Title: A Comprehensive Review of COVID-19 Pathogenesis, Diagnosis, and Management

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A Comprehensive Review of COVID-19 Pathogenesis, Diagnosis, and Management

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ABSTRACT

SARS-CoV-2 has been found to be the leading cause of the outbreak of coronavirus disease 2019 (COVID-19) globally. The disease is triggered by a new form of coronavirus and is characterized by acute respiratory distress syndrome (ARDS) or some primary chills. It was originated from a wet market in Wuhan, China and has engulfed 6.39 million lives globally until September 2022. Historically, the world has witnessed many noticeable epidemics in the form of, SARS-CoV (2002 to 2003), H1N1 influenza in 2009, and the most recent Middle East Respiratory Syndrome coronavirus (MERS-CoV), which erupted in Saudi Arabia in 2012. Different people get this disease with different symptoms including mild to severe illness. The molecular and cellular basis of SARS-CoV-2 pathogenesis gives us in-depth mechanisms involved. Experimental investigations have elaborated bats as the primary host for viral transmission behind COVID-19. Moreover, the anatomy of the virus revealed its RNA based on the genome, which makes its therapeutic interventions more challenging. By the involvement of pre-analytic, analytic, and post-analytical strategies, patients with acute or chronic pneumonia can be distinguished as infected or not. Artificial intelligence has embarked significant importance in the course of viral detection based on computer algorithms. Furthermore, chemical or immune-based therapies were examined for finding a permanent solution to this epidemic issue. This review would cover every emerging aspect of pathogenesis, diagnosis, management, and the latest therapeutic interventions in the course of COVID-19 treatment. By giving rapidly evolving knowledge about this virus, readers are urged to update themselves regularly.

Keywords: Artificial Intelligence, ACE 2, coronaviruses, Immunotherapy, PPE, Spike proteins

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GRAPHICAL ABSTRACT

1. INTRODUCTION

Since ancient times, mankind has been affected by viral diseases. Viruses in the form of polio, HIV, ebola, smallpox, influenza, and many others caused massive causalities around the world [1-6]. The intense viral resurrection can be seen in the Coronavirus disease in 2019 [7]. The Coronavirus (COVID-19), which is caused by the novel β-coronavirus called SARS-CoV-2, has symptoms of chills, high fever, restricted breathing, sore throat, body pains, diarrhea, nausea, myalgia, and cough, reported its first case in December 2019 [8]. The characteristics appearance of the virus is defined by the spike proteins present on the outer surface, which gives it a resemblance to a crown. This spiky arrangement of the surface proteins was the basis of the term, coronavirus. Soon after the first case, the outbreak started in a wet market in the city of Wuhan, China [9-11]. Further studies could unfold many other aspects of the viral foundation for a better cure. The severity of the illness, patient age, immune system, and other variables can all affect the fatality rate from COVID-19 in a given country, because testing facilities are older, the claimed fatality rate may be lower than the actual mortality rate. There have been 1.08 million documented deaths in the United States, 530,630 instances reported in India, 211,893 reported instances in the United Kingdom, 158,708 documented cases in France, 48,133 documented death instances in Canada and more than 183,100 cases in Italy (data taken from: https://covid19.who.int/table).

1.1. Transmission

In the seafood market in Wuhan city where live animals were regularly sold, a large number of people were infected. It was suggested that COVID-19 was
probably of zoonotic origin. Strategies were made for discovering a potent host or middle carriers that could pass the infection to people [12]. At first, it was suspected that SARS-CoV could be transmitted to humans through bats, palm civets or dromedary camels [13]. This concluded the effective human-to-human transmission and the symptomatic patients were also considered to be the most probable source of virus transmission [7]. Particularly, the transmission of SARS-CoV-2 is influenced by the direct or indirect contact of respiratory infectiousdroplets ((particles >5-10 μm in diameter) or fomites with the mucosal membranes (eyes, nose or mouth). Transmission through aerosol is also possible in the event of prolonged exposure in congested spaces with high aerosol levels [14].

Investigations conducted by the CDC China elucidate the viral incubation time stays within 3-7 days or could take up to 2 weeks [15]. Generation time for this novel epidemic is sought to be seven days, however, the basic reproduction number is 2.2[16].

1.2. Taxonomy

Coronavirinae and Torovirinae are the two subfamilies from where coronavirus belongs. These subfamilies originated from the main family of Coronaviridae, which eventually arise from the order Nidovirales [17]. Additionally, the subfamily Coronavirinae is divided into four key genera. These include α-coronavirus, β-coronavirus, γ-coronavirus, and δ-coronavirus. Particulate viruses like HCoV-229E and HCoV-NLQ126 belong to the α genus of the coronaviruses, while others; SARS-CoV, MERS-CoV, HCoV-OC43, and HCoV-HKU1 reside in the genus of β-coronaviruses. Both α and β-coronaviruses are mainly the human infecting viruses, while γ and δ were observed to be involved in birds and a few mammal infections [18]. According to the latest sequencing reports, HCoV-229E, MERS-CoV, SARS-CoV, and HCoV-NL63 are considered to have originated in bats, whereas HCoV-OC43 and HKU1 possibly coined from rodents [19, 20]. The comparative taxonomy of coronavirus is given in Figure 1.

1.3. Pathogenesis

COVID-19 patients exhibit clinical symptoms like fever, non-productive cough, dyspnea, chronic fatigue, tiredness, regular or reduced number of white blood cells, and radiographic confirmation of pneumonia. Patients possessing COVID-19 and SARS both had increased severity and fatality rates when they were older and had more comorbid conditions. In all data sets, the ages of men and women were comparable. However, the instances in the case series tended to be more severe for men than for women (P = 0.035) [21]. In the published data set, there were 2.4 times as many males as females who passed away with COVID-19 (70.3 vs. 29.7%, P = 0.016). The pathogenesis of COVID-19 occurs in stages. The first stage is the asymptomatic phase, which typically starts from 1-2 days after infection and is characterized by fatigue and the flu in the patient. Following the first stage, the virus begins to spread to the respiratory system and the third and final stage is when the pulmonary infiltrates begin to form [22].
A Comprehensive Review of COVID-19...

1.4. Molecular Basis

A study conducted by Xiaowei Li and others [23] delivers the molecular and immune basis of viral pathogenesis. According to the study, the coronavirus S proteins act as a momentous contributing factor for the viral passage to the host [24]. The spike glycoproteins bind to the cellular component of the host by a specific ACE2 (Angiotensin-converting enzyme 2) receptor. Proceeding to the proteolytic cleavage of S proteins, the virus-membrane fusion leads to the viral entry of the host. Other than the membrane fusion pathway, the clathrin-dependent and -independent endocytosis also mediates the entry of SAR-CoV-2 [25]. Viral entry leads to antigenic perception by the host cell. Up till now, the mechanism related to the antigenic perception is still unknown in the case of SARS-COV-2 but it could be hypothesized from the past examinations on MERS-CoV and SARS-CoV. The B cells produced SARS-specific IgG and IgM antibodies that retain a host’s memory for a variable period. For cell-based cytotoxic immunity, researchers discovered the decline of CD4+ and CD8+ T cells in the acute and regular phases of the disease [26, 27]. Acute respiratory distress syndrome (ARDS) is a conjoint immunopathological condition in MERS-CoV, SARS-CoV-2 and SARS-CoV patients. ARDS represents the leading root of death in COVID-19 patients [22, 26]. A schematic representation of immune system involvement in the course of coronavirus infection can be seen in Figure 2.

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**Figure 1.** The Taxonomy of the Novel Coronavirus

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**Order**

**Family**

**Subfamily**

**Genus**

- Alpha Coronavirus
- Beta Coronavirus
- Gamma Coronavirus
- Delta Coronavirus
- Torovirus
- Bafinivirus

- SARS-CoV-2 (HCoV-229E, HCoV-NL63)
- SARS-CoV (HCoV-HKU1, MERS-CoV, HCoV-OCA3)
Figure 2. Display of Molecular Basis of Pathogenesis

Figure 2 shows two aspects of immunity: Adaptive and Humoral. During cell mediated immunity, the viral RNA is perceived by the cell and represented on MHC class I, which in turn recognized by the cytotoxic T cells. On the other hand, in humoral immunity, the APCs engulf virus and represent it on MHC II, which are eventually recognized by Helper-T cells and thus in response of cytokines release other immunity bearing cells get activated.

1.5. Structural Components of CoV

Extensive research on the coronavirus has unveiled that it is not simply a ball-shaped structure with spikes on its surface, but rather a complex entity with numerous features and functions. The Coronavirus belongs to a family of viruses known for their positive-sense RNA viruses that are enveloped and non-segmented. Specifically, they are classified into the sub-genus sarbecovirus, and the subfamily of Orthocoronavirinae, respectively. Depending upon its host-specific infecting ability, it is divided into four classes: α−/β−/γ−/δ-CoV. α−, and β-CoV are involved in causing diseases in mammals, while γ and δ-CoV are involved in infected birds.

Cryo-electron tomography and microscopy depicted that CoV is round shape with a diameter of 125nm. It has several spikes projecting from its structure. As it is enveloped, it contains nucleocapsids behind the envelope. The genome of CoV contains 6-11 open reading frames (ORFs). More than half of viral RNA is present in ORF1a/b which takes part by translating two polyproteins, pp1a and pp2b, and also encodes for other sixteen non-structural proteins. Essential structural proteins such as small envelope (E) proteins, matrix (M) proteins, spike (S) glycoprotein, and nucleo-capsid (N) proteins are encoded by the remaining part of the virus (3’ end of viral genome) [28]. Spike (S) glycoprotein has a role in the attachment of the virus to the host’s receptor, angiotensin-converting enzyme 2 (ACE2). Upon attachment of CoV S proteins to the host’s receptors, the host has a furin-like protease enzyme that
converts the S protein into two polypeptides S1 and S2. The S2 protein forms the stalk of spikes and the S1 protein forms a large receptor-binding domain. Matrix Protein (M) is the most abundant structural protein found in CoV. It is involved in maintaining the shape of the virus. It consists of three transmembrane domains with smaller-sized N-terminal glycosylated ectodomain and a larger C-terminal endo-domain extended 6 to 8 nm into the virus [29]. The structural basis of the novel coronavirus is provided in Figure 3. Coronaviruses belong in the family Coronaviridae and can cause disease in mammals and birds. The coronavirus spike (S) protein mediates membrane fusion by binding to cellular receptors.

Figure 3. Corona Virus Structure and Protein Visualization

1.6. Coronavirus Life Cycle

1.6.1. Attachment and Entry. The attachment of SARS-CoV to host cells depends on the interaction between CoV S protein and its receptors. The tissue tropism of CoV is also very dependent on the S protein. SARS-CoV and HoV-NL63, both viruses use angiotensin-converting enzyme 2 (ACE2) as a receptor for their S proteins. Furthermore, receptors relevant to viruses are enlisted in Table 1. Cathepsin, TMPRSS2, and other proteases do their function in breaking S protein at two different sites. The first cleavage found to be important in the separation of RBD and fusion domains of S protein takes place at the S2 portion of S protein and the second cleavage is important for visualization of fusion peptide at S2′. Cleavage at S2′ is crucial because after exposing of fusion peptide, it enters into the host membrane and two heptad repeats in S2 assemble to form an antiparallel six-helix bundle. Due to the formation of this bundle, viral and host cell membranes mix together leading to the entry of viral RNA into the cytoplasm.

Table 1. Corona Virus Families and their Receptors

<table>
<thead>
<tr>
<th>Alpha Coronaviruses</th>
<th>Receptors</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCoV-229E</td>
<td>APN</td>
<td>[49]</td>
</tr>
<tr>
<td>HCoV-NL63</td>
<td>ACE2</td>
<td>[50]</td>
</tr>
<tr>
<td>PEDV</td>
<td>APN</td>
<td>[51]</td>
</tr>
<tr>
<td>CCoV</td>
<td>APN</td>
<td>[52]</td>
</tr>
<tr>
<td>TGEV</td>
<td>APN</td>
<td>[53]</td>
</tr>
</tbody>
</table>
### Alpha Coronaviruses

<table>
<thead>
<tr>
<th>Coronaviruses</th>
<th>Receptors</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>SARS-CoV</td>
<td>ACE2</td>
<td>[54]</td>
</tr>
<tr>
<td>MHV</td>
<td>mCEACAM</td>
<td>[29]</td>
</tr>
<tr>
<td>MERS-CoV</td>
<td>DPP4</td>
<td>[55]</td>
</tr>
<tr>
<td>BCoV</td>
<td>N-acetyl-9-O-acetylneuraminic acid</td>
<td>[56]</td>
</tr>
</tbody>
</table>

### Beta Coronaviruses

- **APN**: aminopeptidase N
- **ACE2**: angiotensin-converting enzyme 2
- **mCEACAM**: murine carcinoembryonic antigen-related adhesion molecule 1
- **DPP4**: dipeptidyl peptidase 4
- **HCoV**: human coronavirus
- **TGEV**: transmissible gastroenteritis virus
- **PEDV**: porcine epidemic diarrhea virus
- **FIPV**: feline infectious peritonitis virus
- **CCoV**: canine coronavirus
- **MHV**: murine hepatitis virus
- **BCoV**: bovine coronavirus
- **SARS-CoV**: severe acute respiratory syndrome coronavirus
- **MERS-CoV**: Middle East respiratory syndrome coronavirus

Translation of the Replicase gene from viral RNA is the next step in the Coronavirus life cycle. This gene is responsible for the expression of two polyproteins, pp1a and pp1ab, and the encoding of two ORFs, rep1a and rep1b, which is also done by the same gene. For expression of pp1a and pp1ab polyproteins, the viral genome faces frame shifting from the rep1a reading frame into rep1b. This frame shifting takes place because of a slippery sequence 5’-UUAAC-3’ and an RNA pseudoknot. Most of the time the ribosome doing the translation linearizes the pseudoknot structure and continues forming protein until the rep1a stop codon appears. But in this case, due to pseudoknot interruptions, the ribosome stops elongation resulting in a break period at a slippery sequence then changes the reading frame by moving one nucleotide back and continuing elongation in rep1b [30].

### 1.6.2. Replication and Transcription

After the virus dumps his RNA into the host, RNA replicates. CoV replication entails (1) ribosome frame shifting during genome translation and (2) synthesis of both genomic and multiple sub-genomic RNAs. Genomic and sub-genomic RNA both are products of antisense RNA which counts only 1% of total RNA containing poly-uridylate sequences [31]. These RdRps would help in the formation of the Replicase-Transcriptase complex that synthesizes anti-sense RNA via replication of viral RNA. The novel RNA possesses two fates. It can either replicate into new positive-sense RNA that will be repackaged into viral offspring and released to infect other cells or it can synthesize sub-genomic mRNAs of varying lengths with the help of RNA-dependent RNA polymerases, a process called discontinuous transcription.

### 1.6.3. Assembly and Release

After synthesis and replication of sub-genomic RNA, essential structural proteins, S, M, and E is synthesized and inserted into the endoplasmic reticulum [32]. CoV envelope matures when the M protein interacts with it and the E protein assists the M protein in the assembly of the genome. Sometimes S protein that is not assembled, promotes cell fusion and forms multinucleated cells. These multinucleated cells help the virus to infect organisms without being detected by specific antibodies. The entire mechanism involved in coronavirus replication and release is given in the Figure 4.
Figure 4. The Schematic Diagram of the Mechanism of COVID-19 Entry, Viral Replication and Viral RNA Packing in the Human Cell

Figure 5. Various Methods for Diagnosis of SARS-CoV-2
1.7. COVID-19 Diagnosis

For the diagnosis of COVID-19, it is important to look at the initial vitals. These vital or initial diagnoses include symptoms such as cough, flu, allergy, and in some cases high fever or moderate fever [33].

The physical examination of suspected SARS-CoV-2 patients started with performing auscultation, listening to different sounds produced by lungs during respiration [34]. The SARS-CoV-2 virus causes respiratory disorders like coughing, shortness of breath, and others. The sound produced includes bronchial breath sound, which can be an indication of pneumonia. Stridor sound may be due to obstruction in the upper airway. Wheezing can be heard if there is some kind of bronchoconstriction or mucous plugging constricting the passage of air, which is a common sign of asthma. Rhonchus sound was observed due to mucous secretions and was produced in the case of bronchitis. Another sound heard primarily which is called crackles if there are any alveolar edema and fluid accumulation in the lungs. Some other sounds like Squawk and pleural friction rub would be produced. The production of these respiratory sounds is an indication of COVID-19-positive patients [35]. Furthermore, egophony or bronchophony tests can be conducted to confirm the positive results.

1.8. Analytic Stage

1.8.1. Real-time RT-PCR. RT-PCR is a method of diagnosis of the SARS-CoV-2 virus with a gold strand. In the middle of the viral transmission, after the swab is transferred to the laboratory. The PCR test was conducted using that substance, which was suspected to contain the Coronavirus. Coronavirus contains an unusually long genome with a single RNA. To detect these viruses’ using PCR, a reverse transcriptase enzyme would transform the RNA molecules into complementary DNA sequences. The newly synthesized DNA may then be amplified via standard PCR procedures. The main name for this process is Transcriptase-PCR (RT-PCR) [36]. To carry out this procedure, the viral RNA must be isolated. There are several RNA purification kits for comfortable, fast, and efficient insulation. Viral RNA is extracted using a commercial kit. First, the sample is added to the micro-centrifuge tube and then mixed with a solution for lysis. This store is very expensive and typically consists of isothiocyanate phenol and guanidine. Also, an RNase inhibitor is usually present in the buffer for decomposition to ensure proper isolation of the viral RNA [37]. If the degradation buffer is applied, the tube is mixed at room temperature by vortex and incubated and then the virus is decomposed under the high deformation conditions provided by the degradation buffer. When the sample is analyzed, a centrifuge system is used to purify the sample. The sample is placed onto the column of the centrifuge and centrifugation is finished. This is a solid-phase extraction method in which a silica matrix is composed of a fixed phase. RNA molecules bind to the silica gel film under optimum salt and pH conditions, while preserving protein and other contaminants at the same time. The spindle is placed into the clean collection tube, after centrifugation, and the filter is discarded. Then, add a barrier to wash. The spindle is again put in the centrifuge, pulling the laundry store over the membrane. This removes any impurities left in the membrane gel. After washing the samples, the column is transferred into a clean micro-centrifuge tube and a rinse buffer is
added. The centrifugation is then performed forcing the buffer zone onto the membrane. The buffer from the spin column to remove the viral RNA is removed and purified RNA, protein-free, inhibitor, and other contaminants are obtained.

After viral RNA extraction, the next step is to prepare the reaction mixture for PCR amplification. The main mixture consists of dielectric, reverse transcription enzyme, dNTPs, anterior primer, reverse primer, Taqman probe, and DNA polymerase. Finally, to complete, the main mixed RNA template is added. The tube is mixed and the mixture is loaded onto a PCR plate, the plate is placed in a PCR machine, which is a heat circulation tool. The first step in RT-PCR is transcription, which is the first complementary DNA synthesis of the plexus, prepared with a reverse primer for PCR that crosses into an integral part of the viral RNA genome. A polymerase chain reaction (PCR) consists of a series of thermal cycles that consist of denaturation, softening, and extension for each cycle. Double-DNA is obtained after the first cycle. You then anneal the Taqman probe to its complementary segment on DNA [38].

1.8.2. Serology. IgG/IgM test enables the qualitative detection of antibodies to the SARS-CoV-2 virus in human serum, whole blood, and finger-prick sample in less than 10 minutes. The test kit includes a detection cassette, plastic pipettes, and vials of sample diluent. By combining serology with RT-PCR, the sensitivity can reach up to 99%. If someone possessing COVID-19 but shows no symptoms, serology could be used within 3 to 10 days to determine whether he is infected or not [39]. The body of the infected individual has a rise in immunoglobulin M (IgM) first. Following that, the body raises immunoglobulin G typically 7 to 14 days later, depending on the virus (IgG). The IgG response is a later response, which is long-lasting. In a healthy individual, IgM would rise before the IgG level. High IgM level predicts if someone has been infected from the virus. Therefore, usually IgM level is observed to tell if someone has been recently infected or is still infected. IgG starts spiking, as IgM starts coming down. IgG level predicts the long-lasting immunity in a human body. So, even if a person is asymptomatic and have COVID-19, random sampling of a population is done. This indicates that they have been infected with COVID-19. IgG tells us that someone has been infected and that they have successfully recovered from it.

1.9. Post-analytic Stage

1.9.1. Chest X-ray. If the patient typically has COVID-19 symptoms such as fever, coughing or shortness of breath, they may have x-rays of his chest [40]. The most common condition is ground glass opacities, which indicates that certain areas of the lungs tend to be a grey hazy rather than a black shadow for blood vessels with thin white lung markings. It looks like frosted glass, a bit. These x-rays of the chest were not COVID-19 sensitive and may produce false negative results. [40]

1.9.2. Chest CT. Chest scans now offer a more accurate image as compared to x-rays in the chest. In COVID-19 cases, the most common results of computed tomography were ground glass opacities, which spread throughout the lungs. They represent small alveoli filled with air-sac or fluid and transform grey shade on a CT
scan. More and more fluid builds up in the lobes of the lungs in extreme infections, so that the impression of broken glass transforms into a strong white "consolidation"\[41\]. Another result has even been given the moniker “crazy paving pattern” because of enlarging interstitial space in the lung lobe walls. \[42\]. This makes the walls appear thicker, like white streaks on a background of blurred glass. Figure 5 explains the entire diagnostic availabilities for COVID-19.

1.9.3. Artificial Intelligence in Diagnosis. The gold standard method for the detection of COVID-19 infection in a person is reverse transcription PCR (RT_PCR). However, a couple of limitations are associated with the use of this method. Firstly, there is a scarcity of RT-PCR kits available and secondly, it takes almost 2 days to show the results.

Therefore, in this regard, artificial intelligence (AI) algorithms and methods were designed for the fast detection of infection in an individual. A prior study\[43\] examined the sensitivity levels of three artificial intelligence (AI) models. The first one was based on chest CT only, the second on clinical symptoms that a person shows, and the third joint model was based on both chest CT and clinical symptoms. The joint model proved to be very helpful in determining infection very early and fast as well. Although the use of AI is currently limited, it has the potential to be highly beneficial in the future.

1.10. Therapeutic Intervention. COVID-19 is the current global health challenge that was declared a pandemic in Dec 2019. The global bioburden of this life-threatening agent was increasing at a very rapid pace creating a global alarming situation at a large scale. The clinical severity of COVID-19 is present in the respiratory droplets in the air and the absence of pre-existing immunity due to novel characteristics of the virus has made every individual susceptible \[44\]. The entire range of pharmacological interventions in the course of COVID-19 are shown in Table 2.

<table>
<thead>
<tr>
<th>Agents</th>
<th>References</th>
<th>Target</th>
<th>Contraindication</th>
<th>Toxicities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chloroquine phosphate</td>
<td>[57, 58]</td>
<td>Blockage of viral passage by repressing glycosylation of host receptors, proteolytic preparing, and endosomal fermentation.</td>
<td>Hypersensitivity to chloroquine, 4-aminoquinoline compounds, or any component of the formulation.</td>
<td>Loss of appetite, Mild dizziness, Mild diarrhea, Clumsiness, and Mild headache</td>
</tr>
<tr>
<td>Hydroxychloroquine sulfate</td>
<td>[59 - 61]</td>
<td>Hydroxychloroquine shares the same mechanism of action as chloroquine</td>
<td>Known hypersensitivity to hydroxychloroquine, 4-aminoquinoline derivative</td>
<td>Show adverse reactions of a drug but is less common.</td>
</tr>
</tbody>
</table>


<table>
<thead>
<tr>
<th>Repurposed Agents</th>
<th>References</th>
<th>Target</th>
<th>Contraindication</th>
<th>Toxicities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Remdesivir</td>
<td>[62, 63]</td>
<td>Inhibitor of RNA polymerase</td>
<td>It based on special protocol.</td>
<td>Cause kidney failure</td>
</tr>
<tr>
<td>Favipiravir</td>
<td>[64, 65]</td>
<td>Inhibitor of RNA polymerase</td>
<td>It based on special protocol.</td>
<td>Diarrhea, the decrease in neutrophil count</td>
</tr>
</tbody>
</table>

**Adjunctive therapies**

| Tocilizumab | [66, 67] | IL-6 inhibition-reduction in a cytokine storm | Known hypersensitivity to tocilizumab or any components of the formulation. Caution in patients with neutropenia. | Tuberculosis, nasopharyngitis, headache, and hypertension. |

### 1.10.1. Antiviral Therapies

#### 1.10.1.1. Nucleoside Analogs

Generally, it is used as an antiviral agent. It interferes with the nucleotide synthesis pathway and causes the blocking and termination of the viral genome replication by the mutation of the normal nucleotide and blocking the entry of the incoming normal nucleotide [45].

#### 1.10.1.2. Ribavirin

It is an analog of guanine and its targets on the RNA dependent RNA polymerase. It is used as a combination therapy and required a high combination for terminate viral genome replication or necessitating high-dose. It is used in combination with interferon in therapy and it gives no harmful outcomes and no clinical effects on patients [46].

### 1.11. Preventions and Management

1. COVID-19 is a burning issue in these days. Therefore, this is an epidemic disease, preventing and managing it is of utmost importance in order to control the spread of this virus. This can be controlled by the mutual efforts of both govt. and public since the virus can be transmitted from one infected person to a healthy individual through various means, such as direct contact.

2. Protecting homes and hospitals is very important to avoid this epidemic. Therefore, it is essentially important to keep the area clean to minimize infection [47].

3. Another significant prevention is that gathering must be avoided and if people are gathered together, they should not sneeze and cough. People, must avoid going to public place. People should keep social distancing. Avoid going to an area where there is a patient with COVID-19. Govt. should lockdown the areas where COVID cases have been identified in order to save massive people from being infected through this virus.

4. Cleaning your hands with soap and sanitizer, and covering the mouth and nose with mases during sneezing and coughing is important. Properly
washing the food before eating can help to control the spread of COVID-19.

5. It is always best to avoid interaction with anyone, suspecting respiratory problems such as sneezing, coughing, others [48]. To blame for respiratory problems, it is wise to stay at home if a person has cold symptoms such as colds, coughs, respiratory problems, and others. It is also advisable to stay home if a person has severe cold symptoms.

6. It is also better not to go to school, work, and public places, not to use public transportation, such as airplanes, trains, metro, buses, taxi, and others. Other important suggestions may include avoiding travel and gathering somewhere.

7. Drinking hot water after every hour can help in avoiding the virus. A lot of warm water (~ 5 Liter per day) can also help with this.

8. Governments can include facilities for decontamination in public areas. The recommendations are applicable to healthcare practitioners, medical personnel, researchers, and public health professionals. They can also be used to control COVID-19 globally. During the time of COVID-19, it has been reported that the disease was spreading among those who do not take it seriously and do not follow the WHO and local government guidelines. Many people seek to steer a crowd to spread COVID-19 when the virus was blind to every race, sex, age, and religion.

2. CONCLUSION

Over the last few decades; numerous novel members of the coronavirus family have been identified. They retain the property of recombination that enables the swap of genetic material, while infecting via their replication strategy and large-size genome. These viruses have been able to cross species barriers, causing significant devastation to life and resulting in increased mortality rates. Several approaches, like using viruses with high mutation probability are still in testing windows. Due to a lack of effective vaccines and therapies, adhering to guidelines for personal protection with quarantine measures remained recommended strategies for controlling the spread of the virus. Being a global pandemic, this outbreak has grasped the attention of researchers, governments, public health authorities, and healthcare providers worldwide. Thereby, understanding the mechanism of coronavirus infection, replication, and host immunopathological responses would pave the way for the development of drugs and vaccines in the future.

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