

COVID-19, a threat to human and animals and its probable treatment options to mitigate this pandemic

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Abstract

In late December 2019, Wuhan city of Hubei province, China faced a newly emerged highly contagious viral zoonosis mainly characterized by respiratory illness, associated with pneumonia of unknown etiology which claimed many lives. The virus was then provisionally designated as 2019-nCoV by WHO and officially named as Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) by International Committee on Taxonomy of Viruses (ICTV). On 11 Feb 2020, WHO officially announced the name of disease as Coronavirus disease 2019 (COVID-19) and declared the global pandemic on March 11, 2020. Initially, the disease was highly restricted to China but later it scared the world because hugenumber of new cases was reported from the entire world in a short period of 5 months. The dynamic spread of this contagious virus occurred due to exposure of individuals from infected aerosols, community contact and travelling of affected individual worldwide. Bats were thought to be the initial source of this pandemic but the intermediate host of this zoonosis is yet to be established. Many studies reported fever, dry cough, dyspnea, generalized weakness, anosmia, ageusia, muscle ache, rhinorrhea, headache, nausea, conjunctivitis, vomiting and diarrhoea along with many non-specific symptoms as clinical signs of the disease. Many treatment regimen including various antivirals, antibiotics, neutralizing antibodies, repurposed drugs and traditional medicines were being explored but the authorized effective treatment regimen is still awaited. This review is aimed to summarize the current scenario and status of probable treatment options available for ongoing illness caused by the novel coronavirus.

Key words: Coronavirus; COVID-19; SARS-CoV-2; treatment

Introduction

On 31 December 2019, pneumonia of unknown etiology in a cluster of cases, epidemiologically linked to a seafood and game animal market namely Huanan in Wuhan was officially announced by the health commission of Hubei province, China (Huang *et al.*, 2020; Zhu *et al.*, 2020). The newly emerged virus was formerly called as the “Wuhan virus”, and designated provisionally as “2019-nCoV” by WHO but later on, it was officially declared as SARS-CoV-2 (Gorbalenya *et al.*, +2020). The reports on the SARS-CoV-2 provided a clue for the involvement of bats as initial source of this pandemic in China (Rodriguez-Morales *et al.*, 2020). Moreover, the initial transmission of the virus is reported to occur via exposure of the individuals to the seafood market but with time, animal to human and human to human spread was also reported (Chan *et al.*, 2020a; Phan *et al.*, 2020). As per reports, COVID-19 transmission to cats, dogs, tigers, and lions has been documented, with clinical signs such as dyspnoea, dry cough, vomiting, diarrhea, and wheezing suggesting its zoonotic potential leading to its spread in multiple animal species, including domestic and wild animals (Chini, 2020; Gollakner and Capua, 2020). In addition, Pigs, cats, ferrets, and primates have also been identified as good candidates for susceptibility to SARS-CoV-2 (Gollakner and Capua, 2020).

The virus spread like wild fire in short period of time and claimed many lives which forced the WHO to declare it as a pandemic on March 11, 2020. The virus has infected more than 133 millions of people and claimed more than 2.9 millions human lives as of 8th april 2021, (<https://www.worldometers.info/coronavirus/>). The newly emerged SARS-CoV-2 is reported as the 7th coronavirus responsible to infect humans, which mainly targets the lower respiratory tract of humans (Bassetti *et al.*, 2020). As per available report, the clinical signs of the disease includes fever, sneezing, dry cough, chest pain, ageusia, anosmia, pneumonia, conjunctivitis, headache, impaired hearing, dizziness with bilateral consolidation and ground glass appearance of the lungs on computed tomography (CT) (Bassetti *et al.*, 2020; Huang *et al.*, 2020). Recent data revealed the COVID-19 associated deaths were mainly attributed to respiratory failure as a result of pneumonia caused by hyperinflammation (Huang *et al.*, 2020). Moreover, COVID-19 has a higher fatality rate in elderly individuals with immunocompromised state than that of healthy person (Huang *et al.*, 2020). Diagnostic techniques viz. conventional RT-PCR, one step real-time RT-PCR, whole genome sequencing, capture-based next-generation sequencing (NGS), phylogenetic and genome analysis along with advanced diagnostics like microarray-based tests, fluorescence-based quantitative PCR and capture-based NGS are being explored for the rapid and simultaneous detection of SARS-CoV-2 with other pathogens (Huang *et al.*, 2020; Zhu *et al.*, 2020).

So far, no effective antiviral treatment has been reported although drugs (lopinavir, remdesivir and ritonavir) and neutralizing antibodies are found effective in case of other two coronavirus epidemics (SARS-CoV and MERS-CoV) and trials to study the efficacy of these agents in COVID-19 are in pipeline (Huang *et al.*, 2020; Yu *et al.*, 2020). In addition, chloroquine, hydroxychloroquine and ivermectin were found effective against SARS-CoV-2 and are under validation for their use in COVID-19 patients (Gao *et al.*, 2020).

In past two decades, coronavirus epidemics like SARS, MERS and Swine Acute Diarrhea Syndrome (SADS) have always been a matter of concern and interestingly bat corona viruses were linked with these episodes which claims thousands of lives (Perlman, 2020). Therefore, learning from the past detailed study on development of new animal and *in-vitro* models are necessary in order to understand the permissiveness, transmissibility and pathogenesis of the SARS-CoV-2. In this review, the most recent information on our current understanding of available treatment options is discussed.

The virus

An official name for the virus which has left the world in a state of persistent shock has been suggested as SARS-CoV-2 by the International Committee on Taxonomy of Viruses (ICTV) (Gorbalenya *et al.*, 2020). The SARS-CoV-2 is a member of the sub-family *Orthocoronavirinae* under the family *Coronaviridae* in the order *Nidovirales* (Zhu *et al.*, 2020). The sub-family *Orthocoronavirinae* is sub-divided into four genera, viz. *Alphacoronavirus*, *Betacoronavirus*, *Gammacoronavirus*, and *Deltacoronavirus*, as per the ICTV. The genera *Alphacoronavirus* and *Betacoronavirus* originate from bats whereas the *Gammacoronavirus*, and *Deltacoronavirus* are evolved from birds and swine gene pools (Li *et al.*, 2020a). On the basis of molecular characterization, SARS-CoV-2 is considered as a new betacoronavirus, which belongs to the subgenus *Sarbecovirus* (Zhu *et al.*, 2020). Although other important zoonotic viruses such as MERS-CoV and SARS-CoV also belong to the same genera, SARS-CoV-2 was shown to be a distinct virus as the percent identity between SARS-CoV-2 and other *Betacoronavirus* on the basis of conserved ORF 1ab was found to be less than 90% (Zhu *et al.*, 2020). Phylogenetic analysis on the basis of the structural genes also revealed that SARS-CoV-2 was closest to bat CoV. Thus, it was postulated that SARS-CoV-2 might have originated from bats, even though other amplifier hosts such as pangolin could have also been involved (Chan *et al.*, 2020).

Clinical signs and symptoms

The clinical signs and symptoms associated with the COVID-19 mainly depend upon the severity of the disease and immune status of the individuals. The severe form of the disease have been mainly reported in elderly and immunocompromised individual with a history of hypertension, cardiac vascular disease and diabetes (Huang *et al.*, 2020). Moreover, the asymptomatic or mildly symptomatic nature of the illness is a major hurdle in identifying the transmission chains and its subsequent tracing (Lee and Hsueh, 2020).

The incubation period of the disease is highly variable and an estimated incubation period of 3-6 days with a mean value of 5.2 days has been reported (Huang *et al.*, 2020; Li *et al.*, 2020b). Generally, the virus causes fever, generalized weakness, ageusia, anosmia, muscle ache, respiratory distress, rhinorrhea, dry cough, dyspnoea, pleuritic chest pain, headache, haemoptysis, nausea, hearing disorders, vomiting and diarrhoea (Huang *et al.*, 2020; Ollarves-Carrero *et al.*, 2020).

Diagnosis

As per WHO report, the most appropriate clinical samples include nasopharyngeal and oropharyngeal swabs/lavage (Upper respiratory tract), expectorated sputum, endotracheal aspirate, bronchoalveolar lavage (Lower respiratory tract), blood and serum (WHO, 2020). However, the sensitivity of detection in nasopharyngeal and oropharyngeal swab alone is low compared to bronchoalveolar lavage. Currently, the pooled nasopharyngeal and oropharyngeal swab is used for the testing of COVID-19 in molecular diagnostic labs using RT-PCR. Later on, for quick detection of the illness and viral nucleic acid more sensitive and accurate assays were designed. In this context application of imaging techniques like CT imaging along with conventional molecular diagnostic tests targeting primarily *RdRp* and *S* gene viz. in house conventional RT-PCR, one step real-time RT-PCR and whole genome sequencing were widely explored (Huang *et al.*, 2020; Zhu *et al.*, 2020).

Treatment

Till date, there is no definite antiviral drug available for treatment of COVID-19, therefore for treatment and containment of the newly emerging coronaviruses, a novel adaptive cell-based approach is utmost necessary for effective screening of antiviral agents with pan-coronaviral effects (Kilianski and Baker, 2014). The chloroquine, ivermectin, and certain antiviral drugs such as interferon- γ , lopinavir/ritonavir, ribavirin have been used for the treatment of COVID19 currently using the limited evidences available through drug repurposing approaches (Simsek Yavuz and Unal, 2020).

Two important categories of drugs viz. immunomodulators and nucleoside analogues are used in coronavirus infections. And the commonly used antiviral therapies against corona viruses include antiviral agents (ribavirin, lopinavir, ritonavir etc.), interferons or the combination of both (Omraniet *et al.*, 2014). However, agents like oseltamivir, paramivir, zanamivir, ganciclovir, acyclovir and ribavirin used in the treatment of viral infection are not recommended for SARS-CoV-2 (Li *et al.*, 2020c). Combination of lopinavir and ritonavir used in humans for the treatment of human immunodeficiency virus (HIV) have reported to be clinically beneficial in SARS-CoV and MERS-CoV infection, however its safety and efficacy in COVID-19 is yet to be determine (Huang *et al.*, 2020; Lu, 2020). In this context, clinical studies involving early combination therapy of lopinavir-ritonavir, along with interferon-beta in the treatment of COVID-19 patients demonstrated shortening of the duration of viral shedding and reduced hospital stay (Hung *et al.*, 2020). An antiviral drug viz. remdesivir which was reported to be effective in MERS-CoV infection and had also completed phase III trial for Ebola is now thought to be a potential candidate for the SARS-CoV-2, however these data are insufficient to support its application in treatment of COVID-19 (Holshueet *et al.*, 2020; Lu, 2020). Additionally, as per report the *in vitro* application of remdesivir and chloroquine has been found effective in COVID-19 treatment (Gao *et al.*, 2020). Moreover, due to easy availability and cost effectiveness of the chloroquine and its analogue viz. hydroxychloroquine they may prove crucial in clinical management of COVID-19 patients after proper evaluation of its efficacy and safety by clinical trials. As reported earlier, interferons were reported to be effective in SARS-CoV and MERS-CoV infections with little clinical significance (Loutfy *et al.*, 2003; Chan *et al.*, 2013) and therefore its use have also been observed against COVID-19 (Sheahan *et al.*, 2020).

Application of therapeutics like RNA synthesis inhibitors, umifenovir (arbidol), tenofovir disoproxil (TDF), lamivudine (3TC), hormones and conventional Chinese capsules viz. ShuFengJieDu and Lianhuaqingwen were reported in treatment of SARS-CoV-2 infection but their *in-vivo* and *in vitro* efficacy are yet to be determined (Lu, 2020). *In vitro* efficacy of arbidol (an anti-influenza drug) at a concentration range of 10-30 μ M has been reported against COVID-19 (Wang *et al.*, 2017). Moreover, in China, a conventional anti-influenza drug - SFJDC has been recommended against COVID-19 (NHC, 2020). According to Zumla *et al.*, 2020, host-directed therapies

might be a safe alternative against SARS-CoV-2. In this context, drugs like glitazones, fibrates, metformin, sartans, and atorvastin, nutrient supplements, and zinc based supplements or other drugs with a good safety profile can serve the purpose (Zumlaet *et al.*, 2020).

Recently, Defense Research and Development Organisation (DRDO), India proposed treatment 2-deoxy-D-glucose (2-DG) drug as possible treatment option for COVID-19. DRDO, in a statement on Saturday, said the 2-deoxy-D-glucose (2-DG) drug can provide early relief from oxygen dependency among the patients, which can be helpful as the second Covid-19 wave rages on across the country, and more patients continue to need medical oxygen. In this context, The DRDO statement mentioned that “clinical trial results have shown that this molecule helps in faster recovery of hospitalized patients and reduces supplemental oxygen dependence” and a “higher proportion of patients treated with 2-DG showed RT-PCR negative conversion in Covid patients”. Subsequently, the Drugs Controller General of India (DCGI) granted emergency use permission on May 1, “as adjunct therapy in moderate to severe” patients”. The drug has been developed by DRDO’s Institute of Nuclear Medicine and Allied Sciences (INMAS) in collaboration with Dr Reddy’s Laboratories, Hyderabad. (<https://indianexpress.com/article/india/drdo-covid-treatment-drug-gets-emergency-use-nod-7307559/>).

An herbal concoction Coronil, is also classified as a “supportive treatment” for COVID-19 patients by the Ayush Ministry of Indian Government leading to widespread availability of the medicine even without a prescription. In this context, the developer of the medicine i.e. Patanjali has cited a small study featuring around 100 young and healthy Covid-19 patients with mild symptoms to support its claims about Coronil’s effectiveness in treating the disease, but experts warn it is difficult to draw any real conclusions from such a small trial. Tests conducted by Birmingham University also found that the Coronil pills contained plant-based ingredients that cannot protect against COVID-19, according to the BBC (<https://www.forbes.com/sites/siladityaray/2021/05/07/search-interest-in-coronil-a-false-covid-cure-soars-in-india-as-pandemic-rages/?sh=4ce3c68c22fb>).

Rapid spread of the disease and simultaneous enhancement of knowledge in clinical profile of the patients reveals exhibition of cytokine storm syndrome in SARS-CoV-2 infection, where release of proinflammatory cytokines including marked elevation of IL-6 has been noted (Mehta *et al.*, 2020). In severe cases, blocking of cytokine receptor might prove beneficial in COVID-19 patients with hyperinflammation. In this context, the IL-6 receptor targeted monoclonal antibody tocilizumab was found effective in quick control of fever and enhancement in the respiratory function severely affected COVID-19 patients (Cao, 2020). Moreover, the targeting of IL-6 with its receptor by neutralizing monoclonal antibodies like tocilizumab and Siltuximab could prevent the cytokine storm and associated clinical symptoms in severe SARS-CoV-2 infection (Liu *et al.*, 2020).

As reported earlier, neutralizing antibodies specific for receptor binding domain (RBD) in spike (S) protein of SARS-CoV (Traggiai *et al.*, 2004) and MERS-CoV infection (Corti *et al.*, 2015; Chen *et al.*, 2017) were successful in treating those infections, so it was proposed that as long as, the SARS-CoV-2 shares the sequences with other two viruses in the RBD, neutralizing antibodies may be effective in treating the illness (Yu *et al.*, 2020). Moreover neutralizing monoclonal antibodies isolated against SARS-CoV, like CR3022 (terMeulen *et al.*, 2006; Tian *et al.*, 2020), was reported to cross react to the receptor binding domain of SARS-CoV-2 suggesting that SARS-CoV vaccines may also provide protection against SARS-CoV-2. Interestingly, nanobodies identified by a mass spectrometry-based technique in llama’s blood is also reported to bind to SARS-CoV-2 most strongly, hence can be fashioned into inhalable therapeutics to treat the COVID-19 infection (Hanke *et al.*, 2020).

Convalescent plasma is also being explored as treatment option for COVID-19 and in laboratory confirmed COVID-19 cases resolution of ground glass opacities along with lung consolidations were reported after treatment with convalescent plasma. Moreover, convalescent plasma transfusion was found to be safe in the COVID-19 patient under treatment and following the transfusion a rapid increase in the neutralizing antibodies levels was reported (Ye *et al.*, 2020; Duan *et al.*, 2020). Hence, convalescent plasma may prove crucial as an effective prophylactic measure against SARS-CoV-2.

Use of corticosteroids has been reported as a part of routine treatment in SARS-CoV-2 infection to curtail the lung injury induced by cytokines (Th1 and Th2) (Huang *et al.*, 2020; Soyat *et al.*, 2020). Recently, dexamethasone (a corticosteroid) has been proven to significantly decrease the mortality in critically ill COVID-19 patients on ventilation and oxygen by as much as 35% and 20% respectively and declared as the world’s first treatment found effective in reducing the mortality risk among critically ill COVID-19 patients. However, the dexamethasone has been authorized by the U.K. government for treating critically ill COVID-19 patients but no clinical benefits were reported in patients with mild, moderate and hospitalized COVID-19 patients not requiring oxygen or ventilation (Ledford, 2020).

Ventilation and salvage therapy using extracorporeal membrane oxygenation are reported to manage the severity of hypoxia in infected patients. Before discharging the patients it is advisable to perform repeated test for SARS-CoV-2 in respiratory swabs, ensure the improvement in lungs using CT imaging and check for decline in

fever for minimum 10 days (Huang *et al.*, 2020). Identification and development of new treatment regime with potential drug is important to curb the COVID-19 and limit the fatalities.

Conclusion and future prospects

Although an effective vaccine and treatment regimen may reduce the suffering of humankind from this deadly virus but the pandemic raised a serious question over our preparedness and already left the world in a state of great loss. This pandemic revealed all the shortcomings of pandemic preparedness and raised a question to be answered by the global researchers. Moreover, the researchers tried their best to find out the treatment of COVID-19 but they could not succeed up to the satisfactory level. In addition, all the treatment regimen tested against the COVID-19 were from old experiences and traditional medicine as there is no standard protocol and pathway is available to be followed step by step in order to develop a new drug against a highly contagious newly emerged virus. In this context, a holistic approach with one health concept and strategic planning for pandemic preparedness, rapid development of treatment regimen along with strict surveillance and monitoring of pathogens with zoonotic potential is highly warranted.

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