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Insights into the Viral Evolution and Microbial Interactions In COVID-19

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Abstract

The ongoing COVID-19 pandemic, caused by the novel coronavirus SARS-CoV-2, has been largely described in terms of virology and immunology. However, to understand the disease process, it is important to "digest" the microbial content of the disease. In this review, we will try to synthesize the known information on COVID-19 from a microbiological perspective that considers the interaction between the virus and the host, and existing microbes. We will first review the molecular virology and evolutionary biology of SARS-CoV-2, including viral entry, replication, and immune evasion mechanisms, as well as the factors that drive the development of variants of concern. Next, we will review the interplay between the host and the pathogen, considering the lens of viral-induced changes in the host's cellular networks and the mismanaged immune response. An entire core focuses on Infection ecology and covers the prevalence, effect, and mechanisms of bacterial and viral co-infection/secondary infection outcomes. Expanding the lens on the host-virus interaction to the host-microbiome interaction, we will review the gut-lung axis, considering evidence that the gut microbiome influences the severity of the disease and the risk of Post-Acute Sequelae of COVID-19 (PASC, or Long COVID), and the mechanisms by which this might occur. We will also review changes in the lung and oropharyngeal microbiomes during COVID-19 infection. Lastly, we will review the clinical and therapeutic implications of the host-microbiome interaction in

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COVID-19, considering the role of the microbiome in disease, the effect of antimicrobials, and new therapeutic approaches to the host microbiome. In this review, we will argue that COVID-19 is not a viral disease but a systemic microbiological disorder that must be taken into account in the development of new approaches to the disease, including personalized medicine approaches to the treatment and prevention of COVID-19 and future pandemics.

Keywords: COVID-19, Microbial interaction, Viral Evolution, Co-infection, Microbiome, Gut-Lung Axis.

Graphical Abstract:

The review explores COVID-19 from a microbiological perspective, emphasizing the interplay between SARS-CoV-2 and existing microbes. It discusses molecular virology, the virus's replication and immune evasion, and the evolution of variants. Additionally, it examines the host-pathogen dynamics, including immune response and co-infections. The role of the gut microbiome in influencing disease severity and long COVID is highlighted, alongside changes in lung and oropharyngeal microbiomes during infection. Finally, it posits that COVID-19 is a systemic microbiological disorder, advocating for personalized medicine approaches in treatment and prevention.

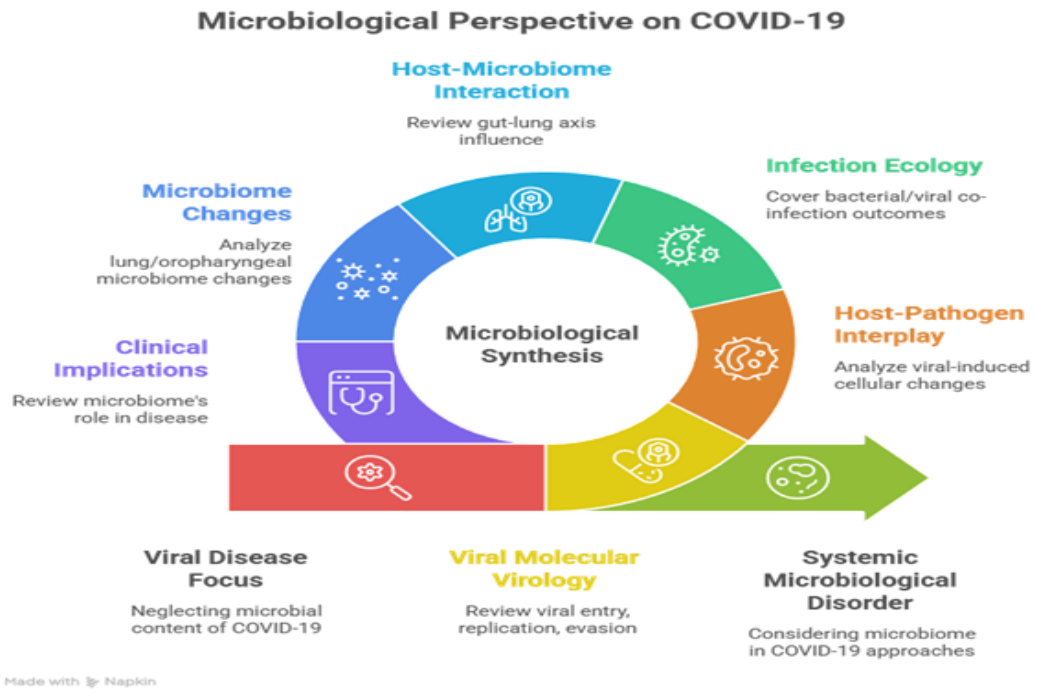

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Figure (1): Conceptual framework of microbiological aspects of COVID-19

1. Introduction

"The emergence of SARS-CoV-2 and the resulting COVID-19 pandemic has triggered an unparalleled scientific response worldwide. In the early stages of the pandemic, the scientific community's attention was fully focused on the virus: determining the virus's structure, sequencing the genome, developing tests, and understanding the acute clinical picture. This virus-centric strategy, reminiscent of classical virology, has been essential for the rapid development of vaccines and antiviral drugs against the virus. However, as the pandemic has persisted, it has become increasingly clear that the outcome of SARS-CoV-2 infection depends neither on the amount of virus nor the type of virus but on the complex interplay between the virus and the biological environment of the host, teeming with microorganisms [1,2].

Each of us is a holobiont, a superorganism comprising human cells and a vast, diverse community of microbes, such as bacteria, archaea, viruses, and fungi, living as commensals, symbionts, and pathogens. This community of microbes, particularly in the gut and lungs, plays a critical role in the process of teaching and fine-tuning the immune system, maintaining barriers, metabolizing nutrients, and excluding pathogenic microorganisms. In this context, the term ‘pathogen’ takes on a different meaning, and the disease process represents the imbalance between the host, the host's microbiota, and the invading microbe [3,4].

A powerful example in the application of such an ecological approach is the COVID-19 pandemic. The symptomatology varies from asymptomatic to lethal multi-organ failure. While the variability in the presentation is partly explained by the host’s genetic make-up and comorbidities, the current review hypothesizes that the human microbiome plays a vital role in the pathogenesis of COVID-19. The infection with the virus SARS-CoV-2 directly and indirectly alters the balance in the microbiome (dysbiosis), which in turn might worsen the symptoms by increasing the inflammatory response and the risk of secondary infections. The pre-existing composition of the microbiome in an individual might prepare the immune system for a better or worse response to the virus. [5,6].

1.2. Objectives and Scope of this Review

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The objective of this article is to present a thorough synthesis of all the various ways that microbiology and COVID-19 intersect. We shall progress sequentially from the virus itself, through immediate cellular interfaces with the virus, and then to the wider world of co-infection and the overall system with regard to the host's microbiome. It is our hope that this article can serve as a means to convince researchers and clinicians alike that a holistic microbiological understanding is a requirement for grasping heterogeneity in disease presentation, predicting outcomes in those with severe disease, finding new targets for therapeutic intervention, and limiting the long-term consequences of this pandemic.

2. The Agent: Molecular Virology and Evolution of SARS-CoV-2

2.1. Viral Architecture and Genome Organization

SARS-CoV-2 is an enveloped virus with a positive-sense single-stranded RNA genome. The ~30 kb genome is one of the largest in the RNA virus world. The genome is encased in a helical nucleocapsid protein (N protein). The viral envelope is studded with the structural proteins essential for viral infection: the spike protein (S), membrane protein (M), and envelope protein (E)[7,8].

The viral genome carries the genes for structural proteins and a set of non-structural proteins (nsp1-16), which make up the viral transcription- replication complex. In addition, the viral genome carries accessory genes like ORF3a, ORF6, ORF7a, ORF7b, ORF8, ORF9b, ORF10. The mutation rate is lower due to the efficient proofreading function of the viral exoribonuclease (nsp14), although the large scale of the virus epidemic ensures that the virus has had the opportunity to evolve significantly [9,10].

2.2. The Spike Protein: Structure, Function, and Host Cell Entry

The S protein trimer acts as the key to the entrance of the virus into the host cell. Each of the S protein monomers has two subunits: S1 and S2. The S1 subunit has the receptor-binding domain (RBD), while the S2 subunit has the membrane fusion activity. The main target of SARS-CoV-2 is the angiotensin-converting enzyme 2 (ACE2), which is found on the epithelial cells of the respiratory system, gastrointestinal system, heart, kidneys, and endothelium. The attachment of the viral RBD to the ACE2 receptor on the target cell surface is the first crucial event in the infection process [11,12].

The cleavage of the viral S protein is essential for the viral entry process. The S1 and S2 subunits are cleaved by the host proteases such as furin at the S1/S2 junction. The S2'

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site of the S protein is then cleaved by the transmembrane protease serine 2 (TMPRSS2), which results in the fusion of the viral envelope with the plasma membrane. Alternatively, the S protein may also enter the host cell by the process of endocytosis in the absence of TMPRSS2. The cathepsins are the proteases responsible for the cleavage of the S protein in the process of endocytosis. The S protein is the major target of the immune system and hence the epicenter of the evolutionary process of the virus.

2.3. Viral Replication Cycle and Intracellular Hija

After entry and uncoating, the viral RNA is translated into large polyproteins pp1a and pp1ab. These polyproteins are cleaved into individual nsps by viral proteases (PLpro and 3CLpro). These nsps assemble to form the replication transcription complex in double-membrane vesicles, protecting the viral RNA from the host immune system. In this compartment, a set of subgenomic mRNAs is generated, enabling the efficient transcription of viral structural and accessory genes. New viral particles assemble in the ER-Golgi intermediate compartment and are secreted via exocytosis. This process significantly reprograms the host cell metabolism and organelles, inducing cell stress and apoptosis and releasing DAMPs [14].

2.4. Viral Evolution in Real-Time: Drivers, Variants, and Fitness

The global pandemic has allowed for the real-time observation of viral evolution. Key drivers include: 1) Neutral genetic drift due to replication errors, 2) Natural selection for increased transmissibility and immune evasion, and 3) Recombination, which can lead to major jumps in phenotype [15].

Variants of Concern (VoCs) like Alpha (B.1.1.7), Beta (B.1.351), Gamma (P.1), Delta (B.1.617.2), and Omicron (B.1.1.529) have sequentially dominated the pandemic. Each carried a constellation of mutations, often concentrated in the S protein. For example, the D614G mutation early in the pandemic increased infectivity. The Delta variant's L452R and P681R mutations enhanced transmissibility and fusogenicity. Omicron represents a stark leap in immune evasion, with over 30 S protein mutations reducing antibody neutralization, while its mutations also appear to shift tropism more towards the upper airways, affecting disease presentation [16].

Fitness is a complex trade-off. Mutations that enhance receptor binding (e.g., N501Y) or furin cleavage (e.g., P681R) may increase transmissibility. Mutations that alter antigenic

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sites (e.g., E484K, K417N/T) aid immune escape. However, these changes can come at a cost to replicative fitness or stability, leading to dynamic shifts in variant predominance [17].

2.5. Animal Reservoirs and Zoonotic Potential

The SARS-CoV-2 virus is of zoonotic origin, suggesting that it came from bats, possibly through an intermediate host. The ability of SARS-CoV-2 to utilize ACE2 from various hosts has been shown. Reverse zoonosis, from humans to animals, has been seen in mink, deer, cats, and dogs, suggesting that SARS-CoV-2 has the ability to create new reservoirs of infection, making eradication of the virus more difficult, particularly since new variants of the virus, as seen in the case of mink, can be transmitted back to humans. This is one of the important microbiological activities that needs to be conducted at the human-animal interface [18].

3. The Host-Pathogen Interface: Cellular Warfare and Immune Dysregulation

3.1. Viral Recognition and the Innate Immune Battle: Interferon Antagonism

The first line of defense is the innate immunity of the host. The viral RNA is recognized by the pattern recognition receptors, like RIG-I and MDA5, which activate the signaling cascade, leading to the production of type I (α/β) and type III (λ) interferons. These, in turn, induce the antiviral state in neighboring cells through the upregulation of hundreds of interferon-stimulated genes (ISGs) [19].

A unique feature of the SARS-CoV-2 pathogenesis is the strong ability of the virus to interfere with the host's interferon system. The virus has developed various strategies to interfere with the IFN system at all stages. For example, the nsp1 subunit blocks the translation of the IFN mRNAs. The ORF6 subunit blocks the nuclear transport of the transcription factors, like STAT1. The ORF3a and M subunits interfere with the IFN signaling pathway. The delayed and reduced IFN response is a significant factor in the severity of the disease. It allows the virus to replicate maximally in the early phase, followed by a hyperactive inflammatory response, leading to the severity of the disease [20].

3.2. Role of Viral Accessory Proteins in Immune Evasion

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The accessory proteins of the virus are not required for the in vitro growth of the virus but are very important in the pathogenesis of the disease. The accessory proteins are multifunctional tools of immune evasion [21]:

1. The ORF3a subunit induces apoptosis and NLRP3 inflammasome activation, leading to inflammation.
2. The ORF6 subunit, as discussed above, is a strong inhibitor of IFN.
3. The ORF7a subunit stimulates the inflammatory response and inhibits the ISGs.
4. The ORF8 subunit regulates the expression of the MHC-I complex, which helps the virus to escape the immune system. It is also associated with the induction of inflammation.
5. The ORF9b subunit is located in the mitochondria and inhibits the innate immunity.

3.3. From Controlled Response to Cytokine Storm: The Path to Hyperinflammation

In severe cases of COVID-19, this inability to control the virus initially triggers massive pyroptosis of infected lung cells and immune cells. This triggers an uncontrollable feedback loop of activation of macrophages and other immune cells due to the massive release of DAMPs and viral components. This triggers the infamous "cytokine storm," where there is an overwhelming release of pro-inflammatory cytokines and chemokines such as IL-6, IL-1β, TNF-α, CXCL10, etc. [22].

It is this overwhelming inflammatory response rather than the cytopathy caused by the virus itself that is responsible for acute respiratory distress syndrome, endothelial dysfunction, and multi-organ failure. It is this uncontrolled host-microbe relationship where the host's immune response is more pathogenic than the virus itself [23].

3.4. Autoimmunity and Molecular Mimicry: Cross-reactive Responses

Another issue that adds complexity is that of "virus-induced autoimmunity." This occurs because, if pieces of viruses look like our own proteins, our immune system will begin to generate antibodies that will then attack our own human tissues. For example, it has been shown that antibodies developed to fight the "S protein" will actually bind to our own human tissue antigens, which could potentially cause thrombotic events or other

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"autoimmune-like syndromes" that occur with acute COVID or Long COVID. This further adds to the "immunological chaos" [24].

4. The Ecology of Infection: Co-Infections and Secondary Infections

4.1. Epidemiology and Clinical Impact of Bacterial Co-infections

Unlike influenza infections, where bacterial co-infection is a main contributor to mortality, preliminary reports indicate low rates (~3-7%) of bacterial co-infection among patients admitted for COVID-19. However, secondary bacterial infections are a significant problem among patients admitted for COVID-19 and are a main contributor to mortality among these patients. These bacterial infections include ventilator-associated bacterial pneumonia and can occur up to 15-20% among critically ill patients [25].

These bacterial infections include Staphylococcus aureus (methicillin-susceptible and methicillin-resistant), *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, and *Escherichia coli*. The compromised lung epithelium and immune system compromise (especially lymphopenia and neutrophil dysfunction) create an ideal environment for these opportunistic pathogens to infect patients with COVID-19[26].

4.2. Viral Co-infections: Influenza, RSV, and Endogenous Virome

In addition, co-infection with other respiratory viruses is not unusual. Various research findings have shown co-detection with other viruses such as rhinovirus, influenza, RSV, and metapneumovirus. The consequences of such co-infection are varied, with some findings indicating increased severity and others failing to do so. The relationship between these viruses can be synergistic, competitive, or neutral, depending on the viruses and host factors [27].

Furthermore, the effect of SARS-CoV-2 on the endogenous respiratory virome, i.e., the viruses that live within our respiratory tract, such as bacteriophages and persistent viruses such as anelloviruses, is an emerging field. Anellovirus load, for example, can be used as an indicator of immune competence. The disruption caused by SARS-CoV-2 could have an impact on the ecological balance of this virome with unknown consequences [28].

4.3. Fungal Co-infections: The Rise of Candida auris and Pulmonary Aspergillosis

Fungal infections represent a particularly deadly complication. COVID-19-associated pulmonary aspergillosis (CAPA) is a major concern in ICU patients, with mortality exceeding 50%. Aspergillus spores, normally cleared by a healthy immune system, exploit

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the COVID-19-induced lung damage and immune suppression (especially from corticosteroid use). Similarly, the multidrug-resistant yeast *Candida auris* has caused outbreaks in COVID-19 units. Its ability to persist on surfaces and its resistance to common antifungals make it a formidable nosocomial threat. These infections highlight how a viral pandemic can directly amplify the burden of other resistant microbial pathogens [29] .

4.4. Mechanisms of Synergy: Viral Damage, Immune Exhaustion, and Niche Creation

The synergy between SARS-CoV-2 and secondary microbes can be explained by several interconnected mechanisms [30]:

1. Physical Barrier Breach: Viral cytotoxicity destroys the mucociliary escalator and epithelial lining, exposing basement membrane and allowing bacterial adherence.
2. Immune Dysregulation: Lymphopenia, neutrophil dysfunction, and macrophage reprogramming impair bacterial clearance.
3. Upregulation of Receptors: Viral inflammation may upregulate host receptors for bacteria (e.g., platelet-activating factor receptor for *S. pneumoniae*).
4. Resource Competition & Altered Microenvironment: Viral consumption of cellular resources and changes in local pH or oxygen tension may favor certain bacteria.
5. Bacterial Superantigens: Toxins from bacteria like *S. aureus* could hyper-stimulate the already dysregulated T-cell response, potentially exacerbating the cytokine storm—a hypothesis that warrants further investigation [31].

5. The Gut-Lung Axis in COVID-19: A Two-Way Street of Dysbiosis

5.1. Evidence Linking Gut Microbiota Composition to Disease Severity

There is an increasing body of evidence from both cross-sectional and longitudinal studies showing the significant disruption of the gut microbiome in COVID-19-infected patients when compared with healthy controls. In severe COVID-19, the gut microbiome appears to be in this condition:

1. Loss of beneficial gut flora, which serve to modulate the immune system, including *Faecalibacterium prausnitzii*, a member of the butyrate-producing bacteria, *Eubacterium rectale*, *Bifidobacterium species*, and *Roseburia*.
2. Increase in Opportunistic Organisms or Pro-Inflammatory Microbes Such as *Enterococcus*, *Actinomyces*, *Clostridium* hatheway Such a dysbiosis is also seen to correlate with the severity of the sick patient and with inflammation levels such as

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IL-6, IL-10, and CRP. Furthermore, the altered microbial composition can extend for months beyond the resolution of the virus in the body of the individual; this may be the reason for the association with long COVID.

5.2. Mechanisms of Communication: Immune Modulation, Metabolites, and Barrier Integrity

The gut influences lung immunity through several pathways:

"A specific immune response to microbes and their metabolites begins in the gut, where they prime the body's total immune response." This occurs as dendritic cells survey the microbes in the gut and later arrive at distant sites, including the lungs, to influence how "T cells differentiate into either regulatory and Th17 responses." Losing certain microbes leads to an overactive inflammatory response in the lungs.

Metabolites from microbes are also very important, such as short-chain fatty acids, particularly butyrate secreted from fiber-loving microbes, which are known for keeping the barrier tight, reducing the inflammation level in macrophages and T cells, and even affecting the levels of ACE2. If short-chain fatty acids are lacking, such as in some COVID-19 patients, it will even lead to uncontrolled lung inflammation.

In the same way, dysbiosis and a leaky gut may also lead to endotoxin translocation, which occurs when live bacteria or their by-products such as lipopolysaccharides are found in the blood.

5.3. Gut Dysbiosis as a Driver of Long COVID: Evidence and Hypotheses

Post-acute sequelae of SARS-CoV-2 infection, also known as PASC or Long COVID, refers to a state of health where a significant percentage of people who were infected with the SARS-CoV-2 virus present with symptoms such as fatigue, cognitive impairment or “brain fog,” dyspnea, among other symptoms. Some of the recent research findings include the following:

“Gut dysbiosis appears to be more pronounced and persistent.” The possible mechanisms for this include:

1. Persistent Inflammation: The “leaky gut” syndrome may be causing persistent inflammation.
2. Autoimmunity: The similarities between SARS-CoV-2 and the gut commensals may be causing a persistent autoimmune response.

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3. Viral Persistence: The presence of SARS-CoV-2 RNA or antigens in the gastrointestinal tract may be causing persistent inflammation.
4. Metabolic Dysfunction: The metabolic dysfunction may be affecting the neurotransmitter system through the brain-gut axis or the metabolic rate.

5.4. Therapeutic Implications: Probiotics, Prebiotics, and Fecal Microbiota Transplantation

This route also offers the possibility for advancement, with various research papers utilizing randomized clinical trials to examine potential strains of probiotics, such as the combination of *Lactobacillus* and *Bifidobacterium*, in relation to COVID-19. The results show reduced duration, severity, and viral load. Prebiotics, which are dietary fibers required to maintain a healthy microbiome, and postbiotics, which are bacterial metabolites, are also being researched [38].

Regarding the case of severe, recurring *Clostridioides difficile* infection co-occurring with COVID-19, fecal microbiota transplantation was found to be therapeutically effective, reducing the symptoms in patients infected with COVID-19. However, this is not recognized as an effective therapy for COVID-19 infection. Nevertheless, these findings support the theory that the human microbiome is involved in the modulation of the disease.

6. Local Microbial Landscapes: Respiratory and Oropharyngeal Micro biome Shifts

6.1. Alterations in the Lower Respiratory Tract Microbiome

The lower respiratory tract, previously considered a sterile site, harbors a small but unique microbiome. In the context of COVID-19, studies of bronchial lavage fluids demonstrate reduced microbial diversity with increased bacterial load. Among the expanded microbiome associated with COVID-19, the relative abundance of *Streptococcus*, *Staphylococcus*, *Prevotella*, and *Veillonella* species increases. Several studies demonstrate the expanded microbiome to include species previously isolated from the human oral cavity, thus supporting the hypothesis of microaspiration. [40]

6.2. Oropharyngeal Microbiome as a Predictor and Modulator

The oropharynx is the primary site for the colonization of viruses and is also the frontline in the initiation of the infection process. The resident microbiota in the oropharynx could be a primary indicator of this process. The viral load in throat swabs could show a pattern that is correlated to the severity of disease and the immune response

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in the host. In particular, high levels of *Neisseria* and *Streptococcus* in the oropharynx are indicative of less severe disease, whereas high levels of *Porphyromonas* and *Fusobacterium* are indicative of severe disease. The resident microbiota in the oropharynx could be responsible for modulating the immune response to viral disease by interacting directly with the virus via resident bacterial communities [41] .

6.3. Interactions Between SARS-CoV-2 and Commensal Bacteria: Adhesion and Amplification

In vitro findings suggest that certain commensal or pathogenic microorganisms may increase the infectivity of SARS-CoV-2. In this case, the *Neisseria* and *Mycoplasma* species have protease activity, which can cleave the spike protein of the virus. Other microorganisms may act as a scaffold to concentrate the virus on the surface of the epithelial cells. Although these findings have yet to be verified in vivo, they demonstrate a very interesting direct microbiological interaction, in which the resident microbiota may play an active role in the life cycle of the virus [41].

7. Diagnostic, Prognostic, and Therapeutic Implications

7.1. Microbiome-Based Biomarkers for Risk Stratification

The integration of microbial information (gut and oropharyngeal signatures) with the clinical and immunological information of the host has the potential to provide a robust prognostic tool. The microbiome risk score can help in the identification of patients at admission who are at a high risk of progressing to severe disease, thus allowing for earlier intervention and efficient resource allocation [42].

7.2. The Dilemma of Antimicrobial Stewardship in COVID-19

The pandemic led to a significant increase in empirical antibiotic use, driven by diagnostic uncertainty and apprehensions regarding co-infection. This is largely unwarranted and puts all efforts to combat AMR at risk. Advances in diagnostic technology, such as rapid multiplex PCR for respiratory pathogens and procalcitonin-guided antibiotic stewardship, are critical in such a situation, as is strict adherence to stewardship principles [43].

7.3. Novel Therapeutic Avenues: Targeting the Microbiome and Bacterial Superantigens

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Besides the antiviral or immunomodulatory strategies, the microbial view of the disease has highlighted several other potential targets for therapy:

1. Next-Generation Probiotics/Symbiotic: Designing specific combinations of bacteria or bacteria with prebiotics to reestablish a healthful, anti-inflammatory microbiome.
2. Phage Therapy: Focusing on the specific multidrug-resistant pathogens responsible for secondary infections in COVID-19 ICU outbreaks.
3. Bacterial Toxin Neutralization: If the role of staphylococcal or streptococcal superantigens in cytokine storm can be confirmed, the use of specific antitoxins might provide a useful adjunctive therapy.
4. Microbial Metabolite Supplementation: Direct administration of postbiotics, such as butyrate or other beneficial microbial metabolites [44].

7.4. Implications for Vaccine Development and Variant Surveillance

It is important to understand the molecular evolution of viruses in order to update vaccine strains. Microbiome surveillance and rates of co-infection in vaccinated versus non-vaccinated groups may provide valuable information about non-specific effects of vaccines. Finally, surveillance for secondary bacterial and fungal infections in COVID-19 endemic areas is important for hospital preparedness and control of antimicrobial resistance [45].

8. Conclusion and future scope

The COVID-19 pandemic also reminds us that human health is situated within a complex microbial environment. The manifestations of SARS-CoV-2 infection are not solely determined by the virus itself but also by its interaction with the resident bacteria, fungi, and viruses within the host, as well as its potential to impact the subtle balance of the human microbiome. From the evolutionary patterns of viral variants to the untoward effects of co-infections, and from the systemic impact of the gut- lung axis to the potential role of dysbiosis in chronic diseases, the science of microbiology is the key to unlocking our understanding of this infectious agent.

Looking to the future, the integrated approach to infectious diseases, pandemics, and personalized medicine must take into account the importance of the microbiome. When we view the patient not simply as the host to the infectious agent, but rather the human body

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as a superorganism, it becomes possible to develop more effective strategies to prevent, treat, and mitigate the effects of COVID-19, as well as future emerging infectious diseases [55–60].

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None.

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Authors' Contributions

Noor Hasan and her team work conceived the idea and wrote the original draft of the manuscript, and the author reviewed and edited the final version.

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References:

1. L. Bao, C. Zhang, J. Dong, L. Zhao, Y. Li, and J. Sun, "Oral microbiome and SARS-CoV-2: Beware of lung co-infection," Front. Microbiol., vol. 11, p. 1840, 2020, doi: 10.3389/fmicb.2020.01840.
2. C. Gaebler et al., "Evolution of antibody immunity to SARS-CoV-2," Nature, vol. 591, no. 7851, pp. 639–644, 2021, doi: 10.1038/s41586-021-03207-w.
3. C. Gallo et al., "The relevance of complementary and alternative medicine in the fight against SARS-CoV-2: Emphasis on microbiota-derived molecules," Front. Pharmacol., vol. 12, p. 649310, 2021, doi: 10.3389/fphar.2021.649310.
4. P. Gutierrez-Castrellon, T. Gandara-Martí, Y. Abreu, A. T. A., C. D. Nieto-Rufino, and E. Lopez-Orduña, "Probiotic improves symptomatic and viral clearance in Covid19 outpatients: A randomized, quadruple-blinded, placebo-controlled trial," Gut Microbes, vol. 14, no. 1, p. 2018899, 2022, doi: 10.1080/19490976.2021.2018899.

   Published by DAC Democratic Arabic Center
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5. A. G. Harrison, T. Lin, and P. Wang, "Mechanisms of SARS-CoV-2 transmission and pathogenesis," Trends Immunol., vol. 41, no. 12, pp. 1100–1115, 2020, doi: 10.1016/j.it.2020.10.004.
6. M. Hoffmann et al., "SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor," Cell, vol. 181, no. 2, pp. 271-280.e8, 2020, doi: 10.1016/j.cell.2020.02.052.
7. S. K. Korang et al., "Interventions for treatment of COVID-19: Second edition of a living systematic review with meta-analyses and trial sequential analyses (The LIVING Project)," PLoS ONE, vol. 17, no. 3, p. e0265708, 2022, doi: 10.1371/journal.pone.0265708.
8. M. M. Lamers and B. L. Haagmans, "SARS-CoV-2 pathogenesis," Nat. Rev. Microbiol., vol. 20, no. 5, pp. 270–284, 2022, doi: 10.1038/s41579-022-00713-0.
9. L. Liu et al., "Anti-spike IgG causes severe acute lung injury by skewing macrophage responses during acute SARS-CoV infection," JCI Insight, vol. 4, no. 4, p. e123158, 2019, doi: 10.1172/jci.insight.123158.
10. Y. López-Hernández et al., "Gut microbiota disturbances in hospitalized patients with COVID-19 and bacterial pneumonia: A case-control study," Sci. Rep., vol. 13, no. 1, p. 3378, 2023, doi: 10.1038/s41598-023-30322-7.
11. A. Mantovani, M. C. Morrone, C. Patrono, M. G. Santoro, S. Schiaffino, G. Remuzzi, and G. Bussolati, "Long Covid: Where we stand and challenges ahead," Cell Death Differ., vol. 29, no. 10, pp. 1891–1900, 2022, doi: 10.1038/s41418-022-01052-6.
12. A. R. Marra et al., "Incidence and outcomes of ventilator-associated pneumonia in critically ill patients with COVID-19: A multicenter cohort study," Infect. Control Hosp. Epidemiol., vol. 42, no. 1, pp. 5–11, 2021, doi: 10.1017/ice.2020.431.
13. E. J. Márquez, J. Trowbridge, G. A. Kuchel, and J. Banchereau, "The lethal triangle of COVID-19, aging, and inflammation: Key role for microbiome dysbiosis," Aging Cell, vol. 21, no. 2, p. e13547, 2022, doi: 10.1111/acel.13547.
14. Y. R. Nobel et al., "Gastrointestinal symptoms and coronavirus disease 2019: A case-control study from the United States," Gastroenterology, vol. 159, no. 1, pp. 373-375.e2, 2020, doi: 10.1053/j.gastro.2020.04.017.

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15. S. Platto, Y. Wang, J. Zhou, and E. Carafoli, "History of the COVID-19 pandemic: Origin, explosion, worldwide spreading," Biochem. Biophys. Res. Commun., vol. 538, pp. 14–23, 2021, doi: 10.1016/j.bbrc.2020.10.087.

16. M. Rawat, P. Chandrasekharan, M. D. Hicar, and S. Lakshminrusimha, "COVID-19 in newborns and infants—low risk of severe disease: Silver lining or dark cloud?," Am. J. Perinatol., vol. 38, no. 4, pp. 370–375, 2021, doi: 10.1055/s-0040-1721659.

17. C. D. Russell et al., "Co-infections, secondary infections, and antimicrobial use in patients hospitalised with COVID-19 during the first pandemic wave from the ISARIC WHO CCP-UK study: A multicentre, prospective cohort study," Lancet Microbe, vol. 2, no. 8, pp. e354–e365, 2021, doi: 10.1016/S2666-5247(21)00090-2.

18. J. Shang, Y. Wan, C. Luo, G. Ye, Q. Geng, A. Auerbach, and F. Li, "Cell entry mechanisms of SARS-CoV-2," Proc. Natl. Acad. Sci. USA, vol. 117, no. 21, pp. 11727–11734, 2020, doi: 10.1073/pnas.2003138117.

19. H. Sokol et al., "SARS-CoV-2 infection in nonhuman primates alters the composition and functional activity of the gut microbiota," Gut Microbes, vol. 13, no. 1, pp. 1–19, 2021, doi: 10.1080/19490976.2021.1893113.

20. X. Tang et al., "On the origin and continuing evolution of SARS-CoV-2," Natl. Sci. Rev., vol. 7, no. 6, pp. 1012–1023, 2020, doi: 10.1093/nsr/nwaa036.

21. W. Tao et al., "Analysis of the intestinal microbiota in COVID-19 patients and its correlation with the inflammatory factor IL-18," Med. Microecol., vol. 5, p. 100023, 2022, doi: 10.1016/j.medmic.2020.100023.

22. R. Viana et al., "Rapid epidemic expansion of the SARS-CoV-2 Omicron variant in southern Africa," Nature, vol. 603, no. 7902, pp. 679–686, 2022, doi: 10.1038/s41586-022-04411-y.

23. B. Wang, L. Zhang, Y. Wang, T. Dai, Z. Qin, F. Zhou, and L. Zhang, "Alterations in microbiota of patients with COVID-19: Potential mechanisms and therapeutic interventions," Signal Transduct. Target. Ther., vol. 7, no. 1, p. 143, 2022, doi: 10.1038/s41392-022-00986-0.

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24. R. Wölfel et al., "Virological assessment of hospitalized patients with COVID-2019," Nature, vol. 581, no. 7809, pp. 465–469, 2020, doi: 10.1038/s41586-020-2196-x.

25. F. Wu et al., "A new coronavirus associated with human respiratory disease in China," Nature, vol. 579, no. 7798, pp. 265–269, 2020, doi: 10.1038/s41586-020-2008-3.

26. D. Yadav and A. Kelkar, "Gut microbiome dysbiosis in COVID-19: Modulation and approaches for prevention and therapy," Int. Immunopharmacol., vol. 117, p. 109945, 2023, doi: 10.1016/j.intimp.2023.109945.

27. Y. K. Yeoh et al., "Gut microbiota composition reflects disease severity and dysfunctional immune responses in patients with COVID-19," Gut, vol. 70, no. 4, pp. 698–706, 2021, doi: 10.1136/gutjnl-2020-323020.

28. M. Zapor, "Antimicrobial resistance in the time of COVID-19," Nat. Microbiol., vol. 5, no. 6, p. 780, 2020, doi: 10.1038/s41564-020-0739-4.

29. F. Zhang, R. I. Lau, Q. Liu, Q. Su, F. K. L. Chan, and S. C. Ng, "Gut microbiota in COVID-19: Key microbial changes, potential mechanisms and clinical applications," Nat. Rev. Gastroenterol. Hepatol., vol. 20, no. 5, pp. 323–337, 2022, doi: 10.1038/s41575-022-00698-4.

30. P. Zhou et al., "A pneumonia outbreak associated with a new coronavirus of probable bat origin," Nature, vol. 579, no. 7798, pp. 270–273, 2020, doi: 10.1038/s41586-020-2012-7.

31. T. Zuo et al., "Alterations in gut microbiota of patients with COVID-19 during time of hospitalization," Gastroenterology, vol. 159, no. 2, pp. 944-955.e8, 2020, doi: 10.1053/j.gastro.2020.05.048.

32. Z. I. Jameel, "CRISPR-Cas9 technology: A breakthrough in cancer gene therapy," Egypt. J. Med. Hum. Genet., vol. 27, no. 1, p. 4, 2026.

33. R. M. J. Ewadh, S. A. Kadhum, A. M. Omran, Z. I. Jameel, and N. H. A. Altaie, "Alterations of basic blood parameters in Iraqi COVID-19 patients with hyperglycaemia and acute kidney injury," Pharmakeftiki, vol. 37, no. 2S, pp. 215–218, 2025.

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34. J. Z. Isam, K. Z. Kamil, and B. R. Shaima, "Review about COVID-19," Res. J. Biotechnol., vol. 16, no. 4, pp. 229–233, 2021.

35. R. N. Ali, Y. F. Alasadi, and Z. I. Jameel, "Estimation some kidney function parameters among covid-19 patients in karbala province," Arch. Venez. Farmacol. Ter., vol. 40, no. 7, pp. 744–747, 2021.

36. S. R. Banoon, Z. K. Kadhim, Z. S. Aziz, Z. I. Jameel, and R. M. J. Ewadh, "Using random amplified polymorphic DNA (RAPD) fingerprinting technique to analyze genetic variation in Staphylococcus aureus isolated from different sources in babylon province hospitals," Indian J. Public Health Res. Dev., vol. 10, no. 9, pp. 1300–1305, 2019.

37. A. Al Shammari, Z. Isam, T. Banimuslem, and A. Neamaa, "Investigation of microRNA 196A2 polymorphism with thalassemia disease among middle and South Iraqi population," Jordan Med. J., vol. 59, no. 2, 2025, doi: 10.35516/jmj.v59i2.1980.

38. Y. F. Alasadi and Z. I. Jameel, "Single nucleotide polymorphism of gene IL8-251A/T (RS4073) associate with coronary artery disease," Int. J. Pharm. Res., vol. 12, no. sp2, 2020, doi: 10.31838/ijpr/2020.sp2.131.

39. A. Didangelos, "COVID-19 hyperinflammation: What about neutrophils?," mSphere, vol. 5, no. 3, p. e00367-20, 2020, doi: 10.1128/mSphere.00367-20.

40. W.-J. Guan et al., "Comorbidity and its impact on 1590 patients with COVID-19 in China: A nationwide analysis," Eur. Respir. J., vol. 55, no. 5, p. 2000547, 2020, doi: 10.1183/13993003.00547-2020.

41. I. Y. Hachim, M. Y. Hachim, K. B. Naeem, H. Hannawi, I. A. Salmi, and S. Hannawi, "Male gender is a risk factor for severe form of COVID-19 illness and worse outcome in the Middle East," Research Square, 2020, doi: 10.21203/rs.3.rs-44433/v1.

42. Z. I. Jameel, "SNPs variety of 3-β-hydroxysteroid dehydrogenase 1 (HSD3B1) gene are related to prostate cancer in some Iraqi individuals," Reprod. Breed., vol. 5, no. 2, pp. 37–43, 2025, doi: 10.1016/j.repbre.2025.03.004.

43. Z. I. Jameel, H. A. Kareem, Z. M. Yahya, A. A. Hussein, and Z. A. Kareem, "Association of MIR196A2 and mir146a polymorphisms and colorectal cancer

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risk: A meta-analysis," Hum. Gene, vol. 45, p. 201448, 2025, doi: 10.1016/j.humgen.2025.201448.

44. Z. Li et al., "Caution on kidney dysfunctions of 2019-nCoV patients," medRxiv, 2020, doi: 10.1101/2020.02.08.20021212.

45. D. Lindner et al., "Association of cardiac infection with SARS-CoV-2 in confirmed COVID-19 autopsy cases," JAMA Cardiol., vol. 5, no. 11, pp. 1281–1285, 2020, doi: 10.1001/jamacardio.2020.3551.

46. S. Naicker, C.-W. Yang, S.-J. Hwang, B.-C. Liu, J.-H. Chen, and V. Jha, "The novel coronavirus 2019 epidemic and kidneys," Kidney Int., vol. 97, no. 5, pp. 824–828, 2020, doi: 10.1016/j.kint.2020.03.001.

47. J. M. Connors and J. H. Levy, "COVID-19 and its implications for thrombosis and anticoagulation," Blood, vol. 135, no. 23, pp. 2033–2040, 2020, doi: 10.1182/blood.2020006000.

48. Y. Shi et al., "COVID-19 infection: The perspectives on immune responses," Cell Death Differ., vol. 27, no. 5, pp. 1451–1454, 2020, doi: 10.1038/s41418-020-0530-3.

49. Z. Wu and J. M. McGoogan, "Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: Summary of a report of 72 314 cases from the Chinese Center for Disease Control and Prevention," JAMA, vol. 323, no. 13, pp. 1239–1242, 2020, doi: 10.1001/jama.2020.2648.

50. L. Yang et al., "COVID-19: Immunopathogenesis and immunotherapeutics," Signal Transduct. Target. Ther., vol. 5, no. 1, p. 128, 2020, doi: 10.1038/s41392-020-00243-2.

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