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TREATMENTS AND MANAGEMENT OF CORONAVIRUS DISEASE 2019 (COVID-19)

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Abstract:

Background: Coronavirus disease 2019 (COVID-19) is a serious public health crisis threatening the world with extremely fast spread and mortality. The disease is transmitted by inhalation or contact with infected droplets and the incubation period ranges from 2 to 14 days or even more. The most common symptoms are fever, dry cough, and tiredness, while the serious symptoms are difficulty breathing or shortness of breath, chest pain or pressure, and loss of speech or movement. There are also less common symptoms such as; aches and pains, sore throat, diarrhea, conjunctivitis, headache, loss of taste or smell, and a rash on the skin, or discoloration of fingers or toes. The disease may progress to pneumonia, acute respiratory distress syndrome (ARDS), and multi-organ dysfunction especially in elderly people and those with comorbidities. However, symptoms of a coronavirus usually go away on their own and many people are asymptomatic. The virus is diagnosed in respiratory secretions by special molecular tests. In some cases, self-isolate to prevent the spread of infection is preferred and advisable. There is no specific treatment for disease caused by a coronavirus. However, many of the symptoms can be treated and therefore treatment based on the patients' clinical conditions.

Objectives: There is currently no vaccine or effective treatment for COVID-19, the treatment is either supportive and/ or the treatment of symptoms. Several strategies in the treatment of the disease were applied including drugs. This review aims to summarize the different strategies and drugs used for the treatment of COVID-19.

Materials and Methods: Different literature and guidelines among different databases were searched. Literature reviewing was conducted using the following search engines, Google Scholar, Medline, Pub Med, EMBASE, Web of Science, and Science Direct. Data also obtained from WHO reports, and the published peer-reviewed articles of 2019-nCoV. The review focuses on the therapeutic drug types and approaches used in the treatment and management of the disease.

Conclusions: The Strategies to end the COVID-19 pandemic are; to slow and stop transmission; provide optimized care for patients; and minimize the impact of the epidemic on health systems, social services, and economic activity. To achieve these; proper management, right actions, and effective treatment of the disease should be considered. To date, there are no specific vaccines or medicines for COVID-19; and treatments are under investigation through clinical trials. Besides, there are no FDA approved drugs for COVID-19 until now. However, an array of drugs approved for other indications, as well as multiple investigational agents, are being studied for the treatment of COVID-19; in several hundred clinical trials around the World. Treatment is essentially supportive and symptomatic.

Keywords: COVID-19, Coronavirus, Treatment, Prevention, Antiviral, 2019-nCoV

Introduction

Coronaviruses are enveloped positive-sense RNA viruses ranging from 60 nm to 140 nm in diameter with spike-like projections on its surface giving it a crown-like appearance under the electron microscope; hence the name coronavirus. Four coronaviruses namely HKU1, NL63, 229E, and OC43 have been in circulation in humans and generally cause mild respiratory disease. The COVID-19 pandemic has exploded since cases have been identified as the cause of an outbreak of respiratory illness in Wuhan, Hubei Province, China at the beginning of December 2019. As of 31 January 2020, this epidemic had spread to 19 countries with 11 791 confirmed cases, including 213 deaths. The World Health Organization (WHO) has declared it a Public Health Emergency of International Concern. By June 4th, 2020, more than 6.5 million cases of COVID-19 have been reported globally, including >380,000 deaths. Cases caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections have been reported in more than 180 countries, including all 50 states of the United States [**1-3**]. While, on May 28th, 2020, the pandemic cases were 5,868,922 and 360,476 deaths worldwide with a 6.14% mortality rate, and in Palestine, the pandemic confirmed cases were 570 with 4 deaths only. The disease spread extremely very fast as by the end of June (within only one month period), the cases have been nearly doubled as the coronavirus cases confirmed were 10,690,566, deaths 516,393 (8%), and recovered are 5,856,464 worldwide. The high incidence rate and cases were in the USA (2,751,571), then Brazil (1,426,913), Russia (654,405), India, UK, Spain, Peru, Chile, Italy, and Iran (230,211) respectively .In Palestine by this time, at the end of June, the reported cases were increased very sharply by about six times; as more than 3,095 cases were reported including East Jerusalem (337 cases), with 11 deaths. The highest cases (1947 cases)

were in Hebron Governorate; with these confirmed cases Palestine ranked 97 among 215 countries that have coronavirus; with the highest outbreak rate in the world; compare to population number. The outbreak of the disease globally was continued raising very sharp as by 11th July 2020, the coronaviruses cases reported was 12,872,339 and the death cases were 568,312, the increase rate of the new cases was ~8% and the rate death increased by 1.125%; within about two weeks period only, which considered high rates. The highest incidences by this time were in the USA with 3,356,242 reported cases, then Brazil (1,840,812), India (854,480), Russia (727,162), and Peru (322,710), etc. as shown in Table-1. In terms of the outbreak of the disease, the rank of the countries is changing every day, but the USA and Brazil remain and still rank first and second respectively for a while. In Palestine by 11th July 2020, the confirmed cases were 6688, and the death cases were 36, with an increased rate of 304%, which extremely very high and considered the highest worldwide. The highest cases were in Hebron Governorate (4620 cases), with about 70% of the total reported cases, as shown in the geographical location of confirmed cases (Figure 1). With these confirmed cases Palestine ranked 87 among 215 countries that have coronavirus; with the highest outbreak rate in the world too; compare to population number. Within only two weeks period the Palestine rank changed from 97 to 87; however, if the outbreak in Palestine remains rising by the same rate, Palestine after a short period will be one of the top countries having the disease, if real and serious precautions did not apply especially the health recommendations, isolation and maintain social distance.

The high outbreak of the disease in this region (Hebron Governorate), as 90% of infections have been caused by people meeting up with their families or attending wedding parties or funerals and failing to follow health recommendations and maintain social distancing according to Palestinian Ministry of Health officials. Figure 1 shown coronavirus disease 2019 (COVID-19) in occupied Palestinian territory by 11th July 2020, cumulative confirmed, recovered and death cases, confirmed cases per day (since April to July 2020), confirmed cases by gender (5th March to 11th July 2020), and confirmed cases by age in Palestine. Some data reported were included and some excluded East Jerusalem. (http://www.emro.who.int/pse/palestine-news/top-story.html). Table-1 shows cases for the top 30 countries including, other information such as daily new cases, total death, totally recovered, a total test of each country, etc. While the actual and accurate causes and effective treatment of COVID-19 are still unknown or unavailable and the number of active cases of the infection is rising every day as mentioned, which rising panic and concern on public health worldwide. Prevention is still the best strategy to face this pandemic. These numbers are possibly an underestimate of the infected and dead due to limitations of surveillance and testing. It is though the SARS-CoV-2 originated from bats, the intermediary animal through which it crossed over to humans is uncertain. Pangolins and snakes are the current suspects [**4**].

The onset and duration of viral shedding and the period of infectiousness are not completely defined. The estimated incubation period for COVID-19 is up to 14 days from the time of exposure or even more, with a median incubation period of 4 to 5 days [**5-7**]. The disease is transmitted by inhalation or contact with infected droplets. The spectrum of illness can range from asymptomatic infection to severe pneumonia with acute respiratory distress syndrome (ARDS) [**4**]. In a report of 1,482 hospitalized patients with confirmed COVID-19 in the United States, the most common presenting symptoms were cough (86%), fever or chills (85%), and shortness of breath (80%), diarrhea (27%), and nausea (24%) [**8**]. Other reported symptoms have included, but are not limited to, sputum production, headache, dizziness, rhinorrhea, anosmia, dyspepsia, sore throat, abdominal pain, anorexia, and vomiting. Asymptomatic or pre-symptomatic individuals infected with SARS-CoV-2 may have viral RNA detected in upper respiratory specimens before the onset of symptoms. Transmission of SARS-CoV-2 from asymptomatic individuals has been described [**9-11**]. The extent to which this occurs remains unknown. Individuals of all ages are at risk for infection and severe disease. The probability of fatal disease is highest in people aged ≥65 years and those living in a nursing home or long-term care facility. However, others at the highest risk for COVID-19 are people of any age with certain underlying conditions, especially when not well-controlled, including hypertension, cardiovascular disease, diabetes, chronic respiratory disease, cancer, renal disease, and obesity [**12-15**].

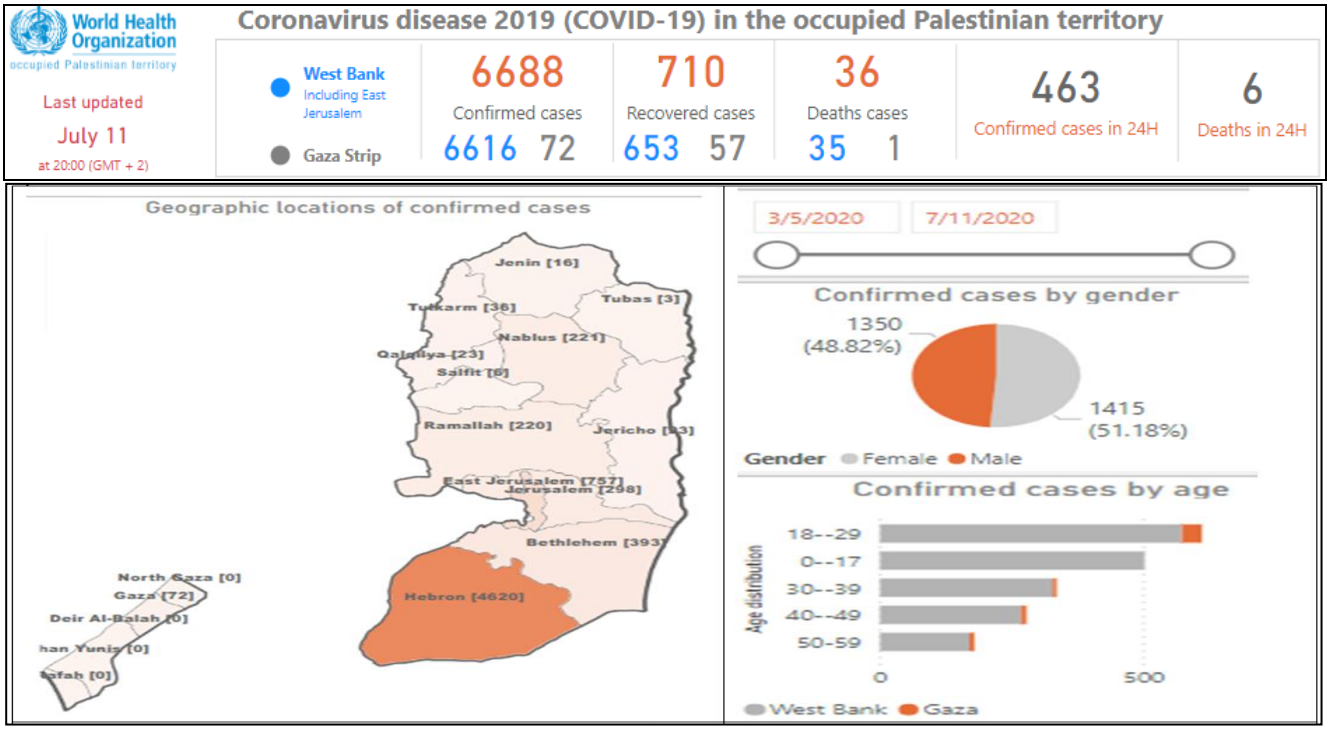
Common laboratory findings of COVID-19 include leukopenia and lymphopenia. Other laboratory abnormalities have included elevations in aminotransferase levels, include normal/ low white cell counts with elevated C-reactive protein (CRP), D-dimer, ferritin, and lactate dehydrogenase, x-ray, and computerized tomographic. The CT chest scan is usually abnormal and varies even in those with no symptoms or mild disease. Imaging may be normal early in infection and can be abnormal in the absence of symptoms [**16**]. Every year an estimated 290,000 to 650,000 people die in the world due to complications from seasonal influenza (flu) viruses. There are about 795 to 1,781 deaths per day due to the seasonal flu. SARS (November 2002 to July 2003). The coronavirus that originated from China and spread to different countries; resulted in more

than ten and a half million people infected; and with about more than half a million deaths; with a fatality rate of 8%, by end of June 2020. Thus, the rates of cases and death of coronavirus are most likely will be more than seasonal influenza viruses; especially the virus outbreak is rising sharply every day; thus, the fatality will higher.

Treatment of the disease is essentially supportive; the role of antiviral agents is yet to be established. Prevention entails home isolation of suspected cases and those with mild illnesses and strict infection control measures at hospitals that include contact and droplet precautions. The virus spreads faster than its two ancestors the SARS-CoV and Middle East respiratory syndrome coronavirus (MERS-CoV) but has lower fatality till now. The global impact of this new epidemic is yet uncertain. Treatment is mainly supportive since no antiviral has been approved yet. Efforts are being made to find effective treatment and to reduce the virus outbreak. However, not much information is known about the virus causes, its survival period, methods of its spreading, biochemical and hematological disorders, its complications, its prevention, and treatments. Therefore, this review provides and focused on the latest treatment and precautions of COVID-19. Slow and stop transmission; provide optimized care for all patients; and minimize the impact of the epidemic on health systems, social services, and economic activity are the main objectives for the management of the disease. More than 150 different drugs are being researched around the world. Most are existing drugs that are being tested against the virus. Here we high light on the most important drugs including herbal medicines used/or tested for the treatment of the disease and the disease complications. In Palestine, the treatment and management protocols of COVID-19 are similar to the strategies and protocols in the other countries which follow the guidelines of WHO.

Materials and Methods

The review discussed the different therapeutic strategies and drugs used for the treatment of COVID-19. Preciously, different literature and guidelines among different databases were searched, summarized, and discussed. The literature review was conducted using various search engines, Google Scholar, Medline, Pub Med, EMBASE, Web of Science, and Science Direct. Data also obtained from the WHO reports, and the published peer-reviewed articles of 2019 novel coronavirus (2019-nCoV). The initial terms “words” that match with the title or abstract or with the topic including 2019-nCoV, 2019 novel coronavirus, SARS, CoV-2, COVID-19, coronavirus disease 2019, NCP, and novel coronavirus pneumonia were used in searching the databases. The further search was also carried out using the keywords, SARS-CoV, severe acute respiratory syndrome, MERS, MERS-CoV, Middle East respiratory syndrome, in combinations of with "pike protein, genome, reproductive number, incubation period, fatality rate, clinical characteristics, pathology, autopsy, protocols, guidelines, treatment, and prevention. Moreover, official documents that have been released by the WHO were accessed for up to date data on COVID-19.



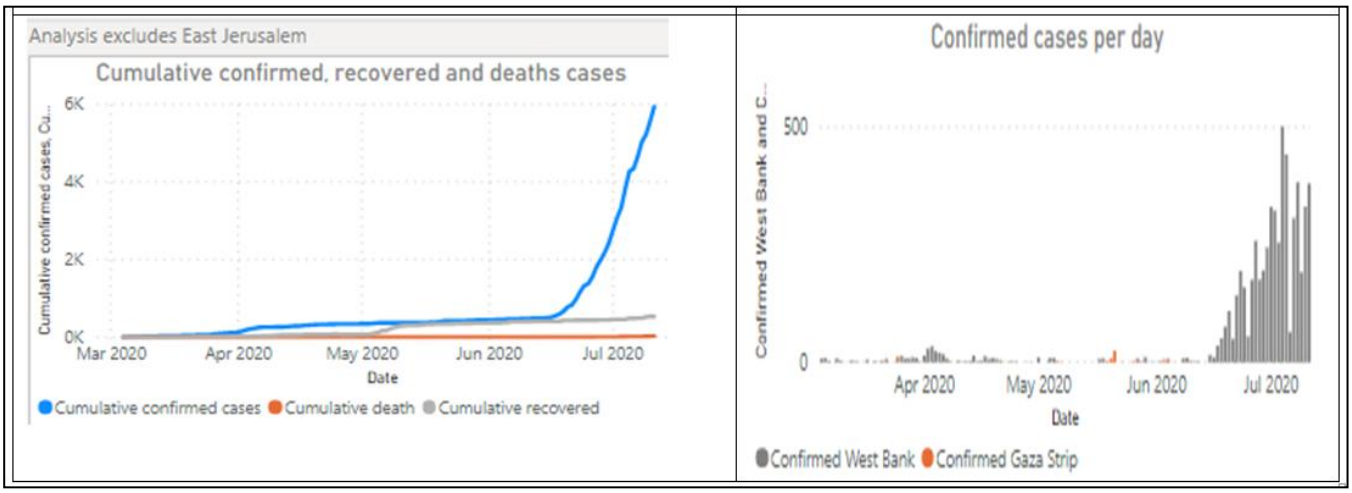


Figure 1: Coronavirus disease 2019 in Palestine (http://www.emro.who.int/pse/palestine-news/landing-page-for-covid19.html)

Table 1: Reported Cases and Deaths by Country as 11^{the} July (https://www.worldometers.info/coronavirus/)

#	Country, Other	Total Cases	Total Deaths	Total Recovered	Active Cases	Serious, Critical	Total Cases/ 1M pop	Deaths/ 1M pop	Total Tests	Population
	World	12,872,339	568,312	7,502,157	4,801,870	58,807	1,651	72.9		
1	**USA**	3,356,242	137,414	1,490,702	1,728,126	15,819	10,138	415	41,773,190	331,060,504
2	**Brazil**	1,840,812	71,492	1,213,512	555,808	8,318	8,658	336	4,572,796	212,603,520
3	**India**	854,480	22,718	537,599	294,163	8,944	619	16	11,587,153	1,380,381,949
4	**Russia**	727,162	11,335	501,061	214,766	2,300	4,983	78	23,031,056	145,936,493
5	**Peru**	322,710	11,682	214,152	96,876	1,315	9,784	354	1,904,242	32,983,682
6	**Chile**	312,029	6,881	281,114	24,034	1,999	16,319	360	1,273,627	19,120,870
7	**Spain**	300,988	28,403	N/A	N/A	617	6,438	607	5,734,599	46,755,366
8	**Mexico**	295,268	34,730	180,852	79,686	378	2,289	269	723,668	128,969,990
9	**UK**	288,953	44,798	N/A	N/A	185	4,256	660	11,782,192	67,896,748
10	**South Africa**	264,184	3,971	127,715	132,498	539	4,453	67	2,108,570	59,328,450
11	**Iran**	257,303	12,829	219,993	24,481	3,359	3,062	153	1,972,207	84,021,254
12	**Pakistan**	248,872	5,197	156,700	86,975	2,118	1,126	24	1,562,638	220,990,656
13	**Italy**	242,827	34,945	194,579	13,303	67	4,016	578	5,900,552	60,458,858
14	**Saudi Arabia**	229,480	2,181	165,396	61,903	2,230	6,589	63	2,226,290	34,827,377
15	**Turkey**	211,981	5,344	193,217	13,420	1,194	2,513	63	3,930,223	84,363,898
16	**Germany**	199,812	9,134	184,500	6,178	278	2,385	109	6,376,054	83,792,278
17	**Bangladesh**	183,795	2,352	93,614	87,829	1	1,116	14	943,524	164,734,934
18	**France**	170,752	30,004	78,388	62,360	496	2,616	460	1,384,633	65,278,075
19	**Colombia**	145,362	5,119	61,186	79,057	875	2,856	101	1,006,093	50,897,758
20	**Canada**	107,347	8,773	71,266	27,308	2,156	2,844	232	3,183,516	37,751,539
21	**Qatar**	103,128	146	98,934	4,048	141	36,729	52	409,199	2,807,805
22	**Argentina**	97,509	1,810	41,408	54,291	688	2,157	40	456,042	45,207,451
23	**China**	83,594	4,634	78,634	326	3	58	3	90,410,000	1,439,323,776
24	**Egypt**	81,158	3,769	23,876	53,513	41	793	37	135,000	102,379,206
25	**Indonesia**	75,699	3,606	35,638	36,455		277	13	1,061,367	273,603,023
26	**Iraq**	75,194	3,055	43,079	29,060	400	1,869	76	671,478	40,241,752
27	**Sweden**	74,898	5,526	N/A	N/A	85	7,415	547	600,019	10,101,130
28	**Ecuador**	67,209	5,031	30,107	32,071	308	3,808	285	181,564	17,649,781
29	**Belarus**	64,932	464	55,380	9,088	89	6,872	49	1,134,653	9,449,221
30	**Belgium**	62,606	9,782	17,196	35,628	32	5,401	844	1,361,830	11,591,164

Results and Discussion

As the coronavirus disease 2019 (COVID-19) spreads, efforts are being made to reduce transmission *via* standard public health interventions based on isolation of cases and tracing of contacts. This contributes to reducing the size of the outbreak but cannot control the outbreak [**17**]. Other interventions that were recommended to reduce the outbreak include strengthening emergency departments, application of strict hygiene measures for the prevention and control of infection, and avoidance of close contact with patients suffering from respiratory tract infections. Efforts are being made to find drugs and vaccines that act against SARS-CoV-2 to control the outbreak of the virus (vaccine is under development). Supportive care is the main strategy for treatment; such as control fever, maintenance of hydration and nutrition, and oxygen therapy, etc.. Up to 76% of patients with COVID-19 require oxygen therapy. Some patients require endotracheal intubation such as patients with hypoxemic respiratory patients. Other patients require oxygen supplementation to maintain an oxygen saturation between 90%-96%. For patients who do not improve with oxygen therapy, high flow nasal cannula (HFNC) is recommended [**18-22**]. Thus, the first step is to ensure adequate isolation to prevent transmission to other contacts, patients, and healthcare workers. Mild illness should be managed at home with counseling about danger signs. The usual principles are maintaining hydration and nutrition and controlling fever and cough. Routine use of antibiotics and antivirals such as oseltamivir should be avoided in confirmed cases. In hypoxic patients, the provision of oxygen through nasal prongs, face mask, HFNC, or non-invasive ventilation is indicated. Mechanical ventilation and even extracorporeal membrane oxygen support may be needed. Renal replacement therapy may be needed in some. Antibiotics and antifungals are required if co-infections are suspected or proven. The role of corticosteroids is unproven; while current international consensus and WHO advocate against their use, Chinese guidelines do recommend short term therapy with low-to-moderate dose corticosteroids in COVID-19 ARDS. Detailed guidelines for critical care management for COVID-19 have been published by the WHO. There is, as of now, no approved treatment for COVID-19 [**19-22**].

Due to the characteristics of this virus, as it has a long incubation period, the infection can be transmitted to many people before symptoms appear, so preventive measures are very necessary, so prevention is very important. The greatest danger is the transmission of the virus to a healthcare worker as the virus has passed on to many of them, however, it is very important to follow a basic protocol to protect them and prevent the transmission of the disease to them and others by them. Those who deal with patients directly are isolated from others and do not deal with ordinary patients. The rooms and surfaces and equipment should undergo regular decontamination. To reduce the spread of the disease in geographical areas, each country quarantines travelers and people who dealt with the injured for 14 days to ensure that they are free of the virus and prevent its spread. As for society, the best ways to prevent coronavirus and other viruses are necessary to move away from crowded places, leave a safe distance between others and follow a healthy lifestyle that is mainly based on maintaining personal hygiene, eating healthy foods, good ventilation, sunlight penetration on all surfaces, adequate rest, using health masks and using sterilizers on an ongoing every 15-20min. People who already have a vitamin C deficiency are more likely and at risk to become infected with the virus. So vitamin C supplementation is very important for prevention according to many studies **[23-28]**.

Currently, no medication is proven to treat COVID-19 effectively, and no cure is available. **Antibiotics** aren't effective against viral infections such as COVID-19. The new coronavirus (COVID19) is a virus and, therefore, antibiotics should not be used as a means of prevention or treatment. However, if the patient hospitalized for COVID19 he may receive antibiotics because bacterial co-infection is possible. There is no evidence that **ibuprofen** or other non-steroidal anti-inflammatory drugs (**NSAIDS**) need to be avoided. Most patients have mild or no symptoms. However, mild cases are asymptomatic patients or patients with mild fever 37.5C^{o}, cough, cold symptoms, nasal congestion, malaise, and without dyspnea, however, isolation of the patients is the most important care step for them and to others.

The other approaches and strategies of the treatment depend upon the patient's situation and the symptoms. For example, if the patient has mild symptoms, it is recommended to stay at home for isolation of a period to avoid spreading the illness to others, as mentioned. If the patient is very ill, he may need to be treated in the hospital. Mild cases need supportive care and symptomatic treatment with antipyretic agents, if needed only, **paracetamol** is the first line and NSAIDs have caution in use, hydration and nutrition supplements should receive and ensure adequate calories intake. Frequent cough and fever monitoring. The organ function should routinely control, and any secondary infection should be prevented. All management is in their houses unless there are severe symptoms. If there is any development in the disease patient must refer to the healthcare center [**29, 30**].

Patients with confirmed COVID-19 disease and develop severe symptoms that have respiratory distress (less than 30 breath/min), oxygen saturation less than 90%, cyanosis, and shock must receive oxygen therapy by including nasal catheter and mask oxygenation and nasal high-flow oxygen therapy. If possible, inhalation of mixed hydrogen and oxygen (H_2/O_2: 66.6%/33.3%) can be applied to target

more than 91% of oxygen saturation in non-pregnant adults and 92-95% to pregnant ones at room air. The nasal cannula is preferred for children with respiratory distress because it is better to tolerate. High flow nasal catheter or non-invasive mechanical ventilation is used when the respiratory distress does not relive after standard oxygen therapy. High flow nasal catheters consider safer than non-invasive ventilation because many scientists suggest that it may associate with the nosocomial transmission of the disease. About one third or two-third of critically ill-patients needs them. If the patient doesn't improve in time nearly 1-2 hour invasive mechanical ventilation should be considered. The invasive mechanical ventilation used to avoid ventilator-induced lung injury while facilitating gas exchange *via* lung-protective ventilation. Patients with severe symptoms should be equipped with pulse oximeters, functioning oxygen systems and disposable, single-use, oxygen-delivering interfaces (nasal cannula, nasal prongs, simple face mask, and mask with reservoir bag), and should have regularly mentoring of the vital sign. In the case series of 99 hospitalized patients with COVID-19 infection from Wuhan, oxygen was given to 76%, non-invasive ventilation in 13%, mechanical ventilation in 4%, extracorporeal membrane oxygenation (ECMO) in 3%. Antiviral therapy consisting of **oseltamivir**, **ganciclovir**, and **lopinavir**-**ritonavir** was given to most patients (see later) **[22, 28. 31]**. Patients with severe COVID-19 develop a systemic inflammatory response that can lead to lung injury and multisystem organ dysfunction, it has been proposed and/ or given a potent anti-inflammatory (**corticosteroids**), which might prevent or mitigate these harmful effects (see later). In Palestine, the treatment and management protocols of COVID-19 are similar to the strategies and protocols in other countries, especially those who follow the guidelines of WHO.

However, Hospitals and research labs all over the world are testing many different therapies on coronavirus-positive patients to find potential COVID-19 treatment. Below we highlight the medications, treatments, and management that have been applied to coronavirus.

Antimalarial Drugs

Chloroquine and its analogs (e.g. **hydroxychloroquine**) are employed for the treatment and prevention of malaria in the 1900s. In addition to that, they possess immunomodulatory effects for the treatment of autoimmune diseases as systemic lupus erythematosus and rheumatoid arthritis. They have also antiviral properties especially for viruses that induced inflammation like Ebola, HIV, and SARS. These agents are non-protonated, when they are introduced intracellularly they become protonated and increase the pH of the corresponding cell. The pH changes inhibit viral infusion with the cell membrane of the host. They can also inhibit nucleic acid replication and appear to interfere with the terminal glycosylation of ACE2 receptor expression which shall prevent SARS-CoV-2 receptor binding and subsequent spread of infection. Studies have shown that chloroquine, has a potent cytotoxic response with 99% inhibition of viral replication, moreover *in-vivo* models show high inhibition of viral spread before viral exposure, it concludes that they may be used as a prophylactic agent. The working group is expressed against the possible use of **chloroquine**, and **hydroxychloroquine** in prophylaxis for COVID-19. At present, there is no evidence of the efficacy of this drug in the prevention of disease COVID-19. Savarino et al hypothesize that chloroquine might block the production of pro-inflammatory cytokines (such as interleukin-6), thereby blocking the pathway that subsequently leads to acute respiratory distress syndrome (ARDS). Based on this finding, the experts and organizers of clinical trials suggested that chloroquine is a promising antiviral agent against SARS-CoV-2. **Hydroxychloroquine** showed a safety profile and three times more potent than chloroquine in cytotoxic response, so less dose of hydroxychloroquine is used. Taking also into account that therapy would be likely required mostly in older patients and/or in case of severe disease (at least for the moment). A study, suggests that SARS-CoV-2 positivity in nasopharyngeal secretions (measured by RT-PCR) is significantly decreased at day 6 after inclusion (i.e. day 10 after symptom onset) in **hydroxychloroquine**-treated COVID-19 patients (n=26) versus patients who received supportive care only (n=16 external controls). However, the study has a limitation of small size and the non-homogeneous group they consider as the first line for severely ill patients. At the same time, it is not recommended for out-patients because there is no sufficient study for efficacy and cost benefits **[30-35].** In *vitro* pharmacokinetic models suggest using a loading dose of **hydroxychloroquine** 400 mg orally twice daily on day one, followed by 200 mg orally twice daily for four days. While it recommends the use of the drug at a dose of 500 mg BID for 10 days, alternatively if this dose is not available, chloroquine and hydroxychloroquine 200 mg BID can be used. These agents have mostly tolerated with patients but it has gastrointestinal adverse effect and toxicity; cause neuropathy, retinopathy, and cardiomyopathy; but that happened with a long time, not in short term use. Concurrent administration of QTc prolonging agents and strong CYP2D6 inhibitors (chloroquine only) should be avoided to minimize cardiac adverse effects. Although the manufacturer's labeling of chloroquine and hydroxychloroquine caution against their use in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency, there are limited data to support this risk and no incidence of hemolytic anemia has been seen in patients with G6PD in 30 years of drug exposure. **Hydroxychloroquine** has been demonstrated to affect SARS-CoV-2 as studies showed the efficacy of hydroxychloroquine in reducing viral nasopharyngeal carriage of SARS-CoV-2 in COVID-19 patients in an average

of three to six days only, but, the FDA invalidates the emergency use authorization (EUA) that permitted the use of **chloroquine** and **hydroxychloroquine** to treat certain patients with COVID-19 [**35, 36**].

Antiviral Drugs

Many clinical trials are testing various potential antivirals, until now there no current evidence to recommend any specific anti-COVID-19 treatment. Investigational anti-COVID-19 therapeutics should be used only if approved by controlled trials. Different antiviral therapies were given to most patients. Based on personal accounts and experience rather than facts or research, **remdesivir**, a broad spectrum anti RNA drug developed for Ebola can be used in the management of COVID-19, further research is going on about this drug. Antiviral drugs such as **ribavirin**, **lopinavir-ritonavir** have been used based on the experience with SARS and MERS.

Remdesivir is pro-drug which contains 1'-cyano-substituted adenosine nucleotide analog, in which its action is to metabolize the cell and tissue to activate the nucleoside triphosphate (GS-443902) which shall inhibit the viral RNA-dependent RNA polymerases in the viral infectious cycle cascade. The second action of this drug, it also may involve lethal mutagenesis and chain termination of the virus. Initially, it is developed for the treatment of Ebola hemorrhagic fever, but it has no approval until now for any indications. Nucleotide analogs use for RNA viral for inhibition of viral replication by suppression of polymerases enzyme, however, many viruses have resistance these agents to result in exo-ribonuclease proofreading and removal; **Remdesivir** has the potential to avoid this. *In vitro* study, **Remdesivir** showed activity in human lung epithelial cells against coronaviruses. In China, two phases 3 randomized, open-label trials, NCT04292899 and NCT04292730, initiated by the manufacturer (Gilead) were carried out to evaluate the safety and antiviral activity of Remdesivir (5- and 10-day regimens of), in conjunction with the standard of care in patients with severe and moderate COVID-19, which are estimated to finalize patient recruitment by May 2020. These clinical trials demonstrating that **remdesivir** improved clinical outcomes by several different measures. The results showed that when treating patients with moderate disease – those with pneumonia who do not require supplemental oxygen – a 5-day course of remdesivir led to greater clinical improvement than the standard of care alone. The totality of clinical data shows that remdesivir has potential benefits to patients with COVID-19 and offers important hope in the treatment of the disease. In the United States, **Remdesivir** has been used for 4-10 days until the respiratory symptoms improved. Remdesivir is used as 200 mg IV loading dose within 30 minutes then 100mg OD for 2-10 days. Some adverse effects appear while using Remdesivir as nausea, vomiting, rectal bleeding, and elevated aminotransferase level. However, it is still not clear that those effects are generally from the disease or the drug itself. No clinical study to elucidate the usage of the drug for pregnant women and drug-drug interaction is still not reported. It is also reported that Remdesivir reduced the viral load in lung tissue in mice affected with MERS-CoV and improved lung function [**37-40**]. Remdesivir is an investigational antiviral drug that is being studied in multiple ongoing international clinical trials, and the safety and efficacy of remdesivir for the treatment of COVID-19 are not yet established. Remdesivir has not been approved by the U.S. FDA for any use until now. However, **remdesivir** is considering the most promising antiviral drug, to be potent against SARS-CoV-2.

Lopinavir is an aspartic acid protease inhibitor. Proteases are essential enzymes for replication and maturation of viruses, so Lopinavir inhibits the spread of the virus in the host cell. **Ritonavir** combined to boots half live of Lopinavir by inhibition of CYP450. The drug has been approved for use in the treatment of HIV. It was found that **lopinavir/ritonavir** has anti-SARS-CoV and MERS-CoV activity *in vitro*. In South Korea, an infected patient with COVID-19 received lopinavir/ritonavir; after eight days of admission, symptoms improved and coronavirus load began to decrease until no longer it's detectable. A recent study also showed that **Lopinavir/Ritonavir** affects the inhibition of 3-chymotrypsin like protease which found to be a novel coronavirus. In another study, Bin Cao et al elucidates that there is no benefit associated with Lopinavir/Ritonavir in severely ill patients. However, there are still trials suggest that Lopinavir/Ritonavir has possible benefits in patients who were treated before 12 days of symptom.; the available doses are 400/100 mg or 200/100 mg. If **Lopinavir/Ritonavir** is used as an adjunctive agent for COVID-19, a dose of 400 mg/100 mg by mouth twice daily for 14 days is recommended. The usage of **Lopinavir/Ritonavir** is associated with gastrointestinal toxicities, diarrhea, and vomiting; however, administering it with food may amend these effects. According to multiple collected data, **Lopinavir/Ritonavir** is not associated with teratogenicity effects in pregnant women with HIV, so it can be used if there isn't a present of any contraindication. These agents still require the second line for COVID-19 treatment in the case when chloroquine is contraindicated [**41-47**].

Ribavirin is a prodrug of purine nucleoside analog with broad-spectrum antiviral activity, which its derivative in the liver to closely mimic the purine analog guanosine which incorporates with RNA. The structural elements prohibit the subsequent addition of nucleoside analogs, effectively stop the synthesis of RNA; **Ribavirin** works by inhibiting RNA synthesis of viruses. It has been used to treat HCV, RSV, hepatitis C, B, and respiratory viruses. In 126 cases treated with ribavirin, hemolysis and anemia occurred in up to 76% and 49% of cases respectively, however, no

effect to use Ribavirin as monotherapy, but it gives potential activity when combined with other anti-viral agents such as Lopinavir/Ritonavir or chloroquine analogs. In a controlled study in patients with SARS, patients treated with lopinavir/ritonavir with ribavirin had better outcomes as compared to those given ribavirin alone; because Lopinavir works by inhibiting the decomposition of gag-pol protein, while ritonavir works by inhibiting the decomposition of gag-pol protein precursor and inhibiting lopinavir metabolism, thus increasing its concentration. Oral ribavirin has been dosed as a 4-gram loading dose followed by 1.2 grams every eight hours in two small studies for SARS. In the management of COVID-19, data is limited to ongoing studies using a dosing strategy of 400 mg by mouth twice daily for 14 days as a part of a combination regimen. Ribavirin needs special precaution while usage, because it is associated with hemolytic anemia, especially after taking a high dose (1-2 gm), which is needed for coronaviruses treatment. **Ribavirin** is a teratogen, with a significant potential for embryonic toxicity and is usually contraindicated in women who are pregnant and in male partners of those pregnant women. Ribavirin in combination with other immunosuppressive therapies, particularly azathioprine or IFN can lead to severe side effects (e.g. myelosuppression, myelotoxicity, pancytopenia, anemia, etc.). **Ribavirin** is usually used in combination therapy to treat MERS-CoV and HCoV-OC43. Ribavirin and INF-α combination therapy are efficient in treating MERS-CoV. A study compared between ribavirin and lopinavir/ritonavir in treating severe acute respiratory syndrome (SARS). Patients treated with lopinavir/ritonavir had a lower risk of acute respiratory distress syndrome and death. More studies about **Ribavirin** still needed to determine whether it is effective in treating COVID-19 or not. However, **ribavirin** side effects like anemia limited its use [**48-50**].

The optimal management of COVID-19 is evolving and updated quickly. However, many antivirals are being under clinical trials to find drugs that are effective against the virus. Several clinical trials are currently looking at **Oseltamivir** in combination with other medications for coronavirus. Other antivirals being tested for COVID-19 include **umifenovir** and **galidesivir**. **Arbidol** (**Umifenovir**) is an antiviral used to treat the influenza virus. A study found that Arbidol can inhibit SARS-CoV-2 *in vitro*. Another antiviral that may have anti-SARS-CoV-2 activity is **Favipiravir**. Favipiravir is an RNA-dependent RNA polymerase (RdRP) inhibitor. It has anti-influenza activity and it can block the replication of filo-, alpha-, arena-, and other RNA viruses. When entering the cells, Favipiravir is converted to its active form Favipiravir-RTP and it is recognized as a substrate by viral RNA polymerase, thus inhibiting its activity [44, 45]. **Favipiravir** *in vitro* studies shown that at high doses was able to prevent human cells from being infected with SARS-CoV-2. The patients who took favipiravir also showed greater improvements in their lungs; based on chest images. **Favipiravir** also found to help to clear the virus faster than lopinavir/ritonavir (4 days vs. 11 days, respectively). Therefore, Favipiravir may be effective against SARS-CoV-2. **Umifenovir** (Arbidol) was not as good as favipiravir in helping patients recover in a study from China. However, it seems to be better than lopinavir/ritonavir at helping patients with COVID-19 clear the virus. **Galidesivir** is a new drug that is currently being developed for a variety of viral infections; it has not yet been approved for human use. Clinical trials for **galidesivir** are starting in Brazil. According to the National Health Commission (NHC) of the People's Republic of China for provisional treatment of COVID-19, several antivirals are recommended including, IFN-α, lopinavir/ritonavir, and ribavirin (Table 2). More evidence is needed before these drugs are recommended. Other drugs proposed for therapy are arbidol (an antiviral drug available in Russia and China), intravenous immunoglobulin, interferons, chloroquine, and plasma of patients recovered from COVID-19. Additionally, recommendations about using **traditional Chinese herbs** find a place in the Chinese guidelines (see later). Chloroquine phosphate and arbidol are also recommended. Azithromycin has been recommended to use with hydroxychloroquine to give a synergistic effect in treating COVID-19. **Azithromycin** has been shown to prevent severe respiratory tract infection and has activity against Ebola and Zika viruses [**51-54**]. **Table-2** Summarized the most important antiviral drugs used and/ or tested in treating COVID-19; including their doses, methods of administration and duration of treatment

Table 2: Antivirals included in the NHC guidelines (version 6) for treatment of COVID-19

Drug	Dosage	Method of Administration	Duration of Treatment
IFN-α	5 Million U or equivalent dose each time, 2 times/day	Vapor inhalation	No more than 10 days
Lopinavir/Ritonavir	200 mg/50 mg/capsule, 2 capsules each time, 2 times/day	Oral	No more than 10 days
Ribavirin	500 mg each time, 2 to 3 times/day in combination with **IFN-α** or **lopinavir/ritonavir**	Intravenous infusion	No more than 10 days
Chloroquine phosphate	500 mg (300 mg for **chloroquine**) each time, 2 times/day	Oral	No more than 10 days
Arbidol	200 mg each time, 3 times/day	Oral	No more than 10 days

Immunosuppressive Drugs

Tocilizumab is a humanized anti-interleukin 6 monoclonal antibody for the treatment of rheumatoid arthritis. It inhibits the interleukin 6 signaling pathway and competes with interleukin 6 binding sites on the cell membrane, so it inhibits the inflammation pathway. It's hypothesized that it works against cytokine storm with raised ferritin and interleukin-6 levels due to SARS-CoV-2. Published data from Wuhan indicates that **tocilizumab** added to **Lopinavir**, **methylprednisolone**, and oxygen therapy in 20 patients with severe COVID-19 resulted in rapid reductions in fever in all patients, improvement in oxygenation for 75%, and facilitated discharged from the hospital in 95% of patients. **Tocilizumab** for most indications is weight-based with a maximum dose of 800mg. The dosing of tocilizumab for COVID-19 is still not well established. When used in a case series of patients with COVID-19, a one-time dose of intravenous tocilizumab 400 mg was administered. However, until now, there are no peer study approved uses of **Tocilizumab**. Other medications that affect the body's immune response are also being tested for COVID-19; these include **acalabrutinib**, **tofacitinib**, **ruxolitinib**, **baricitinib**, **anakinra**, **canakinumab**, **apremilast**, and **sarilumab**, which works similarly to **Tocilizumab**. Early of their results were not promising; it is shown that patients with severe symptoms who given **Sarilumab,** became worse compared to placebo, but patients who had even more severe (critical) symptoms improved compared to placebo. Thus, it is most likely there are other patients factor/s that influenced the treatment. However, the researchers are now scaling back their studies of these drugs to include only COVID-19 patients in critical condition [**55-57**].

Interferon (**INF-α**) is an endogenous protein released by the host cell in action of inflammation and infection. It stimulates the immune response against viral replication. INF-α is a broad-spectrum antiviral that is used in many viral infections, such as hepatitis. This non-specific immune-modulatory response makes this therapy attractive to use in COVID-19 treatment. When interferon used for SARS, it has an action before exposure to infection *via* the inhibition of the virus replication; it inhibits the replication of SARS-CoV and MERS-CoV. It is also used in combination therapy with other antivirals such as **ribavirin** and **lopinavir/ritonavir**. However, still, there is no approved action after viruses' exposure; *In vivo* studies needed to replicate the same benefits. Some studies showed there is no influence on the disease course for MERS, while others suggest a small improvement in survival at 14 days but not 28 days; when used in combination with ribavirin. Due to the lack of established human data with IFNs for COVID-19, this therapy should only be considered for COVID-19 as a part of a clinical trial. There is no established dosing regimen for IFN in the treatment of COVID-19 available. The only available data used for MERS treatment was *via* using a dose of 180 µg per week for 2 weeks [**58-61**].

Convalescent Plasma

The use of **convalescent plasma** was recommended as an empirical therapy during the outbreak of the Ebola virus. It was also recommended as a protocol for the treatment of MERS-CoV. The presence of viruses in the blood usually peaks in the first week and a potential immune response is likely to be developed; in the second weak where serum cytokines increase above the normal range; neutralizing antibodies to various proteins 2-3 weeks following infection are also developed in the patient blood; i.e. IgG immunoglobulin began to increase in the third week of onset, and peaks at the twelfth weak. However, Some studies found that **convalescent plasma** might suppress the presence of viruses in the blood. Other studies also showed that convalescent plasma could reduce serum cytokine response; this indicates that convalescent therapy is only effective in the early stages of the disease. Researchers hope that convalescent plasma can be given to people with severe COVID-19 to boost their ability to fight the virus. Thus, now **convalescent plasma** therapy is considered as another treatment; which is at present under investigation; for its efficacy against the SARS-CoV-2 virus. On March 24, 2020, the FDA issued an Emergency Investigational New Drug (eIND) application for the use of convalescent plasma to treat people with COVID-19. The therapeutic effect of convalescent plasma is dependent upon the level of SARS-CoV-2 neutralizing antibody titer (NAT). One study found that convalescent plasma with NAT ≥ 1:16 reduced mortality of influenza. However, it is better to take plasma from patients who have recovered and are at week 12 of onset with NAT level of ≥ 1:16. Many studies have now reported on the use of **convalescent plasma** to treat severely or critically ill COVID-19 patients, without unexpected or serious adverse events. Many patients improved clinically and cleared the virus, however, the role of the convalescent plasma treatment in these patients is unclear because all patients received at least one additional therapy, including antivirals, antibiotics or antifungals, and corticosteroids. Therefore, more studies are needed to prove **convalescent plasma** effectiveness in treating COVID-19. Convalescent plasma therapy carries the risk of allergic reactions, lung damage and difficulty breathing, and transmission of infections, including HIV and hepatitis B and C. However, donation of the **convalescent plasma** guidelines and protocols should be followed [**62**].

Corticosteroids

Patients with severe COVID-19 develop a systemic inflammatory response that can lead to lung injury and

multisystem organ dysfunction. It has been proposed that the potent anti-inflammatory effects of **corticosteroids** might prevent or mitigate these harmful effects. There are different factors to consider in giving **dexamethasone** to patients with COVID-19 which include; review the patient's medical history and assess the potential risks and benefits of administering corticosteroids, monitor COVID-19 patients for adverse effects (e.g., hyperglycemia, secondary infections) after administration dexamethasone, and review a patient's medication regimens to assess potential interactions as **dexamethasone** is a CYP3A4 inducer. The dose recommended of **dexamethasone** is 6 mg per day for up to 10 days; in patients with COVID-19 who are mechanically ventilated (AI) and in patients with COVID-19 who require supplemental oxygen but who are not mechanically ventilated (BI). It isn't recommended using dexamethasone in patients with COVID-19 who do not require supplemental oxygen (AI). **Corticosteroids** are recommended for patients with sepsis in whom adequate fluids and vasopressor therapy didn't restore hemodynamic stability. In those cases, you should balance the potential small reduction in mortality with the prolonged shedding of coronavirus. Systemic corticosteroids as mentioned previously are indicated as adjunctive therapies for COVID-19, in the case of asthma exacerbation or COPD and septic shock, otherwise, it should be avoided due to the lack of effectiveness and possible harm including avascular necrosis, psychosis, diabetes, and delayed viral clearance; in addition to, higher risk of mortality and secondary infections. When using **corticosteroids**, it is mandatory to monitor and treat hyperglycemia, hypernatremia, and hypokalemia. When stopping corticosteroids taper down the dose, and monitor the recurrence of inflammation and the signs of adrenal insufficiency **[63-65].**

Antenatal corticosteroid therapies are recommended for pregnant women at risk of preterm birth from 24 to 34 weeks of gestation when there is no clinical evidence of maternal infection. However, when a woman presents with mild COVID-19, the benefit of antenatal corticosteroid might outweigh the risks of potential harm to the mother. Due to limited data, there is no evidence suggesting that pregnant are at higher risk of severe illness or fetal compromise; mother-to-child transmission of the virus is still not approved. Samples taken from amniotic fluid, cord blood, vaginal discharge, neonatal throat swabs, or breast milk were negative. Pregnant women in the third trimester especially those who develop pneumonia may suffer from premature rupture of membranes, fetal distress, and preterm birth, preeclampsia, and cesarean delivery for fetal distress. WHO recommends that the cesarean section should be done only when medically justified. Emergency delivery and pregnancy termination decisions are based on many factors such as gestational age, the severity of the maternal condition, and fetal viability and well-being. Neuraxial anesthetic advantages in laboring women providing good analgesia reduce cardiopulmonary stress from pain and anxiety in emergency cesarean by which it limits the need for general anesthesia. The use of nitrous oxide for labor analgesia should be avoided, because of insufficient data about cleaning, filtering, and potential aerosolization of nitrous oxide systems. The use of **magnesium sulfate** for maternal seizure prophylaxis or neonatal neuroprotection may further depress respiration. Consultation with maternal-fetal medicine and pulmonary/critical care specialists is advised. The use of interventions such as a birth ball or peanut ball should be limited because it can increase the risk of infection. Intrapartum oxygen has no proven fetal resuscitation benefit; so it should be abandoned. At delivery of patients COVID-19, institutions have been chosen to prohibit delayed cord clamping in term infants to minimize newborn exposure to the virus. Use **acetaminophen** to relieve postpartum pain if possible, as NSAIDs are needed to use the lowest effective dose. No virus was found in the breast milk of six infected patients. However, close contact during breastfeeding could transmit droplets to the baby. Breastfeeding protects against morbidity in the post-neonatal as it is a passive source of antibodies and other anti-infective factors. Therefore, standard infant feeding guidelines should be followed with appropriate precautions for infection prevention and control. The earlier initiation of breastfeeding results in greater benefits; like increase ability to defense infections, reduce the risk of diarrhea, and increase the survival rate of children. If mother and baby have been separated because the mother is too unwell to breastfeed or express breast milk; the infant is fed expressed breast milk by another healthy caregiver who follows hygiene precautions and uses strict hand washing before pumping and wears a mask during pumping, the pumping equipment should be cleaned by a healthy person. If feeding by a healthy caregiver is not possible, mothers with confirmed COVID-19 should take precautions to prevent transmission of the virus to the infant during breastfeeding such as hand hygiene, use of a face mask, clean and disinfect surfaces which the symptomatic mother has been in contact. Due to the high prevalence of mental disorders among women in the postpartum period more widely interventions should be implemented to these women **[63-65].**

Miscellaneous Drugs

In vitro study found that **ivermectin** can stop SARS-CoV-2 from replicating. **Ivermectin**, an FDA-approved anti-parasitic previously shown to have broad-spectrum antiviral activity *in vitro*. It inhibited the causative virus (SARS-CoV-2), as the single addition of the drug to Vero-

hSLAM cells 2h post-infection with SARS-CoV-2 reduces the virus by about 5000-fold within 48h. **Ivermectin**, therefore, warrants further investigation for possible benefits in humans, and a lot more research is needed to see if the doses studied would be safe and effective against the virus in humans [**66**]. Researchers think that **colchicine** could work similarly to tocilizumab in COVID-19 patients in that it might be helpful if the immune system becomes too activated and a cytokine storm occurs. A large clinical trial is currently running to see if **colchicine**; when given soon after a COVID-19 diagnosis, can lower the chances of hospitalization and death. One research investigated **azithromycin** in combination with **hydroxychloroquine** for COVID-19. They reported that 93% of patients cleared the virus after 8 days, but there was no control group; so we don't know if people would have cleared the virus on their own or due to the medications. There are also concerns about potentially serious side effects; when using azithromycin and hydroxychloroquine together **[67, 68].**

Based on clinical observations; different protocols, guidelines, and recommendations in treating COVID-19 were shown in **Tables 3, and 4**. However, different countries such as Italy, and Belgian established their protocols and guidelines for COVID-19 treatment, which summarized in **Tables 3, and 4**.

Table 3: Italian Society of Infectious and Tropical Diseases Section Therapeutics Protocol [69, 70]. *CPS= Compendium of Pharmaceuticals and Specialties*

Clinical observation	Recommendation
Patient positive for COVI-19 asymptomatic or mild symptoms: (fever (> 37.5 ° C), cough, cold symptoms without dyspnea), age <70 years with no risk factors (COPD, diabetes and heart disease) and RX normal chest	Clinical observation, supportive care
Patient positive for COVI-19 with mild respiratory symptoms but age> 70 years and/or with risk factors (COPD, diabetes and heart disease) or symptomatic or mild symptoms (fever (> 37.5 ° C), cough, dyspnea on mild to moderate) and chest radiography with pneumonia framework	**Lopinavir / ritonavir** 200/50 mg cps, 2 x 2 / day (800 mg **darunavir** alternatively 1 cp / day + **ritonavir** 100 mg 1 cp / day or **darunavir** / **cobicistat** 1 cp 800/150 mg / day) 500 mg + **chloroquine**, 1 x 2 / day or **hydroxychloroquine** cps 200 mg, 1 x 2 / day. Duration of therapy: 5 to 20 days, with timing to be determined according to clinical evolution.
Case of need for oxygen therapy or rapid clinical deterioration (see "supportive measures" and COVID respiratory severity scale)	**Remdesivir** requests for compassionate use. At the time of its availability suspend LPV / RTV (or DRV / b) and continue with: **Remdesivir** vials 150 mg period: 1 day 200 mg IV 30 minutes then 100 mg IV / day for another 9 days in combination with **chloroquine** 500 mg, 1 x 2. day or **hydroxychloroquine** 200 mg, 1 x 2 / day (duration of therapy: from 5 to 20 days, with timing to be determined according to clinical evolution). If the patient has a BCRSS score. Evaluate 2: **dexamethasone** 20 mg/day for 5 days and then 10 mg/day for 5 days (as indicated by intensivistica) and/or **Tocilizumab**
Positive Patient COVID for-19 with the x-ray of severe pneumonia, ARDS or global respiratory insufficiency, hemodynamic failure, need for mechanical ventilation (invasive or not)	**Remdesivir** 1 days 200 mg iv as a loading dose, then 100 mg/day (days 2-10) + **chloroquine** 500 mg, 1 x 2 / day or **hydroxychloroquine** 200 mg x 2 via SNG (duration of therapy: from 5 to 20 days, with timing to be determined according to clinical evolution).
Patients ARDS: after 24 hours from the diagnosis of ARDS.	**Dexamethasone** 20 mg / day for 5 days and then 10 mg / day for 5 days (as indicated by intensivistica) and / or **tocilizumab**.

Table 4: Belgian recommendation for patients with COVID-19 [71]

Clinical observation	Recommendation
Suspicion of COVID-19 (Mild-to-moderate symptoms (no dyspnea), No risk group	Symptomatic treatment. Use **paracetamol** as first-line
Suspicion of COVID-19. Mild-to-moderate symptoms (no dyspnea). Risk group or Suspicion of COVID-19 and alarming symptoms (dyspnea)	Case by case discussion, if possible with a communicable disease Specialist, to initiate an empirical antiviral therapy, supported the potential delay to get results (**antiviral therapy** is anticipated to be more efficient if started early within the course of the disease), or On other considerations (high risk of secondary complications).
Confirmed COVID-19. Mild-to moderate disease (no O2 requirement/no evidence of pneumonia)	Consider start **hydroxychloroquine** (Plaquenil®) IF NO CONTRAINDICATION • 400 mg at suspicion/diagnosis; • 400 mg 12 h later • Followed by 200 mg BID up today 5. If no **hydroxychloroquine** available, consider **chloroquine** base 600 mg (10mg/kg) at diagnosis and 300mg (5 mg/kg) 12 h later, followed by 300 mg (5 mg/kg) BID up to Day 5 or **chloroquine phosphate** 1000 mg at diagnosis and 500mg 12h later, followed by 300mg BID up to day 5.
Confirmed COVID-19 Severe disease ≥ 1 of the following: Respiratory rate ≥30/min (adults), ≥40/min (children < 5), Blood oxygen saturation ≤93%, PaO2/FiO2 ratio 50% of the lung field within 24-48 hours	Start **hydroxychloroquine** (Plaquenil®) IF NO CONTRAINDICATION • 400 mg at diagnosis; • 400 mg 12 h later • Followed by 200 mg BID up today 5. Consider **Lopinavir/ritonavir** 400/100 mg (2 tablets of 200/50 mg) BID for 14 days) as second choice ONLY if **hydroxychloroquine/chloroquine** contra-indicated and provided it can be administered within 12 days after symptoms onset
Confirmed COVID-19 Critical disease ≥ 1 of the following: Acute Respiratory Distress Syndrome, Sepsis, Altered consciousness, and Multi-organ failure	**Remdesivir** (compassionate use) • 200 mg loading dose (IV, within 30 min) • 100 mg OD for 2 to 10 days. If **Remdesivir** unavailable: Consider **hydroxychloroquine**, crushed in the nasogastric tube, at the same dosage and monitoring as above; replace with **Remdesivir** if it becomes available.**Tocilizumab** and other **interleukins** (6 or 1) **blockers**: ***Some Chinese, Italian and (very limited) Belgian clinical experience (unpublished) suggest a favorable effect in the most critical patients***

Herbal Medicine

Herbal medicine is considered one of the alternative approaches in the treatment of COVID-19. Herbal medicine in the past has played an important role in controlling infectious diseases. Clinical evidence from a range of studies of herbal medicine in the treatment of SARS coronavirus (SARS-CoV) has shown significant results and supported the idea that herbal medicine has a beneficial effect in the treatment and prevention of the diseases. The NHC in China has announced using herbal medicine combined with conventional medicines as a treatment for COVID-19 and has issued many guidelines on herbal medicine-related therapy. There are many reports on the effects of the usage of herbal medicines in the treatment of COVID-19. However, different herbal medicines have been evaluated for their effectiveness and adverse reactions in the treatment of COVID-19. This includes **Lianhuaqingwen capsules** and **Jinhuaqinggan granules** for mild conditions, and **Xuebijing** (injectable) for severe conditions. These drugs are now widely used to treat COVID-19 in China. The official claimed that these herbal drugs can effectively relieve symptoms, such as fever, cough, and fatigue, and reduce the probability of patients developing severe conditions, but without giving further details. So far, no clinical trials of herbal drugs have been reported [**72-75**].

Many traditional remedies have been proclaimed as Covid-19 treatments, the two distinguished ones are **Lianhua Qingwen**; containing 13 herbs such as **forsythia suspense** and **Rhodiola rose**, and **Jinhua Qinggan**; which was developed during the 2009 H1N1 outbreak and is made of 12 components including **honeysuckle**, **mint**, and **licorice**. **Table 5** summarized potential Chinese herbal medicines with their effect and mechanism of action as antiviral medications, that may treat COVID-19. Out of these herbal medicines, **six compounds** include **quercetin**, **andrographolide**, **glycyrrhizic acid**, **baicalin**, **patchouli alcohol**, and **luteolin** were discussed below (**Table 5**) [**72-75**].

Table 5: Summary of potential Chinese herbal medicines against SARS-CoV-2 [74].

Potential Natural Compounds	Effect or Mechanism of Antiviral
Quercetin	Inhibits 3CLpro and interacts with viral HA protein to inhibit virus entry into the cell
Andrographolide	Inhibits 3CLpro and virus-induced activation of RLRs signaling pathway
Glycyrrhizin	Inhibits replication, adsorption, and penetration of the virus
Baicalin	Inhibits 3CLpro and HIV-1 Env protein-mediated fusion with cells expressing CD4/CXCR4 or CD4/CCR5.
Patchouli alcohol	Inhibits activation of PI3K/Akt and ERK/MAPK signaling pathways to block viral infection and replication
Luteolin	Inhibits 3CLpro and the expression of the coat protein I complex and interferes with viral replication at an early stage of infection
Hesperidin	Inhibits 3CLpro
Emodin	Blocks the SARS-CoV spike protein and ACE2 interaction and inhibits 3a protein to reduces virus release;
Resveratrol	Inhibits RNA and nucleocapsid expression
Kaempferol	Inhibits 3a channel protein
Lignan	Inhibits virus replication and 3CLpro
Betulinic acid	Inhibits virus replication and 3CLpro
Tanshinone	Inhibits 3CLpro and PLpro
Cryptotanshinone	Inhibits 3CLpro and PLpro
Dihydrotanshinone I	Inhibits 3CLpro and PLpro
Tanshinone IIA	Inhibits 3CLpro and PLpro
Curcumin	Inhibits virus replication and 3CLpro
Shikonin	Inhibits 3CLpro
Matrine	Improves abnormal laboratory parameters and clinical symptoms in patients, and significantly shortens the time to nucleic acid conversion

Quercetin, a flavonoid compound, is widespread in fruit and vegetables. As a dietary source compound, **quercetin** exerts diverse biological activities including anti-inflammatory, anti-oxidant, anti-viral, anti-allergic, anti-cancer, mood-improving as well as vasoprotective. Studies have found that **quercetin** exhibits antiviral properties against a variety of viruses, including Influenza A Virus (IAV), Hepatitis C Virus (HCV), Enterovirus 71 (EV71), and SARS-CoV, etc. It has been confirmed that **quercetin** showed a good inhibitory effect on SARS-CoV 3CLpro expressed in Pichia pastoris, with an inhibition rate of 82 %. Besides, enzyme inhibition assays *in vitro* also showed that **quercetin** had inhibitory activity against SARS-CoV 3CLpro. However, it has not been documented whether quercetin inhibits SARS-CoV-2, but, **Quercetin** has a wide range of sources with relatively low cost, so it is worth testing its efficacy against SARS-CoV-2 infection [**72-75**].

Andrographolide, the main active component isolated from the extract of the herb **Andrographis paniculata**, has a wide range of biological activities including immunity regulation, anti-virus, anti-bacteria, anti-parasite, anti-tumor, and anti-hyperglycemia. Many studies have shown

that **andrographolide** has a broad spectrum of antiviral properties, which inhibits various virus infections including influenza A virus (IAV), human immunodeficiency virus (HIV), Chikungunya virus (CHIKV), dengue virus (DENV), and Enterovirus D68 (EV-D68). It is suggested that **andrographolide** may exert broad-spectrum antiviral activity by interfering with a variety of cellular pathways (including autophagy, unfolded protein response (UPR) pathway and oxidative stress, etc.). It is further found that the anti-dengue virus activity by acting on GRP78, a key regulator of unfolded protein response. Also, it is found that **andrographolide** exerts antiviral activity against H1N1 by inhibiting the activation of RLRs signaling pathways and thereby improving H1N1 virus-induced cell death. Therefore, these indicated that **andrographolide** has potential efficacy against SARS-CoV-2 especially **andrographolide** found to be a potent inhibitor of SARS-CoV-2 3CLpro through in silico studies. Thus, **andrographolide** is widely distributed with low cytotoxicity, and its potent antiviral activity against a variety of viruses needs further investigation [**72-75**].

Glycyrrhizic acid is a plant product isolated from the traditional Chinese medicine **licorice** (Chinese name; **Gan Cao**). **Glycyrrhiza uralensis** contains active ingredients such as **thymol** and **carvacrol**, which have significant antiviral and bactericidal effects. A large number of studies have shown that **licorice** and its chemical components have a protective effect on lung inflammation and damage, and it is a promising herbal medicine for treating SARS. Comparing the effects of conventional antiviral drugs **ribavirin**, **6-azouridine**, **pyrazofurin**, **mycophenolic acid**, and **glycyrrhizic acid** on SARS-CoV; it is showed that **glycyrrhizic acid** had a better viral inhibitory effect than the other four drugs in inhibiting the viral adsorption and penetration. It is also showed that **glycyrrhizic acid** has a good anti-SARS-CoV effect, while SARS-CoV-2 and SARS-CoV belong to different subclasses of coronaviruses with similar structures. However, it is speculated that **glycyrrhizic acid** may have the potential to treat SARS-CoV-2, as **glycyrrhizic acid** plays an important role in inhibiting immune hyperactivation and cytokine storm factor development. Therefore, we believe it is worth testing its efficacy against SARS-CoV-2 infection [**72-75**].

Baicalin, a component of **Scutellaria baicalensis Georgi** (Chinese name; **Huang Qin**), has a wide range of therapeutic effects, including sensitization and anti-apoptosis. It has demonstrated the antiviral activity of **baicalin** against SARS coronavirus, with an EC50 value of 12.5 μg/mL at 48 h, and the activity tended to decrease with incubation time beyond 48 h. Thus, due to the similarities between SARS-CoV-2 and SARS-CoV, it can be speculated that **baicalin** may also have an antiviral effect on SARS-CoV-2. Therefore, **baicalin** can be one of the potential drugs for COVID-19 treatment. Because of the low toxic effect of **baicalin**, and its effect against SARS-CoV-2; these justify further studies about this compound [**72-75**].

Patchouli alcohol (PA), a tricyclic sesquiterpene compound extracted from the traditional Chinese medicine **patchouli**, has a wide range of pharmacological and biological effects including antiviral, immunomodulatory, anti-inflammatory, antioxidative, and antitumor. PA has been found to have anti-influenza A (IAV) effect *in vitro*, while H1N1 virus is the most sensitive to PA. It is suggested that PA may block IAV infection by directly killing viral particles and interfering with some early stages after viral adsorption. Moreover, another study showed that PA also has an effect against influenza virus (IFV) *in vivo* and enhances protection against IFV infection in mice; by enhancing host immune responses and attenuating systemic and pulmonary inflammatory responses. However, **PA** may be a novel and effective antiviral and anti-inflammatory drug for COVID-19 and it is worth testing this drug against COVID-19 [**72-75**].

Luteolin, a natural flavonoid extracted from Chinese herbal medicine; obtained from the plant **Reseda luteola**, It displays multiple biological activities, including anti-inflammatory, anti-cancer, antioxidant, antiviral, and heart protective. It was reported that **luteolin** can interfere with the virus in the early virus life cycle, to a certain extent, block the absorption and internalization of the influenza virus, thereby inhibited the replication of IAV. This suggested that **luteolin** is a potential antiviral drug that inhibits viral replication by regulating host proteins. Considering that **luteolin** has a good antiviral effect, suggested that **luteolin** may be a potential drug for the treatment of COVID-19 [**72-75**].

There is no scientific evidence that any of these alternative remedies can prevent or cure COVID-19. However, their actual effect in the treatment of COVID-19 needs to be confirmed by further studies. The large and rapidly published literature on COVID-19's treatment means that the findings and recommendations are constantly progressed as new evidence arises. The cooperation of all scientists around the world is essential to develop effective drugs to treat current and future potential SARS-CoV-2 infections; to control the further outbreak of the virus. Besides, the attempt to develop drugs from traditional herbal medicine should not be given up too.

Preventions and Precautions

COVID-19 affects the global population in drastic ways; older people face a greater risk of developing a severe illness because of underlying health conditions and many physiological changes that come with age; which shall lead to declines in intrinsic capacity, manifested as the following malnutrition, cognitive decline, depressive symptoms, and

potential underlying health conditions. Early detection of inappropriate medication prescriptions is recommended to prevent adverse effects of drug or potential drug interactions with COVID-19 treatment. Importantly, studies give proof that the transmission of this virus from human-to-human; along with many exported instances across the world. The geriatric population and people who are under some diseases are at risk of infection of this virus and susceptible to serious outcomes; which can be associated with acute breathing distress syndrome (ADRs). The are several limitations such as; the virus outbreaks very fast; thus the actual and accurate causes and effective treatment of COVID-19 are still unknown or unavailable, and the number of active cases of the infection is rising every day. However, the information about the disease including the number of cases and death are changing every day sharply worldwide. The global impact of this new pandemic is yet uncertain. The numbers are possibly an underestimate of the infected and dead due to limitations of surveillance and testing. Since at this time there are no approved treatments for this infection, prevention is crucial and important. Several properties of this virus and/ or lack of precise information; make prevention is difficult; mainly; non-specific features of the disease, the infectivity even before the onset of symptoms in the incubation period, transmission from asymptomatic people, long incubation period, tropism for mucosal surfaces such as the conjunctiva, prolonged duration of the illness and transmission even after clinical recovery. Isolation of confirmed or suspected cases with mild illness at home is recommended. The ventilation at home should be good with sunlight to allow for the destruction of the virus. Patients should be asked to wear a simple surgical mask and practice cough hygiene. Caregivers should be asked to wear a surgical mask when in the same room as the patient and use hand hygiene every 15–20 minutes [**4, 76**].

The greatest risk in COVID-19 is transmission to healthcare workers. In the SARS outbreak of 2002, 21% of those affected were healthcare workers. Almost more than 1500 healthcare workers in China have been infected with 6 deaths and about 600 US healthcare workers have died from COVID-19 (by the end of June). By May 6th, the International Council of Nurses (ICN) reported that at least 90,000 healthcare workers had been infected and more than 260 nurses had died in the novel coronavirus pandemic. The physician in China; who first warned about the virus has died too. It is important to protect healthcare workers to ensure continuity of care and to prevent transmission of infection to other patients. While COVID-19 transmits as a droplet pathogen and is placed in Category B of infectious agents (highly pathogenic H5N1 and SARS), by the China National Health Commission; infection control measures recommended are those for category A agents (cholera, plague). Patients should be placed in separate rooms or cohorted together. Negative pressure rooms are not generally needed. The rooms and surfaces and equipment should undergo regular decontamination preferably with **sodium hypochlorite**. Healthcare workers should be provided with fit-tested N95 respirators and protective suits and goggles. Airborne transmission precautions should be taken during aerosol-generating procedures such as intubation, suction, and tracheostomies. All contacts including healthcare workers should be monitored for the development of symptoms of COVID-19. Patients can be discharged from isolation once they are afebrile for at least 3 days and have two consecutive negative molecular tests at a one-day sampling interval. This recommendation is different from pandemic flu where patients were asked to resume work/school once afebrile for 24 h or by day 7 of illness. Negative molecular tests were not a prerequisite for discharge [**4, 76**].

At the community level, people should be asked to avoid crowded areas and postpone non-essential travel to places with ongoing transmission. They should be asked to practice cough hygiene by coughing in sleeve/ tissue rather than hands and practice hand hygiene frequently every 15–20 min. Patients with respiratory symptoms should be asked to use surgical masks. The use of a mask by healthy people in public places has not shown to protect against respiratory viral infections and is currently not recommended by WHO, but in most countries, they practice this. However, in China, the public has been asked to wear masks in public and especially in crowded places and large scale gatherings are prohibited (entertainment parks, etc). China is also considering introducing legislation to prohibit the selling and trading of wild animals. The international response has been dramatic. Initially, there were massive travel restrictions to China, and people returning from China/ evacuated from China are being evaluated for clinical symptoms, isolated and tested for COVID-19 for 2 weeks even if asymptomatic. However, now with the rapid worldwide spread of the virus, these travel restrictions have extended to other countries. Whether these efforts will lead to the slowing of viral spread still uncertain **[76-79].** Healthcare providers should take travel history of all patients with respiratory symptoms, and any international travel in the past 2 weeks as well as contact with sick people who have traveled internationally. They should set up a system of triage of patients with respiratory illness in the outpatient department and give them a simple surgical mask to wear. They should use surgical masks themselves while examining such patients and practice hand hygiene frequently. Suspected cases should be referred to as government-designated centers for isolation. Patients admitted with severe pneumonia and acute respiratory

distress syndrome should be evaluated for travel history and placed under contact and droplet isolation; regular decontamination of surfaces should be done. They should be tested for etiology using multiplex PCR panels; if logistics permit and if no pathogen is identified, refer the samples for testing for SARS-CoV-2. All clinicians should keep themselves updated about recent developments including the global spread of the disease. International travel should be avoided and people should stop spreading myths and false information about the disease and try to allay panic and anxiety of the public **[76-79].**

Physicians notice a septic shock in some adults when infected with COVID-19, the treatment goal is to maintain mean arterial pressure (MAP) ≥ 65 mmHg, lactate ≥ 2 mmol/L. In absence of hypovolemia, the child will suffer from a septic shock with hypotension when (systolic blood pressure [SBP] < 5th centile or > 2 SD below normal for age) or suffers from two or more of the following: altered mental state; bradycardia or tachycardia (HR < 90 bpm or > 160 bpm in infants and HR < 70 bpm or > 150 bpm in children); prolonged capillary refill (> 2 sec) or feeble pulses; tachypnea; mottled or cold skin or petechial or purpuric rash; increased lactate; oliguria; hyperthermia or hypothermia. When lactate measurement isn't available blood pressure (i.e. MAP) and clinical signs of perfusion can be used to define shock [**77**]. Strategies for the resuscitation of adult and pediatric patients with septic shock include conservative fluid regimens, the crystalloid fluid which include normal saline and Ringer's lactate which is given as bolus infusion, hypotonic crystalloids, starches, or gelatins should not be used for resuscitation. Starches are associated with an increased risk of death and acute kidney injury. Gelatins are more expensive than crystalloids. **Hypotonic** solutions are less effective than isotonic at increasing intravascular volume. Treating Sepsis also suggests the use of **albumin** when patients require substantial amounts of crystalloids, but this recommendation is based on low-quality evidence [**78**]. In adults with septic shock 250–500 mL crystalloid fluid which include normal **saline** and **Ringer's lactate** is given as rapid bolus in the first 15–30 minutes, in children10–20 mL/kg crystalloid fluid is given as a bolus in the first 30–60 minutes, check for signs of fluid overload after each bolus. Reduce or discontinue fluid administration; if there is evidence of no response by the patient to fluid loading; or if signs of volume overload appear on the patient (e.g. jugular venous distension, crackles on lung auscultation, pulmonary edema on imaging, or hepatomegaly in children); especially in patients with hypoxemic respiratory failure. Based on clinical response and improvement of perfusion targets additional fluid boluses may be given (250–500 mL in adults or 10–20 mL/kg in children). The Perfusion targets include MAP (> 65 mmHg or age-appropriate targets in children), urine output (> 0.5 mL/kg/hr in adults, 1 mL/kg/hr in children), and improvement of skin mottling and extremity perfusion, capillary refill, heart rate, level of consciousness, and lactate. Notice indices for volume responsiveness to fluid administration; these indices include passive leg raises, fluid challenges with serial stroke volume measurements, or variations in systolic pressure, pulse pressure, inferior vena cava size, or stroke volume in response to changes in intrathoracic pressure during mechanical ventilation. In pregnant women with sepsis and or septic shock, they may need to be placed in the lateral decubitus position to off-load the inferior vena cava to reduce the hypotension. Management of septic shock in adults includes administration of vasopressors, in case if fluid administration does not restore adequate perfusion. In adults, **norepinephrine** is the first-line agent; **epinephrine** or **vasopressin** are preferred as the second line over **dopamine** .if patients didn't respond to usual doses of norepinephrine consider adding vasopressin rather than further titrating **norepinephrine**. In children, epinephrine is considered the first-line agent, and norepinephrine may be added if necessary. The initial blood pressure target is around 65 mmHg. If signs of septic shock persist despite administration of fluids and vasopressors; the patient shall be given an **inotrope agent** such as **dobutamine** rather than further titrating norepinephrine **[80-84].**

Management of Neurological and Mental Manifestations Associated with COVID-19

COVID-19 is associated with mental and neurological manifestations, including delirium or encephalopathy, agitation, stroke, meningoencephalitis, impaired sense of smell or taste anxiety, depression, and sleep disorders. In many cases, neurological manifestations have been reported even without respiratory symptoms. Anxiety and depression appear to be common amongst people hospitalized for COVID-19; with one hospitalized cohort from Wuhan, China; revealing over 34% of people experiencing symptoms of anxiety and 28% experiencing symptoms of depression. Series cases in France found that 65% of people with COVID-19 in intensive care units (ICUs) showed signs of confusion (or delirium), and 69% experienced agitation. Delirium, in particular, has been associated with increased mortality risk in the context of COVID-19. Moreover, there have been concerns related to acute cerebrovascular disease (including ischaemic and hemorrhagic stroke); in multiple case series from China, France, the Netherlands, and the United States of America. Case reports of Guillain-Barré syndrome and meningoencephalitis among people with COVID-19 have also been reported. It is recommended, in patients with COVID-19, that measures to prevent delirium, an acute neuropsychiatric emergency, be implemented; and

patients be evaluated using standardized protocols, for the development of delirium. If detected, then immediate evaluation by a clinician is recommended to address any underlying cause of delirium and treat appropriately, and providing basic mental health and psychosocial support (MHPSS) for all persons with suspected or confirmed COVID-19. Prompt identification and assessment for anxiety and depressive symptoms in the context of COVID-19 should be considered; and to initiate psychosocial support strategies and first-line interventions, for the management of new anxiety and depressive symptoms. Psychosocial support strategies as the first-line interventions for the management of sleep problems in the context of acute stress also needed [**85**].

In summary, patients with suspected or confirmed mild COVID-19 should be isolated to contain virus transmission according to the established COVID-19 care pathway. This can be done at a designated COVID-19 health facility, community facility, or at home (self-isolation). Patients with mild COVID-19 should be given symptomatic treatment such as antipyretics for fever and pain, adequate nutrition, and appropriate rehydration. Counsel patients with mild COVID-19 about signs and symptoms of complications that should prompt urgent care. Patients with suspected or confirmed moderate COVID-19 (pneumonia) should be also isolated to contain virus transmission. Patients with moderate illness may not require emergency interventions or hospitalization; however, isolation is necessary for all suspect or confirmed cases, and monitoring of signs or symptoms of disease progression for those patients is required. Severe patients should be equipped with pulse oximeters, functioning oxygen systems and disposable, single-use, oxygen-delivering interfaces (nasal cannula, Venturi mask, and mask with reservoir bag). Immediate administration of supplemental oxygen therapy to any patient with emergency signs and any patient without emergency signs and SpO2 < 90%; are recommended. Similar is recommended to those patients closely monitor for signs of clinical deterioration, such as rapidly progressive respiratory failure and shock, and respond immediately with supportive care interventions. Patients with COVID-19 and mild ARDS, a trial of HFNO, non-invasive ventilation – continuous positive airway pressure (CPAP), bilevel positive airway pressure (BiPAP); may be used. Prompt recognition of progressive acute hypoxaemic respiratory failure when a patient with respiratory distress and is failing to respond to standard oxygen therapy and adequate preparation to provide advanced oxygen/ventilatory support and the endotracheal intubation is recommended. Patients with ARDS, especially young children or those who are obese or pregnant, may desaturate quickly during intubation, implementation of mechanical ventilation using lower tidal volumes (4–8 mL/kg predicted body weight [PBW]) and lower inspiratory pressures (plateau pressure < 30 cmH2O) are recommended. In adult patients with severe ARDS (PaO2/FiO2 < 150), prone ventilation for 12–16 hours per day is recommended. It is better to use a conservative fluid management strategy for ARDS patients without tissue hypoperfusion and fluid responsiveness. In patients with moderate or severe ARDS, a trial of higher positive end-expiratory pressure (PEEP) instead of lower PEEP is suggested and requires consideration of benefits versus risks. In COVID-19, we suggest the individualization of PEEP where during titration the patient is monitored for effects (beneficial or harmful) and driving pressure. In patients with moderate-severe ARDS (PaO2/FiO2 < 150); neuromuscular blockade by continuous infusion should not be routinely used. Disconnecting the patient from the ventilator, which results in loss of PEEP, atelectasis, and increased risk of infection of health care workers is avoided. In patients with excessive secretions or difficulty clearing secretions, consider the application of airway clearance techniques. These should be performed only if deemed medically appropriate. Patients with ARDS in whom a lung-protective ventilation strategy fails; to achieve adequate oxygenation and ventilation, the extracorporeal membrane oxygenation (ECMO) is given. Recognize septic shock in adults when the infection is suspected or confirmed; vasopressors are needed to maintain mean arterial pressure (MAP) ≥ 65 mmHg AND lactate is ≥ 2 mmol/L, in the absence of hypovolaemia. Prevention of complications in hospitalized and critically ill patients with COVID-19; such as venous thromboembolism, **low molecular weight heparin** is used. For any other, clinically suspected; such as stroke, deep venous thrombosis, pulmonary embolism, or acute coronary syndrome, appropriate diagnostic and management pathways should proceed immediately [**85-90**].

There are three broad approaches of drugs being investigated for the treatment of CPVID-19; which include: **antiviral drugs;** that directly affect the coronavirus's ability to thrive inside the body, **immunotherapies**; drugs that can calm the immune system; patients become seriously ill when their immune system overreacts and starts causing collateral damage to the body, and **antibodies**; either from survivors' blood or made in a lab, that can attack the virus. WHO recommended that several medicines **shouldn't** be administered or taken as prophylaxis for COVID-19. These drugs include; **chloroquine** and **hydroxychloroquine** (+/- azithromycin), **antivirals**, (Lopinavir/ritonavir, Remdesivir, Umifenovir, Favipiravir), **immunomodulators** (Tocilizumabm, Interferon-β-1a), and Plasma therapy. WHO also against the routine use of systemic corticosteroids for the treatment of viral pneumonia. For

the treatment of other acute and chronic infections in patients with COVID-19; WHO also against the use of antibiotic therapy or prophylaxis in suspected or confirmed mild COVID-19. Besides, antibiotics should not be prescribed in suspected or confirmed moderate COVID-19; unless there is clinical suspicion of bacterial infection. In suspected or confirmed severe COVID-19, the use of empiric antimicrobials to treat all likely pathogens are based on clinical judgment, patient host factors, and local epidemiology; this should be done as soon as possible (within 1 hour of initial assessment if possible); ideally, after blood cultures obtained first. Antimicrobial therapy should be assessed daily for de-escalation [**85, 91**].

Caring for patients with suspected and confirmed COVID19; that have underlying noncommunicable diseases (NCDs); it is recommended to continue or modify their medicines; according to the patient's clinical condition. For example, antihypertensive drugs should not routinely be stopped in patients with COVID-19; but therapy may need to be adjusted; based on general considerations for patients with acute illness; with maintaining normal blood pressure and renal function. Careful consideration should be given to the numerous clinically significant side-effects of medications; that may be used in the context of COVID-19; as well as drug-drug interactions between medications; both of which may affect COVID-19 symptomatology (including effects on respiratory, cardiac, immune and mental and neurological function). Both pharmacokinetic and pharmacodynamic effects should be considered of the medications too [**85, 91**]. The antiviral drug **remdesivir** gained an emergency use authorization from the FDA on May 1, 2020, based on preliminary data showing a faster time to recovery of hospitalized patients with severe disease. However, **remdesivir** is considering the most promising antiviral drug. Also, other antiviral agents, immunotherapies, and vaccines continue to be investigated and developed as potential therapies for COVID-19. Numerous collaborative efforts to discover and evaluate the effectiveness of antivirals, immunotherapies, monoclonal antibodies, and vaccines have rapidly emerged. All infected patients should receive supportive care to help alleviate symptoms; and vital organ function should be supported in severe cases too as mentioned. In Palestine, the treatment and management protocols of COVID-19 are similar to the strategies and protocols in other countries especially those that follow the guidelines of WHO. The high outbreak of the disease in Hebron Governorate-Palestine has been caused by people meeting up with their families or attending wedding parties or funerals and failing to follow health recommendations and maintain social distancing according to the Palestinian Ministry of Health officials. However, isolation and other preventive and precautions are the most important ways in reducing the outbreak of the disease; which prevents the transmission of the virus to others.

Conclusions

The pandemic by COVID-19 is a very dangerous issue affecting people worldwide. Symptoms of this virus may vary from mild symptoms; such as fever and cough to severe symptoms; such as multi-organ failure and ARDS. Still this pandemic is ongoing and no suitable treatments until now. Supportive treatment is still the main strategy in treating this disease; since no curative antiviral has been approved due to the lack of evidence and precise information. Isolating patients and other preventive and precautions are now the most important ways in reducing the outbreak of this virus; as these prevent the transmission of the virus to others or healthcare providers. However, there is an urgent need to develop targeted therapies. Understanding the disease and the different responses to this virus; could help to find immune-based therapeutics or/ and conventional medicines. It is important to have the latest information, but we must ensure that the information is coming from trustworthy sources. Thus, a variety of helpful resources related to COVID-19 treatments and preventions have been collected.

Ethical Considerations

The identities of patients remained unknown and their identities remained confidential and only used for research purposes. The procedures were accomplished upon obtaining permission from the Ethical Committee of Hebron University.

Conflict of Interest and Financial Disclosure

The authors declare no competing financial interests and no conflicts of interest concerning the authorship and/or publication of this article.

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