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Hospital Infections and Microbiota

Songül Türk Aydın[1], **Zerrin Aktaş**[1]

[1]İstanbul University, İstanbul Faculty of Medicine, Department of Medical Microbiology, İstanbul, Türkiye

ORCID ID: S.T.A. 0000-0002-9844-7112; Z.A. 0000-0002-5998-0440

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ABSTRACT

The human body hosts complex communities of microorganisms, collectively known as the "microbiota," predominantly in the lower intestine. This microbiota, which consists of bacteria, viruses, and fungi, plays a vital role in the breakdown of various nutrients and maintenance of homeostasis. The microbiome, which represents the collective genetic content of these microorganisms, is intricately associated with human health and disease. Healthcare-associated infections (HCAIs), a major public health problem, contribute to high morbidity and mortality. Exposure to antibiotics, a primary risk factor for diseases, disrupts the microbiota and compromises its protective role. Age-related changes in the microbiota affect the onset and progression of various diseases by affecting the functional capacity and fitness of the host. Inanimate surfaces in built environments contribute to HCAIs by serving as potential reservoirs for microorganisms. Promising results have been observed with fecal microbiota transplantation (FMT) for treating *Clostridium difficile* infection, which is often associated with healthcare facilities. FMT prevents disease recurrence by restoring a healthy colonic microbiota and breaking the dysbiotic cycle. Furthermore, microbiota-based interventions have the potential to control emerging multidrug-resistant pathogens such as vancomycin-resistant enterococci and carbapenem-resistant Enterobacteriaceae.

Keywords: Microbiota, Healthcare-associated Infections, Microbiome, vancomycin-resistant enterococci and carbapenem-resistant Enterobacteriaceae

INTRODUCTION

The complex communities of microorganisms that live on the body surfaces of vertebrates are termed microbiota, and the region where it is most concentrated is the lower intestine. The microbiota has evolved to break down various plant polysaccharides and other nutrients (1). The collective genome content of the microbiota was earlier known as microbiome; however, both microbiota and microbiome are currently used synonymously (2).

The gastrointestinal application of feces from healthy donors to restore the protective microbiome is known as fecal microbiota transplantation (FMT) (3). In recent years, FMT has been associated with the colonization of multidrug-resistant organisms (MDROs) such as carbapenemase-producing Enterobacteriaceae, vancomycin-resistant enterococci (VRE), extended-spectrum beta-lactamase (ESBL)-producing Enterobacteriaceae, and methicillin-resistant *Staphylococcus aureus* (MRSA) that colonize the intestine. FMT is being attempted as a treatment option to eliminate such colonization, with studies showing successful results, making FMT a promising treatment (4).

Microbiota

In ancient times, Hippocrates emphasized the importance of microbiota by stating that death is in the intestines and inadequate digestion is the source of all evil. Élie Metchnikoff, who lived during 1845–1916, proposed that most diseases begin when good bacteria in the digestive tract can no longer control bad bacteria. He named this situation dysbiosis, which implies an ecosystem in which bacteria do not live together in mutual harmony (5). Humans have evolved with different microorganisms in their microbiota. Dysbioses in the microbiome are associated with several disorders, such as inflammatory bowel disease, multiple sclerosis, diabetes (type 1 and 2), allergies, asthma, autism, and cancer (6).

The pathogenesis, development, severity, and consequences of upper respiratory tract infections may depend on the nasopharyngeal microbiome and immune defense. During early childhood, nasopharyngeal colonization by bacterial

Corresponding Author: Songül Türk Aydın **E-mail:** songulturk07@gmail.com

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respiratory pathogens is a common event and constitutes the first and essential step in the pathogenesis of respiratory bacterial infectious diseases, including acute otitis media, sinusitis, conjunctivitis, chronic obstructive pulmonary disease, and pneumonia. A polymicrobial association exists between high otopathogen loads in children with otitis media or upper respiratory tract infection. The types of microbiomes in the respiratory tract include *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis*. Some strains of *H. influenzae* and *M. catarrhalis* in the middle ear secrete signals that promote biofilm formation. *M. catarrhalis* promotes the growth of *H. influenzae*, especially in the presence of *S. pneumoniae* (7).

Anaerobic bacteria found on the skin, mouth, gastrointestinal tract, and female genital tract are important members of the microbiota (8). The relative abundance of members of these phyla varies among different sites in the body (Figure 1) (9).

Effect of antibiotics on microbiota

Consuming antibiotics orally releases chemicals into the intestine that disrupt the intestinal microbiota. These disruptions may occur through interactions between the normal intestinal microbiota and opportunistic and pathogenic bacteria present in the intestine. The effects of antibiotics on the intestinal microbiota may be temporary or permanent, depending on the type of antibiotic and duration of treatment (10). Mucosal damage caused by antibiotic intake initiates the production of a cascade of inflammatory cytokines, including tumor necrosis factor, type I interferons, interleukin (IL)-1, and IL-6. These cytokines directly alter the gut microbiome and thus create an optimal environment for the development of MDRO induced infections (11).

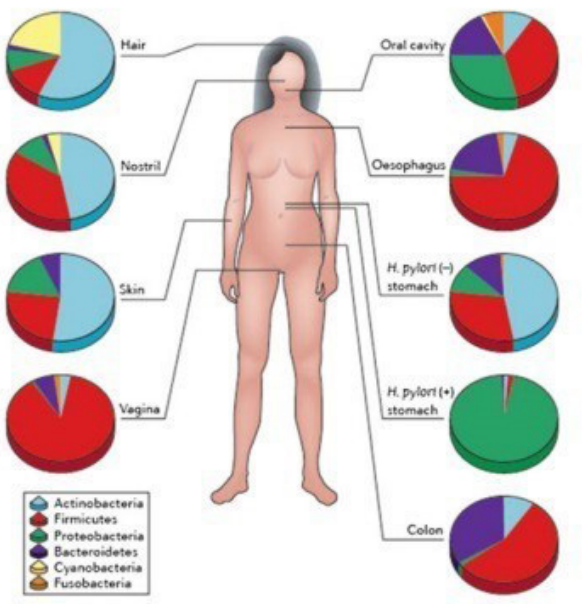

Figure 1: Compositional differences in the microbiome by anatomic site (9)

Antibiotics are released into the environment as a consequence of continuous antibiotic overuse. The release of antibiotics into the environment results in the development of antibiotic resistance genes in bacteria, which reduces the effect of antibiotics on pathogens. This is an alarming situation (12).

Antibiotic use may disrupt the microbiota in the ear, nose, and throat, causing opportunistic pathogens to proliferate in this region. In a microbiota analysis on left and right ear canal swab and nasopharyngeal swab samples obtained from 19 children, a core group of bacterial taxa was identified, including *Corynebacterium*, *Alloiococcus*, *Staphylococcus*, *Haemophilus*, *Turicella*, *Streptococcus*, and *Pseudomonas* (13).

The primary cause of severe bacterial dysbiosis observed in patients in the intensive care unit (ICU) is the widespread use of antibiotics. Nevertheless, as the current evidence is based on preclinical studies, the mechanisms in the microbiota are not completely understood. For instance, although disruption of the gut microbiota by broad-spectrum antibiotics does not affect systemic innate immune responses in healthy humans, it disrupts the host's gut microbiome balance in critically ill patients, causing dysbiosis (14). Gut dysbiosis caused by different factors (environmental factors, antibiotic use, and other factors) can trigger or aggravate inflammatory bowel syndrome, rheumatoid arthritis, obesity, diabetes, nonalcoholic fatty liver disease, depression, and Parkinson's disease (15).

Healthcare-associated infections and microbiota

Healthcare-associated infections (HCAIs) were previously known as nosocomial infections. HCAIs are defined as infections acquired in any healthcare setting, including inpatient/outpatient care (16).

The association between bacteria and humans is related to environmental changes. Anthropogenic factors that alter the environment, chemical pollution that alters microbial biodiversity, new medical technologies, increasing number of highly susceptible hosts, and controlling the access of bacteria to the host are important factors for nosocomial infections. These factors balance colonization/multidrug resistance in the nosocomial microbiota (17).

Inanimate surfaces are potential reservoirs for microorganisms, including bacteria (Gram-positive and Gram-negative), fungi, and viruses. Some microorganisms can survive on dry surfaces for days or even months. A study conducted in the ICU investigated the bacterial species on the floor, workplace, and devices and identified the following seven major bacterial phyla: *Acidobacteria*, *Actinobacteria*, *Bacteroidetes*, *Cyanobacteria*, *Firmicutes*, *Nitrospira*, and *Proteobacteria*. Moreover, the highest bacterial load was detected in hospital devices, followed by the workplace and finally the floors (18).

The microbiota of hospitalized patients is often dysbiotic because of the frequency of treatments such as antibiotics, diet, and chemotherapy (19). Dysbiosis in the gut increases susceptibility to *Clostridium difficile* infection (CDI), which

explains why most CDI cases are associated with healthcare facilities. Microbiota plays a beneficial role in the resistance and resolution stages of infection (20). There is limited research on the changes in the microbiome of patients with recurrent CDI (rCDI). For instance, in a study that investigated microbiome diversity in samples collected from healthy individuals and from patients with primary and rCDI, less bacterial diversity was detected in samples collected from patients with rCDI (21).

Another study by Sereira et al. conducted using rectal, nasal, and hand swab samples collected from 198 patients reported high abundance rates of pathogens associated with HCAIs in all sample types. During hospitalization, 50% of the patients did not experience any HCAI, 43.9% of them experienced an HCAI, and 6.1% of them were colonized by bacteria associated with HCAIs. The authors mentioned that has been an increase in the number of HCAI cases and the detection of pathogens associated with HCAIs, especially bacteria such as *Klebsiella pneumoniae*, Enterobacteriaceae, *Staphylococcus* spp., and *Acinetobacter baumannii*. The usefulness of active surveillance programs based on microbiome monitoring in the evaluation and control of HCAIs indicates the need for a multidisciplinary approach (22).

Hospital plumbing systems are potential reservoir areas for bacteria. There is extensive research demonstrating the isolation of clinically important bacteria from hospital sink and drain water. Multidrug-resistant (MDR) *Pseudomonas aeruginosa* has been widely identified in these areas (23). A study reported that the number of *Bifidobacterium* and *Lactobacillus* bacteria decreases in hospitalized critically ill patients, whereas that of *P. aeruginosa* increases logarithmically. Intestinal microflora can be altered using antibiotics, prebiotics, and probiotics or through fecal transplantation (24). A study conducted using mouse models suggests that the lung immune responses of mice with acute bacterial lung infection are altered by intestinal dysbiosis. Gut dysbiosis caused by broad-spectrum antibiotics results in changes in the IgA response in the lung, causing *P. aeruginosa* infection (25). The results reported by Bacci et al. strengthen the hypothesis of the interaction between the lung and intestinal microbiota concerning *P. aeruginosa* chronic infection (26).

The number of VRE is increasing among nosocomial infections. Stachyose supports probiotic development, and attempts are made to prevent VRE infections using stachyose. For instance, Zhu et al. reported that stachyose supplementation could cause changes in the microbiome, which could result in alterations in the expression of genes and inhibit VRE colonization (27). VRE colonization is essential in liver transplant recipients. VRE colonization as a consequence of intestinal dysbiosis may negatively affect graft function on the microbiota–liver axis and result in adverse outcomes before and after liver transplantation (28). Intestinal commensal bacteria can inhibit dense gut colonization by VRE (29).

Changes in the lung microbiome are observed in respiratory diseases. With alterations in physicochemical properties due to chronic inflammation, the temporary microbiome becomes the permanent microbiome (30). Because the intestinal microbiota can manage lung immune function through the gut–lung axis, this presents a novel option for preventing lung infectious diseases. In this regard, one study reported significant decreases in α-diversity and the presence of various beneficial bacterial species in lung microbiota analysis after MRSA infection, which indicates a decrease in butyric acid content that may play a role in lung inflammation as a result of disruption of the microbiota during MRSA infection (31). Bessesen et al. found no MRSA colonization in the presence of *Streptococcus mitis* and *Lactobacillus gasseri* in the nasal microbial communities of hospitalized patients (32).

Although a high-fat diet (HFD) plays a role in various diseases, the relationship between HFD and antibiotic effectiveness is not completely understood. Antibiotic effectiveness was investigated in a study conducted on HFD-fed mice infected with MRSA and *Escherichia coli*. Lower antibiotic sensitivity was observed in HFD-fed mice than in diet-fed mice. Fecal samples collected from HFD-fed mice were transplanted into diet-fed mice, which resulted in impaired antibiotic activity in the diet-fed mice. This study demonstrated that changes occurred in the intestinal microbiota of HFD-fed mice that played a role in reducing antibiotic activity. Analysis of fecal samples revealed decreased microbial diversity in HFD-fed mice (33).

Therefore, modern approaches require us to consider the human body as a complex ecosystem that must remain in balance to maintain health. Any disturbances to this balance may result in malfunctioning of various organs and promote the development of numerous inflammatory diseases (34).

A novel approach: treatment with microbiota

Interest in microbiota-based therapies has increased due to the success of FMT for treating rCDI. The FMT success rate in rCDI treatment was between 85% and 92% (35). Moreover, FMT was effective in decreasing the development of antibiotic resistance genes in patients with rCDI, which may be effective in reducing colonization by MDROs (36). In the study by Kuraishi et al., FMT was found to be more effective than vancomycin for treating recurrent and resistant CDI (37).

Because dysbiosis is the primary factor for rCDI, microbiome diversity changes due to the excessive use of antibiotics after CDI treatment. Restoring a healthy microbiota can eliminate the dysbiotic cycle (38). Jalanka et al. conducted a study on 84 patients with inflammatory bowel disease, cancer, autoimmune disease, allergies, and neurological diseases, including 45 patients treated with FMT and 39 in the control group receiving antibiotics due to infection. They observed that patients receiving FMT had fewer upper gastrointestinal tract symptoms and irregular bowel function. Thus, FMT was reported as a safe alternative treatment option in patients with rCDI (39).

Davido et al. applied FMT treatment to 15 patients colonized by VRE, and after 3 months, VRE colonization was detected in only three patients. The authors confirmed that FMT is safe and may exert a strong effect on VRE colonization over time (40).

In another study conducted on 17 patients with an average age of 73 years, the duration of infection with CRE and VRE was 62.5 days before FMT. At 1 week after FMT, CRE colonization disappeared in 3 of 8 patients, and VRE colonization disappeared in 3 of 9 patients. At 3 months after FMT, CRE colonization disappeared in 4 of 8 patients, and VRE colonization disappeared in 7 of 8 patients (41). Moreover, a patient with MDR *K. pneumoniae* infection was treated successfully with FMT (42).

A recent study supported a relationship between urinary tract infection and gut microbiota (43), showing that susceptibility to recurrent urinary tract infections (rUTI) may act through the bowel–bladder axis. Patients with rUTI may develop different immune symptoms against intestinal dysbiosis and bacterial bladder colonization (44). This study has demonstrated that FMT is an effective method to treat rUTI (45). Wang et al. demonstrated the benefits of FMT for treating *Escherichia coli* in their study with *E. coli*-infected mice. They recommended FMT as a therapeutic agent for intestinal infections and stomach-related diseases (46).

Bilinski et al. reported that FMT is a suitable treatment option for blood disorders. Colonization was prevented with FMT, but antibiotic treatment after FMT reduced the success rate (47). *Citrobacter murliniae*, *K. pneumoniae*, and *Enterobacter cloacae*, which are among the hospital pathogens, are important in terms of infection risk in hematopoietic stem cell transplantation (HSCT). Acute graft-versus-host disease is a major complication of allogeneic HSCT. Microbiota-based treatment options may be a good option for the prevention and treatment of graft-versus-host disease in patients with HSCT (48).

In a study by Wieërs et al., patients treated with antibiotics were administered a probiotic mixture, which resulted in a significant decrease in *Pseudomonas* colonization from 25% to 8.3% after antibiotic treatment (49).

New treatments are being developed against MDR pathogens, including carbapenem-resistant *K. pneumoniae*. These new treatment options include the application of monoclonal antibodies, use of bacteriophages, genetic editing, and FMT (50).

CONCLUSION

It is crucial to understand the relationship between microbiota and human health to develop strategies for the prevention and management of diseases. Microbiota-based therapies such as FMT are promising in treating conditions such as CDI and addressing the challenges posed by antibiotic resistance. Ongoing research in this area will provide novel insights into the role of microbiota in health and pave the way for innovative therapeutic approaches.

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