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Post-Pandemic Therapeutic Strategies for COVID-19: Current Approaches, Challenges, and Future Directions

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Abstract: ***The coronavirus disease 2019 (COVID-19), caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), has evolved from a global pandemic into an endemic health concern, necessitating a shift in therapeutic strategies. This review provides a comprehensive analysis of post-pandemic drug approaches, highlighting current treatments, emerging challenges, and future directions in COVID-19 management. Initially, treatment relied heavily on repurposed drugs such as remdesivir, hydroxychloroquine, and dexamethasone, with variable efficacy and safety outcomes. Over time, advancements in clinical research led to the development of targeted therapies and evidence-based treatment protocols. In the post-pandemic phase, oral antivirals such as molnupiravir and nirmatrelvir/ritonavir (Paxlovid) have become central to early outpatient management, demonstrating effectiveness in reducing disease severity and hospitalization. Immunomodulatory agents, including corticosteroids, interleukin-6 inhibitors, and Janus kinase inhibitors, play a critical role in managing severe inflammatory responses such as cytokine storm. However, monoclonal antibody therapies have shown reduced effectiveness due to the emergence of viral variants, particularly those with mutations in the spike protein. Vaccination remains a cornerstone of long-term control, with booster strategies and next-generation vaccines enhancing protection against evolving variants. Despite these advances, significant challenges persist, including antiviral resistance, continuous viral evolution, unequal access to therapies in low- and middle-income countries, and the impact of misinformation on rational drug use. Additionally, the growing burden of Long COVID presents new therapeutic challenges, requiring multidisciplinary and symptom-based management approaches. Future strategies emphasize personalized medicine, integration of artificial intelligence in drug discovery, development of broad-spectrum antivirals, and improved global preparedness for emerging infectious diseases. In conclusion, post-pandemic therapeutic strategies for COVID-19 reflect a transition toward targeted, adaptive, and evidence-based approaches, underscoring the need for continuous research and global collaboration to address evolving challenges and improve patient outcomes.***

Keywords: COVID-19; SARS-CoV-2; post-pandemic strategies; Antiviral therapy; Immunomodulators; Monoclonal antibodies; Vaccination; Drug resistance; Long COVID; Drug repurposing; Personalized medicine; Artificial intelligence in drug discovery

1. Introduction

1.1 Overview of the COVID-19 Pandemic

The COVID-19 pandemic is one of the most significant global health crises in modern history. It is caused by the novel coronavirus known as Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), which primarily affects the respiratory system but can also impact multiple organs.

In December 2019, an outbreak of pneumonia of unknown origin was reported in Wuhan, Hubei Province, China. The initial pneumonia cases were epidemiologically linked to the Huanan Seafood Wholesale Market. Laboratory investigations involving inoculation of respiratory samples into human airway epithelial cells, Vero E6, and Huh7 cell lines resulted in the isolation of a novel respiratory virus. Genome analysis revealed that this virus was closely related to Severe Acute Respiratory Syndrome Coronavirus, and it was therefore named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). It is classified as a betacoronavirus belonging to the subgenus Sarbecovirus.

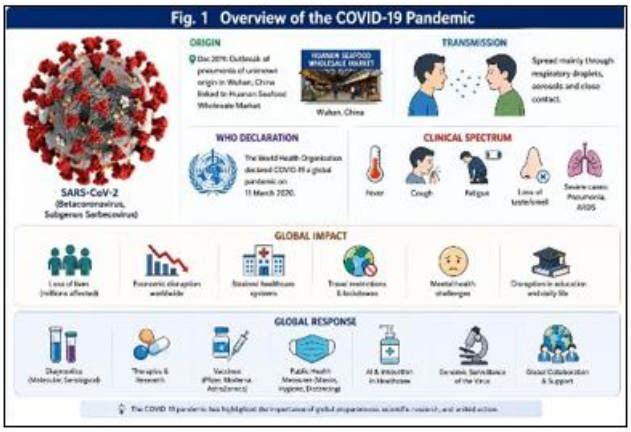
The virus spreads primarily through respiratory droplets, aerosols, and close contact, enabling rapid human-to-human transmission across regions and continents. Due to its widespread transmission and rising mortality, the World Health Organization (WHO) declared COVID-19 a global pandemic in March 2020.

The global spread of SARS-CoV-2 and the thousands of deaths caused by COVID-19 have resulted in an unprecedented crisis. The world has paid a high toll in terms of human lives lost, economic disruption, and increased poverty. Healthcare systems were strained, and governments-imposed lockdowns, travel restrictions, and public health measures to control the spread.

Clinically, COVID-19 presents with a wide spectrum of symptoms ranging from mild illness (fever, cough, fatigue) to severe complications such as pneumonia and acute respiratory distress syndrome (ARDS). Vulnerable populations, including the elderly and those with comorbidities, are at higher risk of severe disease.

In response, significant efforts have been made globally in epidemiological studies, serological and molecular diagnostics, and understanding the origin and pathogenesis of SARS-CoV-2, including its ability to infect human cells. Advances have also been made in developing therapies, vaccines, and innovative approaches such as artificial intelligence to manage the pandemic and limit viral spread.

Vaccination campaigns, led by pharmaceutical companies such as Pfizer, Moderna, and AstraZeneca, have played a crucial role in reducing disease severity and mortality. Additionally, the pandemic has significantly impacted lifestyles worldwide and highlighted the importance of preparedness for potential future waves or pandemics. [(1-8)]



1.2 Transition from Pandemic → Endemic Phase

The global situation of COVID-19 has gradually shifted from a pandemic toward an endemic phase. A pandemic refers to widespread global transmission of a disease, whereas an endemic condition exists when a disease continues to persist within a population at relatively stable and predictable levels over time. During the early phase of COVID-19, rapid transmission of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) led to multiple waves of infection, high mortality rates, and
widespread social and economic disruption across the world.

Over time, several important factors contributed to this transition. Large-scale vaccination programs, particularly with vaccines developed by Pfizer, Moderna, and AstraZeneca, significantly reduced disease severity and mortality. In addition, the development of natural immunity following widespread infections, improvements in clinical management and healthcare infrastructure, and the emergence of viral variants with comparatively lower severity in many cases also played key roles in stabilizing the situation.

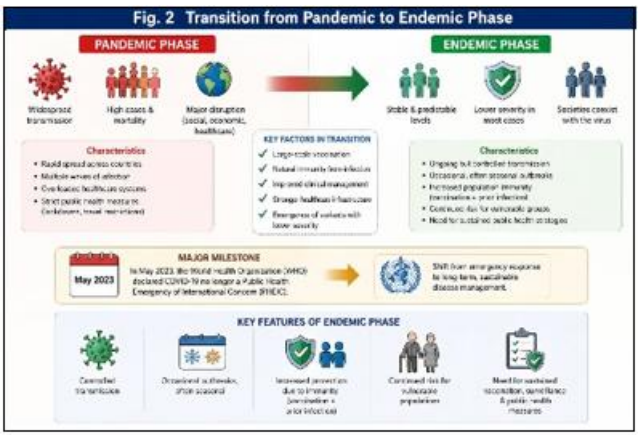
A major milestone in this transition occurred in May 2023, when the World Health Organization declared that COVID-19 was no longer a Public Health Emergency of International Concern (PHEIC). This marked a shift from emergency response measures to long-term, sustainable disease management.

In the endemic phase, the virus continues to circulate within populations, but at lower and more predictable levels. Seasonal or periodic outbreaks may still occur, and high-risk groups—such as the elderly and individuals with underlying health conditions- remain vulnerable. Therefore, continued vaccination, surveillance, and public health strategies are essential.

Key features of the endemic phase:

- Ongoing but controlled transmission of the virus
- Occasional outbreaks, often seasonal
- Increased protection due to immunity (vaccination + prior infection)
- Continued risk for vulnerable populations
- Need for sustained public health measures

Overall, this transition reflects a shift from crisis management to adaptation, where societies learn to coexist with the virus while minimizing its health, social, and economic impacts. [9-13]



1.3 Need for Updated Drug Strategies Post-Pandemic

Even as COVID-19 transitions into an endemic phase, the continued circulation of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) highlights the urgent need for updated and adaptive drug strategies. The pandemic exposed several limitations in existing treatment approaches, making it clear that healthcare systems must be better prepared for both ongoing management and future infectious disease outbreaks. Early reliance on repurposed drugs and limited therapeutic options demonstrated the importance of developing more effective, targeted, and flexible treatment strategies.

One of the major concerns is the continuous emergence of new variants, which can alter transmissibility, disease severity, and response to treatment. Some antiviral drugs and monoclonal antibodies have shown reduced effectiveness against certain variants, emphasizing the need for broad-spectrum antivirals and adaptable treatment protocols. Additionally, the early phase of the pandemic relied heavily on drugs like Remdesivir and Dexamethasone, which, although beneficial, were not universally effective and were mainly useful in specific stages of the disease. This highlighted the need for more targeted antiviral agents, stage-specific therapies, and personalized medicine approaches.

Another important challenge is the growing burden of Long COVID, also known as post-acute sequelae of COVID-19 (PASC), where patients experience prolonged symptoms even after recovery. Managing these long-term complications requires new therapeutic interventions, multidisciplinary care, and long-term treatment strategies. Furthermore, the pandemic revealed significant gaps in global drug development systems and supply chains, underscoring the importance of preparedness. Future strategies should include rapid drug discovery platforms, stockpiling essential medicines, and stronger global collaboration led by organizations such as the World Health Organization.

Although vaccines developed by Pfizer, Moderna, and AstraZeneca have significantly reduced severe disease and mortality, drug therapies continue to play a crucial role in treating infected individuals, protecting immunocompromised patients, and managing breakthrough infections. Modern drug strategies are increasingly supported

by advanced technologies such as artificial intelligence and machine learning for drug discovery, genomic surveillance to monitor viral evolution, and the development of biologics and monoclonal antibodies targeting specific viral mechanisms.

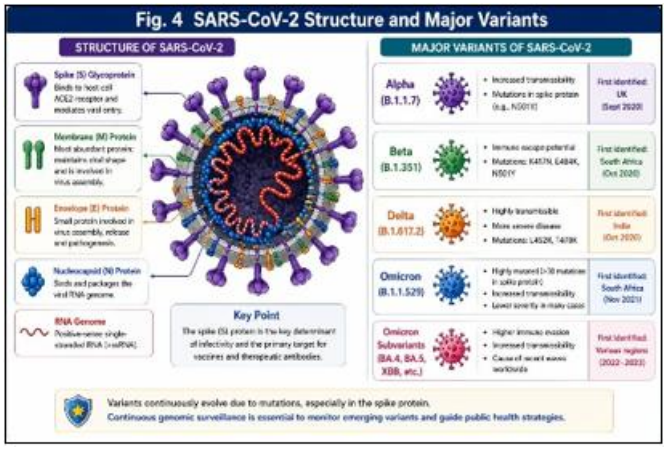
Key focus areas for updated strategies:

- Development of broad-spectrum and targeted antivirals
- Personalized and stage-specific treatment approaches
- Effective management of Long COVID
- Strengthening global drug supply and preparedness
- Integration of advanced technologies in drug development
- Overall, updated drug strategies are essential to ensure effective long-term management of COVID- 19 and to enhance global readiness for future pandemics. [14-23]

2. Pathophysiology of COVID-19

The causative agent of COVID-19, Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), is an enveloped, positive-sense single-stranded RNA virus belonging to the beta coronavirus genus. It has a spherical structure with spike-like projections on its surface, giving it a characteristic "crown-like" appearance under electron microscopy. These structural features play a crucial role in the virus's ability to infect host cells and cause disease.

2.1 Structure of SARS-CoV-2-



The virus is composed of several important structural proteins, each with specific functions:

- Spike (S) glycoprotein: Binds to host cell receptors and facilitates viral entry
- Membrane (M) protein: Maintains viral shape and assists in assembly
- Envelope (E) protein: Involved in viral assembly, release, and pathogenicity
- Nucleocapsid (N) protein: Encapsulates viral RNA and supports replication

Among these, the spike protein is the most critical for infectivity and is the main target for vaccines and therapeutic antibodies.

Variants of SARS-CoV-2- SARS-CoV-2 continuously mutates, leading to the emergence of different variants. These mutations, especially in the spike protein, can affect transmissibility, disease severity, and the ability of the virus to escape immune responses.

Major variants include:

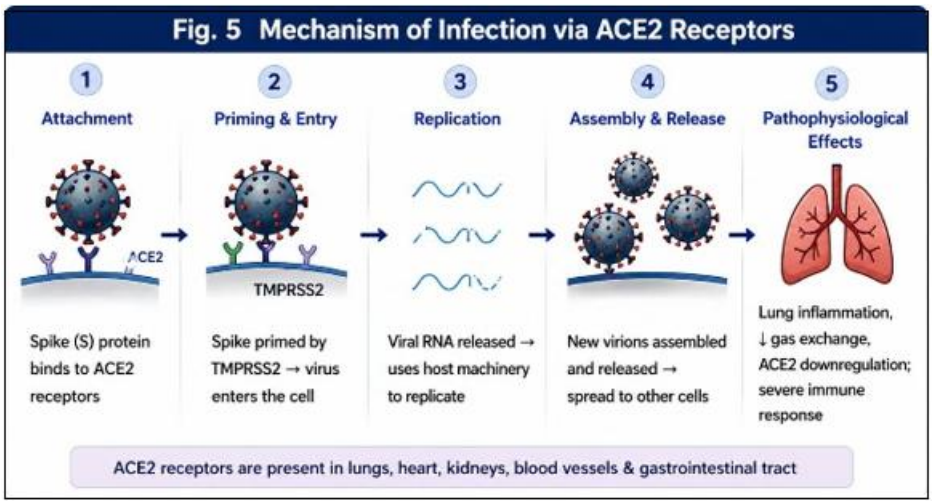
- Alpha (B.1.1.7): First identified in the UK; associated with higher transmissibility
- Beta (B.1.351): Identified in South Africa; showed immune escape potential
- Delta (B.1.617.2): First identified in India; highly transmissible and more severe
- Omicron (B.1.1.529): Highly mutated variant; increased spread but relatively lower severity in many cases

These variants have created challenges for public health by reducing the effectiveness of some treatments and vaccines, highlighting the importance of continuous genomic surveillance and updated therapeutic strategies. [24-29]

2.2 Mechanism of Infection (ACE2 Receptors)

The infection process of COVID-19 begins when Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) enters the human body and targets host cells through specific receptor interactions. The virus primarily utilizes Angiotensin-Converting Enzyme 2 (ACE2) receptors, which are widely present in organs such as the lungs, heart, blood vessels, kidneys, and gastrointestinal tract. The infection starts with the attachment of the viral spike (S) protein to ACE2 receptors on the host cell surface. This is followed by priming and activation of the spike protein by host enzymes like TMPRSS2, which enables the virus to enter the cell. The viral envelope then fuses with the host cell membrane, allowing the viral RNA to enter the cytoplasm.

Once inside the cell, the viral RNA acts as messenger RNA (mRNA) and uses the host cell machinery to synthesize viral proteins and replicate its genome. Newly formed viral particles are then assembled and released from the host cell, spreading the infection to neighboring cells. This process leads to significant pathophysiological effects, including inflammation of lung cells and reduced gas exchange. Additionally, the downregulation of ACE2 disrupts the renin–angiotensin system, contributing to lung injury. In severe cases, an excessive immune response may occur, leading to further complications. Overall, this mechanism explains how SARS-CoV-2 spreads within the body and causes both respiratory and systemic damage. [30-35]



2.3 Immune Response & Cytokine Storm in COVID-19

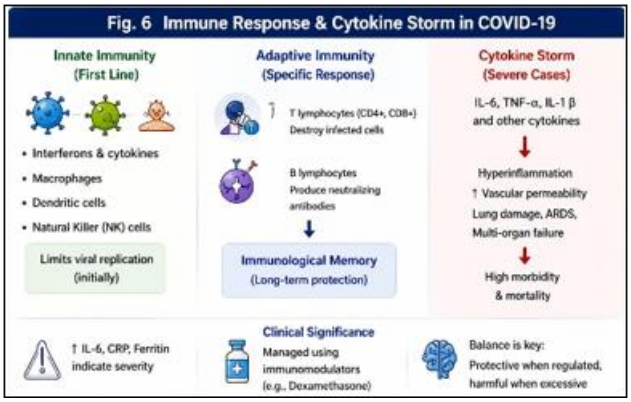
Infection with Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) activates a complex immune response involving both innate and adaptive immunity. Initially, the innate immune system acts as the first line of defense by releasing interferons and cytokines and activating immune cells such as macrophages, dendritic cells, and natural killer (NK) cells. This early response helps limit viral replication, but in some cases, it may not be sufficient to completely control the infection.

As the disease progresses, the adaptive immune system provides a more specific response. T lymphocytes ($CD4^+$ and $CD8^+$) help in destroying infected cells, while B lymphocytes produce neutralizing antibodies, particularly against the spike protein of the virus. This stage also leads to the development of immunological memory, which is important for long-term protection. A balanced immune response is essential for effective recovery.

However, in severe cases, an excessive immune reaction known as a cytokine storm may occur. This involves the uncontrolled release of pro-inflammatory cytokines such as interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and interleukin-1 beta (IL-1β). This hyperinflammatory state leads to widespread inflammation, increased vascular permeability, lung damage, acute respiratory distress syndrome (ARDS), and even multi-organ failure, making it a major cause of mortality in critically ill patients.

Key Points (Clinical Significance):
- Cytokine storm increases disease severity and poor outcomes
- Elevated biomarkers like IL-6, CRP, and ferritin indicate severe infection
- Managed using immunomodulatory drugs such as Dexamethasone

Overall, the immune response in COVID-19 plays a dual role-protective when regulated, but harmful when excessively activated. [36-39]



2.4 Disease Progression Stages of COVID-19

The clinical progression of COVID-19 caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) can be divided into well-defined stages, ranging from mild infection to severe systemic illness. Understanding these stages is important for selecting appropriate treatment and preventing complications.

1) Early Infection Stage (Viral Replication Phase)
This stage occurs during the first few days after exposure and is characterized by active viral replication in the upper respiratory tract. The disease is usually mild at this stage, and early treatment is most effective.
Sub-points:
a) High viral load in upper respiratory tract
b) Mild symptoms:
   - Fever
   - Dry cough
   - Fatigue
   - Sore throat
   - Loss of taste or smell
c) Antiviral drugs are most effective in this phase

2) Pulmonary Stage (Moderate Disease)
In this stage, the infection progresses to the lower respiratory tract, leading to lung involvement and pneumonia. Symptoms become more pronounced and may require medical care.
Sub-points:
a) Spread of virus to lungs
b) Development of viral pneumonia
c) Clinical features:

- Shortness of breath (dyspnea)
- Persistent cough
- Hypoxia (low oxygen levels)

d) Pathological changes:
- Lung inflammation
- Fluid accumulation in alveoli

e) May require hospitalization and oxygen therapy.

3) Hyperinflammatory Stage (Severe Disease)

This stage is marked by an exaggerated immune response (cytokine storm), leading to severe complications and organ damage.

Sub-points:

a) Excessive immune activation
b) Severe lung injury
c) Clinical features:
- Acute Respiratory Distress Syndrome (ARDS)
- Multi-organ dysfunction (heart, kidney, liver)
- Shock and possible death

d) Requires ICU care, ventilatory support, and immunomodulatory therapy

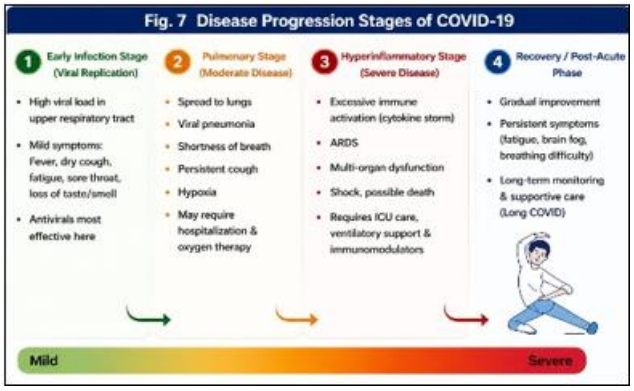
4) Recovery or Post-Acute Phase

In this phase, patients gradually recover, but some may experience prolonged symptoms known as Long COVID.

Sub-points:

a) Gradual improvement of symptoms
b) Persistent symptoms in some patients:
- Fatigue
- Brain fog
- Breathing difficulty (सांस लेने में तकलीफ)

c) Long-term monitoring and supportive care may be required. [40-44]



3. Evolution of COVID-19 Drug Therapy

3.1 Early Pandemic Treatments – Repurposed Drugs

At the beginning of the COVID-19 pandemic, there were no specific antiviral drugs available for Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). Therefore, clinicians relied heavily on drug repurposing, which involves using existing drugs developed for other diseases. This approach allowed rapid use of treatments based on already available safety data, although their effectiveness varied. Over time, several categories of drugs were explored.

1) Antiviral Drugs

These drugs aimed to directly inhibit viral replication.
- Remdesivir: Originally developed for Ebola; inhibits viral RNA polymerase and showed modest reduction in recovery time
- Favipiravir: Used for influenza; inhibits viral RNA synthesis and used in mild-to-moderate cases

2) Antimalarial Drugs

Initially considered due to antiviral and immunomodulatory properties.
- Hydroxychloroquine and Chloroquine
- Later found to have limited benefit and risk of cardiac side effects
- Eventually removed from most treatment guidelines

3) Corticosteroids

These drugs helped control inflammation in severe cases.
- Dexamethasone
- Reduced mortality in patients requiring oxygen or ventilator support
- Became a major breakthrough in treatment

4) Antibiotics (Supportive Use)

Used mainly for secondary bacterial infections, not for the virus itself.
- Azithromycin
- Provided anti-inflammatory effects but no direct antiviral action

5) Convalescent Plasma Therapy
- Plasma from recovered patients containing antibodies was used
- Provided passive immunity
- Showed variable effectiveness and later limited use

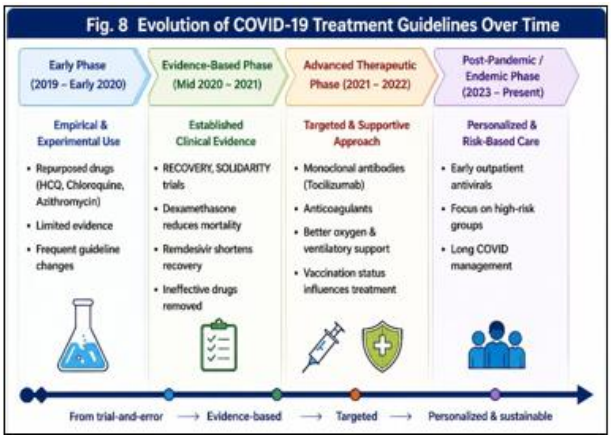
6) Immunomodulators

Used to control excessive immune response (cytokine storm).
- Tocilizumab
- IL-6 receptor blocker used in critically ill patients

Limitations of Early Treatments

Despite rapid use, these therapies had several drawbacks:
- Lack of strong clinical evidence in early stages
- Variable effectiveness among patients
- Risk of adverse effects
- Frequent changes in treatment guidelines

Overall, early COVID-19 drug therapy was largely experimental and based on repurposed drugs. These limitations highlighted the need for more targeted antiviral therapies and evidence-based treatment strategies, which improved with ongoing research. [45-49]



3.2 Changes in Treatment Guidelines Over Time

The management of COVID-19 has evolved significantly since the early stages of the pandemic, driven by emerging clinical evidence, large-scale trials, and global collaboration led by organizations such as the World Health Organization and National Institutes of Health. Over time, treatment strategies shifted from experimental approaches to more structured and evidence-based protocols.

1) Early Phase (2019–Early 2020): Empirical & Experimental Use

During the initial phase, there were no established treatment protocols, and clinicians relied heavily on repurposed drugs such as Hydroxychloroquine, Chloroquine, and Azithromycin. These treatments were based on limited clinical evidence, often derived from in vitro studies and small trials. Due to uncertainty and lack of strong data, treatment guidelines were frequently revised.

2) Evidence-Based Phase (Mid 2020–2021)

As more data became available, large clinical trials such as RECOVERY and SOLIDARITY provided strong scientific evidence. Effective treatments like Dexamethasone were introduced for severe cases, reducing mortality, while Remdesivir was used in hospitalized patients to shorten recovery time. At the same time, ineffective or harmful drugs like hydroxychloroquine and chloroquine were removed from guidelines. This phase marked the development of standardized treatment protocols based on disease severity.

3) Advanced Therapeutic Phase (2021–2022)

In this phase, treatment strategies advanced with the introduction of targeted therapies such as monoclonal antibodies, including Tocilizumab for managing cytokine storm. Greater emphasis was placed on supportive care, including anticoagulants for preventing thrombotic complications and improved oxygen and ventilatory support. Additionally, vaccination status began to influence treatment decisions.

4) Post-Pandemic / Endemic Phase (2023–Present)

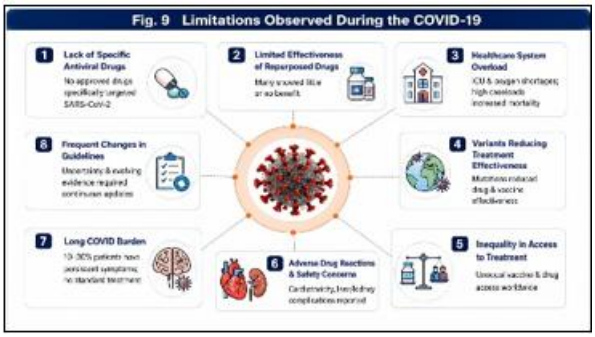
In the current phase, treatment approaches have shifted toward personalized and risk-based management. There is increased focus on early outpatient antiviral therapy and protection of high-risk populations such as the elderly and immunocompromised individuals. Continuous updates in guidelines are necessary due to emerging variants of SARS-CoV-2, along with a growing emphasis on long-term management, including care for Long COVID.

Key Trends in Guideline Evolution

The evolution of COVID-19 treatment guidelines reflects a clear transition from trial-and-error approaches to evidence-based medicine. There has been a shift from the widespread use of general drugs to more targeted and specific therapies. Increasing reliance on real-time data, along with strong global collaboration, has improved treatment outcomes. Furthermore, guidelines are now regularly updated as "living guidelines" by organizations like the World Health Organization to keep pace with new scientific findings. [50-54]

3.3 Limitations Observed During the COVID-19

1) **Lack of Specific Antiviral Drugs:** Early in the pandemic, no approved drugs specifically targeted SARS-CoV-2. According to studies, over 80% of early treatments were based on drug repurposing rather than novel drug development, and many of these repurposed drugs showed limited or inconsistent efficacy.
2) **Limited Effectiveness of Repurposed Drugs:** The WHO Solidarity Trial reported that Remdesivir had little or no effect on overall mortality in hospitalized patients. Hydroxychloroquine was associated with an increased risk of cardiac arrhythmias and showed no significant clinical benefit, leading to discontinuation of many early therapies due to lack of evidence.
3) **Healthcare System Overload:** During peak waves, ICU occupancy exceeded 90–100% in many countries. There were severe shortages, including oxygen supply crises-especially notable in India during the 2021 wave—as well as ventilator and hospital bed shortages. These high caseloads ultimately contributed to increased mortality rates.
4) **Variants Reducing Treatment Effectiveness:** The emergence of variants such as the Delta variant and Omicron variant led to increased transmissibility, with the Delta variant being up to 2–3 times more transmissible. These variants also showed reduced neutralization by some monoclonal antibodies, and continuous mutations required frequent updates in treatment protocols.
5) **Inequality in Access to Treatment:** High-income countries secured over 70% of the global vaccine supply in early phases. In contrast, low- and middle-income countries faced delays in access to essential drugs, vaccines, and adequate healthcare infrastructure, highlighting significant global disparities.
6) **Adverse Drug Reactions and Safety Concerns:** There were increased reports of adverse effects, including cardiotoxicity associated with hydroxychloroquine and liver and kidney complications linked to some antiviral drugs. Additionally, emergency use authorization limited the availability of long-term safety data for many treatments.
7) **Long COVID Burden:** Studies estimate that 10–30% of recovered patients from COVID-19 experienced Long COVID symptoms. These persistent issues include fatigue, respiratory problems, and neurological effects, and there is still a lack of standardized treatment protocols for long-term management. [55-60]



4. Antiviral Drug Strategies (Post-Pandemic Focus)

4.1 Oral Antivirals

In the current phase of COVID-19 management, oral antiviral drugs have become a key component of treatment strategies. These medications are designed for early use in non-hospitalized patients, helping to reduce disease severity, prevent hospitalization, and decrease mortality caused by SARS-CoV-2.

1) **Molnupiravir:** An oral antiviral approved or authorized in several countries for mild-to-moderate COVID-19, Molnupiravir is typically used in high-risk patients who are more likely to develop severe illness and is administered early in the course of infection, usually within a few days of symptom onset. It offers convenient oral dosing suitable for home-based treatment and helps reduce the risk of hospitalization, especially in cases where other preferred antivirals are not suitable. However, it shows moderate clinical effectiveness compared to some alternatives, is not recommended during pregnancy, and requires timely administration to achieve the best results.
2) **Nirmatrelvir/ritonavir (Paxlovid):** Paxlovid is a widely recommended oral antiviral for early treatment of COVID-19, particularly in patients at high risk of progression to severe disease, and is given within the first five days of symptom onset. It is considered a first-line oral treatment in many clinical guidelines and has been shown to significantly reduce hospitalization and death in high-risk individuals, making it suitable for outpatient use. Despite these advantages, it has potential for significant drug–drug interactions, requires cautious use in patients with liver or kidney conditions, and needs proper prescription and monitoring in certain cases.
3) **Role in Post-Pandemic Strategy:** Oral antivirals play an important role in enabling early intervention outside hospital settings, thereby reducing the burden on healthcare systems. They are particularly important for elderly populations, patients with comorbidities, and immunocompromised individuals, as these groups are at higher risk of severe disease. Their use supports the ongoing management of COVID-19 as it transitions into an endemic condition.
4) **Current Focus:** The current focus is on improving the accessibility and affordability of oral antivirals across different regions. There is also emphasis on their integration into updated treatment guidelines by organizations such as the World Health Organization, along with continued monitoring of their effectiveness against emerging variants of the virus. [61-65]

4.3 Effectiveness Against New Variants

The emergence of new variants of SARS-CoV-2, particularly variants such as Delta variant and Omicron variant, has significantly influenced the effectiveness of therapeutic strategies used in COVID-19. These variants contain multiple mutations, especially in the spike protein, which affect transmissibility, immune recognition, and response to treatment.

1) **General Impact of Variants:** Mutations in SARS-CoV-2 may alter viral behavior and reduce immune recognition, which can affect the performance of existing therapies. Treatments such as monoclonal antibodies have shown reduced effectiveness against newer variants due to changes in the spike protein. At the same time, these mutations can also slightly reduce vaccine effectiveness against infection, although protection against severe disease is generally maintained. Because of continuous viral evolution, treatment guidelines require regular updates to remain effective and relevant.
2) **Effectiveness of Oral Antivirals:** Oral antivirals such as Molnupiravir demonstrate activity against a wide range of variants and maintain effectiveness because they target viral replication mechanisms rather than the spike protein. As a result, they show consistent but moderate clinical benefits in reducing disease severity. Similarly, Paxlovid (nirmatrelvir/ritonavir) retains strong activity against multiple variants, including Omicron and its subvariants such as BA.5 and XBB. It is widely recommended due to its high efficacy in preventing severe disease and is considered reliable despite ongoing viral mutations, as it targets conserved viral enzymes that mutate less frequently.
3) **Comparison with Other Therapies:** When compared to other treatment strategies, monoclonal antibodies have shown a significant reduction in neutralizing activity against several newer variants due to spike protein mutations. Vaccines may exhibit slightly reduced protection against infection; however, they continue to provide strong protection against severe disease and hospitalization. In contrast, oral antivirals maintain relatively stable effectiveness across variants because they act on conserved viral processes rather than mutation-prone regions.
4) **Challenges and Future Needs:** Despite current effectiveness, challenges remain due to the risk of future antiviral resistance as the virus continues to evolve. There is a growing need for the development of broad-spectrum antiviral drugs that can act against multiple variants. Continuous genomic surveillance is essential to monitor emerging mutations and guide treatment strategies, along with global coordination by organizations such as the World Health Organization to ensure timely updates in clinical guidelines and effective pandemic management. [66-70]

4.4 Resistance Concerns in Antiviral Therapy

With the continued use of antiviral drugs for COVID-19, there is growing concern about the potential development of

resistance in SARS-CoV-2. Although current therapies remain effective, viral evolution poses a long-term challenge.

1) **Development of Antiviral Resistance:** RNA viruses such as SARS-CoV-2 are characterized by high mutation rates, which increase the likelihood of genetic variations over time. Prolonged viral replication, particularly in immunocompromised patients, further enhances the chances of resistant variants emerging. In addition, the selective pressure exerted by antiviral drugs can promote the survival and dominance of resistant viral strains.
2) **Resistance to Oral Antivirals:** Molnupiravir is generally considered to have a high barrier to resistance, but theoretical concerns exist because of its mechanism of inducing mutations in the viral genome, and therefore continuous monitoring is necessary to detect any resistant strains. In contrast, Paxlovid (nirmatrelvir/ritonavir) may develop resistance due to mutations in viral protease targets, and some laboratory studies have already identified resistance-associated mutations. However, clinical resistance remains relatively rare at present, although it is being closely monitored.
3) **Contributing Factors:** Several factors contribute to the development of antiviral resistance, including incomplete or improper use of antiviral therapy, which may allow partially resistant viruses to survive. The use of these drugs in patients with prolonged infections, such as immunocompromised individuals, also increases the risk of resistance development. Furthermore, the widespread and repeated global use of the same antiviral drugs adds additional selective pressure on the virus.
4) **Clinical Implications:** The emergence of resistance can lead to reduced effectiveness of existing therapies, making treatment less reliable. This situation increases the need for combination therapies that can target the virus through multiple mechanisms and reduce the likelihood of resistance. It also highlights the importance of early and appropriate treatment to limit viral replication and mutation.
5) **Strategies to Overcome Resistance:** To address resistance concerns, there is a need for the development of new and broad-spectrum antiviral drugs that remain effective against multiple variants. The use of combination drug therapy is also an important strategy to minimize resistance development. Continuous genomic surveillance of viral mutations is essential for early detection of resistant strains, along with regular updates in treatment guidelines by organizations such as the World Health Organization to ensure effective clinical management. [71-75]

5. Immunomodulators & Anti-Inflammatory Drugs in COVID-19

The pathophysiology of COVID-19, particularly in moderate to severe cases, involves not only viral replication but also an exaggerated immune response known as a cytokine storm. This hyperinflammatory state leads to lung injury, acute respiratory distress syndrome, and multi-organ dysfunction. Therefore, immunomodulators and anti-inflammatory drugs play a crucial role in reducing morbidity and mortality, especially in hospitalized patients.

5.1 Corticosteroids- Role of Dexamethasone

a) **Overview**- Corticosteroids are widely used anti-inflammatory agents that suppress systemic inflammation, and among them, Dexamethasone emerged as a landmark therapy during the pandemic due to its strong clinical impact.
b) **Clinical Evidence**- The RECOVERY Trial demonstrated that dexamethasone reduced mortality by approximately 30% in ventilated patients and about 20% in patients requiring oxygen, leading to its adoption as a standard of care for severe COVID-19 globally.
c) **Mechanism**-Based Role- Dexamethasone works by suppressing pro-inflammatory cytokines such as IL-6 and TNF-α, reducing immune-mediated lung injury and preventing progression to acute respiratory distress syndrome.
d) **Clinical Use (Post-Pandemic)**- It is recommended for patients requiring oxygen therapy and those who are mechanically ventilated, while it is not recommended in mild or early-stage disease because it may impair viral clearance.
e) **Advantages**- It is widely available, inexpensive, supported by strong clinical evidence, and provides a significant mortality benefit in severe cases.
f) **Limitations**- Its use is associated with risks such as secondary infections, hyperglycemia, and other metabolic effects, and therefore requires careful dosing and monitoring.

5.2 IL-6 Inhibitors – Role of Tocilizumab

a) **Overview**- IL-6 is a key cytokine involved in the inflammatory cascade of severe COVID-19, and Tocilizumab acts by targeting the IL-6 receptor to control hyperinflammation.
b) **Clinical Evidence**- Clinical studies have shown that tocilizumab reduces mortality and the need for mechanical ventilation when used in combination with corticosteroids, particularly in patients with elevated inflammatory markers.
c) **Therapeutic Role**- It is used in severe and critical COVID-19 cases and is especially beneficial in patients experiencing cytokine storm.
d) **Post-Pandemic Clinical Use** - It is administered in rapidly deteriorating patients and those with high CRP and IL-6 levels, often in combination with dexamethasone to achieve a synergistic therapeutic effect.
e) **Advantages**- It provides targeted therapy and helps reduce the progression of severe inflammation.
f) **Limitations**- Its use is limited by high cost, risk of immunosuppression and infections, and the requirement for administration in a hospital setting with proper monitoring.

5.3 JAK Inhibitors

Examples include Baricitinib and Tofacitinib, which inhibit Janus kinase pathways involved in cytokine signaling.

a) **Overview**- JAK inhibitors suppress multiple inflammatory pathways simultaneously, making them effective in controlling systemic inflammation.

b) **Clinical Evidence-** Baricitinib has demonstrated reduced recovery time and decreased mortality in hospitalized patients, supporting its use in COVID-19 management.
c) **Clinical Use**- They are recommended in hospitalized patients requiring oxygen and in patients who cannot receive IL-6 inhibitors.
d) **Post-Pandemic Role-**They serve as an alternative to IL-6 inhibitors and are often used in combination with corticosteroids for better outcomes.
e) **Advantage**s- They offer broad anti-inflammatory action and, in some cases, can be administered orally.
f) **Limitations-** Their use is associated with risks such as thrombosis, increased susceptibility to infections, and the need for monitoring liver and kidney function.

5.4 Updated Clinical Use Post-Pandemic

In the endemic phase of COVID-19, treatment strategies have become more evidence-based and patient-specific, guided by organizations such as the World Health Organization and National Institutes of Health. A severity-based approach is followed in which mild cases do not require immunomodulators, moderate cases receive corticosteroids if oxygen is needed, and severe cases are managed with combination therapy such as corticosteroids with IL-6 inhibitors or JAK inhibitors. Combination therapy, including dexamethasone with tocilizumab or JAK inhibitors, has shown improved outcomes. Treatment decisions are increasingly personalized based on inflammatory markers like CRP and IL-6, comorbidities, and risk of complications. There is also a focus on reducing overuse by avoiding unnecessary immunosuppression in mild disease and ensuring rational drug use. In Long COVID, immunomodulators have a limited role, and management is primarily symptom-based.

5.5 Future Perspectives

Future strategies focus on the development of safer and more targeted immunomodulators, integration of biomarkers to guide therapy selection, and improved approaches to balance antiviral and anti-inflammatory treatments for optimal patient outcomes. [76-81]

6. Monoclonal Antibody Therapy in COVID-19

Monoclonal antibodies (mAbs) were among the earliest targeted therapies developed specifically against SARS-CoV-2. These are laboratory-produced antibodies designed to mimic the body's immune response and neutralize the virus, playing an important role during the early phases of the COVID-19 pandemic.

6.1 Mechanism and Role in COVID-19

Monoclonal antibodies act by binding to specific sites on the spike protein of SARS-CoV-2, which prevents the virus from attaching to host cell receptors such as ACE2. This blockage inhibits viral entry into host cells, reduces viral load, and ultimately slows disease progression.

Clinical Role
These therapies are primarily used in mild-to-moderate COVID-19 cases, particularly in high-risk, non-hospitalized patients. They are most effective when administered early in the course of infection to prevent progression to severe disease.

Examples include Tocilizumab, which has an indirect role by targeting inflammatory pathways rather than the virus itself, and neutralizing antibody combinations such as Casirivimab–Imdevimab that were widely used earlier in the pandemic.

Benefits - Monoclonal antibodies provide targeted antiviral action, help reduce hospitalization rates when used early, and were particularly useful before the widespread availability of vaccines.

6.2 Reduced Effectiveness Due to Variants

Variants of SARS-CoV-2, especially the Omicron variant and its subvariants, contain multiple mutations in the spike protein. These mutations alter the binding sites for monoclonal antibodies, leading to reduced neutralization capacity and loss of effectiveness of several previously approved therapies. As a result, some monoclonal antibody treatments were withdrawn or are no longer recommended. Unlike oral antivirals, monoclonal antibodies are highly sensitive to spike protein changes, making them more vulnerable to viral evolution.

6.3 Current Relevance and Limitations

Current Relevance - At present, monoclonal antibodies have a limited role in routine clinical practice. However, ongoing research is focused on developing newer antibodies that target conserved regions of the virus, which may remain effective against multiple variants. They may still be useful in selected high-risk patients and in situations where variant-sensitive antibodies are available.

Limitations- A major limitation is their sensitivity to viral mutations, which can significantly reduce or eliminate their effectiveness against newer variants. In addition, these therapies are expensive compared to oral antivirals and have limited accessibility in low-resource settings. They are administered via intravenous or subcutaneous routes, requiring a hospital or clinical setup. Furthermore, they provide passive immunity with a limited duration of protection. [82-86]

7. Vaccines and Booster Strategies in COVID-19

Vaccination remains the cornerstone of long-term control of COVID-19 caused by SARS-CoV-2. In the post-pandemic (endemic) phase, strategies have shifted from mass emergency vaccination to sustained protection, booster optimization, and adaptation to emerging variants.

7.1. Role of Vaccines in the Post-Pandemic Phase

a) **Continued Importance-** Vaccines continue to play a crucial role by significantly reducing severe disease,

hospitalization, and mortality, while also helping to maintain population-level immunity against COVID-19.

b) **Shift in Strategy-** There has been a transition from universal mass vaccination to a more targeted approach focusing on high-risk groups such as elderly individuals, immunocompromised patients, and those with underlying comorbidities.

c) **Public Health Impact-** Vaccination helps prevent healthcare system overload, supports the transition toward endemic management of COVID-19, and reduces broader economic and social disruption.

7.2. Booster Dose Strategies

a) **Need for Boosters**- Immunity acquired from primary vaccination declines over time, and the emergence of new variants reduces protection against infection, creating the need for booster doses.

b) **Booster Approach**- Periodic booster doses are recommended, especially for high-risk populations, with timing that may vary between 6 to 12 months depending on public health guidelines.

c) **Types of Boosters**- Boosters may be homologous, where the same vaccine is used again, or heterologous, where a different vaccine is administered to enhance immune response.

d) **Benefits**- Booster doses increase antibody levels, improve protection against severe disease, and broaden immune responses against different variants.

7.3. Vaccine Effectiveness vs Variants

a) **Impact of Variants-** Variants such as the Delta variant and Omicron variant contain mutations in the spike protein, which can reduce vaccine effectiveness against infection and lead to increased breakthrough cases.

b) **Current Evidence-** Despite these challenges, vaccines remain highly effective in preventing severe disease, reducing ICU admissions, and lowering mortality, while booster doses significantly improve protection against variants.

c) **Key Insight-** Although protection against infection may decrease over time, protection against severe outcomes remains strong, highlighting the continued value of vaccination.

7.4 mRNA and Next-Generation Vaccines

mRNA Vaccines- mRNA vaccines developed by companies like Pfizer and Moderna are characterized by high efficacy, rapid development capability, and adaptability to new variants.

Next-Generation Vaccines- Future vaccine development includes variant-specific vaccines designed to target particular strains such as Omicron, multivalent vaccines that can protect against multiple variants simultaneously, and universal coronavirus vaccines aimed at providing broad protection across coronavirus strains. Additionally, nasal vaccines are being explored to induce mucosal immunity, which may help reduce viral transmission more effectively.

7.5 Current Challenges

Challenges in vaccination strategies include waning immunity over time, the continuous emergence of new variants, vaccine hesitancy among populations, and unequal global distribution of vaccines, particularly affecting low-resource regions.

7.6 Future Perspective

Future strategies may involve regular booster programs similar to influenza vaccination schedules, along with the development of broad-spectrum and long-lasting vaccines. There is also increasing focus on integrating vaccination with antiviral therapies for comprehensive disease management, supported by continuous monitoring and guidance from organizations such as the World Health Organization. [87-91]

8. Drug Repurposing vs New Drug Development

Drug development strategies during the COVID-19 pandemic involved both repurposing of existing drugs and the development of new, targeted therapies against SARS-CoV-2.

8.1. Advantages of Repurposing

- Existing drugs have known safety profiles and pharmacokinetics
- Faster availability due to prior regulatory approval
- Lower cost and reduced development time
- Useful in emergency situations
- Enables rapid initiation of clinical trials

8.2. Examples and Outcomes

- Remdesivir showed modest reduction in recovery time but limited effect on mortality
- Hydroxychloroquine showed no significant benefit and raised safety concerns
- Dexamethasone significantly reduced mortality in severe cases
- Many repurposed drugs demonstrated inconsistent or limited efficacy in clinical trials

8.3. Shift Toward Targeted Drug Development

- Focus on drugs specifically designed against viral targets
- Development of antivirals like Paxlovid targeting viral protease enzymes
- Higher specificity and improved clinical outcomes
- Better effectiveness against defined viral mechanisms
- Represents a long-term, evidence-based therapeutic approach [92-96]

9. Challenges in Post-Pandemic Drug Strategy

The post-pandemic management of COVID-19 continues to face several challenges despite advances in therapeutics targeting SARS-CoV-2.

9.1. Drug Resistance

- Continued use of antiviral drugs increases the risk of resistance development
- Mutations in viral targets may reduce drug effectiveness
- Higher risk in immunocompromised patients with prolonged infection
- May require combination therapy and development of new antivirals

9.2 Variant Evolution

- Emergence of new variants such as Omicron variant affects treatment effectiveness
- Mutations, especially in the spike protein, influence transmissibility and immune escape
- Continuous viral evolution requires regular updates in treatment guidelines
- Reduces effectiveness of some monoclonal antibodies and vaccines

9.3. Accessibility and Affordability (Developing Countries like India)

- High cost of newer antiviral drugs limits accessibility
- Unequal global distribution of medicines
- Limited healthcare infrastructure in low- and middle-income countries
- Delayed availability of advanced therapies in resource-limited settings

9.4. Misinformation and Irrational Drug Use

- Spread of misinformation leads to inappropriate and irrational drug use
- Self-medication and overuse of certain drugs observed during the pandemic
- Increased risk of adverse drug reactions and antimicrobial resistance
- Need for public awareness and evidence-based guidelines from organizations such as the World Health Organization (97-101)

10. Long COVID (Post-COVID Syndrome) Management

10.1 Definition and Symptoms

Long COVID, also termed post-acute sequelae of COVID-19, refers to a condition where symptoms persist or newly appear after the acute phase of infection caused by SARS-CoV-2. It typically lasts beyond 12 weeks and cannot be explained by alternative diagnoses. The condition presents with a wide range of symptoms including persistent fatigue, dyspnea, chest tightness, and exercise intolerance. Neurological features such as cognitive dysfunction, difficulty concentrating, headache, and sleep disturbances are common, along with psychological manifestations like anxiety and depression. Some individuals also experience cardiovascular complications such as arrhythmias and postural tachycardia, as well as endocrine, gastrointestinal, and musculoskeletal disturbances, reflecting systemic involvement.

10.2. Drug-Based Management Strategies

Pharmacological management of Long COVID is largely supportive and tailored to individual symptoms due to the absence of a definitive cure. Anti-inflammatory medications may be prescribed to reduce ongoing inflammation, while anticoagulant therapy may be considered in patients with clotting abnormalities or high thrombotic risk. Symptomatic treatments such as inhaled bronchodilators for respiratory symptoms, non-steroidal anti-inflammatory drugs for pain, and medications for sleep or mood disorders are frequently used. In some cases, antihistamines and supplements have been explored for symptom relief, although evidence remains limited. Effective control of pre-existing conditions such as diabetes and cardiovascular diseases is essential to prevent worsening of symptoms.

10.3 Supportive Therapies

Supportive and rehabilitative care plays a vital role in Long COVID recovery. Pulmonary rehabilitation improves lung capacity and breathing efficiency, while structured, low-intensity physical activity programs help restore strength and reduce fatigue. Mental health support through psychotherapy, stress management techniques, and cognitive rehabilitation is crucial for patients with psychological and cognitive symptoms. Nutritional interventions, including balanced diets and micronutrient supplementation, support overall health. Sleep management and gradual return to normal activities are also important components, often requiring coordination between multiple healthcare disciplines.

10.4. Research Gaps

There remain substantial gaps in understanding Long COVID, particularly regarding its underlying biological mechanisms, which may involve persistent viral fragments, immune dysregulation, autonomic dysfunction, and chronic inflammation. There is a lack of standardized treatment guidelines and validated biomarkers for diagnosis and prognosis. Most current management strategies are based on evolving evidence and clinical observations rather than large randomized trials. Continued research efforts are needed to identify targeted therapies, improve diagnostic tools, and establish effective long-term management strategies, with guidance from organizations such as the Centres for Disease Control and Prevention. (102-106)

11. Future Perspectives

11.1 Personalized Medicine in COVID-19 Treatment

Future management of COVID-19 caused by SARS-CoV-2 is expected to increasingly adopt personalized medicine approaches, where treatment is tailored based on patient-specific factors such as genetic makeup, immune response, comorbidities, and disease severity. Advances in genomics, proteomics, and biomarker identification will enable precise selection of therapies, improve efficacy while reduce adverse effects and unnecessary drug use.

11.2 Role of AI in Drug Discovery

Artificial intelligence is revolutionizing drug discovery by enabling rapid screening of large chemical libraries, predicting drug-target interactions, and optimizing lead compounds. AI models also assist in clinical trial design and real-time data analysis, significantly reducing time and cost involved in drug development. During the pandemic, AI contributed to identifying potential antiviral agents and is expected to play an even greater role in future therapeutic innovations.

11.3 Preparedness for Future Pandemics

The COVID-19 crisis has emphasized the need for global preparedness through stronger surveillance systems, early warning mechanisms, and resilient healthcare infrastructure. Enhanced international collaboration, rapid vaccine platforms, and efficient distribution systems are essential to manage future outbreaks. Institutions such as the Coalition for Epidemic Preparedness Innovations are actively working toward accelerating vaccine development and improving global response capabilities.

11.4 Development of Broad-Spectrum Antivirals

There is a growing focus on developing broad-spectrum antiviral drugs that target conserved viral mechanisms rather than specific viral proteins. Such drugs can remain effective against multiple viruses and emerging variants, reducing the need for rapid drug redesign. This approach is crucial for combating future pandemics and ensuring long-term therapeutic preparedness. [107-111]

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