

## Original Article

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# Research progress on human microecology and infectious diseases

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**Abstract:** Human microecology has been extensively investigated. Similar to an important physiologically functioning organ of the human body, the microecological system is one of the leading systems for environmental survival, health, genetics, disease, and aging. It is also an essential carrier for drug metabolism and microbial resistance. The occurrence, development, and deterioration of many infectious diseases are closely related to human microecological systems. This study mainly focuses on the changes in microbial groups associated with various infectious diseases to explore the relevant role of human microecology in the development of infectious diseases and its breakthrough implications in future accurate treatments of infectious diseases.

**Keywords:** infectious disease, human microecology, intestinal flora, immunity

A large number of microbial populations exist on the surface and inside the cavity of the human body. They colonize the gastrointestinal tract, oral cavity, urinary tract, skin, respiratory tract, and other parts, forming the human microecological system with the microenvironment they live in. The intestinal microecological system is the largest and most important microecological system of the human body and is considered an important forgotten “organ” of the human body [1]. More than 1000 kinds of bacteria inhabit the human intestines. The total number is approximately  $10^{13}$ – $10^{14}$ , which is 10 times the number of human somatic cells, and has about 3.3 million genes, which are more than 150 times the number of human genes [2-3]. The human flora plays important physiological functions and participates in various processes, such as metabolism of substances, formation of mucosal barriers, development and maturation of the immune system, and protection of hosts from pathogen attacks [4]. The microbiome acts as the “second set of genomes” of the human body and contains rich data information, which can reflect certain health and disease conditions of the human body. The microbiome can be used to determine early signs of acute and chronic diseases, conduct targeted screening of specific pathogens, develop targeted drugs, and perform relevant procedures. This study focuses on the microecological immune regulation of the human body and the changes in microbial groups in various infectious diseases to explore the important role of human microecology in the development of infectious diseases and its breakthrough implication in future accurate treatments of infectious diseases.

## 1 Colonization of human microecology and development and maturation of the immune function of the human body

The normal flora begins to colonize the human body at birth and accompanies the whole process of immune development. During the maturation of the human immune system, the normal microbiota and the immune system mutually restrict, influence each other, and constitute an important biological barrier of organisms.

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The colonization of normal intestinal microflora can promote the development of gut-associated lymphoid tissues (GALTs) and the differentiation of intestinal-specific immune-responsive cells; in turn, intestinal immune responses activated by the normal flora can regulate the structure of the intestinal microecological flora [5]. GALT is the main site where antigen-presenting cells perform their functions; it is a tissue structure that includes Peyer's patches, lymphatic fossa, and isolated lymphoid follicles essential for cellular immunity and immune tolerance [6]. In sterile mice, the development and maturation of lymphoid fossa and isolated lymphoid follicles require the stimulation of the intestinal flora, but Peyer's patches are remarkably reduced in sterile animals [7]. Isolated lymphoid follicles that are not fully developed show defects in innate immunity and multiple pattern recognition receptors, such as toll-like receptors 2 (TLR2), TLR4, and nucleotide oligomerization domain 2 (NOD2), and other receptors that originally require bacterial stimulation and activation [6]. These receptors may have impaired expression, causing the release of downstream inflammatory cytokines and impairing the immune function of antigen-presenting cells [6].

Human flora colonization can show stable genetic characteristics. For example, the flora structure colonized in the intestinal canal changes with the human diet, and this change manifests in the offspring and becomes difficult to reverse. Sonnenburg *et al.* [8] used a mouse model and found that a high-fiber diet available to microorganisms can affect the intestinal flora of several generations of mice during which the intestinal flora diversity in mice with a low-fiber diet is reduced, and the decrease in the diversity of pseudo-bacteria is the most obvious. This change in the intestinal flora persists in the offspring of mice with a low-fiber diet. Even if a high-fiber diet is restored, changes in diversity cannot be reversed.

## 2 Human microecology and the occurrence and development of infectious diseases

Human microecology is closely related to the occurrence and development of infectious diseases. In the pathogenesis of infectious diseases, on the one hand, human immune and metabolic disorders occur and destroy the mucosal barrier, leading to an imbalance of intestinal microecology. On the other hand, microecological imbalance changes the structure and immune function of the flora and the location of microbial distribution, thereby aggravating infectious diseases. The treatment of infectious diseases and antibiotic abuse can also cause microecological imbalance, resulting in microbial resistance, infection, and multiple organ dysfunction. If microecological imbalance cannot be corrected in time, treatment efficacy is reduced and life-threatening effects are induced.

### 2.1 Respiratory infectious diseases and microecology

Lungs are a sterile environment when they are not infected by pathogens. With the application and development of omics technology, a microecological system that interacts with hosts has been found in the lungs, and the microbiome plays an important role in maintaining the health of the respiratory tract.

Respiratory infections and disease progression are associated with the regulation of microbial immunity in colonization. In lower respiratory tract infections in infants at early stages, changing the colonization structure of the original respiratory tract increases the chances of suffering from allergic reactions and repeated wheezing [9-10]. In addition to infection, the early colonization of the respiratory tract by *Streptococcus pneumoniae*, *Moraxella catarrhalis*, or *Haemophilus influenzae* in infants promotes the progression of chronic wheezing even if no symptoms are shown [11-12]. Biesbroek *et al.* [13] showed that the composition of the microbial flora of the nasopharynx of children in the first 6 weeks is related to the microecological steady state and the probability of pulmonary infection in the next 2 years; the early respiratory microbial structure can determine the pattern of the subsequent succession of the flora, maintaining the health of the respiratory tract.

Although the respiratory microbiome performs immunomodulatory functions in pulmonary infections, the gut microbiota, as a larger microecological system, plays a vital role in the immune and inflammatory responses of respiratory infections through the "intestine-lung" axis.

Patients with acute respiratory infections caused by the H7N9 subtype avian influenza virus suffer from remarkable intestinal microecological imbalances. Lu *et al.* [14] monitored the intestinal microecological structure of patients in real time and found that H7N9 disease can cause large fluctuations in the main flora of the intestine. During antibiotic treatment, fluctuations intensify, the content of beneficial bacteria decreases sharply, the ratio of *Bifidobacteria* to *Enterobacter* (B/E value) is much lower than 1 (i.e., the B/E value in the intestines of healthy people is greater than or equal to 1), and the *Bifidobacteria* in some patients is even lower than the detection line. Through further research involving metagenomic technology, the intestinal pathogenic bacteria *Escherichia coli*, *Enterococcus faecium*, and *Klebsiella pneumoniae* are enriched in the intestinal tract of patients, whereas the anti-inflammatory effect of *Faecalibacterium prausnitzii* is substantially reduced. The diversity of gut microbial species remarkably decreases in patients compared with that in healthy people [15]. Therefore, in the treatment of “four-anti-two balance” of patients with H7N9, the “anti-intestinal microecological imbalance” treatment is emphasized, and a microecological regulator is used to reconstruct the intestinal microecological balance, which promotes the increase in the level of intestinal bifidobacteria, lactobacilli, and butyric acid-producing bacteria; minimizes secondary bacterial infections; and improves patient survival [14,16].

## 2.2 Hepatitis B cirrhosis and chronic acute liver failure with microecology

The liver and the intestines are closely related to the “intestine–liver” circulation through the portal system; the liver metabolizes toxic and harmful substances absorbed by the intestines and secretes bile to promote intestinal function [17]. When liver lesions caused by various factors reach a certain level, especially in the case of liver function decompensation, intestinal microecology changes, thereby aggravating the original pathological modifications in the liver and inducing some complications related to intestinal microecological imbalance, such as infection, endotoxemia, and hepatorenal syndrome, resulting in serious consequences.

Hepatitis B virus (HBV) is the most important cause of liver disease in China. HBV can cause chronic infection in approximately 90% of infected people through vertical transmission from mothers to babies or infection in childhood, whereas less than 5% of adults have chronic hepatitis C [18]. Intestinal microecology has been involved in the host immune regulation of HBV infection. Chen *et al.* [19] used a concanavalin-induced mouse hepatitis model and found that intestinal pathogens can aggravate the immune damage of the liver; its possible mechanism involves the activation of the antigen presentation of dendritic cells by intestinal microbes and the promotion of the proliferation of NK cells, which are key immune cells of HBV infection to exert antiviral effects. Chou *et al.* [20] believed that the intestinal flora is involved in the immune clearance of HBV, and mature intestinal flora can change the immune tolerance of mouse HBV, considerably stimulating the immune response pathway and leading to the rapid removal of HBV virus.

Chronic hepatitis B in some patients is aggravated to cirrhosis. Metagenomics has been applied to study the intestinal flora of 181 patients with cirrhosis and establish the world’s first gut microbiome in patients with cirrhosis. The comparison of the three macrogenes of diabetes in Europeans, Americans, and Chinese has revealed that 790,000 unique genes are found in the gut microbiota of patients with cirrhosis, and changes in the intestinal flora in patients with cirrhosis are clarified. At a genus level, the content of *Bacteroides* in the cirrhosis group is significantly lower than that in the healthy group. The contents of *Veillonella*, *Streptococcus*, *Clostridium prazmowski*, and *Prevotella* significantly increase. Of the 20 species with the highest increase in cirrhosis, four and six belong to *Streptococcus* and *Veillonella*, respectively. A total of 28 bacteria are closely related to cirrhosis. Oral bacteria in patients with cirrhosis invade the intestine, but this phenomenon is not observed in healthy people and may have a remarkable effect on the development of cirrhosis. In a previous study, 15 highly specific and sensitive microbial genes are used, and a predictive model of cirrhosis is established [21]. Hepatic encephalopathy is a common and serious complication in patients with cirrhosis. The intestinal microecology affects disease progression through the “intestine–liver–brain” axis. Ahluwalia *et al.* [22] found that intestinal flora is associated with neuronal damage in patients with hepatic encephalopathy, and a model for end-stage liver disease scores in patients with hepatic encephalopathy is negatively

correlated with the abundance of intestinal ancestral Lachnospiraceae, rumen family, and *Incertae sedis* XIV (Spirulina) but is positively correlated with the abundance of the potential pathogenic bacteria *Enterococcus*.

The gut microbiota of patients with associated acute-on-chronic liver failure is significantly imbalanced. 16S rDNA technology has been utilized to study 79 patients with chronic acute liver failure and found that the overall diversity of intestinal flora in patients with acute-on-chronic liver failure is significantly reduced. The relative abundances of *Bacteroides*, rumen cocci, and *Helicobacter* species are significantly reduced, but the relative abundance of endotoxin-producing bacteria, such as Enterobacteriaceae, Pasteuricaceae, and *Streptococcus*, is significantly increased, revealing that the changes in intestinal flora may be one of the causes of endotoxemia and the progression of chronic acute liver failure [23-24]. Bajaj *et al.* [25] observed that 24% of patients with cirrhosis and co-infection develop into chronically acute liver failure, and their plasma toxin levels significantly increase. Intestinal microbial Gram-positive bacteria significantly decreased, and intestinal microecological imbalance is closely related to the progression of liver failure.

The application of microecological preparations in the prevention of liver diseases has made remarkable progress. In a clinical randomized controlled trial in India, the hospitalization risk and Child–Pugh and model for end-stage liver disease scores of patients with hepatic encephalopathy can be significantly reduced after they take the probiotic preparation VSL#3 for 6 months [26]. Giuseppe *et al.* [27] selected and intragastrically administered *Lactobacillus paracasei* B21060 strain to rats with liver cirrhosis and found that this strain can reduce the level of inflammatory factors in rats and improve liver fibrosis and gastrointestinal mucosal barrier function. Similar studies have been reported in the application of nonalcoholic fatty liver disease and acute liver failure [28-30].

### 2.3 *Clostridium difficile* infection-associated diarrhea and microecology

*C. difficile* infection is a refractory and relapsing disease. The normal intestinal flora of healthy people can inhibit the growth of *C. difficile* through various mechanisms, but the abuse of antibiotics and other reasons can lead to imbalanced intestinal microecology, impaired mucosal barrier, and reduced resistance to pathogenic bacteria [31-32]. Gu *et al.* [33] selected 15 domestic *C. difficile*-infected patients with diarrhea, other patients with diarrhea, and a normal healthy control group and found that patients with *C. difficile* infection show a significantly decreased diversity of gut microbiota compared with the healthy control group. Furthermore, the diversity of aerobic bacteria is reduced, whereas the diversity of endotoxin-producing pathogens and lactate-producing bacteria is significantly increased. Erica *et al.* [34] also observed that intestinal flora participates in the immune regulation of the body to promote interleukin (IL)-25 secretion and increase the number of intestinal eosinophils, thereby resisting *C. difficile* infection. Buffie *et al.* [35] demonstrated that intestinal *Clostridium scindens* can inhibit *C. difficile* infection by altering the components of bile acids in the gut.

In the treatment of *C. difficile*, the application of microecology theory to fecal microbiota transplantation has achieved good results. According to the guidelines for the treatment of *C. difficile* infections as updated by the European Society for Clinical Microbiology and Infectious Diseases, fecal microbiota transplantation is highly recommended for multiple relapses of *C. difficile* infection. Van Nood *et al.* [36] performed fecal transplantation for the clinical treatment of patients with repeated *C. difficile* infection and showed that fecal transplantation is significantly better than antibiotics. However, fecal transplantation is poorly understood, and certain risks have been observed. Therefore, beneficial intestinal flora should be extracted in future investigations. This process will not only achieve treatment goals but also avoid the potential harm caused by fecal transplant therapy.

### 2.4 AIDS and parasitic infections with microecology

The invasion and replication of HIV mainly occur in the mucosal location of the body. For this reason, an increasing number of experts believe that HIV-1 infection is essentially a disease of mucosal systemic damage [37]. GALT is the main site of viral replication at the early stages of HIV infection and can activate

intestinal memory CD4<sup>+</sup> T immune cells to resist HIV infection [38]. The normal intestinal flora plays an important role in the immune regulation of the intestinal tract, which can regulate epithelial development to control the complement of stem cells, affect the permeability of the mucosal barrier, resist the invasion of pathogenic bacteria, promote the development of mucosal lymphocytes, and participate in the body's dependence on IL-17 and IL-22 immune surveillance [39-42]. Intestinal flora can affect not only the host's susceptibility to pathogens but also the host's resistance to parasites. Yilmaz *et al.* [43] found that specific bacteria in the gut flora can express  $\alpha$ -galactosidase, induce the production of natural antibodies to trigger natural defense mechanisms, and prevent the spread of malaria. McClemens *et al.* [44] observed that the use of *Lactobacillus bulgaricus* (JB-1) strains can mediate IL-10 signaling pathways during intestinal parasite infection to promote the elimination of parasites.

### 3 Expectations

Human microecology has been extensively investigated. The microecological system has been regarded as an organ with physiological functions in the human body. The normal flora plays an important role in human immunity, metabolism, development, nutrition, and other essential processes, especially in the prevention, occurrence, and treatment of infection. Research on human microecology has shown remarkable advancements from initial laboratory bacterial cultures, which are time consuming and laborious and have a low positive rate, to second- and third-generation sequencing technologies, which are well known, sensitive, rapid, and more comprehensive than bacterial cultures. In infection microecology, metagenomic sequencing technology has been applied to develop precision medicine, such as rapid monitoring of influenza [45]; research on antibiotic resistance [46]; and accurate screening of unknown pathogen infections [47]. With the widespread application of antibiotics, however, bacterial resistance, dysbacteriosis, double infection, and decreased host resistance have emerged. Therefore, we should examine the occurrence, development, and outcome of infection from a microecological perspective to improve anti-infection strategies and protect the important "organ" of the human body, turning from a pure "sterilization" concept to "sterilization" and "bacterial promoting," which is the new concept of microecological treatments of infection.

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**Conflict of interest:** The authors state no conflicts of interest.

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