COVID-19 pandemic: A review based on current evidence

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Abstract:
In December 2019, severe acute respiratory syndrome-coronavirus-2, a novel coronavirus, initiated an outbreak of pneumonia from Wuhan in China, which rapidly spread worldwide. The clinical characteristics of the disease range from asymptomatic cases or mild symptoms, which include nonspecific symptoms such as fever, cough, sore throat, headache, and nasal congestion to severe cases such as pneumonia, respiratory failure demanding mechanical ventilation to multi-organ failure, sepsis, and death. As the transmission rate is quite alarming, we require an effective therapeutic strategy to treat symptomatic patients and adopt the preventive measures in order to contain the infection and prevent community transmission. Coronavirus disease 2019 (COVID-19) pandemic is a public health emergency of international concern, hence repurposing of the drugs is an attractive and a feasible option because PK/PD profile, toxicity profile, and drug interactions are already known. This review emphasizes on the different aspects of COVID-19 such as the epidemiology, etiopathogenesis, diagnosis, and preventive measures to be adopted in order to fight this pandemic. It also highlights upon the ethics preparedness and challenges faced by a developing country like India during such an outbreak. The review focuses on the various approaches adopted till date for developing effective therapeutic strategies including combination of drugs, vaccine therapy, and convalescent plasma therapy to combat this viral outbreak.

Keywords:
Coronavirus disease-19, drug repurposing, pandemic, severe acute respiratory syndrome-coronavirus-2

Introduction
Coronavirus belongs to the Coronavirus family, Nidovirales order. The name of the genus “Corona” means crown, as the virus appears with crown-like projections on its surface. In the late 1960s, it was first isolated from patients suffering from common cold, named as B814 and visualized under an electron microscope.[1] The subgroups of coronavirus family include alpha (α), beta (β), gamma (γ), and delta (δ). The key reservoirs of the virus are bats, palm civets, livestock, and animals. These viruses were assumed to transmit infection only among animals till the outbreak of severe acute respiratory syndrome (SARS) in the year 2002 in Guangdong, China.[2] Later, there was an outbreak of Middle East respiratory syndrome coronavirus (MERS) in the Middle Eastern countries.[3] Coronavirus is a single-stranded (positive-sense) RNA virus, enveloped (E-protein) with club-shaped/pear-shaped/petal-shaped glycoprotein projections (S-protein). The virus is spherical or pleomorphic with 80–120 nm size. The spikes are made of hemagglutinin-esterase. The S protein mediates the viral attachment and entry to endoplasmic reticulum.[4]

In December 2019, there occurred a novel coronavirus (coronavirus disease 2019 [COVID-19]) outbreak in Wuhan, China. This outbreak was thought to have originated from the Hunan seafood market at Wuhan, China. The patients presented...
with pneumonia of unknown etiology and had a history of travel to the seafood market. Gradually, the number of cases began to rise and few patients had no travel history to seafood market, indicating a possible human-to-human transmission.\textsuperscript{[8]} SARS-coronavirus-2 (SARS-CoV-2) retains the classic coronavirus structure like the presence of spike protein and expression of other nucleoproteins, polyproteins, and membrane proteins such as RNA polymerase, 3-chymotrypsin-like protease, papain-like protease, helicase, glycoprotein, and accessory proteins.\textsuperscript{[6]}

Epidemiology

The outbreak was declared as “a public health emergency of international concern” by the WHO on January 30, 2020, and as a pandemic on March 11, 2020. As of April 28, 2020, there are >29 lakh confirmed cases worldwide with >2 lakh confirmed deaths. The United States have the highest number of confirmed cases.\textsuperscript{[7]} The first case of COVID-19 in India was reported on January 30, 2020, with origin from China. As of April 29, 2020, there are 22,629 active cases in India with 1007 deaths.\textsuperscript{[8]} Keeping in mind the increasing number of COVID-19 cases in India, India observed a 14 h “Janata Curfew” on March 22, 2020, as insisted by our honorable Prime Minister Narendra Modi. Later, the PM of India announced a nationwide lockdown for 21 days on March 24, 2020, so as to break the chain of transmission and the lockdown was then extended till May 3.

Etiopathogenesis

SARS-CoV-2, a type of beta-CoV, is accountable for 5%–10% of acute respiratory tract infections. Around 2% of the population are believed to be healthy carriers of the novel coronavirus.\textsuperscript{[9]} The exponential rise in the number of cases reflected human-to-human transmission. Infection is spread through droplets produced by asymptomatic patients while coughing and sneezing as well as by asymptomatic patients who may later develop symptoms.\textsuperscript{[10]} The virus can persist in the aerosols for nearly 3 h and was detected up to 72 h after application on different surfaces. The virus remains more stable on stainless steel and plastic when compared to copper and plastic. However, a decline in their infectious titer was observed.\textsuperscript{[11]} Hence, transmission can also occur if one comes into contact with such contaminated surfaces and then touches mouth, nose, and eyes.

Given the fact that fecal excretion takes place in case of both SARS-CoV and MERS, it may also be possible that SARS-CoV-2 is also transmitted through this route.\textsuperscript{[12]} It has been reported that patients suffering from SARS-CoV-2 infection have gastrointestinal symptoms and some patients have the presence of viral RNA in feces or even infectious virus. This might suggest that feco-oral transmission might also be a route of transmission of SARS-CoV-2. In China, out of ten pediatric patients suffering from COVID-19, no one required intensive care or respiratory support, but eight patients out of ten had positive rectal swabs for SARS-CoV-2 even after negative nasopharyngeal tests.\textsuperscript{[13]} In another study, 39 patients had a positive SARS-CoV-2 RNA test in stool samples out of 73 patients. In addition, 17 patients still had a positive stool sample even after negative respiratory samples. This could conclude that asymptomatic patients might shed virus, which can possibly infect many other healthy individuals.\textsuperscript{[14,15]}

Role of Renin–Angiotensin System Inhibitors in Coronavirus Disease 2019 Patients

Similar to SARS-CoV, SARS-CoV-2 binds to ACE2 cell receptor expressed by epithelial cells of lung, intestine, kidney, and blood vessels and gains entry into the host cell. Majority of the patients in India suffer from diabetes mellitus and hypertension, and most of them are on ACE inhibitors and angiotensin II receptor blockers (ARBs). Consequently, this will result in an upregulation of ACE2.\textsuperscript{[17]}

As a result, theoretically, this would facilitate the infection with COVID-19. However, there is no robust evidence regarding the use of ACE inhibitors and susceptibility to COVID-19.

In contrast to the above hypothesis, a study by Meng et al. showed that renin–angiotensin system inhibitors improved the clinical outcomes in COVID-19 patients with hypertension. In this study, ACEI and ARB therapies attenuated the inflammatory response as evidenced by a decline in interleukin-16 (IL-16) levels. In addition, an increase in CD3 and CD8 T cell counts in peripheral blood and decrease in the peak viral load were observed.\textsuperscript{[18]}

Severe disease outcomes were observed in patients with diabetes mellitus, hypertension, chronic kidney diseases, and coronary artery diseases, who were most probably on ACE inhibitors and ARBs.\textsuperscript{[10]}

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Hence, with the current evidence, we cannot exactly conclude the role of these drugs in COVID-19 patients.

**Clinical Features**

SARS-CoV-2 infection patients present with a wide range of symptoms from asymptomatic cases to acute respiratory distress syndrome (ARDS), septic shock, and multiorgan failure. In mild-to-moderate cases, patients usually present with fever, cough, sore throat, malaise, headache, shortness of breath, and tachypnea. In severe cases, patients may suffer from pneumonia, acute respiratory symptoms, and septic shock. Patients with comorbidities are known to have high case fatality rate.[19]

Laboratory findings include lymphopenia, elevated prothrombin time, lactate dehydrogenase, creatine kinase, and C-reactive protein. Patients also showed abnormal findings suggestive of myocardial, renal, or hepatic injury.[20] Elevated ILs and tumor necrosis factor-alpha (TNF-α) levels are usually observed in critically ill patients.[10]

**Diagnosis**

As COVID-19 has been declared a pandemic, every case presenting with any of the symptoms discussed earlier or a travel history to any of the affected countries or a history of any contact with infected persons should raise a suspicion of infection with SARS-CoV-2. The WHO recommends sample collection in the form of expectorated sputum, endotracheal aspirate, or bronchoalveolar lavage. Real-time-polymerase chain reaction (RT-PCR) test is used for the detection of viral RNA. Sometimes, if the test is negative but a strong suspicion of COVID-19 is present, then the test has to be repeated for confirmation.[21]

**Challenges for Diagnosis**

A developing country like India may face a problem of limited number of supply of kits and testing facilities. The RNA-based molecular labs need restrictive biosafety levels and expertise. The methods are expensive and also time-consuming. Hence, testing can be performed in only selected centres where well equipped laboratories and expertise are available. The suspected patients have to wait for the confirmation of their report during which they might infect others. The actual number of confirmed cases can be underestimated if the number of testing performed is low.

Another issue with the nucleic acid tests is regarding their sensitivity and specificity. Sometimes, RT-PCR tends to give false-positive and false-negative results.[22] According to the current guidelines, a person can be considered as cured only if he is tested negative twice, 24 h apart by RT-PCR. Apart from the technical challenges, false results can also be generated because of the deletions and mutations in the SARS-CoV-2 genome, which tend to occur during evolution. Therefore, there exists a need for serological tests, which can be performed in any hospital and at a faster rate.

Evidence from the previous SARS epidemic reveal that serological responses, including virus-specific immunoglobulin, immunoglobulin M, and immunoglobulin G, can permit for serological diagnosis.[23] It was shown that patients with COVID-19 also exhibited similar acute serological responses.[19] The testing capacity with 96-well microplate and automated enzyme-linked immunosorbent assay (ELISA) devices is greatly enhanced with a faster turnaround time of 2–3 h. Hence, the serological tests can test a large number of samples in a short span, which is the need of the hour. However, there could be an issue that antigen used in ELISA might cross react with antibodies against other human coronaviruses causing common cold. This cross reactivity may affect the sensitivity and specificity of the test results. Another issue of concern is asymptomatic individuals who can still infect the people being exposed to them. Hence, there is an immense need of rapid viral detection tests. Such tests can be employed as a part of sero-epidemiological studies, thereby helping us to know about the actual burden of the infection [Table 1].

**Role of Drug Repurposing**

Repurposing of already-approved agents for a different medical condition is an effective strategy as it saves considerable amount of time, money, and resources. Sarma et al. have also discussed few potential therapeutic options for treating SARS-CoV-2 infection.[26] Discovering the target, exploration of the signaling pathways, or the mechanism of action are few key steps involved in drug repurposing where the role of a pharmacologist is quite essential. As the safety, efficacy, and toxicity data of the agents being explored are already available, the cost of drug development and time taken are minimized.[27] The requirements of the regulatory agencies are the key factors in determining the production of repurposed drugs. In the United States, there are three possible regulatory pathways, namely section 505(b)(1), section 505(b)(2), or section 505(j), though only one out of them which is section 505(b)(2) applies to drug repurposing.[27,28] A supplemental new drug application must be submitted if slight modifications are to be made to the already-approved agent.[28] The drug repositioning approval process in Europe can be submitted through three different paths: centralized, decentralized, or national. In Europe, article 10 of directive 2001/83/EC provides the principal legal framework for repurposed
drugs and for neglected epidemic. Earlier, fast-track process was used to counter bioterror risks, pandemic risks, and for neglected epidemic. During the Ebola outbreak in 2014, the FDA sought to help speed up the production and delivery of medical items for containing the epidemic. The FDA approach to the Ebola outbreak in 2014 demonstrates the vast array of resources and versatility in regulatory procedures that allowed it to act fairly and quickly during the epidemic. Earlier, fast-track process was used to counter bioterror risks, pandemic risks, and for neglected medical conditions. This fast-track status was provided to therapeutic agents which were to be used against Ebola (TKM-Ebola in 2014 and ZMapp in 2015). The regulatory bodies and the sponsor should be working closely for ensuring that no therapeutic agent, which has the potential for benefitting the patients in the times of urgency, are stuck as it might lead to a calamity-like situation.

As of March 30, 2020, the Drug Controller General of India has issued a notice to all the stakeholders of India regarding the conduct of clinical trial during an outbreak of COVID-19. A clinical trial involving a new drug is regulated under the “New Drugs and Clinical Trials Rules (NDCT), 2019.” A clinical trial should be conducted according to the approved clinical trial protocol and adhere to “Good Clinical Trial Practices” guidelines. In case of an outbreak like COVID-19, there might be various challenges in the conduct of the trial. In such cases, the Central Drugs Standard Control Organisation (CDSCO) states that the sponsor in coordination with the investigator and respective ethics committees.

### Role of Accelerated Drug Approval

It is desirable to accelerate the development of therapeutic agents for serious medical conditions particularly if these agents are the first treatment available or if the benefits of the new drug are more than that of the currently available agents in the market. Four different, yet effective strategies have been established by the FDA for providing the access to these agents as quickly as possible: priority review, breakthrough therapy, accelerated approval, and fast track process. Bearing in mind that the expected therapeutic benefit of a drug may take an excessive amount of time, the FDA introduced the “Accelerated Approval Regulations” in 1992. The FDA approved these drugs quickly based upon the surrogate end points. Surrogate end points are meant to substitute for a clinical endpoint and using these end points, a drug approval process can be shortened considerably.

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| Antigen in target | Number of samples | Outcome | Remarks | Limitation |
|-------------------|-------------------|---------|---------|------------|
| Li et al.[24]     | MK201027          | 525     | Sensitivity: 88.66% Specificity: 90.63% | Comparison was made between fingerstick blood, serum and plasma of the venous blood. There was 100% consistency among the corresponding blood samples | Due to limited time, no complete information for how long each patient was infected and had symptoms when blood samples were collected |
| Guo et al.[25]    | rNP               | Total 208 samples | The detection efficiency by IgM ELISA is higher than that of qPCR method after 5.5 days of symptom onset | Ability to detect subclinical infections effectively | Cross-reactivity was not studied with other coronavirus |

**Table 1: Details of rapid detection methods for COVID 19 (IgG-IgM combined antibody test)**

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RNP=Recombinant nucleocapsid protein, SARS-CoV=Severe acute respiratory syndrome-coronavirus, IQR=Interquartile range, qPCR=Quantitative real-time polymerase chain reaction, ELISA=Enzyme-linked immunosorbent assay
committee should make a decision whether to continue the ongoing clinical trial or not. The safety, well-being, and protection of the rights of trial participants is of utmost importance. Keeping in mind these things, any reason for protocol amendments/declarations should be maintained and a copy of the same is to be submitted to the concerned CDSCO headquarters.

**Potential Therapeutic Options**

SARS-CoV-2 has caused havoc across the globe, yet no therapeutic agent has been approved until now. The current situation demands an approval of the drug as fast as possible and priority should be given to repurposing of the drugs for combating this pandemic. Now, let us highlight on some of the potential therapeutic options against SARS-CoV-2 infection.

**Hydroxychloroquine**

Hydroxychloroquine (HCQ), being a less toxic derivative of chloroquine (CQ), has shown a better activity against SARS-CoV-2 in *in vitro* and a better antiviral activity compared to CQ.  

A study by Gautret *et al.* showed that HCQ reduced the viral load significantly in SARS-CoV-2 infections. Combination of HCQ and azithromycin showed a better reduction in viral load when compared to HCQ alone. However, small sample size is one of the limitations of this study. HCQ is known to cause QT prolongation, and azithromycin has also shown to have pro-arrhythmic potential; the combination of these two therapies is questionable. Due to the absence of a strong evidence regarding the safety of this combination, there is a need of generating data regarding the safety profile. Recently, the ICMR has issued guidelines regarding the use of HCQ as chemoprophylaxis for SARS-CoV2 infection. The use of HCQ has not been advised for the general population but only for high-risk cases like health-care workers who come into direct contact with suspected or confirmed cases and asymptomatic household contacts of COVID-19-positive patients. The ministry has also advised the household contacts of positive cases to remain in home quarantine in addition to HCQ prophylaxis. A recently conducted meta-analysis has shown that HCQ is associated with less number of patients having radiological progression, but the author concluded that more data is required to come to a definitive conclusion.

**Role of antivirals against coronavirus disease 2019**

In a randomized controlled trial, favipiravir has shown some benefit in SARS-CoV-2 infection in terms of clinical recovery rate and effective reduction in the incidence of symptoms except few antiviral-related side effects. Even remdesivir, an antiviral drug, has been tried in SARS-CoV-2 infection. SARS-CoV shares 82% RNA sequence identity with SARS-CoV-2, and their RNA-dependent RNA polymerase (RdRp) shares 96% sequence identity. Hence, drugs that target viral RdRp proteins of SARS-CoV may probably be useful against SARS-CoV-2.

Recently, remdesivir was found to be effective against SARS-CoV-2 infection at the stage after virus entry into Vero E6 cells, thereby exhibiting its antiviral activity. A cohort of severe COVID-19 hospitalized patients with the compassionate use of remdesivir showed a clinical improvement in 36 out of 53 patients. Nevertheless, results of the ongoing randomized controlled trials involving remdesivir therapy are required to elucidate the drug efficacy in SARS-CoV-2 infection.

Currently, clinical trials are ongoing to assess the effect of remdesivir in SARS-CoV-2 infection: NCT04302766, NCT04280705, NCT04315948, NCT04314817, NCT04292899, and NCT04292730. Some of these trials are also evaluating the effect of other treatment options along with remdesivir.

Ribavirin, an antiviral drug, is generally given in combination with interferons (IFNs), and it has shown to be synergistic with any of the two IFN (IFN-α or IFN-β-1a). The drug has shown mixed results when studied in patients with other coronaviruses. In addition to it, the drug exhibits a side effect such as anemia, especially at the dose of ~ 800–3600 mg/day tested for MERS. This may be an unwanted adverse effect in patients suffering from respiratory disorders, hence may not be a better option in SARS-CoV-2 infection.

Lopinavir and ritonavir were found to be effective against SARS-CoV in *in vitro* studies. The main action of ritonavir is to prolong the plasma half-life of lopinavir via the inhibition of CYP P450. Recently, a randomized controlled trial conducted in China to evaluate the effect of combination of lopinavir and ritonavir in addition to standard care in severe COVID-19 patients failed to demonstrate any beneficial effect when compared to standard care alone. However, the possible benefit of the combination cannot be excluded as the study included severely ill patients, which might have failed to demonstrate efficacy against SARS-CoV-2 infection.

**Role of immunomodulators**

**Baricitinib**

Baricitinib is a Janus Kinase inhibitor which has already got FDA approval for treating moderate-to-severe rheumatoid arthritis patients nonresponsive to TNF inhibitor therapies. AP2-associated protein kinase 1 (AAK1) is a known regulator of endocytosis, and the entry of most of the viruses is dependent on the receptor
mediator endocytosis. Hence, the disruption of AAK1 may block the virus entry into the cells. Baricitinib has shown to inhibit AAK1 with therapeutic dosing and may be a promising therapy for the patients. The trials are underway where baricitinib is being given in COVID-19 patients (NCT04320277, NCT04321993).

**Eculizumab**  
It is believed to modulate the activity of terminal complement to inhibit the formation of membrane attack complex. Therefore, it is believed to be beneficial in patients with ARDS/lung injury. A trial is ongoing for evaluating eculizumab in COVID-19 patients (NCT04288713).

**Interferons**  
In a study by Huang et al., out of the 41 COVID-19 patients admitted, six died from ARDS. ARDS is believed to be one of the main causes of death in COVID-19. Cytokine storm is one of the proposed mechanisms for ARDS. It is characterized by the release of large amount of pro-inflammatory cytokines (IFN-α, IFN-γ, IL-12, IL-1ß, IL-18, IL-33, IL-6 TNF-α, transforming growth factor-beta, etc.) and chemokines (CCL2, CCL3, CCL5, CXCL8, CXCL9, CXCL10, etc.) by immune effector cells. The trigger in immune response attacks the body, leading to ARDS and multiorgan failure, ultimately death in SARS-CoV-2 infection. With previous experience of SARS outbreak, the chief pathogenesis of organ dysfunction is cytokine dysregulation. The same is noted even in case of worsening of SARS-CoV-2-infected individuals, characterized by a decline in peripheral lymphocyte counts and elevated cytokines indicative of a triggered immune response.

An open-label, nonrandomized study by Bellingan et al. showed that intravenous IFN beta-1a (FP1201) lowered mortality day 28 in patients with ARDS. However, IFN-associated adverse effects, cost, and intravenous dosage form would pose major challenges in an outbreak. Currently, a clinical trial is ongoing to assess the safety and efficacy of recombinant human IFN-ß1a in COVID-19 patients in Wuhan (NCT04293887). Another trial is being carried out to evaluate the effect of combination of lopinavir/ritonavir, ribavirin, and IFN beta-1B in SARS-CoV-2 infection (NCT04276688).

**Autologous, adipose-derived mesenchymal stem cell therapy**  
Stem cell therapy has attenuated systemic inflammation in Phase I/II clinical trial in rheumatoid arthritis patients. In COVID-19, inflammation is one of the driving forces for disease progression. Therefore, there is an immense need to regulate the immune system as quickly as possible. A Phase II single-arm, nonrandomized study of COVID-19 patients ≥50 years with preexisting comorbid conditions or at high exposure risk has been approved.

**Multistem cell therapy**  
The FDA has approved for the commencement of Phase 2–3 trial for moderate-to-severe ARDS induced by COVID-19 as previous Phase I/II clinical trials have already assessed therapy in ARDS.

**Corticosteroids**  
Corticosteroids were quite commonly used during the previous two SARS and MERS outbreaks. In addition, during the current outbreak of SARS-CoV-2, corticosteroids are being used along with other agents. In both the previous outbreaks, histology revealed inflammatory changes and diffuse alveolar damage associated with the infection. Hence, corticosteroids might play a role in suppressing the inflammation, but in addition, they can also hinder the immune response and clearance of pathogens. Just four studies presented definitive evidence in a meta-analysis of corticosteroid use in SARS patients, all suggesting harm to the patient. In a retrospective observational study involving MERS patients, it was found that patients receiving corticosteroids were at higher risk of requiring mechanical ventilation and also it led to delay in viral RNA clearance. The health-care professionals must carefully assess the benefit versus the risks before attempting to use corticosteroids for patients with COVID-19 and sepsis. There is a small decrease in mortality rate with the use of corticosteroids, but the possibility that these agents might prolong the shedding of virus in respiratory tract as with MERS patients cannot be ruled out. There is no conclusive data to determine that corticosteroids might help patients with SARS-CoV-2 infection. In fact, corticosteroids might do more harm than good. Methylprednisolone is being evaluated in a non-randomized, open-label clinical trial for evaluating the efficacy in COVID-19 patients with severe acute respiratory syndrome.

**Role of teicoplanin**  
According to a previous study by Zhou et al., teicoplanin is believed to inhibit cleavage of the viral spike protein by cathepsin L at low pH, thereby halting viral replication cycle by precluding the release of genomic mRNA. On comparing the cleavage site of cathepsin L in SARS-CoV-2 with SARS-CoV, they observed that it was well preserved. The authors then produced a 2019-nCoV pseudovirus whose entry was inhibited by teicoplanin. Hence, teicoplanin could act as a dual inhibitor in treating SARS-CoV-2 infection and co-infection with Gram-positive bacteria.

**Role of ivermectin**  
An *in vitro* study by Caly et al. showed that ivermectin, a broad-spectrum antiparasitic agent, was able to reduce viral replication (up to ~ 5000 fold decrease in viral RNA) at 48 h in SARS-CoV-2-infected Vero-hSLAM cells.
The postulated mechanism is probably by inhibiting IMPα/β1-mediated nuclear import of viral proteins, as observed with other RNA viruses. This increases the likelihood that ivermectin can also be one of the potential therapeutic options against SARS-CoV-2 infection. Nevertheless, further studies in clinical settings are essential to arrive at a definitive conclusion.

A systematic review by Prajapat et al. has highlighted upon seven major targets and 16 nonstructural proteins, which can be taken into consideration as targets for drug development.

Recently, an in silico study has identified two potential hits, one of them being a theophylline derivative and the other a pyrimidine derivative as inhibitors of RNA binding to N terminal domain of N protein. However, these compounds need in vitro validation in future.

**Role of convalescent plasma therapy**

It has been more than a century, convalescent plasma therapy (CP) has been used for the treatment and prevention of several infectious diseases. The basic principle of this therapy is getting the plasma from a recovered patient if having high titers of neutralizing antibodies. In a patient battling the infection, it can be transfused serving as reinforcement for the immune system. The WHO had also recommended the use of convalescent plasma as an empirical therapy during the outbreaks obtained from recovered patients suffering from Ebola. In a cohort study of the H1N1-infected patients, the mortality was significantly reduced with the use of plasma therapy, and there was a decrease in the respiratory tract viral load. This therapy was also associated with higher discharge rate in patients suffering from SARS. A meta-analysis of 32 studies of SARS and influenza showed that there was reduction of mortality associated with plasma therapy. However, the studies included were not of high quality.

In a recent study by Duan et al., ten patients who were suffering from severe COVID-19 were given convalescent plasma (200 ml) obtained from the recovered patients with the titers of neutralizing antibodies >1:640. All the patients enrolled in the study met the primary and secondary end points such as safety after the transfusion and improvement in clinical symptoms along with the radiological and laboratory parameters within 3 days after the transfusion. All the patients received the standard of care and other antiviral medications, so there might be a possibility that these medications contributed to the desired effect. Nevertheless, the results of this study are promising and more well-designed studies with more number of patients are required to come to a definitive conclusion. The ICMR has also given its nod to Kerala State Government for conducting the trials for convalescent plasma therapy.

**Role of traditional Chinese medicine and AYUSH in severe acute respiratory syndrome-coronavirus-2-infected patients**

In its campaign to control and eliminate SARS-CoV-2, traditional Chinese medicine (TCM) is highly regarded by the China government. Around 85% of the patients are on TCM therapy along with the conventional treatment for SARS-CoV-2 infection. The use of TCM in SARS-CoV-2-infected patients is mainly due to the use of such therapies during the previous SARS outbreak where there was a dramatic decrease in fatality rate in Shanghai which was attributed to the use of TCM therapies. The use of TCM treatment was found to be effective in SARS-CoV-infected patients, as well as improvement of the adverse effects of conventional therapies. Many of the studies evaluating the efficacy of TCM in SARS patients were of poor quality, therefore currently ongoing trials evaluating the efficacy of TCM in COVID-19 patients should take all these points into consideration in order to generate a robust evidence.

The Ministry of AYUSH in its advisory for the prevention of coronavirus recommended the use of *Arsenicum album* 30 as a prophylactic agent against SARS-CoV-2. One dose of *Arsenicum album* 30 for 3 days empty stomach was advised by the ministry. However, no scientific evidence is present to show that this agent has efficacy against SARS-CoV-2. Other Ayurvedic measures which have been advised are consumption of Agastya Harityaki, Samshamani Vati, Tulasi leaves, Trikatu, and Pratimarsa Nasya as prophylactic measures. Many Unani medicines have also been mentioned for coronavirus infections such as Sharbat Unnab, Tiryaq Arba, and Tiryaq Nazla, among many others. Nevertheless, the use of such drugs is controversial with little supporting evidence.

**Vaccines**

Until now, no vaccine has been approved for preventing the infection with SARS-CoV-2. However, clinical trials have been initiated for five vaccine candidates. One of these candidates is mRNA-1273 vaccine being developed by the scientists of the National Institute of Allergy and Infectious Diseases, and it was one of the earliest candidates which entered into clinical trials. This Phase I trial is a nonrandomized, open-label study with an estimated sample size of 45 participants (NCT04283461). Another vaccine candidate being developed by CanSino Biological Inc., in collaboration with the Beijing Institute of Biotechnology based on a nonreplication viral vector vaccine technology which was formerly used in the development of Ebola virus vaccine has entered into Phase II of clinical trials. There are three other vaccine candidates...
candidates which have entered into clinical trials and another 71 vaccine candidates are undergoing preclinical testing.[80] Although the requirement of a vaccine is the need of the hour and governments all over the world are desperately waiting for approval of the vaccine, it should not mean that the vaccines should be approved even before their safety and efficacy is evaluated fully in experimental or clinical studies. Hastening of the development of the vaccines without proper evaluation may be of no value.[82]

An epidemiological study by Miller et al. has also shown that countries without universal policy for Bacillus Calmette–Guérin (BCG) vaccination have shown an increased risk of morbidity and mortality with COVID-19 when compared to countries with universal BCG vaccination policy. They also found that countries that have established BCG vaccination policy earlier showed a decline in the number of deaths per million inhabitants.[83] In a study by Moorlag et al., BCG vaccination has shown to be protective against viral infection and sepsis.[84] Hence, there can be a possibility that BCG might confer some protection against COVID-19 as observed by the epidemiological study.[83] However, there is no evidence that BCG vaccination boosts up immunity in the elderly. It is also contraindicated in the immunocompromised and pregnant women. Therefore, high-level evidence such as randomized controlled trials are essential to explore the role of BCG vaccination in COVID-19 [Table 2].

**Preventive Measures**

As there is no specific treatment against COVID-19 till date, preventive measures play a crucial role at health-care level as well as community level in fighting against this pandemic. Many health-care workers have been affected across the world. Even the doctor who first raised an alarm against this outbreak in China is no more. Protection of health-care workers is important to avoid the spread of infection among colleagues and to other patients. They should be provided with personal protection equipment (PPE) such as N95 masks, protective suits, and goggles. Similar to other CoVs, SARS-CoV-2 is sensitive to ultraviolet rays and heat. In addition, these viruses can be inactivated by lipid solvents such as ether (75%), ethanol, chlorine-comprising disinfectant, peracetic acid, and chloroform except for chlorhexidine.[61]

The infected person should be isolated in a separate room. Special care has to be taken while performing procedures such as intubation, suction, and tracheostomy. Regular decontamination of the equipment preferably with sodium hypochlorite is recommended. Careful monitoring of all the close contacts is essential to check for COVID-19 symptoms. A patient is said to have recovered only when he/she tests negative twice by PCR done at 24 h interval.

At the community level, people should wear masks, maintain social distancing, and follow proper hand hygiene measures. Suspects, patients, and their families should be educated regarding the disease and instructed to follow the guidelines strictly so as to prevent the spread of disease in the community. They should be educated to cover their mouth with tissue paper or handkerchief whenever they sneeze or cough as this would generate multiple droplets carrying virus. Repeated hand washing with soap and water or use of sanitizer is also critical. Avoid public gatherings and unnecessary travel to COVID-19-hit areas. Special care should be taken even in case of immunocompromised patients as there are chances of them having severe disease outcomes. Hence, they should avoid public exposure unless it is an emergency. Avoid close contact with pets as there were few cases reported by media where the animals tested positive for COVID-19.

The WHO has also recommended of collaboration with private and academic sectors for laboratory testing and if possible, the setup of mobile laboratories for testing in remote areas.[80] India can also develop strategies such as Singapore’s Disease Outbreak Response System Condition (DORSCON) in order to fight against the pandemic. DORSCON was drafted in Singapore for the crisis management after the outbreak of SARS in 2003 and swine flu (H1N1) pandemic in 2009. DORSCON is a color-coded framework that provides us information about the present disease situation. It takes into consideration about the disease severity and spread to predict its impact on the community.[86] India being a developing nation and the second most populous country can fight the pandemic successfully only if each one of us follow the preventive measures strictly. Media reports of the suspected/confirmed cases of COVID-19 fleeing from airports, hospitals, not being in quarantine though asked to do so, and violence against the health-care professionals would only lead to more burden on the health-care system and then it will be very difficult to contain this pandemic.

**Ethics Preparedness during an Outbreak of an Infectious Disease**

Ethics preparedness is the ability of the public health system, to safeguard and swiftly respond keeping in mind an ethical framework that would build trust and escort with measures to recuperate from public health emergencies. The most recent version of the National Ethical Guidelines for Biomedical and Health Research Involving Human Participants was launched in October 2017. For the very first time, a separate section
### Table 2: Details of clinical studies involving old pills against severe acute respiratory syndrome coronavirus-2 infection

| Study details | Therapeutic strategy | Sample size | Outcome | Comments |
|---------------|----------------------|-------------|---------|----------|
| **Huang ** et al [10] | Antiviral therapy - 38 (93%); ICU care - 12 (92%), non-ICU care - 26 (93%) (oseltamivir - orally 75 mg twice daily) Antibiotic therapy (oral and intravenous) - 41 (100%); ICU care - 13 (100%), Non-ICU care - 28 (100%) Corticosteroid 9 (22%) ICU care-6 (46%); Non-ICU care - 3 (11%) (methylprednisolone 40-120 mg per day) Oxygen therapy | 41 | Discharge - 28 (68%); ICU care - 7 (54%), non-ICU care - 21 (75%) Hospitalization - 7 (17%); ICU care - 1 (8%), non-ICU care - 6 (21%) Death - 6 (15%); ICU care - 5 (38%), non-ICU care - 1 (4%) | Limited sample size kinetics of viral load and antibody titers not estimated No pediatric or adolescent patients |
| **Wang ** et al [85] | 90% of patients received oseltamivir Antibiotics used were ceftriaxone (25%), moxifloxacin (64%), and azithromycin (18%) Around 45% of patients received additional glucocorticoid therapy 9.4% of patients required additional vasopressor 1.44% of patients required additional renal replacement therapy Severity of disease - determinant of antiviral and corticosteroid therapy | 138 | However, no effective outcomes were observed Admitted=61.6% (n=85) Discharged=34% (n=47) Death=4.3% (n=6) | |
| **Wang ** et al [86] | Combined lopinavir/ritonavir (lopinavir 400 mg/ritonavir 100 mg, q12 h, postoperative) All patients were treated with antivirals for 6-15 days Arbidol - 0.2 g, tid, postoperative SFJDC, a traditional Chinese medicine - 2.08 g, tid, postoperative Antibiotic treatment and oxygen In addition to above therapy, one seriously ill received human serum albumin and γ-immunoglobulin | 4 | 3 patients discharged, one patient still on ventilator (but improved) | Limited sample size |
| **Cao ** et al [49] | Treatment arm - Lopinavir and ritonavir (400 mg and 100 mg, orally; twice daily for 14 days, plus standard care Control arm - Standard care alone | 199 | No beneficial effect by adding lopinavir-ritonavir treatment in terms of time to clinical improvement, 28 days mortality, no reduction in viral RNA loads or duration of viral RNA detectability as compared with standard supportive care alone | 14% of lopinavir-ritonavir recipients were unable to complete full 14-day course of administration due to gastrointestinal adverse events Recruitment of severely ill patients might have led to the absence of efficacy of antivirals |
| **Chen ** et al [87] | Antiviral therapy given to 76% patients (n=75) (oral oseltamivir, intravenous ganciclovir and lopinavir/ritonavir tablets, duration therapy ranged from 3 to 14 days) 70 patients received antibiotic treatment, duration of antibiotic therapy ranged from 3 to 17 days 19 (19%) patients were treated with additional corticosteroids for 3-15 days | 99 | Discharged=31% (n=31) Died=11 (11%) Lymphopenia=8 Bilateral pneumonia=7 Hypertension=3 | Limited sample size |

*Contd...*
Table 2: Contd...

| Study details | Therapeutic strategy | Sample size | Outcome | Comments |
|---------------|----------------------|-------------|---------|----------|
| Jun et al.[89]| Treatment arm - HCQ 400 mg per day for 5 days plus conventional treatments | 30 | Though all patients showed good prognosis, no significant difference between both the arms in terms of median duration from hospitalization to virus nucleic acid-negative conservation, median time for body temperature normalization | Small sample size |
| | Control group - Conventional treatment only | | | |
| Gautret et al.[39] | Treatment arm - Oral HCQ sulfate 200 mg, three times per day during 10 days | Initially estimated 42, finally 36 patients (20 HCQ-treated patients and 16 control patients) | Virological clearance at day-6 postinclusion - 100% of patients treated with HCQ and azithromycin combination were virologically cured Comparing with 57.1% in patients treated with HCQ only | 6 patients receiving HCQ removed - 3 transferred to ICU indicating worsening of symptoms, HCQ could have been given in these patients to evaluate the efficacy Limited sample size, as well as failure to achieve estimated sample size Results of ongoing RCTs are required to measure the efficacy |
| | Control arm Among HCQ-treated patients, six patients received azithromycin (500 mg on day 1 followed by 250 mg per day, the next four days to prevent bacterial super-infection) | | | |
| | Supportive therapy if required (invasive ventilation vs. noninvasive) | | | |
| Grein et al.[41] | Loading dose of 200 mg of remdesivir intravenously on day 1, plus 100 mg daily for the following 9 days (total duration of therapy - 10 days) | 61 patients who received at least one dose of remdesivir, data from 8 could not be analyzed Finally, data of 53 patients was analyzed | 36 patients (68%) had an improvement in oxygen support A total of 25 patients (47%) were discharged 7 patients (13%) died Mortality was 18% (6 of 34) among patients receiving invasive ventilation 5% (1 of 19) among those not receiving invasive ventilation | Results of ongoing RCTs are required to measure the efficacy |
| | Supportive therapy if required (invasive ventilation vs. noninvasive) | | | |

SFJDC=Shufeng Jiedu Capsule, RCTs=Randomized controlled trials, HCQ=Hydroxychloroquine, ICU=Intensive care unit

has been included which talks about research during humanitarian emergencies and disaster conditions.[91] These guidelines include the actions taken to ensure the safety and dignity of the affected population and prevent any stigmatization toward the affected individual. However, the burden of the outbreak is to be notified by public health authorities. During such outbreaks, the ethics committee can conduct unscheduled meetings either through video conference or teleconference even if physical presence would not be possible within a given timeframe.

Research requiring ethics preparedness during an outbreak involves details about the epidemiology of the disease, host/vector description, validation of diagnostics, potential treatment strategies along with safety and efficacy data, preventive measures to be undertaken, storage and transportation of biological samples, teamwork at either regional/national/international levels as well as public/private sectors, and lastly monitoring of all these in order to obtain a rewarding result. Robust ethical review should be carried out by the ethics committee during an emergency. Informed consent is a must if any clinical trial is to be conducted and the participant should be able to read and understand it well. In case of infectious disease outbreak, patients need to be quarantined. In such a situation, apart from the routine standard care and treatment, the patient has to be given supportive care so that he/she is able to overcome the mental stress. Disclosure of patient information to any unauthorized person is not at all acceptable. Under the Drugs and Cosmetics Act 1940, The NDCT Rules was launched in March 2019, which includes provisions to permit fast-track approval process for the usage of unapproved drugs during public health emergencies.[92] Crucial areas of ethics preparedness during an outbreak such as SARS-CoV-2 infections have been discussed below. Building public trust by maintaining transparency, accountability, maintaining their societal value, and proper communication with the patients and representatives are of utmost importance. In addition to it, the community has to be educated regarding the outbreak, mode and rate of transmission, and preventive measures such as maintaining social distancing and hand hygiene in order to prevent the rapid spread of infection. Every measure should be taken at the earliest to prevent community transmission. People should be informed and educated regarding the false information floating in various social media platforms. The WHO and ICMR have been playing an important role in educating people regarding COVID-19 by drafting guidelines and answering to frequently asked questions by the general public. Media has also a major role to play in providing correct information about the ongoing disease in the
country and across the globe. Apart from protecting the public rights, ethics preparedness should also take into consideration the safety of the health-care workers or any frontline workers. They should be provided with PPE as they come into contact with the patients while treating them. It is the responsibility of every citizen of India to follow the rules laid down to fight against this pandemic. Therefore, ethics preparedness ensures standard of care in all the aspects without compromising on human safety and ethical values in order to deal during public health emergencies.

**Conclusion**

COVID-19 is a highly contagious disease caused by SARS-CoV-2. The disease may vary from asymptomatic cases, mild symptoms to life-threatening complications such as ARDS, multiorgan failure, sepsis, and death. In particular, elderly with comorbid conditions are at higher risk. COVID-19 is a pandemic, hence drug repositioning that is “old pills for new indications” is being tried worldwide. Globally, hundreds of clinical trials are ongoing to evaluate the efficacy of these old drugs in SARS-CoV-2 infection. The WHO has also planned a large global trial known as “Solidarity Trial” mainly to generate a robust clinical evidence to combat this pandemic. As there is no specific treatment till date, prevention is the only measure to contain the infection. Even a small negligence in following the preventive measures would be very expensive for the mankind. The ICMR has given some recommendations regarding COVID-19 prevention and treatment. However, these recommendations are based on the present current evidence and may change once robust clinical data is generated. The famous quote says “United we stand and divided we fall.” Therefore, it is the duty of every citizen of India to abide by the rules and regulations led by our government, let’s come together and fight against this pandemic.

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**Conflicts of interest**

There are no conflicts of interest.

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