COVID-19 Pharmacotherapy Treatment Guidance

September 22, 2020
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OVERVIEW

There are many ongoing clinical trials and data is emerging frequently. Use of investigational anti-COVID-19 therapeutics should be done under approved, randomized, controlled trials whenever feasible.

THERAPEUTICS

- This information is provided to share information to help guide treatment conversations. State mandates, medication availability/shortages, and access to Infectious Disease resources may impact some of these recommendations at given sites. As additional information becomes available, this information will be updated accordingly.
- Prophylaxis
  - Evidence does not support use of Hydroxychloroquine, or any other agent, for prophylaxis against COVID-19
- Treatment
  - Given the scarcity of data, the IDSA panel expressed the overarching goal that patients be recruited into ongoing trials whenever possible to provide much needed evidence on the efficacy and safety of various therapies for COVID-19 (IDSA COVID-19 Guidelines).
  - Assessment of Evidence for COVID-19-Related Treatments, updated regularly, is available in the NIH COVID Treatment Guidelines and within the ASHP COVID resource center: ASHP COVID Evidence Assessment

### NON-SEVERE DISEASE

_Hospitalized with confirmed or suspected COVID-19 without any severe disease criteria_

<table>
<thead>
<tr>
<th>Therapeutics</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical observation &amp; supportive care</td>
<td>• Remdesivir is recommended for hospitalized patients not requiring supplemental oxygen with clinical symptoms of COVID-19 and a positive molecular (PCR) test</td>
</tr>
<tr>
<td>&lt; AND &gt; Remdesivir (see comments section)</td>
<td>• See full Remdesivir section below for the FDA emergency approval for use, dose, contraindications, adverse effects, monitoring and drug interactions.</td>
</tr>
</tbody>
</table>

**Remdesivir Comments**
- See Remdesivir comments listed under non-severe disease above
- Duration of 10 days or until hospital discharge.

**Hydroxychloroquine Comments**
- Hydroxychloroquine for treatment of COVID-19 is not recommended

### SEVERE DISEASE

_Confirmed or suspected COVID plus any of the following:

a. Oxygen saturation (SpO2) ≤ 94% on room air
b. Requiring supplemental oxygen
c. Requiring mechanical ventilation
d. Requiring extracorporeal membrane oxygenation (ECMO)

<table>
<thead>
<tr>
<th>Therapeutics</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Supportive Care</td>
<td>• Treatment with convalescent plasma should be approved by Infectious Diseases and/or a Critical Care Provider at sites with these services prior to dispensing</td>
</tr>
<tr>
<td>&lt; AND &gt; Remdesivir (see comments section)</td>
<td>• Scarce supply (remdesivir or convalescent plasma)</td>
</tr>
<tr>
<td>&lt; AND &gt; Convalescent Plasma, if available</td>
<td>• In the setting of limited supplies of or convalescent plasma, consult local Chief Medical Officer after collaboration with an Infectious Disease or Critical Care specialist</td>
</tr>
<tr>
<td>&lt; AND &gt; For patients requiring supplemental oxygen or mechanical ventilation: Dexamethasone 6 mg PO/IV Daily X 10 days*</td>
<td>Remdesivir Comments</td>
</tr>
<tr>
<td>&lt; OR &gt; Methylprednisolone 16 mg PO/IV BID X 10 days*</td>
<td>• See Remdesivir comments listed under non-severe disease above</td>
</tr>
</tbody>
</table>

**Corticosteroid Comments**
- Duration of 10 days or until hospital discharge.

**Hydroxychloroquine Comments**
- Hydroxychloroquine for treatment of COVID-19 is not recommended.
REMDESIVIR PATIENT SELECTION, DOSING, AND MONITORING

- The U.S. Food and Drug Administration (FDA) has issued an Emergency Use Authorization (EUA) to permit the emergency use of the unapproved product remdesivir for treatment of adults and children hospitalized with of suspected or laboratory confirmed coronavirus disease 2019 (COVID-19) EMERGENCY USE AUTHORIZATION (EUA) OF REMDESIVIR
- Remdesivir can be used for the treatment of COVID-19 in patients requiring hospitalization. Based on available clinical data, benefit with remdesivir treatment has been primarily demonstrated for patients in the hospital requiring supplemental oxygen. Treatment with remdesivir earlier in the course of disease has been associated with better outcomes compared to initiation after mechanical ventilation.
- If remdesivir is initiated in a PUI who subsequently tests negative by molecular pcr testing, discontinue remdesivir; consider consultation with Infectious Diseases if COVID-19 still clinically likely
- Prior to treatment the parent/caregiver should be provided information consistent with the "Fact Sheet for Patients And Parent/Caregivers. Emergency Use Authorization (EUA) Of Remdesivir For Coronavirus Disease 2019 (COVID-19)"
  - The following information must be documented in the patient’s medical record: The patient/caregiver was given the Fact Sheet, informed of alternatives to receiving remdesivir, and informed that remdesivir is an unapproved drug that is authorized for use under EUA.

REMDESIVIR CONTRAINDICATIONS AND PRECAUTIONS:

- Remdesivir should not be initiated in patients with ALT ≥ 5 times the upper limit of normal at baseline
- Accumulation of the IV vehicle sulfobutyl-ether beta-cyclodextrin sodium (SBECD) occurs in patients with renal impairment. Use with caution in adults and pediatric patients with eGFR less than 30 mL per minute or in full-term neonates (≥7 days and ≤28 days old) with serum creatinine clearance ≥ 1 mg/dL.

Considerations in pregnancy
- No adverse embryo-fetal events seen in animal models, however there is insufficient data in humans
- Remdesivir should be used only benefit exceeds the potential risk to the mother and fetus.
- Pregnant patients with significant clinical manifestations may qualify for the emergency use program - please see the Remdesivir Availability document on the Trinity Health COVID site

REMDESIVIR DOSING TABLE

<table>
<thead>
<tr>
<th>Adult Dosing</th>
<th>Treatment of hospitalized COVID-19 patients (EUA, Healthcare Provider Factsheet)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• Initial: 200 mg IV (over 30-120 minutes) as a single dose on Day 1</td>
</tr>
<tr>
<td></td>
<td>• Maintenance: 100 mg IV (over 30-120 minutes) once daily for a total duration of 5 days</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Pediatric Dosing</th>
<th>Treatment of hospitalized COVID-19 patients (EUA, Healthcare Provider Factsheet)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• Patients weighing 3.5 to less than 40 kg</td>
</tr>
<tr>
<td></td>
<td>- Initial: 5 mg/kg IV (over 30-120 minutes) as a single dose on Day 1</td>
</tr>
<tr>
<td></td>
<td>- Maintenance: 2.5 mg/kg IV (over 30-120 minutes) once daily for a total duration of 5 days</td>
</tr>
<tr>
<td></td>
<td>• Patients weighing ≥40 kg: See adult dosing</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Duration</th>
<th>Based on current available data, Trinity recommends a 5-day course for all patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• If patient is deemed clinical stable for discharge prior to completion of 5 days course, discontinue remdesivir and discharge to next level of care (per NIH guidelines)</td>
</tr>
<tr>
<td></td>
<td>• The optimal duration of Remdesivir treatment for COVID-19 is unknown</td>
</tr>
</tbody>
</table>

| Dose Adjustments | Renal: No pharmacokinetic data for mild or moderate renal impairment. Hepatic: No pharmacokinetic data for mild or moderate hepatic impairment. Do not use in patients with AST/ALT elevations >5x the upper limit of normal. |

REMDESIVIR MONITORING

- Hepatic laboratory testing should be performed in all patients prior to starting remdesivir and daily while receiving (should discontinue therapy for ALT ≥5x ULN and may be restarted when levels decrease <5x ULN)
- All patients should have eGFR determined before dosing. Remdesivir is not recommended in adults and pediatric patients with eGFR less than 30 mL per minute unless the potential benefit outweighs the potential risk.
- The following laboratory tests should be performed daily while receiving remdesivir: serum chemistries, hematology, ALT, AST, bilirubin, and alkaline phosphatase; renal function tests (creatinine and creatinine clearance).
- If a serious and unexpected adverse event occurs and appears to be associated with the use of remdesivir, the prescribing health care provider and/or the provider’s designee should complete and submit a MedWatch form to FDA as instructed in the Health Care Provider factsheet

**Remdesivir Nursing Considerations**
- Hypersensitivity Including Infusion-Related and Anaphylactic Reactions: Hypersensitivity reactions including infusion-related and anaphylactic reactions have been observed during and following administration of remdesivir. Signs and symptoms may include hypotension, tachycardia, bradycardia, dyspnea, wheezing, angioedema, rash, nausea, vomiting, diaphoresis, and shivering. Slower infusion rates, with a maximum infusion time of up to 120 minutes, can be considered to potentially prevent these signs and symptoms. If signs and symptoms of a clinically significant hypersensitivity reaction occur, immediately discontinue administration of remdesivir and initiate appropriate treatment.

**Remdesivir Adverse Reactions**
- An adverse reaction associated with remdesivir in clinical trials in healthy adult subjects was increased liver transaminases. Additional adverse reactions associated with the drug, some of which may be serious, may become apparent with more widespread use.
- Other adverse effects with incidence ≥10%
  - Constipation (14%) [15% in placebo group]; Hypoalbuminemia (13%) [15% in placebo group]; Hypokalemia (12%) [14% in placebo group]; Anemia (12%) [15% in placebo group]; Thrombocytopenia (10%); Increased bilirubin (10%)

**Remdesivir Drug Interactions**
- Risk of Reduced Antiviral Activity When co-administered with Chloroquine or Hydroxychloroquine: coadministration of remdesivir and chloroquine phosphate or hydroxychloroquine sulfate is not recommended based on in vitro data demonstrating an antagonistic effect of chloroquine on the intracellular metabolic activation and antiviral activity of Remdesivir
- In vitro, remdesivir is a substrate for drug metabolizing enzymes CYP2C8, CYP2D6, and CYP3A4, and is a substrate for Organic Anion Transporting Polypeptides 1B1 (OATP1B1) and P-glycoprotein (P-gp) transporters. In vitro, remdesivir is an inhibitor of CYP3A4, OATP1B1, OATP1B3, BSEP, MRP4, and NTCP. The clinical relevance of these in vitro assessments has not been established. Please refer to [http://www.covid19-druginteractions.org/](http://www.covid19-druginteractions.org/)

**Convalescent Plasma**
The FDA has authorized an Emergency Use Authorization (EUA) for emergency use of COVID-19 convalescent plasma (CP) for the treatment of hospitalized patients with COVID-19. The following information highlights the EUA provider information, please see the full EUA document for complete details. Full details on the collection, testing, labeling, and recordkeeping accompanying the use of CP is available here: [Investigational COVID-19 Convalescent Plasma Guidance for Industry](https://www.fda.gov/emergency-preparedness-response-epore gdyż/warnings-notices/authorization-emergency-use-authorization-convalescent-plasma-covid-19).

In an unpublished, 35,322 patient, open-label trial, the seven-day mortality was 8.7% in patients treated with convalescent plasma within 3 days of diagnosis, and 11.9% if transfused four or more days later in patients hospitalized with COVID-19. Lower mortality was also seen with convalescent plasma that had higher antibody levels. Data from the trial was collected from patients treated through a convalescent plasma expanded access program for COVID-19.

Fact sheets for Convalescent Plasma EUA have been created for both health care providers and patients.

**Convalescent Plasma: Patient Selection**
- The EUA is based on a review of historical evidence using convalescent plasma in prior outbreaks of respiratory viruses, certain preclinical evidence, results from small clinical trials of convalescent plasma conducted during the current...
outbreak, and data obtained from the ongoing expanded access program indicating that it is reasonable to believe that the known and potential benefits of COVID-19 convalescent plasma outweigh the known and potential risks.

- Given that the clinical evidence supporting this EUA was not obtained from prospective, well-controlled randomized clinical trials (RCTs), additional data is needed thus providers are encouraged to continue to enrolling patients in those RCTs.
- COVID-19 convalescent plasma should not be considered a new standard of care for the treatment of patients with COVID-19.

- **Use in specific patient populations:**
  - Safety and effectiveness of COVID-19 convalescent plasma in the pediatric population (< 18 years old), pregnant and nursing women has not been evaluated. Convalescent plasma should be used in these patient populations only if the potential benefit justifies the potential risk for the child or mother and the fetus.

### CONVALESCENT PLASMA: ORDERING AND CONSENT

- Orders for convalescent plasma will be entered in the EMR according via local process to order plasma blood products. A notation should be present on the order to denote the requested product is for Convalescent Plasma.

- Whenever possible, prior to administration the health care provider administering COVID-19 convalescent plasma must provide recipients with the **Fact Sheet for Patients/Caregivers** and must communicate the following information to the recipients:
  - 1) The FDA has authorized emergency use of COVID-19 convalescent plasma, which is not an FDA-approved biological product; 2) The patient or caregiver has the option to accept or refuse administration of COVID-19 convalescent plasma; 3) The significant known and potential risks and benefits of COVID-19 convalescent plasma and the extent to which such risks and benefits are unknown; and 4) Information on available alternative treatments and the risks and benefits of those alternatives.

- If providing the above information will delay the administration of COVID-19 convalescent plasma to a degree that would endanger the lives of patients, the information must be provided to the patients as soon as practicable after convalescent plasma is administered.

- Consent processes per local policies and procedures for administration of blood products should be followed. If applicable based on local product availability, a modified blood product consent with the following additional information should be used: “You are receiving a non-EUA compliant unit of plasma that was manufactured under the prior Emergency Access Protocol (EAP)”

### CONVALESCENT PLASMA: PRODUCT QUALIFICATIONS

- COVID-19 convalescent plasma is human plasma collected by FDA registered blood establishments from individuals whose plasma contains anti-SARS-CoV-2 antibodies, and who meet federal regulation donor eligibility. Under the EUA, authorized COVID-19 convalescent plasma will be obtained from registered or licensed blood establishments from donors in the United States or its territories in accordance with applicable regulations, policies, and procedures. The ordering physician should collaborate with local blood bank for local product availability.

### CONVALESCENT PLASMA: SUGGESTED DOSING AND ADMINISTRATION

- Per the EUA, the initial first dose is suggested as one COVID-19 convalescent plasma unit (about 200 mL). Due to the limited supply, administration of additional COVID-19 convalescent plasma units are currently not recommended.

- Administer COVID-19 convalescent plasma infusion through a peripheral or central venous catheter according to standard institutional medical and nursing practices for the administration of plasma and local policies and procedures.

### CONVALESCENT PLASMA: DOCUMENTATION, ADVERSE REACTIONS, AND RISKS

- Side Effects Known side effects and hazards associated with plasma transfusion include transfusion transmitted infections (e.g. HIV, hepatitis B, hepatitis C), allergic reactions, anaphylactic reactions, febrile nonhemolytic reactions, transfusion-related acute lung injury (TRALI), transfusion-associated cardiac overload (TACO), and hemolytic reactions. Hypothermia, metabolic complications, and posttransfusion purpura have also been described.
• A theoretical risk of administration of convalescent plasma is the phenomenon of antibody dependent enhancement of infection (ADE). ADE has been described in other viral infections and involves an enhancement of disease in the presence of certain antibodies. Another theoretical risk is that antibody administration may attenuate the immune response and make patients more susceptible to re-infection.

• Blood banks must maintain records in accordance with federal requirements and local policies. All suspected adverse reactions should be followed with a thorough investigation according to blood product administration policy.

HYDROXYCHLOROQUINE
• Current IDSA treatment guidelines do not recommend the use of chloroquine (CQ) or hydroxychloroquine (HCQ) in hospitalized patients with COVID-19 outside of a clinical trial. NIH guidelines now recommend against use outside of a clinical trial.
• Recent data from a large randomized controlled trial showed no evidence of benefit for mortality or other outcomes such as hospital length of stay or need for mechanical ventilation of HCQ treatment in hospitalized patients with COVID-19.
• Based on the continued review of the scientific evidence available for hydroxychloroquine sulfate for the treatment of COVID-19, the FDA has revoked the Emergency Use Authorization (EUA) based on this new information and other information discussed in their memorandum.
  o Specifically, the FDA has determined that CQ and HCQ are unlikely to be effective in treating COVID-19 for the authorized uses in the EUA. Additionally, in light of ongoing serious cardiac adverse events and other serious side effects, the known and potential benefits of CQ and HCQ no longer outweigh the known and potential risks for the authorized use.

AZITHROMYCIN
• Evidence to support the combination of hydroxychloroquine with azithromycin improves clinical outcomes for treatment of COVID-19 is lacking. However, the combination of these drugs is known to increase the likelihood of QTc prolongation which can lead to life-threatening arrhythmias and sudden cardiac death.
• Because of the potential for toxicity, routine use of this combination for inpatient treatment of COVID-19 in the absence of secondary bacterial infection is not recommended. If used, cardiac monitoring as outlined in the Cardiovascular section above, should be followed.
• For outpatients the use of antimicrobial regimens, including azithromycin, are only encouraged under approved conditions for treatment of bacterial pneumonia. Routine use in COVID is not recommended.

CORTICOSTEROIDS
A large randomized trial, the RECOVERY trial, has reported a significant mortality benefit with dexamethasone 6 mg daily for up to 10 days in patients requiring supplemental oxygen for COVID. There was no benefit in patients with milder disease who did not require oxygen support. Based on this information, the IDSA and NIH COVID-19 Treatment Guidelines recommends using dexamethasone (at a dose of 6 mg per day for up to 10 days) in patients with COVID-19 who are mechanically ventilated (AI) and in patients with COVID-19 who require supplemental oxygen but who are not mechanically ventilated (BI). The NIH recommends against using dexamethasone in patients with COVID-19 who do not require supplemental oxygen (AI). Other clinical guidelines have not yet been updated to reflect this new information. The World health organization recommends that clinicians may consider using dexamethasone for patients with severe and critical disease while this information is considered. Given the mortality benefit demonstrated in this large randomized trial a course of corticosteroid for up to 10 days is recommended for patients requiring oxygen therapy.33-39 Dexamethasone has been listed on the FDA drug shortage list since February 2019 and is chronically in sporadic supply. While the RECOVERY trial administered dexamethasone, previous retrospective data has also demonstrated benefit with methylprednisolone. Methylprednisolone may be used as an alternative to dexamethasone when necessary. Systemic glucocorticoids cause a dose-dependent, usually mild, hyperglycemia. Patients with diabetes mellitus or critical illness exhibit higher blood glucose levels while taking glucocorticoids, leading to increased difficulty with glycemic control. Patients receiving corticosteroids should be monitored for hyperglycemia. Clinically significant hyperglycemia that is glucocorticoid-induced are generally
treated pharmacologically in the same way that they are in patients with diabetes mellitus or glucose intolerance in the absence of glucocorticoid therapy.

**PROTEASE INHIBITORS**

- NIH Treatment Guidelines recommend against using lopinavir/ritonavir, or other HIV protease inhibitors, to treat COVID-19 outside of a clinical trial. A trial of adults hospitalized with severe COVID-19 treated with Lopinavir–Ritonavir (Kaletra®) has shown no benefit over supportive care and is not recommended (Cao et al.). Darunavir/cobicistat activity against COVID-19 has not been confirmed, activity is extrapolated from other coronaviruses (SARS/MERS).
- The triple combination of lopinavir, ritonavir and ribavirin with or without interferon beta-1b, may reduce duration of symptoms among patients who have been admitted to the hospital with COVID-19 based on preliminary data. Use of this triple antiviral regimen, and interferon beta-1b, should only be within the context of a clinical trial.
- Oseltamivir and other neuraminidase inhibitors do not appear to have activity against other coronaviruses (SARS), and should be reserved for treatment of influenza.

**INTERLEUKIN-6 (IL-6) INHIBITORS**

Due to emerging data signifying a lack of benefit on clinical outcomes, routine use of IL-6 Inhibitors is not recommended. Patients with COVID-19 disease may display an exuberant “cytokine storm” reaction. There are two separate randomized studies, using two IL-6 inhibitor agents that have been halted early due lack of clinical benefit. Preliminary, unpublished data from randomized controlled trials have not demonstrated the efficacy of sarilumab or tocilizumab in patients with COVID-19. The U.S. Phase 3 randomized trial of sarilumab for COVID-19 patients requiring mechanical ventilation was halted early due after it failed to improve outcomes compared to best supportive care. Based on evidence showing lack of benefit, use of Sarilumab (Kevzara®) is not recommended outside of a clinical trial.

Roche announced that in the BARDA sponsored 28-day, 450 patient, Phase III COVACTA trial (NCT04320615), treatment with tocilizumab did not improve clinical status ventilator-free days or mortality compared to placebo in hospitalized patients with severe COVID-19-associated pneumonia. Severe disease was defined as SPO2 </=93% or PaO2/FiO2 <300 mmHg. Patients treated with tocilizumab were discharged sooner than those in the placebo group (20 vs 28 days). Based on available data, routine use of Tocilizumab outside of a clinical trial setting is not recommended.

**ACE INHIBITORS AND ARBS**

There is interest in the potential role of ACE-inhibitors and angiotensin receptor blockers (ARBs) in the pathophysiology of this disease since the SARS-CoV-2 virus binds to the ACE2 receptor for cellular entry. However, current guidance from cardiology organizations (i.e. ACC/AHA/HFSA) state that there is not enough evidence to recommend for or against these medications in the setting of the COVID-19 pandemic.

- The HFSA, ACC, and AHA recommend continuation of RAAS antagonists for those patients who are currently prescribed such agents for indications for which these agents are known to be beneficial, such as heart failure, hypertension, or ischemic heart disease.
- In the event patients with cardiovascular disease are diagnosed with COVID-19, individualized treatment decisions should be made according to each patient's hemodynamic status and clinical presentation. Therefore, be advised not to add or remove any RAAS-related treatments, beyond actions based on standard clinical practice.

**NSAIDS**

The FDA is aware of news reports stating the use of non-steroidal anti-inflammatory drugs (NSAIDs) could worsen coronavirus disease (COVID-19). However, there is no scientific evidence to support these claims to date. The agency is investigating this issue and currently does not have any specific recommendations to withhold NSAID therapy in these patients. The European Medicines Agency has also issued guidance that there is not enough data to recommend avoiding NSAIDS in COVID patients.
OTHER CARE CONSIDERATIONS

COVID AND CO-INFECTION

Although the exact incidence of co-infection with bacterial pathogens among patients with COVID-19 is unknown, current data suggests it is uncommon (<5%). Empiric antibiotic therapy in patients with confirmed COVID is not recommended in the absence of highly suspected or confirmed bacterial co-infection.

MANAGEMENT OF INFLUENZA CO-INFECTION

If a patient with influenza and COVID co-infection, consultation with an Infectious Disease is recommended. Given the benefit of dexamethasone on reducing mortality for patients with severe COVID disease, use should be considered along with the risks and benefits in a co-infected patient. The role of dual antiviral therapy is unknown, but the combination of oseltamivir and remdesivir is not expected to be detrimental.

RESPIRATORY TREATMENTS

Inhaled medications can be delivered either by Metered Dose Inhalers (MDIs) or by nebulization; when delivered by nebulization, these can be aerosol generating. For COVID positive or patients suspected to have COVID, the use of MDIs is preferred when / if available. Collaboration and communication between physician, nursing, respiratory and pharmacy colleagues is necessary to reduce the risk of aerosolizing respiratory secretions induced through nebulization. Please refer to the COVID-19 Patients and Inhaled Respiratory Meds and ED and Urgent Care Inhaled Respiratory Medications for COVID Patients documents on the Trinity Health COVID Resource page.

PATIENT POSITIONING

- For non-intubated patients, please see the “Prone Positioning for the Non-intubated Patient” reference on the Trinity Health COVID site.
- For intubated patients, the American Thoracic Society suggests prone ventilation for patients with refractory hypoxemia due to progressive COVID-19 pneumonia (i.e., ARDS). Refractory hypoxemia refers to an SpO2 consistently less than 90% despite maximal ventilator interventions to increase the SpO2.

USE OF NEUROMUSCULAR BLOCKER AGENTS AND CONSERVATION

Neuromuscular blockade (NMBa) is implemented when needed to facilitate mechanical ventilation for treatment of moderate or severe acute respiratory distress syndrome (ARDS). The historical supply shortages with these agents has been augmented by the surge in demand due to treatment of COVID-19. Conservation methods are necessary to avoid complete exhaustion of drug supply.

The Society of Critical Care Medicine (SCCM) does not recommend routine use of continuous infusion of neuromuscular blockade for all mechanically ventilated patients or for treatment of mild ARDS. For mechanically ventilated patients and with moderate to severe ARDS, the recommendation is as follows:

SCCM Recommendations:
1. For mechanically ventilated adults with COVID-19 and moderate to severe ARDS: We suggest using, as needed, intermittent boluses of neuromuscular blocking agents (NMBa), over continuous NMBa infusion, to facilitate protective lung ventilation (weak recommendation, low-quality evidence).
2. In the event of persistent ventilator dyssynchrony, the need for ongoing deep sedation, prone ventilation, or persistently high plateau pressures, we suggest using a continuous NMBa infusion for up to 48 hours (weak recommendation, low-quality evidence).

Below are the available Trinity Health Formulary Nondepolarizing NMBa agents, suggested dosing, and dose considerations:

<table>
<thead>
<tr>
<th>NMBa</th>
<th>Onset of Action (MIN)</th>
<th>Duration after INITIAL dose (MIN)</th>
<th>Usual Dose Range#</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
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</table>

#For obese patients (BMI ≥ 30), use ideal body weight when calculating NMBa doses
Cisatracurium 1.5-2 20-35 Intermittent bolus dosing: 0.1 to 0.2 mg/kg/dose. Continuous infusion: Initial rate of 0.1 to 0.2 mg/kg/min; Usual dose range of 0.8 to 1.7 mcg/kg/minute

Vecuronium 2.3-3 20-40 Intermittent bolus dosing: 0.1 to 0.2 mg/kg/dose. Continuous infusion: Initial rate of 0.8 mcg/kg/minute; Usual dose range 0.8 to 1.7 mcg/kg/minute

Drug elimination varies based on renal and hepatic function.

Rocuronium 1-2 22-67 (dose dependent) Intermittent bolus dosing: 50 mg initial dose followed by 25 mg dose as needed. Continuous infusion: Initial rate of 8 mcg/kg/min; Usual dose range 8-12 mcg/kg/min

Vagolytic action can cause dose-dependent tachycardia.

USE OF NMBA FOR COVID RECOMMENDATIONS:

1. Implement conservation strategies to mitigate NMBA drug supply exhaustion including:
   a. Limit use of NMBA agents for patients with Severe ARDS (P/F <= 100) or who have failed prone ventilation
   b. Attempt intermittent boluses prior to continuous infusion when appropriated based on SCCM recommendations criteria
      i. Recommend 24 hours of intermittent dosing use prior to converting to continuous infusions
      ii. Local assessment with pharmacy regarding medication supply, available presentations, and dose dispensing should occur with bolus dose strategy to minimize waste
   c. If continuous infusion of a NMBA is required, use the lowest dose to achieve clinical goal and reassess the need for infusion at least twice a day. If train of 4 (TOF) monitoring is used, discontinue infusion if TOF reaches 0/4 and reassess need for infusion.
      i. For obese patients (body mass index (BMI) ≥ 30 kg/m2), use ideal body when calculating NMBA doses

2. Use succinylcholine preferentially, when appropriate, for rapid sequence intubations (RSI) to preserve rocuronium supply. Ensure that a NMBA supply is available for emergent surgeries (succinylcholine or rocuronium).

3. Critical care colleagues should familiarize themselves with alternative agents, dosing, and pharmacodynamic profile in preparation for a potential need to shift to these agents based on availability. Atracurium and Pancuronium are non-formulary alternative NMBA agents. Listed below are the suggested dosing and dose considerations:

<table>
<thead>
<tr>
<th>NMBA</th>
<th>Onset of Action (MIN)</th>
<th>Duration after INITIAL dose (MIN)</th>
<th>Usual Dose Range#</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atracurium</td>
<td>2-3</td>
<td>20-35</td>
<td>Intermittent bolus dosing: 0.4 to 0.5 mg/kg/dose Birthday Continuous infusion: 4 to 20 mcg/kg/minute</td>
<td>Can cause histamine release, however clinical effects unlikely. Histamine release can be reduced by slowing the rate of administration.</td>
</tr>
<tr>
<td>Pancuronium</td>
<td>2-3</td>
<td>60-100</td>
<td>Intermittent bolus dosing: 0.06 to 0.1 mg/kg/dose Birthday Continuous infusion: 0.8 to 2 mcg/kg/minute</td>
<td>Avoid, if possible, if history of coronary artery disease. Vagolytic action and sympathetic stimulation can cause dose dependent tachycardia. Long acting agent. Dose adjustment in renal impairment.</td>
</tr>
</tbody>
</table>

ANTICOAGULATION AND COVID RELATED COAGULOPATHY GUIDANCE

- Patients infected with COVID-19 are at increased risk of venous thromboembolism due to hospitalization, immobilization, active infection and inflammation, and possibly due to a hypercoagulable state unique to the virus itself. Arterial thrombosis has also been reported.
- COVID-19 infected patients display multiple coagulation abnormalities which may be more prothrombotic than hemorrhagic
- Lab derangements may include elevated d-dimers, prolonged PT/PTT high fibrinogen and sometimes mild thrombocytopenia
• This document is based on expert clinical guidance and current best available information, which is still evolving. This guidance should be used in conjunction with latest evidence and patient-specific characteristics and should not supersede clinical judgment

**Anticoagulation Admission Considerations for Highly Suspected or Confirmed COVID**

- **Labs on admission:** D-dimer, INR/PT, PTT, fibrinogen and CBC with differential
  - Elevated D-dimer is of unknown clinical significance and should not be used as a lone criterion in care decisions
- **Inpatient labs every 2-3 days:** CBC, PT, PTT, D-dimer, INR/PT, fibrinogen
  - If worsening parameters, consider more aggressive critical care support
  - Do not use blood products to correct non-bleeding coagulopathy
  - There is no evidence for use of TEG in COVID-19 patients to guide decisions regarding anticoagulation and use is **not** recommended

**Therapeutic Anticoagulation Prior to Admission**

- If a patient was receiving anticoagulation therapy prior to admission for a co-morbid disease state, continue anticoagulation therapy during COVID admission if no contraindications exist
  - Monitor renal function daily
- Consider switching to enoxaparin or heparin infusion if severe illness, possible drug-interactions with COVID investigational therapies, inability to take PO medications or anticipated procedures

**Prevention of Venous Thromboembolism (VTE) in Highly Suspected or Confirmed COVID Patients**

- All highly-suspected or confirmed COVID-19 patients not on anticoagulation therapy should receive VTE prophylaxis unless contraindicated (e.g., Platelet count <25-30K, active bleeding)
- Low molecular weight heparin (enoxaparin), appropriately dose adjusted for renal function and/or weight is the preferred agent for thromboprophylaxis (see Figure 1)
  - Therapy adjustments are required for impaired renal function and/or extremes of weight (see Figure 1)
  - Fondaparinux may be used as an alternative to enoxaparin for patients with heparin induced thrombocytopenia without contraindications
- If pharmacologic prophylaxis is contraindicated, mechanical prophylaxis with intermittent pneumatic compression (IPC) should be consistently applied
- **VTE prevention regimens and recommendations include pregnant COVID+ patients.** Close collaboration with OB and anesthesiology is recommended in the event of delivery and/or need for epidural anesthesia during hospitalization
FIGURE 1: VTE PROPHYLAXIS

VTE prophylaxis for ALL hospitalized highly-suspected or confirmed COVID-19+ patients without contraindications

Non-Critically Ill

<table>
<thead>
<tr>
<th>GrCl</th>
<th>≥ 30 ml/min</th>
<th>29 – 10 ml/min</th>
<th>&lt; 10 ml/min</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enoxaparin SubQ*</td>
<td>Heparin SubQ</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>50-99 kg</td>
<td>40 Daily</td>
<td>30 Daily</td>
<td>5000 Units q8h*</td>
</tr>
<tr>
<td>100-150 kg</td>
<td>40 BID</td>
<td>40 Daily</td>
<td>7500 Units q8h</td>
</tr>
<tr>
<td>&gt;150 kg</td>
<td>60 BID</td>
<td>60 Daily</td>
<td>7500 Units q8h</td>
</tr>
</tbody>
</table>

*For patients <50 kg and age >80 YO, dose adjustment to Heparin 5000 units SubQ q12 hour

Critically Ill (ICU)

<table>
<thead>
<tr>
<th>GrCl</th>
<th>≥ 30 ml/min</th>
<th>29 – 10 ml/min</th>
<th>&lt; 10 ml/min</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enoxaparin 0.5 mg/kg SubQ q12h*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GrCl &gt; 30 ml/min</td>
<td>Enoxaparin 0.5 mg/kg SubQ q24*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GrCl 29 – 10 ml/min</td>
<td>Heparin 7500 Units SubQ q8h*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GrCl &lt; 10 ml/min</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*For patients <50 kg and age >80 YO, dose adjustment based on multidisciplinary discussion is necessary

MONITORING
Every 2-3 days: CrCl, CBC, PTT, PT/INR, D-dimer, fibrinogen

MONITORING
DAILY: CrCl and CBC
Every 2-3 days: PTT, INR/PT, D-dimer, fibrinogen

EMPIRIC THERAPEUTIC ANTICOAGULATION FOR COVID RELATED COAGULOPATHY

- Initiation of therapeutic anticoagulation regimens without confirmed or high clinical suspicion of VTE is controversial is not recommended at this time
- Suspected VTE should be confirmed with diagnostic imaging whenever feasible if patient is stable to do so
- Severe COVID-19 infections may be associated with significant coagulopathy. Reported microvascular thrombosis is a distinctly different entity from embolic DVT/PE and when present in other inflammatory conditions such as sepsis, which does not respond to anticoagulant therapy and bleeding risk is high.
- Currently anticoagulants are not recommended to treat suspected microvascular thrombosis. In contrast, embolic VTE, responds to anticoagulant therapy.
- In the setting of persistent clotting of lines/devices/filters despite COVID-appropriate VTE prophylaxis and worsening clinical course, intensified anticoagulation may be considered via multidisciplinary discussion with critical care attending, coagulation specialist, or others (path, heme) where available

EMPIRIC THROMBOLYTIC THERAPY

- Empiric use of thrombolytic (i.e. alteplase) is NOT recommended for COVID-19 associated coagulopathy (outside of a clinical trial)
- Thrombolysis may be considered for COVID-19 patients with confirmed or high suspicion for indications specific to thrombolytic therapy (i.e., acute ischemic stroke, PE, acute myocardial infarction)

TREATMENT OF VENOUS THROMBOEMBOLISM (VTE) IN HIGHLY SUSPECTED OR CONFIRMED COVID PATIENTS

- Suspected VTE should be confirmed with diagnostic imaging whenever feasible if patient is stable to do so
- Initiate therapeutic anticoagulation (unless contraindicated) only when VTE is confirmed or clinical suspicion is high and diagnostic testing is unavailable or not feasible
- Anticoagulation regimens that require minimal monitoring and RN exposure are preferred when possible (see Figure 2)
- The PTT may be impacted by the virus and thus not reliable in some COVID-19 patients.
  - If available, recommend a correlation is performed between PTT/Anti-FXa at the time IV Unfractionated Heparin (UFH) is started and again if significant worsening of clinical status. Discuss with local laboratory.
- Limit treatment regimens for VTE in COVID+ pregnant patients to enoxaparin or UFH. DOACs are contraindicated in pregnancy and breastfeeding.
FIGURE 2: THERAPEUTIC ANTICOAGULATION FOR TREATMENT OF VTE IN COVID PATIENTS

<table>
<thead>
<tr>
<th>Preferred Treatment Regimens for Highly-suspected or Confirmed VTE</th>
</tr>
</thead>
<tbody>
<tr>
<td>CrCl</td>
</tr>
<tr>
<td>CrCl &gt; 30 ml/min</td>
</tr>
<tr>
<td>Enoxaparin 1 mg/kg SubQ q12h</td>
</tr>
<tr>
<td>CrCl 29 – 10 ml/min</td>
</tr>
<tr>
<td>Enoxaparin 1 mg/kg SubQ q24*</td>
</tr>
<tr>
<td>CrCl &lt; 10 ml/min</td>
</tr>
<tr>
<td>Heparin Infusion for Venous Thromboembolism</td>
</tr>
</tbody>
</table>

**Thromboprophylaxis and Anticoagulation Nursing Considerations**

- Goals of care include prevention of ischemic injury and dehydration, absence of hemorrhage and restoration of homeostatic coagulation. Collaborate with pharmacist and medical staff regarding appropriate anticoagulant dose.
- Management of care include:
  - Regular assessment for signs/symptoms of bleeding
    - Assess skin for hematoma or mottling; Monitor lab values; Assess capillary refill
    - Assess vital signs, watching for arrhythmias, tachycardia and hypotension
  - Assess neuro status
  - Keep venipuncture to a minimum

**Anticoagulation Discharge Considerations**

**Post Hospitalization Considerations for Patients Treated With Therapeutic Anticoagulation for Suspected or Confirmed VTE During COVID Admission**

- If acute VTE was confirmed during admission, continue therapeutic anticoagulation at least 3 months then re-assess
- If VTE was unconfirmed & treated empirically for a patient with high suspicion, continue therapeutic anticoagulation for at least 3 months then re-assess

**Post Hospitalization Considerations - VTE Prophylaxis**

- Severely ill COVID-19+ patients may experience prolonged hospital stay, significant deconditioning, post-ICU syndrome and thus may not fully recover to baseline mobility or health status by time of discharge. Patients being discharged from the Emergency Department (ED) with confirmed COVID-19 diagnosis may also be at risk for VTE.
- While no data specific to COVID-19 exist, extended prophylaxis with LMWH or with direct oral anticoagulants (DOACs) in non-COVID-19 patients can reduce the risk of VTE, at the cost of increase in bleeding events, including major bleeding.
- Each COVID-19 patient should have a careful risk assessment on a case-by-case basis based on the presence ongoing risk factors for VTE at the time of discharge.
- VTE prophylaxis beyond discharge from the hospital, may be reasonable on a case-by-case basis and may include COVID-19+ patients who have:
  - Diminished mobility / weakness
  - Active cancer
  - An ongoing inflammatory state
- Patients considered to be at significant continued risk for VTE AND without elevated bleeding risk factors should be considered (no data exists) for:
  - Short-term use (up to 14 days) of prophylactic dose LMWH or DOAC (dose based on weight, renal function, and drug interaction screening³)
- Prophylaxis dosing with enoxaparin or DOAC for up to 14 days and re-evaluation after beyond hospitalization may be reasonable in appropriately selected patients with reduced mobility and increased thrombotic risk factors
  - Patient education on the potential bleeding risk and expected benefit is required prior to prescribing post-discharge VTE prophylaxis.
- For those patients admitted for treatment of COVID-19 who may have been on thromboprophylaxis for conditions that existed prior to admission, consider transition back to the previous regimen (consider changes in renal function) post-hospitalization (if the pre-hospitalization condition still exists).
COVID VTE Treatment Risk and Treatment Algorithm

Clinical Suspicion for VTE

VTE unlikely (Wells score PE ≤ 4, DVT < 2)
- Continue VTE prophylaxis with close monitoring for further signs and symptoms of VTE
- Consider discharge on VTE prophylaxis for up to 14 days (see Discharge Considerations)

Wells score elevated1 (PE > 4 or DVT ≥ 2) & clinical picture (acute change in oxygenation)
- Low risk for bleeding (VTE-BLEED Score ≥ 2)
- VTE (+) or presumptive
- VTE treatment a

VTE likely (Wells Score PE >4, DVT ≥ 2)
- Assess VTE-BLEED score2
- High risk for bleeding (VTE-BLEED Score ≥ 2)
- Consider PE CT or LE DVT scan as per clinical suspicion

VTE treatment a
- If yes to any of these criteria, no further studies should be performed. Otherwise, continue algorithm
- Patient is end of life or comfort care
- VTE imaging would not change management
- Patient would not consent to therapeutic anticoagulation
- Patient already has dx of VTE from another study or other indications for therapeutic anticoagulation

COVID VTE protocol exclusion criteria
- No
- Consider PE CT or LE DVT scan as per clinical suspicion b
- Yes
- Continue current management
- Consider VTE prophylaxis if not already on

VTE prophylaxis

• For presumptive VTE therapy, arrange for PE CT or LE DVT scan when clinically appropriate and treat accordingly
• Discharge with therapeutic anticoagulation and follow-up as appropriate

VTE (-)

a. See Figure 2. Enoxaparin preferred to IV UFH to minimize need for lab monitoring and RN exposure.
b. If imaging can’t be done but suspicion for VTE is high, may consider cautious use of presumptive therapeutic anticoagulation with close monitoring for bleeding
### Modified Wells Score for Assessment of Clinical Likelihood of VTE

*Not validated in COVID but no other score available*

<table>
<thead>
<tr>
<th>PE Criteria</th>
<th>Pt</th>
<th>DVT Criteria</th>
<th>Pt</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical signs and symptoms of DVT (objectively measured calf swelling and pain with palpation in the deep vein region)</td>
<td>3</td>
<td>Active cancer (patient receiving treatment for cancer within the previous 6 months or currently receiving palliative treatment)</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Paralysis, paresis, or recent casting or immobilization of the lower extremities</td>
<td>1</td>
</tr>
<tr>
<td>An alternative diagnosis is less likely than PE</td>
<td>3</td>
<td>Recently bedridden for 3 days or more, or major surgery within the previous 12 weeks requiring general or regional anesthesia</td>
<td>1</td>
</tr>
<tr>
<td>Heart rate &gt; 100 beats per minute</td>
<td>1.5</td>
<td>Localized tenderness along the distribution of the deep venous system</td>
<td>1</td>
</tr>
<tr>
<td>Immobilization or surgery in the previous four weeks</td>
<td>1.5</td>
<td>Entire leg swollen</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Calf swelling at least 3 cm larger than that on the asymptomatic side (measured 10 cm below the tibial tuberosity)</td>
<td>1</td>
</tr>
<tr>
<td>Previous DVT or PE</td>
<td>1.5</td>
<td>Pitting edema confined to the symptomatic leg</td>
<td>1</td>
</tr>
<tr>
<td>Hemoptysis</td>
<td>1</td>
<td>Previously documented DVT</td>
<td>1</td>
</tr>
<tr>
<td>Malignancy (on treatment, treated in the past six months, or palliative care)</td>
<td>1</td>
<td>Collateral non-varicose superficial veins</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Alternative diagnosis at least as clinically likely as DVT</td>
<td>-2</td>
</tr>
</tbody>
</table>

**OR acute change in O₂ req**

### VTE-BLEED Score

<table>
<thead>
<tr>
<th>Factor</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active cancer</td>
<td>2</td>
</tr>
<tr>
<td>Male with uncontrolled arterial hypertension</td>
<td>1</td>
</tr>
<tr>
<td>Anemia</td>
<td>1</td>
</tr>
<tr>
<td>History of bleeding</td>
<td>1</td>
</tr>
<tr>
<td>Age ≥ 60 years old</td>
<td>1</td>
</tr>
<tr>
<td>Renal dysfunction</td>
<td>1</td>
</tr>
</tbody>
</table>

Other factors that contribute to bleeding:
- Thrombocytopenia
- Cirrhosis
- Other anti-thrombotic use (e.g. aspirin, clopidogrel, ticagrelor)

### Anticoagulation References

REFERENCES:


25. Sarilumab (Kevzara®) https://www.regeneron.com/covid19


47. Peter Horby, Wei Shen Lim, Jonathan Emberson, Marion Mafham, Jennifer Bell, Louise Linsell, Natalie Staplin, Christopher Brightling, Andrew Ustianowski, Einas Elmahi, Benjamin Prudon, Christopher Green, Timothy Felton, David Chadwick, Kanchan Rege, Christopher Fegan, Lucy C Chappell, Saul N Faust, Thomas Jaki, Katie Jeffery, Alan Montgomery, Kathryn Rowan, Edmund Juszczak, J Kenneth Baillie, Richard Haynes, Martin J Landray, RECOVERY Collaborative Group medRxiv 2020.06.22.20137273; doi: https://doi.org/10.1101/2020.06.22.20137273


VERSION HISTORY

<table>
<thead>
<tr>
<th>Version Date</th>
<th>Revisions Made</th>
</tr>
</thead>
<tbody>
<tr>
<td>3/30/2020</td>
<td>Updated Remdesivir compassionate use information.</td>
</tr>
<tr>
<td>4/4/2020</td>
<td>Updated to reflect new FDA released FACT SHEET FOR HEALTH CARE PROVIDERS and expanded information in 'Use of Hydroxychloroquine: Patient Selection, Dosing, and Monitoring&quot; section</td>
</tr>
<tr>
<td>4/28/2020</td>
<td>Added reference to FDA Drug Safety Communication that cautions against use of hydroxychloroquine or chloroquine for COVID-19 outside of the hospital setting or a clinical trial due to risk of heart rhythm problems. Added information on Discharging Patients on Hydroxychloroquine</td>
</tr>
<tr>
<td>05/4/2020</td>
<td>Added outpatient pharmacotherapy guidance.</td>
</tr>
<tr>
<td>05/6/2020</td>
<td>Updated patient categories and therapy guidance for Remdesivir and Hydroxychloroquine. Includes updates for Remdesivir based on FDA emergency use authorization for Remdesivir.</td>
</tr>
<tr>
<td>05/13/2020</td>
<td>Recommendation added to limit use of triple antiviral therapy and interferon beta to use in a clinical trial only</td>
</tr>
<tr>
<td>5/20/2020</td>
<td>Updated recommendations on use of Remdesivir in renal impairment and duration of therapy. Nursing considerations comment added.</td>
</tr>
<tr>
<td>5/28/2020</td>
<td>Hydroxychloroquine no longer recommended</td>
</tr>
<tr>
<td>6/4/2020</td>
<td>Revised criteria for use of IL-6 inhibitors</td>
</tr>
<tr>
<td>Date</td>
<td>Changes</td>
</tr>
<tr>
<td>------------</td>
<td>-------------------------------------------------------------------------</td>
</tr>
<tr>
<td>6/16/2020</td>
<td>Information regarding FDA revocation of emergency approval of Hydroxychloroquine added. Remdesivir information updated with revised warnings for drug interactions and hypersensitivity and anaphylactic reactions.</td>
</tr>
<tr>
<td>6/24/2020</td>
<td>Addition of recommendation for dexamethasone/corticosteroid therapy for patients requiring oxygen therapy</td>
</tr>
<tr>
<td>7/13/2020</td>
<td>Convalescent Plasma guidance is updated and added to guidance document. Updated IL-6 section with results of sarilumab trial. NMBA guidance incorporated into the document. Addition of recommendation for glucose monitoring with corticosteroid use.</td>
</tr>
<tr>
<td>8/27/2020</td>
<td>Removal of option to extend Remdesivir duration from the recommended 5 day to a 10-day duration.</td>
</tr>
<tr>
<td>9/14/2020</td>
<td>Information added on new FDA EUA for convalescent plasma. Remdesivir EUA information updated to reflect the expansion of EUA to all hospitalized patients. Updated IL-6 information; routine use of IL-6 agents is not recommended based on new data. Co-infection (bacterial and influenza) recommendations added.</td>
</tr>
<tr>
<td>9/22/2020</td>
<td>Remdesivir treatment for suspected or confirmed non-severe disease updated &quot;Remdesivir is recommended for hospitalized patients not requiring supplemental oxygen with clinical symptoms of COVID-19 and a positive molecular (PCR) test&quot;</td>
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