

LITERATURE REVIEW SARS-CoV 2 Treatment

By: , Elise Lasker, Cory Nunn, Anjali Prasad, Brian Seegmiller, Michelle Sutanto, and Saraaga Tamirisa; Peer reviewed by: Dr. Kristi Traugott and Dr.

Elizabeth Hand

updated 09/21/2020



UT Health
San Antonio
Long School of Medicine



SUPPORTIVE CARE

IMMUNOSUPPRESSANTS

- Long duration and excessive doses of steroids may adversely affect recovery due to the inhibition of antiviral immunity and may also result in other side effects related to steroids.
- Discontinuation of immunosuppressants and steroid treatment might help faster recovery from COVID-19 pneumonia.
- The risks and benefits of continuing or discontinuing immunosuppressants should be weighed for each individual case.
 - A lower than standard dose of immunosuppressants could be tried in patients requiring immunosuppressants to facilitate and shorten duration of disease with COVID-19.
- However, steroids are still considered standard of care in the management of patients who progress to ARDS

VENTILATION

- Though mostly anecdotal, there is some evidence on the ventilator settings and differing characteristic of COVID-19 associated ARDS. Ventilator setting recommendations include:
 - Low TV, 6 mL/kg ideal body weight
 - PEEP >10 cm H₂O
 - Oxygen administration at an SpO₂ < 90% - 96%
 - Starting RR of 16 breaths/min.
 - Early prone positioning
 - If prone positioning fails, use recruitment maneuvers and high PEEP strategies, pulmonary vasodilators, neuromuscular blocking agents, and/or ECMO.
- The most experienced team member should perform intubation with as few assistants as possible to reduce exposure. Bag-mask ventilation generates aerosols and should be minimized by performing prolonged pre-oxygenation. Rapid sequence induction with muscle relaxants will reduce coughing.
- In patients who develop hypercapnia, increase VT to ~7.7.
- For timing of intubation:
 - If a patient is on nasal high-flow oxygen therapy, the ROX index [SpO₂/(FiO₂ x RR)] can be used. If after 12 hours, patients have a ROX index of <3.85, initiate intubation.
 - For NCP patients, if PaO₂/FiO₂ is <150 mmHg (1mmHg = 0.133 kPa), initiate intubation if receiving more than 2 hours of nasal high-flow therapy or non-invasive ventilation.
- Two recent studies found that self-proning improved oxygenation parameters in adults with COVID-19 with noninvasive ventilation
 - Some patients may be unable to tolerate this or sustain higher oxygenation parameters upon returning to the supine position.

ANTICOAGULATION

- D-dimer and FDP levels may progressively increase with COVID-19 exacerbation, resulting in acro-ischemia.
- The existence of hypercoagulation status in critical COVID-2019 patients should be monitored closely, and anticoagulation therapy with LMWH is recommended for all hospitalized adults with COVID-19. Fondaparinux is recommended in cases of HIT.
- Anticoagulant therapy mainly with LMWH appears to be associated with better prognosis in severe COVID-19 patients meeting SIC criteria or with markedly elevated D-dimer.
- Antiplatelet agent Dipyridamole has been found to suppress SARS-CoV-2 replication in vitro. A proof of concept trial involving 31 patients with COVID-19 found that dipyridamole supplementation was associated with decreased D-Dimer concentration, improved platelet and lymphocyte counts, and improved clinical outcomes compared to control patients.

ECMO

- ECMO should be considered if mortality rate approaches 50%, initiate if 80%.
- ECMO should be considered if one following criteria are met:
 1. PaO₂/FiO₂<100mmHg
 2. P(A-a) O₂>600mmHg
 3. pH<7.2 and plateau pressure >30 cmH₂O with respiratory rate > 35 breaths per minute
 4. <65 years old
 5. NO contraindications
 6. Severe air leak syndrome
 7. Complicated by cardiogenic shock or cardiac arrest
- Contraindications include: multi-organ failure, contraindication to anticoagulation, high mechanical vent for more than 7 days



DIRECT ACTING AGENTS

REMDESIVIR

- Remdesivir shows promise for improved clinical outcomes in one compassionate-use cohort study. Study limitations: lack of control group, lack of uniformity of supportive care, small sample size (n=53).
- Preliminary results from randomized control trial (ACTT-1, n= 1063) show 31% faster median recovery (11 vs 15 days) and improved mortality (8% vs 11.6%) when compared to placebo. Use is recommended in hospitalized patients requiring supplemental oxygen. Benefit is most evident in patients who were hypoxic but not yet intubated.
- The current dose regimen for remdesivir is an IV loading dose of 200mg on the first day of treatment, followed by IV maintenance doses of 100mg for 4 days. However, one study found that this would not achieve adequate plasma concentrations. It is suggested that a combination of IV and pulmonary delivery regimen may be more effective.
- A study comparing the efficacy of 5 days of remdesivir treatment vs 10 days demonstrated no benefit in a longer treatment duration. Therefore, the current recommended dosing regimen is 5 days.
- Adverse events occur more commonly in ventilated patients. Most common adverse events: increased hepatic enzymes, diarrhea, rash, renal impairment, hypotension.

IVERMECTIN

- Ivermectin has been shown to be an effective treatment for SARS-CoV-2 by inhibiting viral replication and greatly reducing viral numbers *in vitro*. *In vivo* trials are merited.

TENOFOVIR

- Tenofovir can tightly bind to the RdRp of the SARS-CoV-2 strain and thus may be used to treat the disease.

TOCILIZUMAB

- A study reviewing clinical trials in China and by the FDA suggest that Tocilizumab may be indicated in patients with cytokine release syndrome (CRS) and diffuse lung injury. The clinical trial found reduction in lung lesions, improvements in oxygen level and respiratory function, and reduction in fever to normal temperature.
 - Study limitations: small sample size (n = 14), all patients treated with methylprednisolone concomitantly
- A multicenter study (n = 63) in showed significant improvement in COVID patients with a pro-thrombotic, pro-inflammatory profile (classified as having 3 of the following: Ferritin >1000 ng/mL, CRP, D-Dimer 10x normal, LDH 2x normal). Administration of TCZ within 6 days of admission was associated with a higher chance of survival. (Sciaccia et al. 05/26/2020)
 - TCZ was administered either IV (8 mg/kg) or SC (324 mg), with a 2nd dose in 52 out of 63 patients.
- Another retrospective study by the University of Maryland confirmed similar improvements in COVID patients
- with CRS due to Tocilizumab treatment combined with lopinavir, methylprednisolone, and oxygen therapy.
 - Both studies reviewed 1-hour infusion of tocilizumab up to 800 mg (max dosage) with some adverse effects including gastrointestinal perforations in patients with diverticulitis and concomitant high dosage corticosteroid use.
- Tocilizumab should not be used in pregnant patients and has not been found to be hepatotoxic or nephrotoxic thus far.

DEXAMETHASONE

- The RECOVERY trial (n=2104) has shown that dexamethasone reduces mortality in ventilated patients by one-third and in patients solely on oxygen by one-fifth.
 - 6 mg PO or IV QD dexamethasone was given to all patients (n=2104) for 10 days and compared to a randomized control group (n=4321) receiving usual care. The compared treatment arms were Lopinavir-Ritonavir, Hydroxychloroquine (discontinued), Azithromycin, Tocilizumab, and Convalescent plasma.
- Dexamethasone has not shown reduction in mortality of patients not using respiratory support
- Preliminary results of the RECOVERY trial have been released, but the study has not been published as of 6/18/20

HYDROXYCHLOROQUINE (HQ)/CHLOROQUINE

- The FDA revoked EUA for COVID-19; cannot be used outside an authorized clinical trial.
- There is no clear evidence for the benefit of hydroxychloroquine in the treatment of patients hospitalized with COVID-19.

For details and references please visit <https://oume.uthscsa.edu/longco/>



DIRECT ACTING AGENTS CONTINUED

CONVALESCENT PLASMA

- Convalescent plasma is FDA approved for use in clinical trials, patients with severe or immediately life-threatening laboratory confirmed COVID-19, and single patient emergency IND approval (FDA 5/1/2020)
- A study performed at Houston Methodist hospitals (n = 25) found that 36% of patients improved from baseline after 7 days and 76% improved after 14 days after 300 mL convalescent plasma obtained from 9 healthy donors who had recovered from COVID-19 was transfused (Salazar et al 5/27/2020)
 - Study limitations: n = 25, no control group, all patients were treated with HQ +azithromycin, 2 patients were treated with remdesvir, some with ribavarin, and some with tocilizumab and methylprednisone
 - Overall decrease in CRP and no increase in LFTs; 20 out of 25 patients were discharged, all but 2 patients on ventilation and ECMO were weaned off
 - Further study is needed to assess efficacy of convalescent plasma as a stand-alone treatment
 - No adverse effects related to transfusion were observed in the study
- Another randomized clinical trial from 7 medical centers in Wuhan, China compared a standard treatment group (n = 51) to a standard treatment plus convalescent plasma group (n=52)
 - 98.3% of patients in the experimental group with severe disease recovered within 28 days compared to the control group (68.2%)
 - There was no statistical difference for recovery within 28 days between the control and experimental group for patients with life-threatening disease
 - No statistically significant decrease in time to clinical improvement between the experimental and control groups

METHYLPREDNISONE*

- A Brazilian study evaluated the use of short-term methylprednisone as adjunct therapy for hospitalized patients, over the course of 28-days. (Prado Jeronimo, C.M. et al, 2020)
- Methylprednisone was given to one group (n=194), dosed for 5 days with twice-daily 0.5 mg/kg IV, and then compared to a randomized control group (n=199). Mortality was not different at day 28 between the two groups; however, mortality among patients over the age of 60 was decreased in the MP group. As a caution, insulin should be monitored in patients receiving MP.

BARICITINIB*

- A press release from the drug company, Lilly, outlined the ACTT-2 trial concerning Baricitinib in combination with Remdesivir in hospitalized patients. The study is as of now unpublished.
 - The trial group (n=1000) compared using a 4-mg dose of Baricitinib in combination with Remdesivir, versus Remdesivir alone. Investigators found a 1-day reduction in median time overall in recovery. They defined recovery as either coming off supplemental oxygen or being discharged.
 - Lilly is seeking an EUA for a 4-mg dose for COVID patients.
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VACCINE DEVELOPMENT

- Moderna has developed an mRNA based vaccine that has progressed to Phase 3 testing. On 09/17/2020, Moderna shared their protocol for determining if their vaccine was safe and effective. It may take until early 2021 to evaluate this.*
 - BioNTech, Pfizer, and Fosun Pharma have developed a two-dose mRNA vaccine that has recently expanded the number of participants in the U.S. Pfizer has stated that they will know if the vaccine works as soon as October 2020 and has been awarded a contract for 100 million doses to be delivered by December from the Trump administration.*
 - AstraZeneca and the University of Oxford have developed a vaccine called ChAdOx1. They have halted trials as of 09/06/2020.*
 - CanSinoBIO, the Gamaleya Research Institute, Sinovac, Sinopharm, and the Wuhan Institute of Biological Products have developed vaccines that are approved for limited use in international countries. None are approved in the U.S. as of 09/21/2020.*
 - As of 09/18/2020, there are 27 vaccines in Phase 1, 15 in Phase 2, 9 in Phase 3, and 5 approved for limited use.*
 - The Murdoch Children's Research Institute is conducting a Phase 3 trial to see if the BCG vaccine partly protects against COVID-19.
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