Current Pharma Research
ISSN-2230-7842
CODEN-CPRUE6
www.jcpronline.in/

Review Article

COVID-19 (SARS-CoV-2): Origin, Virology, Clinical Manifestations, and Treatment.

Supriya Sangram Nikam*, Kalyani Pranav Kayande

Sinhgad Institute of Pharmacy, Narhe, Pune, Maharashtra, INDIA.

Received 08 May 2020; received in revised form 31 May 2020; accepted 05 June 2020

***Corresponding author E-mail address:** *sdeshmukh3105@gmail.com*

ABSTRACT
The rapid spread of the coronavirus disease 2019 (COVID-19), caused by a zoonotic beta-coronavirus entitled 2019 novel coronavirus (2019-nCoV), has become a global threat. Awareness of the biological features of 2019-nCoV should be updated in time and needs to be comprehensively summarized to help optimize control measures and make therapeutic decisions. The genome, clinical presentation, and pathology of COVID-19 much resembled Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV) and indicating a bat origin. Grounded on recently published literature, we studied the virology and origin, epidemiology, clinical manifestations and treatment of COVID-19, in comparison with SARS-CoV and MERS-CoV infection. The COVID-19 generally had long incubation period, high reproductive number, and low case fatality rate (higher in patients with comorbidities). Currently, no confirmed effective therapies for this virus exist. Potential treatments included remdesivir, chloroquine, and tocilizumab. Remdesivir is an utmost promising therapy. It exhibited potent *in vitro* activity against SARS-CoV-2, but then it is not US Food and Drug Administration (US FDA) approved. It is presently is being tested in ongoing randomized trials. Oseltamivir has not been revealed to have efficacy, and corticosteroids are presently not recommended. Current clinical evidence signifies the practice of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers in patients with COVID-19. Additionally, Convalescent Plasma (CP) and vaccine immunization (when possible) is also included. The early experience from the current epidemic and lessons from the prior two pandemics can assist to improve upcoming preparedness strategies and fight against disease progression.

KEYWORDS
COVID-19; SARS-CoV-2; SARS-CoV; MERS-CoV.

1. INTRODUCTION

Corona viruses (CoVs) symbolize a significant group of viruses mostly affecting human beings through the zoonotic transmission. Although human CoVs were recognized for the first time within the year 1960 from respiratory infections in adults furthermore as in children, the most important scientific interest in CoVs research grew only after the occurrence of Severe Acute Respiratory Syndrome CoV (SARS-CoV) within the year 2002-2003 [1,2]. In this SARS-CoV epidemic, about 774 deaths out of 8000 confirmed human cases (9.5% mortality rate) occurred that was a consequence of its world wild spread [3]. Subsequent SARS-CoV incidence in 2003, the same CoV named HKU3-1 to HKU3-3 was identified within the horseshoe bats in 2005 from Hong Kong [4]. Since then, bats are considered to be the natural host and potential reservoir species that could be held accountable for any forthcoming CoVs epidemics and/or pandemics [5]. Subsequently the 2003 and 2005 SARS-CoV epidemics, an identical virus emerged within the Middle East region of the world which results in severe respiratory disorder and was named the Middle East Respiratory Syndrome CoV (MERS-CoV)[6]. These entire relatively pathogenic human CoVs, SARS, and MERS show occurrence over globally posing high risk of human-to-human transmission and fatal effects thereto. In December 2019, a case of unidentified pneumonia was reported in Wuhan, Hubei Province, People's Republic of China (PRC). Its clinical features are analogous to viral pneumonia. PRC Centers for Disease Control (CDC) authorities stated that the pneumonia as novel coronavirus pneumonia (NCP) was caused by novel coronavirus [7]. This virus has high transmissibility and infectivity, in spite of low mortality rate compared with SARS and MERS [8]. Genome investigation of novel coronavirus sequences discovered that the complete genome sequence recognition rates of SARS-CoV and bat SARS coronavirus (SARSr-CoV-RaTG13) were 79.5% and 96% respectively [9]. WHO officially termed the disease COVID-19 and International Committee on Taxonomy of Viruses (ICTV) named the virus severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [10]. This virus belongs to β – coronavirus, a huge class of viruses predominant in nature. Subsequently, within a short period of a one month the disease blowout to other countries all over the place of the globe. COVID-19 was announced as an outbreak prone disease and consequently a Public Health Emergency of International Concern (PHEIC) by WHO on 30th January 2020 as per the International Health Regulation (2005) Emergency Committee [11]. On 11thMarch 2020 WHO categorized COVID-19 as a pandemic. The pandemic has clearly moved in a new phase with speedy spread in many countries exterior China[12]. Around 215 Countries, areas or territories are infected with COVID-19 in which over 36, 79,499 confirmed cases and over 2, 54,199 confirmed deaths worldwide as on May 07, 2020 [13]. Number of confirmed COVID-19 cases till May 07 2020 is represented in graph below (Fig.1).

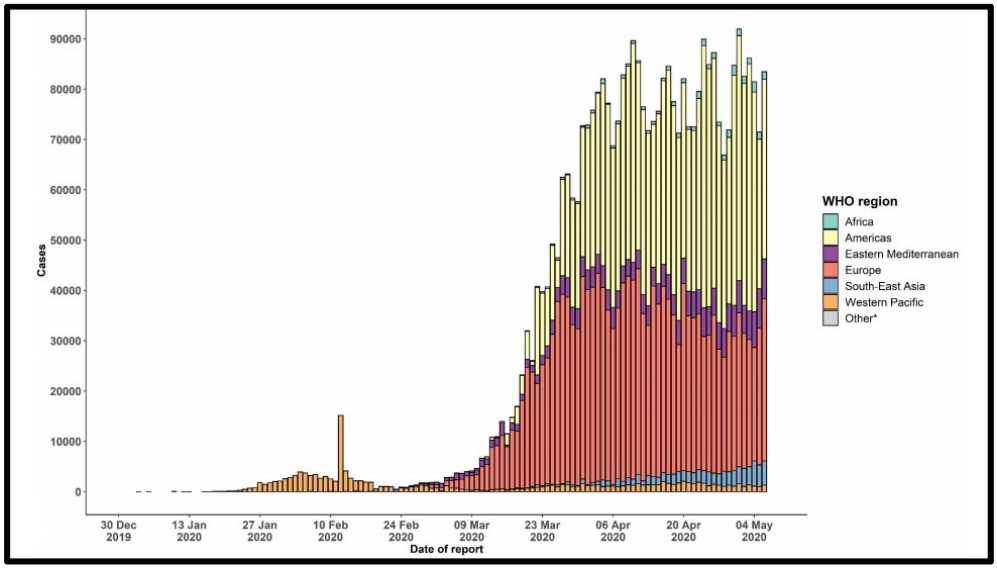

Fig. 1. Number of confirmed COVID-19cases, by date of report and WHO region, 30 December 2019 through 7 May 2020, (Graph was reproduced from WHO Coronavirus Disease (COVID-2019) Situation Reports. May 07, 2020. [13].

There are no definite treatments approved by the U.S. Food and Drug Administration (FDA) for SARS-CoV-2. Some agents are being used under clinical trial and compassionate use protocols based on in vitro activity and on limited clinical experience. Over 300 active clinical trials are in pipeline. This review summarizes Genome structure and key viral factors, epidemiology, clinical manifestations, pathology and treatment.

1.1. Genome structure and key viral factors

Coronaviruses belong to the Coronaviridae family in the Nidovirales order. Coronavirinae is further sub classified into alpha-, beta-, gamma-, and delta COVs. α- and β-CoV are able to infect mammals, while γ- and δ-CoV tend to infect birds. The shape is either pleomorphic or spherical, and it is characterized by crown-like spikes on the outer surface of the virus; therefore, it was entitled as a coronavirus. The SARS-CoV-2 is a β-coronavirus (β-CoV) large family of non-segmented positive-sense, single-stranded RNA (subgenus sarbecovirus, orthocoronavirinae sub family) with a diameter of 80-120 nm and size ranging from 26.2 and 31.7 kb in length. (Fig. 2). It has been revealed that the genome of CoVs comprises a 6–11 number of open reading frames (ORFs) [14]. The 2/3 of viral RNA, primarily positioned with in the first ORF (ORF1a/b) translates two poly-proteins, pp1a and pp1ab, and encodes 16 non-structural proteins (NSP), whereas the residual ORFs encode accessory and structural proteins. The rest part of virus genome encodes four essential structural proteins, including spike (S) glycoprotein, small envelope (E) protein, matrix (M) protein, and nucleocapsid (N) protein and also numerous accessory proteins, that hinder with the host innate immune response. (Fig.2) [15].

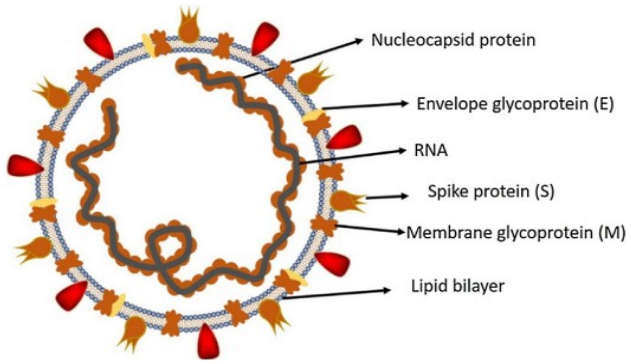

Fig. 2. Structure of coronavirus.

1.2. The life cycle of CoV in host cells

SARS-CoV-2, targets cells with the help of the viral structural spike (S) protein that binds to the cellular receptor angiotensin-converting enzyme 2 (ACE2). Subsequent to receptor binding, the virus particle uses host cell receptors and endosomes to move in cells. A host type 2-transmembrane serine protease, TMPRSS2, assists cell entry through the S protein. When inside the cell, viral poly-proteins are synthesized after that encode for the transcriptase complex. The virus then synthesizes RNA through its RNA-dependent RNA polymerase. Structural proteins are synthesized leading to accomplishment of assemblage and release of viral particles. These viral lifecycle steps give the idea about potential targets for drug therapy (Fig.3) [16].

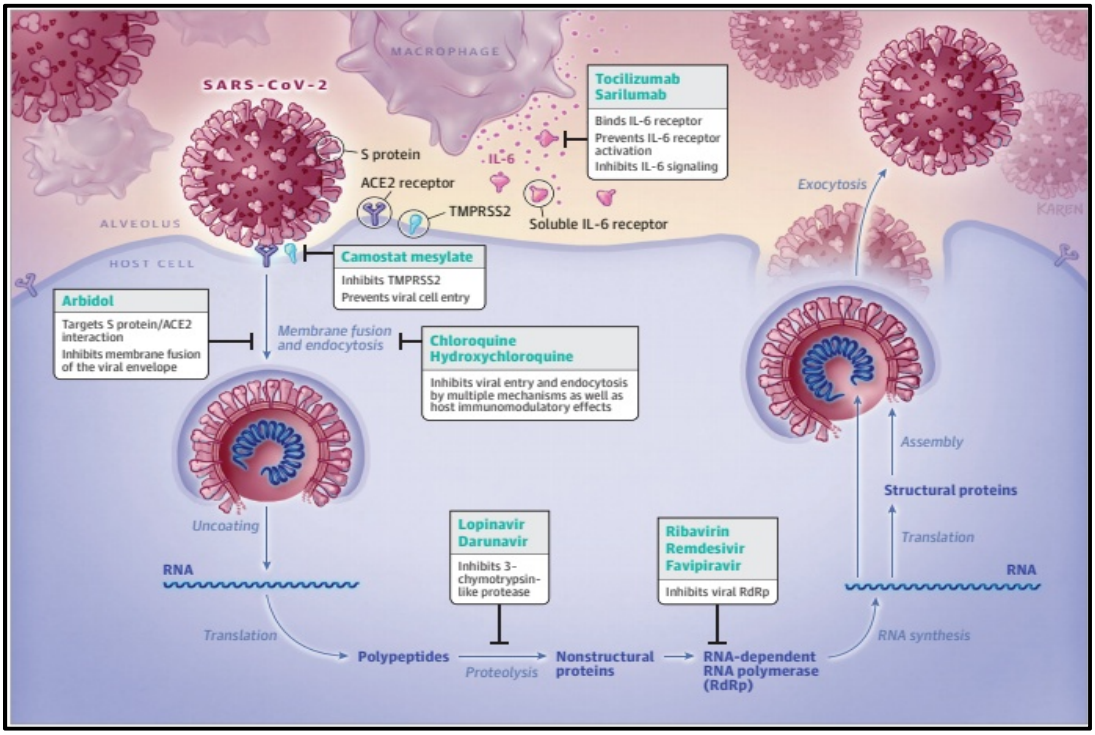

Fig. 3. Simplified Representation of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Viral Lifecycle and Proposed targets of select repurposed and investigational products.

ACE2, angiotensin-converting enzyme 2; S protein, spike protein; and TMPRSS2, type 2 transmembrane serine protease. Promising drug targets comprise nonstructural proteins (eg, 3-chymotrypsin-like protease, papain like protease, RNA-dependent RNA polymerase), which having same homology with other novel coronaviruses (nCoVs). Other drug targets contain viral entry and immune regulation pathways [16].

1.3. Epidemiology

The pandemic worsened exponentially at the beginning of 2020, which may due to delayed case reporting and deficiency in testing kits. The onset of first bunch cases were reported a direct exposure to infected animals (animal-to human transmission) at a Huanan seafood market in Wuhan, China. The proportion of infected cases lacking an exposure history and in health care staffs progressively increased. Person-to-person transmission may occur primarily through droplet or contact transmission [17]. Reproductive number is an indication of the transmissibility of a virus, signifying the average number of new infections caused by an infectious person in an absolutely raw population. For R0 <1, transmission was expected to drop and die out. For R0>1, the figure of infected was estimated to increase. R0 was predictable to be around 3 for SARS and <1 for MERS[18, 19]. The initial R0 of SARS-CoV-2 was reported as 2.24-3.58 [20].

Incubation period is the interval from initial acquaintance to an infectious agent to onset of any signs or symptoms it causes. A long incubation period may lead to an elevation rate of asymptomatic and subclinical infection. The first estimate of mean incubation period was 5.2 days. A latest study composed 1099 cases from 552 hospitals in 31 provinces in China and stated an average incubation period of 3.0 days, fluctuating from 0 to unpredictably 24.0 days. The SARS-CoV-2 generally has a longer incubation time than SARS-CoV(3.6-4.4 days) [21] and MERS-CoV (range 4.5-5.2 days). Comparison of epidemiological characteristics between SARS-CoV, SARSCoV-2 and MERS-CoV were shown in table 1 [22].

Table 1. Comparison of epidemiological characteristics between SARSCoV-2, SARS-CoV, and MERS-CoV.

Features	SARS-CoV-2	SARS-CoV	MERS-CoV
Estimated R0	**2.68**	**2-5**	**>1**
Host of virus	Bats are natural hosts, pangolins are Intermediate hosts, and humans are terminal hosts	Chinese horseshoe bats are natural hosts, masked palm civets are intermediate hosts, and humans are terminal hosts	Bats are natural hosts, dromedary camels are intermediate hosts, and humans are terminal hosts
Transmission mode	Human-to-human through fomites, physical contact, aerosol droplets, nosocomial	Human-to-human through aerosol droplets, opportunistic airborne transmission, nosocomial transmission, fecal-oral	Respiratory transmission, zoonotic transmission, nosocomial transmission, limited human-to-human transmission, aerosol

	transmission, zoonotic transmission	transmission, zoonotic transmission	transmission
Incubation period	6.4 days (range: 0-24 days)	4.6 days	5.2 days

SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SARS-CoV, Severe Acute Respiratory Syndrome Coronavirus; MERSCoV, Middle East Respiratory Syndrome Coronavirus; R0, Reproduction number.

1.4. Clinical manifestations

Clinical exhibition of COVID-19 significantly resembled viral pneumonia such as SARS and MERS. Utmost cases are mild cases(81%), whose symptoms were typically self-limiting and recovery in two weeks. Severe patients developed speedily with acute respiratory distress syndrome (ARDS) and septic shock, ultimately terminated in multiple organ failure. The COVID-19 disease may be categorized into mild, moderate, severe, and critical. The most common symptoms of patients include fever (98.6%), fatigue (69.6%), dry cough, and diarrhea [23].

1.4.1. Mild Disease

Patients with mild infection might present with symptoms of an upper respiratory tract viral infection. These include dry cough, nasal congestion, mild fever, headache, sore throat, muscle pain, and malaise and some time, it is also characterized by absence serious symptoms such as dyspnea. The majority (approximately 81%) of COVID-19 cases are mild in severity. Furthermore, radiograph features are also absent in such cases. Patients with mild disease can quickly worsen into severe or critical cases.

1.4.2. Moderate Disease

These patients present with respiratory symptoms of shortness of breath, cough, and tachypnea. Though, no signs and symptoms of severe disease are present.

1.4.3. Severe Disease

Patient with severe pneumonia, an acute respiratory distress syndrome (ARDS), sepsis, or septic shocks are categories under severe Disease. Diagnosis is clinical, and complications can be excluded with the help of radiographic studies. Other sign and symptoms include presence of severe dyspnea, tachypnea, respiratory distress, and/or greater than 50% lung infiltrates within 24 to 48 hours. Fever can be absent or moderate even in severe forms of the disease [24].

The 5% of patients can progress a critical disease through respiratory failure, septic shock, RNAaemia, cardiac injury, or multiple organ dysfunction. The SARS-CoV was more probably to infect elderly men with pre existing co-morbidities which include diabetes (7.3%), respiratory disease (6.5%), cardiovascular disease (10.5%), hypertension (6%), and oncological complications (5.6%) and have a higher case fatality rate in such patient [25]. Same as SARS-CoV and MERS-CoV studies, males were more prone to SARS-CoV infection due to X chromosome and sex hormones' role on innate and adaptive immunity [26].

Similar to MERS-CoV infection, patient with chronic underlying diseases (mainly hypertension, cardio-cerebrovascular diseases and diabetes) may increase the risk of SARS-CoV infection[27, 28]. Smoking might be a negative prognostic indicator for COVID-19 [28, 29]. Those patients without fever or even without any symptoms might be left un-quarantined as silent carriers.

In addition to the clinical and ventilatory criteria, chest imaging modalities such as chest X-ray, computed tomography (CT) scan, and lung ultrasound can be used to support the diagnosis. The most frequent finding on CT scan includes ground-glass opacity (86%), consolidation (29%), crazy paving (19%), bilateral disease distribution (76%), and peripheral disease distribution (33%) [10]. It is important to note that a chest X-ray has a lower sensitivity (59%) to detect subtle opacities. A CT scan can further detect mediastinal lymphadenopathy, nodules, cystic changes, and pleural effusion. The afore mentioned abnormalities might be detectable before the onset of symptoms.

Besides to clinical and ventilator criteria, to support the diagnosis chest imaging modalities such as chest X-ray, computed tomography (CT) scan, and lung ultrasound can be used. Typical chest CT manifestations of COVID-19 pneumonia were to begin with small subpleural ground glass opacities (86%) that propagated larger with consolidation (29%), crazy-paving pattern (19%), bilateral disease distribution (76%), and peripheral disease distribution (33%). After two weeks of growth, the lesions were progressively absorbed leaving extensive opacities and subpleural parenchymal bands in recovery patients [30]. It is significant to note that a chest X-ray has a lower sensitivity (59%) to identify subtle opacities. A CT scan can auxiliary identify mediastinal lymphadenopathy, nodules, cystic changes, and pleural effusion. The above-mentioned abnormalities might be detectable formerly the onset of symptoms. The patients with normal radiologic findings on initial staging consisted of 23.9% and 5.2% of severe and non-severe cases respectively, which enhance the difficulty to disease control [31].

1.5. Diagnosis

The U.S. CDC has established certain criteria for persons under investigation (PUI) [24]. If a person is considered a PUI, instantaneous prevention and infection control measures are undertaken. Epidemiological features are used to evaluate the prerequisite of testing. These comprise of close contact with a laboratory-confirmed positive SARS-CoV infection patient within 14 days of symptoms or having travel history to an infected area within 14 days of symptom onset. The WHO endorses collecting samples from both the upper and lower respiratory tracts (expectorated sputum, bronchoalveolar lavage, or endotracheal aspirate). These collected samples are then evaluated for viral RNA using polymerase chain reaction (PCR)[32]. If a positive test result is accomplished, it is recommended to do reverification by repeating the test. The test is also repeated in case of negative test with a strong clinical suspicion [24].

1.6. Treatment

1.6.1. General treatments

The first step is to confirm adequate isolation to avoid transmission to other people, patients and healthcare workers. Insignificant infection should be accomplished at home with counseling

about risk signs. The typical ideologies are upholding hydration and nutrition and controlling fever and cough. In hypoxic patients, establishment of oxygen through nasal prongs, face mask, high flow nasal cannula (HFNC) or non-invasive ventilation is designated. General treatments involved nutritional interventions, immuno-enhancers and Chinese medicine [34]. To enhance immune system to fight against SARS-CoV and MERS-CoV plus SARS-CoV-2 use of interferon, intravenous gamma-globulin and thymosin were recommended.

Thus there is an urgent requirement for global surveillance of COVID-19 patients. New therapeutic drugs are developing one after another. However, double-blinded randomized controlled trials along with larger sample size are required to determine the safety and efficacy of these new drugs. As of April 24, 2020, the Covid-19 NMA- Ongoing research initiative collected a number of 506 studies of treatments from the ICTRP (International Clinical Trials Registry Platform). 278 of these trials are recruiting patients. Most of the studies are being conducted in Asia (264 trials) with the majority from China (151 trials). Other countries in Europe (160 trials) and North America (92 trials) are rapidly setting up new trials with the majority being conducted in multiple centers (194 trials) [13].

1.6.2. Repurposed Drugs

Agents who previously used to treat SARS and MERS are potential candidates to fight against COVID-19. Numerous agents with apparent in vitro activity against SARS-CoV and MERS-CoV were used for the period of the SARS and MERS outbreaks, with inconsistent efficacy. Below are some of the most promising repurposed drugs for COVID-19 are reviewed.

1.6.2.1. Chloroquine and Hydroxychloroquine

Chloroquine and hydroxychloroquine have a time-honored history in treatment of malaria, systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA). Chloroquine and hydroxychloroquine had demonstrated significant inhibition in the spread of SARS-CoV via blocking viral access into cells by inhibiting glycosylation of host receptors, proteolytic processing, and endosomal acidification. These agents also show immune-modulatory effects through diminution of cytokine production and inhibition of autophagy and lysosomal activity in host cells. Latest multicenter clinical trials conducted in China have also reported apparent efficacy and adequate safety in COVID-19 patients by reducing exacerbation of pneumonia, encouraging a virus negative conversion, improvement in radiological findings, and shortening the disease duration [16].

1.6.2.2. Antivirals

There is no effective antiviral management for coronavirus infection; even the good candidates such as lopinavir/ritonavir, and abidol demonstrated no significant effect on clinical improvement, day 28 mortality or virus clearance. Belief and attention were shifted to “remdesivir” which may be the utmost potential wide-spectrum drug for antiviral treatment of SARS-CoV-2. Remdesivir formally known as GS-5734 is a monophosphate prodrug that after metabolism converts into an active C-adenosine nucleoside triphosphate analogue, which integrates into viral RNA chains and leads into pre-mature termination. Remdesivir were very effective and safe in the management of SARS-CoV-2 infection in Vero E6 cells and Huh-7

cells. An efficacious utilization of remdesivir on the first SARS-CoV-2 infected case in the United States (US) after his clinical status was getting deteriorate, were recently released. Animal experiments also exhibited advantage of remdesivir above lopinavir/ritonavir collectively with interferon-β, by reducing MERS-CoV titers of infected mice and improving the lung tissue impairment. Clinical trials are continuing to estimate the safety and efficiency of remdesivir in patients with COVID-19 (NCT04292899, NCT04292730, NCT04257656, NCT04252664, and NCT04280705) [40]. Favipiravir, formerly known as T-705, is a prodrug of favipiravir ribofuranosyl-5′-triphosphate a purine nucleotid. The active agent inhibits the RNA polymerase, inhibit viral replication. Maximum of favipiravir's preclinical data are resulting from its influenza and Ebola activity; though, the agent also established broad activity against further RNA viruses. *In vitro*, the EC50 of favipiravir against SARSCoV-2 was 61.88 μM/L in Vero E6 cells [41].

1.6.2.3. Anticytokine or Immuno modulatory Agents

The marked elevations in inflammatory markers were observed in patient with "cytokine storm". IL-6 seems to be a key driver of this dysrhythmic inflammation. Hence the use of monoclonal antibodies as IL-6 receptor antagonists could theoretically inhibit this process and progress clinical outcomes. Tocilizumab, a monoclonal antibody IL-6 receptor antagonist, is FDA approved in treatment of RA and cytokine release syndrome. In 21 patients with COVID-19 treated with tocilizumab exhibited early reports of success with 91% of patient showed clinical improvement by improved respiratory functions, successful discharge, with maximum patients only in receipt of 1 dose. Another IL-6 receptor antagonist approved for RA is Sarilumab, is being studied in a multi-center, double-blind, phase 2/3 trial for severe COVID-19 (NCT04315298) hospitalized patients. Other monoclonal antibody or immunomodulatory agents in clinical trials include bevacizumab (NCT04275414), fingolimod (NCT04280588) and eculizumab(NCT04288713) [42].

1.6.2.4. Immunoglobulin Therapy

One of the hopeful adjunctive treatments that have developed is CP, or immune plasma or hyperimmune globulins. The CP, is the antibodies recovered from an infected patient, such as by COVID-19, is then transfused into infected patients as a post acquaintance prophylaxis. The rationale behind practice using CP therapy help with both free virus and infected cell immune clearance. In the first two decades of the 2000s, Anecdotal reports of CP have been testified as salvage therapy in SARS and MERS. CP-derived antibodies can neutralize a virus by averting replication or by binding deprived of interfering with replication. A review on convalescent plasma for treatment of SARS-CoV suggested a lessening in hospital stay as well as mortality rate, particularly when administered early after symptom commencement. CP, a post infection treatment could aid as a short-term solution to reduced mortality rates in India. As the number of patient with infections increases, the CP of infected patients could be donated or gathered for simultaneous treatment or future use until an effective antibody is discovered [43].

1.6.2.5. Cellular therapy

Mesenchymal stem cells (MSCs) based therapy has a capable therapeutic field to cure incurable diseases. MSCs has fascinated researcher due to source potential, a high proliferation rate, low invasive procedure, and free of ethical issues. Researchers in China administered COVID-19 patients with a mesenchymal stem cell therapy that demonstrated success at treating the condition. (https://www.europeanpharmaceuticalreview.com/). They are easily reachable and can be isolated from different tissues such as bone marrow and adipose tissues, umbilical cord, dental pulp, menstrual-blood, buccal fat pad, fetal liver. They can be store for repetitive therapeutic purposes. In COVID-19, MSC therapy can prevent the blast release of cytokines by the immune system and encourage endogenous repair by reparative properties of the stem cells [44].

1.7. Prophylactic Vaccines

Vaccine platform and target antigen selection are perhaps built on SARS-CoV and MERS-CoV vaccine studies. As summarized in the Table 2, DNA vaccine and nucleic acid based vaccine, exhibited the most improved platform in response to emerging pathogens. According to the existing technological development, mRNA vaccine, alternative nucleic acid-based vaccine, has been deliberated as disruptive vaccine technology. Current mRNA vaccine strategies come up with advantages such as enhanced stability and protein translation competency thus it might induce vigorous immune responses. Different delivery system such as lipid nanoparticle was also well-optimized. Within two months of the SAR-CoV-2 outbreak.

Table 2. Selected antigens and vaccine platforms that have been tested for SARS-CoV and MERS-CoV. [45]

Vaccine platform	Immunogen	Phase	Advantage	Disadvantage
DNA	Full-length Spike, or S1 •IM follow by electroporation	Phase I, II (NCT03721718)	Rapid production • Easy design and manipulation • Induce both B and T cells responses	• Efficient delivery system required • Induce lower immune responses when compare with live vaccine
Viral vector	Full-length Spike or S1 •Vector used: ChAd or MVA	Phase I (NCT03399578, NCT03615911)	• Excellence in immune induction	• Varies inoculation routes may produce different immune responses • Possible TH2 bias
Subunit	Full-length Spike, S1, RDB, nucleocapsid	Preclinical	High safety profile • Consistent production • Can	• Need appropriate adjuvant, • Cost-effectiveness

	•Formulated with various adjuvants and/or fused with Fc		induce cellular and humoral immune responses	may vary
Virus-like particles	RDB, S or Co-expressing of S1, M, and E • Produced in baculovirus	Preclinical	• Multimeric antigen display • Preserve virus particle structure	• Require optimum assembly condition
Inactivated	Whole virus • Inactivated by Formaldehyde or gamma irradiation	Preclinical	• Preserve virus particle structure • Rapid development • Excellence in neutralizing Ab induction • Can be formulated with various adjuvant	• Possible cause hypersensitivity • Possible Th2-bias
Live-attenuated virus	Mutant MERS-CoV and SARS-CoV or recombination with other live attenuated virus	Preclinical	• Excellence in induction of T and B cells responses • Site-directed mutagenesis can be tailor made	Risk of reversion to a virulent strain • Cold chain required • Not suitable or sensitive population such as infants, immune compromised or elderly individuals

Using published literature and patents worldwide, American Chemical Society scrutinized scientific data correlated to therapeutic agents and vaccines in human coronaviruses since 2003. This investigation reported over 130 patents as well as about 3000 potential small molecule drug candidates and approximately 500 patents for biologic agents with probable activity against SARS-CoV-2 comprising of therapeutic antibodies, cytokines, RNA therapies, and vaccines[16, 44].

Recently, on 11 April 2020, WHO released a report stating, Serum Institute of India on said it expect vaccine to combat Covid-19 developed by the University of Oxford in market by October if safety and efficacy is established. Serum Institute of India has patterned with Oxford vaccine project as one of the seven global institutions behind manufacturing the vaccine. University of Oxford researchers have begun testing a COVID-19 vaccine in human volunteers in Oxford[45].

2. CONCLUSION

The COVID-19 pandemic represents the greatest global public health crisis of this generation and, potentially, since the pandemic influenza outbreak of 1918. The speed and volume of clinical trials launched to investigate potential therapies for COVID-19 highlight both the need and capability to produce high-quality evidence even in the middle of a pandemic. No therapies have been shown effective to date. The COVID-19 pandemic symbolizes the greatest global public health disaster of this generation. This novel virus outburst has challenged the economic, medical and public health of whole globe. It still leftovers a challenging task to fight against the SAR-CoV-2. Lessons learned from the MERS and SARS epidemics can offer valuable insight into how to manage the existing pandemic. Certain successful public health epidemic response strategies are wearing masks, hand hygiene, isolation, quarantine and social distancing. The hustle and bulk of clinical trials propelled to investigate potential therapies for COVID-19 highlight both the necessity and competency to produce high-quality evidence even in the middle of a pandemic. The SAR-CoV-2 should be scrutinized of any antigenic conversion or gene variation of antigenic drift to avoid an additional round of epidemic of zoonotic origin. One more lesson from this epidemic will be respect for nature and love for life.

3. REFERENCES

1. Drosten, C., Gunther, S., Preiser, W., van der Werf, S., Brodt, H.R., Becker, S., Rabenau, H., Panning, M., Kolesnikova, L., &Fouchier, R. (2003) Identification of a novel coronavirus in patients with severe acute respiratory syndrome. N Engl J Med., 348(20):1967–1976. doi:10.1056/ NEJMoa030747
2. Ksiazek, T.G., Erdman, D., Goldsmith, C.S., Zaki, S.R., Peret, T., Emery, S., Tong, S., Urbani, C., Comer, J.A.,& Lim, W.,(2003). A novel coronavirus associated with severe acute respiratory syndrome. N Engl J Med., 348(20):1953–1966. doi:10.1056/NEJMoa030781
3. Kahn J.S., &McIntosh, K.,(2005). History and recent advances in coronavirus discovery. Pediatr Infect Dis J., 24 (Supplement): S223-S227. Doi: 10.1097/01.inf.0000188166.17324.60
4. Lau, S.K., Woo, P.C., Li, K.S., Huang, Y., Tsoi H.W., Wong, B.H., Wong, S.S., Leung, S.Y., Chan, K.H., &Yuen, K.Y. (2005). Severe acute respiratory syndrome coronavirus-like virus in Chinese horseshoe bats. ProcNatlAcad Sci. 102 (39): 14040–14045. doi:10.1073/pnas.0506735102
5. Cui, J., Li, F.,& Shi, Z.L. (2019). Origin and evolution of pathogenic coronaviruses. Nat Rev Microbiol. 17(3):181–192. doi:10.1038/s41579-018-0118-9.
6. Zaki, A.M., Van Boheemen, S., Bestebroer, T.M., Osterhaus, A.D., &Fouchier, R.A. (2012). Isolation of a novel coronavirus from a man with pneumonia in Saudi Arabia. N Engl J Med. 367(19):1814–1820.

7. Huang, C., Wang, Y., Li, X., Ren, L., Zhao, J.,& Hu, Y. (2019). Clinical features of patients infected with novel coronavirus in Wuhan, China. Lancet (London, England). 2020;395:497-506.
8. Liu, Y., Gayle, A.A., Wilder-Smith, A.,&Rocklov, J. (2020). The reproductive number of COVID-19 is higher compared to SARS coronavirus. J Travel Med.; 1–4 doi: 10.1093/jtm/taaa021
9. Chen, N., Zhou, M., Dong, X., Qu, J., Gong, F.,& Han, Y. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet. (2020).
10. World Health Organization. Naming the coronavirus disease (COVID-19) and the virus that causes it. https://www.who.int/emergencies/diseases/novel-coronavirus2019/technical-guidance/naming-the-coronavirus-disease-(covid-2019)-and-the-virusthat-causes-it (accessed on 27/04/2020).
11. World Health Organization. Statement on the second meeting of the International Health Regulations (2005) Emergency Committee regarding the outbreak of novel coronavirus (2019-nCoV).https://www.who.int/news-room/detail/30-01-2020-statement-on-the-second-meeting-of-the-international-health-regulations-(2005)-emergency-committee-regarding-the-outbreak-of-novel-coronavirus-(2019-ncov) (accessed 27/04/2020).
12. World Health Organization. WHO Director-General's opening remarks at the media briefing on COVID-19 - 11 March 2020. https://www.who.int/dg/speeches/detail/who-director-general-s-opening-remarks-atthe-media-briefing-on-covid-19-11-march-2020 (accessed 05/05/2020).
13. Coronavirus Disease (COVID-2019) Situation Reports 108, 1-12; World Health Organization, 2020. https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200428-sitrep-99-covid-19.pdf?sfvrsn=119fc382(Accessed on 07/05/2020)
14. Song, Z., Xu, Y., Bao, L., Zhang, L., Yu, P., &Qu, Y. (2019). From SARS to MERS, thrusting coronaviruses into the spotlight. Viruses. 11(1):E59. https:// doi.org/10.3390/v11010059
15. Cui, J., Li, F., &Shi, Z.L. Origin and evolution of pathogenic coronaviruses. Nat Rev Microbiol. 2019; 17(3):181–92.
16. James, M., Marguerite, L., Tomasz, Z., &James, B. (2020). Pharmacologic Treatments for Coronavirus Disease 2019 (COVID-19) A Review. Jama, 5: 185-198.
17. Hoffmann, M., Kleine-Weber, H., &Schroeder, S. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. Cell. Published online March 4, 2020. doi:10.1016/j.cell.2020.02.052
18. Yu, Zhao, Wang, Y.J., Zhou, Y.Q., Ma, Y., Zuo,&Y. Single-cell RNA expression profiling of ACE2, the putative receptor of Wuhan 2019-nCov. BioRxiv(preprint) 2020
19. Bauch, C.T., Lloyd-Smith, J.O., Coffee, M.P.,& Galvani, A.P. (2005). Dynamically modeling SARS and other newly emerging respiratory illnesses: past, present, and future. Epidemiology, 16: 791-801. https://doi.org/10.1097/01.ede.0000181633.80269.4c.

20. Bauch, C.T., &Oraby, T. (2013). Assessing the pandemic potential of MERS-CoV. Lancet, 382: 662-664. https://doi.org/10.1016/S0140-6736(13)61504-4.

21. Liu, Y., Gayle, A., Wilder-Smith, A.,&Rocklov, J. (2020). The reproductive number of COVID-19 is higher compared to SARS coronavirus. J Travel Med. https://doi.org/10.1093/jtm/taaa021.

22. Lessler, J., Reich, N.G., Brookmeyer, R., Perl, T.M., Nelson, K.E., &Cummings, D.A. (2009). Incubation periods of acute respiratory viral infections: a systematic review. Lancet Infect Dis., 9: 291-300. https://doi.org/10.1016/S1473-3099(09)70069-6.

23. Park, J.E., Jung, S., Kim, A., & Park, J.E. (2018). MERS transmission and risk factors: a systematic review. BMC Public Health, 18: 574. https://doi.org/10.1186/s12889-018-5484-8.

24. Wu, Z., &McGoogan, J.M. Characteristics of and Important Lessons From the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72314 Cases From the Chinese Center for Disease Control and Prevention. JAMA 2020.

25. Cascella, M., Rajnik, M., Cuomo, A., Dulebohn, S.C.,& Napoli, R.D. Features, Evaluation and Treatment Coronavirus (COVID-19). StatPearls Publishing, Treasure Island, FL; 2020.

26. Badawi, A., &Ryoo S.G. (2016). Prevalence of comorbidities in the Middle East respiratory syndrome coronavirus (MERS-CoV): a systematic review and meta-analysis. Int J Infect Dis., 49: 129-133. https://doi.org/10.1016/j.ijid.2016.06.015.

27. Jaillon, S., Berthenet, K., &Garlanda, C. (2019). Sexual Dimorphism in Innate Immunity. Clin Rev Allergy Immunol., 56: 308-321. https://doi.org/10.1007/s12016-017-8648-x.

28. Guan, W.J., Ni, Z.Y., Hu, Y., Liang, W.H., Ou, C.Q., He, J.X., Liu, L. Shan, H., Lei, C.L.,&Hui, D.S. Clinical Characteristics of Coronavirus Disease 2019 in China. N Engl J Med 2020. https://doi.org/10.1056/NEJMoa2002032.

29. Badawi, A., &Ryoo, S.G. (2016). Prevalence of comorbidities in the Middle East respiratory syndrome coronavirus (MERS-CoV): a systematic review and meta-analysis. Int J Infect Dis., 49: 129-133. https://doi.org/10.1016/j.ijid.2016.06.015.

30. Chen, N., Zhou, M., Dong,X., Qu, J., Gong, F., Han, Y., Qiu, Y., Wang, J., Liu, Y., &Wei,Y. (2020). Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet.,395: 507-513. https://doi.org/10.1016/S0140-6736(20)30211-7

31. Kanne, J.P.(2020). Chest CT findings in 2019 novel coronavirus (2019-nCoV) infections from Wuhan, China: Key points for the radiologist. Radiology, 295:16-17. 10.1148/radiol.2020200241

32. Guan, W.J., Ni, Z.Y., Hu, Y., Liang, W.H., Ou, C.Q., He, J.X., Liu, L., Shan, H., Lei, C.L. &Hui DSC. (2020). Clinical Characteristics of Coronavirus Disease 2019 in China. N Engl J Med. https://doi.org/10.1056/NEJMoa2002032.

33. Wang, Y., Wang, Y., Chen, Y., &Qin, Q.(2020). Unique epidemiological and clinical features of the emerging 2019 novel coronavirus pneumonia (COVID-19) implicate special control measures [Epub ahead of print]. J Med Virol., 10.1002/jmv.25748

34. Huang, C., &Wang, Y. (2020). Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet.395:497-506. 10.1016/S0140-6736(20)30183-5

35. Cascella, M., Rajnik, M., Cuomo, A., Dulebohn, S.C., &Napoli, R.D. (2020). Features, Evaluation and Treatment Coronavirus (COVID-19). StatPearls Publishing, Treasure Island, FL; 2020.

36. Vincent, M.J., Bergeron, E., Benjannet, S., Erickson, B.R., Rollin, P.E.,Ksiazek, T.G., Seidah, N.G., &Nichol, S.T. (2005). Chloroquine is a potent inhibitor of SARS coronavirus infection and spread. Virol J., 2: 69. https://doi.org/10.1186/1743-422X-2-69.

37. Nosengo, N. (2016). New tricks for old drugs. Nature ,534: 314-6.

38. Zhou, D., Dai, S.M., &Tong, Q. (2020). COVID-19: a recommendation to examine the effect of hydroxychloroquine in preventing infection and progression. [Published online March 20, 2020]. J AntimicrobChemother. 114. doi:10. 1093/jac/dkaa114.

39. Wang, M., Cao, R., Zhang, L., Yang, X., Liu, J., Xu, M., Shi, Z., Hu, Z., Zhong, W., & Xiao, G. (2020). Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. Cell Res., 30: 269-271. https://doi.org/10.1038/s41422-020-0282-0.

40. Mingxuan, X., &Qiong, C. (2020). Insight into 2019 novel coronavirus — an updated intrim review and lessons from SARS-CoV and MERS-CoV. J. Glob. Infect. Dis., 26: 250-272.

41. Xu, X., Han, M., &Li, T. (2020). Effective treatment of severe COVID-19 patients with tocilizumab. chinaXiv. (Preprint posted March 5, 2020.)doi:10. 12074/202003.00026.

42. VanErp, E.A., Luytjes, W., Ferwerda, G.,& van Kasteren, P.B. (2019). Fcmediated antibody effector functions during respiratory syncytial virus infection and disease. Front Immunol., 10: 548. https://doi.org/10.3389/fimmu.2019.00548.

43. Golchin, A., Seyedjafari, E., &Ardeshirylajimi, A. (2020). Mesenchymal Stem Cell Therapy for COVID-19: Present or Future. Stem Cell Rev Rep., 13:1–7. doi: 10.1007/s12015-020-09973-w. Epub ahead of print. PMCID: PMC7152513.

44. Eakachai, P.,Chutitorn, K., &Tanapat, P. (2020). Immune responses in COVID-19 and potential vaccines: Lessons learned from SARS and MERS epidemic. Asian Pac J Allergy Immunol.,38:1-9 DOI 10.12932/AP-200220-0772.

45. Oxford COVID-19 vaccine begins human trial stage, website of Oxford University http://www.ox.ac.uk/news/2020-04-23-oxford-covid-19-vaccine-begins-human-trial-stage (Assessed on 26/04/2020)