COVID-19 Pandemic Between Severity Facts and Prophylaxis

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Abstract
Before COVID-19, many viruses have infected humans, so what caused COVID-19 to be considered as a pandemic? COVID-19 belongs to the coronavirus family that includes severe acute respiratory syndrome (SARS) and Middle East Respiratory Syndrome (MERS). This family has caused a large number of deaths all over the world. How risky is the novel coronavirus? People and their careers were disrupted, and many businesses all over the world are now closed. From here, it seems to us that this virus is something that can make people feel afraid. In this article, we will try to understand the severity of this virus, and then disclose the available ways to confront it and ways that might improve the ability to face it, either now or in the future. Upon comparing COVID-19 with seasonal flu, we have found that COVID-19 is about 10 times more deadly, although it is not the most infectious virus. In this review, we will discuss how healthy nutrition and lifestyle may help to prevent and treat diseases, and especially COVID-19. We will focus on how to follow healthy nutrition habits and lifestyles to stop the dangers of COVID-19.

Keywords
nutrition, lifestyle, stop COVID-19, edible natural products, herbs, natural remedies

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Introduction
Coronaviruses are a wide range of viruses that belong to the RNA type, like influenza hepatitis C, hepatitis E, Middle East Respiratory Syndrome (MERS), severe acute respiratory syndrome (SARS), West Nile fever, Ebola virus disease, rabies, polio, and measles, and recently the novel coronavirus (COVID-19). All of these viruses are of the RNA type, with rapid mutation characteristics, which make them more dangerous than the DNA type. COVID-19 virus may cause serious life-threatening symptoms which can range from none to few, to critical, such as shortness of breath and pneumonia, especially for those who are suffering from chronic diseases such as heart diseases, lung diseases, diabetes, or chronic kidney syndrome.

A healthy lifestyle and physical activity have proved to affect dramatically the progress in chronic diseases. There is a large variation in the way that people deal with their physical and social lives and in their general and private behavior. If we asked how do chronic diseases begin, we will find that long-term unhealthy lifestyle habits increase the risk of developing chronic diseases. Some of these habits may be smoking, drinking alcohol, drug use, unhealthy food (fast, processed, or unbalanced food), and physical inactivity. All of these have helped to increase the possibility of chronic diseases such as obesity, diabetes, heart diseases, stroke, and cancer.

Additionally, healthy nutrition, along with physical activity, have important roles to maintain a healthy life with minimal problems. Unhealthy diets lead to obesity, which contributes critically to many health problems such as type 2 diabetes, high blood pressure, heart disease, osteoporosis, and cancer progression. To avoid many of these health problems, people need to make good and balanced food choices. In this review article, we will try to understand more about the COVID-19 pandemic and will discuss healthy lifestyles and good nutrition habits that may help people stop the progression of this pandemic. Table 1 shows a comparison between SARS, MERS, and COVID-19.

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The novel, severe, acute respiratory syndrome coronavirus 2 (SARS-CoV-2) causing COVID-19 has rapidly turned into a pandemic, infecting millions and causing 1,157,509 (as of October 27, 2020) deaths across the globe. In addition to studying the mode of transmission and evasion of the host immune system, analyzing the viral mutational landscape constitutes an area under active research. COVID-19 is a respiratory disease related to a coronavirus, which has significantly disturbed the socioeconomic balance of the entire world. The outbreak of COVID-19 caused by the SARS coronavirus 2 (SARS-CoV-2, also called novel coronavirus 2019-nCoV) in Hubei Province, China, during late December 2019, has since transformed into a severe pandemic, spreading across more than 200 countries. As of 27 October 2020, 1,157,509 deaths have been reported worldwide, as per recent statistics released by the World Health Organization (WHO) (https://covid19.who.int/, 2020). SARS-CoV-2 belongs to the subfamily Orthocoronavirinae of the Coronaviridae family, classified under the order Nidovirales. After host entry, the 29.9 kb positive-sense, single-stranded RNA genome of this virus is immediately translated to yield 15 nonstructural proteins (nsps, 1-15). These nsps subsequently form multiprotein complexes to execute genomic replication and transcription that produce a genomic RNA template, along with 9 subgenomic RNAs.

The latter are translated to form major structural proteins; spike (S), envelope (E), nucleocapsid (N), and membrane (M) proteins.\(^6,7\) The SARS-CoV-2 virus uses the spike (S) protein to bind to the angiotensin-converting enzyme 2 (hACE2) present on human cells and gain host entry.\(^1\)

Outbreaks caused by members of the Coronaviridae family, including SARS (caused by SARS-CoV) in 2003, MERS (caused by MERS-CoV) in 2012, and currently COVID-19 (caused by SARS-CoV-2), have frequently crossed interspecies barriers to cause zoonotic infections with variable infectivity and transmission rates and case-to-fatality ratios.\(^8\) The genome of SARS-CoV-2 has been found to share a high degree of sequence similarity with SARS-CoV (>80%) and a moderate sequence similarity with MERS-CoV (>50%).\(^9,10\)

The phylogenetic tree was rooted with respect to the sequence from the Wuhan-Wu-1 strain (NC_045512.1), which has been annotated as the base clade 19A. One sample (collected in April 2020) seemed to emerge directly from this base clade. A further, 5 samples belonging to the 19A clade also harbored the C13730T mutation (establishing sub-clade 19A/C13730T). The C13730T mutation has been previously reported to be associated with a more virulent variant of the strain.\(^11\)

### Severity and Health Dangers of This Virus

The clinical features of COVID-19 are varied, ranging from an asymptomatic state to acute respiratory distress syndrome and multiorgan dysfunction. The common clinical features include fever (not in all), cough, sore throat, headache, fatigue, myalgia, and breathlessness. Conjunctivitis has also been described. Thus, they are indistinguishable from other respiratory infections. In a subset of patients, by the end of the first week, the disease can progress to pneumonia, respiratory failure, and death. This progression is associated with an extreme rise in inflammatory cytokines, including IL2, IL7, IL10, GCSF, IP10, MCP1, MIP1A, and TNFα.\(^12\)

The median time from onset of symptoms to dyspnea was 5 days, hospitalization 7 days, and acute respiratory distress syndrome (ARDS) 8 days. The need for intensive care admission was 25% to 30% of affected patients in the published series. Complications witnessed included acute lung injury, ARDS, shock, and acute kidney injury. Recovery started in the second or third week. The median duration of hospital stay for those who recovered was 10 days. Adverse outcomes and death are more common in the elderly and those with underlying co-morbidities (50%-75% of fatal cases). The fatality rate in hospitalized adult patients ranged from 4% to 11%. The overall case fatality rate is estimated to range between 2% and 3%.\(^13\)

Treatment is essentially supportive and symptomatic patients. 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, nutrition and controlling fever and cough. Routine use of antibiotics and anti-viral such as oseltamivir should be avoided in confirmed cases. In hypoxic patients, provision of oxygen through nasal prongs, face masks, high flow nasal cannula, or noninvasive ventilation is indicated. Mechanical ventilation and even extracorporeal membrane oxygen support may be needed. Renal replacement therapy may be needed for some patients. Antibiotics and anti-fungal 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.\(^14,15\)

### Table 1. Comparison Between SARS, MERS, and COVID-19 (Data Till June 3, 2020, According to the Report of the WHO China Joint Mission on COVID-19).

| SARS-CoV-2 | MERS-CoV | SARS-CoV |
|------------|----------|----------|
| Emergence of the disease for the first time | November 2002 | June 2012 | December 2019 |
| Confirmed cases | 8096 | 2494 | 6,382,951 |
| Age average | 44 | 56 | 56 |
| Sex ratio (M:F) | 0.8:1 | 3.3:1 | 1.6:1 |
| Ratios of common symptoms | | | |
| Deaths | 774 | 858 | 380,318 |
| Fever | 99% to 100% | 98% | 87.9% |
| Dry cough | 29% to 75% | 47% | 67.7% |
| Dyspnea | 40% to 42% | 72% | 18.6% |
| Sore throat | 13% to 25% | 21% | 13.9% |

Abbreviations: SARS, severe acute respiratory syndrome; MERS, Middle East Respiratory Syndrome; WHO, World Health Organization; COVID-19, coronavirus disease of 2019.
There is no approved treatment for COVID-19 till now. Antiviral drugs such as ribavirin, lopinavir/ritonavir have been used based on the experience with SARS and MERS. In a historical control study in patients with SARS, patients treated with lopinavir/ritonavir with ribavirin had better outcomes as compared to those given ribavirin alone.12

Ways That Might Improve the Ability to Face the Virus
COVID-19 pandemic has affected healthcare communications at the clinical, institutional, and governmental levels, to solve these problems through structural and customized solutions. Policies have to be developed in a rapid, evidence-based manner and different research methods on a global scale.16

Instructions from Government have been widespread in many parts of the world and have shaped communication with the public, raising a number of challenges that have implications both for those seeking care and for those who provide communication.17

In this paper, we will focus on the critical reflection of these challenges and discussing approaches that could potentially mitigate them, inform policy and practice, and improve healthcare communication as a whole during pandemics. The topics are divided into 2 sections: communicating with the public (eg, uncertainty, risk communication) and communication between healthcare providers and patients, families, and care givers (eg, telehealth, bereavement).16

Uncertainty is a major challenge in communication about COVID-19 pandemic due to the rapidly evolving nature of the disease and situation.17 Research and healthcare are constantly confronted with uncertainty: new hypotheses and constantly emerging evidences undermine previous certainties, clinical and public health decision-makers often deal with unknown aspects. Patients often face uncertainty during their disease trajectory also healthcare providers and researchers are facing the challenges of communicating this uncertainty.17

We know that risk is composed of a materially measurable element of the probability of an event, as well as a socially constructed element of how that probability/event is perceived by the individual and society.18,19

Comparing COVID-19 With Seasonal Flu
The case-fatality rate in COVID-19 appears to be higher than that in seasonal influenza, even though both diseases mainly affect older adults (>65 years) with frailty. The higher case fatality of COVID-19 could be due to differences in underlying comorbidities of patients, the pathogenicity of the virus, population immunity, and host responses to infection. For example, vaccines and approved treatments are available for influenza, but not for COVID-19. Moreover, the considerable strain that was put on hospitals within a short period led to limitations in available care for the most frail patients.20

Few studies have directly compared the respective burdens of the COVID-19 and influenza epidemics.2,21 A comprehensive assessment of the outcomes and mortality of the 2 diseases and risk factors for hospitalization and mortality could be used to identify specific at-risk populations.

This retrospective, nationwide cohort study included 89,530 patients who were hospitalized for COVID-19 between March 1, and April 30, 2020, and 45,819 patients who were hospitalized for seasonal influenza between December 1, 2018, and February 28, 2019. Almost twice as many patients were hospitalized for COVID-19 than for seasonal influenza, over a shorter time period (2 months for COVID-19 and 3 months for seasonal influenza). Patients hospitalized for COVID-19 were more often male than were those hospitalized for influenza. The age distribution also differed, with a median age of 68 years (IQR 52-82) for COVID-19 and 71 (34-84) for influenza. The proportions of patients at the extreme ends of the age categories were significantly greater for influenza (8942 [19.5%] <18 years and 15,366 [33.5%] >80 years) than for COVID-19 (1227 [14%] <18 years and 24,242 [27%] >80 years).20

A recent study reported that the in-hospital mortality of COVID-19 was nearly 3 times higher than that of seasonal influenza, with an age-standardized mortality ratio of 2.82. In addition, patients with COVID-19 were twice as likely to receive invasive mechanical ventilation, and COVID-19 patients hospitalized in the intensive care unit and stayed nearly twice as long as those with influenza.

Of note, the 2018 to 2019 period had the highest case-fatality rate for seasonal influenza in France within the past 5 years (12,300 deaths, including 8100 directly attributable to influenza). Therefore, the excess mortality observed for COVID-19 was not the result of an influenza season that was less severe than usual.

In this nationwide cohort study comparing the COVID-19 epidemic to seasonal influenza, almost twice as many patients were admitted to hospital for COVID-19 over a 2-month period than were admitted for seasonal influenza over a 3-month period. There is a small possibility that some patients hospitalized in 2020 were misclassified as COVID-19 when they actually had influenza. However, the risk of misclassification is low because the period studied in 2020 was at the end of the influenza epidemic in France. In addition, the results of the sensitivity analysis, which was limited to stage 3 of the epidemic, were similar to those of the main analysis. The observed difference in admissions is likely to be an underestimation, considering that the COVID-19 epidemic peaked in the first week of April 2020, and universal lockdown measures were already in place in France by March 17, contributing to a reduction in the rate of hospitalization in the following weeks. However, influenza vaccination coverage against seasonal influenza in France was 29.7% for those under 65 years and 51.0% for those over 65 years from 2018 to 2019, according to the National Public Health Agency. Therefore, the influenza vaccine probably contributed to lower rates of hospitalization for seasonal influenza and associated mortality.14

These factors suggest that the difference in the number of COVID-19 and seasonal influenza cases could be higher in
other settings or periods, or if the residual population immunity acquired from previous seasonal influenza (which cannot be assessed) is lower than usual.

The higher in-hospital mortality observed in younger COVID-19 patients suggests that COVID-19 is intrinsically more severe than influenza. Although children seemed to have a lower risk of being hospitalized with COVID-19 (as shown here by the low rate of hospitalization for COVID-19 compared with seasonal influenza in patients younger than 18 years), the in-hospital mortality of these children was more than 4-times higher than it was for children with influenza.

Recent reports are stating that the clinical manifestations of COVID-19 are very often mild in children. The clinical manifestations of COVID-19 appear to be milder than those of influenza in children younger than 5 years old. Also, it seems to be not more severe than other influenza infections in children younger than 1 year.24

**Healthy Nutrition and Lifestyle**

Eating habits and lifestyle modifications may threaten our health. Maintaining a correct nutrition status is crucial, especially in a period when the immune system might need to fight back. In fact, subjects with severe obesity (body mass index [BMI] ≥40 kg/m²) are one of the groups with the highest risk for COVID-19 complications.25 Obesity is an expansion of the adipose tissue, which produces cytokines and contributes to a pro-inflammatory milieu.26 Moreover, in regards to pulmonary physiology, subjects with obesity have decreased expiratory reserve volume, functional capacity, and respiratory system compliance. In patients with high abdominal fat, pulmonary function is further compromised in the supine position by decreased diaphragmatic excursion, making ventilation more difficult.27

The inflammatory state is also one of the most important factors of the severity of lung disease in COVID-19, which leads to the famous “cytokine storm” associated with acute respiratory distress syndrome and multiple organ failure.28 In this complex scenario, the inflammatory state characteristics in individuals with obesity could further exacerbate the inflammation in patients with COVID-19 and, therefore, exposing them to a higher concentration of pro-inflammatory cytokines compared to normal-weight individuals.29

Following a healthy diet is important because gene expression levels of all the cytokines are influenced by food and are capable of modulating the processes of inflammation and oxidative stress.30 Several studies have confirmed an inverse association between the adherence to the Mediterranean diet (MD) and the overall cancer-related mortality. The healthy MD31 is a proper combination of quality foods, based on macro and micronutrient contents, and the absence of contaminating substances. According to current knowledge, the MD is the key factor against immune-mediated inflammatory responses, such as those occurring in cancer. In particular, their potential clinical applications are, on one side, low cholesterol levels and, on the other hand, high levels of antioxidants contained in fruits and vegetables, and monounsaturated fatty acids, present in fish, nuts, and olive oil.32

Notably, it is well known that the MD, one of the healthiest dietetic patterns in the world, is linked to lower mortality and reduction in obesity, type 2 diabetes mellitus, low-grade inflammation, cancer, Alzheimer’s disease, depression, and Cohn’s disease.32,33

In light of the above, the “Eating Habits and Lifestyle Changes in COVID19 lockdown” project began by using a web survey. The main aim of the project, from a diachronic perspective, was to explore and analyze the changes in eating behavior and adherence to the MD and lifestyle during lockdown among the Italian population, according to the regional distribution of the COVID-19 epidemic and to age. Secondly, it allows achieving nutritional interventions in supporting the health status of different target groups of the population, according to geographical distribution.35

Due to the growing case notification rates at Chinese and international locations, on January 30, 2020, the WHO Emergency Committee declared a global health emergency.34 Lifestyle may be substantially changed due to the containment measures, with the consequent risk of sedentary behaviors, and modification in smoking and sleeping habits. Of interest, different studies reported an association between sleep disturbances and obesity due to an increase in the secretion of pro-inflammatory cytokines by the increased visceral adipose tissue that could contribute to altering the sleep–wake rhythm.35,36 In addition, diet also seems to influence the quality of sleep. In fact, very recently, in a cross-sectional study that included 172 middle-aged adults, it was reported that good sleepers had a higher adherence to the MD and lower BMI compared to poor sleepers.28

Considering smoking, a significant association exists between SARS-CoV-2 infection and air pollution, and in this context, in smokers, more severe COVID-19 symptoms occur.37 Low physical activity levels have been suggested to interact both with body fat and appetite dysregulation.38

**Herbs That can Stop Propagation of COVID-19**

The new coronavirus disease (COVID-19) pandemic has caused global socioeconomic disturbances with a worrisome number of deaths and health issues, and the world has been struggling to find medicine to treat and prevent COVID-19.39

There is a strong inter-relationship between people and plants according to needs.30 People are dependent on plants for different purposes such as for food, medicine, and houses.31 Plant species have always been a fundamental source for the discovery of drugs.34 People have used medicinal plants to fight against pandemics in the past,32,12,15,16 and the dependency of people on medicinal plants might have increased
in these days as they can be an alternative option to prevent COVID-19.40

Different types of misinformation related to COVID-19 have been spreading throughout the world through social media,5 including the use of medicinal plant products to prevent or cure COVID-19. Due to this situation, ethnobiologists should collaborate with local people and document the medicinal plants used with caution to stop the inaccurate sharing of information.41

In China, traditional medicine showed encouraging results in improving symptom management and reducing the deterioration, mortality, and recurrence rates.42 The WHO (2020) claims medicinal plants might be good for health and in supporting the immune system, but not in either preventing or curing COVID-19. WHO Africa (2020) claims unscientific products to treat COVID-19 can be unsafe for people, as they may abandon self-hygienic practices, may increase self-medication, and may be a risk to patient safety.43

After reviewing many research papers from different journals, at least 4 herbs have been shown to complement the treatment of COVID-19 patients. Additionally, we discuss these 4 candidates, including the pros and cons of their effects.44

1. Echinacea purpurea: Echinacea purpurea is one of the most popular herbal medicines in Europe and North America because it shows promising effects against viral infections. Its common name is purple coneflower. Preparations of E. purpurea can be made in the form of extracts, tinctures, teas, and sprays. Many Native Americans use this kind of herb for respiratory infections.8,29 The plant contains several bioactive compounds like chicoric and caffeic acids, alkylamides, and polysaccharides.45

2. Curcumin: Turmeric is the dried rhizome of Curcuma longa, family Zingiberaceae.35 Turmeric is mostly used as a spice, a natural food color, and food flavor. For many years, turmeric has been widely known to treat various diseases and conditions and has been investigated in preclinical and clinical studies.46 C. longa has been used traditionally in Asian countries as a medicine or supplement, as an antioxidant, anti-inflammatory, and anticancer agent, and in the treatment of many other diseases, such as diabetes mellitus, cardiovascular disease, obesity, neurodegenerative disease, inflammatory bowel disease, allergy, asthma, and psoriasis.9,35 C. longa extracts contain curcuminoids, such as curcumin (77%), demethoxycurcumin (DMC; 17%), and bisdemethoxycurcumin (BDMC; 3%). All these curcuminoids are used as either medicines or supplements, especially curcumin.47

3. Cinchona sp: The valuable benefits of Cinchona trees from the Andean mountain forests were first discovered by Jesuit missionaries and gradually expanded throughout the world.36 The tree bark contains quinine alkaloids, which were an effective treatment for malaria for several centuries. Quinine has a mode of action that is similar to that of chloroquine, a synthetic antimalarial agent.48

4. Xanthorrhiza: Java turmeric or Curcuma xanthorrhiza Roxb., family Zingiberaceae, is widely used in Southeast Asian countries. Java turmeric originates from Indonesia and has been spread and grown wild in Thailand, Philippines, Sri Lanka, and Malaysia. It has also been used as a food additive to enhance the flavor of food.49 In addition, this plant has been utilized as a medicine, and its benefits have been scientifically proven.50

Currently, there is no specific treatment for COVID-19. Furthermore, people in the community and researchers are trying to find the best way to cure or prevent the disease, including using herbal medicine. Since the immune status of patients plays an essential role in COVID-19 infection, herbal medicine, which has an immunomodulatory effect, could have potential as a preventive measure and even therapeutic agent for patients with COVID-19 infection.51

A recent trend in the community is the consumption of herbal medicines containing certain active compounds, which have antimicrobial, antiviral, anti-inflammatory, and immunostimulatory activities, such as echinacea, quinine, and curcumin. Phytochemicals such as flavonoids that have the capacity to modulate the immune response are also believed to have beneficial effects on either preventing or treating COVID-19.53

Many branded products contain an active compound that could act as an antiviral and immunostimulator. During the spread of COVID-19, several pharmaceutical companies offered their mainstay herbal products commercially. Consequently, based on the information from the advertisements on television, radio, and online media, people competitively shopped for these herbal products to fight against COVID-19. Unfortunately, this community behavior was undertaken without solid research base on the effects on COVID-19. Studies that describe the relation of some herbal drugs with the molecular mechanisms of COVID-19 infection, treatment, and prevention remain to be explained.34

Traditional Herbal Medicines may help as complementary treatments for COVID-19 as these might have the capabilities to regulate the production and release of proinflammatory cytokines, interfere with the development of the virus in host cells, and modify certain molecular pathways related to the RAA system. Herbal agents might be useful as treatments to fight COVID-19. Finally, a suggestion for the patients is that it is still not recommended to use the supplementation containing one of these compounds to prevent COVID-19 or to heal the disease without specific advice to be under the direct supervision of a clinician. A suggestion for the clinician is that administration of these herbal medicines must be given carefully to patients, even if they are healthy. Because various inconsistent data have been reported about these agents, there is a possibility that these treatments might be associated with the induction of
harmful effects. In addition, preclinical and clinical trial evaluations of these herbal agents for COVID-19 have not specifically been conducted, so further investigations are recommended.

**Pharmaceutical Prophylaxis and Treatment**

Potential treatments should be carefully assessed in randomized controlled trials (RCTs). There are several large-scale, multicenter trials underway that are using an appropriately robust methodology for assessment of potential therapeutics, including the WHO Solidarity Trial, several United States (US) National Institutes of Health studies, as well as international and national trials in Europe.55

Several pharmaceuticals have either been studied or are still undergoing clinical trials to assess their safety and efficacy as potential treatments for COVID-19, including corticosteroids, the antiviral nucleotide analog remdesivir, systemic interferons, in particular interferon β-1a, monoclonal antibodies against components of the immune system such as interleukin-6 (IL-6) and IL-4, and other immune modulators and antibodies against components of SARS-CoV-2.

**For Example**

**Dexamethasone:** On June 16, 2020, preliminary results of an open-label RCT of dexamethasone showed that it significantly reduced the 28-day mortality, particularly among critically ill COVID-19 patients receiving mechanical ventilation. There was no evidence of benefit for patients not requiring oxygen.56,57 Based on these findings, the US National Institutes of Health (NIH) recommends the administration of dexamethasone for COVID-19 patients who are either mechanically ventilated or require supplemental oxygen.58

On July 17, 2020, the Randomized Evaluation of COVID-19 Therapy (RECOVERY) group published findings from 2100 patients concluding that the use of dexamethasone resulted in lower 28-day mortality among those who were receiving either invasive mechanical ventilation or oxygen alone at randomization, but not among those receiving no respiratory support.45 On September 2, 2020, based on a systematic review and meta-analysis of the results of 8 RCTs, WHO published a strong recommendation for the use of systemic corticosteroids in severely ill patients with COVID-19 and a conditional recommendation not to use systemic corticosteroids in patients with nonsevere COVID-19.59

**Remdesivir:** The interim results of the SOLIDARITY trial, an RCT that compared 4 agents to control treatment from 405 hospitals in 30 countries, showed that remdesivir did not have an effect on mortality among 2743 patients compared to 2708 controls (relative risk of death = 0.95, 95% CI 0.81-1.11, P = .50).60 The authors also concluded that there was no effect on the time to discharge, although the study was not designed to address this question. The results from a double-blind RCT, ACTT-1, in 1062 hospitalized COVID-19 patients showed that remdesivir was associated with a shorter median recovery time compared to placebo (10 vs 15 days). The 14-day mortality was 6.7% in the group of patients that received remdesivir and 11.9% in the placebo group, but the difference was not statistically significant.49

A randomized controlled trial that enrolled 584 patients with moderate disease from 105 hospitals in Europe, the United States, and Asia, found a small improvement in the clinical status in the 5-day treatment group, but no difference between the 10-day treatment group and standard care.52 The authors concluded that the finding was of uncertain clinical importance. On June 25, 2020, EMA’s human medicines committee (CHMP) recommended that remdesivir be granted conditional marketing authorization for the treatment of COVID-19 patients with pneumonia requiring supplemental oxygen.61 On July 3, 2020, the European Commission, with the recommendation of EMA, granted conditional marketing authorization for the treatment of COVID-19 in adults and adolescents from 12 years of age with pneumonia who require supplemental oxygen.62 EMA will evaluate the results of the SOLIDARITY trial.63 The US Food and Drug Administration (FDA) has warned against the use of remdesivir in combination with hydroxychloroquine.64

**Hydroxychloroquine/chloroquine:** Data from in vitro experimental studies indicated that hydroxychloroquine (HCQ) and chloroquine have an inhibitory effect on SARS-CoV-2.65

RCTs such as the WHO SOLIDARITY trial and RECOVERY found no evidence of significant benefit of HCQ for the treatment of COVID-19 and discontinued their HCQ arm. Results of the RECOVERY RCT comparing 1542 patients randomized to receive HCQ with 3132 patients that received usual care did not find any difference between the 2 groups in mortality, hospital stay, or other outcomes.66

Two clinical trials that investigated the effect of HCQ when started early (within 4-5 days from symptom onset) in nonhospitalized patients with mild symptoms, did not show any significant effect on symptom severity.67 A RCT for postexposure prophylaxis that enrolled 821 individuals with household or occupational exposure to confirmed COVID-19 cases did not show a statistically significant difference in the incidence of illness compatible with COVID-19 between the group receiving HCQ and the group-receiving placebo.68

Only the British RCT COPCOV continues, aiming to enroll 40 000 healthcare workers and other at-risk staff around the world to study the efficacy of HCQ as a prophylaxis.59

**Lopinavir/ritonavir:** A RCT of lopinavir/ritonavir in 199 COVID-19 patients in China did not show any statistically significant favorable effect on the clinical course or mortality when compared to standard treatment.70 Similarly, the UK RECOVERY trial that randomized 1616 patients to lopinavir–ritonavir and compared with 3424 patients randomized to usual care, identified no benefit of lopinavir–ritonavir on survival, the clinical course, or the length of hospital stay.71 The study did not include a sufficient number of subjects under invasive mechanical ventilation to allow the study of the effect of lopinavir/ritonavir in this category of patients, due to
the difficulty of administration of the drug in such cases. The WHO SOLIDARITY trial discontinued the lopinavir/ritonavir arm after an interim analysis of the trial results.72

Tocilizumab: In the BACC Bay Tocilizumab Trial, a randomized, double-blind placebo-controlled trial of 243 patients with COVID-19 in the United States of America, Tocilizumab was not effective for preventing intubation or death in moderately ill hospitalized patients with COVID-19.75 However, on November 19, the investigators of another RCT, the REMAP-CAP trial, announced in a press release that early analysis of the data showed that treatment with tocilizumab was effective in reducing deaths and time spent in intensive care for critically ill patients with severe COVID-19.76 The full results of this trial are not yet published.

Antibodies: Interim analysis of the Phase II trial (BLAZE-1) of the human antibody Ly-CoV555 were published, which examined the efficacy of LY-CoV555 in the outpatient treatment of mild or moderate COVID-19.77 These preliminary results showed decreased hospitalization, particularly for the age group >65 years. The US Food and Drug Administration authorized casirivimab plus imdevimab, a combination monoclonal antibody treatment, for patients with mild-to-moderate COVID-19 who are at high risk for developing severe disease. The authorization was based on findings from an ongoing randomized trial, in which treatment with casirivimab plus imdevimab was linked to decreased rates of hospitalization or visits to the emergency department.78

Convalescent plasma therapy (plasma with antibodies from recovered COVID-19 patients): The administration of COVID-19 convalescent plasma (CCP) donated by individuals recovered from the disease is both a prophylactic and therapeutic option. Initial results from various non-RCT and expanded emergency use showed no increase of adverse effects after CCP treatment and suggested that the transfusion of CCP containing a high titer of neutralizing antibodies could be effective in reducing the mortality of hospitalized patients.77,78 However, in an RCT that enrolled 333 hospitalized patients with COVID-19, no difference was observed in mortality or other clinical outcomes between the convalescent plasma and placebo groups at day 30.79 More evidence on the safety and efficacy of CCP is expected from several ongoing RCTs.80

The European Commission together with EU/EEA Member States, the European Blood Alliance (EBA), ECDC, and other health professionals developed guidance on the collection, testing, processing, storage, distribution, and monitored use of convalescent plasma for the treatment of COVID-19 patients.81 The Commission also set-up an open-access EU/EEA database to collect data on CCP donations and patient outcomes following transfusions.

On August 23, 2020, based on the scientific evidence available, the US Food and Drug Administration issued an emergency use authorization for investigational convalescent plasma for the treatment of COVID-19 in hospitalized patients.82

Conclusion
COVID-19 is a serious viral infection that started in December 2019 in China and is still causing health problems and deaths all over the world. Different vaccines are now used for COVID-19, but their safety and side effects are not totally clear as yet. So we should keep in mind another strategy such as nutrition and lifestyle. Also, we should find natural products such as herbs instead of drugs or associated with drugs to decrease side effects and to stop the propagation of COVID-19. At the same time, new strains of the virus are still appearing, like the Indian and South African corona strains. Finally, we cannot say there is a definite remedy for coronavirus, but people have to focus on having good nutrition to help their immunity fight against this dangerous infection. Also social distancing is a good strategy to minimize the spread-ability of the disease.

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