

COVID-19: Therapeutics

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LEARNING OBJECTIVES

At the end of this lecture, the learner will be able to:

1. Recognize that the importance of steroids for COVID-19 patients who are hospitalized and have an oxygen requirement
 2. Recognize that there is no evidence to use Chloroquine, Hydroxychloroquine or Convalescent plasma
 3. Limit use of nebulizers because it can aerosolize virus
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LECTURE OVERVIEW

- I. Stages of COVID-19
 - II. Therapeutics
 - III. Inhaled Bronchodilators
 - IV. Fluid Resuscitation
 - V. Vasopressors for Septic Shock
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I. STAGES OF COVID-19

- Beginning: Viral replication
 - Use antiviral therapy
 - Later: Severe inflammatory response
 - Use immunomodulation/immune suppression therapy
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II. THERAPEUTICS

1. Corticosteroids

- Dexamethasone

- o Mortality benefit in hospitalized COVID-19 patients who need supplemental oxygen or mechanical ventilation (RECOVERY trial)
 - Dose: 6 milligrams once per day (IV or PO) for 10 days
 - o Beneficial in patients who are also having an asthma or COPD exacerbation
 - o Decreases the number of days on the ventilator in mechanically ventilated COVID Acute Respiratory Distress Syndrome (ARDS) patients (CODEX trial)
 - Dose: 20 mg/day for 5 days then 10 mg/day for 5 days or until ICU discharge
 - o Still ongoing research about the optimal dose
- Methylprednisolone
 - o Mortality benefit in patients on ventilator when compared to Dexamethasone and usual treatment
 - o Mortality benefit in hypoxic non-intubated patient when compared to usual treatment
 - Dose: 1 mg/kg/day for ≥ 3 days
 - Single center small retrospective study
- Other steroids
 - o If dexamethasone or Methylprednisolone are not available, then use another steroid such as Betamethasone, Prednisone or Hydrocortisone [4].
 - o Here are the following steroid equivalents to Dexamethasone 6 mg
 - Betamethasone: 6 mg
 - Methylprednisolone: 32 mg
 - Prednisone: 40 mg
 - Hydrocortisone: 160 mg
 - o Haven't been robust studies on other steroids
- Steroids can precipitate strongyloides hyperinfection syndrome (SHS) [5]
 - o If your patient is at high risk for strongyloides infection, consider starting empiric Ivermectin before starting steroids to prevent precipitatin of SHS
 - o There are two published case reports of strongyloides hyperinfection syndrome in COVID patients on steroids
- Inhaled Budesonide

- o Small trial, with 139 participants showed that early administration of inhaled budesonide reduced need for emergency medical care in COVID-19 patients (STOIC trial) [6].
- o Dose: 400 ug per puff
- o Frequency: Two puffs twice a day until symptoms resolved

2. Tocilizumab

- IL-6 inhibitor
- Mortality benefit when added to dexamethasone in hypoxemic hospitalized patients with a C-reactive protein >75 (REMAP-CAP and RECOVERY trials) [7,8]
- Dose: 8 mg/kg of actual body weight, up to 800 mg IV once

3. Remdesivir

- Trials have shown conflicting results [9-12]
- The World Health Organization (WHO) doesn't support its use
- The National Institutes of Health (NIH) in the USA suggest using it in hospitalized patients who need oxygen
- Consider using it in hospitalized patients
- Dose: 200 mg IV once, followed by 100 mg IV daily to complete a five-day course

4. Monoclonal antibodies

- Bamlanivimab or Casirivimab plus Imdevimab [13]
 - o Consider use in outpatients who have high risk of clinical progression and if diagnosis is within 10 days
 - o Don't use in hospitalized patients

5. Convalescent plasma

- Randomized controlled trials have shown that convalescent plasma doesn't work for COVID-19 [14]
- We do not recommend its use

6. Hydroxychloroquine and Chloroquine

- Clinical trials have shown no clear benefit to use of Hydroxychloroquine or Chloroquine and can cause harm [15,16]
- We do not recommend their use

7. DVT Prophylaxis in hospitalized patients

- COVID-19 patients are hypercoagulable, therefore, DVT prophylaxis is recommended for hospitalized patients [17]. Follow your local protocol/guidelines.
- Continue unless platelets $< 30 \times 10^9/\text{Liter}$

8. **Antibiotics**

- COVID and Bacterial co-infection on initial presentation
 - o Uncommon, only 3.5% [18]
 - o Do not routinely start empiric antibiotics
 - COVID and Bacterial Secondary infection
 - o Patients who are very sick, are intubated and have long hospital stays have a 14.3% chance of getting a secondary bacterial infection [18]
 - o Consider antibiotics if there is clinical concern
 - o To help decide if you have a bacterial co-infection, look for a focal consolidation on chest x-ray, also obtain blood, sputum and urine cultures as well as procalcitonin
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III. INHALED BRONCHODILATORS

1. **Indication:** if bronchospasm is present (i.e. Chronic Obstructive Pulmonary Disease (COPD) or Asthma exacerbation)
2. **Medication:** Albuterol and Ipratropium
3. **Route of Administration**
 - o **Metered Dose Inhaler (MDI)**
 - Preferred over nebulizer because **MDI doesn't aerosolize virus**
 - 8 puffs are equivalent to 1 nebulizer treatment
 - 8 puffs with a spacer every 20 minutes, 4 breaths in between puffs (see video for demonstration)
 - o **Nebulization treatment**
 - Higher risk of aerosolization of virus, increasing viral transmission, therefore, avoid if possible [19]
 - Use in negative pressure room, if not available, use in well ventilated room
4. **Albuterol dosing**
 - o Intermittent: 2.5-5 mg every 20 minutes for 3 doses, then 2.5-10 mg every 1-4 hours as needed

-OR-

- o Continuous: 0.5 mg per kg per hour (maximum 15mg/hour)

5. **Ipratropium** dosing

- o 0.25-0.5 mg every 20 minutes for 2-3 doses
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IV. FLUID RESUSCITATION

1. Fluid of choice: crystalloids (examples: normal saline, lactated ringer)
 2. Remember #1 problem in COVID-19 is hypoxemic respiratory failure, which can become worse when given fluids
 3. **Initial Resuscitation of hypotensive COVID-19 patient** [17,20]
 - o Give fluid bolus: 500 mL
 - o Check for fluid responsiveness
 - Capillary refill
 - Skin temperature
 - Heart rate
 - Mental status
 - Lactate (if available)
 - o If fluid responsive, repeat above steps
 - o If not fluid responsive and still hypotensive, start vasopressors
 4. **Post-resuscitation fluid management**
 - o Target a normal fluid volume for patient
 - o Lower amount of fluids
 - o Avoid continuous fluids
 - o If patient has a positive fluid balance, consider diuretics
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V. VASOPRESSORS FOR SEPTIC SHOCK

1. Titrate vasopressors to a mean arterial pressure (MAP) of 65 mmHg
2. **Norepinephrine(NE)/Noradrenaline**
 - o 1st line if available
3. **Vasopressin**
 - o Use if NE is not effective alone by adding as 2nd vasopressor if NE is at maximum dose

4. **Epinephrine (Adrenaline)**

- o Use if NE with or without Vasopressin is not available or effective
- o Use as 3rd vasopressor if NE and Vasopressin are at maximum dose

5. **Dopamine**

- o Only use if other vasopressors are not available

SUMMARY

- **Steroids** (use one of the following)
 - **Dexamethasone**: Use if require oxygen or mechanical ventilation. Decreases mortality
 - **Methylprednisolone**: Use if require oxygen or mechanical ventilation. Decreases mortality
- **Tocilizumab**: Use if on dexamethasone, require oxygen and CRP > 75
- **Remdesivir**: Consider in hospitalized patients
- **Monoclonal antibodies**: Consider in outpatients
- Do not use hydroxychloroquine, chloroquine or convalescent plasma
- Do not use nebulizer
- If in septic shock, give 500 mL to 1 L of fluids, check for fluid responsiveness, if responsive, repeat this step, if not responsive, start vasopressors and stop fluids

ADDITIONAL INFORMATION

Asthma and COPD Treatments

1. **Asthma exacerbation**

- o Steroids
 - Dexamethasone
 - 0.6mg/kg IV or by mouth (maximum 16mg); 2nd dose 24 hours later
 - Prednisone
 - 40-80mg/day in one or two divided doses for 5 days
 - Methylprednisolone
 - 1mg/kg IV every 4-6 hours
- o Albuterol/Ipratropium

- *See above in inhaled therapeutics*
- o Magnesium
 - 25-75 mg/kg over 30 minutes (2-3 grams IV needed in most adults)
- o Epinephrine (adrenaline) -OR- Terbutaline
 - Consider if unresponsive to the above treatments
 - Epinephrine (adrenaline): 0.01 mg/kg (max 0.5mg) of the 1 mg/mL concentration subcutaneous or intramuscular every 20 minutes for up to 3 doses
 - Terbutaline: 0.25 mg subcutaneous or intramuscular every 20 minutes for up to 3 doses

2. **COPD exacerbation**

- o Steroids
 - Methylprednisolone 1-2 mg/kg IV daily
 - Prednisone 60 mg on day 1, then 40mg PO daily for 5 additional days
 - o Albuterol/Ipratropium
 - *See above in inhaled therapeutics*
 - o Antibiotics
 - Give if patient has thick phlegm in sputum, increased sputum production, or needs noninvasive positive pressure ventilation
 - Antibiotic choice per local recommendations. Example therapies are listed below.
 - Outpatient and healthy give a 3-5 day course of
 - Azithromycin -OR-
 - Doxycycline
 - Outpatient and unhealthy (age >65 years, known cardiac disease, >3 asthma/COPD exacerbations per year)
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