Online publication ahead of print, AJMHS Vol 53, 2020

Coronavirus Disease (COVID-19): A pandemic emergency

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Abstract

At the end of 2019, a cluster of pneumonia caused by unidentified virus emerged in China. Through the analysis of sequence, this new disease was considered to be caused by a novel coronavirus (CoV) named 2019-nCoV. This new virus looks to be very contagious and has quickly spread from China land borders, infecting people throughout the whole world. On March 11, the WHO made the assessment that COVID-19 can be characterized as a pandemic. The mechanism of COVID-19 infection is not yet known. The most common form of spread of the COVID-19 has been from human to human transmission. After exposure to an infected individual, or less likely a contaminated surface, the mean incubation period of COVID-19 is about from 5 up to 24 days. Management strategies for COVID-19 patients are in a rapidly evolving therapeutic challenge, and the optimal agents to treat or prevent infection or progression to critical illness remain non-well defined. Although certain agents listed and non-listed in this review are encouraging, the evidence remains inconclusive and changes almost daily. Although the pathophysiological mechanisms are still not understood, it has been observed that most severe and fatal cases with COVID-19 have occurred in: elderly patients, patients with comorbidities like cardiovascular diseases (CVDs); diabetes mellitus; chronic lung pathologies; renal disease, hypertension, and cancer. Hand washing for at least 20 seconds after visiting public spaces, avoid touching, avoiding contact with people, are recommended.

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Key words: COVI-19, epidemic, SARS-CoV, treatment

INTRODUCTION

In the last twenty years, viral diseases continue to emerge and represent a serious issue for public health. In recent years the world has witnessed widespread epidemics of infections. Several viral epidemics such as Ebola, Zika, the Severe Acute Respiratory Syndrome coronavirus (SARS-CoV) in 2002-2003, H1N1 influenza in 2009, and Middle East respiratory syndrome coronavirus (MERS-CoV) in 2012 have been recorded (1–6). At the end of 2019, a cluster of pneumonia patients with an unidentified cause emerged in Wuhan, a China province. Through the analysis of sequence, this new pathogen pneumonia was considered to be caused by a novel coronavirus (CoV) named 2019-nCoV (7). On February 11, 2020, the World Health Organization (WHO), announced that the disease caused by this new CoV was a "COVID-19," which is the acronym of "coronavirus disease 2019". Coronaviruses are members of the family Coronaviridae (8–10). This new virus looks to be very contagious and has spread from China crossed borders, infecting people throughout the whole world. At the present time it's easier to count countries that have not declared cases with COVID-19 than the opposite. The WHO declared that COVID-19 has become a global health concern, and it currently results in severe respiratory tract infections in humans. After reaching more than 118,000 cases with over 4,000 deaths in 114 countries, on March 11, 2020 the WHO made the assessment that COVID-19 can be characterized as a pandemic (4,11,12). COVID-19 infected patients are the main source of infection. Modes of transmission are through droplet transmission, fecal-oral route, conjunctiva and fomites, saliva, feces, and urine. Severe patients are considered to be more contagious than mild ones, but asymptomatically infected persons or patients in incubation time, may also be potential sources of infection (7,12–15). Infection in patients can pass in five different outcomes: asymptomatically infected persons; mild to medium cases; severe cases; critical case; and death (7,16–19).

What is the causative agent of disease?

Coronaviruses are members of the subfamily Coronavirinae, the family Coronaviridae and the order of Nidovirales. The recent emergence of a novel coronavirus with an outbreak of unusual viral pneumonia in Wuhan, China and then pandemic outbreak is 2019-nCoV or COVID-19 (11,16,19,20)**.** They as RNA viruses are common in several species of animals. It has been confirmed that coronaviruses have frequently made the jump from animals to human. The seven coronaviruses that can infect humans, including NL63, HKU1, OC43, 229E, SARS, Middle East Respiratory Syndrome (MERS), and COVID-19 (1). The virus particle has a diameter of 60~100 nm. COVID-19 is a spherical or pleomorphic enveloped particles containing single-stranded (positive-sense) RNA associated with a nucleoprotein within a capsid comprised of matrix protein (21,22). There are three or four viral proteins in the coronavirus membrane. The most abundant structural protein is the membrane

(M) glycoprotein. The spike protein (S), which is the inducer of neutralizing antibodies, as a type I membrane glycoprotein constitutes the peplomers. M protein plays a predominant role in the intracellular formation of virus particles without requiring S protein. The mechanism of COVID-19 infection is not yet known. COVID-19 binds to ACE2 (the angiotensin-converting enzyme 2) by its Spike and allows the virus to enter and infect cells. The proteins assembled within the membrane cell and genomic RNA is incorporated because the mature particle forms by budding from the inner membranes cell (7). Most of patients with COVID-19 exhibit fly-like-mild to moderate symptoms, but approximately 10-15% of them achieve severe pneumonia and about 5% eventually develop acute respiratory distress syndrome (ARDS), septic shock and/or multiple organ failure (23). The infection from COVID-19 can activate innate and adaptive immune responses. After the virus bind to alveolar epithelial cells, it activates innate immune and adaptive immune system, which result in the release of a large number of cytokines (23). Uncontrolled inflammatory innate responses and impaired adaptive immune responses may lead to organs damage, both locally and systemically. Most patients with severe COVID-19 infection show principally elevated serum levels of pro-inflammatory cytokines including IL-6: IL-1β, IL-2, IL-8, IL-17, G-CSF, GM-CSF, IP10, MCP1, MIP1α and TNF, characterized as cytokine storm (24). High levels of pro-inflammatory cytokines, as well as C-reactive protein, D-dimer and ferritinemia, may lead to shock and tissue damage in the heart, liver and kidney, respiratory failure or multiple organ failure. On the other hand, high levels of

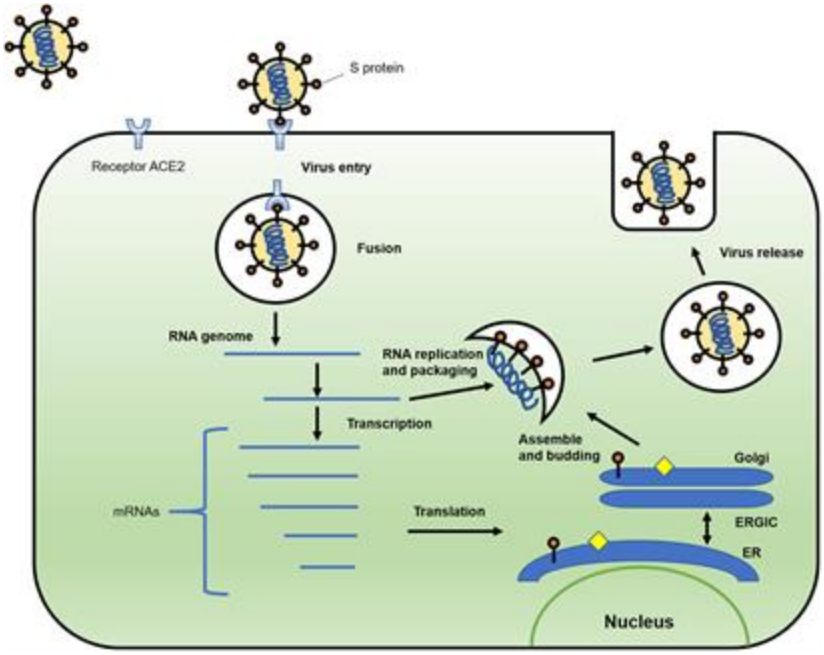

Figure 1. Schematic model of SARS-CoV-2 life cycle. S protein binds to the cellular receptor ACE2 to facilitate the entry of the virus. After the fusion of viral and plasma membranes, virus RNA undergoes replication and transcription

IL-6 were found to be a stable indicator of poor outcome in patients with severe pneumonia and ARDS (22,23). Giannis et al report that preliminary reports on COVID-19 pandemic outcomes have shown that patients commonly develop thrombocytopenia in 36.2% and may have elevated D-dimer in 46.4%. Emerging data support that patients infected by this novel coronavirus are at risk of developing disseminated intravascular coagulation (DIC) (25,26).

The most common transmission form of spread of the COVID-19 virus has been from human to human. This transmission includes contact on 15 minutes or more interaction between infected and uninfected people and facilitating large droplet. After exposure to an infected individual, or less likely a contaminated surface, the mean incubation period of COVID-19 is about from 5 up to 24 days (19,9,27). It has been reported that the virus was more stable on plastic and stainless steel than on copper and cardboard, and viable virus was detected up to 72 h after application to these surfaces.

What characteristics define a "COVID-19 patient case"?

The ongoing coronavirus pandemic is actually responsible for more than 2 397 216 confirmed people in more than 192 countries and territories, and it counts over 162 956 deaths worldwide. It is therefore of crucial importance to identify the suspected cases in order to confirm the diagnosis and investigate their close contacts. As COVID-19 clinical debuted, is very similar to other viruses, many of those who meet the suspect case criteria's will not have COVID-19 (28,29). However, it is of great importance, that people who meet the suspect case criteria, under investigation, probable or confirmed case definitions isolate themselves in order to reduce the transmission (30). The definition of suspected cases has been changing dynamically. At the beginning of COVID 19 pandemic the suspected case criteria's were related to journeys and close contacts with people from China (31). According to standard clinical guidelines, suspected COVID-19 cases were defined as a combination of clinical characteristics and epidemiologic histories. Clinical characteristics of suspected cases must fit at least 2 of the 3 following criteria: "fever and/or symptoms in the respiratory system; radiographic evidence of pneumonia; low or normal WBCc or lymphopenia. Epidemiologic histories must fit at least one of the four following criteria: A traveling history to/from Hubei Province or other districts that has confirmed cases reported within 14 days of symptom onset; a contacting history with a patient who has fever or symptoms in respiratory system from Hubei-Province China or other districts that has confirmed cases reported within 14 days of symptom onset; any person who has had close contact with confirmed cases; cluster cases (32). Ideally, would be tested to confirm or exclude a diagnosis, all people meeting the above symptoms of suspect case definition for COVID-19, or where the clinician has a high degree of

suspicion. The prioritized people for being tested are the following: close contacts of confirmed cases; people meeting the clinical criteria who have travelled overseas in the last 14 days, or have had contact with someone else who has recently travelled overseas; health care workers meeting the clinical criteria; other essential workers meeting the clinical criteria; people meeting the clinical criteria who reside in (or are being admitted into) a vulnerable communal environment including aged residential care; people meeting the clinical criteria who may expose a large number of contacts to infection (including halls of residence, barracks, hostels, shelters etc). Laboratory suggestive evidence requires detection of coronavirus from a clinical specimen using pan-coronavirus NAAT (PCR). A confirmed case is a case that has laboratory definitive evidence and this requires at least one of the following:

- detection of SARS-CoV-2 from a clinical specimen using a validated NAAT (PCR);
- detection of coronavirus from a clinical specimen using pan-coronavirus NAAT (PCR) and confirmation as SARS-CoV-2 by sequencing;
- significant rise in IgG antibody level to SARS-CoV-2 between paired sera (when serological testing is available);

In symptomatic patients, illness may evolve over the course of a week or longer, beginning with flu-like to mild symptoms that progress to organs harmful to ARDS and death. Fever is one of the first symptoms of patients with COVID-19, and pyrexia is present in 85-87% of cases during their illness course, but only 45% are febrile on early presentation. Cough is seen in 67.7% of patients. Usually is a dry cough and sputum is produced in 33.4%. Respiratory symptoms such as dyspnoea, sore throat, and nasal congestion may be present. Other important symptoms are: myalgia, fatigue, bone aches, chills, and headache (29,33). Gastrointestinal (GI) symptoms such as nausea or vomiting and diarrhoea are less frequent (34–36). In severe cases the patient can precipitate in ARDS which can further go to septic shock. The two last complications are the major contributors to intensive care unit (ICU) care and mortality. Patients with moderate to severe disease complain of dyspnoea or short breathing (37). Hypotension, tachycardia, and cool/clammy extremities suggest shock. Age over 60 years, smoking history, and comorbidities are the prognostic factors for case fatality (38–40)**.**

What treatments are effective?

Except of prevention of COVID-19 patients, treatment is a major challenge to physicians. Actually, there isn't any specific effective anti-viral treatment for COVID-19. Hydroxychloroquine is an analogue of chloroquine (CQ), produced by Andersag in 1934, and proven during World War II, it was used as anti-malarial during the 20th and 21st century to prevent and treat malaria (41). Chloroquine blocks viral infection through increase of endosomal pH and interferes with the

glycosylation of cellular receptor of SARS-CoV and inhibits the quinone reductase-2 that makes this agent a broad antiviral agent. Chinese experts recommend chloroquine-based treatment (500 mg twice per day for ten days) as a first line-treatment for mild, moderate and severe cases of COVID-19. Chloroquine phosphate is the first drug reported to display efficacy against COVID-19. It disrupts the ability of the SARS-CoV-2 virus to enter and replicate in human cells (42). The cell culture studies of SARS-CoV-2 revealed that the drug and its derivative hydroxychloroquine (HCQ) undermine the novel virus' replication in a similar way (35,43–45). Some data show HCQ effectively inhibited both the entry, transport and the post-entry stages of SARS-CoV-2, similar to the chloroquine and one study found HCQ to be a more potent agent than chloroquine (45–48). In addition, the combination of hydroxychloroquine and azithromycin on SARS-CoV-2 infected cells showed a considerable synergy when they were used together at doses which mimic the concentrations likely to be obtained in humans (35,49). It is not recommended the general use of HCQ as prophylaxis in the general population for some reasons such are side cardiac effects, dose monitoring etc (41,48,50). A specific antiretroviral therapy combination of lopinavir/ritonavir is widely used in the treatment of HIV and it may play an important role in the treatment of COVID-19 patients (51). In a clinical trial by Cao et al was found that lopinavir–ritonavir treatment didn't reduced viral RNA loads or duration of viral RNA detectability as compared with standard supportive care alone. Lopinavir/ritonavir in combination prolongs bioavailability of lopinavir. This formula in combination with ribavirin was used previously to treat SARS-CoV-2 patients. Currently, lopinavir/ritonavir at 400mg/100 mg twice daily with or without ribavirin is part of the recommended treatment for managing COVID-19 patients in China (52). Maybe the delayed treatment initiation, partially explain the ineffectiveness of this combination on COVID-19 treating. The most commonly used and studied lopinavir/ritonavir dosing regimen treatment is 400 mg/100 mg twice daily for up to 14 days. Ribavirin, a guanine analogue, inhibits viral RNA-dependent RNA polymerase. However, their limitations in daily practice because necessitating high-dose (eg, 1.2 g to 2.4 g orally every 8 hours), hematological side effects, teratogenicity and combination therapy make it a non-first choice drug. Oseltamivir hasn't documented in vitro activity against SARS. Umifenovir (Arbidol) is a promising agent against COVID-19. Its mechanism of action is targeting the S protein/ACE2 interaction and inhibiting membrane fusion of the viral envelope. Arbidol is approved in some countries as anti COVID-19 treatment. Current Chinese guidelines list interferons as an alternative for combination therapy with ribavirin and/or lopinavir/ritonavir. Other drugs such as Nitazoxanide, Camostat mesylate, ACE inhibitors and/or angiotensin receptor blockers

provide additional drug targets for future research (53). Remdesivir is another potential antiviral drug developed for the treatment of COVID-19 patients. Due to its broad-spectrum, potent in vitro activity, it seems a promising potential therapy for COVID-19 (53–57). It is a well-tolerated drug with a single 200-mg loading dose, followed by 100-mg daily infusion. No kidney or hepatic adjustments are recommended. Favipiravir is a prodrug of favipiravir ribofuranosyl-5′-triphosphate. The active agent inhibits the RNA polymerase and prevent viral replication.

Monoclonal antibodies directed against inflammatory cytokines or immune response represents another potential class of adjunctive therapies for COVID-19. Interleukin (IL)-6 and other inflammatory components of the cascade contribute to host defense against infections (58,59) Tocilizumab is listed as a treatment option for severe or critical cases of COVID-19. Given in dose 400mg, was associated with clinical improvement in 91% of patients (57,60). Other formulas such as sarilumab, bevacizumab, fingolimod, eculizumab are under consideration for clinical use (59,61–63). The role of

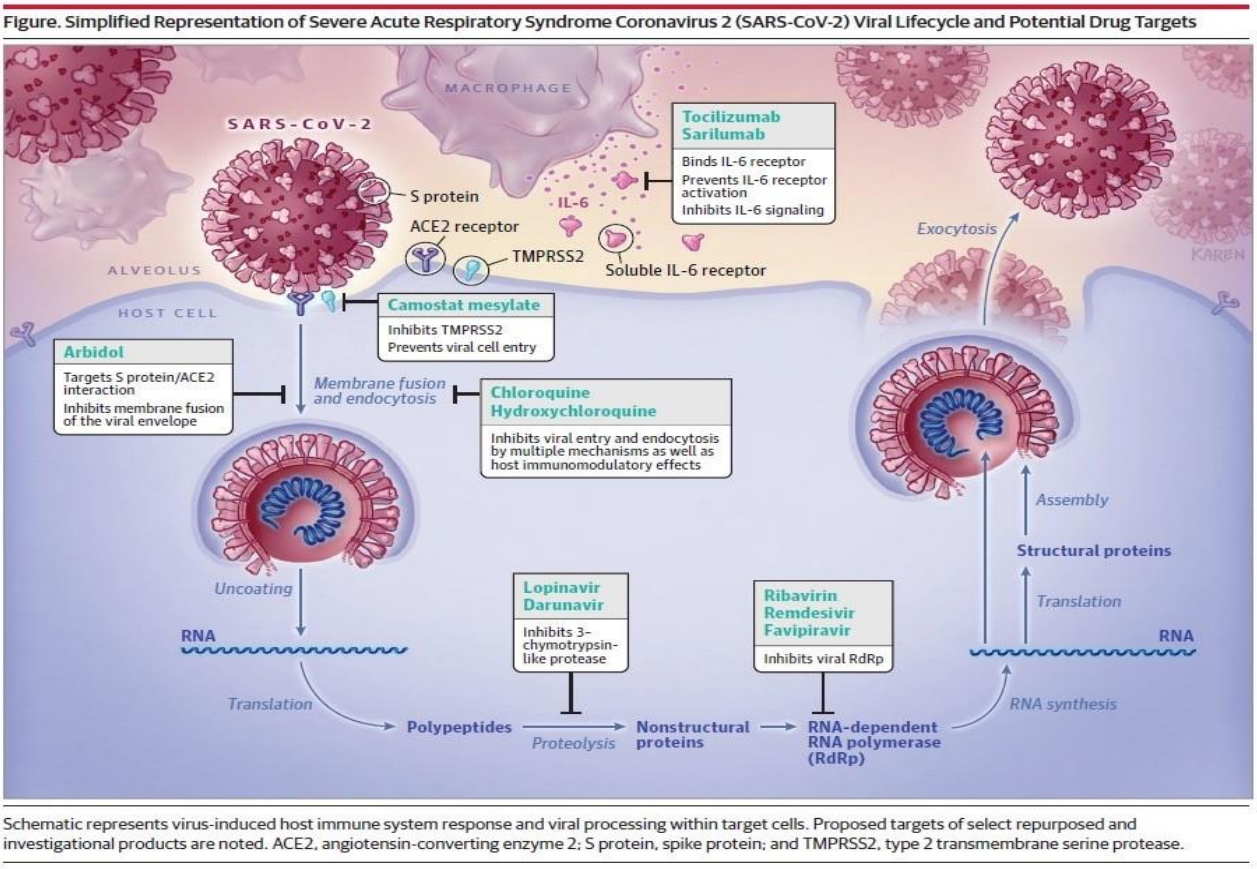

Figure 2. Viral lifecycle and potential drug treatment. Sanders JM, Monogue ML, Jodlowski TZ, Cutrell JB. Pharmacologic Treatments for Coronavirus Disease 2019 (COVID-19): A Review. JAMA. Published online April 13, 2020. doi:10.1001/jama.2020.6019

corticosteroids remains controversial, and their use is not recommended unless another concomitant indication (40,64,65). Another potential adjunctive therapy for COVID-19 is the use of convalescent plasma or hyper immune immunoglobulins that seems as the most promising therapy. Maybe the antibodies from recovered patients may help with both free virus and infected cell immune clearance (53,57,62,66).

Management strategies for COVID-19 patients are in a rapidly evolving therapeutic challenge, and the optimal agents to treat or prevent infection or progression to critical illness remain non-well defined. Although certain agents listed and non-listed in this review are encouraging, the evidence remains inconclusive and changes almost daily. Unfortunately, no antivirals are approved for the treatment of neither COVID-19 infection, nor vaccines are available for prevention. Therefore, the most important way to prevent infection is to avoid being exposed to this virus through measures like hand and respiratory hygiene.

What are the risk factors for infection in the patient population?

Although the pathophysiological mechanisms are still not understood, it has been observed that most severe and fatal cases with COVID-19 have occurred in: elderly patients: patients with comorbidities like cardiovascular (CVDs); diabetes mellitus; chronic lung pathologies; renal disease, hypertension, and cancer (18,67,68). Age seems an important factor that influences in case mortality. Most of the fatal cases to date have involved older adults and patients with comorbidities (67,69). Chen et al on their study report that 27.1% were older than 65 years of age. The main clinical manifestations included fever, dry cough, chest tightness, shortness of breath, and muscle/joint soreness, which are consistent with the previous literature. This study found that the older patients have a poor prognosis (70). Shahid et al report that 80% of deaths among adult patients occurred in those over age 65 (68). Guo et al in their data report that around 15-30% of the COVID-19 patients are with hypertension and 2.5-15% are with coronary heart disease (71). Development of ARDS in COVID-19 infection patients is an another prognostic factor that rise the case fatality (40)**.** In one of Chinese meta-analysis including 1527 patients is showed that the most prevalent cardiovascular metabolic comorbidities were: hypertension; cardio-cerebrovascular disease, and then diabetes. In this report, patients with cardio and cerebrovascular disease had a 3-fold increase in risk of severe disease, while those with diabetes or hypertension had a 2-fold increase (72–74). Hulot at al suggest that patients with previous cardiovascular diseases are at higher risk for developing severe symptoms if infected with COVID-19 (74,75). Madjid et al. in their study, report a series of 44 672 confirmed patients with COVID-19, and among them patients with CVD were 4.2% and patients with hypertension were 12.8%. The mortality was

connected with advanced age, with case-fatality rate of 1.3% in patients aged 50-59, 3.6% in patients aged 60-69, 8% in patients aged 70 to 79, and 14.8% in patients 80 years or older. The case fatality rate for patients with hypertension was 6%, diabetes was 7.3%, and in chronic respiratory disease was 6.3%. COVID-19 infection infect almost equally both sexes; however, men showed a higher case fatality rate than women (3.6% vs 1.6%, respectively) (75). The largest epidemiological data in China indicated that the mortality of COVID-19 patients with diabetes rise up to 7.3%, which is higher with patients without any comorbidities. Bacterial infections are usually regarded as a leading cause of sepsis, and the viral infection can also cause sepsis syndrome. Sepsis occurred in nearly 40% of adults with community-acquired pneumonia due to viral infection. On the other hand elevated IL-6, cardiac troponin I, LDH and lymphopenia were more commonly seen in severe COVID-19 illness (67,70). However in literature are presented a lot of case reports about connection of COVID-19 infection and other diseases. But the better understanding of this topic maybe will be studied latter.

Current state of knowledge for COVID-19

At the time of writing of this review, the COVID-19 pandemic, caused by a completely novel coronavirus, has already affected over 2 397 216 confirmed people in more than 192 countries and territories, and killed over 162 956 people worldwide (32). Recent epidemics of this viral diseases have started from China, and after than Italy, Spain and other European countries (7). Nowadays it's easier to count countries that haven't declared cases with COVID-19 than the other. China established a replacement new web-based service for quick alarming in case of an emerging disease with unknown origin through common closed-circuit surveillance system and has already acknowledged the possibility of a new virus epidemic within the future and scaled up public health measures and quarantined many cities. After distribution in Europe, several countries have instituted temporary restrictions on travel toward slowing the spread of this disease (76). The social distancing measures vary somewhat by state and city but are generally wide-ranging. They include cancelling sports, social and political activities, closing of gyms, restaurants and food courts, closure of schools, banning of mass gatherings, mandated mask wearing, case isolation, recommendations to work from home and to avoid travel (15,77). The closures of school were unprecedented globally. It is unclear how long countries can maintain tight suppression measures before behavioral fatigue within the population occurs. Quarantine is effective at reducing incidence and mortality of covid-19 pandemic (78,79). Albania is applying one among the foremost strictly quarantine rules ever used before. But we don't know how long this pandemic will last and numbers of COVID-19 cases are rising substantially. What we will do? The best way for this moment is not to panic. We must follow the governments rule for

quarantine. Hand washing for at least 20 seconds after visiting public spaces, avoid touching, avoiding contact with people, are recommended (80,81). One of the most relevant concerns in this pandemic is the health care workers infection. The data are not sill published, but it is a real (82).

CONCLUSIONS

The COVID-19 pandemic represents the greatest global public health crisis, since the pandemic influenza outbreak of 1918. Current knowledge for COVID-19 is evolving very fast. The WHO has developed strategies and response attempt to contain the impact of COVID-19. As novel pathogens have emerged and spread, the international response will come, but not soon. Unfortunately, the spread of the virus is ongoing, despite of actions on preventive interventions, which in some contexts are very restrictive. Actually the clinicians doesn't have any target drug to fight the COVID-19, however they're working hardly. Scientists are working in several directions: physpathology, immunology, treatment, prevention and the way the globe should be prepared before a pandemic. Maybe the quarantine is very important in reducing incidence of cases and mortality. The impact of the infection is clear not only from a clinical but also from an economic point of view. In this short review, we gave an overview of epidemiological, etiological, clinical, pathological, diagnosis and the latest advancements in the treatment of covid-19.

Acknowledgments

None declared.

Conflict of interest

None declared.

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