LITERATURE REVIEW SARS-CoV 2 Treatment

By: Laura Berardo, Elise Lasker, Anjali Prasad, Michelle Sutanto, and Saraaga Tamirisa; Peer reviewed by: Dr. Kristi Traugott and Dr. Elizabeth Hand

updated 06/01/2020

UT Health San Antonio Long School of Medicine

SUPPORTIVE CARE

IMMUNOSUPRESSANTS

- 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

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.

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.

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).
- In a preliminary report of a multinational trial of >1000 patients with COVID-19 and pulmonary involvement, remdesivir resulted in faster recovery time.
- 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

- Retrospective study in China suggests that Tocilizumab may reduce inflammation in COVID-19, as indicated by IL-6 levels. This study also suggests that Tocilizumab may be more effective when given in multiple doses to critically ill patients.
  - Study limitations: small sample size (n = 15), all patients treated with methylprednisolone concomitantly
- A multicenter study (n = 63) in Italy 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. (Sciascia 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.
- Tocilizumab should not be used in pregnant patients.

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

- There is no clear evidence for the benefit of hydroxychloroquine in the treatment of patients hospitalized with COVID-19. If a patient is treated with HQ, they should ideally be enrolled in a clinical trial whenever possible.
- One study found that the probability of negative conversion by 28 days in the standard of care alone group was 81.3%. Adverse events were documented in 30% of the patients receiving hydroxychloroquine, while adverse events were recorded in 9% of patients in the control group.
- HQ + AZITHROMYCIN
  - A multinational, retrospective study (n=14,888) using data from 671 hospitals in six continents regarding the outcomes of patients with the use of hydroxychloroquine or chloroquine with or without a macrolide found that patients treated with hydroxychloroquine, hydroxychloroquine with a macrolide, chloroquine, and chloroquine with a macrolide were independently associated with an increased frequency of ventricular arrhythmias when compared to the control group.

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

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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

VACCINE CREATION

- At least 7 different vaccines are currently in phase I of clincial trials (mix of inactivated,mRNA, DNA and Ad5 vector)·
- CanSino Ad5 vaccine (made against CoV2 spike) has been shown to induce peak antibody production at 28 days post inoculation and peak T cell response 15 days post inoculation (Production of antibodies to receptor binding domain of SARS-CoV-2 was increased by 4 fold 90% of participants). Immediate adverse reactions included transient fever and flu like ymptoms (resolved within 48 hrs).
  - Limitations: only 108 people included in study
  - No one below age of 18 or over the age of 60 was included
  - Participants only monitored to 28 days post vaccination
  - Concerning findings of study: seroconversion rates were higher in patients 18-45 than in patients 45-60. Preexisting antibodies to Ad5 vector also seemed to decrease seroconversion for antibody production as well as T cell response. Middle and high dose of vaccine lead to greater T cell response when compared to low dose of vaccine. Possible concern for increased sensitivity to HIV1 infection with activation of CD4 T cells by Ad5 (this relationship is controversial and mechanism still unclear)
- ·The department of Health and Human Services is currently sponsoring Operation Warp Speed, which aims to develop a vaccine. It is providing funding to three companies for stage three trials.