Medical Science Journal for Advance Research

Vol. 4 , No. 2 , July 2023
e-ISSN: 2774-4892

The Development of COVID-19 Treatment Regimen (Article Review)

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ABSTRACT

Background: *Since December 2019, a new human coronavirus outbreak has spread across various nations, causing numerous cases, and deaths. COVID-19 is a disease caused via the brand-new "SARS-CoV-2" virus (a brand-new stress of coronavirus). Wuhan, Hubei Province, People's Republic of China, is a ten-million-person metropolis. The initial and most significant approach to clinical management of COVID-19 is early adjunctive intervention and surveillance, including oxygen supply, organ support, and prevention of complications, and in particular, acute respiratory distress syndrome, organ failure, and secondary health-facility infections.* ***Conclusion:*** *COVID-19 is a pandemic that is causing an increase in the number of infections and deaths. In response to the epidemic, many pharmacologic medicines are being utilized off-label or evaluated for therapy around the world. The four major pharmacologic categories that are supported by international treatment guidelines globally consist of antiviral medications (eight compounds), antimalarial agents (two compounds), systemic corticosteroids (five compounds) and immune-based therapies (seven drugs). There is a lot of difference between these rules in general. These mostly dealt with drug indications, types of pharmaceuticals, dose regimens, treatment periods, and drug safety in various patient groups.*

Key words: COVID-19, Systemic Corticosteroids Drug , Antiviral Medications.

Article Information
Received: May 8, 2023; Revised: June 26, 2023; Online: July 31, 2023

INTRODUCTION

Since December 2019, a new human coronavirus outbreak has spread across various nations, causing numerous cases, and deaths. COVID-19 is a disease caused via the brand-new "SARS-CoV-2" virus (a brand-new stress of coronavirus). Wuhan, Hubei Province, People's Republic of China, is a ten-million-person metropolis. In order to go on their own, most infected people develop minor respiratory illnesses. Some people have no symptoms, while others experience severe symptoms such as pneumonia, which leads to respiratory failure.

The SARS-CoV-2 virus can be spread through droplets formed by infected people coughing, sneezing, or exhaling. If he already has comorbidities, he is also at risk for the next risk. Although droplet contamination is thought to be the most common method of transmission, SARS-CoV-2 is thought to be infectious even in the absence of coughing and sneezing in locations with inadequate ventilation. It is also taken into account to spread through direct and indirect

https://doi.org/10.46966/msjar.v4i2.134

Published by: READ INSTITUTE

contact. The main source of virus transmission is

People who have symptoms. However, there is a possibility of contamination (1).Cough a feeling of being out of breath Muscle ache. Shortness of breath or difficulty breathing, increased airway secretions (i.e. mucous secretion or hemoptysis), gastrointestinal symptoms including nausea, vomiting, and/or diarrhea, and no change in mental state are all possible symptoms of the disease (for example, confusion, lethargy) (2).

The incubation period is 1-14 days, with signs and symptoms appearing 5 days after exposure (WHO). Patients can also be contagious for up to two weeks after their symptoms have gone away. The pathogen is communicable from the start, and its high contagiousness early in the disease is one of the leading causes of community-acquired infections, a trait that sets it apart from SARS and MERS. Both the upper and lower respiratory tracts are infected with SARS-CoV-2. There is a higher likelihood of virus shedding in severe instances. SARSCoV-2's genetic material can be discovered after 3-4 weeks, however finding the disease-causing gene in a patient does not guarantee the patient is infected. The infection phase is thought to begin two days before to the event. The sickness usually appears 7-10 days after the donset. However, infectious SARS-CoV-2 is only found in a small percentage of blood, urine, and stool samples (3). Children's disease appears to be infrequent and minor, with just around 2.4 percent of all documented cases involving adults under the age of 19. The cornerstone and most important management strategy for clinical management of COVID- 19 remains early adjunct care and monitoring, which includes O2 supplementation, organ support, and interference of complications, particularly acute respiratory distress

Syndrome, organ failure, and secondary health facility infections.

Review of the Literature, and Discussion

Therapeutic Recommendations

Many therapy guidelines for COVID-19- inflamed patients have been published. To a great extent, the recommendations are based on the expert opinion and a small amount of clinical information. However, a lack of consensus exists in terms of a clear pharmacological solution to the COVID-19 and the vast majority of recommendations focus on the supportive approach.

The therapeutic guidelines of the COVID-19 suggest varying approaches across jurisdictions, however, they all include four major categories of pharmacologic agents: antivirals, antimalarials, systemic corticosteroids, and antibiotics; they also differ in regards to the specific drug variants, dosage regimens, and treatment periods. These differences are a great burden, considering that there is not much strong evidence to support the effectiveness of a specific pharmacologic intervention. (4).

Antiviral Medicines

In national guidelines for COVID-19 treatment around the world, 9 antiviral medicines (in combination, or monotherapy) were listed. All these pharmacological agents have some antiviral effects against the viral etiological agents causing Middle “East Respiratory Syndrome (MERS)”, “Severe Acute Respiratory Syndrome (SARS)”, Ebola virus disease, influenza and human immunodeficiency virus (HIV) (5). Even though various clinical trials have examined the effectiveness various antiviral agents in treating SARS-CoV-2, a single antiviral, remdesivir, has received regulatory endorsement in treating hospitalized patients with COVID-19. The guidelines of therapeutic mentioned in Table. 1 including the use of antiviral medicines as a

recommended. Apart from remdesivir, no antiviral medications are recommended as first-line treatment for COVID-19 infections in the Netherlands' guideline. In Asia, the usage of three or more words at the same time is common (6).

Remdesivir

Remdesivir is the only antiviral drug, which was approved by the U.S. Food and Drug Administration to manage “COVID-19". “Remdesivir” used intravenously via loading with 200⁻ during the initial stage of treatment in 30 minutes, but the subsequent maintenance doses of 100 milligrams are administered daily during 4 to 9 days. The use of remdesivir early was advised in the treatment protocol of Singapore to reduce the viral replication and minimize pulmonary damage. The Belgian recommendation limited the use of this medication to the people who are not also undergoing other investigational therapies in clinical trials, including hydroxychloroquine/chloroquine and that this medication should be carefully observed when used closely with other medicines. In Nigeria, remdesivir should not be used unless it is used in the framework of a clinical research. Gilead Sciences does not recommend the use of remdesivir, although drug-drug interaction correlations have not been carried out (Gilead Sciences, 2020). Remdesivir can still be used together with CYP450 inducers (like rifampin) to treat COVID-19 in hospitalized adults and in children older than 12 years old or with a body weight greater than 40kg. There is currently no convincing proof of remdesivir treatment's efficacy in pregnant and nursing moms. The In moderate instances requiring oxygen supplementation, A June 2020 Indian clinical care protocol advises the use of remdesivir with the EUA given by the FDA; however, pregnancy and lactation and age under twelve years are contraindications. On the other hand, the Spanish COVID-19 treatment guideline has provided clear dosage prescriptions of patients with the weight exceeding 3.5kg. (7).

The evaluation of the safety and dosage (of remdesivir) in patients with hepatic and renal pathology incomprehensively is insufficient. The medication is contraindicated by renal impairment (CrCl -1Mx Min) and hepatic dysfunction. Yet, the attachment by Gilead of guidelines pertaining to use of extended-access in Italy mentions that there is no modification of dosage needed in patients with liver and kidney impairment (8).

It is used in all nations mentioned in the (table 1), Nigeria does not promote the use of antivirals unless in a clinical trial setting without restriction, except in Africa (Nigeria) which only allows the use of any antiviral unless in a clinical trial setting.

Lopinavir/Ritonavir

The results of the recent LOTUS clinical trial in the case of patients with SARS -CoV-2 suggest that the combination of lopinavir and ritonavir has negligible value in comparison with standard care. As a result, the lopinavir -ritonavir regimen can no longer be recommended by the World Health Organization. The mortality rate decrease experienced in the hospitalized patients undergoing LPV/r therapy was insignificant compared to the traditional therapy. Lopinavir plus rifampicin (400mg) twice daily, 14 days management have been approved as a dosage against COVID-19 management. The regimen was approved under Italian clinical guidelines as the one for moderate illness, but in the July 2020 update, this was disapproved (9). Nationals advise against using lopinavir–ritonavir or other protease inhibitors as a treatment in COVID-19 patients.

The Nigerian guideline mentions that lopinavir/ritonavir are to be used as part and parcel of clinical trials. Lopinavir/ritonavir is used in combination

treatment, which is also including chloroquine or hydroxychloroquine and/or favipiravir, as a specific combination based on the severity of the symptoms in Thailand and Egypt. Lopinavir/ritonavir can be considered a safe alternative in pregnant women. Nevertheless, the Ireland guideline also discussed that the pregnant patients with diabetes were to be considered, and it was recommended that they should pay attention to the levels of glucose regularly when they are taking these drugs (10).

The combination of LPV and r can increase QT segment lengthening and have a negative impact on cardiac rhythm coordination.

The recommendation in the Nigerian guideline was that lopinavir–ritonavir (LPV/r) should only be used in limiting cases of clinical trials only. LPV/r is used in Thailand and Egypt as a part of a combination regimen of ”chloroquine or hydroxychloroquine, azithromycin, and/or favipiravir”, latter of which depends on a severity of the clinical case of a patient. LPV/r has been considered to be safe treatment intervention towards pregnant subjects. However, Irish clinical guidelines note an issue that refers to pregnant, diabetic patients with SARS -CoV-2 infection, which suggests that regular test of glycaemic status should be measured during LPV/r treatment (10).

It is applied in all countries spread in the list except Africa (Nigeria) and Italy. A combination of this was allowed in moderate cases as indicated by the Italian treatment guideline, notwithstanding that this guideline was revoked in July 2020, but it was not endorsed by the Nigerian guideline. Without being used in a controlled clinical study, the combination should not be administered.

Darunavir

Darunavir/Cobicistat (DRV/c) is a combination of Darunavir and Cobicistat. When, a LPV/r combination prohibited, two guidelines (China , and Italy) recommend this antiviral combination as a safer alternative. It is given for 5–7days at a dose of 800mg darunavir, and 150mg cobicistat. The off-label use of these medications, as well as LPV/r, was banned in Italy in the July 2020 update (8). There is currently no evidence that darunavir is effective in the treatment of COVID-19. The next point to consider is the profile of darunavir drug-drug interactions. Long-term co-administration of statin medications (prescribed for dyslipidemia) is particularly dangerous. It is used in all of the countries listed in the table except Italy. In July 2020, the Italian guideline, along with LPV/r, banned off-label usage of these medications. In Japan, favipiravir was licensed for the treatment of influenza in 2014. Focusing on the “COVID-19” virus, a randomized in China demonstrated that favipiravir can reduce the time to fever and cough alleviation in infected patients. Favipiravir has begun phase 2, and 3.

The use of favipiravir cannot be used in Nigeria without controlled clinical-trial use. It should also avoid use even in the course of pregnancy. In addition, since favipiravir may have teratogenic effects on spermatozoa, further observation of male patients is justified. The drug is utilized in all of the listed countries except Nigeria which limits its use to the clinical trial condition (12).

Umifenovir

Umifenovir is an approved medicine in China that has been used to treat influenza virus for a long time. Umifenovir was found to be ineffective in improving “COVID-19” prognosis in nonintensive attention facilities in a retrospective Chinese investigation. For COVID-19 patients, the “Chinese guideline” advised a combined treatment with LPV/r. “COVID-19” patients

are given 200mg of "umifenovir" four times a day for five to seven days. Nigeria advises against using it unless it is part of a clinical trial (6). It is used in all of the countries listed in the table.

Ribavirin

Ribavirin is a generalized antiviral agent that has an action on the broad spectrum of RNA and DNA viruses. In China, the medication is Ribavirin is a broad-ranging antiviral agent, which has its activity on a wide variety of RNA and DNA viruses. In China, the drug is used as 500mg intravenous infusion given two to three a day during ten days, as compared to Saudi Arabia and Singapore where the drug is used orally as 400 mg or twice or three times a day over a period of fourteen days, and use of seven days in the United Arab Emirates. It has been suggested by the Chinese Pharmaceutical Association that ribavirin should be used in combination with lopinavir/ritonavir (LPV/r) or interferon -alpha in a double-therapy regimen. In Hong Kong, a randomised, multicentre clinical trial has shown that an early triple-therapy regimen of ribavirin, LPV/r, and subcutaneous interferon1b -1b was more effective than LPV/r alone in injecting people with mild to moderate symptoms of COVID -19. (11).

This combination therapy is given in the case of moderate-severe cases in Saudi Arabia, but should not be considered against patients who are critically ill. It should only be recommended in case of an emergency in the United Arab Emirates. The treatment is used as a third-line option in extremely sick patients or those who need oxygen supply in Singapore after the remdesivir and convalescent plasma have been used. The majority of Ribavirin is excreted via the kidney, and its build-up can happen in case of kidney failure (13).

Oseltamivir

Oseltamivir a selective neuraminidase inhibitor used to treat influenza (A, and B), with a dosage of 75mg twice daily for five days. The Egyptian Ministry of Health approved the use of oseltamivir in all "COVID-19" cases (14). "Oseltamivir" interacts with the small number of medicines, making it ideal for individuals with chronic diseases.

Antimalarial Medications

Antimalarial medications are "hydroxychloroquine (HCQ), and chloroquine (CQ)" were originally recommended to treat autoimmune illnesses. Both medications were suggested for usage in numerous COVID-19 treatment guidelines around the world during the start of the pandemic (early 2020).

Hydroxychloroquine

Different national guidelines have established a variety of criteria for use of "HCQ in COVID-19" patients. In severe circumstances, India's policy expressly advises against using HCQ. The "HCQ/CQ therapy" choices for critically sick patients have been withdrawn from a new UAE guideline, but they have been retained for other COVID-19 patients who fall into defined categories. Many treatment recommendations have prohibited the use of HCQ in the treatment of COVID- 19 patients. In India, the current treatment guidelines recommend the use of hydroxychloroquine (HCQ) to prevent the virus infection among healthcare staff and caregivers who are put at risk by occupational exposure (15), but in Pakistan, the opposite is clearly preferred. In contrast, the SWAB guideline published in Nigeria and the Netherlands discourages the use of HCQ in an environment other than the strictly designed clinical studies (16).

The backbone from which HCQ was produced is chloroquine (CQ). According to various research, HCQ is more potent and safer than CQ. Treatment is often not

suggested for kids under the age of 12 or weighing less than 50 kg, despite the fact that Spain's and the UAE's treatment guidelines specifically mention doses for the children of several weight groups (13).

Being aware HCQ/CQ is processed in the liver, with some metabolites eliminated through the kidney (22) In Belgium, it is clearly specified that dosage adjustments for HCQ and CQ must be made based on the Glomerular Filtration Rate (GFR). Antimalarial monographs also encouraged to be consulted in UAE for dosage adjustments, and monitoring in patients with liver, or renal failure (12).

Except when a CrCl is less than 15 mL/min, no further dosage adjustments are required in Brazil (17). Although “HCQ, and CQ” are considered safe during the pregnancy, as previously stated, the medication must be constantly monitored. The safety of these substances was clearly mentioned in several standards, such as those in the United Arab Emirates, Belgium, and Italy. HCQ/CQ is a contraindication in pregnancy according to Brazilian and Indian standards (17). CQ is only indicated in Pakistan for serious instances in pregnant women.

Because there are numerous side effects affecting “the heart, eyes, liver, and kidneys”, these medications should only be used after a thorough assessment of the patient. The majority of accessible lines mentioned “HCQ/side CQ's” effect profile, including “ventricular arrhythmias”, and the requirement for the ECG monitoring.

Corticosteroid (Systemic)

Expanding an extreme spectrum of clinical manifestations including mild dyspnea and severe respiratory distress syndrome (ARDS), septic shock, and dysfunction of single and multiple organs is one of the most serious consequences of the exuberant and uncontrolled inflammatory reaction carried out by COVID -19 and other severe respiratory infections. Such a pathological cascade consists of a set of inflammatory mediators, in particular, cytokines and interleukins. The use of dexamethasone 6 mg/day on a maximum of 10 days was found to produce a statistically significant decrease in mortality in mechanically ventilated COVID-19 patients and in patients receiving conventional oxygen supplementation. A partially randomised trial in 85 COVID-19 patients established that methylprednisolone had similar effects of decreasing mortality, intensive-care unit (ICU) readmission, and mechanical ventilation requirement. Nevertheless, a number of post-facto studies have shown no protective value of corticosteroids in COVID-19, which may indicate a potential absence of benefit or even harm in any intensive care group. The Brazilian guidelines show that an anthelmintic prophylaxis regime can be used pre-operative to prevent parasitic infection. During COVID-19, corticosteroid therapy has been used (17).

According to the World Health Organization, it is advisable to give prenatal corticosteroids between 24 and 34 gestational weeks to an infected mother where there is optimum treatment of the neonate and a mother who is also asymptomatic. Dexamethasone (or other agents in case of dexamethasone unavailability) is recommended as a treatment of pregnant women with COVID-19 who need any type of supplemental oxygen in the United States (18). Low-dose prenatal corticosteroid therapy has been approved by the “Society of Obstetricians and Gynaecologists of Canada”, provided there is informed consent of the patients. In particular, during pregnancy in COVID -19 patients, dexamethasone must be replaced with prednisolone 40mg, preferably “orally or intravenously”, or hydrocortisone 80mg twice a day.

Hypocortisolism

The condition is determined as a signal to prescribe dexamethasone when treating COVID -19 in Singapore. An underdose of corticosteroids regimen could be used to treat a range of comorbid situations, specifically, asthma in the United Kingdom, but also in interactions with previous guidelines used in the United States. Pakistani protocols also require all the patients in need of oxygen therapy to be administered of steroids e.g. dexamethasone or methylprednisolone.

Dexamethasone

Dexamethasone is a synthetic long-acting corticosteroid whose biological half-life is 36 to 72 hours, and which has about 25 times better effectiveness than short-acting hydrocortisone. Dexamethasone 6-10mg daily has been demonstrated to lower the occurrence of deaths in COVID-19 patients induced to oxygen supply or mechanical ventilation. Symptomatic disease longer than seven days also becomes another condition of dexamethasone in Switzerland, Malaysia or Singapore.

Methylprednisolone

The duration of action of methylprednisolone is intermediate and is about 5 times higher than that of hydrocortisone with a biological half -life of 12 -36 hours. The ideal dosage regimen is to start with the dosage of 40 mg after every 12 hours and then 20mg after every 12 hours in the first three days. There are many therapeutic guidelines that support this medication. The recommended dosage of the Dutch RIVM treatment guideline is 40mg (0.5mg/kg/day- kg-1) to be taken in three instances daily with a maximum of seven days. A dosage of 32mg per day is recommended in Singapore but different ranges of 0.5-1.0mg kg-kg-1 day -1 are recommended in mild cases with higher oxygenation needs and lasted 3-5 days or longer. The use of extended periods of hypoxia among pediatric COVID-19 patients in Saudi Arabia and Pakistan results in increased periods of treatment. In India and China, use of 1 to 2 to wider dosage of 1 to 2 to harder cases of 3 greater days is suggested.

Prednisone

As a substitute to dexamethasone, prednisone is suggested in the resources about COVID therapeutics in the United States, South Africa, and Singapore. This drug is solely in the form of oral preparations and it has a biological half life between 12-36 hours.

Prednisolone

The potency of prednisolone is similar to prednisone and has a similar biological half-life. The Saudi Arabian guidelines on the use of the treatment are only authorized in a vacuum of pediatric patients infected with COVID-19 and have a content of 1mg / kg -1 once per day. The more frequently used corticosteroid is hydrocortisone, a short acting corticosteroid with a biological half-life of 8-12 hours. In Egypt treatment further recommends a moderate dosage of hydrocortisone against COVID -19 and in the US it could be an alternative to dexamethasone, in the case of unavailability.

Immune-based treatment

Representative agents in this group are immune-based therapies, such as interleukin -2, alpha-interferon, gamma-interferon, and monoclonal antibodies. The importance of these seven compounds has been evaluated in seven COVID-19 patients, but none of the strong evidence of a clinical outcome has been described so far. Current clinical research aims at testing their effectiveness against SARS-CoV-2. (21).

1-Tocilizumab

Tocilizumab is an immunomodulatory therapy that is an interleukin end 6 receptor antagon in form of a recombinant IgG1 monoclonal antibody that

has been employed in antiviral and immunomodulatory treatment of both the acute and convalescent periods of COVID-19 infection. According to Swiss guidelines, it is considered to be necessary in the case of cytokine-storm. Chinese National Health Commission and UAE guidelines suggest it should be used in patients with widespread bilateral lesions of the lungs and/or high levels of IL 6 whilst Spanish guidelines suggest its use in patients with an inflammatory cascade that has affected respiratory performance. In Pakistan, it is recommended against acute respiratory distress syndrome or critically ill cytokine release syndrome in moderate to severe COVID-19. The drug is used in patients with intensive care units with acute cytokine release syndrome.

Guidelines in Singapore do not support the use of tocilizumab; it can only be an option in a cytokine storm or hyper-inflammatory state. In United States and Nigeria the drug is used in the clinical trial settings only. Swiss guidelines are opposed to its application in uncontrolled microbial and fungal infection. Both the Italian and Pakistani guidelines recommend a pre-operative risk-benefit evaluation to pregnant COVID-19 patients. The UAE and Saudi Arabia have categorized it as a contraindication under some situations,

2-Siltuximab

In Spain, an anti-IL-6 monoclonal antibody called siltuximab is used as a compassionate treatment in cases of interstitial pneumonia patients who develop a severe respiratory failure, rapid respiratory deterioration requiring non-invasive or invasive ventilation, extrapulmonary organ failure, or a severe systemic inflammatory response. Its use is not endorsed by the United States when it is not a part of the clinical experiment. Pregnant and lactating women are also contraindicated to use the drug. (18)

3-Sarilumab

The use of sarilumab, an IL 6-inhibitor, suggested in the Spanish guidelines only, is recommended to be used at a single-infusion dose of 200 mg or 400mg, but there are limited evidences in supporting its effectiveness. There is no information on pediatric safety and efficacy.

4-Canakinumab

Canakinumab is a human anti-interferon IL-1 monoclonal antibody. Italy is the only nation that considers canakinumab as compassionate therapy using Managed Access Programme of Novartis, in case other treatments have failed, and the COVID-19 outcome is severe or life-threatening. The intravenous application of the drug comes in two doses of 250 ml of 5 per cent dextrose infused over a two-hour period in patients with a weight of 40-60kg (not to be exceeded by 10mg/kg). (8).

In a cohort of COVID-19 patients with ARDS after the high-dose treatment, anakinra, an interleukin-1 receptor antagonist, produced clinical benefits in 72 per cent of ARDS subjects; an outcome modeled in a model of ARDS with acute respiratory system dysfunction (Tai et al., 2020). Deciding when tocilizumab should not be used, the UAE guideline is the only that assumes anakinra as an option. (12)

5-Ruxolitinib

Ruxolitinib has not proven any effect in diminishing mortality or morbidity in COVID -19 as of December 2020. Italy is also considering their compassionate use with Managed Access Programme of Novartis. The dosage used in Spain is 5mg two times a day in 14 days. Dosage of Italian is subject to variation; 5mg oral per day or twice per day x 7 days in children aged 612 years and those aged over 12 years respectively. (8) The selective and reversible Janus kinase 1/2 selective inhibitor Baricitinib is not advisable

in the United States except in clinical trials. Spanish recommends 4 mg daily during 714 days in adults and 2mg daily in patients aged below 75 years. It has not yet been studied in pediatrics as to its safety.

Interferon (IFN)

The Type I interferons, which include IFN alpha, and IFN beta fall in the antiviral category as well as the immune-modulatory category of therapeutic agents. An empirical study has implicated interferon deficiency with the developing severe disease manifestations, although interferon concentrations are inversely related to viral load. Treatment guide practice in the United States, Canada, the Netherlands (SWAB) and Nigeria do not promote the use of interferon. Therefore, interferon must be reserved to be used as part of the clinical trials in the case of COVID-19 treatment. In case of severely and critically ill patients, the Saudi Arabia and UAE guidelines suggest triple-therapy which includes the use of interferon IFN (IFN 2b: 8 MIU every other day over three doses) in which case it should be combined with ribavirin and Lopinavir/Ritonavir. The use of interferon α1b (5 MIU twice a day) was tested in the Chinese guideline as self-administered therapy or as a combination with antivirals (ribavirin and lopinavir/ritonavir).

In severe and critical cases, interferon 0.25mg once every other day of the 5-7 doses of 0.25 mg (interferon 1b: 0.25## 0.55mg) or 180 mg/kg once weekly (interferon 1b: 0.25## 0.55mg) of interferon 2a can be added as a triple combination, or used as a complement to moderate disease in the UAE. Concerning the administration route, Chinese guidelines prefer use of pulmonary delivery of IFN type 1, but Singapore, Malaysia, the UAE, and Saudi Arabia use subcutaneous routes. Singapore and Saudi Arabia recommend the use of early initiations of interferon, preferably between 6-7 days of onset of symptoms to lessen adverse late-stage symptoms. The maximum number of interferon therapy which is allowed in Singapore is 7 days in order to avoid interfering with hyperinflammatory phase, but Saudi Arabia increases the proposed duration to 14 days.

Antibiotic Treatment

The choice of the antibiotic is based on the severity of the infection and the condition of the patient, and it is mostly applied to infections of the upper respiratory tract. Unexpectedly, antibiotics are usually avoided in viral infections which lack secondary involvement of bacteria. Smaller cases, either therapeutic or prophylactic are not advised to use antibiotics in non-hospitals as per various standards. Malaysian and French guidelines encouraged early empirical antibiotic treatment, e.g. amoxicillin/clavulanate or thirdgeneration cephalosporins (ceftriaxone, cefotaxime, ceftaroline) together with azithromycin when the COVID-19 is severe. WHO did not include Azithromycin in its COVID-19 guidelines. Various recommendations warn of the adverse effects of using azithromycin-hydroxychloroquine combination, and the guideline in Nigeria discourages its use in clinical trials. On the other hand, Thailand and Brazil allow azithromycin in combination with hydroxychloroquine to very ill patients.

WHO indicates that antibiotics are not to be used in mild cases, where only in case of clinical uncertainty, prescriptions should be made in the moderate cases only. Chinese authorities also specify that antibiotics should be used only in those cases of COVID-19 patients with severe acute respiratory infection (SARI) or sepsis, which is also reflected in UAE and Indian guidelines. The Pakistani guidelines relate the use of antibiotics with leucocyte in the event that one suspects infection. The use of linezolid or vancomycin was recommended

by French, UK, and Egyptian guidelines, although doxycycline is preferred to amoxicillin in certain settings, because it has a broader spectrum, including Mycoplasma pneumoniae, a probable secondary infecting bacterium in the pandemic. In Belgium, Brazil, Canada, Ireland, Spain and the United States, no antibiotic prophylaxis is recommended, but empirical treatment is advised in severe cases, depending on comorbidities and situation in the patient, and local epidemiology, and de-escalation without MRSA.

Anticoagulants

Hypercoagulopathy, with increased D -dimer and fibrin degradation products is a significant factor in COVID -19 mortality. People taking chronic anticoagulant or antiplatelet treatment in the United States should stick with their treatment in the case of COVID19, but anticoagulation is not recommended in the case of non-hospitalised individual. The UAE, South African, Egyptian, and Dutch guidelines are consistent with the requirement of the prophylactic anticoagulation of all COVID-19 hospitalized patients with no contraindications. The treatment guideline in Singapore excludes VTE prophylaxis to patients with severe disorders and critically ill. The enoxaparin finds use in recessive patients as well as prophylaxis in those who show signs of pulmonary embolism in Egypt. The Belgian recommendations suggest the replacement of patients on chronic oral anticoagulants with low-molecular-weight heparin (LMWH) to prevent drug-drug interactions that are part of the COVID-19 therapeutics.

The Indian, Saudi Arabian, Belgian and Chinese associations fight in favor of LMWH whereas the Netherlands, India, and Ireland use unfractionated heparin as a preventive and therapeutic agent. The guideline used in Malaysia favorably favors unfractionated heparin in cases of renal inadequacy. The protocols used in the Netherlands prefer dalteparin, nadroparin and fondaparinux sodium. Direct-acting oral anticoagulants are recommended in the context of special treatment, to which they are independently evaluated.

Additional Medications

Many guidelines are referring to medication, complementary treatment, and vitamins. The U.S. and Irish guidelines support the use of NSAIDs in the same condition in patients already taking this medicine in case of a COVID-19 infection. Zinc supplementation against COVID-19 among the Netherlands is not recommended but at 100 mg elemental zinc daily is suggested in the UAE. Vitamin C is prescribed as oral or intravenous in the UAE and dosage varies at 1-3g IV per day. Chinese pharmaco-experts recommend 100-200mg/kg IV daily until considerable improvement of oxygenation, whereas Egyptian instructions recommends 500mg ascorbic acid every 12hours universal. Vitamin D management in the Netherlands states that they have an inadequate amount of data that justifies its prophylactic or curative usage. According to the Nigerian guidelines, multivitamin and mineral supplementation are allowed.

Table 1. Summary of medications used for managing COVID-19 cases as per 24 treatment guidelines.

	Medications																								
	Anti-Virial Drugs							Anti-Malarial Drugs		Systematic Corticosteroids					Immune-Based Therapy						Interferon Type I: IFN Type I		Antibiotic Therapy	Anti-Coagulant
Region	Remdesivir	Lopinavir /Ritonavir	Darunavir/Cobicistat	Favipiravir	Umifenovir	Ribavirin	Oseltamivir	Hydroxychloroquine	Chloroquine	Dexamethasone	Methylprednisolone	Prednisone	Prednisolone	Hydrocortisone	Tocilizumab	Siltuximab	Sarilumab	Canakinumab	Anakinra	Ruxolitinib	Baricitinib				
Reference Guidelines																									
WHO [4]																							√	√	
FDA [5]	√							x	x											√					
EMA [6]	√									√															
Americas																									
Brazil [7]	√							√	√	√													√		
Canada [8]								x		√												x	√		
USA [9]	√	x						x	x	√	√	√		√	√	√				√		x	√	√	
Eastern Mediterranean																									
Egypt [10]		√					√	√						√									√	√	
Pakistan [11]	√							x	x	√	√				√								√	√	
Saudi Arabia [12]	√	√		√		√				√	√		√		√							√		√	
United Arab Emirates [13]	√			√		√		√	√	√	√				√				√			√	√	√	
Europe																									
Belgium [14]	√	√						x	x	√													√	√	
France [15]										x													√		
Ireland [16]		√						x		√					√								√	√	
Italy [17,18]	√	x	x					√	x	√					√			√		√			√		
Netherlands [19,20]								√	√	√	√				√							x	√	√	
Spain [21]	√							√	√						√	√	√		√	√			√		
Switzerland [22]								x	x	√					√										
United Kingdom [23]																							√		

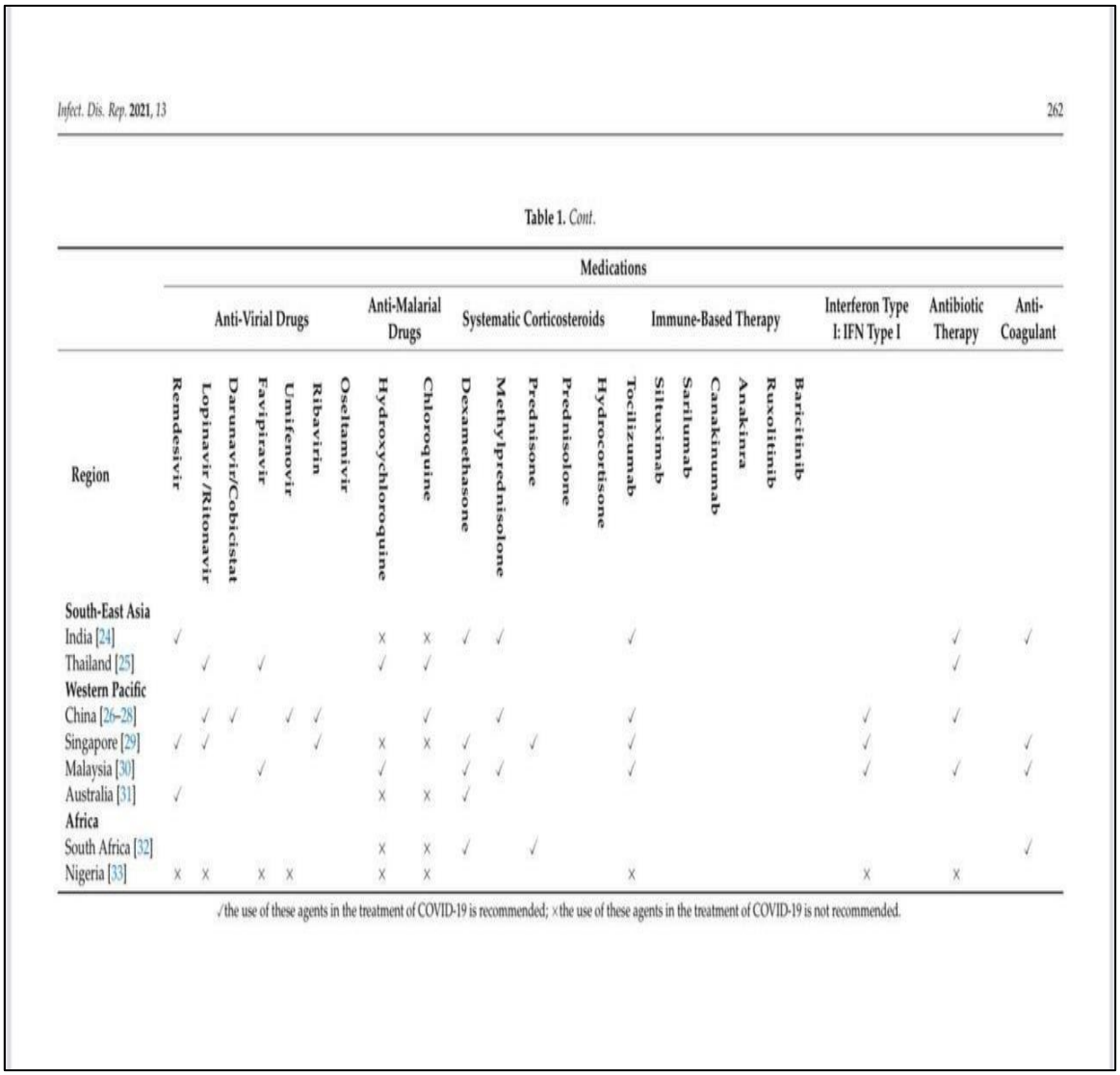

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Table 1. *Cont.*

	Medications																						
	Anti-Virial Drugs							Anti-Malarial Drugs		Systematic Corticosteroids					Immune-Based Therapy						Interferon Type I: IFN Type I	Antibiotic Therapy	Anti-Coagulant
Region	Remdesivir	Lopinavir /Ritonavir	Darunavir/Cobicistat	Favipiravir	Umifenovir	Ribavirin	Oseltamivir	Hydroxychloroquine	Chloroquine	Dexamethasone	Methylprednisolone	Prednisone	Prednisolone	Hydrocortisone	Tocilizumab	Siltuximab	Sarilumab	Canakinumab	Anakinra	Ruxolitinib	Baricitinib			
South-East Asia																							
India [24]	✓							×	×	✓	✓				✓							✓	✓
Thailand [25]		✓		✓				✓	✓													✓	
Western Pacific																							
China [26–28]		✓	✓		✓	✓			✓		✓				✓						✓	✓	
Singapore [29]	✓	✓				✓		×	×	✓		✓			✓						✓		✓
Malaysia [30]				✓				✓		✓	✓				✓						✓	✓	✓
Australia [31]	✓							×	×	✓													
Africa																							
South Africa [32]								×	×	✓		✓											✓
Nigeria [33]	×	×		×	×			×	×						×						×	×	

✓ the use of these agents in the treatment of COVID-19 is recommended; × the use of these agents in the treatment of COVID-19 is not recommended.

CONCLUSIONS

COVID-19 is a pandemic that is causing an increase in the number of infections and deaths. In response to the epidemic, many pharmacologic medicines are being utilized off-label or evaluated for therapy around the world. Antiviral medications (eight drugs), antimalarial drugs (two drugs), systemic corticosteroids (five drugs), and immune-based therapy are the four primary groups of drugs suggested in treatment guidelines around the world (seven drugs).

There is a lot of difference between these rules in general. These mostly dealt with drug indications, types of pharmaceuticals, dose regimens, treatment periods, and drug safety in various patient groups. Corticosteroids are likely to reduce mortality, mechanical ventilation, and ventilator-free days in patients with severe covid-19, according to evidence from an ongoing systematic review. Remdesivir, in combination with steroids or baricitinib, may be explored for hospitalized patients with severe COVID-19 (i.e. SpO2 94 percent on room air, requiring supplementary oxygen). Interferon beta, hydroxychloroquine, and lopinavir/ritonavir may not lower mortality or the need for mechanical ventilation, and they appear to have few other benefits. Patients with severe or critical illness who do not have contraindications should try pharmacologic thromboprophylaxis.

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