MINI REVIEW

COVID-19: Evolving from Myths and Trials to a Potentially Treatable Disease

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ABSTRACT

Since the COVID-19 outbreak has emerged, every nation and every government are trying its best to combat the disease and develop strategies for better prevention, diagnosis, treatment and management of this lethal virus. Though the mortality rate is far less than any other pandemic the world has experienced, still patients with co-morbid conditions and immune system disorders are at high risk of fatal outcome. There are no approved treatments for COVID-19; thus, people with COVID-19 should be referred to clinical trials. Several agents have been touted as treatments for COVID-19, but at this point, the data are insufficient to inform a recommendation for or against the use of these agents outside of clinical trials; well-conducted randomized trials will be critical in determining how COVID-19 should be treated.

KEYWORD: COVID-19, PCR, Hydroxychloroquine, N95 respirator.

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INTRODUCTION

Coronaviruses are RNA viruses that are divided into four genera; alpha-Coronaviruses and beta-Coronaviruses are known to infect humans. SARS-CoV-2 is related to bat Coronaviruses and to SARS-CoV-1, the virus that causes severe acute respiratory syndrome (SARS). Similar to SARS-CoV-1, SARS-CoV-2 enters human cells through the angiotensin-converting–enzyme 2 (ACE2).[1]

Coronaviruses typically cause common cold symptoms, but two beta-Coronaviruses namely SARS-CoV-1 and Middle East respiratory syndrome Coronavirus (MERS-CoV) can cause severe pneumonia, respiratory failure, and death. In late 2019, infection with a novel beta-Coronavirus, named SARS-CoV-2, was reported in people exposed in a seafood market in Wuhan, China, where live animals were sold. Since then, there has been a swift spread of the virus, leading to a global pandemic of COVID-19.[2]

So, there is an expeditious need to manage mild and moderate cases to decrease the morbidity rate and provide awareness to prevent the transmission of the virus.

Transmission

SARS-CoV-2 is primarily spread from person to person through respiratory droplets, which are typically released when an infected person coughs or sneezes. Because droplets usually fall within a few meters, the transmission is possible to decrease if people should remain at least 2 meters away and maintain social distancing. Other routes

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of transmission are still under documentation. SARS-CoV-2 may persist on cardboard, plastic, and stainless steel for days. Therefore, contamination of inanimate surfaces may play a role in transmission. Pre-symptomatic people are infectious, is a major challenge to spread the SARS-CoV-2.[3]

Recent reports suggest that patients may be infectious 1 to 3 days before the onset of symptoms and up to 40 to 50% of cases may be credited to transmit from asymptomatic or pre-symptomatic.[4]

Just before or soon after the onset of symptoms, patients have high nasopharyngeal viral levels, which then fall approximately 1 week. Patients with severe disease may shed the virus for longer periods, although the duration of infectious viral shedding is unclear and need to explore.[5]

Clinical Manifestations

The incubation period, from exposure to symptom onset, is approximately 4 to 5 days, and 97.5% of symptomatic patients will have symptoms within 11.5 days after infection. Symptoms may include fever, cough, sore throat, malaise, and myalgias. Some patients have gastrointestinal symptoms, including anorexia, nausea, and diarrhea. In some cases of hospitalized patients, shortness of breath developed in 5 to 8 days after onset of initial symptoms. Shortness of breath is an indication of the worsening of the disease.[6]

Risk factors for complications of COVID-19 include older age (e.g., > 65 years), cardiovascular disease, chronic lung disease, hypertension, diabetes, and obesity. It is unclear about certain other conditions (kidney disease, immune-suppression, cancer, and uncontrolled human immune-deficiency virus HIV infection) to increase the risk of complications, but after having an infection, these conditions along with opportunistic respiratory pathogens can lead to worse outcomes. So, close monitoring of patients with COVID-19 who have these conditions is mandatory.[7]

Laboratory findings in hospitalized patients may include elevated levels of D-dimer, lactate dehydrogenase, C-reactive protein, and serum ferritin. Result findings associated with poor outcomes in some cases include an increasing white-cell count with lymphopenia, a prolonged prothrombin time, and elevated levels of liver enzymes, lactate dehydrogenase, D-dimer, interleukin-6, C-reactive protein, and pro-calcitonin.[8] On chest imaging, the typical findings are ground-glass opacifications or consolidation.[9]

Diagnosis

The diagnosis of COVID-19 is usually based on polymerase-chain-reaction (PCR) assay to detect SARS-CoV-2. Soon after symptom onset, the sensitivity of PCR testing of nasopharyngeal/ oropharyngeal swabs appears to be high, but false negatives may occur. If a person is suspected to have COVID-19 and having a history to live in an area with active community transmission but has negative testing of a nasopharyngeal swab, repeat testing is prudent.[10]

Nasopharyngeal swabs are mostly collected for PCR assays.[2] There are limited data regarding the use of oropharyngeal swabs. One study indicated testing of these swabs was less sensitive than testing of nasopharyngeal swabs. If a nasopharyngeal swab cannot be obtained, the Centers for Disease Control and Prevention (CDC) recommend the use of an oropharyngeal swab.[11]

The Food and Drug Administration (FDA) recently recognized the on-site self-collection of an anterior nares' specimen as an acceptable method of collection.[12] This option may facilitate home-based testing and reduce the exposures for health care workers.

Evaluation

Evaluation and management of COVID-19 are guided by the severity of the illness. According to initial data from China, 81% of people with COVID-19 had mild or moderate disease (including people without pneumonia and people with mild pneumonia), 14% had severe disease, and 5% had a critical illness.[13]

Patients who have mild signs and symptoms generally do not need additional evaluation, and depending on the risk profile, they may not even need to undergo COVID-19 testing, since the infection usually resolves. However, some patients initially have mild symptoms; approximately 1 week after onset of symptoms can progress to clinical deterioration. Patients, who have risk

factors for severe disease, need close monitoring for clinical progression.[14]

If new or worsening symptoms (e.g., dyspnea) develop in patients with initially mild illness, strict evaluation is warranted. A physical examination should be performed to assess for tachypnea, hypoxemia, and abnormal lung findings. Also, testing for other pathogens (e.g., influenza virus, depending on the season, and other respiratory viruses) should be performed, if available, and chest imaging should be considered.[15]

If the findings on the initial assessment are presenting as moderate or severe illness, hospitalization is compulsory. Patients with moderate disease may have dyspnea, but the blood oxygen saturation is usually at least 94% and the patient can maintain saturation with room air; sometimes need oxygen maintenance. Indicators of severe disease are marked tachypnea (respiratory rate, ≥ 30 breaths per minute), hypoxemia (oxygen saturation, ≤ 93%; the ratio of the partial pressure of arterial oxygen to fraction of inspired oxygen, < 300), and lung infiltrates (> 50% of the lung field involved within 24 to 48 hours).[13]

Laboratory testing in admitted patients should include a complete blood count and a comprehensive baseline investigation. A baseline electrocardiogram should be obtained if the patient has co-morbidities.

Chest radiography is usually the initial imaging method. Some centers also use lung ultra-sonography.

Management of Mild or Moderate COVID-19

According to WHO guidelines patients who have mild illness usually recover with supportive care and isolation at home. Immune-compromised patients who are at risk of complications can self-monitor their oxygen saturation at home by using a pulse.[14]

Patients who have moderate or severe diseases are usually monitored in the hospital. If there is clinical evidence of bacterial pneumonia, empirical antibacterial therapy is a reasonable option but should be stopped as soon as possible. Empirical treatment for influenza may be considered during the period when seasonal influenza transmission is occurring until the results of specific testing are known.[15]

There are no approved treatments for COVID-19; thus, people with COVID-19 should be referred to clinical trials. Several agents have been touted as treatments for COVID-19, but at this point, the data are insufficient to inform a recommendation for or against the use of these agents outside of clinical trials; well-conducted randomized trials will be critical in determining how COVID-19 should be treated.[15,16]

Hydroxy-Chloroquine and Chloroquine With or Without Azithromycin

Hydroxychloroquine also has anti-inflammatory effects. Chloroquine is recommended in China for the treatment of COVID-19, but high-quality data are lacking to show whether it or hydroxychloroquine is safe and effective for this indication. A small open-label, a nonrandomized study from France showed a higher rate of SARS-CoV-2 clearance in 14 patients by day 6 who were treated with hydroxyl-chloroquine than in patients who declined to participate in the study or were at a different clinic. The effects appeared to be greater in the 6 patients who were receiving hydroxychloroquine combined with azithromycin.[17]

A case study showed high rates of viral clearance and clinical improvement in patients treated with hydroxychloroquine plus azithromycin. However, both studies had substantial methodological limitations.[18] Determination of the role of hydroxychloroquine with or without azithromycin for the treatment of COVID-19 hinges on the results of well-conducted clinical trials. The FDA has issued an Emergency Use Authorization (EUA) for the use of chloroquine and hydroxychloroquine from the strategic national stockpile for the treatment of hospitalized adults with COVID-19, but this action does not constitute FDA approval of these agents for this indication. The EUA encourages the conduct and participation in randomized, controlled trials to provide evidence for the effectiveness of these drugs for the treatment of COVID-19.[18,19]

Lopinavir–Ritonavir

Lopinavir–ritonavir, an HIV-1 protease inhibitor, has been proposed as a treatment, but it is not known whether drug levels adequate to inhibit the SARS-CoV-2 protease can be reliably achieved in people with COVID-19 who receive this medication.[20]

Remdesivir

Remdesivir, an inhibitor of RNA-dependent RNA polymerase, has had activity against SARS-CoV-2 in vitro and other Coronaviruses in several animal models.[20,21] In a case series involving patients with severe COVID-19 who received remdesivir through a compassionate-use program, the majority of patients had a decrease in the need for oxygen support, but there was no comparison group. Results of ongoing phase 3, randomized, controlled trials are anticipated.[15]

Immune-modulation

A concern that a hyper-inflammatory state may lead many of the severe manifestations of COVID-19, several immune-modulating therapies including glucocorticoids, Convalescent plasma, and anti-cytokine therapy are under investigation.[15]

Use of Concomitant Medications in People with COVID-19:

As SARS-CoV-2 enters human cells through the ACE2 receptor, questions have been raised regarding whether the use of ACE inhibitors or angiotensin-receptor blockers (ARBs) which may increase ACE2 levels might increase the acquisition of SARS-CoV-2 or the severity of COVID-19.[24]

However, given the absence of definitive clinical data, the current recommendation is that patients who are taking ACE inhibitors or ARBs for another indication (e.g., hypertension or heart failure) should not stop taking these agents routinely, even if they have COVID-19.[25]

Some reports have suggested a possible deleterious effect of non-steroidal anti-inflammatory drugs on the course of COVID-19, but several authoritative organizations have noted the absence of clinical data to support this concern.[26]

Concerns have also been raised about the use of glucocorticoids, and some guidelines suggest that they should not be used in patients with COVID-19 pneumonia. But due to deficient clinical data, the use of systemic or inhaled glucocorticoids should not be stopped in patients who are taking them for other indications.[27]

Infection Control and Prevention

Health care workers must be protected from acquiring SARS-CoV-2 when they are providing clinical care. Using tele-health when possible, reducing the number of healthcare workers who interact with infected patients.[28] Personal protective equipment (PPE) should include, at a minimum, an isolation gown, gloves, a face mask preferably N95 respirator, and eye protection (goggles or a face shield). The use of droplet-contact precautions (a gown, gloves, a face mask, and eye protection) for the routine care of patients with COVID-19 is consistent with guidelines from the World Health Organization (WHO). The CDC prefers the use of a respirator (usually an N95 or N99 filtering face-piece respirator, a powered air-purifying respirator PAPR unit, or a contained air-purifying respirator CAPR unit) instead of a face mask. However, in the context of supply shortages, the CDC recommends the use of face masks as an acceptable alternative. The CDC and the WHO both recommend the use of enhanced protection for aerosol-generating procedures, including the use of a respirator and an airborne infection isolation room.[29]

At sites (Isolation dept.) where enhanced protection is not available, the use of nebulizers and other aerosol-generating procedures should be avoided, whenever possible.

Recent studies indicating that transmission occurs before symptom onset may support universal droplet-contact precautions for all are having patient initial encounters.

Capacity building in our context must be needed to encourage and update the health care workers. Strategies to facilitate infection prevention and control are needed for people with unstable housing and people who live in congregate settings, where physical distancing is inconsistent

or impossible (e.g., dormitories, jails, prisons, detention centers, long-term care facilities and behavioral health facilities).

Area of Uncertainty

Numerous uncertainties remain in our understanding of the spread of COVID-19 and its management. The contribution of transmission from asymptomatic and pre-symptomatic people to the community and nosocomial spread of SARS-CoV-2, and the extent, to which fomites and aerosols (those not generated by medical procedures) contribute to transmission, are unclear.

Data to inform treatment remains limited. Trials are in progress to assess the effects of various medications such as hydroxychloroquine with or without azithromycin, redeliver, and favipiravir (which has anti-influenza activity) on the disease course in patients with different severities of illness, as well as to evaluate hydroxychloroquine as prophylaxis in high-risk or exposed people. Studies are underway to develop an effective vaccine. It is unknown whether infection confers partial or complete immunity (and, if so, for how long time) and whether results of serologic testing can be used to inform when health care workers and others can safely return to work.

Guidelines in Rapidly Changing Pandemic

Many professional organizations have developed interim guidelines for the management and prevention of COVID-19. The National Institutes of Health highlight the fact that there are no proven therapies for COVID-19 and randomized trials are critical.[30]

CONCLUSION

The immune-compromised patient is at high risk of having COVID-19 with potential complications. Dyspnea and risk factors for severe illness is the preference for PCR testing of a nasopharyngeal swab for SARS-CoV-2, along with an examination and chest radiography. Patients should be advised to wear a face mask; after arrival at a health care facility, and promptly escorted to an examination room. Admission would be necessary for close monitoring if dyspnea is present. Based on the limited available data, the patient can continue his ARB and inhaled glucocorticoids. In the absence of high-quality data to support any COVID-19 specific therapy, the recommendation is to enroll in a randomized clinical trial, if possible. When the patient's condition improves sufficiently for discharge, he should be advised to remain isolated for a minimum of 7 days after symptom onset and at least 3 days after resolution of fever and improvement in respiratory symptoms.

Local or national guidelines may be introduced for the isolation period.

LIMITATION OF STUDY

This review is a of narrative type. Critical review of literature and comparison among different studies is lacking.

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CONFLICT OF INETEREST

None to declare.

FINANCIAL DISCLOSURE

None to disclose.

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Author's Contribution

AMN: Conception of data, drafting of manuscript.

SK: Critical review, manuscript drafting, final approval of the version to be published.

MG: Critical review, Design of work, final approval of the version to be published.

SK: Intellectual input into data interpretation.