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REVIEW: COVID-19 – THE PANDEMIC CONTINUES

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ABSTRACT

Coronavirus disease (COVID-19) is a public health emergency. The etiological agent for this health emergency is severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) formerly known as 2019-Novel Coronavirus (2019-nCoV).It is an acute respiratory disease and sometimes potentially fatal. The World Health Organization announced COVID-19 pandemic as a public health emergency on 30 January 2020, and declared it as an emergency for the international community. As of April 20, 2020, there have been 2,420,439 confirmed cases of COVID-19 globally, with 166,205 confirmed deaths globally. Severe acute respiratory syndrome coronavirus 2 utilizes angiotensin-converting enzyme 2 (ACE2) receptor for its entry into the human cell and mode of transmission is via inhalation or contact with infected droplets. The incubation period may be in between 2 to 14 days and clinical symptoms include fever, cough, fatigue, anorexia, dyspnoea whereas some patients remain asymptomatic. Commonly the infection is mild in majority of the patients but patients above 65 years of age (elderly) and patients with concomitant diseases, the infection can worsen and may result in pneumonia, acute respiratory distress syndrome (ARDS), multiple organ dysfunction syndrome with cytokine storm. Currently, treatment is supportive along with the use of some antiviral strategies but their role is not yet established. Prevention along with isolation remains the best option as of now. Many research groups are working on the development of a vaccine against SARS-CoV-2.In this review, we explain the virology, epidemiology, transmission, pathogenesis, clinical presentation, diagnosis, and research progress of the treatment.

INTRODUCTION

In December 2019, there were reports of pneumonia in 27 patients, of which seven patients were gravely ill in Wuhan city of China. At that time the etiology for this illness was still unknown [1]. On 7th January 2020, the Chinese Centre for Disease Control and Prevention (CCDC) reported the etiological agent to be a newly identified β-coronavirus by analyzing the throat swab samples. The World Health Organization (WHO) initially termed this coronavirus as 2019-Novel Coronavirus (2019-nCoV) on 12 January 2020. Later WHO announced the name of this disease as coronavirus disease 2019 COVID-19 on 11 February 2020 [2]. "Viral genomic analysis showed that the new coronavirus is genetically similar to ***severe acute respiratory syndrome coronavirus*** (SARS-CoV)" [3]. Thus various research groups including International Committee on Taxonomy of Viruses (ICTV), Coronavirus Study Group and other virologists named this new strain as **"SARS-CoV-2"** on 11 February 2020 [4].

As of May 1, 2020, there have been 3,181,642 confirmed cases of COVID-19, including 224,301 deaths, as reported by WHO [5]. As of 3 March, the Mortality Rate estimated by WHO is 3.4% [6]. On January 23, estimated R_o (Reproductive number) was in the range of 1.4 and 2.5 [7] whereas various studies have showed a different R_o which is in the range of 3.6 and 4.0, and 2.24 to 3.58 [8].

2. VIROLOGY

SARS-CoV-2 belongs to Coronaviridae family with Orthocoronavirinae as its subfamily, and this virus is enveloped with positive sense-single stranded RNA as its genetic material [9]. This family of viruses causes infection in many vertebrates especially in mammals, wild animals and birds. They are one of the major cause for viral respiratory infections [10, 11]. There are seven varieties of strains of coronaviruses which can infect humans: "HCoV-229E (alpha coronavirus), HCoV-NL63 (alpha coronavirus), HCoV-OC43 (beta coronavirus), HCoV-HKU1 (beta coronavirus), MERS-CoV (the beta coronavirus that causes Middle East Respiratory Syndrome), SARS-CoV (the beta coronavirus that causes Severe Acute Respiratory Syndrome), SARS-CoV-2 (the novel coronavirus that causes Coronavirus diseases 2019 or COVID-19)" [12].

Most of the coronaviruses carry open reading frames (ORFs) in the range of 6 to 11 [13]. The first open reading frame has two sub units that is ORF1a and ORF1b which are translated into several proteins such as pp1a and pp1ab. Viral proteases act on these polyproteins to yield sixteen non-structural proteins (NSPs) [13].During the replication process, the coronaviruses produce subgenomic mRNAs that cause translation of various accessory and structural proteins like spike glycoprotein (S), envelope protein (E), matrix protein (M) and nucleocapsid protein (N) which are essential part of viral replication [14]. Wu et al. carried out a metatranscriptomic analysis of Wuhan-Hu-1 coronavirus (WHCV one strain of SARS-CoV-2) which enclosed 16 predicted NSP and another interesting observation was that WHCV displayed some genetic similarity to SARS-CoV, especially in the receptor-binding domain (RBD) and S-glycoprotein gene thus exhibiting the capability of direct human transmission [15].

Angeletti et al. suggested that mutations in nonstructural proteins like NSP2 and NSP3 may be linked to infectivity and cellular differentiation process of SARS-CoV-2 [16]. A population genetics study was performed by Tang et al. on 103 SARS-CoV-2 genomes and categorized two widespread transforming varieties of SARS-CoV-2 [17]. One is L-type strain affecting 70% of cases and another is S-type strain affecting 30% cases. Furthermore, thy reported that L-type strain were more infectious and hostile [17]. Above studies show that it is essential to closely monitor the novel coronavirus.

3. EPIDEMIOLOGY

As of May 1, 2020, there have been 3,181,642 confirmed cases of COVID-19, including 224,301 deaths, as reported by WHO [5]. The spread of infection through person-to-person transmission was confirmed on 20 January 2020, when two patients with 2019-nCoV who did not have any history of visiting Wuhan were identified in Guangdong region [18]. Later WHO announced that infection spreads via human transmission, thus alerting the worldwide community to follow precautionary steps [19]. "On January 30, WHO declared the coronavirus outbreak a Global Public Health Emergency". Most viral respiratory infection are contagious when the patients is symptomatic, but there is evidence to indicate that spread of the virus via human-to-human transmission may occur during the asymptomatic incubation period, which is approximately estimated to be in between 2 and 10 days [20-22].

4. MODE OF TRANSMISSION

The virus is assumed to be transmitted via droplets when an infected person coughs, sneezes or talks and these

droplets may become infectious when they are in touch with the mucosal surfaces [23]. The spread may also occur via close contacts and also through fecal-oral route. Furthermore, transmission is also possible when the patients are in their incubation period [23]. The possibility of fecal-oral transmission needs more research. Symptomatic patients may be highly contagious [24]. Chinese guidelines suggest three possible way of transmission:

1. **Droplets transmission**: It occurs when respiratory droplets are ingested or inhaled by persons who are near the infected individuals.

2. **Contact transmission**: It occurs when a person comes in contact with virus-contaminated surface or object and then touch their mouth, eyes, or nose.

3. **Aerosol transmission:** It occurs when droplets from the respiratory system combine with air and form aerosols which when ingested in high doses into the lungs may result in infection [25, 26]. Zhang et al. analyzed four datasets with single-cell transcriptomes of the gastrointestinal tract and reported that the digestive system can be a potential route of transmission for COVID-19 infection because enterocytes for absorption located in ileum and colon expressed ACE2 [27].

4.1 Maternal-Child Transmission

Zhu et al. and Chen at al. conducted two separate studies and did not find any clinical evidence or any investigations to support the presence of COVID-19 in neonates who are born to affected mothers. The samples collected during the study like "umbilical cord blood, amniotic fluid, and breast milk" were are all tested negative for SARS-CoV-2 [28, 29]. WHO organized a joint mission consisting of many national and international experts who traveled to China in between 16 and 24 February 2020 [26]. This group investigated 147 pregnant women of which 64 were confirmed cases, 82 were suspected cases and 1 patient was asymptomatic with COVID-19 and reported that 8% had severe disease and 1% were critical. Thus they concluded that pregnant women were not at higher risk of developing the severe disease but this group did not inspect vertical transmission or neonatal outcomes. Schwartz et al. analyzed 38 pregnant women with COVID-19 and their newborn infants. This analysis showed that there were no maternal deaths and also no confirmed cases of intrauterine transmission from infected mothers to their fetuses. All neonates who were born were tested and results were negative for SARS-CoV-2. In this chaos of the global pandemic, there is no corroboration that SARS-CoV-2 can undergo vertical transmission from infected pregnant women to their foetus [30]. However, it is essential to screen pregnant women and carry out aggressive infection control measures.

5. PATHOGENESIS

The pathogenic mechanism and clinical presentation of COVID-19 can be possibly explained by the distribution of viral receptor [31, 32]. **"**Zhou et al. performed bronchoalveolar lavage (BAL) on an infected individual and reported that SARS-CoV-2 makes use of identical cellular entry receptor that is Angiotensin-converting enzyme 2 (ACE2) as SARS-CoV**"** [31]. ACE2 is expressed by the many host cells and it is present at multiple locations like lung AT2 cells, upper esophagus, absorptive enterocytes present in the ileum, and colon and this explains various routes of transmission [33]. The surface spike glycoprotein (S) plays an essential part in the virulence of coronaviruses as a **"**receptor-binding domain (RBD)**"** of virus spikes can attach to the human cell using the receptor ACE2 [34]. **"**Furthermore, the sequence of the RBD of COVID-19 spike glycoprotein is identical to that of SARS-CoV thus above studies strongly advocate that the entry of the virus into the host cell is probably through the ACE2 receptor**"** [35]. **"**Spike glycoprotein is a large trimer with clove shape and includes two subunits S1 and S2**"** [36]. N-terminal S1 subunit consists of RBD which decides the host range as well as host tropism and a C-terminal S2 subunit which mediates virus-host cell membrane

fusion by two tandem domains, heptad repeats 1 (HR1) [37] and heptad repeats 2 (HR2) [38]. **"**The spike glycoprotein shows a variable amino acid sequence among all the other proteins of coronavirus which results from the strongest positive selection among all genes of coronavirus to adapt to its hosts**"** [39]. In contrast, **"**MERS utilizes dipeptidyl peptidase 4 (DPP4, also known as CD26) as a receptor to infect non-ciliary bronchial epithelium and type-II pneumocytes**"** [14, 40] whereas SARS-CoV infects bronchial ciliary epithelium and type-II pneumocytes via ACE2 receptor [14, 41]. Letko et al. performed a methodical identification of β-Coronavirus receptors and reported that human cells that expressed ACE2 but not DPP4 or Aminopeptidase N (APN) showed an increased entry of SARS-CoV-2 [42]. **"**Following receptor binding, in the case of SARS-CoV, the spike glycoprotein is cleaved via acid-dependent cell surface-associated transmembrane protease serine 2 (TMPRSS2) [43] and cathepsin [44] whereas in case of SARS-CoV-2 this is still unclear**"**. Following receptor binding, there is merging of viral envelope to plasma membrane of the cell that results in deliverance of viral RNA into the intracellular region of the host cell which gets uncoated and finally translates into pp1a and pp1ab [45]. Now the RNA material of the virus inside the host cell yields NSPs and also forms a transcription complex [46]. Subgenomic RNAs formed by the replication process encodes for accessory and structural proteins [14].Lastly, newly formed viral RNA, nucleocapsid protein, small envelope protein, endoplasmic reticulum, and Golgi assemble to finally yield viral buds which exit the host cell by merging with plasma membrane [47]. Figure: Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) structure with various proteins influencing the pathogenesis of SARS-CoV-2. Structural proteins like spike glycoprotein (S), envelope protein (E), matrix protein (M) and nucleocapsid protein (N) are also encoded by viral RNA. The surface spike glycoprotein (S) plays an essential part in the virulence of coronaviruses as a **"**receptor-binding domain (RBD)**"** of virus spikes can attach to the human cell using the receptor ACE2. Patients with underlying disease may progress to severe pneumonia.

6. CLINICAL PRESENTATION

Most of the patients diagnosed with COVID-19 show symptoms of dry cough, fever, diarrhea, vomiting, and myalgia but patients with multiple comorbid conditions can develop serious complications like ARDS, acute kidney injury, MODS and may even cause death [48, 49]. **"**Wang et al. reported symptoms of fever, fatigue, dry cough, anorexia, myalgia, and dyspnoea in 138 patients with COVID-19 in Wuhan. Imaging techniques revealed bilateral shadows or ground-glass opacities in the lungs of all 138 patients and also majority of the patients had comorbidities like hypertension, cardiovascular diseases, and diabetes mellitus furthermore 26% of patients were shifted to ICU and 4% of patients died**"** [50]. Also similar to SARS-CoV and MERS-CoV, patients with SARS-CoV-2 had high levels of cytokines in their body [9, 49]. The incubation period of COVID-19 is about 10 days (may range from 2-14 days) from the time of infection to the appearance of symptoms [9, 18, 49, 31]. **"**Wan et al conducted a study on 135 patients and found that most common clinical characteristics at the onset of illness were fever, cough, myalgia, fatigue, and headache. Minority of the reports symptoms were pharyngalgia, dyspnoea, diarrhea, chest tightness, and shortness of breath, fear of cold, and sputum production**"** [51]. Radiological studies can help in diagnosis as well as treatment of the patient. A Chest CT scan was performed in all of the suspected patients and imaging results showed bilateral interstitial pneumonia with multiple patches, flocculent ground glass shadow. There was little pleural effusion and lungs were consolidated in serious disease. Furthermore, among these 135 patients, common complications reported were ARDS, acute cardiac injury, acute kidney injury, secondary infection, and shock. Studies show that COVID-19 in neonates, infants, and children seems to be milder than their

adult counterparts but one case of a child with severe pneumonia and multi-organ dysfunction was reported [52]. Guan et al. reported that 86.2% of patients exhibited abnormalities in chest CT scans with more than 75% of patients among them showed bilateral lung involvement [53]. Furthermore, they found no substantial gender difference in children with respect to COVID-19 susceptibility.

7. DIAGNOSIS

7.1 Case definitions (As per WHO)

7.1.1 Suspect case

A. **"**A patient with acute respiratory illness (fever and at least one sign/symptom of respiratory disease, e.g., cough, shortness of breath), AND a history of travel to or residence in a location reporting community transmission of COVID-19 disease during the 14 days before symptom onset**"** [54]. OR

B. **"**A patient with an acute respiratory illness AND having been in contact with a confirmed or probable COVID-19 case (see definition of contact) in the last 14 days before symptom onset**"** [54];

OR

C. **"**A patient with severe acute respiratory illness (fever and at least one sign/symptom of respiratory disease, e.g., cough, shortness of breath; AND requiring hospitalization) AND in the absence of an alternative diagnosis that fully explains the clinical presentation**"** [54].

7.1.2 Probable case

A. **"**A suspect case for whom testing for the COVID-19 virus is inconclusive**"** [54].

a. Inconclusive being the result of the test reported by the laboratory.

OR

B. **"**A suspect case for whom testing could not be performed for any reason**"** [54].

7.1.3 Confirmed case

"A person with laboratory confirmation of COVID-19 infection, irrespective of clinical signs, and symptoms**"** [54].

7.1.4 Definition of contact

"A contact is a person who experienced any one of the following exposures during the 2 days before and the 14 days after the onset of symptoms of a probable or confirmed case**"** [55]:

1. **"**Face-to-face contact with a probable or confirmed case within 1 meter and for more than 15 minutes**"** [55];

2. **"**Direct physical contact with a probable or confirmed case**"** [55];

3. **"**Direct care for a patient with probable or confirmed COVID-19 disease without using proper personal protective equipment**"** [55]; OR

4. **"**Other situations as indicated by local risk assessments**"** [55].

"Laboratory investigation of majority of the cases show standard or reduced leukocyte count as well as reduced lymphocyte number but in the case of critical patients the neutrophil count, D-dimer, blood urea and creatinine levels were significantly higher and also it was observed that critical patients showed a progressive decrease in lymphocyte count**"** [53,56]. **"**Patients who were admitted to ICU had higher plasma levels of various inflammatory cytokines like interleukin (IL)-6, IL-2, IL-7, IL-10, tumor necrosis factor-α (TNF-α), interferon-gamma induced protein (IP-10), granulocyte colony-stimulating factor (GCSF), monocyte chemoattractant protein-1 (MCP-1) and macrophage inflammatory protein 1-α (MIP-1α)**"** [49]. **"**Patients with a suspected infection should undertake extensive laboratory tests. Patients may have increases levels C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), lactate dehydrogenase (LDH), and also a prolonged prothrombin time (PT)**"** [50].

WHO recommends that all the patients with suspected infections should be

immediately isolated and should undertake the following procedures: **"**Real-time fluorescence Reverse Transcription Polymerase Chain Reaction (RT-PCR)**"** to identify the positive nucleic acid of SARS-CoV-2 in **"**sputum, throat swabs and also secretions of the lower respiratory tract samples**"** [23, 26]. For the swift development of real-time RT-PCR diagnostic test, the genome sequence was used for designing specific primers and probes to detect SARS-CoV-2 [57]. The real-time RT-PCR assay has shown high specificity and sensitivity for the identification of respiratory pathogens in individuals with acute respiratory infection [23]. **"**Nonetheless, the results of RT-PCR for SARS-CoV-2 are influenced by the quality of the testing gear, place of sample taken, volume of sample taken, novel coronaviruses characteristics, shipping environment, storage conditions, and personnel operation**"** [58].

8. PREVENTION AND CONTROL

"WHO and United States Centers for Disease Control and Prevention (CDC) has issued prevention steps to limit the extent of disease spread. The preventive steps include evading travel to high-risk zones, avoiding interaction with symptomatic patients and to shun consumption of meat from COVID-19 outbreak areas. Apart from these, the other recommendations include following basic hand hygiene measures like hand washing with soap and water for a minimum of 20 seconds, especially these measures should be followed while visiting the washroom, prior to food consumption, after cleaning the nose, after sneezing or during cough. Furthermore use of personal protective equipment (PPE) is also essential to curb the infection spread**"** [59, 20]. In case of unavailability of soap and water, alcohol based sanitizer with a minimum of 60% alcohol concentration should be used. Studies have recommended preventive measures for the general public, including regular washing of hands with soap and water, following cough and sneezing manners, use of face mask when visiting public places [23]. However, there is no clear scientific evidence for the effectiveness of wearing masks in a healthy person. Another important concern is protecting the health care workers against hospital acquired infections by providing N95 masks, goggles, and protective gowns [60]. Individuals with close contacts and suspected exposure should follow additional guidelines which are considered as "strong recommendations" like immediate medical care, 14 days of quarantine, wearing N95 masks, use of private transport and also cleaning of transport vehicle with 500mg/L chlorine-containing disinfectant [61] (above recommendations may be subjected to modifications in future).

Strict measures have been adopted by China and the global community in limiting the spread of virus-like temperature detection of incoming and outgoing personnel at places of travel, cancellation of mass gatherings, closure of schools and other educational institutions, work-from-home arrangements and China has also introduced strict laws to prohibit selling and trading of wild animals [62]. **"**SARS-CoV-2 can survive on non-living surfaces like metal, glass, or plastic for up to 9 days so it is essential to follow certain disinfection procedures like using 62-71% ethanol, 0.5% hydrogen peroxide or 0.1% sodium hypochlorite within one minute**"** [63]. However, now declared as a pandemic only future can tell whether all these efforts will result in reduced transmission.

9. TREATMENT

In the current scenario, the therapeutic approaches are only supportive and the best measure is to reduce the transmission. Recently proposed treatment guidelines are largely built on guidelines for SARS-CoV, MERS-CoV, and influenza. The first step is to isolate the patient to reduce the transmission rate. Various health organizations have suggested following recommendations for isolation: isolate the patient confirmed with SARS-CoV-2 infection using laboratory testing at a testing facility approved by the respective governments, individuals with signs of respiratory sickness as well as fever,

individuals who has come in contact with any person with COVID-19 disease or who has a travel history COVID affected region in last 14 days should be isolated, furthermore frontline health care workers with signs of respiratory sickness and fever who are involved in the management of COVID-19 patients or who has come in contact with individuals involved in the management of COVID-19 patients within last 14 days. A mild case of sickness requires home care with adequate nourishment and fluid intake along with management of fever and cough. **"**Patients showing symptoms of hypoxia should be managed by providing supplemental oxygen and WHO recommends extracorporeal membrane oxygenation (ECMO) for cases with acute hypoxemic respiratory failure, renal replacement therapy for cases with reduced kidney function and also patients with suspected or proven co-infections should be given antibiotics and antifungals as appropriate**"** [64].

9.1 Role of corticosteroids

"WHO and various international guidelines are against the use of corticosteroids but Chinese authorities have recommended short term corticosteroid therapy with low-to-moderate doses in patients with COVID-19 ARDS**"** [65, 66]. Chen and his colleagues carried out a case series study in Wuhan. They analyzed 99 COVID-19 patients who were hospitalized and reported that **"**76% of cases received supplemental oxygen, 13% of cases were provided with noninvasive ventilation support, 4% of them were supported with mechanical ventilation, 3% were provided with ECMO, 9% were on dialysis, 71% of patients were prescribed antibiotics, 15% of them received antifungals, 19% of patients were put on glucocorticoid therapy and 27% of patients were received intravenous immunoglobulin therapy**"** [48]. Shang et al. conducted a study on 416 COVID-19 patients and reported that the use of corticosteroid regimen plus gamma globulin is associated with increased mortality rate and concluded that its possible use may be in patients with low WBC count [67]. Therefore the use of corticosteroids in the management of COVID-19 patients is unclear and requires further investigations.

9.2- Role of Hydroxychloroquine/ Chloroquine

Chloroquine as a treatment or prevention option for COVID-19 was first suggested by a French virologist, Prof. Raoult which became viral and the demand for it increased tremendously. Unfortunately, this suggestion was centered on theoretical concept [68], some in vitro studies [69-72] and also based upon investigational data [73] which showed inhibition of SARS-CoV [74]. There was no concrete clinical evidence for the use of chloroquine other than a non-randomized study comprising of 20 patients which seemed to provide results on elimination of the virus [75].

Wang and his colleagues showed that Chloroquine and Remdesivir were efficacious in controlling in vitro 2019-nCoV infection. Chloroquine effect was seen at the entry-level of the virus as well as post-entry-level whereas Remdesivir showed effectiveness only at post-entry-level thus suggesting the possible prophylactic use of Chloroquine [71]. Gao et al. studied the effect of Chloroquine and Hydroxychloroquine (HCQ) in over 100 COVID-19 patients and 10 hospitals spread over different areas of China and they reported that Chloroquine phosphate is efficacious in preventing the severity of pneumonia, reduced lung involvement upon scanning, promoted a virus-negative status and reduced the disease progression, furthermore they added that at therapeutic doses there were no serious adverse effects [76]. **"**Yao et al. also conducted in vitro experiments on the effect of Hydroxychloroquine and Chloroquine and reported that Hydroxychloroquine was more efficacious than Chloroquine for both prophylaxis and treatment**"** [72]. Many randomized clinical trials (RCTs) regarding the use of Chloroquine and Hydroxychloroquine in COVID-19 are being conducted worldwide. **"**Chloroquine as well as Hydroxychloroquine in the future may

emerge as a game-changer but until it is proven they cannot be recommended**"**.

9.3 Role of Anti-viral drugs

In the current situation, there are no fixed antiviral drugs or any vaccines to fight against COVID-19 infection in humans. **"**The only available option is to use broad-spectrum antiviral drugs like nucleoside analogs and HIV-protease inhibitors which could reduce viral infection until more specific antiviral drugs and vaccine becomes available to use**"** [77]. **"**Lopinavir is an HIV-1 protease inhibitor (PI), administered in fixed-dose combination with ritonavir (LPV/r), a potent inhibitor of CYP3A4 which increases lopinavir serum concentration and reports suggest that they have antiviral activity against SARS and MERS**"** [78, 79]. Young and his colleagues announced the results of first 18 SARS-CoV-2 infected patients in Singapore. Among these 18 patients, five patients received Lopinavir and Ritonavir fixed combination in which three patients showed reduced oxygen requirements after initiating the treatment; two patients showed progressive respiratory failure. On treatment, two out of five patients (40%) showed viral load clearance whereas 4 out of 5 patients (80%) showed adverse effects which prevented the completion of a 14-day planned treatment course [80]. **"**Cao et al. conducted an open-label randomized trial comparing LPV/r 400/100 mg twice daily (n=99) to standard care (n=100) in COVID-19 pneumonia and reported that there was no difference between treatment arms in the reduction of viral loads over time between the two groups**"** [81]. From the available data, it is challenging to assess the part played by LPV/r in the management of COVID-19. Remdesivir (GS-5734) is an investigational prodrug which belongs to an analog of adenosine for the management of Ebola virus disease. **"**Remdesivir acts as an RNA-chain terminator by binding to RNA-dependent RNA polymerase (shows high selectivity for viral polymerases) and this drug exhibits effective in vitro activity against SARS-CoV-2 with a half-maximal effective concentration (EC50) of 0.77µM at 48 hours in Vero E6 cells**"** [71]. **"**The first report of a remdesivir-treated patient with COVID-19 within the US was a 35-year-old male who was given treatment on hospital day 7 (which was his illness day 11) owing progressive pneumonia and protracted fever**"** [82].Among the primary 12 patients within US with COVID-19 as confirmed by the CDC, 3 patients were administered with remdesivir through compassionate use [83].The main drawback of this study was that the authors were not able to assess the efficacy or safety of remdesivir based on lack of comparator and cofounding therapy including concomitant use of corticosteroid in one patient. **"**In a Randomized controlled trial (RCT) (ClinicalTrials.gov Identifier: NCT04280705) named as ACTT (Adaptive COVID-19 Treatment Trial) of 1063 patients conducted by National Institute of Allergy and Infectious Diseases (NIAID), it was reported that hospitalized COVID-19 patients with complications of lung recovered 31% faster with remdesivir than with patients who were given placebo**"** [84]. In a multicenter clinical trial conducted at ten hospitals in Hubei province of China, 237 patients with COVID-19 were enrolled. Among them 158 patients received remdesivir, and 79 received placebo. **"**In this trial, remdesivir did not show any statistically significant time difference to clinical improvement and adverse events were reported in 102 patients who were administered remdesivir**"** [85]. However these results are preliminary data and final results will give a clear conclusion. Prominent clinical evidence and existing in vitro studies suggest that remdesivir may be a positive agent for COVID-19 treatment. Additional clinical data is essential to further define the role of this agent in COVID-19.

9.4 Role of Ribavirin and Interferon

"Wang et al. assessed the in vitro activity of Ribavirin against SARS-CoV-2 and reported an EC50 of 109.5µM which was over 100 times less potent than Remdesivir**"** [71]. WHO research and development plan did not consider Ribavirin as a feasible option for further studies due to its ability to cause hematologic toxicity at

high doses, lack of in vitro activity, and poor outcomes. Interferons (α, β) may play a role in activating innate antiviral responses and are likely to possess in vitro activity against SARS-CoV-2 because of their previously described activity against MERS-CoV (EC50 of 175 IU/mL). Interferons are associated with severe cytopenias, hepatotoxicity, neuropsychiatric effects, and increased risk of developing an infection or fatal ischemia, particularly when used along with ribavirin. A combination of ribavirin and interferon was not related to increased viral clearance or reduced mortality during a retrospective study of patients with, MERS-CoV who were started on combined therapy within 1-3 days of ICU, admission [86]. Various clinical trials are being conducted to study ribavirin, interferon, and various antiviral agents in the treatment of COVID-19. With a lack of clear animal or human data, poor in vitro activity and severe toxic profile makes ribavirin a poor candidate in the management of COVID-19 disease.

9.5 Role of Oseltamivir

Oseltamivir was include in the treatment strategy along with broad-spectrum antibiotics for the management of COVID-19 patients in Wuhan city [49].Here in this study oseltamivir was not used as a targeted therapy against SARS-CoV-2 but rather the driving force behind its use was lack of knowledge about the pathogen and the need to empirically treat influenza. **"**Furthermore, the authors of this study do not suggest the use of oseltamivir for COVID-19 patients in the publication and there is no strong evidence which can suggest in vitro activity of oseltamivir against SARS-CoV-2**"** [49]. **"**Tan et al. showed that oseltamivir was ineffective against SARS-CoV-1 even at a degree of 10 000μM/L**"** [87]. Thus coronavirus does not neutralize neuraminidase and this holds for other neuraminidase inhibitors. So once influenza has been ruled out these agents should not be used in the management of COVID-19 patients.

9.6 Role of Convalescent plasma therapy

Convalescent plasma therapy was used earlier to treat SARS-CoV-1, Ebola, HINI influenza, and MERS with reported success by taking from patients who recovered these viral infections [88]. **"**A meta-analysis showed a significant decline in mortality and viral load in studies that used convalescent plasma as a treatment option for severe acute respiratory infection of viral origin including those affected by other coronaviruses**"** [89].Clinical trials to examine this treatment strategy are underway in China (Clinical Trials.gov:NCT04264858) [90] and compassionate use protocol has been lately underway in the US. However, the safety and efficacy of this treatment strategy has not been established in SARS-CoV-2 patients.

9.7 Role of Vaccine

"SARS-CoV-2 was recognized early and its genomic sequence was made public by Chinese researchers**"** [9, 15, 31]. **"**Studies from SARS-CoV-1 and MERS-CoV immunizations provide information that spike (S) glycoprotein located on the viral surface is a perfect target for the vaccine because, in SARS-CoV-1 and SARS-CoV-2, this protein associates with ACE2 receptor in the host cell and antibodies directed against the spike glycoprotein can interrupt the binding of the virus and thus neutralizing the virus**"** [91-93]. In this way we have a target antigen that can be consolidated into cutting edge and different immunization stages. As of now, there are no affirmed human coronavirus immunizations and numerous ongoing clinical trials with funding from various organizations are working towards the development of vaccines. Apart from the above treatment options, use of an antiviral fusion inhibitor Arbidol [94, 95]. **"**Another strategy is the utilization of polyclonal human immunoglobulin G (IgG) acquired from transgenic bovines since this approach has been successfully tested against MERS-CoV in animal models**"** [96]. The results of these trials will be coming soon and hopefully, they would be used widely in a short duration.

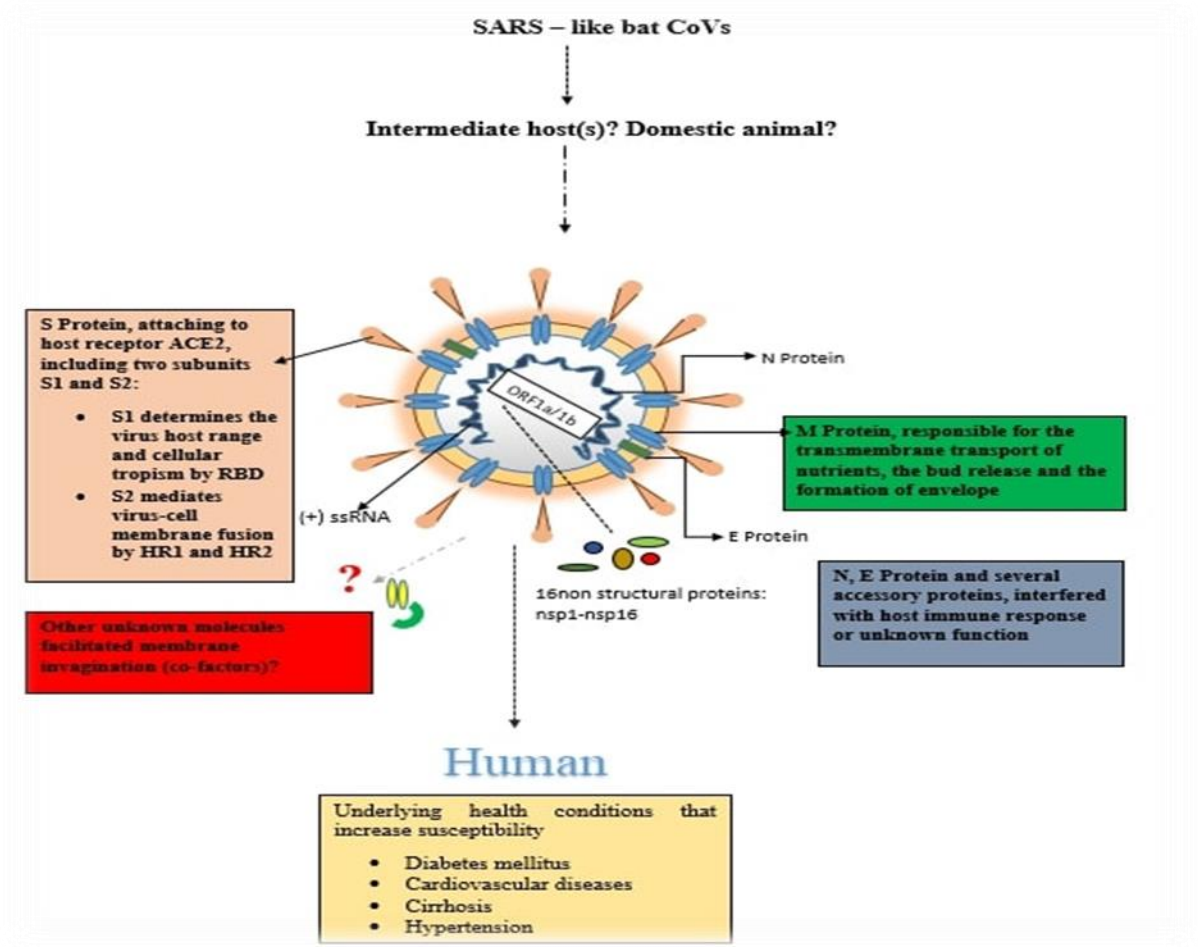

Figure 1: Structural proteins like spike glycoprotein (S), envelope protein (E), viral RNA also encodes matrix protein (M) and nucleocapsid protein (N). The surface spike glycoprotein (S) plays an essential part in the virulence of coronaviruses as a **"**receptor-binding domain (RBD)**"** of virus spikes can attach to the human cell using the receptor ACE2. Patients with underlying disease may progress to severe pneumonia.

Table No 1: List of agents that are under investigation and/or being theoretically considered for the management of SARS-CoV-2 patients. In the current scenario, no recommendation can be made for any of these agents.

AGENT	COMMENTS
Anakinra	Interleukin-1 (IL-1) receptor antagonist, which hypothesizes to curb cytokine storming. As of now, no information exists for treatment of COVID-19. There are no current clinical trials in China or the US for investigating this agent.
Arbidol (Umifenovir)	The antiviral agent utilized for the influenza in Russia and China. It is under investigation for COVID-19 alleging potent in vitro activity in Chinese clinical trials. The recommended dose is 200mg orally 3 times a day for no more than 10 days. There are currently no clinical data available.
Baricitinib	**"**A Janus Kinase family (JAK) enzyme inhibitor that is suggested by artificial intelligence as a COVID-19 treatment**"** [97]. There are no clinical results.
Bevacizumab	Recombinant humanized monoclonal antibody that prevents the interaction of the vascular endothelial growth factor (VEGF) with endothelial receptors Flt-1 and Kinase insert domain receptor (KDR) inhibitor licensed in the United States for multiple cancers. It is being assessed for COVID-19 (NCT04275414) in a clinical trial in China [98], there are no data to support

	its use at this time.
Brilacidin	A host defense peptide mimetic used by Innovation Pharmaceuticals in clinical research. The company recently announced that they would begin testing the molecule against SARS-CoV-2 starting March 16, 2020.
Convalescent plasma	**"**Convalescent plasma from patients recovering from viral infections has previously been used with documented success for SARS-CoV-1, Middle East Respiratory Syndrome, Ebola, and H1N1 influenza**"** [88]. The safety and efficacy of convalescent plasma transfusion in patients infected with SARS-CoV-2 has not been developed, and there are no guidelines currently in place in the United States.
Darunavir/cobicistat	**"**The HIV-1 protease inhibitor currently being tested in a clinical trial (NCT04252274)**"** [99], but there are no in vitro or human trials evidence to support its use.
Disulfiram	Thiuram derivative that blocks the oxidation of alcohol. Established ability to inhibit the papain-like SARS proteases; however, there is no clinical data [100]. There is no in vitro or clinical evidence for COVID-19.
Eculizumab	Humanized, monoclonal IgG antibody binding to complement protein C5 and preventing complex membrane attack (MAC) formation. Being tested to quench immune response in a clinical trial (NCT04288713) [101] for COVID-19, no evidence exist at this time to support its use.
Favipiravir	**"**RNA-dependent RNA polymerase inhibitor with widespread antiviral activity; however, high EC50 (decreased potency) was demonstrated against SARS-CoV-2 but was successful in shielding mice from Ebola virus despite similarly high EC50 values**"** [71]. This agent is not approved by FDA or available in the USA.
Galidesivir (BCX4430)	Nucleoside RNA polymerase inhibitor with a reported broad spectrum of antiviral activity, currently in the Biocryst Pharma pipeline and previously tested for Ebola and other viral infections.
Griffithsin	**"**Algae-derived lectin and potent HIV entry inhibitor agent showing in vitro activity against SARS-CoV-1**"** [102].
Niclosamide	**"**Anthelminthic drug with in vitro efficacy against SARS-CoV-1; however poor absorption and oral bioavailability resulting in a broad range of serum concentrations in healthy volunteers after administration of a single dose can limit the usefulness of antiviral treatment**"** [103].
REGN3048	**"**The human monoclonal antibody that Regeneron has discovered is reportedly bound to the MERS-CoV spike protein. Right now the molecule is in phase 1 of clinical trial in healthy volunteers (NCT03301090)**"** [104].
Sarilumab	FDA-approved IL-6 receptor antagonist for rheumatoid arthritis. Under clinical trials.
Sofosbuvir	**"**Antiviral used to treat hepatitis C infection. It shows in vitro activity against SARS-CoV-1**"** [105], no clinical data exist yet.
Vitamin C	**"**There is an ongoing clinical trial in China for the treatment of COVID-19 (NCT04264533 [106] using 12 grams IV BID vitamin C**"**. Not recommended for use at this time.
XueBiJing	Chinese herbal medicine extract given at 100 mL IV twice daily, suggested in the National Health Commission of the People's Republic of China as a "may consider" treatment for severe and critical cases. **"**This previously demonstrated improved mortality in patients with severe community-acquired pneumonia in China**"** [107].

9.8 Investigative Agents for "SARS-CoV-2"

In the **Table,** We have provided a list of agents that are under investigation and/or being theoretically considered for the management of SARS-CoV-2 patients. In the current scenario, no recommendation can be made for any of these agents. **10.**

CONCLUSION AND FUTURE PERSPECTIVE

SARS-CoV-2 pandemic continues. Extensive measures to prevent human-to-human transmission of COVID-19 are essential to control the outbreak as well as measures to curb the trading of wild animals and to improve health infrastructure to combat the virus. Therapeutic agents to treat or prevent the disease progression remain ill-defined and several pharmaceutical companies and research institutions have started to develop a vaccine but it requires enormous funding and time. Global pandemic not only results in the severe human loss but also affects global economies. More studies are needed to reveal the mystery of mechanism of entry of the virus which will provide the platform for the development of antiviral agents and vaccines. However, the rapidly evolving nature of COVID-19 pandemic, rapidly changing statistics and new findings present a major limitation to this present review.

11. MATERİALS AND METHOD

In this review, we have used PubMed, Google Scholar databases for our search using the terms 'SARS-CoV-2', 'COVID-19', 'Coronavirus', 'treatment', 'pandemic', 'vaccine'. Furthermore we have used Google search engine for obtaining information and also for selecting our articles regarding COVID-19 from reputed journals. The collected articles include latest research done on SARS-CoV-2 including in vitro studies and articles related to other coronavirus members. Most of the articles evaluated were latest and published in 2020. Titles and abstracts of collected articles were screened with complete evaluation of full text of the articles.

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