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REVIEW ARTICLE

Influence of Gut Microbiota on Progression, Maintenance, and Control of Sepsis: A Comprehensive Review

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METADATA

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ABSTRACT

Background: Sepsis is a medical condition that is characterized by an unbalanced immune response to an infection, leading to organ damage. The dysfunction of gut microbes due to sepsis has significant impact on body organs and tissues. Several therapies include fecal microbiota transplantation, dietary fiber intake and antibiotic scavengers which reduce the impact of antimicrobial agents on gut microbiota while enhancing their presence at main infection sites.
Objective: The aim of this review is to explore recent development in the field, evaluate microbiota based therapeutic options, and highlights the need for further research to evaluate their role in sepsis management.
Methodology: A comprehensive search of databases, including PubMed, Scopus, and Web Science was conducted to identify relevant studies published up to 2023. The inclusion criteria covered clinical trials and observational studies assessing the effect of fecal microbiota transplantation, probiotics and prebiotics, postbiotics, synbiotics and antibiotics in sepsis management.
Results: The review included studies that have beneficial impact of prebiotics, probiotics, fecal microbiota transplantation on sepsis. Specifically, these interventions were found to improve intestine barrier characteristics, restore intestine microbial variety and decrease infection.
Conclusion: The gut microbiota plays a crucial role in sepsis pathogenesis, affecting immune responses, gut barrier function, and bacterial translocation. Modulating the gut microbiota through various therapeutic interventions holds promise in sepsis management. However, further research is required to fully understand the underlying mechanisms and optimize treatment strategies for personalized care.

INTRODUCTION

Sepsis is a fatal syndrome resulting in abnormal functioning of body organs due to host systemic inflammatory reaction to infection. This disorder is a serious, global health concern leading to both morbidity and death (20%) in worldwide (Singer *et al.* 2016). It is the major cause of health expenses in United States that leads to the public health problem (Rudd *et al.* 2020). Therefore, to understand the cause of dysregulation, research of sepsis condition has target point for researchers on the host immune' response (Rhee *et al.* 2017). The vital role of the gut microbiota in both the progression as well as persistence of sepsis especially in predispose sepsis in adults and post-operative sepsis (MacFie *et al.* 1999).

When an individual has sepsis, their microbial community generally experiences a drop in variety, loss of helpful bacteria, and a rise in the development of dangerous bacteria such as Enterococcus and Staphylococcus (Dickson *et al.* 2016). The host body's inflammatory reactions and increased intestinal microbiota permeability that result from gut microbiota dysbiosis cause infections to spread to organs like the liver. (Fox *et al.* 2012). As a result, changed microbiota compositions in the sepsis state, the precise root cause for the beneficial function of gut microorganisms in sepsis, and the lack of diagnostic procedures or treatments targeting the gut microbiome in the treatment of sepsis are all unresolved issues (Knoop *et al.* 2016).

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ROLE OF GUT MICROBIOTA IN THE MANAGEMENT OF SEPSIS

In gastrointestinal tract, microbiota refers to the diverse group of microorganisms that ultimately inhabit the gastrointestinal tract. Microorganisms such as bacteria, viruses, fungus, and archaea are all part of the microbiome. Numerous facets of host physiology, metabolism, and immune response are significantly influenced by this intricate ecosystem. The microbiome, a varied group of microorganisms that live in both internal and external body parts, is found in the human body (Gilbert *et al.* 2018).

Metabolites produced by commensal gut bacteria are considered important for the characteristics of immune cells and contribute to the various systemic effects that intestinal microbes have on host defense (Fox *et al.* 2017). Recent research has focused on the key immunological pathways influenced by these metabolites. One example is the role of Kupffer cells, the macrophages in the liver, which capture and eliminate circulating pathogens. Gut commensal bacteria produce D-lactate, which is transported to the liver via the portal vein and helps maintain the integrity of the intravascular barrier regulated by Kupffer cells (Schlechte *et al.* 2022). Butyrate, a short-chain fatty acid (SCFA) produced through anaerobic bacterial fermentation, plays a role in the differentiation of monocytes into macrophages. Butyrate promotes the production of antimicrobial peptides and enhances antimicrobial activity in both mice and in vitro (McDonald *et al.* 2020).

Oral administration of short-chain fatty acids (SCFAs) has been shown to boost macrophage phagocytic activity against Klebsiella pneumoniae. This effect is triggered by the activation of G protein-coupled receptor 43. SCFAs also significantly enhance the macrophage-driven removal of the bacteria during infection. The antimicrobial effector LAMTOR2 is overexpressed, which leads to pneumonia infection. The LAMTOR2 receptor activates extracellular signal-regulated kinase, facilitating phagosome-lysosome fusion (Schulthess *et al.* 2019). Metabolites produced by the gut microbiota have a multifaceted effect on the host immune response. In addition to influencing the host's immune system, commensal bacteria can alter their metabolic activity in response to immune stimuli. For example, when mice colonized with four anaerobic commensal bacteria were exposed to acute immune stimulation via flagellin or anti-CD3 antibody, rapid transcriptional changes were observed. Although the overall abundance of the bacteria remained relatively unchanged, this reprogramming led to an increase in the expression of strain-specific reaction mediators. Intestinal metabolite production was observed to change within six hours of immune activation, with a marked reduction in the levels of short-chain fatty acids (SCFAs) like acetate and propionate (Wu *et al.* 2020)

SEPSIS AND ITS TREATMENT AFFECTS THE GUT MICROBIOME

There are several factors that affect sepsis (Miller et al. 2020; Fig. 1). The unclear underlying cause of the beneficial role of gut microorganisms in sepsis, and the lack of diagnostic approaches or therapies targeting the gut microbiota that are effective in sepsis treatment, are still unresolved issues involve the changes in microbiota composition during sepsis (Ubeda *et al*. 2010; Taur *et al*. 2012). One finding is that stress by itself can change the makeup of the gut microbiota. Artificial nutrition feeding is one of the many necessary strategies to help septic patients. Given that food composition is one of the most well researched elements that might alter the makeup and function of the intestinal microbiota, careful study is warranted here (David *et al*. 2014). An instance of this phenomenon involves human participants who were given a meal heavy in animal protein, fat, and low in fiber. Remarkable alterations in the makeup of their gut microbiota were seen during a just 24-hour period. In contrast to those who consume a diet mostly based on plants and rich in fiber, those who follow a different dietary pattern exhibit reduced levels of short-chain fatty acids (SCFAs) and increased levels of secondary bile acids. These secondary bile acids possess the ability to impede the proliferation of beneficial bacteria such as Firmicutes and Bacteroidetes, which are known to contribute to overall health. However, it is common for sepsis patients who are hospitalized to receive casein-based, sterile, chemically specified meals via an enteric tube, which are devoid of dietary fiber (Reis *et al*. 2018).

Gut barrier integrity and bacterial translocation

An initial line of defense in case of infections and dietary antigens is the gut barrier (Paone *et al.* 2020). The intestinal barrier is selectively permeable in a healthy organism, which implies that while it is impenetrable to macromolecules, poisons, food allergies, and infections, it is permeable to ions, water, and low-molecular compounds (Thoo *et al.* 2019). When these compounds leave the colon, the immune system becomes hyperactive, leading to inflammation. Prolonged inflammation can significantly impact health (Paone and Cani et al. 2020). The intestinal barrier is composed of the mucus layer, intestinal microbiota, intestinal epithelial cells (IECs), and lamina propria (Takiishi *et al.* 2017). Intestinal epithelial cells and bacteria are essential for maintaining the integrity of this barrier. The IECs act as a physical barrier, preventing harmful substances from leaking out of the intestinal lumen (Vancamelbeke and Vermeire 2017).

Role of gut microbiota in bacterial translocation

Inflammatory illnesses that can impact the gut and distant organs can be brought on by microorganisms, bacterial

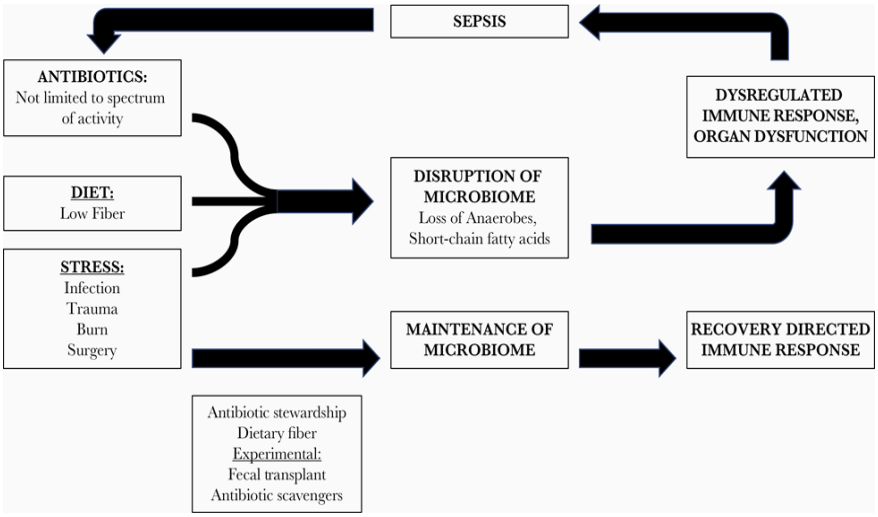

Fig. 1: Factors affecting microbiome in sepsis (derived from Miller *et al.* 2020)

chemicals, or toxins that are unable to pass through the epithelium due to anomalies in the gut barrier (Sorini *et al*., 2019). Mucins comprise the majority of intestinal mucus and are complex clusters of glycoproteins with distinct O-linked glycan's that are produced by goblet cells (Sicard *et al.* 2017). There are several sources of verification that show functional and structural changes to the intestinal barrier are connected to dysbiosis and occur in both human and animal models (Camara-Lemarroy *et al*. 2018). Chronic exposures to molecules from microbial translocation and ongoing dysbiosis, which are to responsible for the rise of bacterial species that are harmful, are to fault. (Mirza *et al*. 2017). In mice, changes in the microbiota of the gut brought on by antibiotic therapy can cause enteric bacteria to move across the epithelium (Knoop *et al*. 2016). Due to changes in the gut microbiota, this relationship may become pathogenic in critical disease, resulting in bacterial translocation, gut-derived sepsis, intestinal homeostasis disruption, and harmful clinical consequences (Wischmeyer *et al.* 2016).

Alteration in gut barrier function in sepsis

Sepsis is a life threatening medical emergency. As our body shows extreme response towards a particular infection. Organ not performing their particular function properly are linked with high risk of death and disease, as the disease turns sever, several abnormalities begin to appear across multiple organs. Sepsis and septic shock frequently result in damage to the digestive system (Fig. 2).

The very first signs are increased permeability, passage of viable bacteria from GI tract to GI sites, and difficulty in absorption are the primary signs of shock (Longhitano *et al.* 2020). Three main lines of defense make up the gut barrier function. the typical intestinal flora (gut microbiota), which makes up the intestinal barrier. Important metabolic, immune, and gut-protective functions are carried out by the

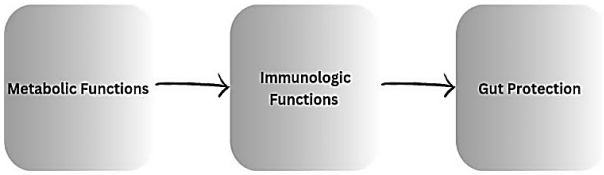

Fig. 2: Major functions of microbiota

microbiota (Assimakopoulos *et al.* 2007). Multiple organ dysfunction syndrome in sepsis is hypothesized to be influenced by intestinal barrier disruption. Although there are some commonalities in the clinical course of sepsis, the host response varies significantly depending on the initiating organism, disease time course, and pathways of gut injury in several preclinical models of sepsis (Yoseph *et al*. 2016). Critically sick individuals have leaked gut malabsorption which leads to the emergence of multiple organ dysfunction syndrome (MODS) and various health issues like systemic inflammatory response syndrome (Assimakopoulos *et al.* 2018). Strange assumptions of gut related sever issues and MODS awaited clinical validation.

In 1991, a researcher took 20 seriously injured individuals in an effort to gather information about bacterial translocation in critically ill patients. 60% added prevention of patient shock 30% of patients develop MODS, 2% test positive, and no one develops systemic endotoxemia (Moore *et al.* 1991). The investigation shows fair doubts about the validity of the gut hypothesis of sepsis, but it was challenging to conduct similar trials with badly damaged individuals (Assimakopoulos *et al.* 2018). Group randomized multicenter trial with surgical 2762 and non-surgical patients 3165 showed that the SDD patients had a fair chance of surviving. An extensive clinical trial in which researchers and patients knows the given drug or treatment, clustered group-randomized crossover study in 13 intensive care units in the

Netherlands with 5927 patients revealed comparable effects of the two treatments in terms of infection rate, as well as low levels of colonization with antibiotic-resistant pathogens. It is similar to the comparison of SDD and SOD strategies (Oostdijk *et al.* 2013).

Sepsis's systemic effects have been deeply studied, and proof of local changes and effects in the intestinal mucosal compartment is increasingly defining changes related to the gut during sepsis (Neish 2014). Six pertinent studies conducted between 1998 and 2006 on 2125 patients found that 5% of patients had post-operative infections, which escalated to 45% of infections overall, whereas 19% of patients were in perfect health. A bigger randomized experiment is being conducted to examine the impact of immune-nutrients, and 1223 critically ill adults with multiple organ failure who are hospitalized to 40 ICUs across different nations are included. To increase mortality, glutamine is administered to them (Goodrich *et al.* 2014). The risk factor of sepsis is due to the disturbance of gut microbiome as shown by circumstantial confirmations, according to two recent large epidemiologic studies (Gergianaki *et al.* 2018).

A meta-analysis of all randomized clinical trials was conducted in 2012 to upshot the effects of micronutrients and antioxidants. Because selenium is highly effective and has shown the survival by 28 days in these patients, a high dose of selenium was given in this study (David *et al.* 2018). A test is carried out in 2004 to determine the overall impact of beneficial bacteria on gut health. After one week of therapy, occurrences of pathogen diminish pathogenic bacteria 43% and multi-organism 39%, there is no discernible difference among the 90 patients admitted to the ICU who received the RCT, received a placebo effect, and experienced the symbiotic effect. Prebiotics and probiotics are employed in two major clinical therapies for intestinal bacterial over-growth, and 5393 individuals are treated using this approach. As a result, there is a 50% reduction in incidence and an 11% reduction in mortality. SDD in 28 days, SOD reduces mortality by 2.9% while reducing motility by 3.5%. 10,000 beneficiaries in this cohort study were studied in 2015 (Sori *et al.* 1988)

GUT MICROBIOTA BASED THERAPEUTIC INTERVENTIONS IN SEPSIS

Gut microbiota, a set of microorganisms dwelling with inside the GI tract that has been diagnosed as the critical factor for human fitness. Recent studies have shed mild at the massive position of intestine microbiota in sepsis, a life-threatening situation characterized through systemic inflammatory reaction syndrome (SIRS) as a result of excessive contamination. Therapeutic interventions concentrated on intestine microbiota in the sepsis that have emerged as a promising location of investigation, aiming to modulate the microbial composition and feature to enhance affected person consequences (Wang *et al.* 2022). Fig. 3 explains some of the strategies used for the treatment of sepsis.

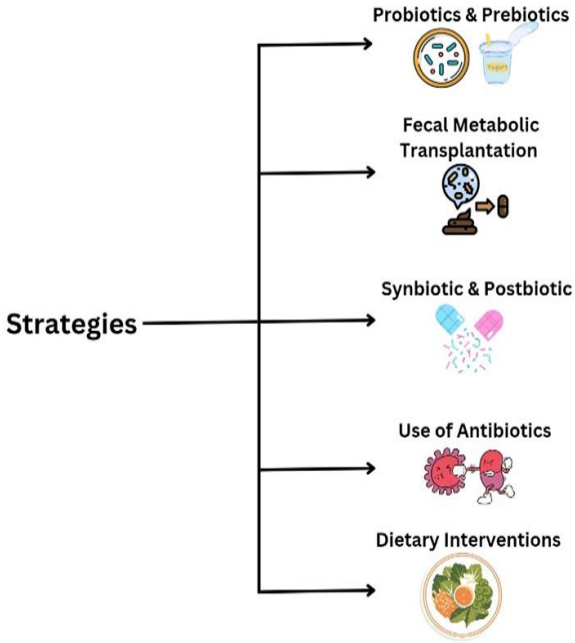

Fig. 3: Strategies used for treatment of sepsis

Probiotics and prebiotics

Probiotics, stay microorganisms that confer fitness advantages whilst administered in ok amounts, have received interest as an ability healing choice for sepsis. Lactobacillus and Bifidobacterium species, generally used as probiotics, have proven promise in restoring intestine microbial variety, improving intestine barrier characteristic, and modulating immune responses in animal fashions of sepsis (Shimazu *et al.* 2012). Clinical trials have proven that probiotic management in septic sufferers improves intestine barrier characteristic, reduces infection markers, and reduces mortality charges (Petrof *et al.* 2012). However, in addition studies is important to validate the efficacy and protection of probiotics in sepsis. Prebiotics, indigestible compounds that selectively stimulate the boom and pastime of useful intestine microorganisms, have additionally emerged as capability interventions for sepsis. Fructo-oligosaccharides and galacto-oligosaccharides, not unusual place prebiotics, were proven to enhance intestine barrier feature, sell the boom of useful bacteria, and decrease intestine-derived irritation in sepsis animal fashions (Ciorba 2012). Although medical research investigating using prebiotics in septic sufferers are limited, initial proof shows that prebiotic management may also lessen contamination costs and enhance medical results (Schulthess *et al.* 2019).

Fecal microbiota transplantation (FMT)

The FMT includes shifting wholesome donor fecal fabric to a recipient's gastrointestinal tract, aiming to repair a balanced

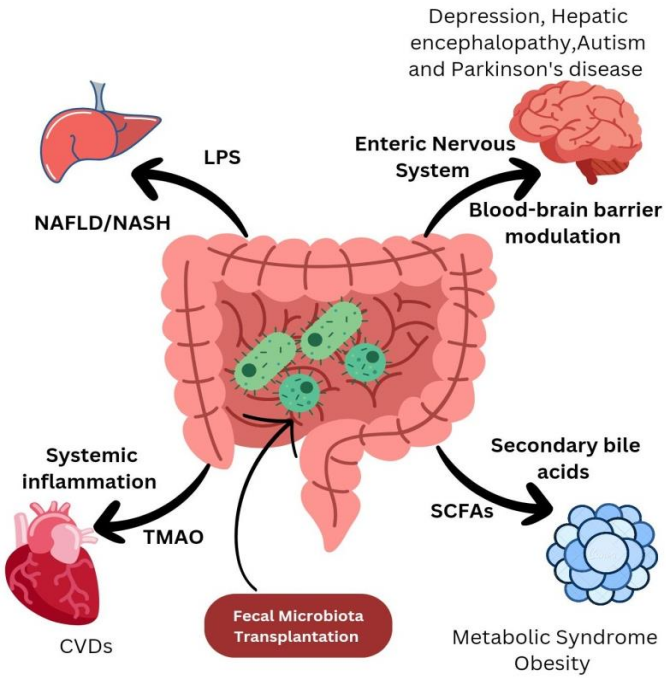

Fig. 4: Illustration of proposed methods via which FMT might influence the development and progression of particular diseases

microbial community. Several research has explored the capacity of FMT in modulating intestine microbiota in sepsis (Fig. 4). Animal fashions have proven that FMT restores microbial variety, improves intestine barrier feature, and decreases infection (Li *et al.* 2016). While medical proof concerning FMT in septic sufferers is limited, early research has said high quality results in phrases of decreased contamination costs and advanced medical parameters (Zuo *et al.* 2018). However, similarly studies and scientific trials are had to set up the protection and efficacy of FMT in sepsis management.

The manipulation of the blood-brain barrier and signaling via the enteric nervous system by microbial metabolites has been shown to have an impact on several mental and neurological illnesses. These disorders include autism spectrum disorders, depressive disorder, hepatic encephalopathy, and Parkinson's disease. The modulation of the metabolic disorder and obesity seems to be influenced by the presence of short-chain fatty acids (SCFA) and secondary bile acids, which are generated by bacterial activity. The introduction of lipopolysaccharides (LPS) together with other structural molecules derived from bacteria into the portal circulation has an impact on the overall health of the liver. The regulation of cardiovascular health has been seen to be influenced by the production of Trimethylamine-N-oxide (TMAO) by bacteria, as well as the induction of systemic inflammation caused by the existence of circulatory bacteria and their byproducts. Fecal microbiota transplantation (FMT), short chain fatty acids (SCFA), lipopolysaccharide (LPS), and Trimethylamine-N-oxide (TMAO) are the respective acronyms for the following terms (Baggs *et al.* 2018).

Postbiotics and synbiotics

Postbiotics are non-feasible microbial mobileular additives or metabolites which have proven capacity blessings in sepsis interventions. These additives, which includes mobileular wall fragments, secreted proteins, and short-chain fatty acids, exert anti-inflammatory and immunomodulatory effects, thereby mitigating sepsis-related complications. In a current observe via way of means of, postbiotics derived from Lactobacillus traces have been discovered to lessen organ dysfunction, decorate microbial diversity, and enhance survival costs in sepsis models. Synbiotics, the mixture of prebiotics and probiotics, have additionally proven promise in sepsis intervention (Meszaros *et al.* 2021). The state-of-the-art studies through proven that synbiotics intervention stepped forward intestine barrier integrity, attenuated systemic inflammation, and ameliorated sepsis-caused lung injury. These findings underscore the capability of postbiotics and synbiotics as novel healing procedures for sepsis management (Shimizu *et al.* 2021).

Antibiotics and gut microbiota

Antibiotics play a critical position in sepsis interventions through focused on and killing the infectious pathogens. However, they also can disrupt the sensitive stability of the intestine microbiota, main to dysbiosis and impaired immune

response (Hutchings *et al.* 2019). Strategies together with antibiotic stewardship and aggregate treatment options with probiotics or fecal microbiota transplantation may also preserve promise in mitigating the negative outcomes of antibiotics on sepsis results (Arora and Backhed 2016).

Dietary modifications

Dietary changes constitute any other road to modulate intestine microbiota in sepsis. High-fiber diets, wealthy in fruits, vegetables, and entire grains, were related to elevated microbial variety and progressed intestine barrier characteristic, probably lowering the danger of sepsis (Jandhyala *et al.* 2015). Conversely, diets excessive in saturated fat and occasional in fiber content material had been related to dysbiosis and elevated susceptibility to infections (Gutierrez *et al.* 2015). However, in addition studies is needed to set up top-rated nutritional techniques for sepsis prevention and management.

Visual acuity for all participants was measured, and those with clinically significant macular edema (CMO) or pre-proliferative/proliferative retinopathy were excluded from the study. Color vision impairment was most pronounced along the tritan axis, particularly in diabetic pseudophakes with background retinopathy. A significant association was found between color vision defects and the presence of background retinopathy ($p = 0.05$). The distribution of color vision defects in the study population was as follows: 16.9% with normal color vision, 10.2% with red-green defects, and 61% with tritan defects. Tritan discrimination sensitivity changes were determinant for figuring out patients liable to excessive retinopathy. The poorer color changes following cataract surgical operation in diabetic pseudophakes can be due to extended short-wavelength transmission thru the intraocular lenses, that could lead to retinal damage. This is mainly true inside the case of phacoemulsification, in which there's a shorter period of exposure to radiation all through lens removal, probably aggravating retinal harm.

FUTURE PERSPECTIVES AND CHALLENGE

- Provision of proper approaches of treatment as well as carefully selected probiotics to the identified patients well helpful for selecting future therapies for gut microbiota for the treatment of sepsis. It will be helpful in the upcoming years in targeting and curing sepsis disease.
- Mostly in practice setting, clinical trials are needed for benefiting septic patients and among them, fecal microbiota transplant (FMT) is helpful in the treatment of sepsis but may be its only beneficial for a fixed number of patients and there's possibility of occurrence of different factors that can cause alteration in the treatment of sepsis via using FMT therapy. These factors included selection of patient, proper rout for administration, timing etc. It is expected that by improving mechanistic insights into the interaction between gut microbiome and sepsis will allow the development of microbiome-based therapeutics for mitigation of sepsis morbidity and mortality.
- Probiotics are helpful in treating gastrointestinal disorders through changes in the gut microbiota but there are still various aspects remaining that will have to address better results such as safety issues, evaluation models, stress resistance etc.
- Hopefully in the future research, there must be some mechanisms or ways to use gut microbiome composition as biomarkers for getting better results of sepsis and this is all possible when all the aspects of the gut microbiome are fully studied. This may be effective in changing the level of mortality and morbidity of sepsis.
- As the world is becoming more advanced day by day, still a lot of things are hidden and need more research to find out the main reasons behind the alterations of gut microbiota normal mechanism and will need more research regarding the factors affecting the normal mechanism of gut bacteria which play an important role in the growth and maintenance of gut

CONCLUSIONS

The gut microbiota plays a crucial role in sepsis pathogenesis, affecting immune responses, gut barrier function, and bacterial translocation. Modulating the gut microbiota through various therapeutic interventions holds promise in sepsis management. However, further research is required to fully understand the underlying mechanisms and optimize treatment strategies for personalized care. Gut microbiota healing interventions maintain enormous ability for enhancing sepsis consequences. Probiotics, FMT, prebiotics, and nutritional changes have proven promise in restoring intestine microbial balance, improving intestine barrier feature, and modulating immune responses in septic sufferers. Nevertheless, the efficacy, protection, and finest dosage of those interventions want to be in addition elucidated thru large-scale scientific trials. Manipulating intestine microbiota represents a promising approach to lessen mortality and enhance affected person effects in sepsis.

AUTHOR CONTRIBUTIONS

Both the authors contributed equally to the write up.

CONFLICTS OF INTEREST

The authors affirm that they possess no conflicts of interest.

DATA AVAILABILITY

Not applicable

ETHICS APPROVAL

Not applicable

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