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From Belly to Bedside: The Gut Microbiota's Influence on Septic Shock: A Review Article

Choudhury A[1*], Rathore SS[2], Gangadharan J[3], Kumar S[4] and Bairwa M[5]

[1,2]Department of Medicine, Military Hospital, Mall Road, Ambala Cantt, Haryana, India

[3]Department of Critical Care, Narayana Health, Bangalore, India

[4,5]Department of Medicine, All India Institute of Medical Sciences, Rishikesh, Uttarkhand

[*]Corresponding author:

Dr Arnab Choudhury, MD, DM,
Classified Specialist & Critical Care, Department of Medicine, Military Hospital, Mall Road, Ambala Cantt, Haryana. Pin-133001, India

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1. Abstract

The gut microbiota and sepsis are closely related, and there has been increased research recently on the role that microbial dysbiosis plays in the development of sepsis. The dysregulated host response to infection that is characterized by changes in the gut microbiota and gut microbiome is known as sepsis. Modern studies have revealed that sepsis patients have lower microbiota richness and higher pathogenic bacteria. Probiotics, prebiotics, FMT, and diet are known to affect the gut microbiota; therefore, these therapeutic approaches may be helpful in attempting to restore the balance of the microbial flora and enhance the prognosis for sepsis. Probiotics support immune system function and gut health, whereas FMT restores a balanced bacterial flora. Dietary sources of fiber, polyphenolic compounds, and omega-3 fatty acids are known to improve the stability of the microbiota. Some of the limitations include the fact that the microbiota can be different in different people and there is a need for large-scale human intervention for microbiota-modulating therapies. Microbiota-directed therapy is applied together with traditional sepsis treatment, and this approach might be a new way of improving patient outcomes. This underlines the involvement of gut microbiota in sepsis development and its possible management.

2. Highlight of the Article

This article highlights the gut microbiota's role in septic shock, emphasizing microbial diversity as crucial in sepsis progression. It advocates combining probiotics, prebiotics, FMT, and diet with standard treatments, offering a novel approach to improve sepsis outcomes while stressing the need for further research.

3. Introduction

The human gut microbiota is thus defined as a microbial ecosystem, bacterial and archaeal, viral and fungal, residing in the gastrointestinal tract. This microbial community has multiple functions in physiological functions like digestion, metabolism, the immune system, and the structural framework of the gastrointestinal tract [19,23].The overreaction of the host to an infection, followed by the development of organ dysfunction and a pro-inflammatory state, is known as sepsis [1, 13]. Changes in the makeup and function of the gut microbiota have been connected to this illness [1]. This review article will describe the relationship between microbiota and sepsis how microbial disruption causes sepsis, and how the manipulation of microbiota can be therapeutic for sepsis treatment.

4. The Gut Microbiota: Composition and Functions

The gastrointestinal microbiota is mostly bacterial such as Firmicutes and Bacteroidetes, Actinobacteria, Proteobacteria, and others. Each individual has his or her microbiome type depending on his or her genetic code, diet, environment, and usage of antibiotics [19]. These microorganisms have various roles which are a positive effecton the host.

1. Digestive Functions: It aids in the breakdown of proteins, fiber, and carbohydrates that are difficult for their own enzymes to break down. Short-chain fatty acids (SCFAs), such as butyrate, propionate, and acetate, are produced by this process and are utilized in colonocyte energy requirements and immune system modulation. [16].

2. Metabolic Functions: Microbiota produces certain essential vitamins (K and B vitamins) and plays a role in the host's lipid metabolism. Such disruption of metabolic processes can be blamed on dysbiosis as it causes metabolic disorders like obesity and diabetes [2].

3. Immune Modulation: The host's immune system regulation and proper operation are influenced by the gut microbiota. It sustains the integrity of the intestinal tract barrier, stimulates the growth of GALT, and gives immune cells information [14].

4. Barrier Function: By secreting more mucus and tight junction proteins, the gut microbiota improves barrier function and lowers the likelihood that toxins and pathogens will pass through the intestinal barrier and enter the bloodstream [23].

5. Sepsis: Pathophysiology & Clinical Impact

Sepsis results from an infection that in turn triggers an inflammatory process in the body and this leads to more harm to the body tissues and organs and death. The pathophysiology of sepsis involves several key mechanisms:

1. Systemic Inflammatory Response: The host's immune system produces inflammatory cytokines (e.g.,TNF-α,IL-1β,IL-6) when infected & these cytokines may become overproduced resulting in inflammation and tissue injury [8].

2. Immune Dysregulation: Sepsis is characterized by the dysregulated immune response that is at the same time both overactive and inactive. This dysregulation hampers the body's capacity to regulate the infection and results in secondary infections and poor outcomes [24].

3. Microcirculatory Dysfunction: Inflammatory mediators lead to endothelial dysfunction, capillary leak, and microcirculatory abnormalities, resulting in inadequate tissue perfusion and organ failure [15].

4. Metabolic and Coagulation Disturbances: Sepsis disrupts metabolic homeostasis and coagulation pathways, contributing to disseminated intravascular coagulation (DIC) and metabolic acidosis [17].

6. The Role of Gut Microbiota in Sepsis

Through multiple mechanisms, the gut microbiota plays a crucial role in the pathogenesis of sepsis.

1. Microbial Dysbiosis and Barrier Dysfunction: Dysbiosis, another name for changes in the intestinal microflora's makeup, is typically present in patients with sepsis. The intestinal barrier may be weakened by this dysbiosis, which could encourage the translocation of harmful bacteria and endotoxins into the bloodstream and worsen systemic inflammation [13].

2. Immune Modulation and Dysregulation: The immune system and the body's capacity to fight infections can both be weakened by dysbiosis. Some of the beneficial bacteria including Bifidobacteria and Lactobacilli are known to influence immune response and enhance anti-inflammatory effects. Disruption of these friendly microbes may result in uncontrolled inflammation and immune system problems [3].

3. Metabolite Production: There is proof that the "SCFAs produced by gut bacteria have anti-inflammatory properties and help to maintain the intestinal barrier's" integrity. In dysbiosis, levels of SCFAs are lowered, which leads to a pro-inflammatory condition and disruption of the barrier [22].

4. Secondary Infections: Secondary infections can arise as a result of immunosuppression brought on by dysbiosis, worsening the conditions of sepsis patients and potentially influencing their prognosis [10].

7. Evidence from Clinical and Preclinical Studies

Numerous investigations have shown a correlation between sepsis and gut microbiota:

1. Clinical Studies: Sepsis patients have been reported to present low microbial richness and pathogenic dominant dysbiosis with Enterococcus and Escherichia coli being the most predominant. These alterations are connected to the prognosis and severity of the illness [25].

2. Preclinical Studies: The use of antibiotics or altering one's diet to promote dysbiosis has been shown in certain animal models of sepsis to exacerbate the illness. On the other hand, FMT, or the use of probiotics to replace a healthy microbiota can reduce sepsis severity and increase the survival rate [1].

8. Therapeutic Implications and Future Directions

Numerous therapeutic approaches are being investigated in light of the critical role the gut microbiota plays in sepsis.

1.Probiotics: Probiotic strains of Lactobacillus and Bifidobacterium have shown promise in helping sepsis patients regain their normal intestinal barrier integrity, restore their normal flora, and control their immune responses [18]. Nevertheless, more clinical trials are required to determine the effectiveness as well as the side effects of the treatments.

2. Prebiotics: Prebiotics, or indigestible fibers, are another kind of diet that helps boost SCFA levels and promote the growth of good bacteria. Together with probiotics, they can have a co-advantageous effect on sepsis treatment [20].

3. Fecal Microbiota Transplantation (FMT): FMT is a procedure in which a dysbiosis patient is given donor feces.This approach has been found helpful in restoring favorable gut flora and a better outcome of sepsis but more work needs to be done and guidelines

have to be established [11].

4. Dietary Interventions: It can be seen that depending on the type of food that an individual takes then the type of gut microbiota that a person will have. That's why there is a need to trace the impact of the dietary supply of fibers, polyphenols, and omega-3 fatty acids on sepsis severity and microbiome health [12].

5. Antibiotic Stewardship: Thus, one of the measures to prevent dysbiosis is the proper application of antibiotics, with rational usage being one of the key aspects.Preventing the overuse of antibiotics is the purpose of antibiotic stewardship programs, which help maintain the health of the gut microbiota and decrease sepsis-associated complications [9].

9. Detailed Mechanisms Linking Gut Microbiota and Sepsis

Understanding the detailed mechanisms through which gut microbiota influences sepsis is essential for developing targeted therapies:

1.Intestinal Barrier Integrity: The gut barrier is made of epithelial cells, mucus layer, and tight junction proteins that act as barriers to prevent the pathogens from translocating. This disrupts the barrier, and products such as lipopolysaccharides (LPS) produced by microbes get into the bloodstream and cause sepsis and inflammation [4].

2.Pattern Recognition Receptors (PRRs): SSP from the gut microbiota stimulates the PRRs including TLRs and NLRs on immune cells that trigger inflammation. Dysbiosis can increase the activation of these receptors and thus inflammation [21].Immune Cell Modulation: The gut microbiota affects T cells, B cells, macrophages, and other immune cell differentiation and function. Beneficial microbes promote regulatory T cells (Tregs) and anti-inflammatory cytokines, whereas pathogenic microbes can induce pro-inflammatory Th17 cells and cytokines [3].

3.Metabolic Endotoxemia: This results in enhanced permeability of the gut and hence LPS and other endotoxins enter the circulation to cause metabolic endotoxemia. This illness "is thought to play a role in the onset of sepsis and is linked to low-grade inflammation [6].

4.Neuro-Immune Axis: The gut-brain axis, which influences the immune and stress systems, is the conduit through which the gut microbiota and the brain interact.Dysbiosis may" impede this interaction, which in turn may change the body's capacity to mount a suitable defense against infections [7].

10. Therapeutic Strategies Targeting Gut Microbiota in Sepsis

1.Probiotics and Synbiotics: Synbiotics are products that contain both "probiotics and prebiotics, whereas probiotics are live microorganisms that are good for the host. The restoration of microbiota, improvement of the intestinal barrier's quality, and control of immunological inflammation in sepsis are the goals of these interventions [18].

2.FMT: FMT is an action, that involves the movement of fecal material from a healthy person to" the patient with dysbiosis.It has been described to be useful in eradicating C. difficile infection and other conditions which are characterized by dysbiosis. They are being applied in sepsis, and studies indicate that the treatment can result in the normalization of bacterial colonies and the patient's general well-being [11].

3.Dietary Modifications: Among other things, diet has a big impact on the type of microbes that live in the stomach. Short-chain fatty acids, or ScFas, improve the lining of the stomach and lower inflammation. They are produced by beneficial bacteria that can be found in high-fiber diets. Polyphenols and omega-3 also have a positive contribution to the microbiome [12].

4.Antibiotic Stewardship: When antibiotics are used excessively, dysbiosis arises, and sepsis and other related complications are likely to occur. Antibiotic stewardship programs are designed to promote the rational use of antibiotics so as to minimize disruption of the healthy bacterial flora in the gut and hence the emergence of antibiotic-resistant infections [9].

5.Targeted Therapies: New strategies are focused on the manipulation of certain elements of the microbiota or their products. Some of these are bacteriophages that are selective for pathogenic bacteria, and small molecules that influence the metabolism of microbes or interaction between the microbes and the host [5].

11. Challenges and Future Directions

1.Individual Variability: Individual differences exist in the gut microbiota composition as a result of lifestyle, environment, diet, and genetic predispositions. This means that patient-specific treatments are required to address this variation in therapeutic interventions [19].

2.Mechanistic Understanding: There are already other related studies about gut microbiota and sepsis, but the process is still not very well understood. Subsequent effort needs to be invested in the elucidation of these processes and the identification of key microbial players and activities [3].

3.Clinical Trials: Randomised controlled trials of sufficient sample size need to be conducted to determine the efficacy and safety of microbiota-directed therapies in sepsis. Such aspects as patients, time of the intervention, and more than one agent should be considered in these trials [18].

4.Standardization and Regulation: Even more, the guidelines for the application of such interventions as FMT and probiotics should be clearly defined to improve the use and approval of the interventions by the governing bodies. This comprises donor profiling, method of food preparation, and precautions that are taken in order to make sure that the foods to be prepared are quality ones [7].

5.Integrative Approaches: Adding microbiota-directed treatments to other sepsis treatments such as antibiotics and supportive care

could help the outcomes. These diseases' treatment is said to need the collaboration of microbiologists, immunologists, and clinicians [1].

12. Conclusion

The body of research demonstrates that both the onset and severity of sepsis are influenced by gut microbiota. Sepsis deteriorates because of dysbiosis and its effects on the immune system, metabolites, and intestinal barrier. This awareness increases the potentiality of creating new therapies that might influence the gut microbiota. Probiotics, prebiotics, FMT, changes in diet, and antibiotics are some of the approaches through which the microbiota can be restored, and the prognosis of sepsis improved. Future research should try to describe the precise function of gut microbiota in sepsis and these approaches should be beneficial in treatment trials.

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14. Conflict of Interest

The authors declare no conflict of interest

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