Volume 10, Issue 7, July – 2025 International Journal of Innovative Science and Research Technology
ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/25jul144

Gut Microbiota Modulation in Leptospirosis: Exploring Pathogenic Mechanisms and Novel Therapies

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Publication Date: 2025/07/14

Abstract: Leptospirosis, an emerging global zoonotic disease caused by Leptospira species. A wide range of clinical symptoms are present in this condition, from a low-grade fever to potentially fatal side effects like Weil's disease and pulmonary hemorrhage syndrome. The pathophysiology remains incompletely understood despite being a disease of epidemic proportions, particularly in tropical regions. Recent developments have indicated the gut microbiota to be a potent modifier of systemic immunity and its potential to modulate disease severity in infectious diseases. The review discusses how the gut microbiota modulates the pathogenesis of leptospirosis through dysbiosis, leading to immune dysregulation and systemic inflammation while causing localized damage to specific organs. Related bacterial infection research indicates that disruptions in gut microbiota worsen immune system imbalances and cytokine storms while intensifying multi-organ failure in severe leptospirosis cases. Microbiota-directed therapeutic approaches including probiotics, prebiotics, fecal microbiota transplantation and dietary modifications may decrease disease severity and improve clinical outcomes. There are several knowledge gaps in leptospirosis research that require comprehensive microbiota profiles, mechanisms of action and clinical trials to address and evaluate these therapeutic approaches. This review emphasizes that combining microbiota approaches with leptospirosis research will provide a novel, and potentially fruitful, direction for therapeutic development and address the acute need for new therapeutic against the neglected tropical disease.

How to Cite: Afnan Ahmed Khan; Israt Jerin Tonni; Md. Shohel Al Faruk; Shormin Akter (2025) Gut Microbiota Modulation in Leptospirosis: Exploring Pathogenic Mechanisms and Novel Therapies. *International Journal of Innovative Science and Research Technology*, 10(7), 551-561. https://doi.org/10.38124/ijisrt/25jul144

I. INTRODUCTION

Leptospirosis, a disease that can be transmitted from animals to humans. It is caused by a harmful bacteria belonging to the genus *Leptospira* [1]. It can be fatal for human health. It has a different range of clinical symptoms, which can vary from mild fever to serious complications such as Weil's disease and pulmonary hemorrhage syndrome [2,3]. While leptospirosis has a widespread around the world, it continues to be inappropriately diagnosed and poorly studied, especially in tropical and subtropical areas where it represents a major public health concern [4]. The disease's pathogenesis is complex, involving strategies by *Leptospira* to evade immune system, excessive inflammatory responses, and multi-organ involvement. Comprehending the factors that increases disease symptoms and progression is important for developing specialized therapeutic systems [5,6].

In recent years, the gut microbiota has come into focus as a vital host health regulator that influences the progression of many infectious diseases and aids in immunological homeostasis [7]. The gut microbiota, which is made up of trillions of microorganisms such as bacteria, viruses, fungi, and archaea, cooperates to regulate systemic immunity [8]. Changes in the composition of the gut microbiota, referred to as dysbiosis, have been associated with the development of several bacterial illnesses, including sepsis, pneumonia, and gastrointestinal problems. These findings raise the intriguing potential that

ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/25jul144

leptospirosis severity and progression may possibly be influenced by the gut microbiome [9 -12].

According to research, gut dysbiosis can increase systemic inflammatory responses by disrupting the balance of pro- and anti-inflammatory signals [13]. In viral diseases, this imbalance may lead to enhanced immune activation, increased cytokine production, and ultimately organ failure [14]. Given the systemic character of leptospirosis and its reliance on immune system interactions, it is pertinent and urgent to investigate the relationship between gut microbiota and the disease's progression [15]. Although the gut microbiota has been thoroughly investigated in relation to other bacterial infections, its role in leptospirosis remains mostly unknown [16].

The aim of this study, therefore, is to investigate the potential contribution of gut microbiota to the pathophysiology of leptospirosis in order to fill this knowledge gap. We shall discuss how gut microbiota can modulate host immune responses in Leptospira infection and whether dysbiosis may lead to exacerbated leptospirosis-related outcomes, such as acute renal impairment and liver dysfunction. Other new interventions that aim to target gut microbiota with the aim of disease course limitation include probiotics, prebiotics, and fecal microbiota transplantation.

Current knowledge regarding microbiota and the pathophysiology of leptospirosis from two key areas of research is summarized to arrive at a comprehensive view with respect to the role played by gut microbiota in this NTD. Having used this approach, we are allowed to emphasize critical research gaps within the area and point toward new directions of developing microbiota-based therapeutic interventions. The resultant multidisciplinary view can provide depth to our understanding of leptospirosis, while offering a new approach for the mitigation of infectious disease via commensal organisms of the gut.

II. LEPTOSPIROSIS PATHOPHYSIOLOGY

Leptospirosis is a zoonotic disease with an array of clinical manifestations from a mild, self-limiting febrile illness to severe, life-threatening complications caused by pathogenic *Leptospira* species [17]. Understanding this host and virulence factor interplay in positive human studies will be critical in determining future strategies for making an effective vaccine against systematics leptospirosis [18]. The disease follows a distinct course, with traditional bacterial spread, immune response, and organ-specific injury defining each step along the way [19, 20].

A. Entry and Dissemination of Leptospira

Pathogenic *Leptospira* gain access to the host via abrasions of the skin or mucous membranes, or via direct contact with contaminated water or soil [21]. Once entry is achieved, the spirochetes spread quickly through the bloodstream, exploiting their unique shape and motility to do so [22, 23]. The migratory ability and mechanical barrier bypassing capacity offered by flagella allow *Leptospira* to penetrate competitive host tissue [24]. In contrast to several other pathogens, *Leptospira* show extraordinary resistance to host complement-mediated killing, allowing them to survive in the early phase of infection [25 -27].

After dissemination, bacteria colonizes various organs, especially liver, kidneys, lungs and CNS. Such a systemic distribution is characteristic of leptospirosis and is aided by the ability of *Leptospira* to bind extracellular matrix proteins including laminin and fibronectin [28, 29]. These bacteria generate adhesins and surface proteins (e.g., LipL32), responsible for vertical adhesion and tissue colonization [30].

B. Host Immune Response and Inflammatory Pathways

The immune response of the host to leptospirosis is two-edged: it protects but at the same time contributes to the destruction of tissues.

➢ *Innate Immune Response:*

During the early phase of infection, macrophages, dendritic cells, and neutrophils recognize *Leptospira* via PRRs, including TLR2 and TLR4 [31]. This recognition induces the production of pro-inflammatory cytokines, including tumor necrosis factor-alpha (TNF-α), IL-6, and IL-1β [32]. These cytokines mediate the recruitment of immune cells to the site of infection but can also cause systemic inflammation [33].

➢ *Adaptive Immune Response:*

The humoral immune system has an important role in the control of *Leptospira* [34]. Antibodies to antigens of *Leptospira*, such as LPS and LipL32, enhance bacterial clearance. In some instances, however, the delayed adaptive response promotes tissue damage by deposition of immune complexes and activation of complement.

➢ *Cytokine Storm:*

In the severe state of the disease, dysregulated immune response results in cytokine storm with overwhelming levels of IL-1β, IL-6, IL-10, and TNF-α. Hyperinflammatory status contributes to endothelial dysfunction, vascular leakage, and multiorgan failure [35].

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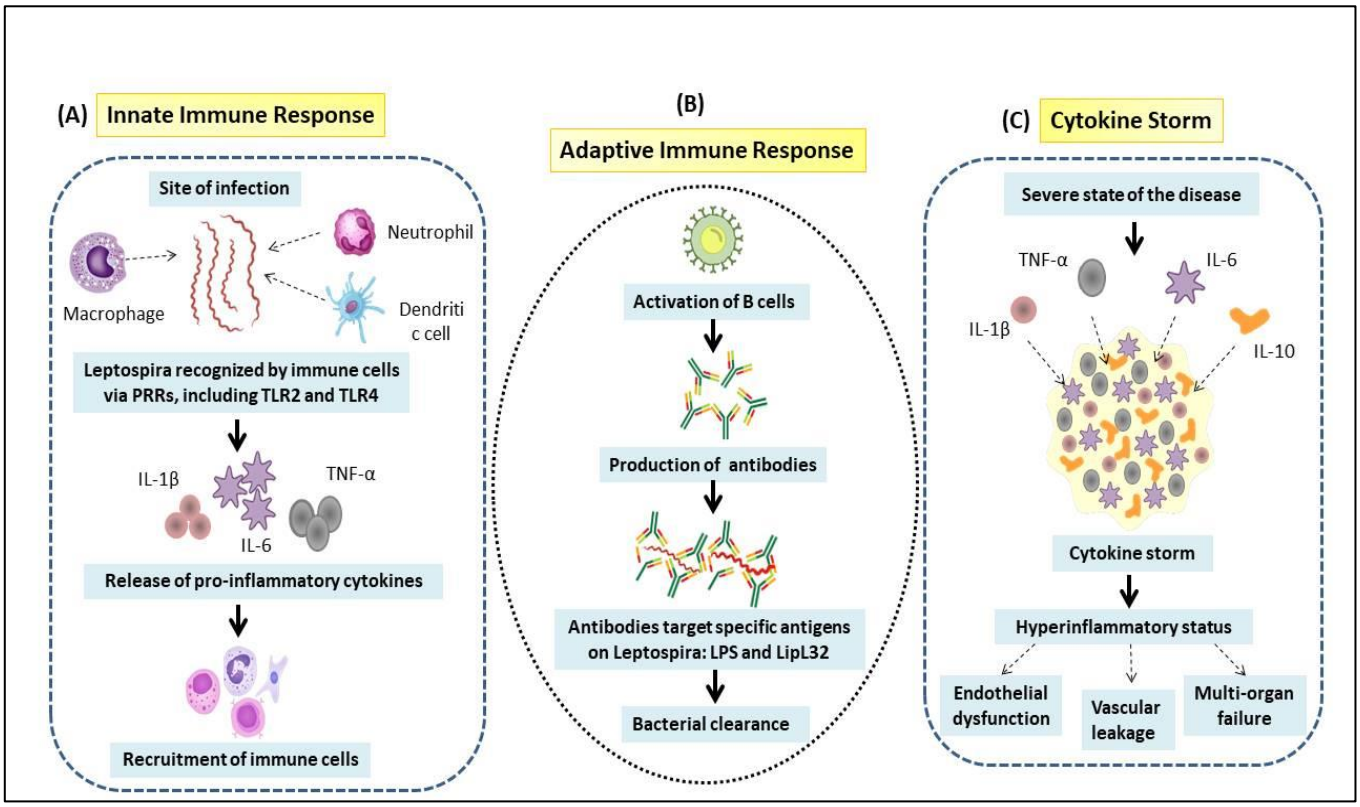

Fig 1: Demonstration of Immune Cells Triggering Inflammatory Pathways

C. Organ-Specific Pathogenesis

➢ *Kidney Injury:*

Human leptospirosis pathology focusses on the kidneys. Leptospirosis is linked with excessive activation of inflammasomes and proinflammatory cytokines in the early stages, resulting in kidney inflammation and injury. Leptospira can be identified in proximal tubular cells on day 10 and in the tubular lumen on day 14 [36]. Leptospiral outer membrane proteins (OMPs) contain harmful compounds like lipoproteins, LPS, and peptidoglycan, which trigger immune responses [37]. LPS is a major antigen affecting immunity and plays a key role in infection [38]. When OMPs were tested on mouse kidney cells, they activated genes linked to kidney damage and inflammation [39]. A key protein, LipL32, causes kidney injury and is a major target of the immune system in human infections. LipL32 also acts as a toxin, breaking down red blood cells during infection [40].

➢ *Liver Dysfunction:*

Weil's disease actually represents the most severe form of leptospirosis disease, involving liver damage with jaundice, with a lethal rate of (19%), which is serious [41]. The mechanisms responsible for jaundice in leptospirosis have not been determined, nor is it clear if jaundice is caused by the liver injury [42]. In recovery of patients, evidence for liver damage includes changes to various liver structures, including the mitochondria, bile ducts, lacteals, and tight junctions [43, 44]. Indeed, leptospires invade the space between liver cells, and therefore can in theory lead to disruption of the tight junctions causing bile to flow in the blood alongside the potential for liver cell injury to involve other structures, which could lead to jaundice [45, 46]. Indeed studies of leptospirosis afflicted hamsters and guinea pigs demonstrated the presence of leptospires and/or remnants located between liver cells that have been damaged [47]. The events occurring in typical liver disease called jaundice are thought to occur when bile duct is obstructed and bile is retained in liver involving bile duct cells. In leptospirosis, it could be said that an obstructed bile duct is analogous to cellular or organ injury to the biliary structures enabling some type of leakage of bile after injury leading to jaundice [48]. Understanding the causations of the events describing jaundice in horrible cases of leptospirosis may provide useful understanding of liver failure in serious leptospirosis and the potential value of early laparotomy or liver isolation and treatment.

➢ *Pulmonary Hemorrhage Syndrome (PHS):*

Leptospiral pulmonary hemorrhage syndrome (LPHS) is the most fatal complication of leptospirosis, with mortality amongst cohorts observed to be greater than 50% [49, 50]. The LPHS process is complex and involves interactions between bacterial mechanisms and host mechanisms; therefore clear mechanistic delineation and understanding will be a challenge. Whereas lung tissue is typically devoid of leptospires, the pulmonary damage from distal sites of infection is thought to involve circulating bacterial toxins (i.e. hemolysins and proteases) [51 - 53]. Immune-mediated mechanisms are also implicated in the pulmonary hemorrhage process. Immunoglobulin and complement has been demonstrated in deposits along the alveolar septa in LPHS human patients and in experimental animal studies in the LPHS disease process. These immune complexes may have roles in hosting a milieu for pulmonary

ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/25jul144

hemorrhage [54]. Finally, the pathophysiology of LPHS also includes mechanisms that impair normal aluminum fluid clearance , such as infection-induced impairments in ENaC along lung membranes while carrying simultaneous increases in NKCC1 along the basolateral membrane transepithelial conductance. These mechanism breaks that osmotic gradient to dynamic fluids for absorption, together allows fluid to remain in the alveolar spaces [55]. Further, though AQP5 and Na-K-ATPase expression did not appear to be perturbed in a manner consistent with present health complaints, the fluid clearance mechanics resembled impaired physiology described in ARDS. The increased vascular permeability caused by inflammatory damage, along with the lack of regulation of fluid, creates a situation ripe for severe pulmonary hemorrhage and respiratory failure, mimicking the lung injury patterns observed in sepsis. The present findings highlight the dual roles of bacterial toxins and host responses in driving the devastating pulmonary complications of leptospirosis [56].

III. GUT MICROBIOTA ALTERATIONS IN BACTERIAL INFECTIONS

Manipulation of the gut microbiota should improve host homeostasis, especially by maintaining immune system function and by preventing pathogenic invasion [57]. However, gut microbiota composition is frequently disturbed during bacterial infections (a phenomenon referred to as dysbiosis). Such disruption can aggravate disease progression through impaired immune homeostasis and enhanced systemic inflammation [58]. Much of the insight on the mechanisms and ramifications of microbiota perturbations stems from studies performed in the context of a wide range of bacterial infections [59].

A. Dysbiosis During Systemic Bacterial Infections

Even bacterial infections outside the gastrointestinal tract may cause serious changes in gut microbiota. Most systemic infections compromise the gut epithelial barrier, promoting translocation of gut bacteria and their metabolites into the bloodstream and further altering microbiota composition [60]. For example, during *Salmonella* infection, the inflammation caused by the pathogen reconfigures the intestinal microbiota, diminishing the abundance of the commensal bacteria *Lactobacillus* and *Bacteroides* and giving rise to blooms of opportunistic pathogens, including *Enterobacteriaceae* [61]. In contrast, systemic infections such as sepsis are characterized by loss of microbial diversity with overrepresentation of pro-inflammatory bacteria that further contribute to immune dysregulation [62]. These findings suggest that not only do bacterial infections cause disruption of gut microbiota, but dysbiosis in return exacerbates systemic inflammation through a feedback loop.

B. Gut Dysbiosis and Immune Modulation in Bacterial Infections

The gut microbiota significantly mediates the host's immunity both within the gut and systemically. Dysbiosis, due to bacterial infection, impairs both the innate and adaptive immune responses [63]. *Clostridioides difficile* infection serves as an example of how disturbance of gut microbiota and decreased efficacy in short-chain fatty acid (SCFA) production by bacteria critical to intestinal epithelial barrier and regulatory anti-inflammatory pathways disrupt localized immunity [64]. Loss of SCFA-producing bacteria creates a 'window of opportunity' for *C. difficile* to attach to and colonize the intestinal epithelium and produce severe inflammation [65]. Loss of gut homeostasis is also a sequela of dysbiosis and is associated with impaired T cell responses, as well as increased incidence of systemic infection in contexts such as *Staphylococcus aureus* bacteremia [66]. Ultimately, these studies demonstrate that disturbances of gut microbiota composites (functional to structural) during bacterial infection can substantially alter immune responses and disease outcomes.

C. Evidence from Animal Models of Gut Dysbiosis

The evidence from animal models strongly support the role of gut dysbiosis in the altered disease progression of bacterial infections. Mice treated with antibiotics recognize that gut microbial diversity decreases with this treatment, as the ability of the mucosal immunity to respond is impaired, increasing the occurrence of systemic infections [67]. For example, in an infection with *Streptococcus pneumoniae*, colonizing gut dysbiosis was found to impair alveolar macrophage function, which could exacerbate pulmonary infections [68]. In these examples, how type 1 systemic infections in mammals could also reflect a bidirectional interaction between affected gut and mucosa were demonstrated. Pneumonia has been shown to be the leading cause of mortality for all infectious disease and is influenced by the gut microbiota, which has been shown to influence mucosal immunity locally and systemic immunity [68]. Additionally, an imbalance in gut microbiota signaling can be expressed through clinical models for the development and progression of disease continues to illustrate how the gut can influence systemic inflammation and infection [69]. The gut-lung axis has captured the interest of researchers and speaks to the complex interplay between the gastrointestinal and respiratory systems [70, 71].

IV. GUT MICROBIOTA AND IMMUNE RESPONSES IN LEPTOSPIROSIS

The gut microbiota has established itself as a significant regulator of host immune function, influencing both the innate and adaptive sides of the immune response [72]. This relationship is especially interesting when considering systemic bacterial infections such as leptospirosis, where immune dysregulation plays a major role in the severity of the disease. While there not an abundance of direct scientific literature linking gut microbiota and leptospirosis, other bacterial infections and theoretical models have discussed this wider dynamic relationship leading to inferences on the possible relationship in the context of leptospirosis [73]. The underlying features of the relationship between gut microbiota and host immune function is complex, and it has been recognized to involve a wide range of interactions involving microbial metabolites, immune signaling pathways, and gut barrier function [74]. The gut microbiota, a complex ecosytem within the gut, plays a central role in

ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/25jul144

many aspects of host physiology and multi-faceted tasks including nutrient metabolism, immune system development, and providing a protective barrier against pathogenic bacteria [75].

A. Modulation of Innate Immunity: Role of Macrophages and Neutrophils

The innate immune response is the relevant mediator of the first line of defence against *Leptospira* infection, and the macrophage and neutrophil response is critical for the recognition and clearance of the pathogen, and importantly all the immune-mediated effects are strongly modulated by the gut microbiota [76].

➢ *Macrophages:*

The function and activity of macrophages is reported to be enhanced by commensal gut bacteria and their metabolites such as short-chain fatty acids (SCFAs) [77]. Macrophages are important for recognising leptospira during leptospirosis, via pattern recognition receptors such as toll-like receptors (TLRs) [78]. Gut dysbiosis may decrease effective macrophage responses, and associated impairment of bacterial clearance and prolonged inflammation responses [79].

➢ *Neutrophils:*

The process of neutrophil mobilisation and maturation is governed by gut microbiota-derived signals. Some studies indicate neutrophil responses are impaired in dysbiosis [80]. This could compromise the host response to avoid Leptospira dissemination, especially because excessive neutrophil activation, that is typically caused by a microbial imbalance, may promote tissue damage and perpetuate systemic inflammation during leptospirosis [81, 82].

B. Modulation of Adaptive Immunity: Role of Tregs and Th17 Cells

The adaptive immune response, particularly the activity of T helper cells, is a major factor in the regulation of the inflammatory process that occurs in leptospirosis. The gut microbiota affect a balance between pro-inflammatory Th17 cells and regulatory T cells (Tregs), maintaining immune homeostasis **[83]**.

➢ *Th17 Cells:*

Gut microbiota are essential to the differentiation and maintenance of Th17 cells, which mediate many of the inflammatory responses that occur in response to bacterial infections [84]. Th17 cell responses in leptospirosis are likely to contribute to tissue injury and damage, especially when they are overactive [85]. Dysbiosis - an overgrowth of inflammatory gut microbes - would amplify the cytokine production mediated by Th17, and cause a hyper-inflationary response with potential for cytokine storm seen in severe cases of leptospirosis [86].

➢ *Tregs:*

Regulatory T cells promote suppression of excessive inflammation and inflammation mediates tissue repair; the effects are less pronounced in the presence of absence of systemic inflammation - therefore it could be seen as a competing factor with regard to inflammation and infection [87]. Commensal bacteria (*Clostridia*) have been shown to induce Treg expansion through SCFA [88]. Dysbiosis or lower proportions of SCFA-producing bacteria reduce Treg activity and function may lead to a reduced capacity for inhibition of inflammation, ultimately tipping the intra-host balance towards leakage and amplification of the inflammation during infection [89].

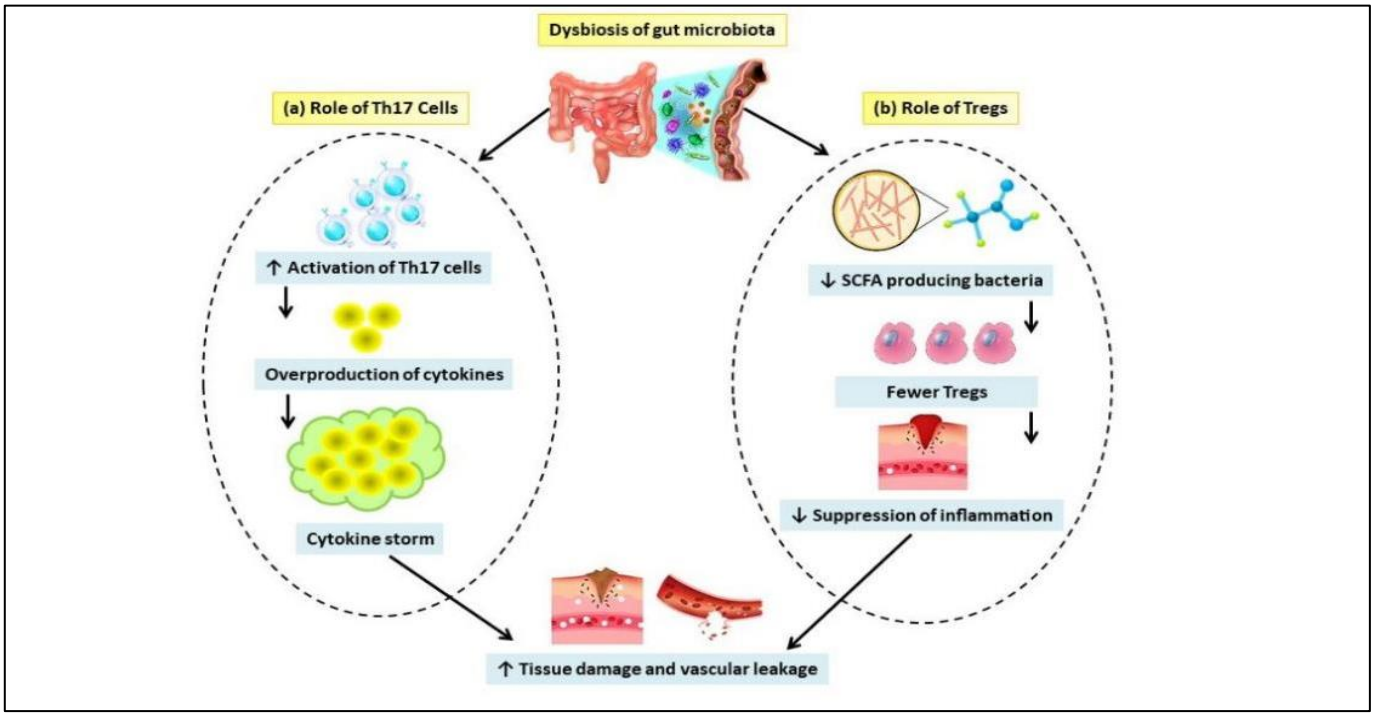

Fig 2: Visualization of Role of Th17 & Tregs

ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/25jul144

C. Hypothetical Models: Gut Dysbiosis, Cytokine Storms, and Organ Damage in Leptospirosis

Severe lethal leptospirosis is associated with systemic inflammation, including cytokine storms, potentially through the gut microbiota's translocation to the immune system [90]. Theoretical models have proposed multiple paths by which limited gut dysbiosis might lead to greater immune dysregulation and organ injury:

- *Barrier Dysfunction and Systemic Inflammation*

Gut dysbiosis often leads to increased permeability of the gut, and bacterial endotoxins such as lipopolysaccharide (LPS) are translocated into the blood circulation. In LPS endotoxic shock (i.e., sepsis), high endotoxin exposures can lead to increasing systemic inflammatory response (i.e., catastrophic inflammation) [91]. In leptospirosis, this may represent an increased risk for cytokine storms, with excessive levels of pro-inflammatory cytokines such as TNF-α, IL-6, and IL-1β that promote endothelial dysfunction, increased vascular permeability, and subsequent multiple organ failure phenomena associated with severe forms of leptospirosis [92].

- *Improved Cytokine Production:*

Changes in the gut microbiome composition attributed to dysbiosis can lead to increased concentration of pro-inflammatory cytokines such as IL-17 and IL-22 [93]. These cytokines are necessary for the resolution of pathogens; however, dysregulated levels can lead to tissue injury. In the case of leptospirosis, exaggerated cytokine production can result in additional renal and pulmonary injury [94]. Microbial Metabolites and Immune Regulation: Dysbiosis causes a reduction in beneficial microbial metabolites like short chain fatty acids (SCFAs) which can disrupt immune regulation and induce hyper-inflammation [95]. The primary SCFAs were shown to promote anti-inflammatory pathways and protect epithelial barrier integrity which has potential consequences with increasing susceptibility of multi-organ dysfunction from leptospirosis [96, 97].

V. THERAPEUTIC PERSPECTIVES

The gut microbiota is an attractive therapeutic target to attenuate the progression and severity of infectious diseases like leptospirosis [98]. Immune dysregulation and systemic inflammation associated with dysbiosis, indicates a potential rationale for the use of microbiota-based approaches to restore immune homeostasis, facilitate pathogen clearance, and decrease injury to tissues and organs [99]. Although we could not find studies on microbiota-based therapy specific to leptospirosis, studies performed with other bacterial infections revealed potential microbiota-based approaches using probiotics, prebiotics, fecal microbiota transplantation (FMT), and dietary approached [100].

A. Probiotics: Modulating Immune Responses and Restoring Gut Homeostasis

Probiotics, or live microorganisms (bacteria and yeasts) that can improve the health of a host, have been shown to have effective roles for restoring microbial balance and regulating immune responses related to bacterial infection [101]. Probiotics exhibit protective mechanisms, notably *Lactobacillus rhamnosus* and *Bifidobacterium bifidum*, that provide improved integrity of the epithelial barrier and associated decreased permeability of the gut leading to decreased systemic translocation of bacterial endotoxins [102, 103]. This is relevant and likely important in the case of leptospirosis since the greatest driver of disease severity is systemic inflammation due to release of endotoxin. Probiotics may also regulate cytokine production by stimulating production of anti-inflammatory cytokines (e.g., IL-10) and decreasing pro-inflammatory cytokine production (e.g., TNF-α) [104]. These immune-modulatory advantages may mitigate cytokine storms and decrease tissue damage associated with leptospirosis. Animal models of sepsis study show that probiotics reduce mortality through the reduction of inflammation and improvements in bacterial clearance [105, 106]. Overall, probiotics have potential for alleviation of complications due to uncontrolled inflammation in patients suffering from severe leptospirosis.

B. Prebiotics: Supporting Beneficial Microbial Populations

Prebiotics, which are non-digestible dietary fibers that selectively stimulate the growth and activity of beneficial gut bacteria, represent another treatment option. Prebiotic compounds such as fructooligosaccharides (FOS) and inulin promote SCFA-producing bacterium, including *Clostridia* and *Bacteroides*, and these organisms play important roles in immune homeostasis [107]. SCFAs, especially butyrate, have anti-inflammatory effects and help to fortify the gut barrier, two useful effects that help with controlling systemic inflammation during leptospirosis [108]. The benefits of prebiotic supplementation for gut microbiota diversity and decreasing severity of bacterial infections, such as *Clostridioides difficile* infections and colitis, has been demonstrated [109]. While direct studies on leptospirosis are currently lacking, prebiotics can help promote biodiversity and recovery of microbiota after dysbiosis induced by infection from *Leptospira* species.

C. Fecal Microbiota Transplantation: Rebuilding Microbial Ecosystems

Fecal microbiota transplantation (FMT), the procedure of transferring stool from a healthy donor to a recipient has been demonstrated to be successful restoring gut microbiota diversity in acute and chronic settings such as recurrent C. difficile infections and inflammatory bowel disease (IBD) [110, 111]. FMT has been suggested to restore gut microbial diversity, increase the production of short-chain fatty acids (SCFAs) and decrease pro-inflammatory immune responses [112]. This restoration of intestinal microbiota diversity may help restore immune homeostasis in cases of leptospirosis where dysbiosis and systemic inflammation are substantial. In mouse models of sepsis, FMT reduced mortality by restoring intestinal barrier function which limited the systemic translocation of bacterial endotoxins [113]. Collectively, these findings suggest that FMT has potential as a rescue therapy in severe cases of leptospirosis where underlying gut barrier dysfunction is concern.

ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/25jul144

D. Dietary Interventions: Enhancing Gut Microbiota Resilience

Dietary changes to influence gut microbiota composition and function may also be used as an adjunct approach to the treatment of leptospirosis. Specifically, diets that incorporate fiber, polyphenols, and omega-3 fatty acids, tend to increase microbial diversity and lead to the production of SCFAs that modify immune responses and lower the level of inflammation [114]. These dietary contents could support recovery of the microbiota and reduce organ damage that may arise from inflammation in leptospirosis. On the other hand, diets high in saturated fats and refined sugars, are associated with gut dysbiosis, and have increased overall inflammatory responses [115]. Therefore, dietary considerations for leptospirosis patients should focus on microbiota supporting foods to improve treatment outcomes.

VI. CONCLUSION

Leptospirosis is a zoonotic disease that is still poorly researched despite being globally active, it leads to severe cases with immune dysregulation, systemic inflammation and multi-organ damage. While there is much established knowledge of its clinical presentation and pathophysiological underpinnings, the potential contribution of gut bacteria in controlling the progress of leptospirosis is a new and largely uninvestigated area of study. Information from research investigating other bacterial pathogens overwhelmingly supports our hypothesis that disruption of gut dysbiosis may worsen immune dysregulation, contribute to cytokine storm biologically and enhance organ damage in cases of leptospirosis. These observations advocate for further study of the interactions between gut microbiota and leptospirosis pathogenesis. The microbiota's role on both innate and adaptive immunity present unique opportunities for therapeutic methods. Probiotics, prebiotics, fecal microbiota transplantation (FMT) and dietary strategies targeting gut microbiota recovery and immune modulation demonstrated success in other infection-mediated diseases. Especially for severe cases that are associated with systemic inflammation and organ failure, using these techniques to modify the course of illness in leptospirosis has the possibility of reducing symptoms and improving clinical outcomes. Nonetheless, considerable knowledge gaps persist. More research is required to define the changes in microbiota during leptospirosis, and identify microbiota-derived biomarkers that may relate to disease severity, as well as to develop an understanding of how gut dysbiosis can affect immune responses and organ damage. More rigorously designed clinical studies are needed to assess the safety and efficacy of microbiota-based treatments in patients with leptospirosis. By combining findings from multi-variable sources, we have developed a review that demonstrates the potential of including microbiota study in leptospirosis studies, which could not only enhance our knowledge of the disease, but ultimately, improve treatment. As such, by outlining the role of gut microbiota in leptospirosis represents an exciting means by which innovative, microbiota-based interventions could be developed to add to current therapies, and to alleviate the global burden of this neglected tropical disease.

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