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A REVIEW ON THE COMMON THREAT WORLDWIDE: CORONAVIRUS DISEASE (COVID-19)

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ABSTRACT

At the end of 2019, there was a new public health crisis threatening the world with the emergence and spread of the 2019 novel coronavirus (2019-nCoV), which was originated at the sea food market of Hubei province in Wuhan, China. The virus was originated in bats and was transmitted by unknown intermediary animals in China. . In humans they're typically spread via airborne droplets of fluid produced by infected individuals. Some rare but notable strains, including SARS-CoV-2 (responsible for COVID-19), and those responsible for severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS), can cause death in humans. Currently all the countries are on the COVID-19 alert and on the major lockdown.

This review aims to establish the current knowledge on COVID-19 by highlighting about the coronavirus genomic organization along with its pathogenesis, mode of transmission, various diagnosis and treatment strategies, precautionary measures and the treatment and vaccines available.

Keywords: Coronavirus (CoVs), Sever Acute Respiratory Syndrome (SARS), Severe acute respiratory syndrome coronavirus (SARS-CoV), 2019 novel coronavirus (2019-nCoV or COVID-19), Acute Respiratory Distress Syndrome (ARDS)

INTRODUCTION

Coronavirus are positive- sense RNA virus having vast and heterogeneous range of natural host which affect various systems. Coronavirus cause various clinical disease in humans ranging from common cold to sever respiratory diseases like SARS and MERS **[1, 2]**. Coronavirus are enveloped viruses and have single-stranded RNA genome with genome sizes ranging from 26 to 32 kilobases (kb) in length. It was first described in detail in the 1960s. The coronavirus got its name from a distinctive corona or 'crown' of sugary-proteins that project from the envelope surrounding the particle. Encoding the virus's make-up is the longest genome of any RNA-based virus **[3, 4]**. Coronaviruses (CoVs) are the largest group of viruses belonging to the Nidovirales order, which includes Coronaviridae, Arteriviridae, Mesoniviridae, and Roniviridae families. The Coronavirinae comprise one of two subfamilies in the Coronaviridae family, with the other being the Torovirinae. The Coronavirinae are further subdivided into four genera, the alpha, beta, gamma, and delta coronaviruses. The viruses were initially sorted into these genera based on serology but are now divided by phylogenetic clustering **[5]**.

There are seven human coronaviruses cause infection in humans including HCoV-229E (alpha coronavirus), HCoV-NL63 (alpha coronavirus), HCoV-OC43 (beta coronavirus), HCoV-HKU1 (beta coronavirus), Middle East Respiratory Syndrome, or MERS-CoV (beta coronavirus), Severe Acute Respiratory Syndrome, or SARS-CoV (beta coronavirus), and the newly identified 2019 Novel Coronavirus (2019-nCoV) (CDC, 2020), defined as SARS-CoV2, causing the Coronavirus Virus Disease of 2019 (COVID-19) **[6]**.

GENOMIC ORGANIZATION

Coronaviruses possess an unsegmented, single-stranded, positive-sense RNA genome of around 30 kb, enclosed by a 5'- cap and 3'- poly(A) tail (30). The genome of SARS-CoV-2 is 29,891bp long **[7]**. These viruses are encircled with an envelope containing viral nucleocapsid. The nucleocapsids in CoVs are arranged in helical symmetry. The organization of the coronavirus genome is 5′-leader-UTR- replicase-S (Spike)-E (Envelope)-M (Membrane)- N (Nucleocapsid)-3′ UTR-poly (A) tail with accessory genes interspersed within the structural genes at the 3′ end of the genome. The most prominent feature of coronaviruses

is the club-shaped spike projections emanating from the surface of the virion. These spikes are a defining feature of the virion and give them the appearance of a solar corona, prompting the name, coronaviruses. Within the envelope of the virion is the nucleocapsid. Coronaviruses have helically symmetrical nucleocapsids, which is uncommon among positive-sense RNA viruses, but far more common for negative-sense RNA viruses. Coronavirus particles contain four main structural proteins. These are the spike (S), membrane (M), envelope (E), and nucleocapsid (N) proteins, all of which are encoded within the 3′ end of the viral genome **[5, 7]**.

S Glycoprotein

S glycoprotein is a large, multifunctional class 1 viral transmembreane protein consisting of 1160 to 1400 amino acids. It lies on the virion surface giving it a crown-like appearance. Functionally it is required by the virus to enter into the host cell.Furthermore, it acts as a critical factor for tissue tropism and the determination ofhost range. S protein is an essential immunodominant protein of CoVs which is capable of inducing host cell response **[8, 9]**.

M protein

The M protein is the most abundant structural protein in the virion.The M protein exists as a dimer in the virion, and may adopt two different conformations, allowing it to promote membrane curvature as well as to bind to the nucleocapsid **[10]**.

E protein

The E protein (~8–12 kDa) is found in small quantities within the virion. The coronavirus E protein is the most enigmatic and smallest of the major structural proteins. It plays a multifunctional role in the pathogenesis, assembly, and release of the virus. It is a small integral membrane polypeptide that acts as a viroporin (ionchannel). The inactivation or absence of this protein is related to the altered virulence of coronaviruses due to changes in morphology and tropism **[11, 12, 13]**.

N Protein

The N protein of coronavirus is multipurpose. Among several functions, it plays a role in complex formation with the viral genome, facilitates M protein interaction needed during virion assembly, and enhances the transcription efficiency of the virus **[14, 15]**. It contains three highly conserved and distinct domains, namely, an NTD, anRNA-binding domain or a linker region (LKR), and a CTD. The NTD binds with the 3’ end of the viral genome, perhaps via electrostatic interactions, and is highly diverged both in length and sequence. The

charged LKR is serine and arginine rich and is also known as the SR (serine and arginine) domain **[16]**. The LKR is capable of direct interaction with in vitro RNA interaction and is responsible for cell signaling. It also modulates the antiviral response of the host by working as an antagonist for interferon (IFN) and RNA interference **[17, 18, 19]**.

PATHOGENESIS

The life cycle of the virus with the host consists of the following 5 steps: attachment, penetration, biosynthesis, maturation and release. Once viruses bind to host receptors (attachment), they enter host cells through endocytosis or membrane fusion (penetration). Once viral contents are released inside the host cells, viral RNA enters the nucleus for replication. Viral mRNA is used to make viral proteins (biosynthesis). Then, new viral particles are made (maturation) and released **[20]**. Coronavirus mainly attack to the respiratory tract and based on the cells that are likely infected, COVID-19 can be divided into three phases that correspond to different clinical stages of the disease.

- Stage 1: Asymptomatic Stage (initial 1-2 days of infection)
- Stage 2: Upper airway and conducting airway response (next few days)
- Stage 3:Hypoxia, ground glass infiltrates, and progression to Acute Respiratory Distress Syndrome (ARDS) **(Figure:1), [21]**.
- **Stage 1: Asymptomatic Stage (initial 1-2 days of infection)**

  The inhaled virus SARS-CoV-2 binds to epithelial cells in the nasal cavity and starts replicating. Angiotensin converting enzyme 2 (ACE2) was identified as a functional receptor for SARS-CoV2 and SARS-CoV. Following the binding of SARS-CoV-2 to the host protein, the spike protein undergoes protease cleavage. It is a two-step sequential protease cleavage to activate spike protein of SARSCoV and MERS-CoV. After the cleavage at the S1/S2 cleavage site, S1 and S2 subunits remain non-covalently bound and the distal S1 subunit contributes to the stabilization of the membrane-anchored S2 subunit at the perfusion state **[22, 23, 24]**. There is local propagation of the virus buta limited innate immune response. At this stage the virus can be detected by nasal swabs. Although the viral burden may be low, these individuals are infectious. The RT-PCR value for the viral RNA might be useful to

predict the viral load and the subsequent infectivity and clinical course **[25, 26]**.

- **Stage 2: Upper airway and conducting airway response (next few days)**

  The virus propagates and migrates down the respiratory tract along the conducting airways, and a more robust innate immune response is triggered. Epithelial cells, alveolar macrophages and dendritic cells (DCs) are three main components for innate immunity in the airway. DCs and macrophages serve as innate immune cells to fight against viruses till adaptive immunity is involved. T cell responses are initiated by antigen presentation via DCs and macrophages. DCs and macrophages can phagocytize apoptotic cells infected by virus. Nasal swabs or sputum should yield the virus (SARS-CoV-2) as well as early markers of the innate immune response **[27, 28]**. For about 80% of the infected patients, the disease will be mild and mostly restricted to the upper and conducting airways. These individuals may be monitored at home with conservative symptomatic therapy **[29]**.

- **Stage 3: Hypoxia, ground glass infiltrates, and progression to Acute Respiratory Distress Syndrome (ARDS)**.

  Unfortunately, about 20% of the infected patients will progress to stage 3 disease and will develop pulmonary infiltrates and some of these will develop very severe disease. Initial estimates of the fatality rate are around 2%, but this varies markedly with age **[30]**. The virus now reaches the gas exchange units of the lung and infects alveolar type II cells. Both SARS-CoV and influenza preferentially infect type II cells compared to type I cells. SARS-CoV propagates within type II cells, large number of viral particles are released, and the cells undergo apoptosis and die **[31]**. The end result is likely a self-replicating pulmonary toxin as the released viral particles infect type II cells in adjacent units. The pathological result of SARS and COVID-19 is diffuse alveolar damage with fibrin rich hyaline membranes and a few multinucleated giant cells **[32]**. Elderly individuals are

particularly at risk because of their diminished immune response and reduced ability to repair the damaged epithelium. The elderly also have reduced mucociliary clearance, and this may allow the virus to spread to the gas exchange units of the lung more readily **[33]**.

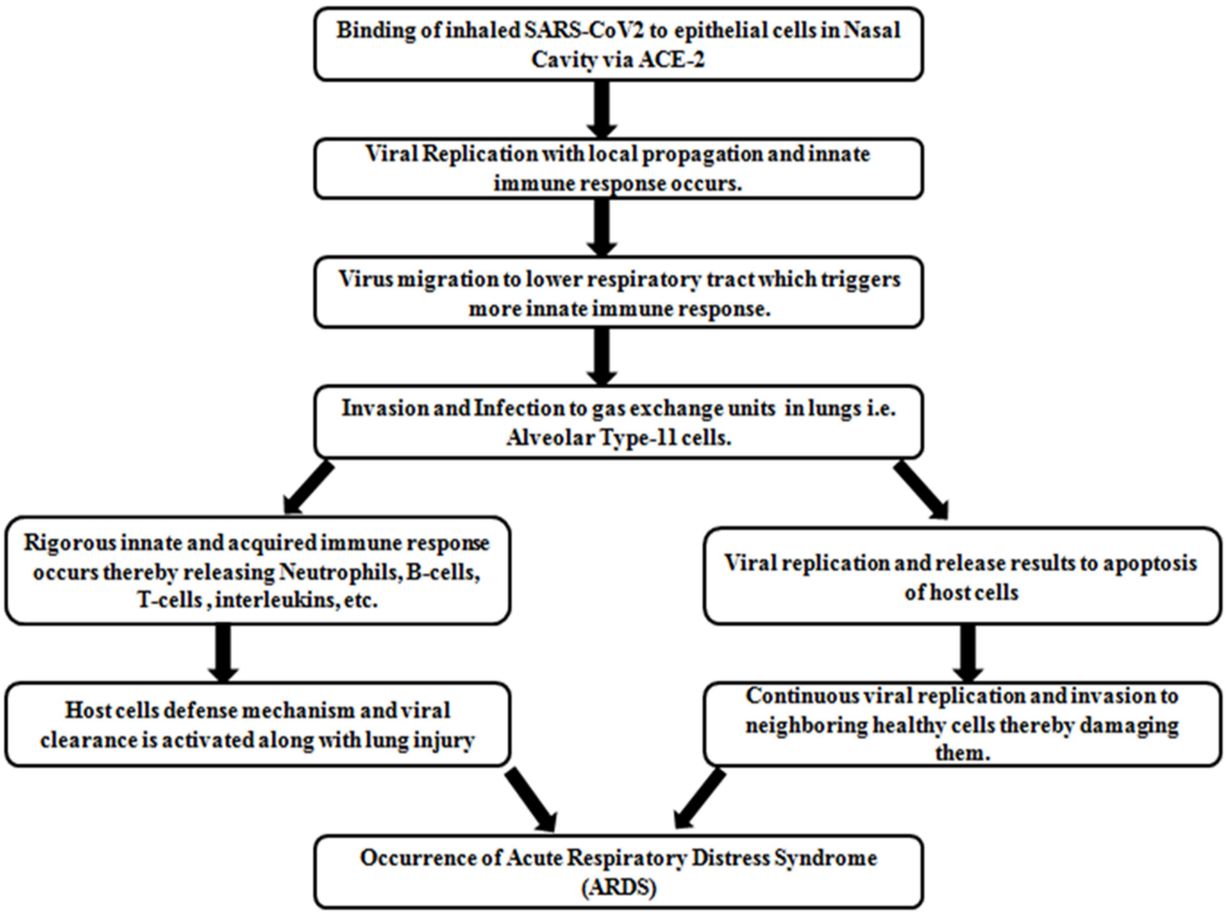

Figure 1: Pathogenesis of COVID-19

EPIDEMIOLOGY

All ages are susceptible. Infection is transmitted through large droplets generated during coughing and sneezing by symptomatic patients but can also occurs from asymptomatic people and before onset of symptoms **[34]**. At the beginning of the outbreak, COVID-19 cases were mostly observed among elderly people. As the outbreak continued, the number of cases among people aged 65 years and older increased further, but also some increase among children (< 18 years) was observed **[35]**. The chronology of COVID-19 infections is as follows. The first cases were reported in December 2019. By January 2,

2020, 41 admitted hospital patients had been identified as having laboratory-confirmed COVID-19 infection, less than half of these patients had underlying diseases, including diabetes, hypertension, and cardiovascular disease **[36]**. As of January 30, 2020, 7734 cases have been confirmed in China and 90 other cases have also been reported from a number of countries that include Taiwan, Thailand, Vietnam, Malaysia, Nepal, Sri Lanka, Cambodia, Japan, Singapore, Republic of Korea, United Arab Emirates, United States, The Philippines, India, Australia, Canada, Finland, France, and Germany. The case fatality rate was calculated to be 2.2% (170/7824) **[37]**. On the 31st of January 2020, the World Health Organization (WHO) announced that COVID-19 was listed as the Public Health Emergency of International Concern (PHEIC), meaning that it may pose risks to multiple countries and requires a coordinated international response **[38]**.

DIAGNOSTIC MODILITIES

A suspected case is defined as one with fever, sore throat and cough who has history of travel to China or other areas of persistent local transmission or contact with patients with similar travel history or those with confirmed COVID-19 infection. However cases may be asymptomatic or even without fever **[39]**.Clinical diagnosis of COVID-19 is mainly based on epidemiological history, clinical manifestations and some auxiliary examinations, such as nucleic acid detection, CT scan, immune identification technology (Point-of-care Testing (POCT) of IgM/IgG, enzyme-linked immunosorbent assay (ELISA)) and blood culture **[40]**.

a) Rapid Test

Recently, in response to the COVID-19 outbreak, 1-step quantitative realtime reverse transcription-PCR assays were developed that detect the ORF1b and N regions of the SARS-CoV-2 genome [**41]**. That assay was found to achieve the rapid detection of SARS-CoV-2. Nucleic acid-based assays offer high accuracy in the diagnosis of SARS-CoV-2, but the current rate of spread limits its use due to the lack of diagnostic assay kits. In such situations, conventional serological assays, like enzyme-linked immunosorbent assay (ELISA), that are specific to COVID-19 IgM and IgG antibodies can be used as a high-throughput alternative. At present, there is no diagnostic kit available for detecting the SARS-CoV-2 antibody **[42]**. The specific antibody profiles of COVID-19 patients were analyzed, and it was found that the IgM level lasted more than 1 month, indicating a prolonged stage of virus replication in SARS-CoV-2-infected

patients. The IgG levels were found to increase only in the later stages of the disease. These findings indicate that the specific antibody profiles of SARS-CoV-2 and SARS-CoV were similar. A major problem associated with this diagnostic kit is that it works only when the test subject has an active infection, limiting its use to the earlier stages of infection. Several laboratories around the world are currently developing antibody-based diagnostic tests against SARS-CoV-2 **[43]**.

b) Molecular Diagnosis

RNA tests can confirm the diagnosis of SARS-CoV-2 (COVID-19) cases with real-time RT-PCR or next-generation sequencing. At present, nucleic acid detection techniques, like RT-PCR, are considered an effective method for confirming the diagnosis in clinical cases of COVID-19.Several companies across the world are currently focusing on developing and marketing SARS-CoV-2-specific nucleic acid detection kits **[42, 44]**. Till date, 34 real-time PCR kits have been validated by ICMR validation centres, and some of them are Altona Diagnostics, Seegene, MY LAB, SD Biosensor, etc. Nucleic acids of SARS-CoV-2 can be detected from samples (64) such as bronchoalveolar lavage fluid, sputum, nasal swabs, fiber bronchoscope brush biopsy specimen, pharyngeal swabs, feces, blood, and urine, with different levels of diagnostic performance **[45, 46]**. The viral loads of SARS-CoV-2 were measured using N-gene-specific quantitative RT-PCR in throat swab and sputum samples collected from COVID-19-infected individuals. The results indicated that the viral load peaked at around 5 to 6 days following the onset of symptoms, and it ranged from 104 to 107 copies/ml during this time. The viral load detected in asymptomatic patients resembled that of symptomatic patients as studied in China, which reflects the transmission perspective of asymptomatic or symptomatic patients having minimum signs and symptoms. Studies are required to establish any correlation betweenSARS-CoV-2 viral load and cultivable virus. Recognizing patients with fewer or no symptoms, along with having modest detectable viral RNA in the oropharynx for 5days, indicates the requirement of data for assessing SARS-CoV-2 transmission dynamics and updating the screening procedures in the clinics. Further, novel SARS-CoV-2 infections have been detected in a variety of clinical specimens, like bronchoalveolar lavage fluid, sputum, nasal swabs, fibrobronchoscope brush biopsy specimens, pharyngeal swabs, feces, and blood. Recently, it was found that

the anal swabs gave more positive results than oral swabs in the later stages of infection. Even though the viral loads in stool samples were found to be less than those of respiratory samples, strict precautionary measures have to be followed while handling stool samples of COVID-19 suspected or infected patients **[47, 48, 49]**. Children infected with SARS-CoV-2 experience only a mild form of illness and recover immediately after treatment. It was recently found that stool samples of SARS-CoV-2-infected children that gave negative throat swab results were positive within ten days of negative results. It has also been observed that the initial screening of COVID-19 patients infected with RT-PCR may give negative results even if they have chest CT findings that are suggestive of infection. Hence, for the accurate diagnosis of COVID-19, a combination of repeated swab tests using RT-PCR and CT scanning is required to prevent the possibility of false-negative results during disease screening**[50]**.

c) Additional Test

For the diagnosis of COVID-19, although RT-qPCR is specific, its false-negative rate cannot be ignored because of the severe consequences of missed diagnosis. So many clinicians proposed CTscans should be one necessary auxiliary diagnostic method because it is more sensitive. **[51]** Chest CT is an ideal diagnostic tool for identifying viral pneumonia. The sensitivity of chest CT is far superior to that of X-ray screening. The chest CT findings associated with COVID-19-infected patients include characteristic patchy infiltration that later progresses to ground-glass opacities. Early manifestations of COVID-19 pneumonia might not be evident in X-ray chest radiography. In such situations, a chest C Texamination can be performed, as it is considered highly specific for COVID-19 pneumonia. Those patients having COVID-19 pneumonia will exhibit the typical ground-glass opacity in their chest CT images. The chest CT imaging abnormalities associated with COVID-19 pneumonia have also been observed even in asymptomatic patients **[52]**.

Other laboratory investigations are usually non specific. The white cell count is usually normal or low. There may belymphopenia; a lymphocyte count <1000 has been associated with severe disease. The platelet count is usually normal or mildly low. The CRP and ESR are generally elevated but procalcitonin levels are usually normal. A high procalcitonin level may indicate a bacterial co-infection. The ALT/AST, prothrombin time, creatinine, D-dimer, CPK and LDH maybe elevated and high levels are

associated with severe disease **[53]**. The patients infected with COVID-19 had elevated plasma angiotensin 2 levels. The level of angiotensin 2 was found to be linearly associated with viral load and lung injury, indicating its potential as a diagnostic biomarker **[54]**.

PREVENTION AND CONTROL

Persons with close contacts and suspicious exposure: Persons with close contacts and suspicious exposure should be advised to have a 14-day health observation period, which starts from the last day of contact with the 2019-nCoV infected patients or suspicious environmental exposure. Once they display any symptoms, especially fever, respiratory symptoms such as coughing, shortness of breath, or diarrhea, they should reach out for medical attention immediately **[55]**.

Patients with suspected 2019-nCoV infection: Patients with a suspected infection should be isolated, monitored, and diagnosed in hospital as soon as possible. Doctors should make recommendations based on the patient's situation. Patients with mild symptoms and suspected infection may consider in-home isolation and home care (weak recommendation). Suspected infected with severe symptoms and those who need to stay in hospital for observation by doctor's judgment should follow the isolation guidelines for suspected patients. It should also be noted that: (1) whether the suspected patients should be given in-home isolation and care or not requires careful clinical evaluation and safety assessment by professionals. (2) If the suspected patients do not get improvement in the symptoms or even worsened in condition during home care, they need to go to the doctor for treatment. (3) During the period of home care, the patients' medication and symptoms should be closely recorded and their caregivers should also monitor their body temperature daily **[56, 57]**.

Prevention for travelers (Strong recommendation): International visitors should take routine precautions when entering and leaving the affected areas, including avoiding close contacts with people with acute respiratory infection, washing hands frequently, especially after contacting with the sick or their surrounding environment; following appropriate coughing etiquette; and avoiding close contact with live or dead farming animals or bats or other wild animals. Passengers should avoid unnecessary travel, if possible **[58, 59]**.

TREATMENT AND CONTROL

Treatment plans:

- The patient should rest in bed, being monitored for vital signs (heart rate, pulse oxygen saturation, respiratory rate, blood pressure) and given supportive treatment to ensure sufficient energy intake and balance for water, electrolytes, acid base levels and other internal environment factors (Strong recommendation).
- The patient should be monitored for blood routine, CRP, PCT, organ function (liver enzyme, Bilirubin, myocardial enzyme, creatinine, urea nitrogen, Urine volume, etc.), coagulation function, arterial blood gas analysis and chest imaging (Strong recommendation).
- The patient should be given effective oxygen therapy, including nasal catheter, mask oxygen, high flow nasal oxygen therapy (HFNO), non-invasive ventilation (NIV) or invasive mechanical ventilation (Strong recommendation).
- Extracorporeal Membrane Oxygenation (ECMO) should be considered for the patients with refractory hypoxemia that is difficult to be corrected by protective lung ventilation. (Strong recommendation).

To date, no specific antiviral treatment has been confirmed to be effective against COVID-19. Regarding patients infected with COVID-19, it has been recommended to apply appropriate symptomatic treatment and supportive care along with some antiviral medication (Weak recommendations). Various clinical trials are being done to fine the appropriate vaccine and cure for COVID-19 **[60, 61]**.

Recent Studies on COVID-2019

1. Most people that became ill with COVID-19 will be able to recover at home.
2. There is still no specific treatment that exist for COVID-19, but there are certain things that one should take care of by getting adequate amount of rest, staying well hydrated, taking medication for relieving fever, body aches and pain may also help in relieving COVD-19 **[62]**.
3. Promising drugs to treat COVID-19 undergoing Tests.
4. **Convalescent plasma Technique-** In this technique antibody-containing plasma from a recovered patient is transfused to a patient who is suffering from COVID-19. The donor antibodies help by possibly shortening the length or reducing the

severity of the disease. On March 24th, the FDA began allowing convalescent plasma to be used in patients with serious or immediately life-threatening COVID-19 infections. This treatment is still considered experimental. *Criteria for donors:* They have to be tested positive for COVID-19 previously and recovered. They should have no symptoms form past 14 days and currently should be tested negative for COVID-19. These previously exposed patients to COVID-19 should have high enough antibody levels in their plasma **[62, 64]**.

S. No.	Drugs	Current Use	Mode of Action	Being Tested?
1.	Chloroquin	Antimalarial	Heme Polymerase Inhibitor	Yes
2.	Kaletra (Ritonavir + Lopinavir)	HIV	Protease Inhibitor	Yes
3.	Interferon α-2b	Hepatitis-C	Immune Modulator	Yes
4.	Remdesivir	Experimental	Nucleotide analogue	Yes
5.	Favipiravir	Influenza	RNA Polymerase Inhibitor	Yes
6.	Actemara (Tocilizumab)	Rheumatoid Arthritis, COVID-19	Anti-inflammatory	Approved *
7.	Kevzara (Sarilumab)	Rheumatoid Arthritis	Anti-inflammatory	Trial expected
Source: WHO, adapted from landscape analysis,17th Febuary,2020 *For use of COVID-19 in China, March 2020.[62]				

5. A study conducted showed that Anti-malarials (Hydroxychloroquine and chloroquine) have been shown to kill COVID-19 virus under the laboratory conditions. They work by making it harder for the virus to get attached to the cells thereby inhibiting the virus to enter inside the cell and multiplying within it. If by chance the virus enters inside the cell the drugs kill the virus before it starts multiplying. However, the most recent human studies suggest no benefit and possibly a higher risk of death due to lethal heart rhythm abnormalities with both hydroxychloroquine and chloroquine.**[65]**
6. Azithromycin is a commonly prescribed antibiotic for streptococcal throat and bacterial pneumonia. Drug is inexpensive and is readily available. Azithromycin is never used for viral infections. However, this antibiotic does have some anti-inflammatory action. There has been speculation, but never proven that azithromycin may help to dampen an overactive immune response to the COVID-19 infection **[66, 67]**.
7. Antiviral Drug (remdesivir) has received a lot of attention for

providing its beneficial effect in treating COVID-19. Remdesivir works by inhibiting the ability of the coronavirus to reproduce or multiply. This drug was used in first case of severely ill COVID-19 patient in Washington State, January 2020. The drug showed beneficial effects and the patient was cured **[68]**.

8. Some critically ill patients with COVID-19 have been treated with high doses of intravenous (IV) vitamin C in the hope that it will hasten the recovery. However, there is no clear or convincing scientific evidence that it works for COVID-19 infections. While standard doses of vitamin C are generally harmless, high doses can cause a number of side effects, including nausea, cramps, and an increased risk of kidney stones **[69]**.
9. Another drug which is used for the treatment of COVID-19 *in vitro* is Ivermectin. It was observed that a treatment with single dose was able to effect approximately 5000-fold reduction in virus at 48 h in cell culture. Ivermectin is FDA-approved drug for parasitic infections, and therefore it has a potential for repurposing. Ivermectin is widely available, due to its inclusion on the WHO model list of essential medicines **[70]**.
10. A study done on the Chinese COVI-19 patients stated that Hydroxychloroquine (an analogue of chloroquine) has been demonstrated to have an anti-SARS-CoV activity *in vitro* along with better clinical safety profile than chloroquine in higher daily dose and has fewer drug-drug interactions. Hydroxychloroquine is efficient in clearing viral nasopharyngeal carriage of SARS-CoV-2 in COVID-19 patients in only three to six days, in most patients **[71]**.
11. Coronavirus has a five spike protein structures in its outer cell which when enters in the human respiratory cells attaches itself to the ACE-2 Receptors or TMPRSS-2 Receptors and enters inside the cell where uncoating of virus is done and ssRNA is formed. Then this ssRNA with the help chymotrypsin like protease take part in translation and helps in the multiplication of ssRNA thereby forming more virus copies inside the cell. After they have multiplied the

virus then enters in the plasma and fight against the host cell immunity.

Generally there are various categories of the drug which act at different stages of virus multiplication and work by inhibiting the process and thereby killing the virus and curing the patient. Different drugs act at different stages like:

i) *Entry inhibitors*- Hydroxychloroquine, Nafamostat or Camostat (they block TMPRSS-2 Receptors), Umefenovir or Arbidol (they inhibit S protein and TRMPSS-2 interaction).

ii) *Endocytosis Inhibitors*- Hydroxychloroquine (Increase pH to alkaline in endosome.)

iii) *Protease Inhibitors*- Lopinavir or Darunavir (they inhibit the translation process).

iv) *RNA Polymerase Inhibitor*- Remdesivir or Galidesvir (fake adenosine), Ribavirin (fake guanosine), Favipiravir (direct RNA Polymerase damage), Merimepodis (Deplete guanosine), β-Hydroxycytidine (fake cytidine).

v) *Importin Inhibitor*- Ivermectin

vi) *Immunomodulators*- Corticosteroid, Hydroxychloroquine, Tocilizumab and Sarilumab (Anti interleukin 6), Bevacizumab (Anti VEGF), Plasma Exchange.

vii) *Miscellaneous*- Antihelmenthics (Niclosamide, Emetine, Ivermectin), Plitidepsin (Elongation factor inhibitor), Bemcentinib (AXL kinase Inhibitor), Rintatolimod (Toll like receptor-3 inhibitor) **[72, 73, 74, 75]**.

CONCLUSION

This review shows a comprehensive picture of the current research in response to the outbreak of COVID-19. The occurrence of outbreak of CoVs due to changes in the climate, and ecological conditions is generally associated with human animal contact. Live-animal markets, such as the China Seafood Market, represent ideal conditions for interspecies contact of wildlife with domestic birds, pigs, and mammals, which substantially increases the probability of interspecies transmission of CoV infections and could result in high risks to humans due to adaptive genetic recombination in these viruses. The COVID-19-associated symptoms are fever, cough, expectoration, headache, and myalgia or fatigue. During this early period, many

studies have been published exploring the epidemiology, causes, clinical manifestation and diagnosis, and prevention and control of the novel coronavirus. This study shows a holistic picture of the current research in response to the outbreak of COVID-19.However, advances in designing antiviral drugs and vaccines against several other emerging diseases will help develop suitable therapeutic agents against COVID-19 in a short time. Until then, we must rely exclusively on various control and prevention measures to prevent this new disease from becoming a pandemic.

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