



## THE IMPACT OF GUT MICROBIOTA ON LONG COVID: INSIGHTS AND CHALLENGES

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Study performed Postgraduate Program in Biotechnology at Potiguar University/ UnP.

Financial support: None.

Conflicts of interest: None.

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Submitted: feb 21; accepted after revision, apr 29, 2024.

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### ABSTRACT

Long COVID-19, characterized by persistent symptoms following acute COVID-19 infection, presents a multifaceted challenge. Recent research has unveiled the potential role of gut microbiota in shaping the course of Long COVID, offering insights into its consequences and therapeutic avenues. Dysbiosis in the gut microbiota, marked by a reduction in beneficial commensal bacteria and an increase in pro-inflammatory taxa, appears to be a common feature in Long-term COVID patients. Notably, microbiota composition correlates with symptom severity and duration, suggesting a link between gut microbiome composition and Long COVID's clinical manifestations. Various interventions, such as antibiotics, probiotics, and dietary modulation, have been explored as potential strategies to mitigate gut dysbiosis and its effects on Long-term COVID-19. Parallels between Long-term COVID and myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) have been drawn, indicating potential shared mechanisms, including gut microbiota involvement. Longitudinal studies highlight the persistence of gut microbiota alterations beyond the acute phase of COVID-19, emphasizing the need for long-term monitoring and interventions. While these findings offer promise, standardized and comprehensive research is essential to establish causality and elucidate the intricate mechanisms underlying the gut microbiota's influence on Long COVID. Understanding this relationship holds the potential to develop novel approaches

for managing and improving Long COVID outcomes, addressing a pressing public health concern.

**Keywords:** post-acute COVID-19 syndrome, post-acute COVID-19 syndromes, Long COVID, PASC post-acute sequelae of COVID-19, gastrointestinal microbiome, gut microbiota.

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## INTRODUCTION

The ongoing global COVID-19 pandemic caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has resulted in a spectrum of clinical manifestations, ranging from asymptomatic or mild respiratory symptoms to severe pneumonia and multi-organ dysfunction<sup>1</sup>.

While the acute phase of the disease has been extensively studied, the emergence of a condition known as "Long COVID" or "Post-Acute Sequelae of COVID-19 (PASC)" has raised significant concern due to its persistent and debilitating nature. Long COVID is characterized by symptoms that persist for weeks or even months after the acute infection has resolved, affecting various organ systems and significantly impairing patients' quality of life<sup>1-3</sup>.

Recent research has shed light on the potential role of gut microbiota in the pathogenesis of Long COVID, as alterations in the composition and dynamics of the gut microbiome have been observed in patients with both acute COVID-19 and Long COVID<sup>2,3</sup>.

The gut microbiota regulates the host's immune response, metabolic processes, and overall health. Dysbiosis, or an imbalance in the gut microbiome, can lead to immune dysfunction and chronic inflammation, hallmarks of Long COVID<sup>4</sup>.

This emerging connection between gut microbiota and Long-term COVID has prompted investigations into its potential as a therapeutic target for alleviating symptoms and improving outcomes in affected individuals<sup>5-7</sup>.

Several studies have explored the dynamics of gut microbiota in patients with long-term COVID-19, shedding light on how changes in microbial composition may correlate with symptom severity and persistence<sup>2,3,5</sup>.

Additionally, research has examined the impact of factors such as antibiotics, probiotics, and dietary interventions on gut microbiota in Long-term COVID patients. Understanding the relationship between the gut microbiome and Long-term COVID is crucial, as it may open new avenues for therapeutic interventions and improve the management of this complex and poorly understood condition<sup>8,9</sup>.

In this comprehensive review, we aim to synthesize the existing literature on the role of gut microbiota in Long COVID. We will analyze findings from recent studies investigating alterations in gut microbiota composition, diversity, and function in

patients with Long-term COVID and their potential implications for disease pathogenesis and symptomatology<sup>9-11</sup>.

Additionally, we will explore the impact of various interventions, including dietary modifications and probiotics, on modulating the gut microbiome in Long COVID patients. Our objective is to provide a thorough overview of the current knowledge regarding the gut microbiota's involvement in Long-term COVID and its potential as a target for therapeutic interventions.

## **METHODS**

The research methodology involved a comprehensive search of multiple reputable databases to ensure the inclusion of relevant studies while minimizing the risk of bias. PubMed, Scopus, Scielo, Embase, and Web of Science were chosen due to their comprehensive coverage of peer-reviewed literature in the medical field. Additionally, Google Scholar was utilized to access gray literature, which often includes valuable insights not found in traditional peer-reviewed articles. The study's selection criteria were centered on the study's focus, which was artificial intelligence's impact on general surgeons' training. To refine the search and capture relevant studies, a combination of keywords was used, including "post-acute COVID-19 syndrome", "post-acute COVID-19 syndromes", "long COVID, PASC post-acute sequelae of COVID-19", "gastrointestinal microbiome," and "gut microbiota." This approach ensured that the selected studies were directly related to the topic of interest. The inclusion criteria encompassed various studies, such as systematic reviews, case-control studies, cross-sectional studies, case series, and review articles. This broad inclusion criteria aimed to gather a comprehensive range of evidence and perspectives on the subject matter. The process of analysis, review, and selection of materials was conducted rigorously to maintain the quality and relevance of the chosen studies. It involved a systematic and blinded approach, with pairs of reviewers independently assessing the title and abstract of each study. In cases of disagreement between the two reviewers, a third reviewer was involved to reach a consensus and ensure the final selection of studies was based on well-founded criteria. This meticulous research methodology guarantees that the findings and conclusions drawn in the article are rooted in a robust and diverse body of evidence, enhancing the credibility and reliability of the study's outcomes.

## **RESULTS AND DISCUSSION**

Long COVID has emerged as a perplexing and debilitating condition characterized by persistent symptoms following acute COVID-19 infection. Recent research has shed light on the potential role of the gut microbiota in influencing the course of long-term COVID, offering intriguing insights into the consequences and effects of microbial alterations<sup>12</sup>.

A recurring theme in these studies is the presence of dysbiosis within the gut microbiota of Long COVID patients. This dysbiosis typically involves a decrease in

beneficial commensal bacteria like *Bifidobacterium* and *Lactobacillus*, coupled with an increase in pro-inflammatory taxa<sup>5-8</sup>.

Such microbial imbalances are thought to trigger immune dysregulation and chronic inflammation, potentially contributing to the prolonged and diverse symptomatology observed in Long COVID<sup>4</sup>.

One significant finding is the association between gut microbiota profiles and the severity and duration of Long COVID symptoms<sup>5</sup>. Liu et al. revealed that individuals experiencing more severe Long COVID symptoms exhibited distinct microbiota profiles, implying a potential link between gut microbiome composition and symptom severity<sup>5,6</sup>.

This observation was further corroborated by Ancona et al., who reported dysbiosis in both gut and airway microbiota, suggesting its potential role in influencing respiratory symptoms associated with long-term COVID<sup>3</sup>.

Recognizing gut microbiota involvement in Long COVID has opened doors to therapeutic exploration. Su et al. (2022) delved into the impact of antibiotics and probiotics on gut antimicrobial resistance gene reservoirs, highlighting the potential of these interventions to modulate gut microbiome composition and, consequently, Long-term COVID outcomes<sup>7,11,12</sup>.

Furthermore, Wang et al. demonstrated the alleviation of severe gastrointestinal symptoms in a Long COVID patient through nutritional modulation of the gut microbiota, suggesting the promise of dietary interventions<sup>13</sup>.

Intriguingly, parallels have been drawn between long-term COVID and myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS), prompting investigations into potential shared mechanisms<sup>4-6</sup>.

Komaroff and Lipkin proposed that insights from ME/CFS research might contribute to unraveling the pathogenesis of long-term COVID-19, hinting at possible commonalities that potentially involve the gut microbiota<sup>2-4</sup>.

Vestad et al. provided valuable insights into the persistence of gut microbiota alterations beyond the acute phase of COVID-19<sup>14-17</sup>. Their study suggested that the impact of gut dysbiosis might extend for months, emphasizing the necessity for long-term monitoring and interventions to address the consequences of these microbial changes<sup>18</sup>.

Mundula et al. explored the implications of chronic low-grade inflammation in various diseases, including the potential modulation through gut microbiota interventions. This perspective highlights the crucial role of gut microbiota in regulating host inflammatory responses and its potential influence on disease outcomes<sup>19</sup>.

Moreover, Nguyen et al. conducted a metagenomic assessment of gut microbial communities, offering a deeper understanding of their potential influence on COVID-19 severity<sup>15</sup>. Their study unraveled the intricate interplay between gut microbiota and

host responses, providing critical insights into how microbiota composition may shape the course of the disease<sup>18-20</sup>.

While these studies collectively suggest a role for gut microbiota in long-term COVID, it is essential to acknowledge the variability in findings and methodologies. Robust and standardized research is necessary to establish causality and unravel the intricate mechanisms by which the gut microbiota influences long COVID.

## **CONCLUSION**

In conclusion, the emerging evidence underscores the potential significance of gut microbiota alterations in the pathogenesis and clinical progression of long-term COVID-19. Dysbiosis in the gut microbiome appears to be associated with symptom severity and duration, offering promising avenues for therapeutic interventions.

Longitudinal studies indicate that the impact of gut dysbiosis may extend well beyond the acute phase of the disease. However, comprehensive, and standardized research is crucial to establish causality definitively and unlock the intricate mechanisms underlying the influence of the gut microbiota on COVID. Understanding this relationship holds the promise of novel approaches to managing and improving the outcomes of Long COVID patients, addressing a pressing public health concern.

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