

Management of COVID-19: Review of Literature

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Abstract

COVID 19 has taken the world by surprise. Slowly transforming into a pandemic, COVID-19 has taken the lives of thousands and affected millions. The emerging data on diagnosis and management of COVID-19 is rapidly changing and physicians have remained on toes to keep themselves well updated so as to diagnose and manage the patients in the best possible way. This review highlights the management of COVID-19 focusing on the emerging data with respect to the severity of the disease.

Keywords: COVID-19; SARS- CoV-2; Management; Antiviral Drugs

Introduction

Initially identified in Wuhan, China as a cause of cluster of cases causing pneumonia, Corona virus disease (COVID-19) has emerged as one of the fatal and contagious diseases that has affected people in all aspects of their lives [1]. The organism was isolated by Chinese Centre for Disease Control and Prevention and it was named as Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) later to be named as COVID-19 by WHO [2]. Majority of the patients usually manifest symptoms of mild or moderate disease. While few especially those with co-morbidities and those who are elderly progress to severe disease leading to ARDS and multi-organ dysfunction [3].

Disease has been broadly classified into mild, moderate, severe and critically ill stage. A mild disease is one in which there is low grade fever with symptoms of upper respiratory tract infection followed by moderate disease which consists of shortness of breath with high grade fever but with no changes in mental status. A severe disease is one which has Respiratory rate $> 30/\text{min}$, $\text{SPO}_2 \leq 93\%$, $\text{PaO}_2/\text{FiO}_2$ less than 300 with confusion, agitation and restlessness. A patient with septic shock, multiorgan dysfunction and respiratory failure requiring mechanical ventilation is classified as critically ill [4]. Severity of the disease along with management is briefly mentioned in table 1.

Review of selected drugs

Anti-viral

Lopinavir/ritonavir

Lopinavir and ritonavir were initially approved by FDA for HIV. Both of these drugs have shown some *in vitro* activity against other novel corona viruses [5,6]. The addition of lopinavir/ritonavir to the treatment of severe acute respiratory syndrome has also shown association with decreased death rate and improved clinical outcome in certain studies [7]. A randomized controlled open label trial involving hospitalised patients infected with SARS-CoV-2 was conducted. No benefit was observed in lopinavir/ritonavir group beyond

Severity	Symptoms	Management
Mild disease	<p>Symptomatic patients without any hemodynamic compromise including:</p> <ul style="list-style-type: none"> • Cough • Fever • Muscular pain • Loss of sense of smell and taste • Malaise • Sore throat • Gastrointestinal distress like nausea, diarrhea 	<p>Supportive treatment including:</p> <ul style="list-style-type: none"> • Antipyretics • Proper nutrition • Hydration • Antibiotics are not recommended until there is evidence of superimposed bacterial infection • Watch for warning signs and symptoms like shortness of breath, hypoxia, agitation, confusion, chest pain.
Moderate disease	<p>Signs of pneumonia:</p> <ul style="list-style-type: none"> • Fever • Cough • Fast breathing • SpO₂ ≥ 90% • Infiltrates on Chest X-ray 	<p>Supportive treatment including:</p> <ul style="list-style-type: none"> • Oxygen via nasal cannula/face mask • Proning • Antibiotics are not recommended until there is evidence of superimposed bacterial infection <p>Pharmacotherapy:</p> <ul style="list-style-type: none"> • Remdesivir • Tocilizumab/Corticosteroids if there is an evidence of cytokine release syndrome
Severe disease	<ul style="list-style-type: none"> • Fever • Suspected respiratory tract infection with fever, cough, dyspnea including any one of the following: <ol style="list-style-type: none"> 1. Respiratory rate > 30 breaths/min 2. severe respiratory distress 3. SpO₂ < 90% on room air 	<p>Supportive treatment including:</p> <ul style="list-style-type: none"> • Supplemental oxygen therapy • Prone positioning • Non-invasive ventilation • Invasive ventilation if severe respiratory distress, shock, cyanosis, shock, coma or convulsions • Antibiotics as per local guidelines <p>Pharmacotherapy:</p> <ul style="list-style-type: none"> • Remdesivir • Convalescent plasma • Tocilizumab/Corticosteroids if there is an evidence of cytokine release syndrome • Anticoagulation if no contraindication

<p>Critically ill</p>	<p>Any one or more of the following:</p> <ol style="list-style-type: none"> 1. ARDS 2. Septic shock 3. Multiorgan dysfunction 	<p>Supportive treatment including:</p> <ul style="list-style-type: none"> • Supplemental oxygen therapy via <ol style="list-style-type: none"> 1. Nasal cannula/Face mask 2. High flow nasal oxygen • Prone positioning • Non-invasive ventilation • Invasive ventilation if severe respiratory distress, shock, cyanosis, shock, coma or convulsions • Antibiotics as per local guidelines • Vasopressors <p>Pharmacotherapy:</p> <ol style="list-style-type: none"> 1. Remdesivir 2. Convalescent plasma 3. Tocilizumab/Corticosteroids if there is an evidence of cytokine release syndrome 4. Anticoagulation if no contraindication
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Table 1: Severity of the disease and management of COVID-19.

standard care [8]. Lopinavir and ritonavir are also associated with adverse effects like hepatotoxicity and gastrointestinal distress including diarrhea and nausea which can be further exacerbated in a setting of viral illness like SARS-CoV-2. Hence for now this combination of Lopinavir/Ritonavir is reserved for HIV patients and not routinely recommended for the management of SARS-CoV-2.

Ribavirin

Ribavirin an antiviral agent has been used effectively in past against hepatitis C. It gets incorporated in the RNA of virus and prevents its elongation, hence hindering its replication [9]. Although *in vitro* studies have shown promising role of this drug against COVID no studies are available in to assess its role in treating COVID-19 in human beings [10]. Moreover, its side effect of decreasing hemoglobin makes its unfavorable to use in patients with respiratory distress [11,12]. Hence its use is not recommended in treatment of COVID.

Favipiravir

Favipiravir is a broad-spectrum antiviral agent active against RNA viruses. It acts by inhibiting RNA dependent RNA polymerase and hence prevent its proliferation [13]. It has activity against several RNA viruses including influenza and viruses causing hemorrhagic fever like Ebola virus. Covid-19 is a positive sense RNA virus and studies have evaluated activity of Favipiravir against it [14,15]. A nonrandomized control study in china including 80 patients with moderate COVID-19 showed radiological improvement in 91.4% of patients receiving Favipiravir as compared 62% in control arm receiving lopinavir/ritonavir [14]. Although preliminary results seem promising there is still need of RCTs evaluating its role and comparing its efficacy with other antiviral agents.

Remdesivir

Remdesivir (RDV) is an investigational antiviral drug, which is a nucleotide prodrug that is currently being tested in extensive clinical trials for the treatment of COVID-19. It was first developed by Gilead Sciences, an American pharmaceutical company, to the response of 2014 Ebola virus outbreak in West Africa. RDV is metabolized to its active triphosphate form and inhibits the action of RNA-dependent RNA polymerase of SARS-COV-2. Though the RDV is not approved by the FDA, still the “Emergency Use Authorization” (EUA) for compas-

sionate use in severe cases is recommended [16]. Recently in Lancet published a trial that found no reduction in deaths with RDV, however in the preliminary report of randomised, double-blinded, placebo-controlled trial involving 1063 patients, conducted by National Institute of Allergy and Infectious Diseases (NIAID), they reported that RDV was better in terms of time of recovery. Their results revealed patient on RDV has 31% faster time to recovery than who received placebo ($p < 0.001$) and there was difference of 4 days in recovery between two groups. Results also suggested a survival benefit, with a mortality rate of 8.0% for the group receiving RDV versus 11.6% for the placebo group ($P = 0.059$) [4,17]. These early findings support the use of RDV for patients who are hospitalized with Covid-19 and require supplemental oxygen therapy. On the other hand, given high mortality despite the use of RDV, it is clear that treatment with an antiviral drug alone is not likely to be sufficient. Future strategies should be made to evaluate antiviral agents in combination with other therapeutic drugs. The suggested dose of RDV for treatment of COVID 19 is 200 mg intravenous (IV) on day 1 followed by 100mg daily for 9 days (days 2 through 10) infused over 30 - 60 minutes [18]. A lot of important trials and studies are underway as the safety and efficacy of this drug in COVID-19 cases require high-quality evidence from well-designed and adequately-powered clinical trials with proper sample size for precise decision.

Anti-parasitic

Hydroxychloroquine/chloroquine

Hydroxychloroquine (HCQ) and Chloroquine (CQ) are currently being used for treatment and prevention of malaria, amebiasis, and many autoimmune diseases like Rheumatoid Arthritis and Systemic Lupus erythematosus. HCQ (an analogue of Chloroquine) clinical safety profile is better than that of CQ and has been found to have an anti-SARS-CoV activity *in vitro* [19]. Despite the lack of robust evidence HCQ and CQ are among the proposed drugs and are the most widely used so far. On March 28, FDA issued an Emergency use Authorization (EUA) and recommended initial evaluation and monitoring when using HCQ or CQ under the EUA or in clinical trials. ECG, electrolyte and LFTs monitoring are required while its use [20]. Some preliminary reports have suggested that HCQ, alone or in combination with antibiotic azithromycin (AZM) may benefit people with COVID-19. However, several case series and other small randomized trials reported in the National Institute of Health (NIH) treatment guidelines reported conflicting results [21]. The suggested dose under the EUA for CQ to treat adults and adolescents who weigh 50 kg or more is 1 gram of CQ phosphate on day one, followed by 500 milligrams daily for four to seven days of total treatment based on clinical evaluation [22]. The suggested HCQ regimen was a loading dose of 600 mg twice on day 1, followed by 400 mg daily for 4 additional days.

HCQ and CQ are currently being studied in several clinical studies, the evidence for the use of HCQ or CQ in COVID-19 is not good so far, not only because of the negative results but also because of their serious adverse effects. Still there are no significant studies on assessments of HCQ or CQ for prophylaxis against COVID-19.

Ivermectin

Presently being used as a broad- spectrum anti-parasitic agent [23], Ivermectin has shown *in vitro* effects against certain arboviruses and Zika virus. Ivermectin has shown to unlink the preformed IMP $\alpha/\beta 1$ heterodimer which is responsible for the nuclear transport of viral protein cargos. This inhibition interferes with the viral invasion [24,25]. Similar mechanism have been used to test SARS-CoV-2 with Ivermectin and positive results have been obtained with 5000 fold reduction in viral RNA after 48-hours in Ivermectin group [26]. Because of these promising results, Ivermectin warrants further investigation and can play an integral role in the management of COVID-19 as we gather further evidences.

Anti-inflammatory

Azithromycin

Azithromycin (AZM) is a broad spectrum macrolide antibiotic with its well-known action in respiratory tract infections and soft tissue infections. Synergistic antiviral effects of AZM in combination with HCQ on SARS-CoV-2 infection has been seen, which has led to the widespread use of this combination therapy for the COVID-19 pandemic [27]. Recently in France, the combination AZM and HCQ was tried

in the treatment of COVID-19. They studied 1061 patients and suggested the use of AZM and HCQ combination before the occurrence of COVID-19 complications showed low fatality rates [28].

However, many other studies are not supportive of the extensive use of AZM for the treatment of COVID-19 outside of the context of clinical trials, except in possible superimposed bacterial infections [29]. The suggested dose of AZM is 500 mg on day 1 and then 250 mg daily for 4 more days. QT interval prolongation is potential serious side effect of AZM both individually and in combination with HCQ/CQ, therefore caution must be applied if AZ is prescribed to elderly patients with high baseline risk of cardiovascular disease, who are already vulnerable to complications from COVID-19. AZ, CQ and HCQ have long half-life (72 hours, 5 days, 40 days respectively), So, discontinuing one drug and starting another too soon may result in a similar adverse event [30,31]. There are many trials being carried out worldwide to look for efficacy of AZA as alone and in combination with HCQ, the results of which are still pending [20,21].

Tocilizumab

Severe pneumonia in COVID 19 has been linked to dysregulated immune response also known as Cytokine release syndrome (CRS) [32]. The syndrome has been documented in several autoimmune diseases and viral infections including MERS and SARS. IL6 is one of cytokine which has major role in acute inflammation and elevated levels of IL6 have been found in patients with CRS. Tocilizumab is a humanized antibody against IL 6, it has been approved for treatment of Rheumatoid arthritis and Juvenile idiopathic arthritis [33,34]. Considering its role in treatment of CRS its use in severe disease associated with COVID-19 has been studied in several centers with promising results. A single center prospective study from Italy reported the efficacy of Tocilizumab in 100 patients admitted to Spedali Civili University Hospital in Brescia (Italy). All the patient had pneumonia required ventilatory support. Tocilizumab was given in a dose of 8 mg/kg by two consecutive iv infusions and a third dose being optional on basis clinical response. It was noted that 77% of the patients improved or remained stable with 61% showing significant improvement in bilateral opacities and 15% being discharged. 24% showed worsening of respiratory status and 20% died [35]. Although the study shows promising results lack of a comparator decreases its credibility. Several clinical trials are underway to evaluate the role of Tocilizumab in COVID-19 including a double-blind placebo control phase 3 trial approved by FDA [36]. Current recommendation of use of Tocilizumab is at a dose of 8 mg per kg through IV route with a maximum dose of 800 mg [37]. Another case series reported positive results of subcutaneous injection as an alternate route of Tocilizumab administration with clinical improvement and resolution of fever [38]. Common side effects associated with Tocilizumab treatment include serious infections, GI perforation, infusion reactions, anaphylaxis and thrombocytopenia [37].

Corticosteroids

The role of corticosteroids in viral infections has remained controversial, as there has always been concerns of delayed viral clearance and superinfections [39]. These observations lead to reluctance of use of steroids in COVID infection. However, COVID-19 is a complex disease with broad spectrum of manifestations and disease processes. Hence extrapolating findings from other viral infections would be oversimplification of processes. Several observational studies from china and other parts of world have reported potential benefits of steroids in severe pneumonia and ARDS especially if associated with CRS. In retrospective study done in china included 46 patients with severe pneumonia defined by a low saturation and decreased arterial oxygen, were given methylprednisolone in a dose of 1 - 2 mg/kg for 5 - 7 days via IV route. 43 out of 46 patients were discharged and 3 died, common side effect identified was superimposed bacterial infections [20]. In conclusion use of methyl prednisolone leads to improvement in clinical outcomes when used in severe pneumonia associated with COVID-19, however side effects like secondary infections should be kept in mind, which can be dealt with early use of broad spectrum antibiotics. Nonetheless there is imminent need of RCTS to evaluate role of steroids in COVID-19.

Miscellaneous

Convalescent plasma therapy

The concept of passive immunity is quite old and has proved its role time and again in several diseases. The use of convalescent plasma therapy was approved by WHO for Ebola outbreak [40]. Plasma therapy has been used for severe pneumonia caused by COVID-19 and

has showed promising results including resolution of lung infiltrates as well as acceleration of viral clearance from body [41]. However, it is both time dependent and not free from side effects. Convalescent plasma therapy helps in decreasing viremia and hence is beneficial in early phase of disease [42]. Moreover, it can aggravate immune response and mechanism associated with it like Cytokine release syndrome. Common side effects associated with plasma therapy include transfusion related events like fever transfusion associated lung injury and infections like hepatitis B and C [43]. A recent RCT done in Wuhan, China (although terminated early) in which convalescent plasma therapy was added to standard therapy in patients with severe and life threatening COVID-19 showed no statistically significant clinical improvement within 28 days hence more clinical trials are required to evaluate the efficacy as well as side effects profile of convalescent plasma therapy [44].

Conclusion

COVID-19 pandemic is one of the greatest global health crisis seen in the centuries. The fast upcoming data on the management emphasizes the need of evidence to tackle this pandemic. The rapid pace at which the data is getting published and the new evolving recommendations remains the top most limitation of this review.

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