LITERATURE REVIEW SARS-CoV 2 Treatment

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

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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.
- 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.

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

MEDICAL AGENTS

DIRECT ACTING ANTIVIRALS

REMDESIVIR

- Remdesivir is the only FDA approved COVID treatment as of 10/26/2020
- 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 of 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%). 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.
- On March 5, 2021, the COVID-19 Treatment Panel updated its recommendations on the use of remdesivir and dexamethasone in hospitalized patients requiring conventional oxygen therapy.
  - They recommend using one of the following options: remdesivir, dexamethasone + remdesivir, or dexamethasone alone

NONSPECIFIC ANTI-INFLAMMATORIES

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.
- ·The primary short-term adverse effect of corticosteroids are hypoglycemia
- ·Adverse events associated with prolonged use include glaucoma, cataracts, fluid retention, hypertension, psychological effects, weight gain, or increased risk of infections and osteoporosis
- ·Dexamethasone has shown to be a moderate inducer of CYP3A4 and thus its use must be monitored for drug interactions

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)
- ·Methyprednisone 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.

COLCHICINE

- ·A press release from the Montreal Heart Institute announced on Jan. 22, 2021 the preliminary results of a clinical trial using Colchicine to treat COVID-19. The results showed that Colchicine reduced the risk of death or hospitalizations by 21% compared to placebo. The colchicine was effective at preventing the cytokine storm.
  - The trial (n=4488) included people who had tested positive via naso-pharyngeal PCR, and randomly assigned them to colchicine or placebo cohorts. The colchicine was shown to reduce hospitalizations by 25%, the need for ventilation by 50%, and deaths by 44%.
  - This would be a good candidate for an oral treatment for non-hospitalized patients.

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

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MEDICAL AGENTS CONTINUED

MONOCLONAL ANTIBODIES

BAMLANIVUMAB+ ETESIVIMAB

- On Nov. 9, 2020, Emergency Use Authorization was given to the drug company Eli Lilly by the FDA for use of Bamalnivimab in the treatment of adult and pediatric patients mild to moderate COVID-19, who are at high risk of progressing to severe COVID-19.
- High risk defined as having:
  - BMI ≥ 35, chronic kidney disease, diabetes, immunosuppression, ≥ 65 years old,
  - ≥ 55-year-old with CVD, HTN, or COPD,
  - 12–17-year-old with BMI ≥ 85th percentile of CDC growth chart, sickle cell disease, heart disease, neurodevelopmental disorders, medical technology dependence, asthma, reactive airway, or other chronic respiratory disease that requires daily meds for control.
- Dosing for Bamlanivimab is a single infusion of 700 mg IV over 60 minutes. It should be given as soon as possible after a positive viral test within 10 days of symptom onset. There are no contraindications.
- There is potential for an infusion reaction to cause anaphylaxis. Discontinue infusion if a serious reaction occurs.B
  - It is not authorized for use in patients who are hospitalized, require oxygen therapy, require an increase in baseline oxygen flow rate due to COVID-19, or are on chronic oxygen therapy due to other comorbidities.
- BLAZE-2 concluded a Phase 3 trial in residents and staff of high-risk nursing and assisted living facilities to test the efficacy of Bamlanivimab (LY-CoV555) in preventing COVID-19 infection. A press release by Eli Lilly on Jan. 21, 2021 stated that patients who received the Bamlanivimab were found to have significantly lower frequency of COVID-19 infections.
  - The trial assigned 965 participants (299 residents and 666 staff) to receive 200mg of either Bamlanivimab or placebo, and then assessed for symptomatic COVID-19 infection 8 weeks later.
- On February 23, 2021, Emergency Use Authorization was given for the use of Bamlanivimab 700 mg and Etesevimab 1,400 mg combo for outpatient treatment of patients with mild to moderate COVID-19 infection who are at high risk of progressing to severe disease and/or hospitalization
  - They recommend against the use of this combination treatment in hospitalized COVID-19 patients, with exceptions for those in clinical trial

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. (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.
- ·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.
- ·According to COVID-19 treatment guidelines, patients who require ICU-level care are recommended against the use of tocilizumab or sarilumab for the treatment of COVID-19, except for clinical trials
- ·On February 2021, a New England Journal of Medicine paper revealed that the use of tocilizumab did not result in significantly better clinical status or lower mortality.
- ·On March 5, 2021, the COVID-19 Treatment Panel updated its recommendations on the use of tocilizumab:
  - They recommend the use of tocilizumab + dexamethasone in certain hospitalized COVID patients who are in rapid respiratory decompensation. These patients include:
    - ICU patients admitted within 24 hours and require respiratory support
    - Recently hospitalized patients (not ICU) with increasing oxygen requirements and have significantly increased markers of inflammation

KINASE INHIBITORS

BARICITINIB

- ·Baricitinib has received EUA approval for treatment of COVID-19 in patients 2 years of age or older as of 11/23/2020
- oThe ACTT-2 trial was published on Dec. 11,2020, which showed that Baricitinib in combination with Remdesvir was more effective in reducing recovery time and accelerating recovery time than Remdesvir alone. The trial group (n=1033) 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.
- ·Patients receiving combination therapy on high-flow oxygen or non-invasive ventilation at enrollment recovered faster (within 10 days versus 18 for control) and there were fewer serious adverse events and infections in the combo cohort. The 28-day mortality was 5.1% in the combination cohort and 7.8 in the control.Baricitinib received EUA for a 4-mg dose for COVID patients.

ADVANCED THERAPY MEDICINAL PRODUCTS (ATMP)

REGEN-COV ANTIBODY COCKTAIL

- · The REACH Trial (COVPN 3502/REGN 2069) is testing the ability to prevent the acquisition of SARS-COV-2 through the combination treatment of casirivimab and imdevimab antibody cocktail.
- · This cocktail is designed to bind the SARS-COV-2 virus and prevent the virus from entering into healthy cells
- · Study enrollment consists of ~3,500 adults and adolescents who share a household with a person who recently tested positive for COVID-19
- ·Preliminary results from Regeneron show decreased viral loads and decreased disease burden, measured by fewer weeks of viral shedding, fewer weeks of high viral load shedding, and fewer total symptomatic weeks.

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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
- 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

AGENTS NO LONGER RECOMMENDED FOR USE

HYDROXYCHLOROQUINE

IVERMECTIN

TENOFOVIR

NIH RECOMMENDATIONS

VACCINE DEVELOPMENT

AUTHORIZED AND RECOMMENDED COVID-19 VACCINES

PFIZER VACCINE

- BioNTech, Pfizer, and Fosun Pharma have developed a two-dose mRNA vaccine that has recently expanded to testing the vaccine on children as young as 12 years old. They have also reported results stating that individuals who received the first dose experienced mostly mild to moderate side effects. The vaccine is reported to be 95% effective. On 12/11/2020, the FDA gave the Pfizer vaccine EUA in the United States. The vaccine is recommended for people aged 16 years and older. Side effects have been mild to moderate, and start within 1-2 after getting the vaccine, but should go away in a few days. Most common side effects reported include pain, swelling, and redness in the injection site and chills, tiredness, and headaches. Side effects such as fevers, chills, tiredness, and headaches are more common after the 2nd dose of the vaccine. Based on clinical trials, The Pfizer-BioNTech vaccine was 95% effective.

MODERNA VACCINE

- oModerna 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. On 11/16/2020, Moderna announced that preliminary data demonstrates that the vaccine is 94.5% effective. Data analysis also indicates that the vaccine may protect against severe disease. On 12/2/2020, Moderna registered a trial to test the vaccine on adolescents 12-18 years of age. On 12/18/2020, the FDA gave the Moderna vaccine EUA in the United States. The vaccine is recommended for people aged 18 years and older. People who are allergic to polyethylene glycol or polysorbate should not get this vaccine. Side effects have been mild to moderate and more common after the 2nd dose. Most common side effects reported include pain, swelling, and redness in the injection site, and chills, tiredness, and headaches. Based on clinical trials, The Moderna vaccine was 94.1% effective.

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VACCINE DEVELOPMENT

AUTHORIZED AND RECOMMENDED COVID-19 VACCINES

JANSSEN VACCINE

- On February 27, 2021, the FDA announced the emergency use authorization (EUA) of the single-dose COVID-19 vaccine developed by Johnson&Johnson. The vaccine is recommended for people aged 18 years and older. The vaccine was 66.3% effective in clinical trials. People had most protection 2 weeks after getting the vaccine. This vaccine had high efficacy in preventing hospitalizations and death in people who did not get sick. This vaccine may provide protection against asymptomatic infection.

COVID-19 VACCINES IN PHASE 3 CLINICAL TRIALS

ASTRAZENCA VACCINE

- AstraZeneca and the University of Oxford have developed a vaccine called ChAdOx1. After halting global trials in September due to a volunteer who had developed transverse myelitis, the FDA authorized the restart of the trial on October 23.

NOVAVAX VACCINE

- Novavax is a vaccine based on the genetic sequence of the SARS-CoV-2 and does not contain any live or inactivated virus. It was created using Novavax's nanoparticle technology and contains a patented adjuvant (Matrix-MTM) for immune boosting and neutralizing antibody stimulation, allowing a stronger immune response at a lower vaccine dose. In November 2020, they recently started Phase 3 trials in adults 18 years and older in the United States and Mexico. The trial has also been opened at UT Health Antonio, and study participants will be followed for 2 years.

INTERNATIONAL COVID-19 VACCINE STUDIES

- The Murdoch Children's Research Institute is conducting a Phase 3 trial in Australia to see if the BCG vaccine partly protects against COVID-19.
- CanSinoBIO, the Gamaleya Research Institute, Bektop, 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 10/24/2020.