

Understanding and Dealing the SARS-CoV-2 Infection: An Updated Concise Review

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Abstract

Viral infection has made the world to pass through the most critical time of the current century. In December 2019, the Wuhan city of China faced a novel etiological viral agent with atypical secondary pneumonia. The unique virus was severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) that caused coronavirus disease 2019 (COVID-19) pandemic. According to the worldometer data, as of December 24, 2020, the world lost more than 1.74 million lives and infected more than 79.3 million people with the novel coronavirus-2. As there is no approved drug to combat the disease or vaccine against the virus, the infection continuously triumphed over the current medical system. The epidemiological analysis showed that geriatric patients are generally the most susceptible to the viral infection, and pediatric patients exhibited milder complications. The clinical characteristics of COVID-19 displayed that the most frequent symptoms are dry cough, fever, dyspnea, and sputum production. Herd immunity is a tested strategy that could moderate viral transmission in developing countries. In this study, authors abridged the epidemiological outcomes, clinical features, and pathophysiology of SARS-CoV-2 infection. The article also focused on vaccine development, herd immunity, and the most promising repurposed therapeutics for the treatment of COVID-19 with their clinical trial updates.

Key words: COVID-19, SARS-CoV-2, clinical characteristics, pathophysiology, herd immunity, repurposed therapeutics, clinical trials

Introduction

The first fatal case of coronavirus disease 2019 (COVID-19) was surfaced from Wuhan, Hubei province, China, during late December of 2019 as severe infectious respiratory disorders leading to death (Zhang and Holmes, 2020; Yu *et al.*, 2020). Soon after that, a novel Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) was found responsible for this. The source of this unique virus was primarily envisaged through a zoonotic transmission from a seafood market of Wuhan and recognized to have a stronger capacity to cause a

human to human transmission (Andersen *et al.*, 2020; Zhang and Holmes, 2020), even though many claims for artificially creating this virus in the laboratory was also noticed (Latham, 2020). The International Committee of Taxonomy of Viruses named this virus as SARS-CoV-2 due to its ~80% genetic homology to SARS-CoV (also known as SARS-CoV-1), causing an infection outbreak in 2002-2003 starting from China to many other places of the world (Yuki *et al.*, 2020). The World Health Organization (WHO) has assessed the alarming condition of severity and spreading of COVID-19 and declared this novel

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outbreak as a pandemic on March 11, 2020 (Hossain et al., 2020).

Numerous scientific articles addressed this virus as the seventh member of the β coronavirus genus and *coronaviridae* family (Wrapp et al., 2020). The largest known single-stranded, positive sense spherical enveloped RNA virus has already extended its pervasiveness to more than two hundred and fifteen countries throughout the six continents of the world (Ceraolo and Giorgi, 2020; Li and Clercq, 2020; Wang et al., 2016). The SARS-CoV-2 virus mainly attacks the respiratory tract and causes primary symptoms like fever, dry cough, sore throat, dyspnea, headache, dizziness, nausea, and vomiting (Huang et al., 2020). A large percentage of COVID-19 infected patients in China exhibited septic shock, coagulation dysfunctions, and metabolic-acidosis in the critical phase. It is well established that the symptoms of COVID-19 disease are now highly heterogeneous, from simple clinical symptoms to hypoxia with acute respiratory distress syndrome (ARDS) for critically ill patients (Huang et al., 2020; Guan et al., 2020). Recent epidemiological studies have reported that the SARS-CoV-2 mortality rate is the highest for geriatric patients and the lowest for pediatric patients (Zhou et al. 2020; Qiu et al. 2020).

As there is no approved drug or vaccine against the SARS-CoV-2 infection, the clinical managements are the ubiquitous weapons to recover the infection. Here, the article was intended to review the current updates of epidemiology, clinical features, pathophysiology, and promising treatments of COVID-19.

Epidemiology

Sources, spectrum, and routes of the infection: Currently, the primary source of the virus is SARS-CoV-2 infected patients. The people who are not showing significant signs and symptoms, i.e., the asymptomatic patients, might be considered potential sources of this viral infection. Critically ill patients are envisaged as more contagious than mild or moderate patients (Jin et al., 2020). It has been

reported that most of the COVID-19 cases recovered within 1-2 weeks, where 1.2 % were asymptomatic patients (Lu et al., 2020a).

The main transmission routes of the virus have been identified as the respiratory droplets and physical contact of the infected patients (Jin et al., 2020). Morawska and Milton (2020) have recently reported the significant airborne transmission of the virus. They suggested taking preventive measures to prevent this potential route of transmission. However, it was not confirmed that the people would be infected or not after consumption of contaminated food products, and no clear evidence has been proved that the virus may transmit from mother to child during pregnancy or childbirth (Jin et al., 2020).

Basic reproduction number and incubation period: The basic reproduction or reproductive number (R_0) of infection means the average number of infected patients from one patient in a population over the infectious period. Zhao et al. (2020) estimated the R_0 value in mainland China 2.24 (95% confidence interval, CI = 1.96-2.55) to 3.58 (95% CI = 2.89-4.39) by a data-driven analysis during the early phase of the outbreak. Tang et al. (2020a) indicated the R_0 value by deterministic compartmental model analysis for COVID-19 during late January 2020, and it was 6.47 (95% CI = 5.71-7.23). The WHO measured the R_0 value as 1.4-2.5 (Tang et al., 2020b). The R_0 value was less than one for infection of Middle East Respiratory Syndrome coronavirus (MERS-CoV), and it was reported to be 2-5 for SARS-CoV infection (Zhao et al., 2020).

The incubation period assists in making case definitions and measure the quarantine durations during the pandemic. The model-based basic reproductive number is the most vital epidemiological factor, which is a prerequisite to determine the viral transmissibility. A dynamics study on confirmed 425 COVID-19 patients (median age 59 and male 56%) regarding the early transmission in Wuhan, China, reported that the average incubation period was five days (95% CI = 4.1-7.0). The same study also estimated the basic reproductive number, and it was 2.2 (95% CI = 1.4-

3.9) (Li *et al.*, 2020a). Another study with 88 COVID-19 positive patients found the average incubation period 6.4 days (95% CI = 5.6-7.7), and it was ranged from 2.1 to 11.1 days (2.5th to 97.5th percentile) (Backer *et al.*, 2020).

Worldwide current COVID-19 cases: As of December 24, 2020, the worldometer counted near 79.4 million SARS-CoV-2 infected patients, and around 1.75 million patients lost their precious lives. The good news is that more than 55.8 million patients got the medical declarations as COVID-19 negative.

Table 1 represented the total SARS-CoV-2 infected patients of the most 30 countries of the world and their percentage of contribution of global cases up to December 24, 2020. The United States of America (USA) contributed the highest percentage of infections (n=18,923,693; 23.89%) followed by India (n=10,130,066; 12.79%), Brazil (n=7,366,677; 9.37%), and Russia (n=2,963,688; 3.74%). In the perspective of COVID-19 infections, Bangladesh (n=506,102; 0.64%) was staying at 27th position of the worldwide cumulative cases (Table 1).

Table 1. Countrywise cases distribution up to December 24, 2020. (Data source: <https://www.worldometers.info/coronavirus/worldwide-graphs/>).

Serial no.	Country	First reporting date	Total cases	% of global cases
1	USA	January 20, 2020	18,923,693	23.89
2	India	January 30, 2020	10,130,066	12.79
3	Brazil	February 25, 2020	7,366,677	9.37
4	Russia	January 31, 2020	2,963,688	3.74
5	France	January 24, 2020	2,505,875	3.16
6	UK	January 31, 2020	2,114,551	2.71
7	Turkey	March 11, 2020	2,082,610	2.63
8	Italy	January 31, 2020	1,991,278	2.51
9	Spain	January 31, 2020	1,847,874	2.33
10	Germany	January 27, 2020	1,599,177	2.02
11	Argentina	March 3, 2020	1,563,865	1.97
12	Colombia	March 6, 2020	1,544,826	1.95
13	Mexico	February 29, 2020	1,350,079	1.70
14	Poland	March 4, 2020	1,239,998	1.57
15	Iran	February 19, 2020	1,183,182	1.49
16	Peru	March 6, 2020	1,002,263	1.27
17	Ukraine	March 3, 2020	1,001,132	1.26
18	South Africa	March 5, 2020	954,258	1.20
19	Netherlands	February 27, 2020	721,071	0.91
20	Indonesia	March 2, 2020	692,838	0.87
21	Czech Republic	March 1, 2020	660,461	0.83
22	Belgium	February 4, 2020	632,321	0.80
23	Romania	February 26, 2020	608,561	0.77
24	Chile	March 3, 2020	590,914	0.75
25	Iraq	February 22, 2020	588,803	0.74
26	Canada	January 27, 2020	528,354	0.67
27	Bangladesh	March 8, 2020	506,102	0.64
28	Philippines	January 30, 2020	465,724	0.59
29	Pakistan	February 26, 2020	465,070	0.59
30	Switzerland	February 25, 2020	428,197	0.54

COVID-19 and Bangladesh perspectives: The current novel epidemic in Bangladesh is a part of the COVID-19 global pandemic. Dhaka, the capital city of Bangladesh, has faced its first three SARS-CoV-2 infected patients on March 8, 2020, whereas two of them were returnees from Italy (Hossain, 2020a). To protect the country's people from this new threat, the Government of Bangladesh has declared 'lockdown' in the whole region and taken precautionary measures to spread awareness among the population of the country (Mamun, 2020). Although the infection rate was negligible until March, it grew up at an exponential rate from early May. On May 6, all districts of the country have experienced COVID-19 infected patients. Among them, Rangamati was the last one. The recovery number of patients from SARS-CoV-2 infection has exceeded the number of active cases on July 12 (<https://corona.gov.bd/>). According to worldometer data, as of December 24, 2020, Bangladesh counted its total cases of infection of 506, 102 with 7,378 deaths, and till the same date, 446,690 patients got recovered from COVID-19 infection.

Clinical characteristics

The most frequent symptoms of COVID-19 infected patients are fever, dry cough, sore throat, chest tightness, dyspnea, sputum production, fatigue, and diarrhea. More than 80% of cases were reported as mild to moderate illness (Lake, 2020). The clinical features of 2,985 patients with COVID-19 from six distinct sources (Guan *et al.*, 2020; Wang *et al.*, 2020a; Xiong *et al.*, 2020; Chen *et al.*, 2020; Wang *et al.*, 2020b; Huang *et al.*, 2020) were observed. The number of patients from the six references were 1099, 1012, 421, 274, 138, and 41, respectively (Guan *et al.*, 2020; Wang *et al.*, 2020a; Xiong *et al.*, 2020; Chen *et al.*, 2020; Wang *et al.*, 2020b; Huang *et al.*, 2020). All the patients were adult-aged, and the mean age of the patients was 50.53 years. The males and females were 1,639 (54.90%) and 1,343 (44.99%), respectively, 21.31% were 65 years or more. Among the total patients, 1,914 (64.12%)

patients suffered from fever, and almost 61% of patients faced coughing. From the four studies (Guan *et al.*, 2020; Chen *et al.*, 2020; Wang *et al.*, 2020b; Huang *et al.*, 2020), it was reported that 1,552 patients showed fatigue. The other prevalent symptoms were sputum production (n=753; 25.22%), shortness of breath (n=662; 22.17%), myalgia or arthralgia (n=556; 18.62%), chills (n=405 out of 2,532; 15.99%), sore throat (n=423 out of 2,670; 15.84%), and headache (n=389; 13.3%). Diarrhea was noted as the least (n=292; 9.95%). The observed coexisting complications were chronic obstructive pulmonary disease (COPD), hypertension, diabetes, coronary heart disease (CHD), cerebrovascular disease, chronic kidney disease (CKD), hepatitis, tuberculosis, human immunodeficiency virus (HIV), chronic liver disease, cancer, malignancy, and other disorders.

Hematological profile: Most patients showed the normal range of neutrophil count ($1.8-6.3 \times 10^9/L$). Notably, the ICU patients showed higher neutrophil count than the non-ICU patients [median (IQR): 4.6 (2.6-7.9) vs. 2.7 (1.9-3.9); $p < 0.001$] (Wang *et al.*, 2020b). In white blood cell (WBC) count from the four studies (Guan *et al.*, 2020; Wang *et al.*, 2020b; Chen *et al.*, 2020; Huang *et al.*, 2020), 28.59% (n=537 out of 1,878) patients showed the decreased level than the normal range ($3.5-9.5 \times 10^9/L$), and 7.34% (n=137 out of 1,878) exhibited the elevated level. The ICU patients exhibited higher WBC count than the non-ICU patients [6.6 (3.6-9.8) vs. 4.3 (3.3-5.4); $p = 0.003$]. The lymphocyte count was found 0.8 (0.6-1.1) [ICU vs. non-ICU = 0.8 (0.5-0.9) vs. 0.9 (0.6-1.2); $p = 0.03$] which is lower than the normal range ($1.1-3.2 \times 10^9/L$). The median monocyte and platelet counts were observed in the normal range (Wang *et al.*, 2020b).

Pathophysiology

Cell entry and infection stages: The SARS-CoV-2 virus enters the body via respiratory droplets or contact from the infected patients, and potentially oral route. Initially, the virus is presumed to use in

the nasal cavity, pharynx, i.e., the upper respiratory tract. Then it utilizes the lower respiratory tract and gastrointestinal mucosa to proliferate the viral counts (Xiao *et al.*, 2020). Very few SARS-CoV-2 infections are dominated at that point, and it was reported as asymptomatic (Figure 1). The asymptomatic stage may be as long as 1 or 2 days after the viral infection, where some local replication might be happened (Mason, 2020). In some cases, it was reported as a non-respiratory illness like acute kidney, liver, and cardiovascular disorders (Jin *et al.*, 2020). Angiotensin-converting enzyme 2 (ACE 2) has been proven as a principal receptor for binding the cell surface to enter into the cell (Hoffmann *et al.*, 2020). After the cell entry, the virus propagates more,

conducts the airway regulation, and triggers the innate immune responses. This is the second stage, and approximately 80% of patients recover from this mild stage via symptomatic therapy (Mason, 2020). Unfortunately, around 20% of the most vulnerable patients develop the third stage of severe SARS-CoV-2 infection. Initially, the mortality rate is about 2%, which is varying reportedly with the age groups (Wu and McGoogan, 2020). In the third stage, the virus infects the units of the lung, the type II alveolar cells which are responsible for exchanging the gas. Scientists suggested monitoring this progression of the third stage of SARS-CoV-2 infection, which might be required to serve as the best facility to recover (Mason, 2020).

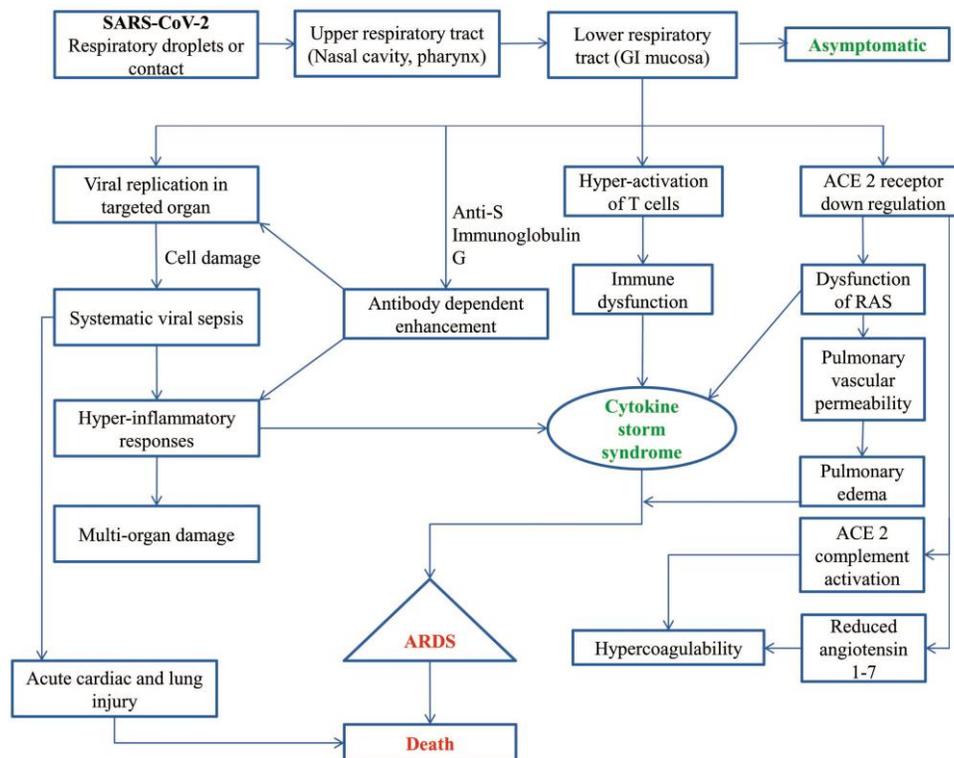


Figure 1. Plausible pathogenesis of SARS-CoV-2 infection in the human body. SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; GI mucosa: Gastrointestinal mucosa; ACE 2: angiotensin-converting enzyme 2; RAS: renin-angiotensin system; ARDS: acute respiratory distress syndrome. The figure was examined and supported by previous published literatures (Jin *et al.*, 2020; Mason, 2020).

Genetical and biochemical features: The novel SARS-CoV-2 virus has shown a similar characterization and genomic sequencing at around 80% with SARS and 50% with MERS bat-derived

coronavirus. In contrast, the phylogenetic analysis suggested the dissimilarity of SARS-CoV-2 with the previous both coronavirus (MERS-CoV and SARS-CoV), as it has belonged to the β -coronavirus genus

(Lu *et al.*, 2020b). It was reported that there are four significant glycoproteins in the surface of the SARS-CoV-2 virus [(Spike (S), membrane (M), envelop (E), and nucleocapsid (N)]. Amongst them, the spike protein significantly binds with the ACE 2 receptor located on the surface of the host cell, which is highly expressed in the lung, heart, kidney, and bladder (Zou *et al.*, 2020). The spike protein consists of two subunits (S1 and S2), which are responsible for binding to the ACE 2 receptor binding and for the cell fusion, respectively (Kuhn *et al.*, 2004). Moreover, the S protein forms a crown-like appearance of the virus by extending itself from the membrane. Homology modeling analysis showed that the SARS-CoV also used to enter the host cell via the same receptor, while MERS-CoV utilized the dipeptidyl-peptidase-4 (DPP-4) receptor (Wan *et al.*, 2020; Li *et al.*, 2020b). However, this novel virus transmits with a 3 and 10 fold higher transmission rate than the SARS and MERS-CoV viruses, respectively (Jiang and Shi, 2020).

Mechanism of SARS-CoV-2 invasion: In brief, the life cycle of the SARS-CoV-2 virus in the host cell consists of five processes: attachment, penetration, biosynthesis, maturation, and release

(Figure 2). Firstly, the virus binds to the host cell receptor ACE 2 (attachment process) and enters into the cell via the endocytosis process (penetration). Then the viral cell is supposed to be released in the cytoplasm and thrusts into the nucleus for its replication. The viral proteins are biosynthesized by utilizing viral mRNA. Then the new viral particles are matured and released (Yuki *et al.*, 2020). Among all proteins of the virus, the envelope protein plays a major role during the maturation and budding, as it localizes in the Golgi or endoplasmic reticulum (ER). After the S1 subunit of the spike protein of the virus binds with the ACE 2 receptor, the conformation change of the protein provokes the envelope fusion via the endosomal process in the cell membrane. Then the virus releases its genetic material into the cell. By the effect of viral proteinases, the RNA cleaves into some small products. A series of sub-genomic mRNA materials which are finally translated to the viral proteins through transcription and translation processes. Then the viral proteins are assembled into the ER/Golgi apparatus, which are transported through vesicles. Finally, the viral genomic materials and proteins are released out of the cell (Sherren *et al.*, 2020).

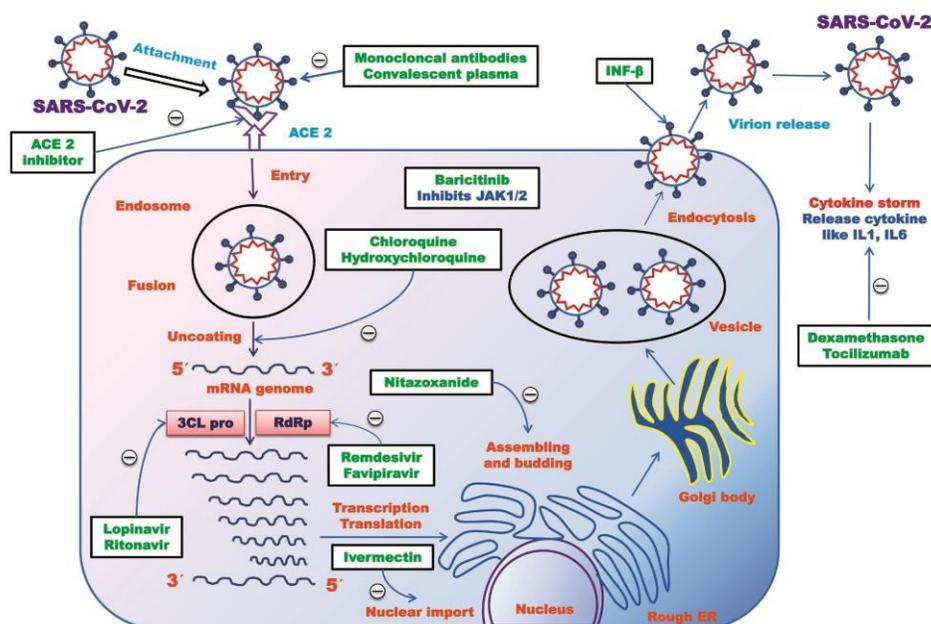


Figure 2. The life cycle of SARS-CoV-2 in the host cell and the proposed drug targets against the virus. The figure was verified and supported by previous published literatures (Pandey *et al.*, 2020; Hossain and Rahman, 2020).

Concurrent treatments of COVID-19

Promising repurposed therapeutic options: Due to the novelty of COVID-19, the world community still lacks any approved vaccine or effective therapeutic option against the virus. The primary treatment of SARS-CoV-2 infection is palliative care. Currently, outpatient management to intensive care is based on supportive and symptomatic treatments to save lives. As the SARS-CoV-2 virus is an RNA virus, it was also reported that the virus is 80% similar to genetically with SARS-CoV; the drugs used to fight the SARS-CoV, MERS-CoV successfully or potentially, can be repurposed to combat this novel virus. The new drug development process is also long. Therefore, drug repurposing is the best strategy to fight pandemics instantly. Since the outbreak, some antivirals, anti-parasitic, and immune-modulating drugs are being prescribed urgently to the COVID-19 positive patients (Hossain and Rahman, 2020).

Antiviral therapy: Numerous antiviral drugs like remdesivir, favipiravir, lopinavir/ritonavir, interferon-beta, darunavir, oseltamivir, etc., were reported as promising drugs against COVID-19. Remdesivir is an approved drug to treat the Ebola virus (Al-Tawfiq *et al.*, 2020), and favipiravir is used against the influenza virus (Shiraki and Daikoku, 2020). As both drugs are the blockers of RNA-dependent RNA polymerase (RdRp) enzyme (Figure 1), these antiviral drugs showed *in vitro* anti-COVID-19 property (Sheahan *et al.*, 2017; Shiraki and Daikoku, 2020). Both antiviral drugs are nucleoside analog-based drugs, which act on the RdRp enzyme and inhibit the replication of RNA viruses, like coronavirus (Li and Clercq, 2020). Recently, a preliminary report of a double-blind, placebo-controlled, randomized trial (NCT04280705) has been published by analyzing data obtained from 1,059 COVID-19 patients (remdesivir=538 and placebo=521) (Beigel *et al.*, 2020). The drug has been observed to minimize the median recovery time from 15 to 11 days and decreased the mortality rate from 11.9% to 7.1%. In the meantime, the United States Food and Drugs Administration (USFDA)

published an authorization letter for the emergency use of remdesivir (USFDA, 2020).

The health ministry of Russia issued a temporary approval of favipiravir (Avifavir) to use in the treatment of COVID-19 after getting a positive outcome of a clinical trial on 330 patients. The drug showed a safety profile with no significant adverse effects (Trial Site News, 2020). Another double-blind, placebo-controlled, randomized trial was conducted in Bangladesh (Dhaka Trial) on 50 patients with COVID-19. The study found 44% more viral clearance than placebo (RT-PCR negative: favipiravir vs. placebo = 96% vs. 52% after 10 days) (Hossain and Rahman, 2020).

Another potential anti-COVID-19 therapy is the combination of lopinavir/ritonavir (Pandey *et al.*, 2020). Lopinavir is used in conjunction with ritonavir to treat the human immune deficiency virus (HIV). Lopinavir acts as an HIV-1 protease enzyme inhibitor, where ritonavir blocks the CYP3A4 metabolizing enzyme and enhances the plasma level of lopinavir (Kaplan and Hicks, 2005; Podzamczar *et al.*, 2015). A trial (ChiCTR2000029308) on 199 hospitalized COVID-19 patients showed no significant benefit of lopinavir/ritonavir compared to standard care only (Cao *et al.*, 2020). Another open-label, randomized phase II clinical trial (NCT04276688) for triple combination therapy of LPV/RTV (400 mg/100 mg twice daily), ribavirin (400 mg twice daily), and INF beta-1b (3 doses of 8 million IU on alternate days) was conducted by Hung *et al.* (2020) on 127 COVID-19 patients. The study established the triple therapy safety profile and found superior activity than the lopinavir/ritonavir alone to reduce complications and shorten the viral clearance time. However, WHO Solidarity Trial Consortium (2020) has recently reported its interim results that the repurposed drugs like remdesivir, hydroxychloroquine, lopinavir, and interferon beta-1a exhibited little or no effect on COVID-19 hospitalized patients in the duration of hospital stay, initiation of ventilation, and overall mortality.

Anti-parasitic therapy: Chloroquine or hydroxychloroquine, is an approved antimalarial and autoimmune disease drug. During the early phase of the COVID-19 pandemic, hydroxychloroquine was reported as promising anti-SARS-CoV-2 therapy in numerous scientific articles. It has a weak basic property that increases the endosomal pH. The high pH prevents cell fusion and enzyme activation, which is essential for viral replication (Salata *et al.*, 2017). The drug also blocks viral entry by halting the glycosylation of ACE 2 on the surface of the host cell (Vincent *et al.*, 2005). The use of hydroxychloroquine with azithromycin had been excellent breaking news after the publication of a non-randomized, open-label clinical trial in March of the year 2020 (Gautret *et al.*, 2020). Unfortunately, hydroxychloroquine has failed to be established as an anti-COVID-19 drug finally, due to its high side effects concluded by a big open-label, randomized, controlled, and multicenter clinical trial (Tang *et al.*, 2020c).

Another proposed anti-COVID-19 drug, ivermectin, is an FDA-approved broad-spectrum anti-parasitic drug to treat river blindness (Pandey *et al.*, 2020). Many studies found ivermectin's activity against RNA viruses like HIV, flavivirus, influenza, dengue, West Nile virus, and a few cancer cells (Hossain and Rahman, 2020). It was recently reported that ivermectin showed the *in vitro* anti-COVID-19 activity (Caly *et al.*, 2020). A pilot study of phase I trial on 87 COVID-19 patients in Iraq showed more efficacious of ivermectin group (100% cure), smaller hospital stay (7.62 ± 2.7 vs. 13.22 ± 0.90 days), and comparatively safer than its control group (hydroxychloroquine + azithromycin) (Hossain and Rahman, 2020). Another recently published double-blind, placebo-controlled, randomized trial conducted in Dhaka, Bangladesh, on 72 COVID-19 patients reported that a 5-day course of ivermectin was found to be safer and effective against mild COVID-19 adult patients (Viral clearance: ivermectin group vs. placebo group = 9.7 days vs. 12.7 days; $p = 0.02$) (Ahmed *et al.*, 2020). However, some larger clinical trials (for example, NCT04381884, NCT04429711, NCT04391127, NCT04360356) have

been started to ensure its safety and efficacy against COVID-19.

Nitazoxanide is a broad-spectrum antiviral drug that has been repurposed for the treatment of some RNA viruses which was originally developed and commercialized as an antiprotozoal agent (Rossignol, 2014). Initially, nitazoxanide was developed as an antiprotozoal drug. This safe drug showed high potency against broad-spectrum DNA and RNA virus in cell culture assays (Rossignol, 2014). In LLC-MK2 cell culture, the EC_{50} value for NTZ was found $0.92 \mu\text{M}$ which indicated the potency of NTZ against COVID-19 (Rossignol, 2020). Some clinical trials (for example: NCT04360356) are ongoing to establish its final safety and efficacy against the SARS-CoV-2 infection (Table 2).

Immune-modulating therapy: Baricitinib is a Janus kinase (JAK) inhibitor, which is currently prescribed to treat mild to severe rheumatoid arthritis (Favalli *et al.*, 2020). It also blocks the viral entry to the cell by blocking adapter protein-2 associated kinase protein 1 (AAK1). A group of scientists recently proposed that baricitinib might be a potential anti-SARS-CoV-2 drug as regular dosing (Richardson *et al.*, 2020). Kalil *et al.* (2020) conducted a randomized, double-blind, placebo-controlled clinical trial on 1033 adult patients with COVID-19. They reported that baricitinib plus remdesivir was better than remdesivir alone to shorten recovery time and improve clinical status. However, some clinical studies (for example: NCT04320277, NCT04321993) have been started to establish the safety and efficacy of the drug against COVID-19.

Tocilizumab, another potential drug in the treatment of COVID-19, is an interleukin-6 (IL-6) receptor blocker. This recombinant monoclonal antibody is frequently prescribed in rheumatoid arthritis (Abdallah *et al.*, 2017). Since COVID-19 is recognized with hyper-inflammation, with extreme production of interleukin that causes cytokine storm syndrome (Mehta *et al.*, 2020). In this regard, tocilizumab or JAK inhibitor may prevent the cytokine storm (Xu *et al.*, 2020). A large

observational cohort study on 1,351 hospitalized SARS-CoV-2 infected patients with severe pneumonia has demonstrated that tocilizumab decreased the fatality rate of critically ill patients and need for the mechanical ventilation (adjusted hazard ratio, 0.61; 95% confidence interval [CI], 0.40-0.92; $p = 0.020$) (Guaraldi *et al.*, 2020). These preliminary

promising outcomes motivated for large randomized clinical trials. However, a recently published randomized, double-blind, placebo-controlled trial on 243 SARS-CoV-2 infected patients showed that the drug was not effective to avert intubation or death in moderately ill hospitalized patients (Stone *et al.*, 2020).

Table 2. Ongoing clinical trials of the most promising therapeutics for COVID-19 (data source: <https://clinicaltrials.gov/ct2/home>)

Sr no.	Drug	Drug type	ROA	Phase	ClinicalTrials.gov identifier	Duration of study
1	Remdesivir	Antiviral	IV infusion	III	NCT04431453 NCT04330690	Jul, 2020 to Jan, 2021 Mar, 2020 to May, 2022
2	Favipiravir	Antiviral	Oral	III	NCT04336904	Mar, 2020 to Jul, 2020
3	Lopinavir/ritonavir	Antiviral	Oral	II	NCT04330690	Mar, 2020 to Mar, 2022
4	Ivermectin and nitazoxanide	Antiparasitic, Antiviral	Oral	II, III	NCT04360356	May, 2020 to Dec, 2020
5	Hydroxychloroquine, Oseltamivir, Azithromycin	Antiparasitic, Antiviral, Antibiotic	Oral	III	NCT04338698	Apr, 2020 to Nov, 2020
6	i) Lopinavir/ritonavir ii) Hydroxychloroquine sulfate, iii) Baricitinib, iv) Sarilumab.	Antiviral, Antiparasitic, Immune-modulating	i, ii, & iii Oral route, iv. S.C injection	II	NCT04321993	Apr, 2020 to Mar, 2022
7	Baricitinib	Immune-modulating	IV	II, III	NCT04340232	Jun, 2020 to Oct, 2020
8	Lopinavir/ritonavir vs Hydroxychloroquine sulfate	Antiviral, Antiparasitic	Oral	III	NCT04403100	Jun, 2020 to Nov, 2020
9	i) Remdesivir, ii) Lopinavir/ritonavir, iii) interferon β -1A, and iv) hydroxychloroquine	Antiviral, Antiparasitic	I.V infusion, oral route, SC injection, and oral route, respectively	III	NCT04315948	Mar, 2020 to Mar, 2023
10	Dexamethasone	Corticosteroid	IV	IV	NCT04325061	Apr, 2020 to Oct, 2020
11	Convalescent plasma	Immune-modulating	IV	III	NCT04372979 NCT04343755 NCT04390178	May, 2020 to May, 2021 Apr, 2020 to Apr, 2021 Apr, 2020 to Dec, 2020
12	Tocilizumab	Immune-modulating	IV injection	II	NCT04317092 NCT04335071	Jun, 2020 to Dec, 2020 Mar, 2020 to Dec, 2022 April, 2020 to Oct, 2020
13	i). Hydroxychloroquine and ii). Nitazoxanide	Antiparasitic	Oral	II, III	NCT04361318	May, 2020 to Dec, 2020

Note: ROA=Route of administration; IV= Intravenous; SC = subcutaneous.

Dexamethasone (Corticosteroid) is an immune-modulating agent that contributes significantly to immune homeostasis (Stockman *et al.*, 2006). A randomized controlled, open-label, clinical trial on

6,425 COVID-19 patients, conducted by the RECOVERY collaborative group (2020), has been published that dexamethasone reduced the 28-day fatality rate of critically ill patients on ventilator

support. However, the drug did not show any improvement in moderate or mild patients.

Convalescent plasma therapy is a process of enhancing passive immunity by providing plasma containing neutralizing antibodies. A donor who has recently recovered from SARS-CoV-2 can donate plasma to a COVID-19 patient (Hui and Wong, 2005). As there is no approved vaccine or drug, this low risk therapy can boost the patient's immunity (Arabi *et al.* 2016). Recently, Simonovich *et al.* (2020) have published the outcomes of a randomized, double-blind, placebo-controlled, clinical trial of convalescent plasma therapy on 228 patients, where they reported that this therapy exhibited neither decreasing mortality rate nor any clinical improvement. However, currently, some more extensive randomized, double-blind, controlled clinical trials are under investigation to finalize its safety and efficacy for the treatment of COVID-19 (Rajendran *et al.*, 2020).

Vaccination against SARS-CoV-2 infection: The most wanted and long-term effective solution of the current pandemic is to develop a vaccine against the SARS-CoV-2 virus. The undertaken previous attempts to develop a vaccine against the SARS and MERS outbreak introduced sufficient knowledge about the new virus's anatomy and physiology. The established preliminary conceptions expedited the vaccine development against COVID-19 (Diamond and Pierson, 2020). According to WHO, no vaccine is approved for the virus. Till the date, more than 137 vaccine candidates are ongoing under preclinical development, and 23 are in clinical development for COVID-19 prevention (WHO, 2020). Among them, very few vaccines like mRNA (Moderna), ChAdOx1 nCoV-19 (Oxford), Ad5-nCoV (CanSino Biologicals), INO-4800 (Inovio), LV-SMENP-DC, and pathogen-specific aAPC (Shenzhen Geno-Immune Medical Institute) are promising which have already entered into clinical trial phases. Another significant breakthrough was created on July 20, 2020, through publishing the preliminary report of phase 1/2, single-blind, randomized, controlled trial of ChAdOx1 nCoV-19 potential vaccine (Folegatti *et*

al., 2020). A total of 1,077 participants (18-55 years) were recruited in the trial, where 543 received the vaccine. In the vaccine group, a dual immune response, i.e., spike-specific T-cell response and anti-spike IgG response, were observed on days 14 and 28, respectively, with no serious adverse effects. The ChAdOx1 nCoV-19 vaccine showed well tolerability with an acceptable safety profile. Moreover, the study supported the bigger scale Phase III trial (Folegatti *et al.*, 2020). Recently, UK's medicines and healthcare products regulatory agency (MHRA) has given temporary use approval of the world's first vaccine BNT162b2 (developed by Pfizer and BioNTech) to fight COVID-19 pandemic based on its 95% protection against SARS-CoV-2 virus in an ongoing placebo-controlled, observer-blinded, multinational trial on 43,548 participants (EPR, 2020; Polack *et al.*, 2020).

Herd immunity and COVID-19: Herd immunity or herd effect or indirect protection is not a novel concept. It indicates the incorporation of a pathogen to a human or animal population to attain immunity against the pathogen. Individuals with no development of self-immunity are defended from the infection indirectly, according to the theory (Rashid *et al.*, 2012). The stated doctrine of herd immunity had been popular in the case of animal husbandry. However, it can protect a large population by restricting the transmission of infectious diseases. The R_0 value is utilized to determine the threshold percentage (P) of the population required to be immunized for developing herd immunity. The whole community will get rid of the pandemic (Hossain, 2020b).

$$P = \frac{R_0 - 1}{R_0} \times 100\%$$

Most of the study showed that the R_0 value was lying between 2 to 3 for SARS-CoV-2 infection (Liu *et al.*, 2020). Therefore, the threshold percentage is 50 to 66.67% population required for achieving indirect protection from the COVID-19 outbreak (Syal, 2020).

During the pandemic time, the hot spots for the infection are the hospitals or clinics, diagnostic

centers, airports, stations, immigration points, etc. should be covered by the recovered volunteers from COVID-19 as per their expertise setting. The immunized people would be able to limit the spread of the virus and act as a root of indirect protection (Liu *et al.*, 2020). It is important to note here, after the recovery of all symptoms of COVID-19 for 14 days, approximately 14% of patients got RNA test positive in China (An *et al.*, 2020). However, it has been disputable that COVID-19 recovered subjects can be re-infected. It has been considered the reactivation of dormant SARS-CoV-2 infection (Guzman, 2020). Recently, Batisse *et al.* (2020) published a national case series of 11 re-infected patients with acute COVID-19 and recommended to perform a more extensive study to comprehend the mechanism of these reactivations. Unfortunately, indirect protection will not be effective if the virus would mutate. Nevertheless, herd immunity is an experimented approach. In developing countries, all the places are not homogeneously susceptible to the infection. Therefore, localized herd immunity may help in mitigating the spread of COVID-19 (Syal, 2020; Hossain, 2020b).

Conclusions

Undoubtedly, the COVID-19 outbreak caused by the zoonotic virus has created vigorous troublesome in public health and the international economy. Although the symptoms of SARS-CoV-2 infection are mild to moderate in most of the cases, the infectivity is so high compared to SARS and MERS coronavirus. Until an effective, safe, and approved vaccine is available for everyone, potential repositioned drugs might be suitable candidates to fight COVID-19. Numerous repurposed drugs are undergoing clinical trials, and some of them have already been endorsed in different countries of the world for emergency use or as adjuvant treatment options in COVID-19 in addition to standard of care.

However, the approved vaccines or drugs are far away; therefore, the transmission of COVID-19 must be controlled by concerted efforts. The strict protocols of social distancing, wearing masks, routine washing of hands, and maintaining isolation and

quarantine protocols may be the instant solution to prevent its rapid transmission. Particular attention should be given to vulnerable populations, including older adults, children, and health care providers. It is inevitable to monitor the strength and potential routes of human to human transmission of SARS-CoV-2 globally. Anti-COVID-19 drugs or vaccines development must be accelerated, and comprehensive steps should be promoted to prevent any future pandemic.

Conflict of interests

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