Dartmouth Center for Global

COVID-19 Treatment in LMIC Settings

20 May 2020

This document summarizes existing technical guidance and lessons from other settings responding to the COVID-19 pandemic on COVID-19 treatment. It is designed to help inform high-level planning and is not intended as a comprehensive national planning document or to substitute for professional medical advice, or expert clinical or epidemiological guidance. This document is not intended to recommend or endorse any specific tests, procedures, opinions, or other information that may be referenced.

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Overview

Approximately 20% of COVID-19 positive patients may require hospital care.[1] This document outlines current evidence behind COVID-19 symptoms and treatment for patients with severe or critical COVID-19 in resource-limited settings.

Section 1. Presenting Signs and Symptoms of COVID-19

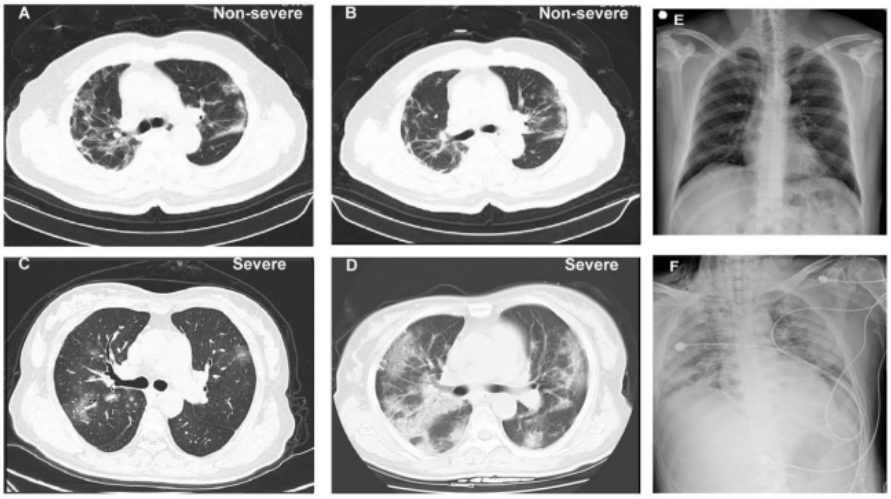
Common symptoms of COVID-19 include:[2,3]

- Cough
- Shortness of breath or difficulty breathing
- Fever
- Chills
- Muscle pain
- Sore throat
- Sputum production
- New loss of taste or smell
- Gastrointestinal distress

Growing anecdotal accounts indicate that some patients may also have a rash, most frequently pink or purple with papules and often involving the tips of the toes.[4] These symptoms are most common in pediatric patients.

Radiological Presentation

Figure S1. Representative chest radiographic manifestations in a non-severe and a severe case with COVID-19



From Guan et al. 2020[5]

COVID-19 respiratory illness primarily looks like atypical or organizing pneumonia in radiological images. Bilateral or multibar involvement is common, often with a lower zone distribution. However, up to 18% of cases demonstrate normal chest x-rays or CTs early in the disease course.[6]

In a chest x-ray there are typically patchy or diffuse airspace opacities, whether consolidation or ground-glass opacity (GGO).[7] Pleural effusion is rare.

CT can be a useful diagnostic tool but will not be available in many settings. In a CT, primary findings are ground-glass opacities, crazy paving appearance, air space consolidation, bronchovascular thickening in the legion, traction bronchiectasis.[8,9]

Parenchymal image findings are variable and depend on time course. Late findings may include fibrotic changes[10]

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Laboratory Findings

Laboratory findings in hospitalized COVID-19 patients may include:[11]

- Lymphopenia
- Elevated levels of:
    - D-dimer
    - Lactate dehydrogenase
    - C-reactive protein
    - Ferritin

Findings that have been associated with poorer outcomes in some series include:[12,13]

- Increasing white cell count with lymphopenia
- Prolonged prothrombin time
- Elevated levels of:
    - Liver enzymes
    - D-dimer (> 1 ug/ mL on admission)
    - Lactate dehydrogenase
    - C-reactive protein
    - Ferritin
    - IL-6
    - Procalcitonin

Section 2. Criteria for Hospitalization

Currently, inpatient care is recommended for people with an oxygen saturation ~ < 94 or 92 (though this may vary with altitude), or those with any other symptoms for which they would normally be admitted to the hospital.[14] Emerging evidence and accounts suggest that patients with COVID-19 may experience hypoxia that is more severe than their symptoms. These patients may have low oxygen saturation levels without experiencing respiratory distress. Limited evidence suggests that early detection and intervention of these patients may limit the need for more intensive treatment (such as ventilation and dialysis) and lead to higher survival rates.[15]

Patients with the following should be considered for treatment in the ICU, if available:[16]

- Respiratory distress
    - Need O2 > 6 LPM to maintain SPO2 > 92%
    - Rapid escalation of O2 requirement
    - Significant work of breathing
- Hemodynamic instability after initial conservative fluid resuscitation
    - SBP< 90, mean arterial pressure < 65, or heart rate > 120
- Severe comorbid illness or high risk for deterioration

- High risks groups with increased risk of severe cases and mortality include older people (65+)[17], hypertension[18], diabetes[19], cardiovascular disease[20], cancer[21], chronic respiratory disease[22], current smoker[23], severe obesity[24], liver disease[25], asthma.[26]

Section 3. Treatment of Hypoxia

Hypoxemia, or SpO2 of < 90% despite oxygen supplementation, is associated with higher mortality rates. In one study that examined symptoms, laboratory findings, and demographic variables, hypoxemia was the most robust risk factor for fatal outcomes.[27]

Graded Oxygen Administration:[28]

Give supplemental O2 to patients with O2 saturation < 90% and mild to moderate work of breathing. Ideally, the goal is to maintain O2 sat between 92-96% and a respiratory rate < 24.

O2 administration options:

1. Humidified Nasal Cannula (NC) from 1-6 liters per minute (LPM)
2. If goals of therapy are not met, advance to either:
    a. Oxymizer mustache (if available)
        i. Initiate at 6 LPM, titrate to 12 LPM maximum
    b. Venturi mask
        i. Initiate at FiO2 40%, titrate to maximum FiO2 60%
3. If O2 saturation, respiratory rate, and work of breathing are not improved, consider intubation if ventilation is available.

Note: **High flow nasal cannula (HFNC) and non-invasive positive pressure ventilation (NIPPV) should be avoided for COVID-19 patients or PUI due to risk of aerosolization**. It is unclear whether or not HFNC or NIPPV reduces the eventual need for intubation, but it may be used if there are no alternatives. If HFNC must be used, patients should wear surgical masks (if available) and flow rate should be < 30 L/min. If NIPPV must be used, ensure devices fit well and there is minimal air leak. Airborne precautions (including an N95 mask for providers) should be used. These therapies should be given in a negative pressure room if available.

Ventilator Use:

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Some COVID-19 patients may require mechanical ventilation. However, survival rates for patients who require intubation are relatively low. A recent ICNARC report (n = 4855) found that 56.8% of patients receiving advanced respiratory support died in critical care.[29]

If mechanical ventilation is available, **airborne precautions are required for providers** (including N95 mask, face shield, gloves, gown).

Initial Ventilator Settings:[30]

- Initial tidal volume (Vt) = 6mL/kg
- Initial respiratory rate: 16-24 titrated to goal minute ventilation of 5-8 L/min or 24-28 titrated to goal minute ventilation of 8-12 L/min in setting of acidosis (pH < 7.25) pre-intubation
- Initial PEEP based on BMI: PEEP 5 (BMI < 35), PEEP 10 (BMI > 35)
- Initial FiO2: 100% on intubation and then rapidly wean to SpO2 92-96%

Target oxygenation is SpO2 92-96%. Brigham and Women's Hospital has guidelines for determining PEEP and mechanics and for daily ventilator management, located here: https://covidprotocols.org/protocols/respiratory/#initial-mechanical-ventilation).

If ventilators are not available, anesthesia machines may be used for prolonged ICU ventilation. See guidelines here: https://www.asahq.org/in-the-spotlight/coronavirus-covid-19-information/purposing-anesthesia-machines-for-ventilators. Alternatively, continue to administer high flow oxygen using airborne precautions (the risk of aerosolization is higher with higher flows of O2).

It is not currently recommended to put multiple patients on the same ventilator.[31]

Proning

Proning is recommended for both ventilated and non-ventilated patients.[32]

Growing evidence supports the use of proning for both ventilated and non-ventilated patients with COVID-19.[33,34] Proning is thought to provide physiologic benefits for COVID-19 patients by improving recruitment of alveoli in dependent areas of the lungs. Additionally, it may improve perfusion to ventilated areas which improves V/Q mismatching.[35] Proning can reduce mortality, particularly when patients are ventilated with a low tidal volume, proning starts within 48 hours of disease evolution, and when patients have severe hypoxemia.[36]

Self-proning for non-ventilated patients

Self-proning can be used on stable patients (on room air or on supplemental oxygen) and as a "rescue" for those who have escalating supplemental O2 requirements.[37]

Patients who self-pronate must be able to move on their own so they can supinate themselves if they become uncomfortable.[38]

Patients with the following should not self-pronate:[39]

- Inability to independently supinate or pronate safely
- Imminent risk of intubation
- Spinal instability
- Facial or pelvic fractures
- Open chest or unstable chest wall
- Open abdomen

Self-proning Protocol[40]

If possible, tilt the bed so that the patient's head is 10 degrees above their feet. Arrange tubing so that it travels towards the top of the bed, and not across the patient to minimize the risk of dislodging.

The Brigham Hospital recommends that a nurse document prone/supine at every vitals check, and document just before proning, 1 hour after proning begins, and when proning ends in order to identify how patients respond to the treatment. Continuous O2 monitoring is required during self-proning.[41]

Patients who are awake can self-prone every 4 hours for as long as they can tolerate the position.[42] Ideally, patients will prone for 16 of every 24 hours, but it is unlikely that they will be able to tolerate it for that amount of time.[43]

Proning may be stopped by the patient at any time. Consider ending proning if the patient has an escalating oxygen requirement that may require intubation.

Prone Position

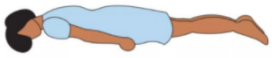
The patient should lie on their abdomen with their arms at their sides or in "swimmer" position. If they cannot tolerate that position, they may be partially propped to one side (can use pillows to help stabilize if necessary).

Elmhurst Hospital in New York recommends the following proning schedule:[44]

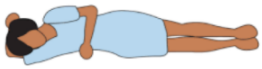
PHOTOS BELOW TO DEMONSTRATE THIS:

LAS FOTOS DEBAJO DEMUESTRAN ESTO:

1. 30 minutes – 2 hours: laying on your belly
1. 30 minutos – 2 horas: acostado sobre su estómago (boca abajo)

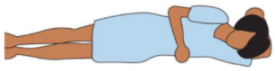


2. 30 minutes – 2 hours: laying on your right side
2. 30 minutos – 2 horas: acostado sobre su lado derecho

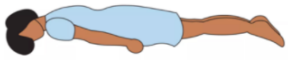


3. 30 minutes – 2 hours: sitting up
3. 30 minutos – 2 horas: sentado

4. 30 minutes – 2 hours: lying on your left side
4. 30 minutes – 2 horas: acostado sobre su lado izquierdo



Then back to Position 1. Lying on your belly!
Luego, vuelva a la posición 1. ¡Acostado sobre su estómago (boca abajo)!



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Proning for Ventilated Patients

Proning can be used as an adjuvant therapy for improving ventilation in patients with ARDS.[45] Proning should be applied for at least 12 hours per day.[46]

Section 4. Therapeutic Interventions

Therapeutics Overview

Currently, there are no proven therapeutics for COVID-19. Treatment is primarily by supportive care. Some drugs have been proven effective in vitro but have not been effective in vivo. Several drugs are currently undergoing trials. The table below lists possible therapeutic drugs being considered for COVID-19, outlines why they are used, and details current evidence behind them. The table is in order based on likelihood of availability in low-resource settings rather than on current evidence of efficacy.

Drug	Use	Evidence
Hydroxychloriquine	Thought to act by inhibiting cytokine storm.[47] Thought to shorten disease course of pneumonia Some medical experts are advocating for caution because the drug has potential for cardiac implications.[48]	**Use of hydroxychloroquine is not yet routinely recommended.** Initial anecdotal evidence supporting the use of hydroxychloroquine has led to disagreement as to its use, with little scientific evidence to support its efficacy. Positive Evidence: One study found that hydroxychloroquine significantly reduced treatment time to clinical recovery and improved pneumonia symptoms.[49] Neutral Evidence: A few small studies have shown that hydroxychloriquine makes no significant difference in alleviating symptoms or improving outcomes.[50,51,52] Negative Evidence: One study from the US found that hydroxychloroquine increased mortality for patients hospitalized with COVID-19.[53]One study found drug-related Qtc prolongation, leading to early study termination.[54]
Hydroxychloriquine + Azithromycin	May decrease viral loads in patients, leading to reduced need for ventilation and decreased mortality.	**Evidence is conflicting and widely disputed. Further evidence is needed to evaluate the safety and efficacy of the combination.** One small study (n=22) in France found that the combination significantly decreased viral loads in COVID-19 patients.[55] However, this study has

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		been widely criticized.[56] A study from the US (n = 368) found that the risk of ventilation and COVID-19 mortality was similar between the treatment and control groups.[57]
Lopinavir-Ritonavir	Tested because of evidence that it improves outcomes for patients with ARDS and SARS and because there is evidence that is has activity against MERS-CoV.[58]	**Evidence does not support the use of Lopinavir-Ritonavir** Two studies failed to show that Lopinavir-Ritonavir was an improvement over standard care.[59,60]
Remdesivir	Remdesivir inhibits SARS-CoV-2 replication in human nasal and bronchial airway epithelial cells.[61]	**Remdesivir represents a promising treatment but is currently not available in most settings.** Emerging evidence suggests remdesivir may decrease time to recovery and mortality. Evidence from an NIH RCT showed a median time to recovery of 11 days for patients with remdesivir vs. 15 days for patients given placebo.[62] The NIH study demonstrated positive results but has not been peer-reviewed. A smaller study did not find statistically significant benefits, but also found that remdesivir may decrease treatment time.[63]
Favipiravir	An antiviral drug used to treat influenza.[64]	**Limited evidence supports the use of Favipiravir, though further research is required.** One study found that favipiravir led to shorter latencies for both pyrexia and cough, as compared to another influenza drug, arbidol.[65]
Tocilizumab (IL-6 inhibitor)	For hospitalized patients with severe or critical COVID-19. Thought to act by addressing cytokine storm, a hyper-immune response induced by viral pneumonia.[66]	**Preliminary studies are promising, clinical trials are underway.** One small study in China found that tocilizumab significantly improved the condition of COVID-19 patients in a few days (temperature returned to normal day 1, reduced oxygen therapy intake and increased percentage of lymphocytes in peripheral blood by day 5).[67] Another (unpublished) study in France found that the drug significantly reduced mortality and need for life support as compared to standard care.[68]
Convalescent plasma	Convalescent plasma, using	**Limited early evidence indicates that**

	antibodies from people who have recovered from the virus, has been successful in the 1918 pandemic flu, MERS-CoV, and SARS.[69]	**convalescent plasma can improve clinical status for severe COVID-19 cases.**[70,71] Emerging evidence suggests that treatment is most effective when given earlier in the disease course (before day 14).[72] RCTs are currently being conducted to verify the results of these small studies.[73]
Antibiotics	Some are using antibiotics because of bacterial superinfection in influenza associated with pneumonia[74] However, it is unclear how many patients have pneumonia with bacterial superinfection. Secondary worsening is common in days 7-9 and is often attributable to the hyperinflammatory phase rather than a bacterial superinfection.[75]	**There is little research regarding antibiotic use for COVID-19, and recommendations vary by country**.[76] Physicians are calling on responsible antibiotic use, recommending that it be used sparingly for the most severe cases to avoid antimicrobial resistance.[77]

Section 5: Prothrombotic Complications of COVID-19

Growing evidence suggests that thrombotic processes may play a role in mortality and significant morbidity in COVID-19 patients.[78] It is unclear whether COVID-19 causes thrombotic complications or if these complications are a result of local or systemic complications.[79] COVID-19 may predispose venous and arterial thromboembolism due to excessive inflammation, hypoxia, immobilization, and intravascular coagulation. One study in the Netherlands (n = 184) found a 31% incidence of thrombotic complications in ICU patients with COVID-19[80]

Commented [5]: maybe it should be respiratory failure instead of mortality: Recent observations suggest that respiratory failure in COVID-19 is not driven by the development of the acute respiratory distress syndrome (ARDS) alone (10), but that (microvascular) thrombotic processes may play a role as well. (Oudkerk, et al)

In ICU patients, cumulative incidences range from 11% to 70% in patients on varying levels of prophylactic anticoagulation.[81,82,83,84]At the Brigham and Women's Hospital (BWH), physicians found that 10 out of 104 (9.6%, cumulative incidence ~14%) COVID-19 patients "developed venous thromboembolic events (VTE, largely DVTs), and 5 individuals were empirically anticoagulated for other thromboembolic indications, despite 100% compliance with VTE ppx (i.e., enoxaparin 40mg qday for standard patients). Historic BWH ICU VTE rates for patients on prophylactic anticoagulation are approximately 7%, indicating that there may be a 1.5-2-fold increase in VTE in COVID patients specifically. However, only 1% of SPU (Covid-19

floor) patients developed VTE."[85] One case series indicates that COVID-19 may be associated with large vessel stroke in younger patients (under age 50).[86]

Higher D-dimer and FDP levels are associated with multi-organ dysfunction syndrome and poorer prognosis.[87]

Treatment recommendations for COVID-19 patients

Some recommend applying pharmacological thrombosis prophylaxis in all COVID-19 patients in the ICU.[88] Researchers from the Netherlands found that prophylactic doses of heparins in COVID-19 patients "might be associated with improved survival (20%) in patients with evidence of sepsis induced coagulopathy."[89] Others recommend that physicians remain vigilant for signs of thrombotic complications and order necessary diagnostic tests at a low threshold.[90]

Physicians in the Netherlands recommend the following course of action in relation to D-dimer values:[91]

Action	D-dimer at admission <1,000 mg/L	D-dimer at admission 1,000-2,000 mg/L	D-dimer at admission >2,000 mg/L
Close monitoring of D-dimer	+	++	++
Imaging for pulmonary embolism or DVT	Based on clinical signs/symptoms Lower threshold for imaging if D-dimer levels increase progressively (e.g. >2,000-4,000 mg/L)	Based on clinical signs/symptoms Lower threshold for imaging if D-dimer levels increase progressively (>2,000-4,000 mg/L)	Based on clinical signs/symptoms Low threshold for imaging
Anticoagulation	Routine thrombosis prophylaxis	Routine thrombosis prophylaxis If imaging is not feasible and D-dimer levels increase progressively (>2,000-4,000 mg/L), therapeutic anticoagulation can be considered	Routine thrombosis prophylaxis If imaging is not feasible and D-dimer levels increase progressively, therapeutic anticoagulation should be considered

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