Bon Secours Mercy Health
Use of Therapies for Treatment of COVID-19 Disease

NOTE: most data is likely to be extrapolated from other coronaviruses
This is a living document and will continuously be updated
4/8/20 update
This is not meant to endorse any specific treatment or even any anti-viral therapy at all
Supportive care is the current standard of care.

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Questions? Email Josh Crawford at Joshua_crawford@bshsi.org

I. Potential Treatment Algorithm for COVID-19

Table 1. Factors associated with severe COVID-19
Age > 65 years
Age > 40 and chronic cardiovascular, diabetes, pulmonary, hepatic, renal, hematologic or neurologic conditions
Requiring ICU admission +/- poor O2 saturation (<93% on RA) or mechanical ventilation
Immunocompromised
Residents of nursing homes, long term care facilities, group homes
Lab findings: D-dimer ≥ 1mcg/mL, LDH > 250 U/L, CRP > 40, and/or ferritin > 300mcg/L, Fever > 39°C (102.2°F), elevated troponin

Hydroxychloroquine	Lopinavir/Ritonavir	Ribavirin	Azithromycin
400mg PO BID x 1 day, then 200mg PO BID x 4 days	Lpr 400mg/r 100mg PO BID x 14 days	1200mg PO BID x 13 days	500mg IV/PO x1 then 250mg IV/PO x 4 doses

Figure 1. Potential Treatment Algorithm for COVID-19

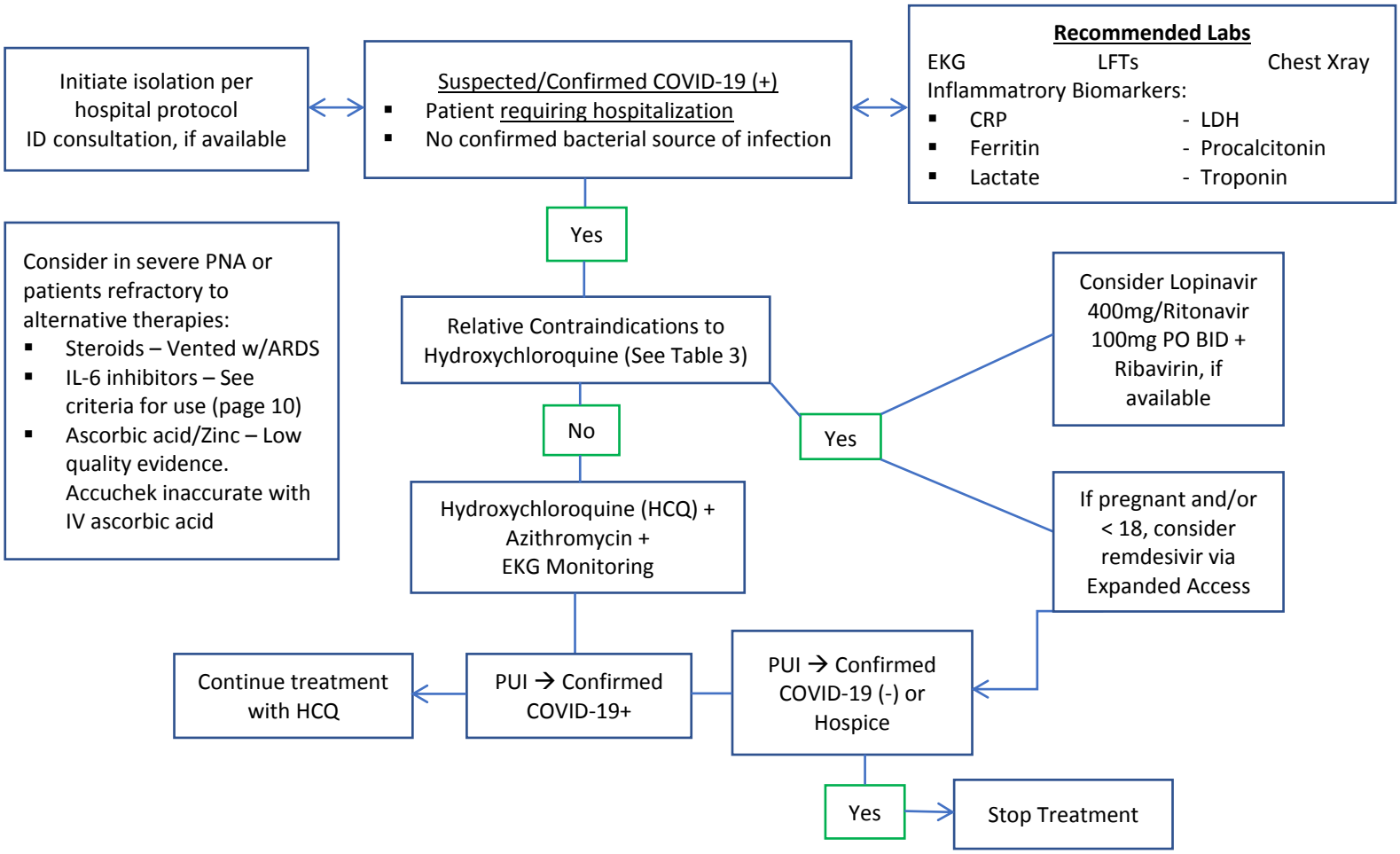

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Table 3. Relative Contraindications to Hydroxychloroquine (HCQ)
▪ QTc > 500msec ▪ Drug interactions - consult pharmacy ▪ Myasthenia gravis ▪ Porphyria ▪ Retinopathy ▪ Epilepsy ▪ Known G6PD Deficiency (do not test empirically or delay HCQ for this test)

Table 4. Remdesivir Criteria - https://rdvcu.gilead.com/ - Pregnant and < 18 years of age only	
Key Inclusion criteria: ▪ Hospitalization ▪ Confirmed SARS-CoV-2 by PCR ▪ Mechanical Ventilation	Key Exclusion criteria: ▪ Evidence of multi-organ failure ▪ Pressor requirement to maintain blood pressure ▪ ALT levels > 5 X ULN ▪ Cr Clearance <30 mL/min or dialysis or CVVH

Table 5. Clinical Considerations
▪ As these treatments are in high demand, shortages of the above medication are occurring and supply may be limited ▪ Corticosteroids are not currently recommended for COVID-19 unless other compelling indications exist ▪ No pharmacologic option listed has proven clinical efficacy in the management of COVID-19 ▪ To date, data does not exist supporting pharmacologic prophylaxis for COVID-19 exposure

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Ia. Chloroquine/Hydroxychloroquine

- Hydroxychloroquine
  - Overview
    - Traditionally an anti-malarial agent, should have similar activity on viruses as chloroquine (see MOA of chloroquine below)
    - Widely available in the USA, inexpensive
    - Not as well studied as chloroquine in coronavirus treatment (in vitro)
  - Clinical Data
    - Found to be more potent than chloroquine
    - Generally better tolerated than chloroquine (especially at high doses)
      - Less risk of retinopathy
    - Precautions:
      - Pregnancy - Association with fetal ocular toxicity in animal studies and secreted in breast milk
      - Known G6PD deficiency
    - Suggested dosing: 400mg PO BID on day 1, 200mg PO BID x 4 days (total 5 days)
    - Only available in PO formulation
      - Suspension can be made (see page 4) BUD is 30 days
      - ERX # 3100567 in CC, ERX 4081815 in CP
- Chloroquine phosphate
  - Overview
    - Chloroquine, a widely-used anti-malarial and autoimmune disease drug, has recently been reported as a potential broad-spectrum antiviral drug. Chloroquine is known to block virus infection by increasing endosomal pH required for virus/cell fusion, as well as interfering with the glycosylation of cellular receptors of SARS-CoV. Besides its antiviral activity, chloroquine has an immune-modulating activity, which may synergistically enhance its antiviral effect in vivo. Chloroquine is widely distributed in the whole body, including lung, after oral administration. The EC_{90} value of chloroquine against the 2019-nCoV can be clinically achievable in patients who receive 500 mg administration.
    - Traditionally an anti-malarial agent, but known to block viral infections by increasing endosomal pH required for virus/cell fusion; interferes with glycosylation of cellular receptors of SARS-CoV[2].
    - Commercially-available in the USA, but limited supply, next resupply expected for late March.
  - Clinical Data
    - The first results obtained from more than 100 patients showed the superiority of chloroquine compared with treatment of the control group in terms of reduction of exacerbation of pneumonia, duration of symptoms and delay of viral clearance, all in the absence of severe side effects. This has led in China to include chloroquine in the recommendations regarding the prevention and treatment of COVID-19 pneumonia
    - Multiple studies have demonstrated *in vitro* effectiveness against a variety of coronaviruses
    - Dosing data is available (500mg PO BID x 10 days) – Recommended by Italian and Chinese infectious diseases societies and government

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Hydroxychloroquine Criteria for Use During COVID-19 Epidemic

Confirmed/suspected COVID-19 (+)

- Patient requiring hospitalization with factors associated with severe illness (see factors below)
  - No other confirmed viral pathogen
  - No confirmed bacterial source of infection

Table 1. Factors associated with severe COVID-19
Age > 65 years
Age > 40+ and chronic cardiovascular, pulmonary, hepatic, renal, hematologic or neurologic conditions
Requiring ICU admission +/- poor O2 saturation (<93% on RA) or mechanical ventilation
Immunocompromised
Residents of nursing homes or long term care facilities
Lab findings: D-dimer ≥ 1mcg/mL, LDH > 250 U/L, and/or ferritin > 300mcg/L, fever > 102.2°F (39°C)

- **Retail pharmacy restrictions:**
  - **Previously hospitalized patients with confirmed/suspected COVID-19+ infections who are finishing their course of hydroxychloroquine following hospital discharge**
  - **Patients with a history of using hydroxychloroquine for maintenance of chronic disease (such as RA, sickle-cell anemia, etc).**
  - **Follow applicable state laws on quantity and day supply restrictions**
- Board of Pharmacy regulatory updates
- On March 22, the State of Ohio Board of Pharmacy to filed emergency rule 4729-5-30.2 of the Administrative Code, which reads:
  - No prescription for chloroquine or hydroxychloroquine may be dispensed by a pharmacist or sold at retail by a licensed terminal distributor of dangerous drugs unless all the following apply:
  - The prescription bears a written diagnosis code from the prescriber; and
  - If written for a COVID-19 diagnosis, the diagnosis has been confirmed by a positive test result, which is documented on the prescription and both of the following apply:
    - The prescription is limited to no more than a fourteen-day supply; and
    - No refills may be permitted unless a new prescription is furnished.
- On March 25, Virginia BOP required the following:
  - Prescriptions for chloroquine, hydroxychloroquine, mefloquine and azithromycin should be restricted in the outpatient setting and should require a diagnosis “consistent with the evidence for its use.”
  - Community pharmacists should use professional judgement to determine whether a prescription is valid and that there is a bona fide practitioner-patient relationship prior to dispensing.
  - Prioritize treatment for continuation of existing medication therapy, inpatient settings, and other indications where there is not an alternative therapy.
  - Advise against hoarding these medications or stockpiling.
- Do not dispense a “go-pack” containing hydroxychloroquine, lopinavir/ritonavir, or inhalers from the ED for patients being discharged home with suspected COVID
- Once PUI test results, if negative, discontinue treatment immediately
- If patient enters hospice care, discontinue treatment immediately

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Hydroxychloroquine Sulfate Oral Suspension 25 mg/mL

Ingredients:

Hydroxychloroquine 200 mg tablets	15 tablets
Ora-Plus	60 mL
Sterile Water for Irrigation	QS AD 120 mL

Preparation:

Remove coating of hydroxychloroquine tablets with alcohol swab. Crush tablets in a mortar; triturate to a fine powder and levigate with 15 mL Ora-Plus to form a viscous, but smooth and uniform paste. Add remaining 45 mL Ora-Plus in increasing amounts while mixing thoroughly. Transfer contents to graduated cylinder. Rinse mortar and pestle with sterile water for irrigation and pour into graduated cylinder until almost final volume. QS to 120 mL with sterile water for irrigation. Stir well.

Additional Information:

Dispense in amber bottle
Shake Well
Refrigerate

Storage:

Refrigerate

Expiration Date:

30 days

References:

Pesko LJ. Compounding: Hydroxychloroquine. *Am Druggist*. 1993; 207-257.
Nahata MC, Pai VB, Hipple TF. Hydroxychloroquine. Pediatric Drug Formulations 2004; (5): 145.

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Ib. Remdesivir – See research

- Overview
  - Anti-viral agent that has shown to be effective against MERS-CoV, SARS-CoV, which are related to SARS-CoV-2 (Causes COVID-19)
  - May be effective against COVID-19. This drug is not commercially available but we have worked to identify how to obtain from the manufacturer and built the drug records in Epic so we are prepared to use. There would be no direct cost to obtain but it would take a lot of time equity to participate in clinical trials.
  - Has shown superior efficacy to lopinavir/ritonavir + ribavirin which led to better outcomes in the treatment of MERS-CoV.
  - Not commercially-available in the USA
    - **Expanded Access program** (see below)
      - Gilead may accept patients via expanded use program – Pregnant or < 18 only
      - Reports note it can take 3-6 days to receive drug therapy
      - IRB approval is required for use in Expanded Use program
    - Available via clinical trials, but BSMH does not have any sites nerolled in a trial
  - Dosing: Intravenous (IV) infusion of 200mg loading dose on day 1, followed by 100mg daily doses for 9 days
  - Preparation and administration:
    - Each single-use vial contains 100mg of remdesivir
    - Reconstitute each vial with 19 mL sterile water for injection for a concentration of 5 mg/mL
    - Further dilute into 0.9% Normal Saline for intravenous infusion with total volume of up to 250 mL
    - Administer over 30 - 60 minutes
    - After administration is complete, flush the IV line with at least 30 mL of 0.9% normal saline
  - Storage:
    - Up to 4 hours at room temperature
    - Up to 24 hours at refrigerated temperature
  - Acquisition via Expanded Access Program with the following requirements:
    - Patient must be hospitalized with confirmed COVID-19 infection with significant clinical symptoms

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  - Contact Gilead (https://rdvcu.gilead.com/) and submit the following information:
    - Requestor's name/phone/email
    - Requesting physician's name/institution, contact info, address
    - Patient information (initials, DOB, sex, brief description of clinical course, imaging results, oxygen requirements, certain lab values)
      - Other information: Pregnancy status, confirmation of SARS-CoV-2 infection, intubation/ventilation status, ECMO requirements, vasopressor requirements, current therapy including other potential treatments for COVID-19

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        - Hospital pharmacy name, contact info, address
            - Note must be able to receive drug 24 hours a day
        - At the conclusion of the drug's use, sumit a request to withdraw the EIND
    - Helpful websites
        - Emergency Investigational New Drug Applications for Antiviral Products
        - Gilead Expanded Use and Access to Investigational Medicines

    - Connect Care Build
        - ERX 5000501 - REMDESIVIR 100 MG IV INJECTION
        - Custom NDC - 11111-501-01
        - ERX 5000502 - REMDESIVIR IVPB
        - OSQ 386870 – RX Remdesivir Ordering Panel
    - Carepath Build: Search terms: "Remdesivir", "COVID-19" "COVID19", "COVID 19", "COMPASSIONATE", "CORONA VIRUS"

- Pros
    - Potentially effective in treatment of COVID-19 infections
    - Available in IV form, so can use in patients who are NPO
    - No direct cost to obtain the medication (although time to obtain via Expanded use and a clinical trial are substantial)
    - If enrolled in one of three clinical trials, may have access to the results early from across the world to gauge effectiveness
        - If enrolled in clinical trial, we would likely have drug on hand, which prevents a delay in treatment of confirmed cases
- Cons
    - Only available for Extended Use from manufacturer for patients meeting the following criteria:
        - Patients < 18 years of age and/or Pregnant
        - No BSMH hospital is currently enrolled in a clinical trial with remdesivir

Ic. Lopinavir/ritonavir (Kaletra)

Overview

- Lopinavir/Ritonavir (LPV/r) is a combination of protease inhibitors typically used in HIV, including post-exposure prophylaxis (lopinavir is the actual antiviral agent, with ritonavir functioning to inhibit metabolism of lopinavir, thereby boosting levels of lopinavir)
- *In vitro*, Lopinavir/Ritonavir has activity against SARS-CoV-1 and functions *synergistically* with ribavirin (the addition of ribavirin increases Lopinavir's potency four-fold). Ribaviron dose = 4 g oral loading dose followed by 1.2 g every 8 hours x 14 days.
- *In the two studies in which* LPV/r was effective (albeit retrospective trials) it was combined with IV/PO ribavirin (IV not available in US). The LPV/r dose used in these studies was 400mg/100mg twice daily.
- In a recent study from Singapore in 18 patients with COVID-19, LPV/r was dosed at 200mg/100mg (which is a dose we could not make in USA as it only comes in 200mg/50mg strength) and patients did well. No patients died, one (5%) patient was intubated, five experienced hypoxemia (28%) and some carried the virus as demonstrated by nasopharyngeal viral load for up to 24 days. In prior MERS studies, viral clearance was demonstrated. Please note, LPV/r was given at a lower dose and NOT with ribavirin.

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Id. Azithromycin (Zithromax)

- Macrolide antibiotic with activity against gram-positive, gram-negative and atypical bacterial pathogens.
- Treatment of COVID-19
    - Twenty (20) confirmed COVID-19 positive hospitalized patients were treated with hydroxychloroquine (200mg PO TID) and compared with 16 patients who were not treated with a targeted anti-viral agent.
    - Of these 20 patients, azithromycin (AZ) was added to hydroxychloroquine (HCQ) in six (6) patients confirmed positive for COVID-19 in France.
    - In this trial, 5 of 26 patients (20%) originally stratified to the hydroxychloroquine treatment group died or went to the ICU and were not included in the analysis.
    - When comparing the effect of HCQ treatment as a single drug and the effect of HCQ and AZ combination, the proportion of patients that had negative PCR results in nasopharyngeal samples was significantly different between the two groups at days 3, 4, 5 and 6 post-inclusion. At day 6 post-inclusion, 100% of patients treated with HCQ and AZ combination were virologically cured comparing with 57.1% in patients treated with HCQ only, and 12.5% in the control group ($p<0.001$).
    - The HCQ + AZ group had significantly lower baseline viral loads compared with HCQ group.
- **Summary: Small study, HCQ + AZ group had a lower baseline viral load, which may have skewed results in its favor. No clinical data reported in this study. 20% of patients in the intent-to-treat group were removed from the study, so the population severity was relatively mild.**
- Risk of Torsades de Pointes (TdP) arrhythmia: 116 healthy subjects who received either chloroquine (1000 mg) alone or in combination with oral azithromycin (500 mg, 1000 mg, and 1500 mg once daily). Co-administration of azithromycin increased the QTc interval in a dose- and concentration-dependent manner. In comparison to chloroquine alone, the maximum mean (95% upper CI) increases in QTcF were 5 (10) ms, 7 (12) ms and 9 (14) ms with the co-administration of 500 mg, 1000 mg and 1500 mg azithromycin, respectively.
    - Patients receiving both hydroxychloroquine and azithromycin concomitantly should be placed on telemetry monitoring.

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Ie. Interleukin-6 (IL-6) Inhibitors

- Emerging evidence suggests that hyperinflammation, as seen in cytokine storm syndromes, can contribute to the severity of COVID-19. Inflammatory stimuli increase circulating IL-6 levels, leading to further cytokine release. A recent multicenter, retrospective study of 150 COVID-19 patients in Wuhan, China identified elevated IL-6 levels as a predictor for fatality. Tocilizumab (Actemra) and sarilumab (Kevzara) are IL-6 inhibitors being investigated in COVID-19 patients for virally-induced hyperinflammation.
  - **Per clinician's discretion, if the patient is rapidly deteriorating consider using an IL-6 inhibitor earlier in the treatment course than later.**
  - **Therapy needs to be prioritized for patients when cytokine storm is first recognized who also have a reasonable chance of survival.**

<table>
<tr><td colspan="3">Tocilizumab (Actemra) or Sarilumab (Kevzara) - Adjunct to standard of care and antiviral therapy</td></tr>
<tr>
<td><u>INCLUSION Criteria</u>
Consider adding to antiviral therapy for patients meeting <u>all 3 criteria below</u>:
1. Hospitalized COVID-19 positive patient
2. One of the following respiratory findings:
• Rapidly worsening respiratory gas exchange
• Radiographic infiltrates by imaging (chest x-ray, CT scan, etc.),
• SpO2 ≤93% on room air OR greater than 6 L/min O2
3. One of the following laboratory findings:
• Elevated serum IL-6
• Ferritin >300 ug/L (or surrogate) with doubling within 24 hours
• Ferritin >600 ug/L at presentation and LDH >250
• D-dimer > 35

<u>EXCLUSION Criteria</u>
• Unlikely survival
• ALT / AST > 5 x ULN
• Known TB or history of incompletely treated TB
• Current suspected or known active bacterial, other viral, or fungal infection (untreated)
• History Diverticulitis (unless family/patient signs waiver)
• Pregnancy (unless family/patient signs waiver)
• Active chemotherapy</td>
<td>DOSING

Should be ordered via shared decision making by critical care and infectious diseases physicians on the patient's treatment team

Tocilizumab (Actemra)
▪ Dose: 400mg IVPB
▪ Duration: 1 dose
▪ Consider giving additional dose 8-12 hours later if continued clinical decompensation

Kevzara (sarilumab)
▪ Dose: 200mg SQ
▪ Duration: 1 dose
▪ Consider use if cannot obtain Tocilizumab (Actemra)</td>
<td>Adjunct therapy may improve oxygenation and time to symptom resolution in patients at high risk of cytokine storm.

<u>Contraindications:</u>
▪ Avoid in pregnancy
▪ Not recommended during breastfeeding

<u>Adverse effects:</u>
▪ Gastrointestinal perforation
▪ Anemia
▪ Hepatitis
▪ Infusion reaction</td>
</tr>
</table>

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Actemra (tocilizumab)

- **Xu H, Han M, Li T, et al. Effective Treatment of Severe COVID-19 Patients with Tocilizumab (2020)**
  - http://www.chinaxiv.org/abs/202003.00026
  - **Methods:** This is a recent retrospective trial of 21 patients in Wuhan, China with severe COVID-19. The diagnosis of severity was defined by the presence of any of the following criteria: 1) respiratory rate ≥30 breaths/min, 2) SpO2 ≤93% on room air, and 3) PaO2/FiO2 ≤300 mmHg; a case was critical if the patient met any of the following criteria 1) respiratory failure requiring mechanical ventilation, 2) shock, 3) combined with other organ failure, and required ICU admission. Patients received the standard of care per the Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia: lopinavir, methylprednisolone, and agents for symptomatic control as well as supportive care, with the addition of tocilizumab 400mg IV as a one-time dose (3 patients received a second 400 mg dose due to fever within 12 hours). An IL-6 test was conducted in all study participants to confirm increased levels of IL-6. Treatment was analyzed between February 5 and February 14, 2020 (10 days of therapy). Clinical manifestations, CT imaging, and laboratory data were then evaluated retrospectively.
  - **Results:** Researchers reported that the temperature of all patients returned to normal the first day after receiving tocilizumab. 75% of patients (15 of 20) required less oxygen intake; one patient no longer required oxygen therapy. CT imaging improvements were noted in 90.5% (19 of 21) patients. Further, researchers reported a significant change in lymphocyte levels following administration of tocilizumab; within five days, a lower percentage of lymphocytes was observed in 85% (17 of 20) patients and returned to normal in 52.6% of those patients (10 of 19). This is an important finding, as a study of 138 COVID-19 patients in Wuhan found the percentage of lymphocytes to be an important indicator for diagnosis and severity of COVID-19. Additionally, CRP decreased significantly and returned to normal in 84.2% of patients on the fifth day following tocilizumab treatment. White blood cell count increased initially following treatment and normalized by day five of treatment with only two of the nineteen patients.
  - Nineteen (90%) patients were discharged, including two critical patients. The remaining study subjects were kept in the hospital; however, it was noted that these patients were afebrile, and their symptoms had improved.
  - No adverse effects due to tocilizumab or secondary pulmonary infections were noted. Additionally, there were no reports of worsening illness or death.
  - The researchers concluded that due to symptomatic improvement, tocilizumab is efficacious in treating COVID-19 patients. Of note, due to the small study size and low external validity, the authors suggested further studies need to be completed to confirm this recommendation.
  - See research section at end of document for more information on potential clinical trials
- Preparations Available in US:
  - Available as brand name Actemra only. Available in 3 formulations, IV solution (Actemra IV), Auto-Injector Pen (Actemra ACTPen, Subcutaneous) and a Prefilled syringe (Actemra Subcutaneous). Actemra IV comes in 80mg/4mL, 200mg/10mL and 400mg/20mL containers. Both the syringe and auto-injector come as 162mg/0.9mL. IV formulation recommended for COVID-19 patients.
- Dosing:
  - Per trial: 400 mg IV once
  - If clinical improvement does not occur after the 1st dose, may administer up to 3 additional doses. Must be administered at least 8 hours after the last dose, however some studies have

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recommended waiting 12 hours in COVID-19 patients. May be used as a monotherapy or in combination with corticosteroids.
    - https://www.chinalawtranslate.com/wp-content/uploads/2020/03/Who-translation.pdf
- Preparation and administration:
    - IV: Should reach room temperature prior to administration. Tocilizumab should be infused over 60 minutes with a dedicated IV line. No other agents should be given through the same line. No IV push, no bolus. If additional doses are necessary, 8 hours must elapse from prior dose. Do not use if there are opaque particles present or if there is any discoloration.
    - May be diluted to 100 mL by slowly adding NS or ½ NS. Withdrawal equal volume of NS or ½ NS to the volume of tocilizumab required for selected dose. Slowly add tocilizumab to the infusion bag/bottle. Gently invert to mix to avoid potential foaming. Diluted solutions are compatible with any of the following: polypropylene, polyethylene, polyvinyl chloride and glass containers. Be sure to allow solution(s) to reach room temperature before administration.
- Storage: Intact vials, prefilled syringes and auto injectors should be refrigerated at 2°C-8°C (NOT to be frozen). Should be protected from light. Solutions that are diluted in NS for administration may be stored in refrigerator or room temperature for 24 hours. Solutions diluted in ½ NS should be stored in the refrigerator for 24 hours or at room temperature for 4 hours. If any product is remaining in the vial, it should be discarded.
- Acquisition Cost: 400mg (20mg/mL) = $2,248.16
- Pros
    - Mortality benefit demonstrated in one small study
    - Promising discharge rate
    - No documented severe adverse reactions
- Cons
    - Limited number of patients in study
    - Cost
    - Low external validity

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Kevzara (sarilumab):

- Preparations Available in the US:
  - Solution available in Auto-Injector and Prefilled Syringe formulations which are both 150mg/1.14 mL and 200 mg/1.14 mL. Kevzara is available as a brand only formulation.
- Dosing:
  - For Rheumatoid arthritis, it is dosed at 200 mg once every 2 weeks. **Note**: Do not use if ANC <2000, platelets <150,000 or if ALT/AST are >1.5x ULN.
- Preparation and Administration:
  - **RA**: Sarilumab should be administered subcutaneously with standard rotation of injection sites. Prefilled syringes and pens should be allowed to get to room temperature for 30-60 minutes. Do not warm in any other way. Solution should be clear and colorless to pale yellow. Do not shake medication prior to use. Ensure to administer the entirety of the syringe/pen. Do not inject into tender, damaged, scarred or bruised skin.
  - **COVID-19:** Sarilumab is being utilized IV for the treatment of SARS-CoV2. This is based on clinical trials and has limited data about the use of IV administration of sarilumab.
- Storage:
  - Sarilumab should be stored at 2°C-8°C (Not frozen or shaken). May store above 25°C for ≤14 days. After sarilumab is removed from the refrigerator, it must be used within 14 days.
- **Acquisition cost: 200mg SQ syringe = $1,696.23**
- Pros:
  - Sarilumab is in the same therapeutic class as tocilizumab and thus it is hoped to provide a similar mortality benefit.
- Cons:
  - Cost
  - Not yet studied in COVID-19
  - Unknown optimal dose
  - Only available as SQ formulation (although clinical trial uses an IV formulation)

<u>Interluekin-6 (IL-6) Inhibitors References:</u>

1. Mehta P, McAuley DF, Brown, M, et al. COVID-19: consider cytokine storm syndromes and immunosuppression. *The Lancet.* 2020 March 16. [cited 2020 March 20]. Available From: https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)30628-0/fulltext?rss=yes
2. Xu H, Han M, Li T, et al. Effective Treatment of Severe COVID-19 Patients with Tocilizumab. *ChinaXiv.* 2020 March 3. [cited 2020 March 20]. Available from: http://www.chinaxiv.org/abs/202003.00026
3. Roche initiates Phase III clinical trial of Actemra/RoActemra in hospitalized patients with severe COVID-19 pneumonia. *F. Hoffmann-La Roche Ltd*. 2020. [cited 2020 March 20]. Available from: **https://www.roche.com/media/releases/med-cor-2020-03-19.htm**
4. Lexi-Comp: [Internet]. Toclizumab. Hudson OH: Lexi-Comp. c1978-2019 [Updated ; cited 2020 March 20]. Available From: http://online.lexi.com.onu.ohionet.org/lco/action/search?q=tocilizumab&t=name&va=tocliz
5. Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia (Trial Version 7). *National Health Commission & State Administration of Traditional Chinese Medicine.* 2020 March 3 [Cited 2020 March 20]. Available from: https://www.chinalawtranslate.com/wp-content/uploads/2020/03/Who-translation.pdf
6. Regeneron. An adaptive phase 2/3, randomized, double-blind, placebo-controlled study assessing efficacy and safety of sarilumab for hospitalized patients with COVID-19 (NCT04315298). Available from:

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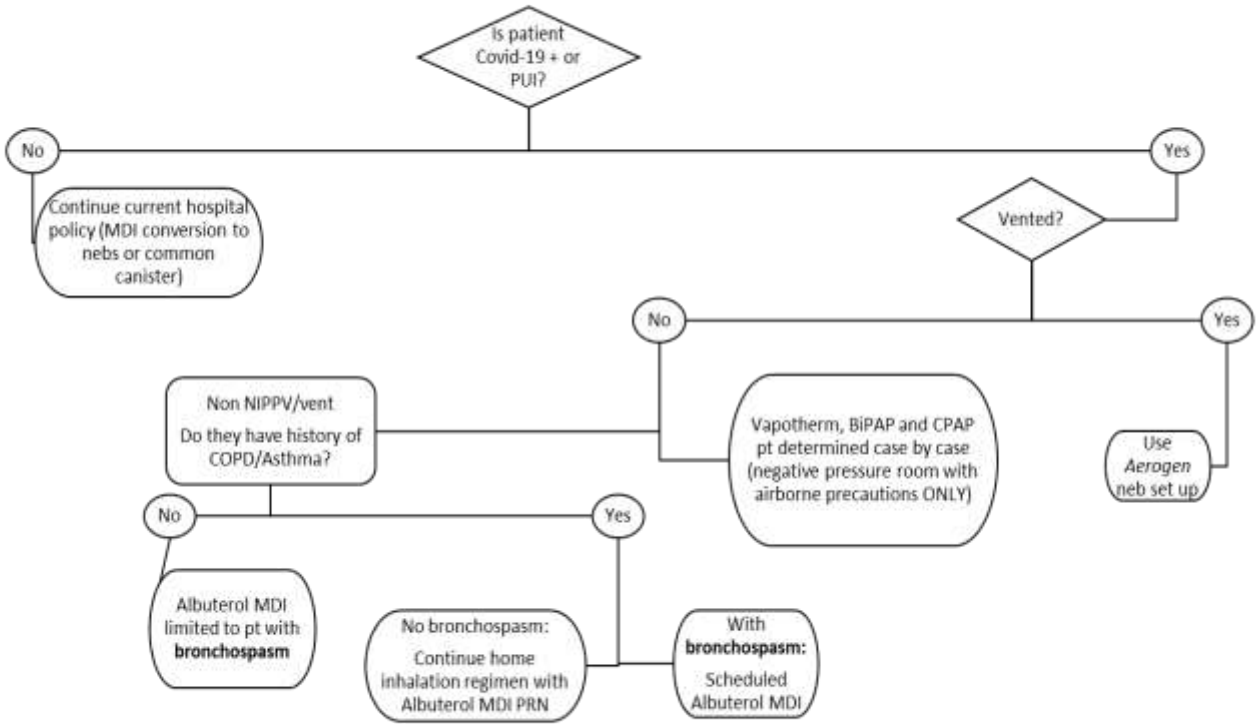
https://clinicaltrials.gov/ct2/show/NCT04315298?term=kevzara&cond=covid19&draw=2&rank=1#contacts.

7. Lexi-Comp: [Internet]. Sarilumab. Hudson OH: Lexi-Comp. c1978-2019 [Updated 2020 March 19; cited 2020 March 20]. Available From: http://online.lexi.com.onu.ohionet.org/lco/action/doc/retrieve/docid/patch_f/6491723?cesid=2LQg0OKpjtD&searchUrl=%2Flco%2Faction%2Fsearch%3Fq%3Dkevzara%26t%3Dname%26va%3Dkevzara#doa

II. Inhaler and Nebulizer Overview

Inpatient Guide for Bronchodilator Administration During COVID-19 Pandemic (Can be applied to non-negative pressure rooms unless otherwise stated)



Alternative to Albuterol MDI, bronchodilator nebulizer with filtered neb set up…. See next page for example or contact RT Manager for direction

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Filtered Neb Example

Metered Dose Inhaler Considerations

- Be diligent with MDIs, other inhalers due to nationwide shortage
  - Albuterol MDIs under extreme shortage
  - Auto-verification of albuterol and Combivent inhalers have been turned off in CC and CP.
  - An alternative alert (LMA) has been implemented to reserve for use in COVID/PUI patients
  - Pharmacists should evaluate all orders to ensure inhalers are used in COVID/PUI patients only
  - Do not dispense inhalers for patients discharging home.
- Follow recommended cleaning procedures for inhalers that can be reused
  - We must continue the use of common canister in non-PUI patients (at sites currently using common canister)
  - May reuse inhalers in PUIs who test negative
- Consider use of home medication inhalers when possible
- Pharmacy may substitute another brand of inhaler within the respective class at an equivalent dose/frequency (see page) based on availability

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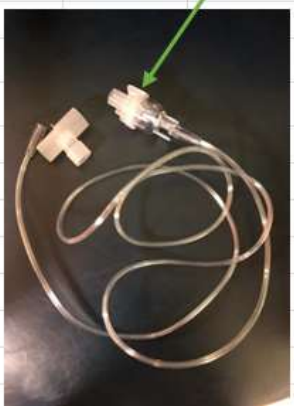
Aerosol Treatment in line on Anesthesia Vent

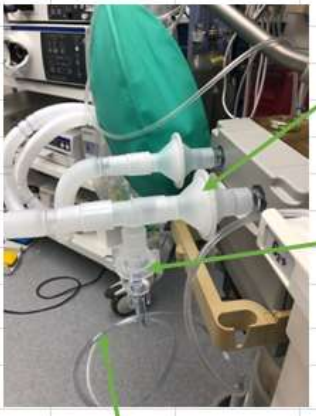
Supplies needed

1. Aerosol Setup
2. Filters
3. Flipable HME (if available)

You will only need these 3 Pieces



Place filters on inspiratory and expiratory side of circuit



Place aerosol set up on the inspiratory side of the circuit

Take off HME on the circuit.

Leave off or add flipable HME

Plug Oxygen tubing into flowmeter and run flow meter at 6-8 LPM

Arrow goes toward the patient

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Use of Patient-Supplied Inhalers

Patient Scenario	OK to use home meds?	Who can identify home med & compare to MD order?	Self-administered? (Hospital to provide spacer)	OK to use nebulizers?
Non-PUI NOT under investigation for flu or COVID-19	YES If patient cannot supply, use nebulizers.	Nurse or RT (Do not send to Pharmacy) Other home meds should be sealed in a plastic bag, left in room with patient name on the bag Upon discharge all patient-supplied meds should be returned to the patient	Patient to self-administer if possible. Order can be placed per protocol by RN, RT, or Prescriber. (and verified by pharmacy via Epic)	**YES** Nebs preferred over hospital stock inhalers (due to shortage)
PUI Person Under investigation for flu or COVID-19	YES If patient does not have home inhalers, pharmacy will provide inhalers via a therapeutic interchange based on class/classes of prescribed regimen		Patient to self-administer if possible. Order can be placed per protocol by RN, RT, or Prescriber (and verified by pharmacy via Epic)	**NO** Preferentially use inhalers. If inhalers are unavailable, nebs may be used with a bacterial/viral filter and appropriate PPE (N95/CAPR/PAPR). Do not use common canister as these are isolation patients. If patient tests negative for COVID-19 and flu, the patient is to be automatically switched per protocol to nebulizers at an equivalent class/dose/frequency. The used inhaler(s) can be cleaned and used for another patient who has confirmed/suspected COVID-19 A NURSE, RT, or PHARMACIST may enter the switch to nebulizers per protocol.
Confirmed COVID-19 or flu	YES If patient does not have home inhalers, pharmacy will provide inhalers as close as possible to therapeutic class/classes		Patient to self-administer if possible. Order can be placed per protocol by RN, RT, or Prescriber (and verified by pharmacy via Epic)	**NO** Preferentially use inhalers. If inhalers are unavailable, nebs may be used with a bacterial/viral filter and appropriate PPE (N95/CAPR/PAPR). Do not use common canister as these are isolation patients.
Mechanically **Vented** Patients	YES If it fits with vent circuit (ie: Respimat)		Not applicable	**YES** Use *Aerogen* product to ensure closed circuit and minimize AGPs

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Drug Class	Preferred Inhaler	Preferred Nebulizer	Inhaler Alternative	Inhaler alternative	Inhaler alternative	Inhaler alternative	Inhaler alternative	Inhaler alternative	Nebulizer alternative
ICS	Fluticasone 110 mcg 1 puff BID (Flovent HFA)	Budesonide 0.25mg/2ml BID (Pulmicort)	Budesonide 90 mcg 1 puff BID (Pulmicort Flexhaler)	Beclomethasone 40 mcg 1 puff BID (Qvar)	Fluticasone 100 mcg 1 puff daily (Arnuity Ellipta)	Fluticasone 50 mcg 2 puffs BID (Flovent Diskus)	Mometasone 220 mcg 1 puff daily (Asmanex)	Ciclesonide 80 mcg 1 puff BID (Alvesco HFA)	
ICS	Fluticasone 110 mcg 2 puff BID (Flovent HFA)	Budesonide 0.5mg/2ml BID (Pulmicort)	Budesonide 180 mcg 2 puffs BID (Pulmicort Flexhaler)	Beclomethasone 80 mcg 2 puffs BID (Qvar)	N/A	Fluticasone 100 mcg 2 puffs BID (Flovent Diskus)	Mometasone 220 mcg 2 puffs daily (Asmanex)	Ciclesonide 80 mcg 3 puffs BID (Alvesco HFA)	
ICS	Fluticasone 110 mcg 4 puff BID (Flovent HFA)	Budesonide 1mg/4ml BID (Pulmicort)	Budesonide 180 mcg 4 puffs BID (Pulmicort Flexhaler)	Beclomethasone 80 mcg 4 puffs BID (Qvar)	Fluticasone 200 mcg 1 puff daily (Arnuity Ellipta)	Fluticasone 250 mcg 2 puffs BID (Flovent Diskus)	Mometasone 220 mcg 2 puffs BID (Asmanex)	Ciclesonide 160 mcg 3 puffs BID (Alvesco HFA)	
ICS + LABA	Budesonide-Formoterol 80/4.5 mcg 2 puffs BID (Symbicort HFA)	Budesonide 0.25mg/2ml BID (Pulmicort) + Arformoterol 15mcg/2ml (Brovana) BID	Fluticasone-Salmeterol 45/21 mcg 2 puffs BID (Advair HFA)	Fluticasone-Salmeterol 100/50 mcg 1 puff BID (Advair DPI)	Fluticasone-Vilanterol 100/25 mcg 1 inhalation daily (Breo Ellipta)	Fluticasone-Vilanterol 200/25 mcg 1 inhalation daily (Breo Ellipta)	Mometasone-Formoterol 100/5mcg 2 puffs BID (Dulera)		
ICS + LABA	Budesonide-Formoterol 160/4.5 mcg 2 puffs BID (Symbicort)	Budesonide 0.5mg/2ml BID (Pulmicort) + Arformoterol 15mcg/2ml (Brovana) BID	Fluticasone-Salmeterol 115/21 mcg 2 puffs BID (Advair HFA)	Fluticasone-Salmeterol 230/21 mcg 2 puffs BID (Advair HFA)	Fluticasone-Salmeterol 250/50 mcg 1 puff BID (Advair DPI)	Fluticasone-Salmeterol 500/50 mcg 1 puff BID (Advair DPI)	Mometasone-formoterol 200/5 mcg 2 puffs BID (Dulera)		
LAMA	Tiotropium Respimat 2 Inh (5mcg) once daily (Spiriva Respimat)	Ipratropium 0.5mg/2.5mL every 8 hours scheduled (can be q 6-8h)	Aclidinium 1 Inh BID (Tudorza Pressair)	Tiotropium 1 inh daily (Spiriva Handihaler)	Glycopyrrolate 1 inh BID (Seebri Neohaler)	Umeclidinium 1 inh once daily (Incruse Ellipta)			Revefenacin 175mcg/3mL same frequency (Yuperli)
LABA	Olodaterol Respimat 2 inhalations once daily (Striverdi Respimat)	Arformoterol 15mcg/2ml BID (Brovana)	Indacaterol 1 inhalation (75 mcg cap) daily (Arcapta)	Salmeterol 1 puff BID (Serevent Diskus)					Formoterol 20 mcg/2mL same frequency (Perforomist)
LAMA + LABA	Glycopyrrolate/Formoterol (Bevespi Aerosphere) 2 inhalations twice daily	Aformoterol 15 mcg/2mL BID (brovana) + Ipratropium 0.5mg/2.5mL every 8 hours (Atrovent)	Glycopyrrolate/Indacaterol 1 inhalations twice daily (Utibron Neohaler)	Tiotropium/ Olodaterol 2 inhalations once daily (Stiolto Respimat)	Umeclidinium / Vilanterol 1-2 inhalations once daily (Anoro Ellipta)				
LAMA + LABA + ICS	Budesonide-Formoterol 80/4.5 mcg 2 puffs BID (Symbicort HFA) AND Tiotropium Respimat 2 Inh (5mcg) once daily (Spiriva Respimat)	Budesonide 0.25mg/2ml BID(Pulmicort) + Arformoterol 15mcg/2ml (Brovana) BID AND Ipratropium every 8 hours scheduled (can be q 6-	May use any combination using available products at comparable doses (see above categories)						

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		8h)							
SABA	Albuterol MDI 2 puff (Proair HFA)	Albuterol Neb 2.5mg same frequency	Pirbuterol MDI 2 puff (Maxair)	Levalbuterol MDI 2 puff (Xopenex 45 mcg HFA) frequency	(Other brand name products? ProAir Respiclick, Proventil HFA, Ventolin HFA)				Levalbuterol Nebs 0.693mg/3mL same frequency (Xopenex)
SAMA	Ipratropium (Atrovent HFA)	Ipratropium 0.5mg/2.5mL neb frequency							
SAMA + SABA	Ipratropium & Albuterol (separate inhalers)	Ipratropium & Albuterol Nebulizer 2.5mg/0.5mg /3mL, same dose/frequency	Combivent	Combivent Respimat					Ipratropium + Levalbuterol nebs

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IV. Other Potential Therapies

There are less data in the use of these medications for COVID-19 treatment, however providers may consider using them or have questions about their use.

Darunavir/cobicistat (Prezcobix)

Overview

- Antiretroviral, protease inhibitor
- Used with low doses of cobicistat to increase bioavailability and half life
- Proposed dose = 800mg/150mg daily PO

Mechanism/Virology/In vitro data

- "Janssen (manufacturer) has no *in vitro* or clinical data to support the use of darunavir as a treatment for Covid-19. The drug is in the process of being evaluated *in vitro* for any potential activity against the coronavirus."
    - https://www.clinicaltrialsarena.com/analysis/coronavirus-mers-cov-drugs/

Trials in Progress

- "Efficacy and Safety of Darunavir and Cobicistat for Treatment of Pneumonia Caused by 2019-NCoV - Full Text View - ClinicalTrials.Gov." Accessed March 1, 2020.
    - https://clinicaltrials.gov/ct2/show/NCT04252274.

Atazanavir or Indinavir

Overview

- Indinavir is a protease inhibitor used in HIV (Only manufactured by one company)
    - Shown to possess docking sites that strongly overlap with the protein pockets, and could be potential therapeutic agents. These docking sites were conferred from the proteins of SARS coronavirus and may not be compatible with the docking site of COVID-19. It did perform similarly well as remdesivir in this theoretical analysis.
- Atazanavir is a protease inhibitor used in HIV –Manufactured by many companies
    - An international collaboration between researchers at Deargen and Dankook University in the Republic of Korea, and Emory University in the United States, have published a prediction model for antiviral drugs that may be effective on 2019-nCoV
        - Predicting commercially available antiviral drugs that may act on the novel coronavirus (2019-nCoV), Wuhan, China, through a drug-target interaction deep learning model
- The result showed that atazanavir is the most promising chemical compound. The authors noted that the model showed that atazanavir has an inhibitory potency with Kd of 94.94 nM against the 2019-nCoV 3C-like proteinase, followed by efavirenz (199.17 nM), ritonavir (204.05 nM), and dolutegravir (336.91 nM). Atazanavir was predicted to have a potential binding affinity to multiple components of the virus, binding to RNA-dependent RNA polymerase (Kd 21.83 nM), helicase (Kd 25.92 nM), 3'-to-5' exonuclease (Kd 82.36 nM), 2'-O-ribose methyltransferase (Kd of 390 nM), and endoRNAse (Kd 50.32 nM), suggesting that "all subunits of the 2019-nCoV replication complex may be inhibited simultaneously by atazanavir.

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Zinc

- Increasing the intracellular Zn2+ concentration with zinc-ionophores like pyrithione (PT) can efficiently impair the replication of a variety of RNA viruses, including poliovirus and influenza virus. For some viruses this effect has been attributed to interference with viral polyprotein processing. In this study we demonstrate that the combination of Zn2+ and PT at low concentrations (2 mM Zn2+ and 2 mM PT) inhibits the replication of SARS-coronavirus (SARS-CoV) and equine arteritis virus (EAV) in cell culture. The RNA synthesis of these two distantly related nidoviruses is catalyzed by an RNA-dependent RNA polymerase (RdRp), which is the core enzyme of their multiprotein replication and transcription complex (RTC). Using an activity assay for RTCs isolated from cells infected with SARS-CoV or EAV—thus eliminating the need for PT to transport Zn2+ across the plasma membrane—we show that Zn2+ efficiently inhibits the RNA-synthesizing activity of the RTCs of both viruses. Enzymatic studies using recombinant RdRps (SARS-CoV nsp12 and EAV nsp9) purified from E. coli subsequently revealed that Zn2+ directly inhibited the in vitro activity of both nidovirus polymerases. More specifically, Zn2+ was found to block the initiation step of EAV RNA synthesis, whereas in the case of the SARS-CoV RdRp elongation was inhibited and template binding reduced. By chelating Zn2+ with MgEDTA, the inhibitory effect of the divalent cation could be reversed, which provides a novel experimental tool for in vitro studies of the molecular details of nidovirus replication and transcription.

Ascorbic Acid (Vitamin C)

- **Accuchek inaccurate can't not be used if intravenous administration of ascorbic acid results in blood concentrations of ascorbic acid >3mg/dL. It will cause an overestimation of blood glucose results. Must send blood glucose measurements to the lab.**
- There is no robust scientific evidence to support the usage of IV ascorbic acid in the management of COVID-19. A trial is underway to provide more information for this specific use, but overall use of ascorbic acid has not been associated with any consistent clinical benefit in critical illness and is not currently recommended for treatment or prevention of COVID-19.
- Fowler et al. JAMA 2019;13:1270-1261. Doi:10.1001/jama.2019.11825
    - Effect of Vitamin C Infusion on Organ Failure and Biomarkers of Inflammation and Vascular Injury in Patient with Sepsis and Severe Acute Respiratory Failure: The CITRIS-ALI Randomized Clinical Trial.
- In this randomized clinical trial that included 167 patients in the intensive care unit, intravenous infusion of high-dose vitamin C vs placebo for 96 hours resulted in no significant differences in the modified Sequential Organ Failure Assessment (SOFA) score at 96 hours, or in levels of C-reactive protein and thrombomodulin at 168 hours.
- Putzu A, et al. The Effect of Vitamin C on Clinical Outcome in Critically Ill Patients: A Systematic Review with Meta-Analysis of Randomized Controlled Trials.
    - In a mixed population of ICU patients, vitamin C administration is associated with no significant effect on survival, length of ICU or hospital stay. In cardiac surgery, beneficial effects on postoperative atrial fibrillation, ICU or hospital length of stay remain unclear.
- Surviving Sepsis Campaign: Guidelines on the Management of Critically Ill Adults with Coronavirus Disease 2019 (COVID-19) and The Australian Government Department of Health (Therapeutic Goods Administration) states the following: There is no robust scientific evidence to support the usage of this vitamin in the management of COVID-19.
- CITRUS-ALI Trial
    - Authors randomized 167 adults at 7 centers diagnosed with sepsis and acute respiratory distress syndrome (ARDS) to receive ascorbic acid infusion (50 mg/kg) or placebo every 6 hours for 4

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days. Patients had to develop ARDS within 24 hours of ICU admission. Patients were similarly vitamin C-deficient between groups. There was a remarkable reduction in 28-day all-cause mortality rate among the patients receiving vitamin C: **29.8% in the treatment group and 46.3% in the placebo group**, which was statistically significant (P = .01) without adjusting for the multiple comparisons performed. There were also improvements in ICU-free days and days out of the hospital at day 60. (These tend to correlate with reductions in mortality.)

Corticosteroids

Limited evidence supporting use of corticosteroids:

- Prior studies assessing outcomes in patients receiving systemic corticosteroids for infections due to closely related viruses (SARS-CoV and MERS-CoV) found a lack of effectiveness and possible harm. However, corticosteroids may still be warranted for other medical indications (i.e., ARDS, COPD exacerbation). If steroids are utilized, continue anti-COVID-19 therapy.
- From SCCM COVD-19 Guidelines: "For adults with COVID-19 and refractory shock, we suggest using low-dose corticosteroid therapy ("shock reversal"), over no corticosteroid therapy (weak recommendation, low quality evidence.
    - A typical corticosteroid regimen in septic shock is intravenous hydrocortisone 200mg per day administered either as an infusion or intermittent doses.
    - Since no data exist on the use of steroids inpatients with COVID-19 and shock, the panel based this recommendation on indirect evidence from critically ill patients in general. Both a 2018 systematic review of 22RCTs (n=7297patients) comparing low-dose corticosteroid therapy versus no corticosteroid therapy in adult patients with septic shock and a clinical practice guideline report no significant difference in short-term mortality (RR 0.96, 95% CI 0.91 to 1.02), long term mortality (RR 0.96, 95% CI 0.90 to 1.02), or serious adverse events (RR 0.98, 95% CI 0.90 to 1.08). However, time to resolution of shock and length of stay in ICU and in hospital were shorter with corticosteroid therapy.
- **From the WHO:** Do not routinely give systemic corticosteroids for treatment of viral pneumonia or ARDS outside of clinical trials unless they are indicated for another reason. Remarks: A systematic review of observational studies of corticosteroids administered to patients with SARS reported no survival benefit and possible harms (avascular necrosis, psychosis, diabetes, and delayed viral clearance). A systematic review of observational studies in influenza found a higher risk of mortality and secondary infections with corticosteroids; the evidence was judged as very low to low quality due to confounding by indication. A subsequent study that addressed this limitation by adjusting for time-varying confounders found no effect on mortality. Finally, a recent study of patients receiving corticosteroids for MERS used a similar statistical approach and found no effect of corticosteroids on mortality but delayed lower respiratory tract (LRT) clearance of MERS-CoV. Given lack of effectiveness and possible harm, routine corticosteroids should be avoided unless they are indicated for another reason.

B. Ibuprofen versus Acetaminophen for Fever Associated with COVID-19

- The Health Minister of France has recommended that acetaminophen be used instead of ibuprofen or other nonsteroidal anti-inflammatory medications for the treatment of systems associated with COVID-19 infections. This recommendation is based on anecdotal information from France and a letter published in Lancet that hypothesized that anti-inflammatory medications such as ibuprofen could lead to an increased expression of angiotensin-converting enzyme 2 (ACE2).[1] Human pathogenic coronaviruses (severe acute respiratory syndrome coronavirus [SARS-CoV] and SARSCoV-2) bind to their

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target cells through angiotensin-converting enzyme 2 (ACE2), which is expressed by epithelial cells of the lung, intestine, kidney, and blood vessels. The letter suggests that patients who use medications that increase ACE2, ibuprofen for example, are at a theoretical higher risk of severe COVID-19 infection. Other scientists postulate that ibuprofen's anti-inflammatory properties could "dampen down" the immune system, which could slow the recovery process. It may be likely, based on similarities between the new virus SARSCoV-2 and SARS-CoV, that COVID-19 reduces a key enzyme that part regulates the water and salt concentration in the blood and could contribute to the pneumonia seen in extreme cases. Ibuprofen aggravates this, while acetaminophen does not[2]. Acetaminophen is also associated with less overall adverse effects when compared to NSAIDs, such as acute kidney injury and gastrointestinal complications. For the treatment of fever, acetaminophen is a safe and effective choice.

- FDA Statement on Nonsteroidal Anti-inflammatory Drugs (NSAID) Use in COVID-19
    - FDA is aware of news reports stating the use of non-steroidal anti-inflammatory drugs (NSAIDs), such as ibuprofen, could worsen coronavirus disease (COVID-19). These news reports followed a March 11, 2020 letter in The Lancet medical journal, which hypothesized that an enzyme (a molecule that aids a biochemical reaction in the body) is increased by NSAIDs and could aggravate COVID-19 symptoms.
    - At this time, FDA is not aware of scientific evidence connecting the use of NSAIDs, like ibuprofen, with worsening COVID-19 symptoms. The agency is investigating this issue further and will communicate publicly when more information is available. However, all prescription NSAID labels warn that "the pharmacological activity of NSAIDs in reducing inflammation, and possibly fever, may diminish the utility of diagnostic signs in detecting infections."
    - For those who wish to use treatment options other than NSAIDs, there are multiple over-the-counter (OTC) and prescription medications approved for pain relief and fever reduction. FDA suggests speaking to your health care professional if you are concerned about taking NSAIDs and rely on these medications to treat chronic diseases.
    - FDA advises the public to read the full Drug Facts Label on OTC medications prior to use. OTC medications are safe and effective when you follow the directions on the label and/or as directed by your health care professional. Patients who use prescription drugs should take these medications as directed by their health care professional and in accordance with instructions on the label.

1. Fang L, Karakiulakis G, Roth M. Are patients with hypertension and diabetes mellitus at increased risk for COVID-19 infection? Lancet 2020. https://doi.org/10.1016/S2213-2600(20)30116-8.
2. Day M. Covid-19: ibuprofen should not be used for managing symptoms, say doctors and scientists. B*MJ* 2020; 368 doi: https://doi.org/10.1136/bmj.m1086 (Published 17 March 2020)

C. ACE Inhibitors/Angiotensin II Blockers in COVID-19

- The largest Chinese study with 44,672 confirmed cases of COVID-19 shows a high overall case fatality rate (CFR) of 2.3%. Important co-morbidities are hypertension (CFR 6.0%), diabetes (CFR 7.3%), cardiovascular disease (CFR 10.5%) and age >70 (CFR 10.2%). Similar co-morbidities were noted for the SARS outbreak in 2003.
- The commonality of these risk factors is not clear. This is somehow surprising as compared to for example the 2009 pandemic H1N1 influenza outbreak, immunosuppressant patients were primarily affected. Cardiac patients seem to be at higher risk in Covid-19. One possible answer could be the following: Patients with the comorbidities of hypertension, diabetes and cardiovascular disease might fulfill the indication for the use of angiotensin converting enzyme inhibitors or angiotensin II receptor antagonists.

- The question is, does a connection exist between the use of these drugs and severe sequela of Covid-19? While the epidemiological association has not been investigated yet, several indicators underline the hypothesis of the link between ACE inhibitors and Covid-19.
- On the one hand, it has been shown that the Covid-19 agent (also known as SARS-CoV-2), uses the SARS-COV receptor angiotensin converting enzyme (ACE) 2 for entry into target cells [4]. The interface between ACE2 and the viral spike protein SARS-S has been elucidated and the efficiency of ACE2 usage was found to be a key determinant of SARS-CoV transmissibility.
- On the other hand, it could be shown in animal experiments that both the ACE-inhibitor lisinopril and the angiotensin-receptor blocker losartan can significantly increase mRNA expression of cardiac ACE2 (5-fold and 3-fold, respectively) [5]. Further, losartan also significantly increases cardiac ACE2 activity [5].
- Is a link between these observations possible? Is the expression of ACE2 receptor in the virus targeted cells increased by the use of ACE-inhibitor/angiotensin-receptor blocker and is the patient therefore more at risk for a severe course? We need rapid epidemiological and preclinical studies to clarify this relationship. If this were the case, we might be able to reduce the risk of fatal Covid-19 courses in many patients by temporarily replacing these drugs.
- Position Statement of the ESC Council on Hypertension on ACE-Inhibitors and Angiotensin Receptor Blockers
    - Based on initial reports from China, and subsequent evidence that arterial hypertension may be associated with increased risk of mortality in hospitalized COVID-19 infected subjects, hypotheses have been put forward to suggest potential adverse effects of angiotensin converting enzyme inhibitors (ACE-i) or Angiotensin Receptor Blockers (ARBs). It has been suggested, especially on social media sites, that these commonly used drugs may increase both the risk of infection and the severity of SARS-CoV2. The concern arises from the observation that, similar to the coronavirus causing SARS, the COVID-19 virus binds to a specific enzyme called ACE2 to infect cells, and ACE2 levels are increased following treatment with ACE-i and ARBs.
    - Because of the social media-related amplification, patients taking these drugs for their high blood pressure and their doctors have become increasingly concerned, and, in some cases, have stopped taking their ACE-I or ARB medications.
    - This speculation about the safety of ACE-i or ARB treatment in relation to COVID-19 does not have a sound scientific basis or evidence to support it. Indeed, there is evidence from studies in animals suggesting that these medications might be rather protective against serious lung complications in patients with COVID-19 infection, but to date there is no data in humans.
    - The Council on Hypertension of the European Society of Cardiology wish to highlight **the lack of any evidence** supporting harmful effect of ACE-I and ARB in the context of the pandemic COVID-19 outbreak.
    - The Council on Hypertension **strongly recommend that physicians and patients should continue treatment with their usual anti-hypertensive therapy because there is no clinical or scientific evidence to suggest that treatment with ACEi or ARBs should be discontinued because of the Covid-19 infection.**
- **In summary, based on the currently available evidence, treatment with RAAS blockers should not be discontinued because of concerns with coronavirus infection.**

D. Statin Use in COVID Positive Patients

- Statin therapy is associated with reduced serum inflammatory markers, such as C-reactive protein and erythrocyte sedimentation rate. Statins interfere with the body's inflammatory response through multiple mechanisms including: integrin inhibition, decreased T-cell activation, and interference with monocytic cytokine expression. Due to these anti-inflammatory mechanisms, the effects of statin therapy on infectious

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processes has been the subject of clinical research. While no clinical data yet exists for a protective role for statins for COVID-19 infection, there are some data that are suggestive that they may be associated with less severe viral pneumonia.

- There is no clinical evidence to date that statins are beneficial for patients with COVID-19. Their positive effects on inflammatory markers, widespread use, and relatively safe profile make them acceptable options for managing a disease with inflammatory components without any established treatments.
- Continue statins if already prescribed. If no contraindication, and for those who have a guideline indication for a statin, consider starting a high-intensity statin with predicted LDL lowering of >50% (either atorvastatin 40 mg daily or rosuvastatin 20 mg daily).
- References:
  - Ferro D, Parrotto S, Basili S, Alessandri C, Violi F. Simvastatin inhibits the monocyte expression of proinflammatory cytokines in patients with hypercholesterolemia. J Am Coll Cardiol. 2000;36(2):427-31.
  - Frenette PS. Locking a leukocyte integrin with statins. N Engl J Med. 2001;345(19):1419-21.
  - Frost FJ, Petersen H, Tollestrup K, Skipper B. Influenza and COPD mortality protection as pleiotropic, dose-dependent effects of statins. Chest. 2007;131(4):1006-12.
  - Kwak B, Mulhaupt F, Myit S, Mach F. Statins as a newly recognized type of immunomodulator. Nat Med. 2000;6(12):1399-402.
  - Vandermeer ML, Thomas AR, Kamimoto L, Reingold A, Gershman K, Meek J, et al. Association between use of statins and mortality among patients hospitalized with laboratory confirmed influenza virus infections: a multistate study. J Infect Dis. 2012;205(1):13-9.
  - Weitz-schmidt G, Welzenbach K, Brinkmann V, et al. Statins selectively inhibit leukocyte function antigen-1 by binding to a novel regulatory integrin site. Nat Med. 2001;7(6):687-92.

E. Convalescent sera/plasma

- An individual who is infected with COVID-19 and recovers has blood drawn and screened for virus-neutralizing antibodies. Following identification of those with high titers of neutralizing antibody, serum containing these virus-neutralizing antibodies can be administered in a prophylactic manner to prevent infection in high-risk cases, such as vulnerable individuals with underlying medical conditions, health care providers, and individuals with exposure to confirmed cases of COVID-19. Additionally, convalescent serum could potentially be used in individuals with clinical disease to reduce symptoms and mortality. The efficacy of these approaches is not known, but historical experience suggests that convalescent sera may be more effective in preventing disease than in the treatment of established disease.
- This does not appear to be commercially-available, potential to produce in house is being assessed.
- https://www.jci.org/articles/view/138003

Summary of limited evidence - Convalsecent sera/plasma

A case series was conducted in 5 critically ill COVID-19 patients that received convalescent plasma transfusions in China. All five patients had severe pneumonia with rapid progression, high viral load, P_{AO2}/F_{IO2} <300, mechanically ventilated, 4/5 (80%) had no preexisting medical conditions, age range was 36-65 and they all had received antiviral agents such as lopinavir/ritonavir and methylprednisolone. They received two consecutive transfusions of 200-250 ml of ABO compatible convalescent plasma on the same day of donation to preserve natural activity. They also received CoV-2-specific antibody(IgG) binding titer and a neutralization titer that had been obtained from 5 patients who fully recovered from COVID-19. It was administered between 10 and 22 days

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after admission. The main findings from this case series displayed body temperature normalization within three days in 4 of 5 patients (80%), SOFA score decreased, P_{AO2}/F_{IO2} increased, viral loads decreased and became negative within 12 days after infusion. Four patients had resolution of their acute respiratory distress syndrome after 12 days and 3 patients were weaned off of mechanical ventilation within two weeks of treatment. However, with a small study and delayed use of convalescent plasma while using antivirals and steroids, it is unclear if patients would have improved without the transfusion.

Mount Sinai Health system will begin plasmapheresis. They will inject critically ill patients with antibodies from patients who have recovered from COVID-19 in hopes that the antibodies will neutralize the virus. Last week, scientists in Australia were the first to develop an antibody test that will help identify people who are already immune to the virus and detects infected patients as early as 3 days after the onset of symptoms. This discovery used recombinant or manufactured antigens from the spike protein on the surface of SARS-CoV-2 virus. Once it enters the cell, it creates antibodies that recognizes the protein to kill the virus. Researchers found we do not have natural immunity to the SARs-CoV-2 virus, however once we make antibodies against the virus, there is no evidence we lose our immunity and become re-infected.

FDA Regulatory status Change – Convalsecent sera/plasma

The FDA is granting clinicians permission to use convalescent plasma as treatment for an individual patient by a license physician through single patient emergency Investigational New Drug Application (eINDs) however does not include the use for prevention of the infection. COVID-19 convalescent plasma must be collected from recovered individuals if they are eligible to donate blood. Here are additional considerations for donor eligibility

- Prior diagnosis of COVID-19 documented by a laboratory test
- Complete resolution of symptoms at least 14 days prior to donation
- Female donors negative for HLA antibodies or male donors
- Negative results for COVID-19 either from one or more nasopharyngeal swab specimens or by a molecular diagnostic test from blood. A partial list of available tests can be accessed at https://www.fda.gov/medical-devices/emergency-situations-medical-devices/emergency-use-authorizations.
- Defined SARS-CoV-2 neutralizing antibody titers, if testing can be conducted (e.g., optimally greater than 1:320)

- **Eligible patients for use under expanded access provisions:**
    - Must have laboratory confirmed COVID-19
    - Must have severe or immediately life-threatening COVID-19, for example:[1]
        - Severe disease is defined as:
            - dyspnea,
            - respiratory frequency ≥ 30/min,
            - blood oxygen saturation ≤ 93%,
            - partial pressure of arterial oxygen to fraction of inspired oxygen ratio < 300, and/or
            - lung infiltrates > 50% within 24 to 48 hours
        - Life-threatening disease is defined as:
            - respiratory failure,
            - septic shock, and/or

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        - multiple organ dysfunction or failure
    - Must provide informed consent

In order to obtain authorization for the use of COVID-19 convalescent plasma,

- For request that are not highly time sensitive (response from FDA provided within 4 to 8 hours), the requesting physician may contact FDA by completing form 3926 (https://www.fda.gov/media/98616/download) and submitting the form by email to CBER_eIND_Covid-19@FDA.HHS.gov.
- In the event of an emergency that is highly time sensitive (response required in less than 4 hours) or where the provider is unable to complete and submit form 3926 due to extenuating circumstances, the provider may contact FDA's Office of Emergency Operations at 1-866-300-4374 to seek verbal authorization.
    - If verbal authorization is given, the requestor must agree to submit an expanded access application (e.g., form 3926) within 15 working days of FDA's authorization of the use.

Antibodies

It is possible that convalescent plasma contains antibodies to SARS-CoV-2 that is allowing it to be effective against the infection. Several studies have shown convalescent plasma to decrease hospital stay and lower mortality in patients with COVID-19 as well as patients who had Ebola. Investigators believe that the plasma contains antibodies that suppress viremia. It may be more effective to administer the plasma in earlier stages of the disease because patients develop a primary immune response by 10-14 days. Then is followed by virus clearance.

https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(20)30141-9/fulltext#articleInformation

F. Ivermectin

Review of the recent study of ivermectin in SARS-CoV2 *in vitro.*[1]

- 5 µM of ivermectin added to Vero/hSLAM cells with SARS-CoV2 isolates.
- 93% reduction in viral RNA present in the supernatant, 99.8% reduction in cell-associated viral RNA at 24 hours post-ivermectin.
- Viral RNA reduction seen up to ~5000 fold by 48 hours post-ivermectin compared to control samples, resulting in the effective loss of all viral material both in the supernatant and cell pellets.
- By 72 hours, no further reduction in viral RNA observed.
- No toxicity of ivermectin observed.
- The IC_{50} of ivermectin treatment was ~2 µM in vitro.
- Potential mechanism can be explained by ivermectin inhibiting IMPα/β1-mediated nuclear import of viral proteins of SARS-CoV2.
- Ivermectin is thought to block the cargo transporter and thus prevents the virus from getting into the nucleus, and so can't make copies of itself.
- No dosing information for human use provided.

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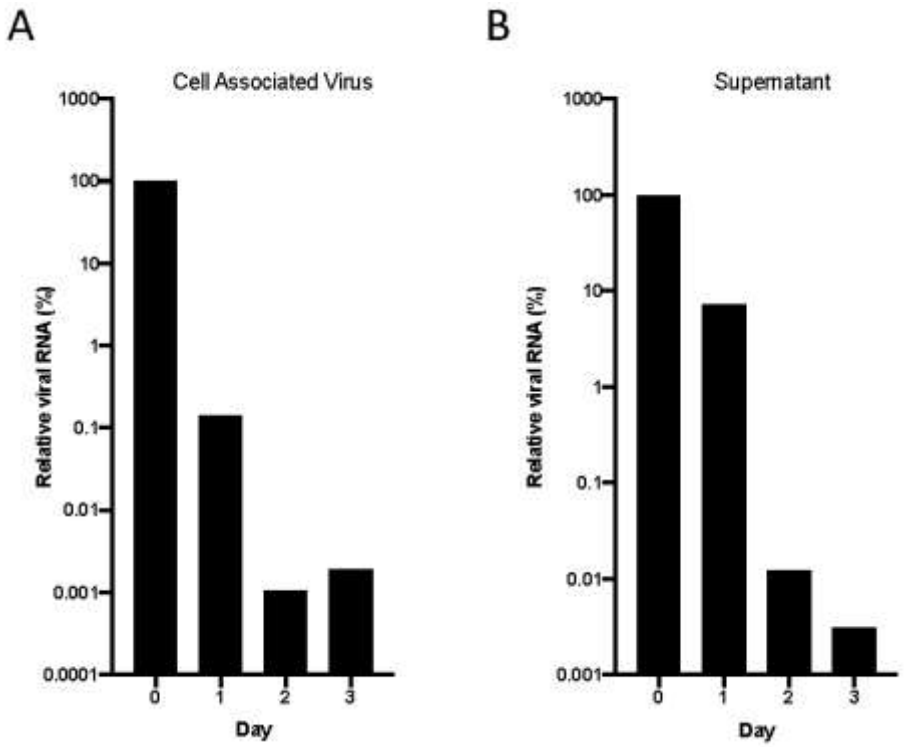

Ivermectin Uses in Other Viruses[1,3]

- Ivermectin uses have been studied in HIV, Dengue virus (DENV), West Nile virus, Venezuelan equine encephalitis virus (VEEV), yellow fever virus (YFV), chikungunya virus (CHIKV) influenza, and pseudorabies virus (PRV).
- Efficacy has not been observed in Zika virus (ZIKV).
- Most are *in vitro* studies except one phase III trial.

Dosing Information[,2,4]

- FDA-approved dose of Ivermectin use for onchocerciasis is 150 µg/kg as a single dose; for strongyloidiasis is 200µg/kg/day for 1-2 days.
- Phase III trial in Thailand for Dengue infection reported use of 400 µg/kg orally once daily for 3 days:
    - Median plasma dengue viremia clearance 80.5hr in ivermectin group vs. 82hr in placebo group (p=0.766)
    - Median fever clearance time 79 hr in ivermectin group vs. 79 hr in placebo group (p=0.736)
    - Median dengue nonstructural protein 1 (NS 1) antigenemia clearance 90hr in ivermectin group vs. 102hr in placebo group (p=0.027)
    - No serious adverse events observed
- *In vivo* study on Pseudorabies virus (PRV) reported using ivermectin 200 µg/kg in mice with successful suppression of virus replications.
    - One caveat is that PRV is a DNA virus, unlikely to SARS-CoV2 which is a single stranded RNA virus.
- Currently, no study available for review to evaluate the optimal dose for the treatment of SARS-CoV2.

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Pharmacokinetics/Pharmacodynamics of Ivermectin[3,5]

- In US, ivermectin is supplied as oral 3mg tablet for human use.
- Ivermectin is available as a 1% cream for rosacea
- Ivermectin is a common drug used to prevent heartworm infestations in canines (sold as Frontline, Heartguard)

Absorption	Well absorbed
Distribution	High concentration in liver and adipose tissue; dose not readily cross the blood-brain barrier
Protein binding	93% primarily to albumin
Metabolism	Hepatic via CYP3A4 predominantly
Half-life elimination	18 hours
Excretion	mainly via feces, only 1% via urine
Pregnancy/lactation	• Adverse events observed in animal reproduction studies • Measurably low concentration of ivermectin observed in breast milk – advise to weight risk vs. benefit before initiating ivermectin in lactating mothers
Drug/food interaction	• Antagonist effect against vitamin K (interfere with vitamin K metabolism) – enhance effect of vitamin K antagonists • No bleeding disorders were observed; but prolonged prothrombin ratios • Increased plasma concentration with alcohol consumption • Decreased AUC and C_{max} with fruit juice (i.e. orange juice)

Toxicity[5,6,7,8,9]

Ivermectin is generally considered safe and well-tolerated, and most adverse effects are mild and temporary. Rarely, serious neurologic adverse effects have been reported with therapeutic doses. The proposed mechanism of these events has been debated in the literature, and may be explained in part by high-burden parasitic infection (ie. *L. loa*). Other proposed mechanisms include disruption of the blood-brain barrier due to genetic variants in mdr-1 (P-glycoprotein) or illness (ie sepsis or malignancy), or drug interactions with CYP3A4 inhibitors. Neurologic toxicity has also been associated with acute and chronic overdose. Ivermectin should not be used in pregnancy or in pediatric patients <2 years old or <15 kg.

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Signs of toxicity:

- *Mild/moderate toxicity:* rash, edema, headache, dizziness, nausea, vomiting, abdominal pain, diarrhea, tachycardia
- *Severe toxicity:* inability to walk, consciousness disturbed, depressed level of consciousness, or loss of consciousness, seizure, encephalopathy, metabolic acidosis, coma, tremor, death

Treatment of toxicity generally involves supportive/symptomatic care. Contact the Poison Control Center immediately (1-800-222-1222) if intentional or unintentional ivermectin overdose is suspected.

References:

1. Caly L, Druce JD, Catton MG, Jans DA, Wagstaff KM. The FDA-approved Drug Ivermectin inhibits the replication of SARS-CoV-2 in vitro [published online ahead of print, 2020 Apr 3]. Antiviral Res. 2020;104787. doi:10.1016/j.antiviral.2020.104787
2. Yamasmith, E., et al., Efficacy and Safety of Ivermectin against Dengue Infection: A193 Phase III, Randomized, Double-blind, Placebo-controlled Trial, in the 34th Annual194 Meeting The Royal College of Physicians of Thailand- 'Internal Medicine and One195 Health'. 2018: Chonburi, Thailand.
3. Lv C, Liu W, Wang B, et al. Ivermectin inhibits DNA polymerase UL42 of pseudorabies virus entrance into the nucleus and proliferation of the virus in vitro and vivo. Antiviral Res. 2018;159:55–62. doi:10.1016/j.antiviral.2018.09.010
4. González Canga A, Sahagún Prieto AM, Diez Liébana MJ, Fernández Martínez N, Sierra Vega M, García Vieitez JJ. The pharmacokinetics and interactions of ivermectin in humans--a mini-review. AAPS J. 2008;10(1):42–46. doi:10.1208/s12248-007-9000-9
5. Ivermectin. Lexi-Drugs. Lexicomp. Wolters Kluwer Health, Inc. Riverwoods, IL. Available at: http://online.lexi.com. Assessed April 7, 2020
6. Chandler RE. Serious neurological adverse events after invermectin – do they occur beyond the indication of onchocerciasis? *Am J Trop Med Hyg*. 2018; 98(2):382-388.
7. Chung K, Yang CC, W ML et al. Agricultural avermectins: an uncommon but potentially fatal cause of pesticide poisoning. *Ann Emerg Med.* 1999;34(1):51-7.
8. DeBonis K and Pierre JM. Psychosis, ivermectin toxicity and "Morgellons disease". *Psychosomatics.* 2011;52(3):295-296.
9. Poison Control - National Capital Poison Center. Ivermectin Safety. https://www.poison.org/articles/ivermectin-your-dogs-heartworm-medicine-173 (accessed 2020 Apr 7).

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V. Supporting Literature

Chloroquine/Hydroxychloroquine Supporting Literature

Philippe Colson ,Jean-Marc Rolain ,Jean-Christophe Lagier ,Philippe Brouqui ,Didier Raoult. Chloroquine and hydroxychloroquine as available weapons to fight COVID-19, International Journal of Antimicrobial Agents (2020)

- https://doi.org/10.1016/j.ijantimicag.2020.105932
- Nine studies have demonstrated *in vitro* activity against various coronaviruses.

- Gao, Jianjun, Zhenxue Tian, and Xu Yang. "Breakthrough: Chloroquine Phosphate Has Shown Apparent Efficacy in Treatment of COVID-19 Associated Pneumonia in Clinical Studies." *BioScience Trends* advpub (2020).
  - https://doi.org/10.5582/bst.2020.01047.
  - Breakthrough: Chloroquine phosphate has shown apparent efficacy in treatment of COVID-19 associated pneumonia in clinical studies.
  - The first results obtained from more than 100 patients showed the superiority of chloroquine compared with treatment of the control group in terms of reduction of exacerbation of pneumonia, duration of symptoms and delay of viral clearance, all in the absence of severe side effects. This has led in China to include chloroquine in the recommendations regarding the prevention and treatment of COVID-19 pneumonia

- Multicenter collaboration group of Department of Science and Technology of Guangdong Province and Health Commission of Guangdong Province for chloroquine in the treatment of novel coronavirus pneumonia. "[Expert consensus on chloroquine phosphate for the treatment of novel coronavirus pneumonia]." *Zhonghua Jie He He Hu Xi Za Zhi = Zhonghua Jiehe He Huxi Zazhi = Chinese Journal of Tuberculosis and Respiratory Diseases* 43, no. 0 (February 20, 2020): E019.
  - https://doi.org/10.3760/cma.j.issn.1001-0939.2020.0019.
  - https://www.ncbi.nlm.nih.gov/pubmed/32075365
  - Comprehensive review of using chloroquine in the treatment of COVID-19 pneumonia.
  - Proposed dosing: Dosage, usage, and treatment plan: Chloroquine phosphate tablets, 500 mg each time, 2 times / d for 10 days. If severe gastrointestinal reactions occur, the dose can be reduced to 1 time / d, 500 mg each time, or even discontinued. During the course of treatment, if the nucleic acid of the throat swab becomes negative and is negative for 3 days, the drug withdrawal can be considered, but the minimum course of treatment needs 5 days.

- Cortegiani A, Ingoglia G, Ippolito M, Einav S. A systematic review on the efficacy and safety of chloroquine for the treatment of COVID-19. *J Crit Care*. In Press.
  - https://www.sciencedirect.com/science/article/pii/S0883944120303907
  - Review of chloroquine and hydroxychloroquine in treatment of COVID-19 pneumonia.
  - Summarizes ongoing clinical trials evaluating use in this context.

- Zhaowei C, et al. Efficacy of hydroxychloroquine in patients with COVID-19: results of a randomized clinical trial. Pre-publication

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- https://www.medrxiv.org/content/10.1101/2020.03.22.20040758v2
- 62 patients suffering from COVID-19 were included in the trial at a Chinese hospital
- All participants were randomized in a parallel-group trial, 31 patients were assigned to receive an additional 5-day HCQ (400 mg/d) treatment and 31 patients received standard of care treatment.
- Time to clinical recovery (TTCR), clinical characteristics, and radiological results were assessed at baseline and 5 days after treatment to evaluate the effect of HCQ.
- Key findings
  - TTCR, the body temperature recovery time and the cough remission time were significantly shortened in the HCQ treatment group.
  - A larger proportion of patients with improved pneumonia in the HCQ treatment group (80.6%, 25 of 32) compared with the control group (54.8%, 17 of 32).
  - All 4 patients that progressed to severe illness that occurred in the control group.
  - 2 patients with mild adverse reactions were observed in the HCQ treatment group.
- Among patients with COVID-19, the use of HCQ could significantly shorten TTCR and promote the absorption of pneumonia.

Mechanism/Virology/In vitro data

- Yao, Xueting, Fei Ye, Miao Zhang, Cheng Cui, Baoying Huang, Peihua Niu, Xu Liu, et al. "*In Vitro* Antiviral Activity and Projection of Optimized Dosing Design of Hydroxychloroquine for the Treatment of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2)." *Clinical Infectious Diseases: An Official Publication of the Infectious Diseases Society of America*, March 9, 2020 (pre-publication).
  - https://doi.org/10.1093/cid/ciaa237.
  - Hydroxychloroquine (EC_{50}=0.72 µM) was found to be more potent than chloroquine (EC_{50}=5.47 µM) *in vitro*. Based on PBPK models results, a loading dose of 400 mg twice daily of hydroxychloroquine sulfate given orally, followed by a maintenance dose of 200 mg given twice daily for 4 days is recommended for SARS-CoV-2 infection, as it reached three times the potency of chloroquine phosphate when given 500 mg twice daily 5 days in advance. Hydroxychloroquine was found to be more potent than chloroquine to inhibit SARS-CoV-2 *in vitro.*
- Keyaerts E, Vijgen L, Maes P et al. (2004). In vitro inhibition of severe acute respiratory syndrome coronavirus by chloroquine. Biochem Biophys Res Commun 323: 264.
  - https://www.sciencedirect.com/science/article/pii/S0006291X0401839X?via%3Dihub)
  - Chloroquine, a 4-amino-quinoline, is an effective inhibitor of the replication of the severe acute respiratory syndrome coronavirus (SARS-CoV) in vitro. Chloroquine is a clinically approved drug effective against malaria. We tested chloroquine phosphate for its antiviral potential against SARS-CoV-induced cytopathicity in Vero E6 cell culture. Results indicate that the IC_{50} of chloroquine for antiviral activity (8.8 ± 1.2 µM) was significantly lower than its cytostatic activity; CC_{50} (261.3 ± 14.5 µM), yielding a selectivity index of 30. The IC_{50} of chloroquine for inhibition of SARS-CoV in vitro approximates the plasma concentrations of chloroquine reached during treatment of acute malaria. Addition of chloroquine to infected cultures could be delayed for up to 5 h post infection, without an important drop in antiviral activity. Chloroquine, an old antimalarial drug, may be considered for immediate use in the prevention and treatment of SARS-CoV infections.

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- Vincent MJ, Bergeron E, Benjannet S et al. (2005). Chloroquine is a potent inhibitor of SARS coronavirus infection and spread. Virol J 2: 69. (SARS-CoV;
    - Chloroquine is a potent inhibitor of SARS coronavirus infection and spread)
    - Chloroquine has strong antiviral effects on SARS-CoV infection of primate cells. These inhibitory effects are observed when the cells are treated with the drug either before or after exposure to the virus, suggesting both prophylactic and therapeutic advantage. In addition to the well-known functions of chloroquine such as elevations of endosomal pH, the drug appears to interfere with terminal glycosylation of the cellular receptor, angiotensin-converting enzyme. This may negatively influence the virus-receptor binding and abrogate the infection, with further ramifications by the elevation of vesicular pH, resulting in the inhibition of infection and spread of SARS CoV at clinically admissible concentrations.

- Savarino A, Boelaert JR, Cassone A, Majori G, Cauda R. Effects of chloroquine on viral infections: an old drug against today's diseases? Lancet Infect Dis. 2003; 3:722- 727.
    - Includes description of mechanism of action
    - https://www.sciencedirect.com/science/article/pii/S1473309903008065?via%3Dihub

    - Chloroquine is a 9-aminoquinoline known since 1934. Apart from its well-known antimalarial effects, the drug has interesting biochemical properties that might be applied against some viral infections. Chloroquine exerts direct antiviral effects, inhibiting pH-dependent steps of the replication of several viruses including members of the flaviviruses, retroviruses, and coronaviruses. Its best-studied effects are those against HIV replication, which are being tested in clinical trials. Moreover, chloroquine has immunomodulatory effects, suppressing the production/release of tumor necrosis factor α and interleukin 6, which mediate the inflammatory complications of several viral diseases. We review the available information on the effects of chloroquine on viral infections, raising the question of whether this old drug may experience a revival in the clinical management of viral diseases such as AIDS and severe acute respiratory syndrome, which afflict mankind in the era of globalization.

- Wang M, Cao R, Zhang L, et al. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. *Cell Research*. 2020;30(3):269-271.
    - Proposed mechanism: "Chloroquine is known to block virus infection by increasing endosomal pH required for virus/cell fusion, as well as interfering with the glycosylation of cellular receptors of SARS-CoV"
    - "The EC90 value of chloroquine against the 2019-nCoV in Vero E6 cells was 6.90 µM, which can be clinically achievable as demonstrated in the plasma of rheumatoid arthritis patients who received 500 mg administration"
        - doi:10.1038/s41422-020-0282-0

Remdesivir Supporting Literature

- Sheahan TP et al. Comparative therapeutic efficacy of remdesivir and combination lopinavir, ritonavir, and interferon beta against MERS-CoV. *Nat Commun* 2020 Jan 10; 11:222.
    - (https://doi.org/10.1038/s41467-019-13940-6)
    - Using a recombinant MERS-CoV engineered to express a reporter nanoluciferase, Sheahan and colleagues now show that remdesivir and interferon beta (IFN-β) have superior antiviral activity to lopinavir/ritonavir (LPV/RTV) in cultured human lung cells. In this manufacturer-sponsored

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trial, the activity of IFN-β was not enhanced by LPV/RTV in vitro. In a murine model, remdesivir at both prophylactic and therapeutic doses improved lung function, reduced lung injury, and reduced virologic loads, whereas LPV/RTV–IFN-β results were significantly less pronounced.

- de Wit E et al. Prophylactic and therapeutic remdesivir (GS-5734) treatment in the rhesus macaque model of MERS-CoV infection. *Proc Natl Acad Sci U S A* 2020 Feb 13; [e-pub].
    - (https://doi.org/10.1073/pnas.1922083117)
    - The efficacy of prophylactic and therapeutic remdesivir was also examined by de Wit and colleagues in a rhesus macaque model of MERS-CoV. Remdesivir prophylaxis initiated 24 hours before inoculation with MERS-CoV caused significantly lower viral loads than control treatment in the lungs and prevented clinical infection in this model. Remdesivir therapy initiated 12 hours after inoculation significantly reduced MERS-CoV loads in other respiratory tissues, decreased lung disease, and strongly attenuated clinical signs of infection compared with control treatment.

Lopinavir/Ritonavir Supporting Literature

- Yao TT, Qian JD, Zhu WY, Wang Y, Wang GQ. "A Systematic Review of Lopinavir Therapy for SARS Coronavirus and MERS Coronavirus-A Possible Reference for Coronavirus Disease-19 Treatment Option." J Med Virol. 2020 Feb 27.
    - https://onlinelibrary.wiley.com/doi/epdf/10.1002/jmv.25729

- Chan, Jasper Fuk-Woo, Yanfeng Yao, Man-Lung Yeung, Wei Deng, Linlin Bao, Lilong Jia, Fengdi Li, et al. "Treatment With Lopinavir/Ritonavir or Interferon-B1b Improves Outcome of MERS-CoV Infection in a Nonhuman Primate Model of Common Marmoset." The Journal of Infectious Diseases 212, no. 12 (December 15, 2015): 1904–13.
        - Improved clinical scores and lower viral loads in necroscopied lungs in animals treated with lopinavir/ritonavir OR interferon
            - Pathology of MMF and untreated lungs much more extensive than lopinavir/ritonavir and interferon
        - Note: worsened disease and viral load in animals treated with mycophenolate
    - https://doi.org/10.1093/infdis/jiv392.

- Sheahan TP et al. Comparative therapeutic efficacy of remdesivir and combination lopinavir, ritonavir, and interferon beta against MERS-CoV. *Nat Commun* 2020 Jan 10; 11:222.
    - (https://doi.org/10.1038/s41467-019-13940-6)
    - Using a recombinant MERS-CoV engineered to express a reporter nanoluciferase, Sheahan and colleagues now show that remdesivir and interferon beta (IFN-β) have superior antiviral activity to lopinavir/ritonavir (LPV/RTV) in cultured human lung cells. In this manufacturer-sponsored trial, the activity of IFN-β was not enhanced by LPV/RTV in vitro. In a murine model, remdesivir at both prophylactic and therapeutic doses improved lung function, reduced lung injury, and reduced virologic loads, whereas LPV/RTV–IFN-β results were significantly less pronounced.

- Includes both *in vitro* (human lung cell) and *in vivo* (transgenic mouse model) of MERS-CoV
    - TL;DR: high EC50 + low levels of free LPV in plasma → authors conclude that LPV is unlikely to be efficacious against MERS-CoV in human host
        - doi:10.1038/s41467-019-13940-6

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- "Treatment of Severe Acute Respiratory Syndrome with Lopinavir/Ritonavir: A Multicentre Retrospective Matched Cohort Study | HKMJ." Accessed March 1, 2020.
    - cohort study of treatment of SARS.
    - Case control study: patients who received LPV/r as initial therapy OR LPV/r as rescue therapy were compared to controls
    - Conclusion: "The addition of lopinavir/ritonavir to a standard treatment protocol as an initial treatment for severe acute respiratory syndrome appeared to be associated with improved clinical outcome."
        - https://www.hkmj.org/abstracts/v9n6/399.htm.

- Zhou F, Yu T, Du R et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet. Published online March 9, 2020
    - A retrospective, multicenter cohort study including all adult inpatients with laboratory confirmed COVID-19 from Jinyintan Hospital and Wuhan Pulmonary hospital who had been discharged or died by 1/31/20
    - Included 191 patients of whom 137 were discharged and 54 died in-hospital
    - Included univariable and multivariable logistic regression to evaluate risk factors associated with in-hospital death
    - 41 (21%) received antiviral therapy (LPV/r). Among 29 patients who received LPV/r and were discharged (survived), the median time from illness onset to initiation of therapy was 14 days and the median duration of viral shedding was 22 days. The median duration of viral shedding was 20 days among all 137 survivors. This study did not observe shortening of viral shedding duration after LPV/r.
        - https://wwxfw.thelancet.com/lancet/article/S0140-6736(20)30566-3
- Chu CM, Cheng VCC, Hung IFN, et al. Role of lopinavir/ritonavir in the treatment of SARS: initial virological and clinical findings. *Thorax*. 2004;59(3):252-256.
    - Retrospective case control study - 41 patients who received LPV/r + ribavirin compared to 111 patients who received ribavirin only
    - "The adverse clinical outcome (ARDS or death) was significantly lower in the treatment group than in the historical controls (2.4% v 28.8%, p<0.001) at day 21 after the onset of symptoms...Lopinavir/ritonavir treatment was associated with a better outcome even when adjusted for baseline lactate dehydrogenase level."
    - Of note, both the treatment group and control group also received ribavirin (x14 days; dose 4 g oral loading dose followed by 1.2 g every 8 hour or IV if unable to take PO)
        - doi:10.1136/thorax.2003.012658

- Young BE, Ong SWX, Kalimuddin S, et al. Epidemiologic Features and Clinical Course of Patients Infected With SARS-CoV-2 in Singapore. *JAMA.* Published online March 03, 2020. doi:10.1001/jama.2020.3204
    - Singapore descriptive case series of 18 cases. Five of six patients requiring supplemental oxygen were given lopinavir/ritonavir 200mg/100 mg BID for up to 14 days. Only one individual finished 14 days due to adverse events (N/V/increased LFTs). Two patients continued to deteriorate and shed virus. Two of the five cleared viral shedding in two days, three of the five had decreases in supplemental oxygen requirement. "Evidence of clinical benefit equivocal. Decline in viral load as indicated by the cycle threshold value from nasopharyngeal swabs also appeared similar between those treated and not treated with lopinavir-ritonavir."

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  - https://jamanetwork.com/journals/jama/fullarticle/2762688
- Cao, B et al. A Trial of Lopinavir-Ritonavir in Adults Hospitalized with Severe Covid-19. New England Journal of Medicine. March 18, 2020. DOI: 10.1056/NEJMoa2001282
  - 199 patients with laboratory-confirmed SARS-CoV-2 infection were assigned to receive either lopinavir/ritonavir 400mg/100mg twice daily with standard of care or standard of care alone.
  - Treatment with lopinavir–ritonavir was not associated with a difference from standard care in the time to clinical improvement (hazard ratio for clinical improvement, 1.24; 95% confidence interval [CI], 0.90 to 1.72). Mortality at 28 days was similar in the lopinavir–ritonavir group and the standard-care group (19.2% vs. 25.0%; difference, −5.8 percentage points; 95% CI, −17.3 to 5.7). The percentages of patients with detectable viral RNA at various time points were similar. In a modified intention-to-treat analysis, lopinavir–ritonavir led to a median time to clinical improvement that was shorter by 1 day than that observed with standard care (hazard ratio, 1.39; 95% CI, 1.00 to 1.91). Gastrointestinal adverse events were more common in the lopinavir–ritonavir group, but serious adverse events were more common in the standard-care group. Lopinavir–ritonavir treatment was stopped early in 13 patients (13.8%) because of adverse events.
  - Overall mortality rate was much higher than previous observed, showing this was a sick population.
  - Accelerated clinical recovery (16.0 days vs. 17.0 days) and reduced mortality (19.0% vs. 27.1%) were observed in a post hoc subgroup of those treated within 12 days after the onset of symptoms, but not in those treated later.

Surviving Sepsis Campaign COVID-19 Guidelines

Surviving Sepsis Campaign COVID-19 Guidelines – preliminary key observations that may influence hospital protocols

1. Fever management
   a. Recommendation to use acetaminophen first line as NSAID safety is unknown
2. Corticosteroids
   a. Recommend against routine use of systemic steroids in ventilated patients with COVID-19 **without ARDS**
   b. Suggest using systemic corticosteroids over not using corticosteroids in mechanically ventilated adults **with COVID-19 and ARDS**
3. ID and COVID-19 “treatments”
   a. Recommendation FOR use of empiric antibiotics vs. none
   b. Insufficient evidence for tocilizumab in critically ill
   c. Insufficient evidence for hydroxychloroquine/chloroquine in critically ill
   d. Recommend against IVIG
   e. Recommend against lopinavir/ritonavir
4. Hemodynamics and shock management
   a. Recommend goal MAP of 60 – 65 vs. higher MAP targets (obviously based on patient baseline and other considerations)
   b. Recommend against use of dopamine if norepinephrine is available
   c. If norepinephrine unavailable, recommend vasopressin or epinephrine as first line agents for vasopressors
   d. Recommend adding vasopressin as second line agent to norepinephrine if cannot maintain MAP goal

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   e. Recommendation for adding dobutamine over increasing norepinephrine doses in patients with shock and evidence of cardiac dysfunction with persistent hypoperfusion despite fluids and vasopressors
   f. Recommend considering the addition of low-dose corticosteroids (up to 200 mg of IV hydrocortisone per day) as bolus or infusion
   g. Recommendation for bolus vs. continuous paralytics in patients with ARDS
5. Fluid management
   a. Recommend conservative fluid strategy over a liberal fluid strategy
6. Fluid selection
   a. Recommend crystalloids over colloids for acute resuscitation
   b. Recommend against routine use of albumin for initial resuscitation
   c. Recommend against hrydroxyethyl starches, gelatins, and dextrans
   d. Recommend buffered/balanced crystalloids over unbalanced crystalloids
   e. Recommend conservative fluid strategy (similar strategy in ARDS management)
7. Paralytics
   a. Recommendation for bolus vs. continuous paralytics in patients with ARDS to facilitate protective lung ventilation
   b. For patients with persistent ventilator dyssynchrony, the need for ongoing prone ventilation, or persistently high plateau pressures, we suggest using a continuous NMBA infusion for up to 48 hours
8. Pulmonary vasodilators and nitric oxide
   a. Recommend against routine use of inhaled nitric oxide for COVID-19 ARDS
   b. Recommend a trial of inhaled pulmonary vasodilators as recue therapy in patients with severe ARDS and hypoxemia despite optimizing ventilation; if no rapid improvement noted then should be tapered off

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V. Clincal Research Summary - COVID-19

Clinical Research within BSMH Office of Research and Innovation is proactively reviewing research opportunities during this rapidly changing COVID-19 pandemic. For questions or inquiries please email ClinicalResearch@BSMHealth.org . All emails are monitored daily.

Please note that all COVID-19 related research, clinical trials or expanded access (also know as compassionate use) of drugs requires IRB involvement.

Remdesivir Overview: • Anti-viral agent that has shown to be effective against MERS-CoV, SARS-CoV, which are related to SARS-CoV-2 (Causes COVID-19) • May be effective against COVID-19. This drug is not commercially available but we have worked to identify how to obtain from the manufacturer and built the drug records in Epic so we are prepared to use. There would be no direct cost to obtain. • Has shown superior efficacy to lopinavir/ritonavir + ribavirin which led to better outcomes in the treatment of MERS-CoV. Dosing: • Intravenous (IV) infusion of 200mg loading dose on day 1, followed by 100mg daily doses for 9 days Preparation and administration: • Each single-use vial contains 100mg of remdesivir • Reconstitute each vial with 19 mL sterile water for injection for a concentration of 5 mg/mL • Further dilute into 0.9% Normal Saline for intravenous infusion with total volume of up to 250 mL • Administer over 30 - 60 minutes. After administration is complete, flush the IV line with at least 30 mL of 0.9% normal saline Storage: • Up to 4 hours at room temperature • Up to 24 hours at refrigerated temperature *_**There are no clinical trials are currently enrolling at**	**Not commercially available in the USA** **Manufacturer: Gilead** **Expanded Access program** Gilead may accept patients via expanded use program – Pregnant or < 18 years **ONLY** **https://rdvcu.gilead.com/** **Criteria for Expanded Access:** • Patient must be hospitalized with confirmed COVID-19 (SARS-CoV-2) infection by PCR with clinical systems and on mechanical ventilation • Key Exclusion Criteria: Evidence of multi-organ failure, pressor requirements to maintain blood pressure, ALT levels > 5 X ULN, Cr Clearance < 30 mL/min or on dialysis/CVVH • IRB approval is required for Expanded Access program

Questions? Email Josh Crawford at Joshua_crawford@bshsi.org

BSMH facilities	
Actemra (tocilizumab) ● **Phase III clinical trial of Actemra/RoActemra in hospitalized patients with severe COVID-19 pneumonia (COVACTA)** ○ https://www.roche.com/media/releases/med-cor-2020-03-19.htm ○ Roche as well as the Biomedical Advanced Research and Development Authority (BARDA) are working together to complete a clinical trial studying Actemra (tocilizumab) in patients who have severe COVID-19 pneumonia requiring hospitalization. ○ The study is hoped to be randomized, double-blind, and placebo controlled. ○ The treatment group will receive standard of care treatment as well as tocilizumab; the placebo group will receive standard of care treatment as well as placebo. ○ Primary and secondary endpoints include: "Clinical status, mortality, mechanical ventilation and ICU variables." ○ It is hoped that the trial will enroll 330 patients throughout the world. ○ The trial is set to start enrolling patients in early April. ○ Participants will be studied for 60 days following initial randomization. ○ Researchers plan to complete an interim analysis to determine if there is data to suggest early efficacy. ○ Dosing, preparation, and storage to be determined by study ******There are no clinical trials are currently enrolling at BSMH facilities*	**Commercially available in the USA** **Manufacturer: Roche** **Expanded Access to be determined by sponsor and FDA**
Kevzara (sarilumab) ● **An Adaptive Phase 2/3, Randomized, Double-Blind, Placebo-Controlled Study Assessing Efficacy and Safety of Sarilumab for Hospitalized Patients with COVID-19 (NCT04315298; recruiting)**	**Commercially available in the USA** **Manufacturer: Sanofi and Regeneron Pharmaceuticals** **Expanded Access to be determined by**

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https://clinicaltrials.gov/ct2/show/NCT04315298?term=kevzara&cond=covid19&draw=2&rank=1#contacts ○ This trial was posted March 19, 2020, anticipating an enrollment of 400 patients in New York medical centers. The primary objective of phase 2 is to evaluate the clinical efficacy of sarilumab versus a control arm in adult patients hospitalized with severe COVID-19; the primary objective of phase 3 expands its evaluation to adult patients hospitalized with severe and critical COVID-19. ○ Key inclusion criteria: ▪ Laboratory confirmed SARS-CoV2 infection ▪ Hospitalization with illness of any duration with evidence of pneumonia and severe disease, critical disease, or multi-system organ dysfunction at baseline ○ Key exclusion criteria: ▪ Unlikely to survival for >48 hours from screening (clinical judgment) ▪ ANC <2000, AST/ALT >5x ULN, plt <50,000 ▪ Treatment with anti-IL 6, anti-IL-6R antagonists, or JAKi in the past 30 days or plans to receive during study ▪ Current treatment with DMARDs/immunosuppressive agents ▪ Chronic oral corticosteroids (non-COVID-19-related condition) >prednisone 10 mg or equivalent per day ▪ Autoimmune or inflammatory systemic or localized disease(s) other than rheumatoid arthritis ▪ Known active TB, Hx of incompletely treated TB, suspected or known extrapulmonary TB, suspected	**Sanofi** https://www.sanofi.com/en/science-and-innovation/clinical-trials-and-results/compassionate-use-expanded-access • IRB approval is required for Expanded Access program

or known systemic bacterial or fungal infections ▪ Immunosuppressive antibody therapy within the past 5 months, including IVIG or plans to receive during study ○ Patients will receive either a high or low single IV dose of sarilumab or placebo. ○ The primary outcome for phase 2 is time to resolution of fever for at least 48 hours without antipyretics for 48 hours; the primary outcome for phase 3 is the percentage of patients reporting each severity rating on a 6-point ordinal scale: death; hospitalized, on invasive mechanical ventilation or ECMO; hospitalized, non-invasive mechanical ventilation or high flow oxygen devices; hospitalized, requiring supplemental oxygen therapy; hospitalized, not requiring supplemental oxygen therapy; and not hospitalized. ○ Dosing, preparation, and storage determined study ***There are no clinical trials are currently enrolling at BSMH facilities***	

Anectdotal Corner

Questions? Email Josh Crawford at Joshua_crawford@bshsi.org

SmartSet: BSMH IP UNKNOWN RESPIRATORY PATHOGEN (COVID) FOCUSED (ID:5961)

General Information

Display name: Unknown Respiratory Pathogen (COVID) Focused

Type: General

Merge priority:

Version comment:

Content source:

Synonyms:
1. coronavirus
2. COVID-19
3. corona virus
4. wuhan
5. hydroxychloroquine
6. chloroquine
7. PLAQUENIL

SmartSet notes:

Description: Identify a Decision Maker and address Ventilation and Resuscitation preferences for all COVID-19 hospitalized patients.

Web information:

	Title	URL
1.		

Questionnaire:

Configuration

General

Isolation

☑ DROPLET PLUS	Routine, CONTINUOUS, Starting S at 4:00 AM, Droplet Plus Isolation consists of: Droplet plus Contact plus Eye Protection (face shield/goggles)

Nursing Interventions

☑ PPE Instructions	Routine, CONTINUOUS, Starting S at 4:00 AM Description of Order: PPE required for any aerosolizing procedure (ie, intubation, bronchoscopy). Surgical mask on patient for any transport outside room. Patient should be single room, closed door with notification of droplet plus isolation.

Labs

Labs

☐ RESPIRATORY VIRAL PANEL, PCR	
☐ RESPIRATORY VIRAL PANEL, PCR	ONE TIME For 1 Occurrences Specimen source: Nasopharyngeal
☐ RESPIRATORY PANEL,PCR,NASOPHARYNGEAL	
☐ RESPIRATORY PANEL,PCR,NASOPHARYNGEAL	STAT, ONE TIME For 1 Occurrences
☐ RESPIRATORY PATHOGEN PROFILE, PCR	
☐ RESPIRATORY PATHOGEN PROFILE, PCR	ONE TIME For 1 Occurrences, Specimen source: Nasopharyngeal
☐ LEGIONELLA PNEUMOPHILA AG, URINE	
☐ LEGIONELLA PNEUMOPHILA AG, URINE	STAT, ONE TIME For 1 Occurrences Specimen source: Urine
☐ LEGIONELLA AG, URINE	
☐ LEGIONELLA AG, URINE	ONE TIME For 1 Occurrences
☐ S.PNEUMO AG, UR/CSF	
☐ S.PNEUMO AG, UR/CSF	STAT, ONE TIME For 1 Occurrences Specimen source:
☐ STREP PNEUMO AG, URINE	
☐ STREP PNEUMO AG, URINE	STAT, ONE TIME For 1 Occurrences
☐ PROCALCITONIN	ONE TIME For 1 Occurrences
☐ CBC WITH AUTOMATED DIFF	STAT, ONE TIME For 1 Occurrences
☐ METABOLIC PANEL, COMPREHENSIVE	STAT, ONE TIME For 1 Occurrences
☐ PROTHROMBIN TIME + INR	STAT, ONE TIME For 1 Occurrences
☐ CULTURE, RESPIRATORY/SPUTUM/BRONCH W GRAM STAIN	
☐ CULTURE, RESPIRATORY/SPUTUM/BRONCH W GRAM STAIN	STAT, ONE TIME For 1 Occurrences
☐ LOWER RESPIRATORY CULTURE	
☐ LOWER RESPIRATORY CULTURE	STAT, ONE TIME For 1 Occurrences
☐ C REACTIVE PROTEIN, QT	STAT, ONE TIME For 1 Occurrences

☐ LD	STAT, ONE TIME For 1 Occurrences
☐ FERRITIN	STAT, ONE TIME For 1 Occurrences
☐ D DIMER	STAT, ONE TIME For 1 Occurrences
☐ TROPONIN I	STAT, ONE TIME For 1 Occurrences
☐ LACTIC ACID	STAT, ONE TIME For 1 Occurrences

COVID-19 Labs

☐ EMERGENT DISEASE PANEL	
☐ EMERGENT DISEASE PANEL	STAT, ONE TIME For 1 Occurrences Has CDC form been completed?
☐ NOVEL CORONAVIRUS (COVID-19)	
☐ NOVEL CORONAVIRUS (COVID-19)	STAT, ONE TIME For 1 Occurrences
☐ SARS-COV-2	
☐ SARS-COV-2	STAT, ONE TIME For 1 Occurrences
☐ COVID-19	
☐ COVID-19	STAT, ONE TIME For 1 Occurrences
☐ MISC. LAB TEST	
☐ MISC. LAB TEST	STAT, ONE TIME For 1 Occurrences Test description: Specimen type:

Imaging

Imaging - Chest

☐ XR CHEST PA LAT	Routine, ONE TIME Transport: Reason for Exam: Is Patient Pregnant?
☐ XR CHEST PORT	Routine, ONE TIME Reason for Exam: Is Patient Pregnant?

Medications

Pain/Fever Management

☑ acetaminophen PO or PR panel	**"Or" Linked Panel**
☑ acetaminophen (TYLENOL) tablet	650 mg, Oral, EVERY 6 HOURS AS NEEDED, Mild Pain, Fever, For temp greater than 100.4 F (38 C)
☑ acetaminophen (TYLENOL) suppository	650 mg, Rectal, EVERY 6 HOURS AS NEEDED, Pain, Fever, For temp greater than 100.4 F (38 C)

Experimental Medications

- ☐ hydroxychloroquine (PLAQUENIL) PO tablet panel — **"Followed by" Linked Panel**
  - ☐ hydroxychloroquine (PLAQUENIL) tablet — 400 mg, Oral, EVERY 12 HOURS For 2 Doses
  - ☐ hydroxychloroquine (PLAQUENIL) tablet — 200 mg, Oral, EVERY 12 HOURS For 4 Days

- ☐ hydroxychloroquine (PLAQUENIL) PO suspension panel — **"Followed by" Linked Panel**
  - ☐ hydroxychloroquine (PLAQUENIL) 25 mg/ml oral suspension — 400 mg, Oral, EVERY 12 HOURS For 2 Doses
  - ☐ hydroxychloroquine (PLAQUENIL) 25 mg/ml oral suspension — 200 mg, Oral, EVERY 12 HOURS For 4 Days

- ☐ hydroxychloroquine PO tablet AND azithromycin PO tablet panel
  - ☐ hydroxychloroquine (PLAQUENIL) PO tablet panel — **"Followed by" Linked Panel**
    - ☐ hydroxychloroquine (PLAQUENIL) tablet — 400 mg, Oral, EVERY 12 HOURS For 2 Doses
    - ☐ hydroxychloroquine (PLAQUENIL) tablet — 200 mg, Oral, EVERY 12 HOURS For 4 Days
  - ☐ azithromycin (ZPACK) panel — **"Followed by" Linked Panel**
    - ☐ azithromycin (ZITHROMAX) tablet — 500 mg, Oral, NOW Starting S For 1 Doses
    - ☐ azithromycin (ZITHROMAX) tablet — 250 mg, Oral, DAILY Starting S+1 For 4 Doses
  - ☐ EKG, 12 LEAD, INITIAL — Routine, TOMORROW AM, Starting S+1 at 4:00 AM For 1 Occurrences
    Reason for Exam: R/o QTc abnormality

- ☐ hydroxychloroquine PO suspension AND azithromycin PO tablet panel
  - ☐ hydroxychloroquine (PLAQUENIL) PO suspension panel — **"Followed by" Linked Panel**
    - ☐ hydroxychloroquine (PLAQUENIL) 25 mg/ml oral suspension — 400 mg, Oral, EVERY 12 HOURS For 2 Doses
    - ☐ hydroxychloroquine (PLAQUENIL) 25 mg/ml oral suspension — 200 mg, Oral, EVERY 12 HOURS For 4 Days
  - ☐ azithromycin (ZPACK) panel — **"Followed by" Linked Panel**
    - ☐ azithromycin (ZITHROMAX) tablet — 500 mg, Oral, NOW Starting S For 1 Doses
    - ☐ azithromycin (ZITHROMAX) tablet — 250 mg, Oral, DAILY Starting S+1 For 4 Doses
  - ☐ EKG, 12 LEAD, INITIAL — Routine, TOMORROW AM, Starting S+1 at 4:00 AM For 1 Occurrences
    Reason for Exam: R/o QTc abnormality

Criteria

Suggestions:

Filter:

Restrict SmartSet: ☐

Settings

Discontinue action:	
Deselect sections for Pended/Held orders:	☐
Pended/Held orders display:	
Release date:	Use System Definitions Setting
Disallow user override:	☑

SmartSet: UNKNOWN RESPIRATORY PATHOGEN (COVID) FOCUSED (ID:3040002318)

General Information

Display name: Unknown Respiratory Pathogen (COVID) Focused

Type: General

Merge priority:

Version comment:

Content source:

Synonyms:
1. CORONAVIRUS
2. CORONA VIRUS
3. COVID-19
4. WUHAN
5. hydroxychloroquine
6. chloroquine
7. PLAQUENIL

SmartSet notes:

Description: Identify a Decision Maker and address Ventilation and Resuscitation preferences for all COVID-19 hospitalized patients.

Web information:

	Title	URL
1.		

Questionnaire:

Configuration

General

Nursing Interventions

☑ PPE Instructions	Routine, ONE TIME, Starting S PPE required for any aerosolizing procedure (i.e., intubation, bronchoscopy). Surgical mask on patient for any transport outside room. Patient should be single room, closed door with notification of droplet plus isolation.

Isolation

☑ Droplet Plus Isolation	Routine, CONTINUOUS Droplet Plus Isolation consists of: Droplet plus Contact plus Eye Protection (face shield/goggles)

Labs

COVID-19 Labs

☐ Emergent Disease Panel	STAT, ONE TIME, Starting S, Specimen Requirements: - Upper respiratory - Nasopharyngeal AND Oropharyngeal swabs (swabs must be synthetic and have plastic shafts) in separate transport media, 3-4ml - Lower Respiratory - (if productive cough) - Sputum in sputum cup or sterile container OR Bronchoalveolar lavage, tracheal aspirate 2-3ml in sputum cup or sterile container - Call lab and alert them of PUI - Add "red dot" label to specimens - Double bag specimen before sending to the lab
☐ COVID-19	STAT, ONE TIME, Starting S

Labs

☐ CBC Auto Differential	STAT, ONE TIME, Starting S
☐ Comprehensive Metabolic Panel	STAT, ONE TIME, Starting S
☐ Protime-INR	STAT, ONE TIME, Starting S
☐ Procalcitonin	STAT, ONE TIME, Starting S
☐ C-Reactive Protein	STAT, ONE TIME, Starting S
☐ Lactate Dehydrogenase	STAT, ONE TIME, Starting S
☐ Ferritin	STAT, ONE TIME, Starting S
☐ D-Dimer, Quantitative	STAT, ONE TIME, Starting S
☐ Troponin	STAT, ONE TIME, Starting S
☐ Lactic Acid, Plasma	STAT, ONE TIME, Starting S
☐ Legionella antigen, urine	STAT, ONE TIME, Starting S
☐ Strep Pneumoniae Antigen	STAT, ONE TIME, Starting S
☐ Culture, Respiratory, Sputum	STAT, ONE TIME, Starting S

Respiratory Panel- Toledo, Lorain, Summa, and Kentucky

☐ Respiratory Virus PCR Panel	STAT, ONE TIME, Starting S

Respiratory Panel- Springfield

☐ Respiratory Disease Panel PCR	STAT, ONE TIME, Starting S

Respiratory Panel- Cincinnati, Youngstown, and Lima

☐ Respiratory Panel, Molecular	STAT, ONE TIME, Starting S

Imaging

Imaging - Chest

☐ XR CHEST STANDARD (2 VW)	Routine, 1 TIME IMAGING For 1 Reason for exam: Portable?
☐ X-ray chest AP portable	Routine, 1 TIME IMAGING For 1 Reason for exam: Portable?

Medications

Pain/Fever Management

☑ acetaminophen PO or PR panel	**"Or" Linked Panel**
☑ acetaminophen (TYLENOL) tablet	650 mg, Oral, EVERY 6 HOURS PRN, Pain Mild (1-3), Fever, For temp greater than 100.4 F (38 C)
☑ acetaminophen (TYLENOL) suppository	650 mg, Rectal, EVERY 6 HOURS PRN, Pain Mild (1-3), Fever, For temp greater than 100.4 F (38 C) Administer if oral route cannot be used.

Experimental Medications

☐ hydroxychloroquine PO tablet panel	**"Followed by" Linked Panel**
☐ hydroxychloroquine (PLAQUENIL) tablet	400 mg, Oral, EVERY 12 HOURS, For 2 Doses
☐ hydroxychloroquine (PLAQUENIL) tablet	200 mg, Oral, EVERY 12 HOURS, Starting H+24 Hours, For 4 Days
☐ hydroxychloroquine PO suspension panel	**"Followed by" Linked Panel**
☐ hydroxychloroquine (PLAQUENIL) oral suspension	400 mg, Oral, EVERY 12 HOURS, For 2 Doses
☐ hydroxychloroquine (PLAQUENIL) oral suspension	200 mg, Oral, EVERY 12 HOURS, Starting H+24 Hours, For 4 Days
☐ hydroxychloroquine PO tablet AND azithromycin PO tablet panel	
☐ hydroxychloroquine PO tablet panel	**"Followed by" Linked Panel**
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☐ hydroxychloroquine (PLAQUENIL) tablet	200 mg, Oral, EVERY 12 HOURS, Starting H+24 Hours, For 4 Days
☐ azithromycin (ZPACK) panel	**"Followed by" Linked Panel**
☐ azithromycin (ZITHROMAX) tablet	500 mg, Oral, DAILY, For 1 Doses
☐ azithromycin (ZITHROMAX) tablet	250 mg, Oral, DAILY, For 4 Doses
☐ EKG 12 Lead	Routine, TOMORROW AM, Starting S+1 at 6:00 AM For 1 Occurrences Reason for Exam? Other
☐ hydroxychloroquine PO suspension AND azithromycin PO tablet panel	
☐ hydroxychloroquine PO suspension panel	**"Followed by" Linked Panel**
☐ hydroxychloroquine (PLAQUENIL) oral suspension	400 mg, Oral, EVERY 12 HOURS, For 2 Doses

☐ hydroxychloroquine (PLAQUENIL) oral suspension	200 mg, Oral, EVERY 12 HOURS, Starting H+24 Hours, For 4 Days
☐ azithromycin (ZPACK) panel	**"Followed by" Linked Panel**
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☐ EKG 12 Lead	Routine, TOMORROW AM, Starting S+1 at 6:00 AM For 1 Occurrences Reason for Exam? Other

Criteria

Suggestions:

Filter:

Restrict SmartSet: ☐

Settings

Discontinue action:

Deselect sections for Pended/Held orders: ☐

Pended/Held orders display:

Release date: Use System Definitions Setting

Disallow user override: ☑