CLINICAL PATHWAY: Therapies for COVID-19

Inclusion Criteria:
- Positive for COVID-19 infection AND
- Fever with signs/symptoms of respiratory disease (e.g. cough, increased WOB) or chest X-ray with pulmonary infiltrates OR
- Risk factors for severe disease (active oncologic disease or chemotherapy within 1 year of presentation, chronic pulmonary disease or requiring chronic ventilation, hemodynamically significant corrected or uncorrected congenital heart disease, heart failure, chronic hypertension, significant neurologic/neuromuscular disease, immune deficiency (e.g. HIV, SCID), solid organ/bone marrow transplant, patients on immunosuppressant medications (e.g. SLE, vasculitis, IBD), poorly controlled diabetes mellitus [Hgb A1c ≥ 8], morbid obesity (BMI ≥ 30), etc.)

Exclusion Criteria:
- Infants < 6 months old

May consider treatment while COVID-19 test pending if critically ill and meets other criteria above (discuss with ID service)

Initial Management:
- Labs:
  - CBC with differential, chem 10, PT/PTT, fibrinogen, D-dimer, CRP, ESR, procalcitonin, LFTs, LDH, ferritin, triglycerides, 66PD assay, HIV screen if patient has risk factors, Hgb A1C in diabetic patients
  - If ferritin >500 mcg/ml: obtain cytokine panel* (IL-6, IL-1, NK cell activity)
  - If COVID-19 testing at outside location uncertain or projected TAT > 48 hours, send COVID-19 test
- Studies:
  - EKG
  - Chest-Xray
- Consults:
  - Infectious Disease (required)
  - Rheumatology if suspected clinical/laboratory evidence of cytokine storm syndrome
  - Note: In order to conserve PPE, consultants will strongly consider waiving the physical examination. Nevertheless, a formal consult should be placed.

Treatment Considerations: Primarily supportive in nature with a focus on treatment of pneumonia, respiratory failure, ARDS, sepsis and septic shock (see Septic Shock Pathway)

See Appendix A for Medication/Treatment Concepts

Daily Laboratory Monitoring:
The lab schedule is recommended based on algorithms used at other medical centers. The frequency and labs obtained will be dependent on the patient’s clinical status and judgment of the healthcare team.

- CBC with differential, chem 10, PT/PTT, fibrinogen, D-dimer, CRP, procalcitonin, ferritin
- In patients with suspected clinical or laboratory evidence of cytokine storm syndrome, add: LFT’s, LDH, triglycerides

Children and Adults
1) Start hydroxychloroquine sulfate (in conjunction with ID consult)
   - Dosing:
     - o Dose for Day 1: 6.5 mg/kg/dose PO/NG q12hr x 2 doses (max 400 mg/dose)
     - o Dose for Days 2 to 5: 3.25 mg/kg/dose q12hr (max 200 mg/dose)
     - o In patients with extended ventilation or immunosuppression, duration may be extended
   - Can be started before 66PD screen resulted.
     - o If 66PD positive, consult Hematology/Oncology
   - Obtain EKG after 2nd loading dose to monitor QTc
     - o In patients with known prolonged QTc, consult Cardiology before initiating therapy to help assess risk benefit ratio for treatment
     - o If QTc after 2nd loading dose is prolonged, consult Cardiology service to discuss ECG monitoring and drug management
   - If limited supply of hydroxychloroquine, use chloroquine phosphate Dose: 8.3 mg/kg/dose PO/NG q12hr for 5-10 days (max 500 mg/dose or 1000 mg/day)
2) Patients with prolonged QTc or other contraindications for hydroxychloroquine:
   - Begin lopinavir/ritonavir (Kaletra)
   - Dosing per Infectious Disease

* Consider placing patient in prone position

1) Initiate or continue hydroxychloroquine, chloroquine, or Kaletra
   (hydroxychloroquine is the 1st choice treatment, followed by chloroquine then Kaletra)
2) For patients who are <18 years of age or pregnant
   - Begin application process for compassionate use of remdesivir Appendix B
   - If approval obtained, add remdesivir
   - Patients ≥ 18 years of age are not eligible for remdesivir

* Consider placing patient in prone position

For patients with evidence of CYTOKINE STORM SYNDROME (e.g. high fever, worsening coagulopathy, ARDS, elevated ferritin):
- Consult Rheumatology
- Begin tocilizumab
  - o Wt <30 kg: 12 mg/kg IV x1 dose
  - o Wt ≥30 kg: 8 mg/kg IV x1 dose (max 800 mg/dose)
  - o A 2nd dose can be given separated by at least 12 hours based on clinical response
- If tocilizumab unavailable, consider adding anakinra or emapalumab
- Steroids may be added following consultation with the ID and Rheumatology services

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Appendix A: Medication/Treatment Concepts

1. Therapy for patients with COVID-19 is primarily supportive in nature with a focus on treatment of pneumonia, respiratory failure, ARDS, sepsis and septic shock.

2. The agents recommended in these guidelines (hydroxychloroquine, lopinavir-ritonavir, remdesivir) are investigational or for compassionate use in symptomatic patients with COVID-19 infection.
   a. It is essential that we communicate to parents and guardians that the therapy their child is receiving is investigational in nature and is based on experience at other centers as well as data from published case series.
   b. Due to the investigational nature of these therapies, the Infectious Disease service should be consulted on all patients with COVID-19 infection to assist in management.

3. Hydroxychloroquine and chloroquine: Hydroxychloroquine and chloroquine have in vitro activity against SARS-CoV, SARS-CoV-2, and other coronaviruses, with hydroxychloroquine having relatively higher potency against SARS-CoV-2. Initial data from China indicated that chloroquine treatment of patients with COVID-19 had clinical and virologic benefit, and therefore, was recommended as antiviral for treatment of COVID-19. Based upon limited in-vitro and anecdotal data, chloroquine or hydroxychloroquine are currently recommended for treatment of patients hospitalized with COVID-19 in several countries. We are recommending use of hydroxychloroquine for COVID-19 positive patients who have oxygen saturations < 94%, or are immunosuppressed or medically compromised with fever, increased WOB, and/or pulmonary infiltrates on chest X-ray. Chloroquine may be used as an alternative if supplies of hydroxychloroquine diminish.

4. Antiviral therapy:
   a. Lopinavir-ritonavir (Kaletra): Kaletra did not show promise for treatment of patients with COVID-19 hospitalized with pneumonia in a recent clinical trial in China. Due to small sample size of that study, a follow up investigation by the World Health Organization (WHO) study is underway. Due to the lack of treatment options in patients with contraindication to hydroxychloroquine use, we are recommending use of Kaletra for COVID-10 positive patients who meet criteria but cannot receive another antiviral agent.
      i. Kaletra tablets should be used in patients who are able to swallow pills. In those unable to swallow pills, may use solution instead. Crushing tablets leads to approximately 50% loss of drug exposure. Solution should only be given with food. When feeding tubes are necessary, must note that silicone or polyvinyl chloride tube are compatible with this medication.
      ii. Kaletra is a very potent CYP 450 3A4 inhibitor. Its concentration will be decreased by potent CYP inducers (e.g. rifampin), and it can increase other medications that are substrates of CYP 3A4.
b. Remdesivir: Remdesivir is an investigational antiviral drug produced by Gilead Sciences that inhibits viral replication and has \textit{in vitro} activity against SARS-CoV-2 and in-vitro and in-vivo activity against related betacoronaviruses. There are currently one phase 2 and two phase 3 trials for treatment of COVID-19 infection. Remdesivir is currently available on a compassionate use basis for intubated COVID-19 patients who are < 18 years of age or are pregnant. Current inclusion and exclusion criteria are listed in the table below. If a patient is eligible and remdesivir is approved for use by Gilead Sciences, we are recommending use of remdesivir for intubated patients with COVID-19 infection. Tocilizumab may be used concomitantly with remdesivir. Currently, antiviral agents with potential activity against COVID-19 (e.g., hydroxychloroquine, chloroquine, Kaletra) need to be discontinued 24 hours before the first dose of remdesivir is begun. If approved for remdesivir, follow current information from Gilead Sciences regarding its use.

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5. \textit{Antibiotics}: Based on the study in adults by Zhou, \textit{et. al.}, approximately 15% of hospitalized patients with COVID-19 infections developed a secondary bacterial infection (pneumonia or bacteremia with a positive culture). If there is clinical evidence or concern for pneumonia or sepsis, antibiotic therapy should be initiated as delineated in the CT Children’s pneumonia and septic shock clinical pathways.

6. \textit{Cytokine Storm Syndrome}: Reports from China have reported clinical signs of cytokine storm syndrome (CSS) in patients with COVID-19 infections, such as fever, hepatomegaly, splenomegaly, acute respiratory distress syndrome (ARDS), and coagulopathy. In addition, patients with COVID-19 have shown laboratory abnormalities consistent with CSS such as lymphopenia, thrombocytopenia and elevation of CRP, coagulation times, D-dimer, hepatic transaminases, ferritin, and soluble IL-2. The ideal treatment of COVID-19 induced CSS is unknown. However, there is anecdotal evidence that the IL-6 inhibitor tocilizumab may be beneficial in these patients. We recommend monitoring for laboratory evidence of CSS. If there is clinical or laboratory evidence suggestive of CSS, we recommend rapid initiation of tocilizumab. The Rheumatology Service should be consulted for all patients with signs of CSS. They can provide assistance in management and consideration of alternative treatment options.
therapies such as anakinra, an IL-1 blocker, and emapalumab, a gamma interferon blocker if supplies of tocilizumab are depleted.

7. **Azithromycin**: The study by Gautret, *et. al.*, showed that monotherapy with hydroxychloroquine led to a similar proportion of negative testing at day 6 of illness compared to combination therapy of azithromycin and hydroxychloroquine. Therefore, *routine* use of azithromycin is not recommended. Azithromycin may be used if no other medication options are available.

8. **Corticosteroids**: Use of corticosteroids should be avoided unless there is a clear indication for use, such as status asthmaticus or Cytokine Storm Syndrome. This recommendation is based on studies in related viruses, such as SARS-CoV and MERS-CoV, that have shown lack of effectiveness and possible harm. Steroids may be added to a patient’s treatment regimen following consultation with the ID and Rheumatology Services.

9. **Angiotensin-Converting Enzyme (ACE) Inhibitors, Angiotensin II Receptor Blockers (ARBs), and other Related Agents**: Theoretical concerns exist regarding the use of ACE inhibitors and ARBs, which may continue to increase viral entry into cells leading to a more severe disease course. At this time, there are no clinical or epidemiological data to confirm or dispel this hypothesis. A joint statement by Heart Failure Society of America, American College of Cardiology, and American Heart Association recommends continuation of these medications for patients for whom they are currently prescribed for indications known to be beneficial, such as heart failure or hypertension.

10. **Nonsteroidal Anti-inflammatory Drugs (NSAIDs)**: It has been hypothesized that NSAIDs may worsen COVID-19. There are no data suggesting an association between COVID-19 clinical outcomes and NSAID use. The Centers for Disease Control and Prevention (CDC) is currently not aware of scientific evidence establishing a link between NSAIDs (e.g., ibuprofen, naproxen) and worsening of COVID-19. The U.S Food and Drug Administration, the European Medicines Agency, the WHO, and CDC are monitoring the situation and will review new information regarding the effects of NSAIDs on COVID-19 infection as it becomes available.
References

CCMC Remdesivir Compassionate Use Request – March 2020

1. Drug availability
The manufacturer of remdesivir is Gilead Sciences, Inc.
• Gilead is willing to consider on a case-by-case basis providing the drug to individual patients via compassionate use requests. We’ve heard via a pharmacist listserv about hospitals that have already been able to get it.
• Gilead is only allowing pediatric patients (< 18 years old) or adult pregnant patients to still receive compassionate use remdesivir. Adult non-pregnant patients are required to be enrolled in a clinical trial or a soon to be released expanded access protocol.

2. Patient eligibility
• Please make careful note of Gilead’s inclusion and exclusion criteria:

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• Given these criteria, it is crucial to request the drug once a patient is intubated and on mechanical ventilation because once a patient develops multi-system organ dysfunction/ failure, he or she is no longer eligible for the drug.
• Patients who are receiving other experimental antiviral agents still may be considered for remdesivir, but these other drugs must be stopped before initiating remdesivir.

3. Involvement of ID service in compassionate use requests:
• We have recommended that the ICU team consult the Infectious Diseases Service as soon as a patient has a confirmed diagnosis of COVID-19 independent of the level of respiratory support required
• The Infectious Diseases Service will assist the PICU attending physician in the process applying for compassionate use of remdesivir.
• If Gilead Sciences has approved use of remdesivir, the PICU and Infectious Diseases attending physicians will document that they have discussed the rationale for use, potential benefits and risks of this agent with the patient’s parents or legal guardian.

4. Instructions for submitting remdesivir compassionate use requests:
A. Gilead application (to be completed by the PICU attending physician):
• Gilead has created a web-based application form. See separate pdf of current information required in web-based form.

Advance Prep – Print and fill out a blank copy of the form for your specific case so you’ll have the responses ready when you need to complete the online form.
• Once your patient meets inclusion criteria, go to https://rdvcu.gilead.com
• Click “I’m a healthcare professional,” then click “Next” to access the web-based application form.
• Fill out the form completely, check off the Confidential Disclosure Agreement (CDA) and Gilead case review policy boxes, then click submit. Save an electronic copy of the CDA for team distribution.
• Contact the team members below by email with an attached copy of the CDA once the request for compassionate use of remdesivir is submitted:
  o Matthew Wallace, Director of Pharmacy
    Email: mwallace@connecticutchildrens.org
    Cell phone: 860-208-0925
  o Paulette Grocki, Lead Pharmacy Clinical Specialist
    Email: pgrocki@connecticutchildrens.org
    Phone: 860-545-8017
  o Laurie Boan, Research Pharmacist
    Email: lboan@connecticutchildrens.org
    Phone: 860-545-9935
  o Alison Oville, Director Clinical Trials
    Email: aoville@connecticutchildrens.org
    Phone: 860-837-5879
  o James Santanelli, Lead Clinical Research Assistant
    Email: jsantanelli@connecticutchildrens.org
    Phone: 860-837-5873
  o Francis DiMario, Director CCMC IRB
    Email: fdimario@connecticutchildrens.org

B. FDA application: (responsible individual: James Santanelli Lead Clinical Research Assistant)
• Refer to the guidance document titled “Instructions for compassionate use request (eIND) application” for details about requesting FDA authorization and completing the eIND application process using Form FDA 3926.
• The guidance document includes a sample completed Form FDA 3926 for remdesivir for a hypothetical patient.

Advance Prep – Fill out Form FDA 3926, leaving the field for the IND number blank. Upon receiving initial FDA authorization via telephone or email, you will be assigned an IND number and can then submit the form.

C. IRB application: (responsible individual: Allison Oville, Director Clinical Trials)
• Remdesivir will be used on an individual basis for treatment of COVID-19 infection and will require a formal process to request deferral of prospective IRB review.
• A letter to must be submitted to the IRB within 5 days of use of remdesivir including the clinical circumstance and absence of any other treatment option in light of a risk to life or limb. This letter be signed by the treating MD and a second MD NOT directly involved in the patient’s care attesting to these facts.
• The treatment protocol and an informed consent or information sheet for parent/patient must be submitted with that request. The IRB provide a template letter for this purpose. A letter from the IRB will be sent back to the requesting MD who in turn provides it to the pharmaceutical company so they can send the drug.
**CLINICAL PATHWAY:**
Therapies for COVID-19
Appendix B: CCMC Remdesivir Compassionate Use Request – March 2020

**Advance Prep** – Prepare the consent form and fill out and save the application. Once the FDA has provided initial authorization, you will be able to upload the approval email and Form FDA 3926 and enter the IND number in the appropriate section, then submit the application.

**Note to IRB for Emergency Exemption to Prospective IRB Review**

The IRB Chair or HRPP Director needs to be notified in writing within 5 days of use that;

(I) Dr. ________ is seeking emergency exemption to prospective IRB review.

(II) The elements of a report from Dr. ________ to the IRB should include a statement; that the subject is in a potentially life or limb-threatening situation in which no standard acceptable treatment is available, and in which there is not sufficient time to obtain prior IRB approval.

(III) A parental permission/informed consent to the treatment must be documented in writing.

(IV) There must be a signature from a colleague not directly caring for the subject who acknowledges the need for the treatment.

(V) The IRB must be notified within 5 working days.

[NOTE: Any subsequent use of this treatment/product is subject to IRB review. So, if it is likely that this intervention will be used repeatedly in the future then there should be an IRB application submitted prior to the next circumstance. An IND, IDE or HUD may also be needed in support of this application.]