

Management of Coronavirus 2019

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J Card Crit Care:2020;4:40–46

Abstract

Keywords

- ▶ coronavirus
- ▶ COVID-19
- ▶ Outbreak

Coronavirus 2019 (COVID-19) disease is the most recent global public health problem. It is caused by SARS-CoV-2 (severe acute respiratory syndrome related coronavirus 2), which is a RNA virus with a high mutation rate, belonging to the genus *Coronavirus*. The objective of this communication is to provide an initial understanding regarding pathophysiology, clinical manifestations, management, and prevention of this devastating disease.

Introduction

An outbreak of pneumonia of unidentified etiology started in Wuhan district of China in the month of December 2019. Soon, scientists were able to identify it as a novel coronavirus referred to as 2019-nCoV. It has been assigned a new name, that is, severe acute respiratory syndrome related coronavirus 2 (SARS-CoV-2). Disease caused by SARS-CoV-2 was termed as coronavirus disease 2019 (COVID-19) by the World Health Organization (WHO) soon after. In a short span, COVID-19 has afflicted populations across all boundaries globally. Unlike the SARS outbreak, where it took 5 months after the outbreak to identify the etiological organism, identification of SARS-CoV-2 was within 2 weeks of the outbreak. This allowed a rapid development of real-time polymerase chain reaction diagnostic test specific to SARS-CoV-2. Despite this, it has had a devastating effect worldwide and continues to do so till now.¹

SARS-CoV-2 is a positive-sense single-strand RNA virus that is distinct from other coronaviruses such as SARS-CoV and Middle East respiratory syndrome coronavirus (MERS-CoV). The incubation period is not exactly known, but according to the WHO, it is between 2 and 14 days. Understanding of the risk of transmission is not complete yet. Person-to-person spread of SARS-CoV-2 occurs through contact, droplet, and, sometimes, airborne route. Droplets travel around 2 m, but apparently the virus can remain viable in aerosols for about 3 hours. It is estimated that the virus persists for approximately 5 days on plastic, paper, wood, and glass surfaces. Transmission is more likely during the early stage of infection as viral RNA level appears to

be highest soon after the onset of symptoms. Viral translocation has been documented from asymptomatic persons as well or from individuals within the incubation period. SARS-CoV-2 has been isolated in blood and stool specimens as well. But fecal–oral transmission does not seem to play a role as per the current understanding.^{2,3}

More than 471,820 cases and 21,297 deaths from COVID-19 have been reported globally. Updated case counts can be checked on the WHO and Centers for Disease Control and Prevention (CDC) Web sites.

Case Definition of COVID-19

A suspected case has been defined as a patient with acute onset respiratory infection with fever, cough, sore throat, and an epidemiological link in the form of a history of travel 14 days prior to the onset of symptoms to countries afflicted with COVID-19, or a close contact with a confirmed or probable case of COVID-19 14 days prior to symptom onset, or some acute respiratory infection requiring hospitalization with no other etiology fully explaining the clinical presentation, as per WHO guidelines.

A probable case has been defined as a suspected case in whom the laboratory testing for COVID-19 has turned out to be inconclusive. It has been advised to repeat the test 2 to 3 days later in such cases.

A confirmed case is a patient with laboratory confirmation of infection with COVID-19. This is irrespective of the patient's clinical signs and symptoms as per the WHO. These definitions are, however, dynamic, and therefore practitioners may follow updates closely.

published online
24 April 2020

DOI <https://doi.org/10.1055/s-0040-1710401>
ISSN 2457-0206.

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Pathophysiology

The primary pathophysiology is acute respiratory distress syndrome (ARDS). There may also be an associated exuberant cytokines storm reaction as well. Viral infection seems to move through two stages. First is the replicative stage, when viral replication occurs and innate immune responses of an individual fail to contain it. It is followed by the adaptive immunity stage, where adaptive immune responses result in falling titers of virus. This phase is associated with increased levels of inflammatory cytokines that may lead to tissue damage with clinical deterioration.⁴ There may be an associated hemophagocytic syndrome. Clinical markers such as C-reactive protein (CRP) or ferritin may be used to track disease and mortality.⁵

Screening

Potential patients of COVID-19 requiring critical care may present either to an emergency department or through an interfacility transfer. Routine careful questioning about the risk of COVID-19 exposure is a must to ensure that appropriate infection control precautions are taken by the attending staff. If in doubt, any patient with unexplained several respiratory illnesses should be treated with standard contact/droplet ± airborne precautions. All intensive care units (ICUs) should have a “ready bed” for airborne isolation capacity.³

Infection Control Precautions

The following practices have been broadly recommended:

- The patient should be isolated in a single room with negative pressure and frequent air exchanges.
- The second best option should be a single room with closed doors.
- Portable high-efficiency particulate air filters may be used.
- Cohort COVID-19 ICUs can be made.
- If possible, the entire ICU can be converted to a negative-pressure airflow ward rather than just an individual patient room.
- Recommended personal protective equipment (PPE) are fluid-resistant gown, eye protection, and full-face shield if possible. Three-layer surgical mask would do, but N95 respirator masks are recommended during aerosol-generating procedure.
- Shoes that are impermeable to fluids and can easily be decontaminated should be worn.
- Staff should wear surgical scrubs under the PPE.
- Some international societies have recommended the use of powered air-purifying respirators instead of N95 masks for aerosol-generating procedures.³

Clinical Presentation

Patients infected with COVID-19 present with constitutional, upper and lower respiratory tract, and gastrointestinal symptoms. The frequency of fever varies between 43 and 98%.

The absence of fever does not rule out COVID-19 though. Sore throat occurs in up to 14% of patients. Shortness of breath, cough, and sputum are seen in up to 80% of patients. Gastrointestinal symptoms such as diarrhea and nausea can occur in up to 10% of patients and may, in fact, be the presenting symptom that precedes the development of fever and dyspnea.⁶ Silent hypoxemia, that is, respiratory failure without dyspnea may also be a presenting feature in some patients, especially in the elderly age group.⁷

Physical findings are usually nonspecific. The most associated comorbidities with ICU admission have been found to be diabetes and hypertension. The China CDC report⁸ has divided clinical manifestation severity-wise as follows:

- Mild disease: mild or no pneumonia occurring in 81% of cases.
- Severe disease: this includes respiratory rate of more than 30 per minute, oxygen saturation (SpO₂) of less than 93%, PaO₂/FiO₂ ratio of less than 300 mm Hg, and lung infiltrates of more than 50% within 24 to 48 hours, occurring in up to 14% of cases.
- Critical disease: this includes respiratory failure, septic shock, acute kidney injury, and multiorgan failure, occurring in up to 5% of cases.

The WHO has divided clinical syndromes associated with COVID-19 into mild illness, pneumonia, severe pneumonia, ARDS, sepsis, and septic shock.

Risk factors for severe COVID-19 disease are divided into three categories. Epidemiological risk factors are age more than 55 years, preexisting pulmonary disease, chronic kidney disease, diabetes mellitus with HbA1C more than 7.6%, hypertension, coronary artery disease, immunosuppressed state due to HIV (regardless of CD4 count), posttransplant or history of immunosuppressive therapy, and severe obesity (body mass index > 40).

Clinical risk factors identified are respiratory rate of more than 24 per minute, heart rate of more than 125 per minute, and oxygen saturation of less than 90% on room air. Laboratory risk factors are D-dimer more than 1,000 ng, creatine phosphokinase more than twice the upper limit of normal, CRP of more than 100 mg/L, lactate dehydrogenase (LDH) of more than 245 U/L, elevated troponins, admission absolute lymphocyte count less than point 0.8, and serum ferritin levels of >300 g/L.^{9,10}

Laboratory Work-Up

All routine investigations including D-dimer, CRP, procalcitonin, LDH, ferritin, and troponins should be performed. Routine blood and sputum cultures should be taken. Arterial blood gas analysis may show mild acidosis with normal lactate and high anion gap. White blood cell counts tend to be normal. Lymphopenia is observed in approximately 80% of patients. Mild thrombocytopenia is common, but platelet counts are rarely below 100 × 10⁹/L. Elevated D-dimer is seen with normal coagulation profile initially, with the progression of disease, severe thrombocytopenia, and disseminated intravascular coagulation set in, indicating a poor prognosis.

Liver function tests are abnormal in approximately 30% of patients. Procalcitonin levels have been found to be less than 0.5 in 95% of patients in the largest series.^{6,10-12}

COVID-19 infection, however, results in an increase in CRP levels. This may be used to track the disease severity and prognosis. In a patient with severe respiratory failure and a normal CRP, non-COVID-19 etiologies such as heart failure may be considered.

Imaging Findings

Chest X-ray usually reveals bilateral diffuse infiltrates with gravitational distribution. Pleural effusion is uncommon. The typical finding of a computed tomography (CT) scan is patchy ground-glass opacities, mainly peripheral and basal. The crazy-paving pattern may also be seen. COVID-19 does not appear to cause cavitation on lymphadenopathy. Lung ultrasound usually shows diffuse B lines and can be used bedside to optimize ventilatory settings and follow the disease.

Chest CT is not indicated routinely due to a high risk of transport and spread of the contagion. It should be reserved for patients in whom an alternative diagnosis needs to be ruled out. An echocardiogram may show dyskinesia due to stress cardiomyopathy secondary to the virus. Elevated troponin should not give a false suspicion of acute coronary syndrome.¹³

Bronchoscopy

The utility of bronchoscopy in COVID-19 is quite dubious. It may be associated with an enormous risk of transmission and may result in clinical deterioration. It should be considered where it would otherwise normally be done like for fungal pneumonia. It should not be performed routinely in these patients.¹⁴

Evaluation and Diagnosis

The initial approach should be early suspicion, early recognition, immediate isolation, and institution of infection control precautions of COVID-19 patients.

Patients who meet the criteria should urgently undergo testing for SARS-CoV-2 in addition to testing for other respiratory pathogens such as influenza and respiratory syncytial virus. SARS-CoV-2 RNA is detected by reverse transcriptase polymerase chain reaction (RT-PCR). A positive test confirms the diagnosis of COVID-19. In case the initial test is negative but suspicion is high, resampling from multiple respiratory tract sites is recommended by the WHO. The CDC recommends that nasopharyngeal swab specimen should be collected to test for SARS-CoV-2. The WHO considers the collection of oropharyngeal swab also essential. If it is collected, then it should be placed in the same container as the nasopharyngeal specimen. Other preferred samples are bronchoalveolar lavage, tracheal aspirate, and sputum. In confirmed patients, blood, urine, and stool samples may also be tested. The sample should be tested within 3 days of symptom onset and no later than 7 days. Standard

Table 1 Differential diagnosis of COVID-19

Viral pneumonia such as adenovirus, influenza, human metapneumovirus, respiratory syncytial virus, and rhinovirus
Community-acquired pneumonia
Hospital-acquired pneumonia
Acute exacerbation of chronic obstructive pulmonary disease

Abbreviation: COVID-19, coronavirus 2019.

triple packing should be followed for the transport of the samples as per WHO.¹⁵

PCR seems to have a sensitivity of around 75%. For safety reasons, it is recommended that specimens from suspected or confirmed COVID-19 patients should not be submitted for viral cultures.

Differential diagnosis of COVID-19 is given in ► **Table 1**.

Management

Pharmacological Therapy

- No antiviral therapy has been proven to work against COVID-19 in humans. Several randomized control trials are ongoing.
- It is unknown whether a single antiviral agent is enough or a combination of multiple antiviral agents is required.
- Earlier treatment, that is, within 1 to 2 days of admission may be more effective than reserving it for a later date when organ failure has already set in.
- Maximum patients should do well without any therapy except for supportive care. Among hospitalized patients, 10 to 20% of patients need ICU admission, of which 3 to 10% require intubation. Such patients would likely benefit from early therapy.
- Predictors of poor outcome as previously discussed, if present, should be an indication to start early antiviral therapy.

There is currently scant evidence regarding appropriate antivirals to be used in COVID-19. Some of the therapies that are being used on a trial basis by practitioners world over are remdesivir, lopinavir/ritonavir with ribavirin, and chloroquine.

Lopinavir/ritonavir in combination with ribavirin is being used commonly in the doses of 400/100 mg twice daily plus a 2-g loading dose of ribavirin followed by 1 to 2 g thrice a day orally for 14 days or 1 mg per kg thrice a day intravenously for 14 days in moderate and severe cases. Remdesivir has been found to have a superior activity than lopinavir/ritonavir in in vitro and animal studies on MERS-CoV, but the availability of this drug is a big issue.

Some institutes are using the following investigational therapies, but as per the WHO, these can be used only in approved, randomized controlled trials:

- In mild illness, use of lopinavir/ritonavir plus hydroxychloroquine 400 mg (two tablets) 12 hourly for 1 day followed by 400 g (two tablets) orally daily for 9 to 14 days.
- In patients with COVID-19 with no symptoms, hydroxychloroquine alone is being used.

- In patients with severe COVID-19 infection requiring supplemental oxygen, lopinavir/ritonavir combination plus hydroxychloroquine plus favipiravir 1,600 mg (eight tablets) twice daily as a loading dose followed by 600 mg (three tablets) every 8 hours for 14 days is being used.
- In patients with COVID-19 ARDS, intravenous (IV) remdesivir 200 mg IV as a loading dose on day 1 followed by IV remdesivir 100 mg once daily for 9 days is being given as a part of clinical trials at various centers such as Cleveland Clinic, Abu Dhabi.

The Surviving Sepsis Campaign guidelines on COVID-19 recommend against the routine use of lopinavir/ritonavir or any other antiviral or chloroquine. There is insufficient evidence to issue a recommendation as per them. Similarly, in certain refractory or progressive patients, with infectious disease expert approval, interferon- β 1b and tocilizumab are being considered, although the Surviving Sepsis Campaign guidelines do not support their use.¹⁶⁻²¹ Oseltamivir and other neuraminidase inhibitors do not seem to be effective against COVID-19. Initial empiric therapy may include this till the time influenza infection is ruled out.

Antibiotic Therapy

There is no role of prophylactic antibiotics in COVID-19 infected patients, but they may be used empirically at the physician's discretion in the presence of atypical presentation. The Surviving Sepsis Campaign guidelines support the use of empirical antibiotics over no antibiotics in these patients. Antibiotics may, however, be required later as bacterial pneumonia can develop during the hospital course. In one series, 16% of patients developed secondary infection.²⁰

Steroids

The WHO and the CDC recommend not using glucocorticoids in patients with COVID-19 pneumonia unless there are indications such as acute exacerbation of chronic obstructive pulmonary disease. The Surviving Sepsis Campaign guidelines on COVID-19 recommend the use of steroids in low doses in septic shock and in mechanically ventilated adults with COVID-19 and ARDS. Steroids may cause a delay in viral clearance.^{19,20}

Ascorbic Acid

Although the CITRIS-ALI (Vitamin C Infusion for Treatment in Sepsis Induced Acute Lung Injury) trial did not show improved mortality with ascorbic acid, some studies still recommend the use of vitamin C in moderate doses (i.e., 1.5 g IV six hourly) along with 200 mg of IV thiamine twice daily in such patients. There is no high-quality evidence at present to support the use of ascorbic acid in viral pneumonia routinely.

Nonsteroidal Anti-Inflammatory Drugs

The use of acetaminophen or paracetamol over other antipyretics is recommended for temperature control in COVID-19 patients.^{19,20}

Hemodynamic Support

Patients with COVID-19 have rarely been found to have shock. The Surviving Sepsis Campaign guidelines and some institutional guidelines recommend using conservative fluid strategy over liberal fluid strategy for acute resuscitation of patients with COVID-19 infection. The cause of death from COVID-19 is almost always ARDS, and this may worsen by fluid administration. Dynamic parameters are preferred over static parameters for assessing fluid responsiveness. Resuscitation with balanced crystalloids is preferred. The use of hydroxyethyl starches and gelatin is contraindicated. Noradrenaline should be used as the first-line vasoactive agent in case of septic shock.^{19,20} Epinephrine/vasopressin may be added as required.

Oxygenation

Supplemental oxygen should preferably be provided through a mask than nasal prongs. Use of high-flow nasal cannula (HFNC) is preferred over noninvasive positive-pressure ventilation (NIPPV) for treating COVID-19-related acute respiratory failure. NIPPV can be provided through a mask, although there is a high risk of droplet production and transmission. Helmets have also been used for this purpose at some centers. All patients with acute respiratory failure should be closely monitored for worsening respiratory status, and early intubation in a controlled setting is recommended in such a situation.^{19,20} Bronchodilators, if required, should be administered through metered dose inhalers to decrease the risk of viral aerosolization.

Airway Management

The principles of airway management^{20,22} are given in ► **Table 2**.

Ventilation

Lung protective strategy, which is the standard recommendation for ARDS, should be used. Target a plateau pressure of less than 30 cm of H₂O. COVID-19 patients have been found to require high positive end-expiratory pressure (PEEP) and usually respond well to recruitment maneuvers. If recruitment maneuvers are used, the Surviving Sepsis Campaign guidelines recommend against the use of staircase or incremental PEEP recruitment maneuver. In case of a PaO₂/FiO₂ ratio of less than 150, early prone ventilation can be performed for a duration of at least 12 to 16 hours. Intermittent or continuous neuromuscular blocking agent may be used to facilitate lung-protective ventilation. Early airway pressure release ventilation could be useful in some patients.^{20,22}

Extracorporeal Membrane Oxygenation

Mechanically ventilated COVID-19 patients with refractory hypoxemia, despite the use of rescue therapies, can be put on VV or VA extracorporeal membrane oxygenation depending on hemodynamic stability.^{20,22}

Table 2 Airway management in COVID-19

Before the procedure
Minimize personnel during aerosol-generating procedures
Use airborne infection isolation room if available
Hand hygiene to be ensured
Full personal protective equipment should be used
Early preparation of drugs and equipment
Ensure meticulous airway assessment
Connect viral/bacterial filter to circuits and manual ventilation system
Use close suctioning system
Use video laryngoscopy
Avoid awake fiberoptic intubation
During the procedure
A thorough preoxygenation with 100% oxygen and rapid sequence intubation should be performed
Intubation by a health care worker most experienced with airway management
Lowest airflow to be used for oxygenation
Clear communication of airway plan to the entire team
Ensure paralysis to avoid coughing
Positive-pressure ventilation to be initiated only after the cuff is inflated
Tracheal intubation rather than the use of laryngeal masks is preferred
After the procedure
Avoiding unnecessary circuit disconnection
Full PPE to be used if any disconnection is needed
Adherence to proper degowning steps
Proper hand hygiene
Team debriefing

Abbreviation: PPE, personal protective equipment.

Protected Code Blue

This concept was created during the SARS outbreak. This highlighted procedures that required extra precautions due to the associated risk of viral transmission and aerosolization. These high-risk procedures were identified as HFNC, bag-mask ventilation, CPAP/BiPAP (continuous positive airway pressure/bilevel positive airway pressure) use, endotracheal tube insertion, bronchoscopy, gastrointestinal endoscopy, and cardiopulmonary resuscitation (CPR). The primary care provider team enters the room with full PPE with minimal team size to avoid viral exposure during resuscitation.^{3,22}

Complications of Coronavirus 19

Anticipated complications in COVID-19 patients are ARDS, acute liver injury, acute cardiac injury, acute kidney injury, septic shock, and disseminated intravascular coagulation. Acute liver injury is the second most commonly reported

complication as per the recent case reports. Around 70% of patients have been found to die due to fulminant myocarditis. Heart failure and arrhythmia have been found to occur even when respiratory illness is recovering. Troponin elevation seems to strongly predict mortality in these patients. Renal failure occurs in less than 10% of COVID-19 patients.^{2,22}

Discharge Criteria

The patient can be shifted to a ward if his/her physiological condition has stabilized and there is no need for intensive monitoring. Since the virus scan persists for 7 to 12 days in moderate cases and up to 2 weeks in severe cases, the patient should be shifted to a single room with a closed door or to a cohort ward/area. However, it is important that the patient is noninfectious at the time of discharge from the hospital. The following criteria have been recommended as per the latest guidelines:

- *For symptomatic patients:* patient should be afebrile for 3 days with improvement in respiratory symptoms, lung imaging must show resolution of infiltrates, and the nucleic acid test should be negative for SARS-CoV-2 from two consecutive samples of nasopharyngeal swabs taken at least 24 hours apart.
- *For asymptomatic patients who are quarantined:* patients must be SARS-CoV-2 negative 14 days after the first test, that is, at the time of quarantine.^{19,22}

Additional Considerations

Pregnancy

- Minimal information regarding COVID-19 in pregnant patients is known at present. Considering the possibility of asymptomatic transmission, they should be closely followed if there is epidemiological history. Their testing for COVID-19 should also be prioritized.
- No vertical transmission to fetus has been documented so far.
- Infants born to suspected or confirmed COVID-19 mothers should receive breast milk as per standard feeding guidelines but of course with appropriate infection prevention and control measures.
- As per the American College of Obstetricians and Gynecologists, infants born to COVID-19 afflicted mothers should be treated as patients under consideration and therefore should be appropriately isolated and evaluated.^{2,19}

Angiotensin-Converting Enzyme Inhibitors/Angiotensin Receptor Blockers

There is currently no evidence to suggest that angiotensin-converting enzyme (ACE) inhibitors/angiotensin receptor blockers (ARBs) should be discontinued in a patient with COVID-19 due to a risk of adverse events.^{2,19} In fact, COVID-19 virus enters the cells through ACEII receptors, and patients on ACEI or ARB may theoretically have some protective effects.

Immunosuppressed Patients

- In immunocompromised patients with COVID-19 infection, decision to discontinue any of the immunosuppressive agents or biologics should be undertaken on a case-to-case basis.
- Currently, there is a scarcity of data on transplant patients with COVID-19 infection. It is presumed that transplant patients would likely have greater infectivity and more potential to spread the disease due to high viral load.^{2,23}

Adjunctive Therapies

Theoretically, there may be a role of extracorporeal therapies such as CytoSorb filter (CytoSorbents Europe GmbH, Berlin, Germany) in patients with COVID-19 sepsis and septic shock. Clinicians have used the same in some cases. It has been mainly used in Wuhan, China, and Germany.²⁴ Ulinastatin is a protease inhibitor, which has been tried in some patients. An expert consensus statement on COVID-19 from Shanghai recommends the use of ulinastatin in large doses to reduce pulmonary interstitial inflammation.²⁵

Medanta Experience

Seventeen patients have been admitted to our facility with COVID-19 patients to date. Out of these, 11 patients have successfully recovered and discharged home. Three patients were put on a combination of lopinavir and ritonavir for high CRP levels (cutoff being taken as twice the normal value). The maximum CRP level observed was 365 mg/L. All patients received ascorbic acid in 1.5-g six hourly IV dosages. Out of these three patients, one patient was given interleukin-6 (IL-6) inhibitor in lieu of hypotension and ARDS. This patient also received steroids in septic doses. After IL-6 inhibitor therapy, a significant fall in CRP levels was observed, which persisted for the next 5 days. Out of these three patients, one has been discharged, and the other two have stabilized as of now. Other four patients received a combination of hydroxychloroquine and azithromycin due to worsening respiratory symptoms. This was following the recent French study published that showed a decrease in viral load with hydroxychloroquine, which got further strengthened with additional azithromycin.²⁶ These patients are being closely monitored.

Conclusions

The COVID-19 outbreak story is still evolving at present and needs to be closely followed for further developments. There has currently been no breakthrough as far as any therapeutic or preventive therapy is concerned. It is highly contagious, and the most risky ones are the asymptomatic carriers. The only preventive measure is isolation and infection control precautions. Supportive therapy remains the mainstay. The psychological impact of perceived risk on the attending hospital staff cannot be undermined. Each institute should have protocols ready to take care of COVID-19 patients and their health care workers.

Conflict of Interest

None.

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