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The effect of neonatal nursing care on clinical symptoms and intestinal flora of children with acute diarrhea

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ABSTRACT

Nursing care for infants in the neonatal intensive care unit (NICU) is very complex and may affect the function of the infant microbiome. Several factors inherent in staying in the intensive care unit, such as the use of antibiotics, non-antibiotic drug interventions, nutritional components, and various invasive procedures, including surgery, are associated with disruption of the host microbiota. Therefore, the NICU nurse needs to consider effect factors on the microbial growth and the role that the microbiome may play in causing disease since admission to the NICU. In this study, we describe the association between the gut microbiome and neonatal nursing care at the NICU and the cellular and molecular factors affecting the intestinal flora of children with acute diarrhea.

Introduction

The human gut covers 500 different species of forced anaerobic microbes (Bifidobacterium, Clostridium, Eubacterium, Fusobacterium, Peptococcus, Peptostreptococcus) and Optional Anaerobic (Lactobacillus, Bacillus, Streptococcus, Clostridococcus and Streptococcus) (1). Numerous studies have shown that the use of probiotics can reduce the risk of respiratory infections as well as fever and cough in children (2). Commensal bacteria play a direct role in the growth and differentiation of intestinal epithelium and its immune system and produce a balanced inflammatory response in terms of safety (1). Intestinal bacteria regulate the human immune system by increasing the number of extraintestinal T cells, and the production of short-chain fatty acids (3).

Disorders in the intestinal flora of children

The microbiome is the presence and coexistence of millions of microbes in the body of every person, which contains beneficial and harmful microbes. Bacteria are by far the most abundant member of the human microbiome. Bacteria in the human colon feed on the cellulose contained in it, and in contrast, the human body needs the activity of intestinal microbiota to increase the absorption of nutrients, vitamins (K, B12), growth, maturity and immunity (4). Microbial invasion, including pathogenic bacteria, and their spread into the bloodstream leads to systemic inflammatory response syndrome (SIRS), also called Sepsis. Systemic inflammatory response syndrome is a term used to describe the widespread inflammation that occurs in infection, pancreatitis, ischemia, burns, multiple trauma, hemorrhagic shock, and immune-mediated organ damage (1). Studies have shown that the neonatal gut microbiome in the neonatal intensive care unit (NICU) differs from healthy neonates in composition and diversity (5).

In critical diseases, poor intestinal perfusion, hypoxia, and antimicrobial therapy lead to changes in intestinal microbiome diversity (6). Microbial imbalances in the body are known as dysbiosis, which leads to secondary infection and death in humans, especially children. The composition of the NICU neonatal microbiome can change due to parturition methods, disinfection methods, and health conditions in different hospitals after parturition (4). Evidence suggests that maternal diet during pregnancy and Breastfeeding play a role in the composition of

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infants' intestines (7).

Bacteria, cells, and other immune compounds in breast milk, after passing through the infant's intestine, promote the growth and maturation of gastrointestinal lymph nodes by establishing and inducing differentiation. Also, by inducing an immune tolerance mechanism, they prevent the development of ectopic immunity to environmental factors and food antigens and beneficial microbes, and also, the cytokines in it prevent the proliferation of pathogens. While dry milk has an effect on the exacerbation of Enterobacter, which causes various diseases (4). Hence, changes in breast milk at the NICU alter beneficial gut bacteria. Clostridium species are abundant in the intestinal microbiome of preterm infants with a milk allergy who die to age 8 (8). Injections of prebiotics and probiotics maintain the balance of intestinal microbiomes in premature infants. Prebiotics are indigestible foods that cause the growth and activity of anaerobic flora in the colon (9).

Bacteria are involved in the extraction of energy from foods containing polysaccharides, as well as in the metabolism of bile acids for intestinal microbial activity. In this regard, Wijeyesekera et al. (10) believe that continuous use of systemic antibiotics affects the recovery rate of intestinal microbial activity, and also, the profile of bacterial metabolites shows the functional capacity of the intestinal microbiome. Thus, the decrease in the frequency of these metabolites is associated with the severity of clinical disease (10).

Diseases related to disorders of the intestinal flora of children

Changes in the intestinal microflora are associated with obesity, diarrhea, type 1 diabetes, nonalcoholic fatty liver disease (NAFLD), asthma, and allergic diseases (11). Diarrhea in children causes malnutrition by reducing nutrient absorption and mucosal damage, which leads to weight loss and height gain (12). In one study, a persistent increase in *Fusobacterium mortiferum*, *Escherichia coli*, and oral microorganisms was reported in the fecal microbiome of children with diarrhea (13). The fetal intestine of a human is sterile and free of any bacteria. Cloning of these bacteria in the human gut begins with the transfer of bacteria from mother to fetus, and this is influenced by factors such as gestational age, type of parturition, type of infant nutrition, use of antibiotics, and health status. Nutrition and the environment play a vital role in the acquisition of microbiota, such as the adult microbiota, in the first three years of life. The coexistence of millions of genes of these bacteria with humans has an important role in metabolism, immune and nervous system function and expression of human genes (14). In this regard, studies have shown that probiotic microorganisms prevent the course of diarrhea, especially acute and chronic infectious diarrhea caused by *Clostridium difficile* viruses and bacteria, Shigella and Salmonella, and some strains of Escherichia coli (15). Amoebiasis (traveler's diarrhea) is also one of the most common diseases caused by consuming sewage-contaminated water and lack of hygiene, which changes the composition of the intestinal microflora. In addition to infecting the colon, this disease can also infect the human liver. Symptoms of the disease include mild or severe diarrhea with mucus and blood. A meta-analysis study with 12 clinical trials and 5,171 patients showed that administering probiotics two days before the trip and during the trip reduced the risk of traveler's diarrhea to 15% (16).

Microbiome imbalance may alter the feeling of satiety and hunger by affecting the function of the pituitary gland and ultimately lead to obesity. On the other hand, the pituitary gland also affects the balance of intestinal bacteria. Based on the results of studies, bacteria of the family of Firmicutes and Bacteroidetes have been identified in the small intestine, which is related to body weight. Firmicutes are a type of bacterium that is found in higher amounts in obese people and plays a role in Calorie extraction from complex sugars and saving them as fat. Bacteroidetes are also less common in obese people (17).

In addition, an association between changes in intestinal bifidobacteria and Escherichia coli and animal obesity has been identified in studies by Gao et al. (18). These researchers used the second-generation sequencing platform, Illumina Miseq, a high-power 16SrDNA sequencing technology to characterize participants' fecal DNA. Based on the results of operational taxonomic unit analysis for valid 16SrDNA sequences, a significant difference was observed between the operational classification unit and the relative frequency between obese and control groups. They believe that the intestinal flora may play

a role in obesity, and identifying them in children provides important information about the role of specific bacteria in obesity. In this regard, researchers have suggested that in order to eliminate obesity and other diseases, it is necessary to regulate the balance of intestinal bacteria through the use of appropriate probiotic supplements daily (18, 19).

Researchers believe that the intestinal flora is influenced by various geographical, ethnic, diet, lifestyle, DNA damage and exercise factors (18). Exercise can increase the number of beneficial microbial species, and improve the growth of intestinal bacteria (20). Also, changes in the composition of the gut microbiota are associated with a variety of digestive disorders such as constipation. Children with functional constipation have higher levels of Clostridium and Bifidobacterium in their feces (21). In adults with constipation, a decrease in Bacteroides, Roseburia and Coprococcus phyla organs has been observed in the intestinal microbiota (20).

On the other hand, children with malnutrition have low nutrients and poor growth. According to the World Health Organization, childhood malnutrition is a major global health problem, affecting 150 million children under the age of five. In this regard, Huey et al. (22) reported that growth, diet, and nutrition patterns are associated in malnourished children whose gut microbiota is composed primarily of proteobacteria (22). Animal studies have also shown that this immature microbial population leads to abnormal immune systems and metabolic problems, and the adaptation of dietary supplements to improve the growth of the intestinal microbiome leads to the treatment of malnutrition in children. Infections caused by bacteria, viruses and parasites damage the intestinal wall. Because of this, food cannot pass through it and enter the bloodstream. In this case, nutrients are excreted through the (23). Thus, the gut microbiota acts as a bridge between reactions and the modulation of host metabolism (24).

Children with recurrent respiratory tract infections (RRTIs) also suffer from an imbalance in the intestinal flora, which manifests as a significant decrease in the number of bifidobacteria and lactobacilli and an increase in the number of Escherichia coli. Evidence suggests that probiotics work in the body in two ways: First, they improve the digestive system because the digestive system needs to balance the beneficial and harmful bacteria. When the digestive system is working properly, it becomes a filter for harmful substances such as toxins, harmful bacteria, chemicals and other food waste. Second, probiotics protect the immune system against toxins, and when they do not work properly, a person may suffer from allergic reactions, immune system disorders, and skin infections (2). The beneficial effects of probiotics on upper respiratory tract infections have been confirmed. Intestinal probiotics can regulate IgA production by regulating pulmonary dendritic cells (2). In addition, influenza pulmonary infection increases the production of interleukin-17 and activates Th17 cells by increasing IFN-1 levels. Thus, it produces proinflammatory cytokines and chemokines and destroys intestinal epithelial cells (25).

Changes in the intestinal microflora are associated with gastrointestinal tumors such as gastric cancer, liver cancer, colon cancer, and non-digestive tumors such as breast cancer (26). Van Vliet et al. (27) reported that, during chemotherapy, the total number of bacteria in the feces samples of patients with acute myeloid leukemia was 100 times lower than in healthy individuals, and the number of anaerobic bacteria and potentially pathogenic aerobic enterococci decreased and increased, respectively (27). Intestinal microbiota also affects the central nervous system. In the gut, there are nerve cell terminals that, connect to the brain. This relationship is called the gut-brain axis. Lactobacillus and Bifidobacterium attenuate inflammatory responses by stimulating the production of interleukin-10 (a suppressor of depression and inflammation). The microbial synthesis potential of dopamine 3, 4-dihydroxyphenyl acetic acid is positively correlated with mental quality of life, and the production of microbial γ-aminobutyric acid may play a role in the development of depression (28). In addition, stress increases the concentration of cortisol and decreases the concentration of T3 and T4. Finally, it changes the composition of intestinal bacteria. Meanwhile, the administration of probiotics in people with chronic depression has been shown to have beneficial effects on gastrointestinal symptoms. Lactobacilli have anti-inflammatory properties on human intestinal epithelial cells, and oral treatment of Bifidobacterium has beneficial effects on ulcerative colitis (11).

In autism, children have less variety of gut microbiota and a variety of beneficial bacteria such as Bifidobacteria and Prevotella. Altered levels of intestinal microbiota lead to hyperactivity of inflammatory mediators. These inflammatory mediators cause inflammation of the blood-brain barrier, which is essential for nerve development. The intestine-brain axis is a two-way communication path between the intestine and the brain. In autism, there is an increase in intestinal permeability, which causes bacterial metabolites to cross the intestinal barrier. This disorder, along with disruption of the blood-brain barrier integrity, may affect childhood neurodevelopment in people with autism. Maternal intestinal microbiota may play a key role in the development of autism in children during pregnancy. In addition, maternal factors, including the mother's diet, factors during parturition, postpartum factors, genetics, and antibiotic use during breastfeeding may alter the microbial composition of the offspring. Also, the mother's high-fat diet during pregnancy reduces the amount of bacteria and Campylobacter in infants (29) In this regard, studies have shown that the use of common probiotics can target the maternal microbiome, or reduce the risk of autism by blocking a specific inflammatory molecule called interleukin-17a, which is produced by the immune system (30).

The effect of nursing level on clinical symptoms and intestinal flora of children with acute diarrhea

Infant nursing care in the neonatal intensive care unit (NICU) is complex and may affect the functioning of the infant microbiome (8). Health buildings are the main sources of microbial diversity due to the habitat of drug-resistant microbes (31). Therefore, it is important for the NICU nurse to thoroughly investigate the factors that affect microbial growth, and also the role of the neonatal intestinal flora (8). The fetal intestine before birth is completely or largely sterile. As the baby passes through the mother's birth canal, it is exposed to microorganisms in the vagina, which are the source of the microbiome population. Hence, they have a higher relative abundance than *Bifidobacterium longum*. Babies born by caesarean section, who do not pass through the birth canal, do not have one of the major groups of gut bacteria, called Bacteroidetes, or get it later than babies who are born naturally. Bifidobacteria, Bacteroides and Escherichia coli are colonized in caesarean section infants, and the abundance of *Clostridium perfringens* and *Clostridium difficile* is relatively high (4). NICU nurses can promote optimal microbiome growth by encouraging mothers to breastfeed their infants. They can also educate parents on the basics of baby care and the importance of skin-to-skin contact in the neonatal intensive care unit, for preventing potential illnesses in infants (8). In one study, McDonald et al. (32) examined the fecal microbiota of 115 patients in the intensive care unit (ICU) within 48 hours of admission to the ICU and the tenth day of ICU stay. Their results showed that the relative abundance of Firmicutes and Bacteroidetes at the branch level decreased in the feces of ICU patients, and that of proteobacteria increased. Faecalibacterium, which has anti-inflammatory properties, decreased sharply at the genus level, but common pathogens Enterobacter and Staphylococcus increased (32).

Numerous factors, including the use of antibiotics, non-antibiotic drug interventions (such as proton pump inhibitors, and Vasopressors) and various invasive procedures, including endotracheal intubation and surgery, are associated with a disturbance of the host microbiota to stay in the ICU (33). In addition, these factors alter the nutritional components (carbohydrates, lipids, and proteins) in a person's health (34). Opioid use in mechanically ventilated patients causes intestinal atony and bacterial overgrowth. As a result, the proliferation of highly dangerous microorganisms disrupts the balance of the host-pathogen, causing an adverse activation of local inflammation by mucosal-derived cytokines (1). Antibiotics kill harmful bacteria in the gut. However, they also kill beneficial bacteria. Other drugs and processed foods affect the level of beneficial bacteria. Stress is also one of the factors in this change (35). Selective gastrointestinal decontamination affects Staphylococcus aureus and intestinal yeasts, while through the selective use of antibiotics, it maintains anaerobic populations with uncertain clinical consequences (33). The use of antibiotics during maternal parturition, with a longer course of antibiotics, causes a more significant reduction than a shorter period (8).

Using molecular biology techniques, the composition of the intestinal microbiota of patients, which was normal before admission to the intensive care unit, after 1 week of serious illness, and the treatment of intensive care including antibiotics, observed a marked change in the overall composition of the microbiota with Enterococcus (36). Some gut bacteria may be involved in the link between cholesterol and heart disease. When consumed on a high-fat diet, these bacteria produce a compound that is converted by the liver to trimethylamine N-oxide (TMAO). This compound causes cholesterol sediment in the blood vessels. Excessive TMAO may also cause chronic kidney disease. People with chronic kidney failure cannot excrete this compound well, which can lead to heart disease (37). Aardema et al. (33), before, during and after admission of cardiac-surgical intensive care patients, a significant decrease in the abundance of Blautia, Roseburia and Dorea bacteria and an increase in enterococcus, and a relative increase in the abundance of non-pathogenic species Akkermansia, Bifidobacterium and methanobrevibacter were observed in the intestines of these patients. In their study, the most obvious dynamic change in intestinal microbiota during hospital stay was a decrease in the abundance of bacterial members of a healthy microbiota, including butyrate producers, which may be had a direct impact on clinical outcome (33).

Studies have shown that exposure to multiple antibiotics, host physiological abnormalities, or the presence of nosocomial pathogens increases the frequency of nosocomial pathogens in all parts of the body and decreases the frequency of intestinal compounds, such as Faecalibacterium, in children in the ICU (38).

Cellular and molecular evaluation of the effect of nursing level on clinical symptoms and intestinal flora of children with acute diarrhea

The growth and proliferation of the human intestinal flora begin with the birth of a baby through breathing, physical contact with the environment, breastfeeding, and eating. In fact, the microbiota of the mother's body (skin, intestines, and vagina) and the surrounding microorganisms cause the baby's body to gradually form a variety of intestinal flora, which reaches adulthood by about 2 to 3 years of age. These bacteria affect the digestion and the proper functioning of the immune system (39). When the intestinal flora becomes unbalanced, it releases inflammatory agents that can be harmful to the human body (40). The cause of microbiome instability in critical diseases is multifactorial. Critical disease, alone, causes profound changes in the gut microbiota that may be due to general changes in the host environment (34). External factors (such as diet and medication) and internal factors (such as the host genome) can affect the baby's microbial colonization. Changes in the microbiome can produce metabolites, some of which (such as DNA methylation and histone modification) are essential elements for epigenetic regulation. Changes in the epigenome will subsequently lead to altered gene expression and modified functions (4). In intestinal diseases, dysfunction of the intestinal flora significantly alters the executive function of the mucosal immune system, thereby, increasing the expression of IL-6, IL-1β, TNF-α and other inflammatory factors, and decreasing the expression of IL-31 (41, 42). Kim et al. (43) analyzed the serum of patients with diarrhea and found that serum C-reactive protein could distinguish between non-inflammatory diarrhea and inflammatory diarrhea (43). In diarrhea, the maturation of IL-1 depends on the activation of caspase-1 and intensifies the proinflammatory response. At different stages of diarrhea, IL-6 expression levels may change and indicate a prognosis. In the study by Qin et al. (14), serum levels of IL-1, IL-6, IL-17 and TNF-α were significantly higher in children with non-infectious diarrhea than healthy children. In their study, these levels were positively correlated with the prevalence of Escherichia coli and Enterococcus in children with non-infectious diarrhea. These researchers believe that, changes in the intestinal flora may affect the secretion of inflammatory factors in vivo (14).

Genetic evaluation of pediatric intestinal flora

Genetics plays an important role in determining microbiome diversity among individuals. According to this view, genes determine the location of the microbiome, and each specific environment allows certain bacteria to survive. In addition, the composition and interaction of the developing intestinal microbiome with the host genomics may play an important role in the early development of the

infant. Using genetic sequencing methods, the researchers found that healthy people had up to 10 times more lactobacilli in some parts of their noses. The researchers then identified the types of bacteria that were found only in healthy people. They showed that a subset of Lactobacillus bacteria called Lactobacillus Casei AMBR2 is particularly adapted to living in the nose. Lactobacillus Casei AMBR2 has unique genetic characteristics that enable it to survive in the high levels of oxygen in the nose. The researchers then grew Lactobacillus Casei AMBR2 in the laboratory with upper respiratory tract epithelial cells, along with specific pathogens that normally infect this part of the body. They found that this bacterium not only inhibited the growth of these pathogens but also reduced the inflammatory response of these cells (44). Thus, using target regions to study microbiota composition or genetic sequencing to catalog existing genes can reveal patterns and diversity of intestinal microbiota (7). The host-microbial relationship is driven by host genetic diversity in immune-related pathways associated with microbiome-related disorders including inflammatory bowel disease (IBD) and obesity (45). Studies have shown that the LAMB1 and HNF4a16 genes can explain intestinal barrier dysfunction in IBD. AHR, CCL20, CD28, LY75, NFATC1, and NFKBIZ, which are members of the newly identified candidate gene, can modulate the T cell response to some extent (46). Stilling et al (47) reported that the lack of microbes in germ-free mice was significantly associated with genes that promote transcription, which is associated with neural activities and established during early life. These researchers believe that the reduction of immune-related genes may reflect some of the effects of microbiota on brain physiology and behavioral responses (47)

On the other hand, evidence suggests that the IL-10 receptor mutation causes severe colitis and severe IBD. IL-10 activates Tyrosine kinase 2(Tyk2) and Janus kinase 1(JAK1), and ultimately promotes the expression of anti-inflammatory agents (48). Than et al. (49) showed changes in gene expression in hemostasis, immune cell inflammation, cell growth regulation, detoxification, stress response, lipid metabolism, stem cell regulation, and decreased intestinal microbiota diversity in the intestine of cystic fibrosis transmembrane conductance regulator (CFTR) mutant mice (49). Dayama et al. (50) observed host colon gene expression and mucosal microbiome composition data, enrichment of cancer-related unregulated genes, and changes in intestinal microbiome in cystic fibrosis patients compared with healthy individuals (50). The global spread of antibiotic resistance among Enterobacteriaceae is mainly due to the transfer of multidrug-resistant plasmids between different strains of bacteria. Horizontal transfer of resistance plasmid genes can complicate the prevalence of nosocomial diseases, and cause problems in epidemiological detection (51). It is difficult to treat infections caused by antibiotic-resistant bacteria and to find the mechanism of resistance to several classes of antibiotics, including β-lactams, aminoglycosides, and fluoroquinolones. In molecular evolution, microbes adopted various mechanisms to maintain genomic flexibility. Pseudomonas aeruginosa is one of the most worrying pathogens involved in antibiotic resistance, whose mechanism of intrinsic resistance includes the presence of a higher flow pump, and low permeability of its outer membrane (31).

Conclusion

This study describes the effect of outpatient intensive care, nursing level on clinical symptoms and intestinal flora of children with acute diarrhea in ICU. Several groups have reported vulnerabilities in the intestinal flora of children in the ICU. Overall, studies have shown that the profile of bacterial metabolites provides insight into the functional capacity of the intestinal microbiome, and a decrease in the frequency of these metabolites is associated with the severity of the clinical disease. Overall, the present study should help to increase the awareness of physicians who are associated with patients with intestinal microbiota disorders.

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Interest conflict

The authors declare no conflict of interest.

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