%	216,000
Multiple sclerosis	0.06%	174,900
Systematic lupus erythematosus	0.03%	96,000
Temporal arteritis	0.03%	90,000
Scleroderma	0.02%	72,000
Antiphospholipid syndrome	0.02%	64,500
Autoimmune hepatitis type 1	0.02%	48,300
Primary biliary cirrhosis	0.01%	43,800
Sjogren's syndrome	0.01%	43,200

Adapted from References 107-109.

review provides insight into the mechanism of action and an update of key data most relevant to autoimmune diseases. Table 1 lists the 20 most prevalent autoimmune diseases in the United States.

Interaction Between the Gut Microbiome and the Immune System

The human gastrointestinal tract harbors an enormous number of microbes that include up to 10^{14} microbes per gram of feces in the distal gut.[3] Emerging data suggest colonization begins in utero,[7] but the majority of early colonization occurs during the birthing process and infant feeding.[8]

Through coevolution, a mutualistic relationship developed between the human host and his or her microbial residents, in which the host provides a living environment and nutrients to the gut microbiota in exchange for microbial support in nutrient metabolism, regulation of immunity, and protection from pathogenic microorganisms.[9] Interfacing with the external environment, the gastrointestinal tract is at high immune challenge. During daily exposure to a nonsterile food and water supply, ingested pathogens, and their by-products, the intestine is protected against these antigens by a layer of mucus and commensal microbes, an epithelial barrier, and gut-associated lymphoid tissue (GALT) within the lamina propria. Goblet cells secrete mucus and Paneth cells secrete defensins in response to bacterial exposure.[10] An adaptive immune response can be orchestrated in the GALT, where immune cells (including T lymphocytes, B cells, and eosinophils) are concentrated. Moreover, specific subpopulations of T cells have their specialized functions. As such, T helper (Th1) cells lead to increased cell-mediated responses against intracellular bacteria and protozoa, whereas Th2 cells lead to humoral immune responses, such as extracellular parasites (eg, helminths). Furthermore, regulatory T cells (Treg) dampen proliferation of effector T cells to avoid autoimmunity, whereas Th1 17 (Th17) cells are a proinflammatory subset of Th1 cells that inhibit Treg differentiation and induce pathogen clearance at mucosal surfaces. Loss of Th17 cell populations at mucosal surfaces has been linked to chronic inflammation and microbial translocation[11] (Figure 1).

It is, therefore, unsurprising that the gut microbiome and metabolome play a critical role in the development of the immune system. Gut microbiota have been shown to be required for normal immune system maturation.[12] Indeed, development of GALT is reduced drastically in germ-free (GF) mice, with decreased numbers of T cells, B cells, and antimicrobial peptides, as well as a thinner mucus layer and reduced Peyer's patches.[13] Whereas this results in decreased production of immunoglobulin A (IgA), IgE production is increased by a relative Th2 abundance in GF mice.[14] As a consequence, GF mice develop less immunotolerance to autoantigens[15] and severe allergic responses to food antigens.[16] Interestingly, exacerbated allergic responses to foods can be prevented by colonization with selected bacterial species, suggesting a causal relationship with the gut microbiota.[16] Furthermore, the spleen and lymph nodes are abnormally developed in GF mice, with decreased numbers of B and T cells in the germinal centers and parafollicular region, respectively.[17] In humans, colonization of the gut, skin, and lungs during vaginal delivery triggers and forms the newborn's immune responses with regard to Th2 to Th1 and drives Treg development. Although Th1 responses protect against many infections, they can promote autoimmunity when dysregulated. On the other hand, weak Th1-mediated immunity results in Th2 polarization, which is observed in children who develop allergic diseases later in life.[18]

Intestinal immune responses are regulated by several bacterial species, including segmented filamentous bacteria, *Bacteroides fragilis*, Clostridia, *Lactobacillus*, and *Bifidobacterium*. Gram-positive bacteria play a crucial role in the generation of proinflammatory Th17 lymphocytes, *Clostridium* cluster IV and XIVa,[19] and *Bacteroides* Th1 and Th17 immune responses. *Lactobacillus* and *Bifidobacterium* also have anti-inflammatory capacities by inducing tolerogenic dendritic cells and Tregs, which suppress

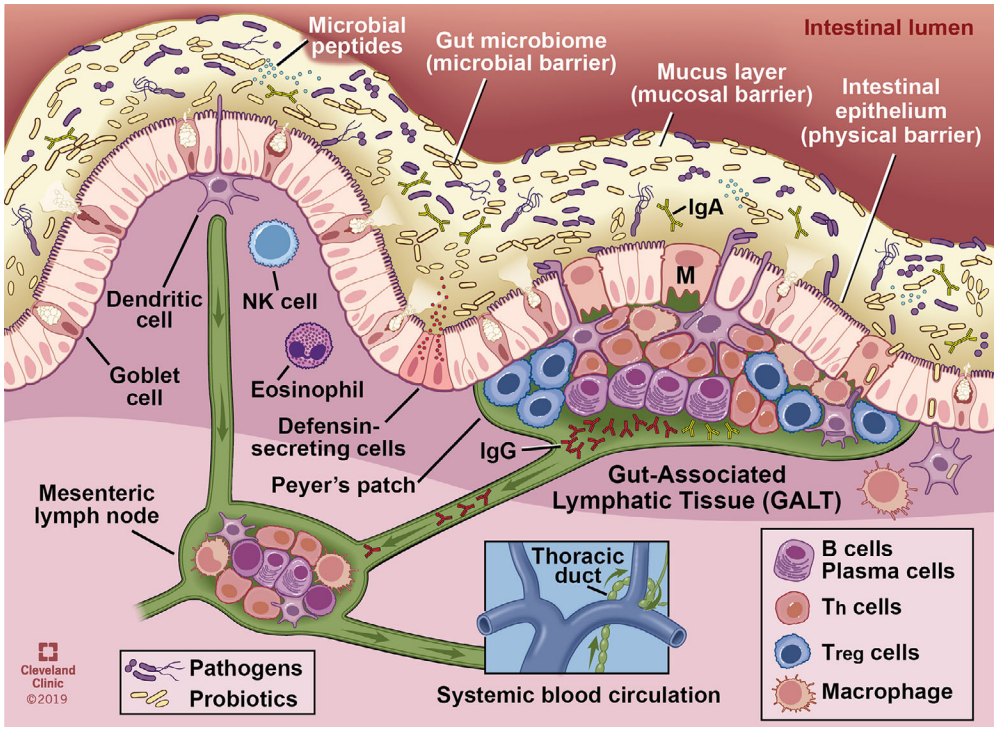

Figure 1. Interaction between the gut microbiome and the gut-associated lymphoid tissue. Commensal microflora and probiotics (light shades) form a microbial barrier where microbial pathogens (dark shades) have to compete for nutrients and adhesion to the epithelial surface. A mucosal barrier formed by mucin secreted by goblet cells and defensins secreted by Paneth cells protects the epithelial barrier. Dendritic cells endocytose bacterial products either via extending into the enteric lumen throughout epithelial tight junctions, via bacterial transit through microfold M cells, or via pinocytosis of probiotics/microflora by epithelial cells. Macrophages and natural killer (NK) cells patrol the submucosa as part of the innate immune system. Adaptive immune responses are triggered by dendritic cells, macrophages, and epithelial cells, which process and present pathogenic peptides to the aggregations of B and T lymphocytes, referred to as Peyer's patch. Here, proinflammatory responses from cytotoxic T-cells T helper (Th)-1 and immunoglobulin A (IgA) secretion are balanced by regulatory T (Treg) and Th2 cells. If pathogens surpass the gut-associated lymphoid tissue, whether by pathogenic virulence or aberrant immune response through genetic predisposition, systemic inflammation or autoimmunity can develop. Illustration by Dave Schumick, BS, CMI. Reprinted with the permission of the Cleveland Clinic Center for Medical Art & Photography © 2020. All Rights Reserved.

undesired immune responses in the periphery. It is intriguing to note that patients with autoimmune diseases have a distinct microbiota profile, characterized by decreased numbers of *Bacteroides*, *Clostridia* clusters IV and XIVa in relapsing-reemitting MS, or decreased Bifidobacteriales in the early stages of rheumatoid arthritis.[37]

However, it is important to realize that microbial effects are caused not only by the microbiota themselves but also by microbial by-products and metabolites. Short-chain fatty acids (SCFAs) such as acetate, propionate, and butyrate are produced during bacterial fermentation of indigestible polysaccharides and are widely recognized as modulators of immune response in the periphery.[20]

Although the direct cause of most autoimmune diseases is not known, most diseases have been shown to arise following an environmental exposure in a genetically susceptible person. The notions that environmental antigens are presented within the gastrointestinal tract and that increased intestinal permeability precedes most autoimmune diseases place the gut microbiome in the center of the hypothesis that a permeable gut epithelial barrier is involved in the inadvertent antigen delivery to the GALT, or that a miscommunication occurs between the host immune system and the antigen, triggering the multiorgan process leading to the autoimmune responses.[21]

Recently, spontaneous translocation of a gut pathobiont, *Enterococcus gallinarum*, to the liver and other systemic tissues was shown to trigger autoimmune responses in a mouse model with a genetic background that predisposes to lupus kidney disease.[22] Antibiotic treatment suppressed growth of *E gallinarum* in tissues and eliminated pathogenic autoantibodies and T cells, preventing mortality from thrombosis in this model. Also, an intramuscular vaccine targeting the pathobiont *E gallinarum*–specific DNA prevented

development of autoantibodies and mortality.[22] These discoveries show that a gut pathobiont can translocate and promote autoimmunity in genetically predisposed hosts.

Antibiotics and the Gut Microbiome

In the early 20th century, arsphenamine was found to be an effective treatment for syphilis, which is caused by the Gram-negative bacterium *Treponema pallidum*. However, it was only when Alexander Fleming accidently discovered penicillin in 1928[23] and Selman Waksman introduced the term antibiotic[24] that the antibacterial approach became public.

Since then, the use of antibiotics has increased steadily. In 2010 alone, 70 billion single doses of antibiotics have been prescribed worldwide.[25] Repeated antibiotic treatment can exert long-term effects on microbial communities long after the medication is removed. One case series describes how the antibiotic ciprofloxacin induced a loss of diversity and a shift in gut microbial community within 3–4 days of antibiotic administration and that the resolution was incomplete after 10 months.[26]

Antibiotic delivery at early stages of life affects gut microbiota development during the critical first weeks of life.[27-29] As such, intrapartum antimicrobial prophylaxis (IAP) with ampicillin into group B *Streptococcus*–positive women has been effective in reducing sepsis-associated deaths.[28] However, the consequences to the newborn have only recently been described. Compared with control infant deliveries, fecal samples from newborns delivered vaginally to mothers receiving IAP showed a poor microbial biodiversity, with a high predominance of Enterobacteriaceae and low level of *Bifidobacterium* members.[28] These changes are in agreement with the antibiotic spectrum of ampicillin. Interestingly, overgrowth of the Gram-negative bacterial family also includes potentially pathogenic bacteria such as *Salmonella* sp, *Shigella* sp, *Enterobacter* sp, *Klebsiella* sp, and *Escherichia coli*. The reduced microbial biodiversity due to IAP could increase newborn vulnerability to health problems such as atopic disorders and gastrointestinal diseases.

Compounding the impact of antibiotics on microbiome shifts is that many preexisting medical conditions are associated with gut dysbiosis, characterized as less diverse (eg, obesity, IBD, diabetes), which could reinforce the negative effects of antibiotic treatment.[30]

Restoration of the microbiota can take months or even years and may be incomplete, as shown by Jernberg et al, who noted that the effects of a 7-day clindamycin treatment on the human intestinal microbiota persisted up to 2 years post exposure.[31] Similarly, after 5 days of treatment with ciprofloxacin, 4 weeks were required for the gut microbiota to recover, and some bacteria failed to restore up to 6 months later.[32]

Microbial Disruptions in Key Autoimmune Diseases

Changes is microbial composition in key autoimmune diseases are presented in Table 2.

Inflammatory Bowel Disease

IBD, of which Crohn's disease (CD) and ulcerative disease (UC) are the 2 major subtypes, results in part from an inappropriate immune response to gut microbes in a genetically susceptible host. UC is a continuous inflammation of mucosa and submucosa of the (distal) colon, whereas CD is characterized by patchy lesions of transmural inflammation throughout the terminal ileum and colon. Disease etiology remains largely unknown, but it is accepted that it affects mainly Caucasians[33] and that CD is a Th1/Th17 T cell–driven process, whereas UC is a Th2-like T cell–driven process.[34]

The gut microbiome has been shown to be an essential factor of intestinal inflammation in IBD.[35] Patients with IBD have a decreased bacterial α diversity and species richness, with a reduced total number of species in a community compared with that of healthy people,[36] or monozygotic twins discordant for CD.[37] The dysbiosis in patients with IBD is characterized by decreases in Bacteroidetes and Firmicutes, including Lachnospiraceae, and increases in Proteobacteria and Bacilli.[38] Even during clinical remission, the biodiversity of the fecal microbiota in UC patients is low, and the temporal instability is high compared with that of healthy controls.[39] Recently, Lloyd-Price and colleagues reported on the intensive 1-year follow-up of 132 patients with IBD as part of the Human Microbiome Project.[40] They demonstrated characteristic taxonomic perturbations in the enrichment of facultative anaerobes (eg, *E coli*) and losses in obligate anaerobes, including *Faecalibacterium prausnitzii* and *Roseburia hominis*. Furthermore, periods of disease activity were also marked by disruptions in microbial transcription (eg, among *Clostridia*), metabolite pools (eg, acylcarnitines, bile acids, and SCFAs), and levels of antibodies in the host's serum.[40]

Some bacterial species have emerged with specific beneficial effect with regard to IBD development. For instance, *Lactobacillus*, *Bifidobacterium*, and *Faecalibacterium* have been shown to protect the host from mucosal inflammation by induction of the anti-inflammatory cytokine interleukin (IL)-10.[41] One such anti-inflammatory commensal strain, *F prausnitzii*, was underrepresented in IBD patients,[42] particularly in postoperative CD patients with disease relapse.[41] In contrast, restoration of *F prausnitzii* after disease recurrence was associated with maintenance of clinical remission of UC.[43]

Another intriguing observation is that *Helicobacter pylori* infection seems to have a beneficial immunomodulatory

Table 2. Changes in Gut Microbiome Compared With Healthy Controls.

Bacteria	Function	IBD	T1D
Akkermansia	Anti-inflammatory		↓
Bacillus		↑	↑
Bacteroides	Bacterial translocation, activate CD4+ T cells	↓	↑
Bifidobacterium spp	SFCA production	↓	↓
Clostridium groups IV and XIVA	Generation Th17 cells	↓	
Clostridium perfringens	Intestinal integrity	↓	↑
F prausnitzii	SFCA production, anti-inflammatory effects	↓	↓
Lachnospiraceae		↓	
Lactobacillus			↓
Prevotella			↓
Proteobacteria		↑	
Ruminococcus		↑	↑
Roseburia spp	SCFA production	↓	↓
Suterella spp		↓	

↑, increased; ↓, reduced; IBD, inflammatory bowel disease; T1D, type 1 diabetes; SCFA, short-chain fatty acid.

effect in IBD, as it is negatively associated with IBD regardless of ethnicity, age, and use of aminosalicylates and corticosteroids.[44,45] Moreover, this effect is especially noted for the virulent cagA-positive *H pylori* strain that is known for increased risk for gastric carcinoma and esophageal adenocarcinoma and that seems to have a protective effect on IBD.[46]

The essential and potential causal relationship between the microbiome and IBD has been explored and confirmed in several rodent models of genetic or chemically induced colitis. It has been shown that commensal microbes protect the host via colonization resistance[47] and that commensals also have functional effects on pathogens, such as dampening virulence-related gene expression[48] or modulating the host's mucosal immune response. *Clostridium* and *Bacteroides* species have been shown to induce the expansion of Tregs cells and to mitigate intestinal inflammation.[19]

The gut microbiota also influence intestinal homeostasis by fermenting dietary complex polysaccharides to yield SCFAs, including acetate, propionate, and butyrate. SCFAs are the primary energy source for colonic epithelial cells[49] and can induce the expansion of colonic Treg cells.[19] Not only is a lack of dietary fiber consumption associated with the development of IBD,[50] but numbers of several SCFA-producing bacteria, including *Faecalibacterium*, *Phascolarctobacterium*, and *Roseburia*, are also reduced in CD patients.[51]

Finally, inflamed colonic biopsy samples from UC patients fueled the "leaky gut" hypothesis in IBD nearly 20 years ago.[52] Recently, Chang et al associated impaired intestinal permeability with ongoing bowel symptoms in patients with mucosal healing, suggesting that only resolution of mucosal permeability beyond mucosal healing might improve outcomes in patients with IBD.[53] There is research investigating the role of diet and other microbes (virus, fungi, helminths) and IBD; this discussion is beyond the scope of this paper, but a review can be found by Zuo et al.[54]

Given these microbial signatures and the disruptive potential that broad-spectrum antibiotics might have during the maturation process of the microbiome and the immune system in early life, researchers have tried to assess whether antibiotic exposure could be causally related to IBD development. Indeed, in a retrospective cohort study from 464 United Kingdom ambulatory medical practices following more than a million children for at least 2 years during 1994 to 2009, antibiotic prescriptions throughout childhood were associated with IBD development.[55] This relationship decreased with increasing age at time of exposure, but each antibiotic course increased the IBD hazard by 6%.[55] In search of a potential underlying mechanism, Scheer et al examined the effects of antibiotic treatment during gestation and in early life on the development of IBD in adult mice. They found a faster onset of IBD with T cells from adult mice that had been exposed to an antibiotic cocktail during gestation and in early life.[56] Furthermore, gentamicin has been shown to activate cytotoxic T cells by expression and major histocompatibility complex class I presentation, substantiating the possibility of an autoimmune response to cryptic epitopes by aminoglycoside use.[57]

Type 1 Diabetes

T1D is the most prevalent autoimmune disease in children and adolescents and one of the few autoimmune diseases that does not have a higher prevalence in females. It is characterized by a T cell–mediated destruction of pancreatic β cells. The incidence of T1D varies because of genetic and environmental factors.[58]

As with IBD, T1D patients harbor specific changes in the composition and diversity of their gut microbiome. Genetically predisposed infants from 3 to 36 months old have reduced α diversity and an overabundance of *Blautia*, Rikenellaceae, *Ruminococcus*, and *Streptococcus* genera.[59] Children with T1D have an overrepresentation of the *Bacteroidaceae* family together with a decrease of intestinal microbiota dominant species *Bifidobacterium adolescentis* and *Bifidobacterium pseudocatenulatum*.[60] Similarly, biobreeding diabetes-prone rats, a widely used animal model for studying human T1D, demonstrate more beneficial bacteria, such as *Bacterioides*, *Eubacterium*, and *Ruminococcus* in their stool samples.[61]

In the Environmental Determinants of Diabetes in the Young (TEDDY) study, the use of β-lactam or macrolide antibiotics early in life and before seroconversion was not associated with an increased risk of autoimmunity in children at genetic risk for T1D or celiac disease.[62] Similarly, in the framework of the Norwegian Mother and Child Cohort Study, looking at 541,036 children of whom 836 were diagnosed with T1D, antibiotic or acetaminophen use during pregnancy or in early childhood was not associated with risk of T1D.[63] In male nonobese diabetic (NOD) mice, a single early-life antibiotic course accelerated T1D development.[64]

As in IBD, there is also evidence supporting a relationship between T1D and intestinal permeability, based on studies by transmission electron microscopy, evaluation of lactulose and mannitol urinary excretion,[65] and increased blood zonulin, a protein that modulates intestinal permeability.[66] In a NOD mouse model of T1D, oral gavage with wild-type *Citrobacter rodentium* at a young and prediabetic age resulted in higher intestinal permeability and induced earlier inflammatory destruction of the islets of Langerhans.[67] Importantly, the mutant strain of *C rodentium* that lacks the ability to disrupt the intestinal barrier was unable to induce inflammatory harm to those islets.[67]

These studies suggest the possibility of a direct mechanistic link between antibiotic use and development of autoimmunity and warrant further attention to a potential causal relationship. However, most of the aforementioned studies are associations in observational and relative short-term studies. It is important to note that many alterations in the human environment have occurred concurrently, such as reduced infectious diseases and improved diagnostics, which are very difficult to disentangle when looking for the causal factor. Moreover, studying the impact of early-life antibiotic exposure on the incidence of autoimmune diseases (mostly in adulthood) is challenging because of the limitations of interpreting animal studies, the extension in time with human studies, and the fact that many patients might have altered microbiota composition by the disease itself.

Microbial Intervention in Key Autoimmune Diseases

Antibiotics

Although antibiotics can have a negative impact on gut microbiota, evidence suggests that antibiotics can be helpful in treating autoimmune diseases. Rosman et al have reviewed the usefulness of antibiotic therapy in autoimmune disorders through their anti-inflammatory and immunomodulatory properties.[68] Known effects of antibiotic, prebiotic, probiotic and fecal microbiota transfer interventions in key autoimmune diseases are summarized in Table 3.

Antibiotics have been used for the treatment of autoimmune diseases based on the knowledge that infections play a role in the development and progression of these diseases. First, infections can result in the cross-activation of autoreactive T or B cells by a common epitope, termed "molecular mimicry."[69] Second, infections may trigger an autoimmune reaction including "epi-tope spreading," in which an epitope is switched from a dominant to a cryptic position resulting in the creation of autoantibodies against the new epitope. Finally, infection-related tissue damage can result in the release of new antigens, which activate lymphocytes and induce an autoinflammatory microenvironment, leading to the destruction of neighboring, uninfected cells in a process known as "bystander activation."[69] In that sense, antibiotics used to curtail infections can be seen as a prevention or limitation of the autoimmune cascade.

A major role for antibiotic therapy in relation to autoimmune disease has been attributed to penicillin in the treatment of rheumatic fever, a systemic disease affecting the heart, joints, central nervous system, and skin following streptococcal infection. The antibodies that the host's immune system generates against group A β-hemolytic *Streptococcus* are also active against host targets, including the heart and joints. Antibiotic treatment with penicillin is known to prevent the autoimmune reaction when given during the acute infection or may prevent the continued deterioration when given for a longer period of time, even after elimination of the infection.[70]

Molecular mimicry has also been postulated to be responsible at least in part for the association between *H pylori* infection and autoimmune thrombocytopenic purpura,[71] next to nonspecific immune activation and modulation of macrophage function.[72] *H pylori* eradication should now be offered to all patients with autoimmune thrombocytopenic purpura.[73] Similarly, treatment with co-trimoxazole reduces the incidence of relapses in patients with Wegener's granulomatosis in remission, through an unknown mechanism.[74]

Furthermore, some antibiotics are also utilized for their specific anti-inflammatory and immunomodulatory

Table 3. Summary of Known Effects of Antibiotic, Prebiotic, Probiotic, and FMT Interventions in Key Autoimmune Diseases.

	IBD	T1D	RA	MS
Exposure to antibiotics	Early-life exposure associated with development of disease	Early-life exposure not associated with development of disease	?	Increased risk of disease development
Antibiotic therapy				
β-lactam	Reduced disease activity (in mice)	?	?	Reduced disease activity
Glycopeptide	Reduced disease activity in CD (not UC)	?	?	Reduced disease activity
Fluoro-quinolone	Reduced disease activity in CD (not UC)	?	Reduced disease activity	?
Macrolide	?	?	Reduced disease activity	Reduced disease activity
Nitroimidazole	?	?	?	Reduced disease activity
Rifamixin	Reduced disease activity in CD (not UC)	?	?	?
Tetracyclin	?	?	Reduced disease activity	Protective
Prebiotics/probiotics therapy				
VSL#3	Reduced disease activity	Reduced incidence (mice)	?	Reduced incidence (mice)
Tungstate	Reduced disease activity	?	?	?
Lactobacilli		Reduced incidence (mice)	Reduced disease activity	Reduced disease activity
FMT	Reduced disease activity in CD, less UC	Trial ongoing	Trial ongoing	Trial ongoing

?, Unknown; CD, Crohn's disease; FMT, fecal microbiota transplantation; IBD, inflammatory bowel disease; MS, multiple sclerosis; RA, rheumatoid arthritis; T1D, type 1 diabetes; UC, ulcerative colitis.

properties. For instance, tetracyclines were shown to inhibit the activity of antiphospholipase A2, scavenge free radicals, and inhibit various matrix metalloproteinases,[75] as well as impair lymphocyte activity.[76] Also, macrolide antibiotics are reported to decrease the number of neutrophils and the concentrations of IL-8, IL-6, IL-1β, tumor necrosis factor α, eosinophilic cationic protein, and matrix metalloproteinase 9 (reviewed in Zimmermann et al[77]).

Clinical studies indicate a beneficial effect of antibiotics in CD. As such, metronidazole combined with ciprofloxacin,[78] ciprofloxacin alone,[79] and rifaximin[80] all have been shown to be effective alternatives to anti-inflammatory therapies in patients with CD. Studies in mouse models of dextran sulfate sodium–induced colitis[81] and spontaneous colitis in IL-10−/− mice[82] showed that vancomycin can reduce the severity of colitis and even prevent development of colitis when antibiotics were given prior to disease induction.[81]

In contrast to CD patients and the murine studies, no benefits of antibiotic therapy have been found in UC. The addition of vancomycin,[83] ciprofloxacin,[84] and rifaximin[85] to standard therapy did not improve disease severity in UC patients compared with standard therapy in the control groups.

To our knowledge, no studies have examined a potential beneficial effect of currently available antibiotics on T1D.

Prebiotics and Probiotics

A probiotic is a live organism that provides a benefit to the host when provided in adequate quantities, whereas a prebiotic is a food compound that induces the growth or activity of beneficial gut microorganisms.[86]

Probiotics have been considered as adjuvant therapy for autoimmune diseases, with the notion that they support homeostasis of the gut microbiota and immune system.

Potential mechanisms supporting this include increased mucus secretion, antimicrobial peptide production, enhancement of the gastrointestinal–epithelial barrier function, and support of gut microbiota–mucosal immune cell crosstalk, which includes optimal orchestration of the host immune system in response to pathobionts (reviewed in detail by Liu et al[87]). Indeed, induction of immunotolerance by treatment with antigens, bacteria, or engineered immune cells could reprogram the immune system and have the potential to cure a range of autoimmune disorders.

Despite the high number of gut microbiome studies and the evidence for the gut microbiome's involvement in IBD pathogenesis, the data supporting the use of probiotics for the treatment of IBD remain limited. The probiotic preparation of 8 live freeze-dried bacterial species, including *Lactobacillus casei*, *Lactobacillus delbrueckii* subsp *bulgaricus*, *Lactobacillus acidophilus*, *Lactobacillus plantarum*, *Bifidobacterium longum*, *Bifidobacterium infantis*, *Bifidobacterium breve*, and *Streptococcus salivarius* subsp *thermophiles* (VSL#3),[88] and the probiotic *E coli* Nissle were shown to reduce active inflammation and sustain remission[89] in UC pouchitis but not in CD. Because of the known protective effects of *F prausnitzii* on the intestine by producing barrier-enhancing and immunosuppressing SCFAs and stimulating Tregs, providing dietary prebiotic substrates, such as oligosaccharides and fiber, to selectively increase the abundance of SCFA-producing commensals is tantalizing; however, results to date in humans have not been satisfactory.[90] Another approach is to selectively block the virulence products of pathogenic microbes or their activity to diminish the IBD-associated dysbiotic gut bacteria. As such, blocking the protease activity of *E faecalis* or protease receptor binding has been shown to inhibit mucosal permeability.[91,92]

Recently, precision approaches have emerged to modulate specific microbial pathways. For instance, anti-flagellin antibodies or glycopolymer antagonists have been shown to reduce epithelial adherence, invasion, and translocation of pathogens.[93,94] Furthermore, the inorganic compound tungstate ameliorated colitis in mice.[95] Tungstate treatment prevented gut inflammation as well as the dysbiotic expansion of Enterobacteriaceae by selectively inhibiting molybdenum-cofactor–dependent microbial respiratory pathways and caused minimal changes in the microbiota composition under homeostatic conditions.[95]

Current interventions for arresting autoimmune diabetes have yet to strike the balance between sufficient efficacy, minimal side effects, and lack of generalized immunosuppression. In the TEDDY study—a prospective multicenter cohort study of probiotic supplementation for 7473 children with genetic risk for T1D in the USA, Finland, Germany, and Sweden—various mixtures of *Lactobacillus* and *Bifidobacterium* were administered to newborns. There was a decreased risk of islet autoimmunity when compared with the group that received probiotics after 27 days of life or no supplementation.[96] Takiishi et al have shown that development of T1D can be diverted in an autoantigen-specific manner in NOD mice, using oral administration of *Lactococcus lactis* genetically modified to secrete the whole proinsulin autoantigen along with the immunomodulatory cytokine IL-10.[97] The research group suggests that the biologically contained *L lactis* could be an appealing method for induction of antigen-specific tolerance.[98] However, currently the need for coadministration of immunosuppressive therapy during tolerance induction with potential serious side effects is the Achilles' heel of this approach.[99]

Further studies in NOD mice aimed at the immune mechanisms that mediate protective effects of SCFAs. NOD mice fed specialized diets with specific cellulose and starch variations, resulting in high bacterial release of the SCFAs acetate and butyrate, were almost completely protected from T1D.[100] The use of the probiotic mixture (VSL#3) has been successful in reducing the susceptibility to developing autoimmune diseases, such as T1D and colitis, by enhancing the production of IL-10 in Peyer's patches and the spleen.[101]

Fecal Microbial Transplantation

The shotgun approach of fecal microbial transplantation (FMT) has been shown to be highly effective in treatment of recurrent *Clostridium difficile* infections.[102] In a pooled analysis of 18 studies that included 122 patients with IBD, about 40% of patients achieved clinical remission of IBD after FMT.[103] Importantly, the clinical remission rate was 61% for CD but only 22% for UC.[103] Patients with IBD have been shown to harbor a significantly higher virome richness than healthy household controls,[104] which may partly account for the higher failure rate of FMT in treating IBD than in treating *C difficile*. These data highlight the importance of donor selection for FMT, and more insight is needed in the most beneficial or required profiles for each type of disease. In T1D-prone mice, the incidence of diabetes development could be dramatically reduced when they were cohoused with normal mice or received oral gavage with fecal samples from healthy mice.[105] In humans, FMT trials are ongoing for T1D (ClinicalTrials.gov NCT04124211), rheumatoid arthritis (ClinicalTrials.gov NCT03944096), and MS (ClinicalTrials.gov NCT03975413, NCT03183869). Improvement of neurological symptoms in MS was reported after FMT in a case report in which the indication for FMT in a MS patient was *C difficile* and in an abstract that described FMT in 3 patients with MS after FMT for constipation.[106]

Summary and Future Directions

In conclusion, the gut microbiome is extremely important in development and maturation of a normal immune system. A range of microbial disturbances have been associated with

the development and disease activity of several autoimmune diseases. Some signals suggest that widespread use of antibiotics is associated with dysbiosis and autoimmunity, but antibiotics also hold the potential for improving disease activity. Currently, the effects of fecal microbiota transplantation on several autoimmune diseases are being studied in clinical trials, and preclinical studies are revealing promising results with probiotic and prebiotic therapies.

Future research should be focused to identify specific microbial culprits in autoimmune diseases including bacteria, viruses, fungi, helminths, and their active metabolites. Emphasis should be on defining specific outcome measures and considerations for a "normal and healthy" microbiome, taking into account all complex confounding factors such as diet, lifestyle, and comorbidities. Conversely, clinicians will need to be cognizant of that fact that interventions in the microbiome might alter host metabolism, including drug metabolism.

As the knowledge and understanding of the human microbiome expands with improved technology into metatranscriptomics and metagenomics, we will gain understanding for causal effects of microbial driven pathology in the context of genetic susceptibility. These advancements may lead to replacement of the current broad-spectrum antibiotic therapies with specific and targeted therapies to prevent development of autoimmunity or restore microbial balance and immune tolerance.

Statement of Authorship

R. Vangoitsenhoven and G. A. M. Cresci contributed to the conception and design of the research; R. Vangoitsenhoven and G. A. M. Cresci contributed to the design of the research; R. Vangoitsenhoven and G. A. M. Cresci contributed to the acquisition and analysis of the data; R. Vangoitsenhoven and G. A. M. Cresci contributed to the interpretation of the data; and R. Vangoitsenhoven and G. A. M. Cresci drafted the manuscript. All authors critically revised the manuscript, agree to be fully accountable for ensuring the integrity and accuracy of the work, and read and approved the final manuscript.

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