Inpatient Therapies for COVID-19

Inclusion Criteria:
- Positive for COVID-19 infection AND
- Oxygen saturations < 94% AND/OR
- 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.)

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

Initial Management:
- CBC with differential, chem 10, PT/PTT, fibrinogen, D-dimer, CRP, ESR, procalcitonin, LFTs, LDH, ferritin, triglycerides
- If suspected cardiac involvement: add troponin, NT-proBNP, CKMB
- IFN-
- IV (IL-6, IL-1, NK cell activity)
- If COVID-19 testing at outside location uncertain or projected turnaround time > 48 hours, send COVID-19 test

Consults:
- Infectious Diseases (required)
- Rheumatology if suspected clinical/laboratory evidence of cytokine storm syndrome* and need for escalation of treatment

General Treatment Considerations:
- Consider placing patient in prone position
- Management is primarily supportive in nature with a focus on treatment of pneumonia, respiratory failure, ARDS, sepsis and septic shock (see Septic Shock Pathway)
- Please utilize COVID-19 VTE algorithm to determine interventions to prevent or treat for thrombosis
- If concern for Multi-system Inflammatory Syndrome in Children (MIS-C), see MIS-C Clinical Pathway
- Consider other signs of systemic severe illness, in consultation with ID

Medications:
- See Appendix A for Ordering, Dosing and Administration Guidelines

Remdesivir:
- Begin in patients with suspected or confirmed COVID-19 infection with SpO2 ≤94% on RA or requiring supplemental oxygen, mechanical ventilation, and/or ECMO
  - Can be considered in other severe cases without hypoxia, in consultation with ID
- Considerations:
  - If patient is on chloroquine phosphate or hydroxychloroquine sulfate at baseline (i.e., lupus), co-administration with remdesivir is not recommended (see Appendix B for more information)

Dexamethasone:
- Consider routine use in patients who require supplemental oxygen

Baricitinib:
- Consider for patients requiring HFNC, BIPAP, mechanical ventilation or ECMO
- To be used in conjunction with remdesivir, in consultation with Rheumatology and ID

Daily Laboratory Monitoring:
The lab schedule is recommended based on algorithms used at other medical centers. The labs obtained and frequency of labs 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
- For patients who are on remdesivir, add: LFTs (can space to every other day if baseline LFTs normal)
- In patients with suspected clinical or lab evidence of cytokine storm syndrome**, add: LFTs, LDH, triglycerides

Discharge Considerations:
- Follow up with ID (and Rheumatology, if involved)
- Refer to COVID-19 Cardiology Return to Play Algorithm

**For patients with evidence of CYTOKINE STORM SYNDROME (e.g. high fever, worsening coagulopathy, ARDS, elevated ferritin):
- Consult Rheumatology for escalation of treatment
- Begin treatment with one of the following:
  - Tocilizumab: 8mg/kg/dose IV x 1 dose for weight < 30 kg, 8 mg/kg (max 800mg/dose) IV x 1 dose for weight ≥ 30 kg. A 2nd dose can be given separated by at least 12 hours based on clinical response (caution should be used in cases of leukopenia or transaminitis) OR
  - Anakinra: 2 mg/kg/dose (max 100 mg/dose) IV q4h OR
  - If these treatments are unavailable, may consider emapalumab
- Steroids should be added if not already receiving, following consultation with the ID and Rheumatology services

Important References:
Refer to CT Children’s COVID-19 Intranet site, under “Care for COVID-19 Patient” for more resources.

If there is a clinical suspicion for Multi-System Inflammatory Syndrome in Children (MIS-C), please follow the MIS-C Clinical Pathway.

Clinical suspicion would include:
- Fever ≥100.4°F for ≥24 hours AND any one of the following:
  - GI: abdominal pain, diarrhea, vomiting
  - CV: chest pain, arrhythmia, signs of shock, hypotension
  - Musculoskeletal: rash, oral changes, conjunctivitis, extremity swelling/peeling
  - Resp: cough, shortness of breath, difficulty breathing
  - Neuro: altered mental status, headache, irritability
(Bolded symptoms are most common presenting symptoms)

* Cytokine studies
- IL-1 and IL-6: 1 ml red top
  - IL-1 levels are done at Quest labs on Wed with~7 day turnaround time
  - IL-6 levels are done at Quest labs on Tues with~5-12 day turnaround time
- NK cell killer activity is done at Quest Labs from Fri with a 4-8 day turnaround time. A 5 ml (preferred 10 ml) sample in a green sodium heparin tube must be sent to the lab between 2-3 PM Mon-Thurs for direct shipping to Quest

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- Begin treatment with one of the following:
  - Tocilizumab: 8mg/kg/dose IV x 1 dose for weight < 30 kg, 8 mg/kg (max 800mg/dose) IV x 1 dose for weight ≥ 30 kg. A 2nd dose can be given separated by at least 12 hours based on clinical response (caution should be used in cases of leukopenia or transaminitis) OR
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  - If these treatments are unavailable, may consider emapalumab
- Steroids should be added if not already receiving, following consultation with the ID and Rheumatology services

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This pathway is subject to change, based on evolving recommendations from the CDC and CT DPH.
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REMDESIVIR

- Inclusion:
  - Suspected or confirmed COVID-19 infection with SpO2 ≤94% on RA of requiring supplemental oxygen, mechanical ventilation, and/or ECMO
    - Can be considered in other severe cases without hypoxia, in consultation with ID
  - Note: if patient is on chloroquine phosphate or hydroxychloroquine sulfate at baseline (ie, lupus), co-administration with remdesivir is not recommended
- How to obtain:
  - Utilize Emergency Use Authorization – see Appendix B for appropriate utilization.
- Dosing if NOT on mechanical ventilation or ECMO: (IV infusions are run over 30-120 minutes)
  - ≥40 kg: Day 1: load with 200 mg IV once; then days 2-5: 100 mg IV once daily
  - 3.5 kg - <40 kg: [powdered formulation only]: On day 1, load with 5 mg/kg IV once; then days 2-5, administer 2.5 mg/kg IV once daily
  - Consider prolonged duration in individual situations, in consultation with ID
- Dosing if ON invasive mechanical ventilation or ECMO:
  - ≥40 kg: Day 1: load with 200 mg IV once; then days 2-10: 100 mg IV once daily
  - 3.5 kg - <40 kg: [powdered formulation only]: On day 1, load with 5 mg/kg IV; then days 2-10, administer 2.5 mg/kg IV once daily

DEXAMETHASONE:

- Inclusion:
  - Consider routinely using dexamethasone in patients who require supplemental oxygen (with or without remdesivir)
- Dosing:
  - 0.15 mg/kg IV or PO once daily (max 6 mg/dose) for up to 10 days (or until discharge, whichever is shorter)

BARICITINIB:

- Inclusion:
  - >2 year olds who require mechanical ventilation or higher level of support, in conjunction with remdesivir, in consultation with Rheumatology and ID
- How to obtain:
- Dosing:
  - <2 yrs old: not authorized
  - 2 yrs old – <9 yrs of age: 2 mg once daily
  - ≥9 yrs old: 4 mg once daily
  - Dosing adjustments are recommended for laboratory abnormalities, including renal impairment
- Duration:
  - For 14 days, or until hospital discharge, whichever comes first
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. 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.

2. The agents recommended in these guidelines (remdesivir, baricitinib) 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. Antiviral therapy:
   a. Remdesivir: Remdesivir is an antiviral drug produced by Gilead Sciences that inhibits viral replication and has in vitro activity against SARS-CoV-2 and in-vivo activity against related betacoronaviruses.
      i. Remdesivir is FDA approved for those who are ≥ 12 years of age and ≥ 40 kg. It is only available by Emergency Use Authorization (EUA) for patients with suspected or confirmed COVID-19 disease who are less than 12 years old and weigh at least 3.5 kg, and for patients who are ≥ 12 years old and weigh between 3.5 and 40 kg. Please see below regarding important requirements for EUA usage. Please see the Inpatient Therapies for COVID-19 algorithm for indications for use.
      ii. Emergency Use Authorization:
          1. Utilize Health Care Provider FAQs and Patient/Family FAQs
          2. Provide patient/family the Patient/Family FAQ sheet and explain that the drug is not FDA approved, but available through the emergency use authorization. Patient and families have the option to refuse treatment. Providers should discuss potential risks and benefits, and that the full extent of these risks and benefits are unknown. Providers should discuss alternative treatments that are available (and those associated risks and benefits).
          3. Please note that providers need to report any serious adverse effects within 7 days (see Health Care Provider FAQs)
          4. Additional EUA information including educational information in Spanish is available at: https://www.gilead.com/remdesivir
iii. Remdesivir use is currently only recommended for patients with severe disease who require supplemental oxygen or have SpO2 <94% on room air. Remdesivir may also be considered in other severe cases without hypoxia, in consultation with the ID team.

b. **Baricitinib:** Baricitinib is a Janus kinase (JAK) inhibitor, and has FDA approval to treat adults with moderate-severe rheumatoid arthritis who have inadequate responses to tumor necrosis factor antagonist therapies. A randomized, double-blind, placebo-controlled clinical trial showed improved clinical outcomes in adults with COVID-19 infection, when used in conjunction with remdesivir.
   
i. Baricitinib has obtained Emergency Use Authorization to be used in combination with remdesivir, for treatment of suspected/laboratory confirmed COVID-19 in patients 2 years of age or older, who require supplemental oxygen, invasive mechanical ventilation, or ECMO. It can be obtained through EUA (see Healthcare Provider FAQs).
   
ii. Please consult the Rheumatology Team when considering this medication.

4. **Hydroxychloroquine:** To date, data regarding the benefit of hydroxychloroquine in COVID-19 positive patients with symptomatic disease remains unclear, with increased rates of toxicity noted in the adult population. In addition, co-administration of remdesivir and chloroquine phosphate or hydroxychloroquine sulfate is not recommended based on in vitro data demonstrating an antagonistic effect of chloroquine on the intracellular metabolic activation and antiviral activity of remdesivir. As such, we are no longer recommending the use of hydroxychloroquine for the treatment of COVID-19 positive patients.

5. **Antibiotics:** Based on the study in adults by Zhou, *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. **Cytokine Storm Syndrome:** Clinical signs of cytokine storm syndrome (CSS) have been recognized in some patients with COVID-19 infections, including fever, hepatomegaly, splenomegaly, acute respiratory distress syndrome (ARDS), and coagulopathy. In addition, these patients have demonstrated laboratory abnormalities 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 continues to be investigated, but there is increasing evidence that the IL-6 inhibitor tocilizumab and the IL-1 inhibitor anakinra can be beneficial in these patients. We recommend monitoring for laboratory evidence of CSS in patients with COVID-19. If there is clinical or laboratory evidence suggestive of CSS, we recommend rapid initiation of one of these medications. The Rheumatology Service should be consulted for all patients with signs of CSS. They can provide assistance in management and consideration of these medications or of alternative therapies (such as emapalumab, a gamma interferon blocker) if tocilizumab or anakinra are unavailable.

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.

8. **Corticosteroids**: The safety and efficacy of dexamethasone or other corticosteroids for COVID-19 treatment have not been sufficiently evaluated in pediatric patients. Importantly, the RECOVERY trial did not include a significant number of pediatric patients. As mortality rates are significantly lower among pediatric patients with COVID-19 than among adult patients with the disease, caution is warranted when extrapolating the results of this trial to patients aged less than 18 years old. Nevertheless, newer data in the adult literature suggest benefit of using dexamethasone in those who require a low level of oxygen support rather than reserving its use only for those who require a higher level of support. As such, utilization of dexamethasone should be considered for patients who are on supplemental oxygen.

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