Review Article

Home management of mild-moderate coronavirus disease-19 patients in low-resource countries: Reducing the burden on hospitals and a guide to clinical excellence

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ABSTRACT

The severe acute respiratory syndrome coronavius-2 (SARS-CoV-2) pandemic since when it was reported from Wuhan, China, in December 2019 has spread dramatically and rapidly affecting all countries and territories of the world. The morbidity and mortality rates of coronavirus disease (COVID-19) continue to climb each day with over 88 million people infected and more than 2 million deaths reported worldwide. This puts health-care systems and health-care professionals/providers (HCPs) at risk. At present, the health-care systems of the poor and low resource are unable to cope with these extremely difficult circumstances. The main objective of this article is to serves as a guideline for treating patients with mild or moderate symptoms of COVID-19 at home in over to reduce the already over burden health infrastructure, especially in developing nations. With the permission of the ethical committee of the institutions COVID-19 case management team, this article reviewed protocol-based guideline aimed at infection prevention and control to protect the health worker, the patient, his relatives, and the community and also drug treatment to help prevent the progression of the disease to severe or critical. The home treatment guideline will help poor and low-resource countries cope with the increase in number of patients with COVID-19 and ameliorate the negative effects on health-care resources for such countries that are already burden by poor or limited health system infrastructure, low workforce, and inadequate expertise to cope with the rapidity with which the virus spread.

KEYWORDS: Coronavirus Disease; Hydroxychloroquine; Azithromycin; Antithrombotic; Personal Protection Equipment

INTRODUCTION

More than 1 year since the first case of coronavirus was reported from Wuhan in China, the virus has continued to spread globally leading to widespread of coronavirus disease (COVID-19) infection. Worldwide over 88 million (88M) people have been infected with over 2 million (2M) deaths recorded and over 50 million (50M) recoveries.[1] Because of the rapidity and highly communicable nature of spread of COVID-19, the numbers of patients who test positive to the SARS-CoV-2 by reverse transcription polymerase chain reaction (rt-PCR) far outnumber the available bed spaces in the designated COVID-19 isolation and treatment centers and also hospitals designated as COVID-19 treatment centers.[2] Unlike what is obtained in the developed countries, low-resource countries suffer from lack of public awareness, inadequate infrastructures, and low human resources and they do not have adequate experts to manage patients with COVID-19 which is rapid spreading, especially the severe cases who may require mechanical ventilation or

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high-flow oxygen therapy.[3] The inadequate workforce found in low-resource countries is already overburdened by patients with common diseases of the tropics such as malaria, HIV/AIDS, cholera, and pneumonia and high maternal mortality rate from hemorrhage, hypertensive disorders in pregnancy, anemia, obstructed labor in addition to surgical patients, and diseases such as hypertension, diabetes, asthma, and sickle cell diseases seen on outpatient basis. This problem is further compounded by elevated cost of drugs, the scarcity of personal protection equipment (PPE) such as Tyvek suits, N95 face masks, inadequate daily consumables, and the lack of ventilators and intensive care unit beds.[3,4]

During epidemic or pandemic, these low-resource countries with poor financial resources must prioritize patients based on presentation.[4] Patient who requires in-hospital management is admitted and attended to while those who will do well at home are seen and attended to before they are allowed to go home and continue home care. Prioritization must be science based to avoid increase in morbidity and mortality. With the rapid spread of COVID-19, even developed countries find some difficulties in decisions that have to do with allocation of health-care supplies. A critical care specialist may experience difficulty in allocating a mechanical ventilator to two patients who both require assisted ventilation in a setting with only one ventilator available.

Despite these enormous challenges, low-resource countries must try as much as possible to prevent the rapid spread of this virus in other to reduce the morbidity and mortality associated with contracting the disease while at the same time protecting the healthcare workers, members of the family, and the public through strict adherence to infection prevention and control measures.

It is desirable also for these countries to derive and adopt methods to learn to leave with the virus while going about their normal daily life activities as was done with tuberculosis.

PROTECTING THE HEALTH WORKERS

Health care workers (HCWs) play a key role in relieving the pains and sufferings of the sick while also doing their best to save lives. The pandemic has placed extraordinary levels of psychological stress on health workers ranging from family separation, long hours of shift, fear of contracting the virus themselves, social stigmatization, etc. It is important to protect them from contracting diseases during pandemic so that they can continue to provide care to the sick.

For the HCW involve in home management, review of patients should mostly be by phone calls and occasional in person visit if necessary. Where in person visit is necessary, appropriate PPE should be worn (Tyvek's suits with head hood, goggles, boots, gloves, etc.).[5-7]

Simple but detailed instructions should be given to the patient on what to do if they become ill or their symptoms progresses. There should be an uninterrupted communication link between the HCW and the patient and members of his family.

PROTECTING THE PATIENT'S FAMILY AND THE COMMUNITY

The patient's family members and the community should also be protected from contracting the virus. The HCWs should educate both patient and the entire household members about infection prevention and control measures. These include but not limited to regular hand washing and use of hand sanitizers, wearing of facemask, improve cleanliness, and disinfection with chlorinated solutions. Patient should stay and remain isolated in a well-ventilated room if possible separated from the main house with limited movement in the house. The number of caregivers should be limited and both patient and family should be advised to seek care if there is change in the condition of the patient.

SELECTION OF PATIENTS FOR HOME CARE

Hospitalization of patients who tested positive to rt-PCR for SARS-CoV-2 presenting with mild-to-moderate symptoms may not be possible because of the burden on the health-care system. In patients with mild-to-moderate illness, providing care at home may be considered, as long as they can be followed up and cared for by family members and are without underlying chronic conditions such as lung or heart disease, renal failure, or immune-compromising conditions. This decision requires careful clinical judgment and should be informed by an assessment of the safety of the patient's home environment. Home care may also be considered when inpatient care is unavailable or unsafe (e.g., capacity is limited, and resources are unable to meet the demand for health-care services). Good patients for home management include those aged ≤50 years, who are asymptomatic or have mild symptoms, oxygen saturation on room air ≥95%, and available space for self-isolation at home. Cautiously, patients aged 50–70 years who are clinically stable, asymptomatic without any history of comorbidity may be considered.[8]

RECOMMENDED THERAPY

Medical therapies to treat COVID-19 is growing and evolving rapidly. It is recommended that clinicians regularly update their knowledge with treatment guidelines that are regularly reviewed based on scientific evidence and expert opinion. Where drug treatment is needed, early and effective treatment can help avert progression to more serious illness, thereby helping to reduce the burden on health-care system.

HYDROXYCHLOROQUINE (HCQ)

HCQ is an antimalarial/anti-inflammatory drug that impairs endosomal transfer of virions within human cells. HCQ is also a zinc ionophore that conveys zinc intracellularly to block the SARS-CoV-2 RNA-dependent RNA polymerase, which is the core enzyme of the virus replication. Studies have suggested that HCQ is effective in fighting COVID-19.[9,10] A global HCQ/CQ study involving 230 HCQ studies and 165 peer review showed that early treatment is most successful, with 100% of studies reporting a positive effect and an estimated reduction of 67% in the effect measured (death, hospitalization, etc.) using a random effects meta-analysis, RR 0.33 (0.25–0.43). In late treatment, 74% reported positive effect. The probability that an ineffective treatment generated results as positive as the 192 studies to date is estimated to be 1 in 1 quadrillion ($P = 0.00000000000000097$).[11]

Effectiveness of HCQ may be related to its anti-virus, anti-inflammatory, and anti-thrombotic function. HCQ has been shown to possess antiviral activity against various viruses, such as human immunodeficiency virus (HIV), hepatitis A virus, hepatitis C virus, influenza A and B viruses, influenza A H5N1 virus, and others.[12] Recommended HCQ regimen is 200 mg twice daily for 5–7 days, however, this can be extended for up to 2 weeks. Side effects reported in patients with long-term use of HCQ include gastrointestinal disorder, skin rash, retinopathy, blurred vision, and cardiac toxicity. Retinopathy is a more serious toxicity of HCQ though rare; it can, however, progress to irreversible loss of vision.[13-15]

AZITHROMYCIN (AZM)

AZM is a macrolide antibiotic with antiviral properties and is being used in combination with other drugs as path of a regimen for the treatment of SARS-CoV-2 pneumonia given its antiviral and immune modulatory activity with a well-known safety profile. It has a synergistic antiviral effect against SARS-CoV-2 when combined with HCQ both *in vitro* and in clinical settings. It exhibits its antiviral activity by appearing to decrease the virus entry into cells and also enhances the immune response against viruses by several actions. AZM upregulates the production of type I and III interferon (especially interferon-β and interferon-λ), and genes involved in virus recognition such as MDA5 and RIG-I. These mechanisms are universally involved in the innate response against infectious agents and potentially against SARS-CoV-2. The activity of AZM against respiratory syncytial virus has been demonstrated in a randomized study in infants. The combination of HCQ and AZM has been used as standard of care in more than 300,000 older adults with multiple comorbidities.[16-18] Recommended dosing of AZM is 500 mg once daily for 3–5 days or 500 mg on the 1st day followed by 250 mg once daily on days 2–5. As an antibacterial, AZM provides additional coverage of bacterial upper respiratory pathogens that could potentially play a role in concurrent or secondary infection thus serving as a safety net for patients with COVID-19 against clinical failure of the bacterial component of community-acquired pneumonia. AZM is contraindicated in patients with hypersensitivity to any macrolide drug and with a history of cholestatic jaundice or AZM associated hepatic dysfunction. Caution should be taken in patients with hepatotoxicity, infantile hypertrophic pyloric stenosis, *Clostridoides difficile* associated diarrhea, myasthenia gravis, and previous prolongation of QTc interval.[19,20]

ZINC SULFATE

Zinc is a trace element and very important in the development and function of the immune system.[21] It is a known inhibitor of viral replication and also has a direct antiviral activity by preventing fusion with the host membrane, decreasing the viral polymerase function, impairing protein translation and processing, blocking viral particle release, and destabilizing the viral envelope. Deficiency in zinc can result in dysfunction of all immune cells and an increased risk for infectious diseases, autoimmune disorders, and cancers. During infectious disease such as COVID-19, zinc helps to balance the immune response by inducing the production of IFN-α and IFN-γ and reduce mononuclear cell tumor necrosis factor (TNF) production and interleukin (IL)-1β. Zinc also enhances cell's resistance to apoptosis through inhibition of caspases-3, −6, and −9, and an increase of the Bcl-2/Bax ratio and such antiapoptotic effects at both the peripheral and thymic level could result in an increase in the number of T helpers. Zinc-induced alteration of the capillary epithelium might inhibit transcapillary movement of plasma proteins and reduce local edema, inflammation, exudation, and mucus secretion.[21-23] A daily dosage of 15–30 mg is recommended daily for 5–7 days in combination with HCQ and AZM has been used in the management of mild-to-moderate COVID-19. Do not exceed 40 mg/day as this can cause flu-like symptoms such as fever, cough, headache, and fatigue thus masking as worsening of COVID-19 symptoms. Common side effects include nausea, vomiting, diarrhea, stomach pain, metallic taste in mouth, and copper deficiency.

ANTITHROMBOTICS

Patients with COVID-19 have presented with complains of chest heaviness, difficulty in breathing associated with oxygen desaturation on pulse oximetry. This is highly suggestive of a possible pulmonary thrombosis.[24] Studies across the globe have indicated that COVID-19 is associated with coagulopathy and is marked by a state of profound inflammation with endothelial dysfunction, abnormal flow dynamics, platelet activation, and hypercoagulability resulting in higher rates of thrombotic complications such as deep venous thrombosis (DVT), pulmonary embolism

(PE), and microvasculature thrombosis.[24-26] Based on reports available, the use of anticoagulants (low-molecular-weight heparin LMWH, unfractionated heparins, and antiplatelet) may reduce the burden of thrombotic disease and the hyperactivity of coagulation, and may also hold beneficial direct anti-inflammatory effects against sepsis and the development of acute respiratory distress syndrome (ARDS).[27] Aspirin or clopidogrel is antiplatelet and anti-inflammatory and a daily dose of 75 mg daily can be used. LMWH such as Clexane 40 mg daily for 7–14 days can be used in patients with moderate symptoms or obese. Do not use antiplatelet of LMWH if initial platelet count is ≤25,000.

DOXYCYCLINE

Doxycycline is a tetracycline derivative used to treat bacterial infections and also dermatological conditions. It has both antiviral and anti-inflammatory properties.[28] A known mechanisms through which doxycycline's action can prevent or ameliorate the effect of COVID-19 include inhibition of metalloproteinases (MMPs), in particular MMP-9, which is likely required for initial viral entry into the cell, inhibition of IL-6, with both IL-6 and MMPs key regulators of the "cytokine storm" often associated with severe viral pneumonitis and establishing ionophore that helps to transport zinc intracellularly with increased cellular concentrations of zinc shown *in vitro* to inhibit coronavirus replication.[29] Doxycycline has no effect on cardiac conduction and has similar advantage to AZM of offering antibacterial coverage for superimposed bacterial infection in the upper respiratory tract.[30] Where combination of HCQ-AZM is undesirable, doxycycline may be useful. Recommended dosing is 100 mg orally twice daily for 5–7 days.

CORTICOSTEROIDS

Corticosteroids such as hydrocortisone and dexamethasone have anti-inflammatory, anti-fibrotic, and vasoconstrictive effects, which intensivists have been trying to leverage for decades to improve outcomes in patients with ARDS and septic shock.[31] Corticosteroids are not generally recommended for the treatment of viral pneumonia. They can induce harm through immunosuppressant effects during the treatment of infection. The WHO guidelines for use of 6 mg oral or intravenous dexamethasone or hydrocortisone 50 mg iv 8 hourly are reserved for seriously ill patients.[32] We, therefore, do not recommend oral or intravenous corticosteroids in mild-to-moderate cases that are fit for home management.

ANTIVIRAL DRUGS

SARS-CoV-2 replication leads to many of the clinical manifestations of COVID-19, several antiviral therapies are being investigated for the treatment of COVID-19 while some such as remdesivir, lopinavir, ritonavir, and favipiravir are already available for use though as at now, there is no large-scale randomized trial that has been completed. Antiviral drugs inhibit viral entry through the angiotensin-converting enzyme 2 receptor and trans membrane serine protease 2, viral membrane fusion and endocytosis, or the activity of the SARS-CoV-2 3-chymotrypsin-like protease and the RNA-dependent RNA polymerase.[33] Viral replication may be particularly active early in the course of COVID-19, so antiviral therapy may have the greatest impact before the illness progresses into the hyperinflammatory state that can characterize the later stages of disease, including critical illness. Where available, we recommend the use of antivirals in home management protocol for treating mild-to-moderate cases and also in facility-based care for severe, and critical ill COVID-19 patients. Regular monitoring of full blood count, electrolytes, urea and creatinine, and clotting profile is advised in persons taking antivirals. Caution should be taken when treating children and pregnant women.

VITAMINS C & D

Vitamin C, a water-soluble vitamin and an antioxidant and free radical scavenger, has anti-inflammatory properties, influences cellular immunity and vascular integrity, and serves as a cofactor in the generation of endogenous catecholamines. These properties are thought to have beneficial effects in patients with severe and critical illnesses.[34] Its role in management of mild-to-moderate COVID-19 is still being studied.

Vitamin D is critical for bone and mineral metabolism. Its supplements may also increase T regulatory cell activity. Based on its immunomodulatory effects (Vitamin D is thought to modulate innate and adaptive immune responses), Vitamin D could potentially protect against COVID-19 infection or decrease the severity of illness.[35] We, therefore, recommend Vitamin D supplements for patients with COVID-19.

CONCLUSION

This home treatment guideline will help poor and low-resource countries cope with the increase in number of patients with COVID-19 and ameliorate the negative effects on health-care resources for such countries that are already burden by poor or limited health system infrastructure, low workforce, and inadequate expertise to cope with the rapidity with which the virus spread.

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