PROTOCOL FOR INPATIENT DIAGNOSIS AND MANAGEMENT OF COVID-19

Diagnosis

Consider testing of any hospitalized patient with signs and symptoms of viral lower respiratory tract infection. Limit testing for other viruses through rapid antigen or PCR as swabs in low supply. Coinfection is well-described and does not exclude COVID-19.

Suspect COVID-19 and test in patients with 2 or 3 of the following signs or symptoms

1. Fever
2. Cough
3. Shortness of breath/sign and symptoms of lower respiratory infection (tachypnea, retractions, nasal flaring)

These patients do not need to be in negative pressure rooms unless they undergo aerosol generating procedures. NP swab is not aerosol generating.

Also test patients the following patients presenting with any respiratory symptoms (fever, cough, shortness of breath, congestion or sore throat):

1. CF patients admitted with pulmonary exacerbation as it could be difficult to determine if these patients have clinical disease consistent with COVID-19. In addition, their inpatient management requires multiple, daily, aerosol-generating procedures[§] so they should be placed in a negative-pressure room (or PICU cohort area) while awaiting test results.
2. Patients requiring airway suctioning with tracheostomy or other patients (infants, patients with impaired airway clearance) requiring airway suctioning. These patients should be placed in a negative pressure room (or PICU cohort area) pending results as these are aerosol generating procedures. May consider testing of patients who have been in the hospital and have a worsening of respiratory status only if they have been exposed to a caregiver with new respiratory illness (family member or healthcare worker).
3. Immunocompromised patients (transplant; high dose steroids for more than 2 weeks; use of biologics including TNF inhibitor, IL-1 inhibitors; other medications including methotrexate, cyclophosphamide, tacrolimus, cyclosporine) with any respiratory symptoms needing hospitalization. These patients are expected to have higher viral loads with longer shedding than healthy patients and, thus, may be more contagious. These patients do NOT need to be in negative pressure rooms unless they undergo aerosol generating procedures.
4. Patients with any other co-morbid cardiac or lung conditions (including severe asthma) who could be at higher risk for disease progression should be tested. These patients do NOT need to be in negative pressure rooms unless they undergo aerosol generating procedures.

Do not test:

1. Asymptomatic patients
2. Patients with lobar pneumonia on CXR as these patients more likely to have bacterial pneumonia even if associated with viral respiratory tract symptoms. These patients should still be placed in contact and droplet precautions (if associated viral RTI) as usual but do not need testing for respiratory viruses including SARS CoV-2.

[§]Aerosol generating procedures include procedures that stimulate coughing and promote generation of aerosols including aerosolized or nebulized medication administration, diagnostic sputum induction, bronchoscopy, airway suctioning, endotracheal intubation, positive pressure ventilation via face mask (NIPPV, CPAP, BiPAP) and high frequency oscillatory ventilation.

Management

Supportive care

1. Place patients who are likely to have aerosol generating procedures[§] (see above) in a negative pressure room. Can be moved to a regular room if testing for SARS CoV-2 is negative and no concern for another airborne infection (measles, varicella, TB) or if not requiring aerosol generating procedures.
2. Patient should not have rapid antigen testing for influenza or RSV or have respiratory virus PCR testing in order to conserve swabs which are in short supply. All patients with any signs or symptoms of viral upper or lower respiratory infection should be placed in contact and droplet precautions regardless of testing (syndromic precautions)
3. Consider the following labs at the time of confirmation of COVID-19 diagnosis (especially if patient moderately to severely ill at admission) and/or if increasing oxygen requirement:

- CMP, CBC, CRP, Ferritin, Fibrinogen, D-dimer, LDH, Triglycerides, Troponin, IL-6 level (plasma)
    - Severe disease associated with hyperinflammatory response
    - Myocarditis as a cause of deterioration and death also reported

Pharmacotherapy

1. There is no direct clinical evidence that NSAIDs, ACE inhibitors or ARBs worsen disease although there are theoretical concerns. The risk-benefit ratio for use of these agents in individual patients with suspected or confirmed COVID-19 should be assessed. Using acetaminophen as a safe alternative to NSAIDs for systemic symptoms of infection is reasonable.

2. There are no targeted antiviral therapies known to be efficacious in COVID-19. Agents with in vitro activity and/or limited evidence for efficacy are listed below and on subsequent pages. Treatment decisions based on disease severity stratification

Table 1 COVID-19 targeted treatment recommendations
(Note that prescribing of all targeted medications is restricted to Infectious Diseases)

Disease severity	Recommendations
Mild – may include fever, sore throat, cough and/or myalgias	• Supportive care
Moderate – may include fever, dyspnea, and/or chest imaging consisted with COVID-19 pneumonia. No change from baseline respiratory support requirement	No comorbidity, stable • Supportive care • No targeted pharmacotherapy No comorbidity, worsening disease • Consult ID, Consider hydroxychloroquine if no contraindication[¥] or lopinavir-ritonavir Comorbidities (especially immunocompromised)

Severe - additionally new or increased supplemental O2 and/or ventilatory support	• consult ID
Critical – respiratory failure requiring mechanical ventilation, ARDS, SIRS and/or multiorgan failure	All patients: • ID consult • Consider hydroxychloroquine if no contraindication[¥] or lopinavir-ritonavir • Apply for Remdesivir compassionate use (for patients receiving invasive mechanical ventilation)

[¥]Likely excludes most cardiac patients but can discuss on case by case basis

1. **Hydroxychloroquine***

Efficacy

- In vitro studies show effective viral suppression in Vero cells (Wang et al, Lui et al)
- Clinical efficacy unknown, studies from China and France showed reduced virus shedding but have several important limitations (very small, non-randomized, potentially misleading endpoint (nasopharyngeal viral clearance, not clinical outcome; Gao et al (abstract only in English), Gautret et al)
- In studies of hydroxychloroquine in Chikungunya virus infection there was no evidence of benefit in terms of reducing viremia and subjects with treatment had higher incidence of late arthralgia (De Lamballerie 2008). In a separate study, chloroquine was also associated with greater late arthralgia and early reductions in inflammatory markers without reductions in virus clearance (Roques 2018)

Dosing

- 6.5 mg/kg PO q12h [max 400 mg/dose] for 2 doses, then maintenance dose: 3.5 mg/kg/dose PO q12h [max 200 mg/dose] for 8 doses (**5 days total**)
- Pharmacy can prepare a suspension for patients who cannot take tablets

Indications

- Due to questions of efficacy and potential for harm, as well as limited supply, recommending only for a duration of **5 days** (at least initially with discussion about prolongation if needed) in children with known (or strongly suspected) COVID-19 admitted to PICU. Prescribing restricted to ID only.

Contraindications

- QTc > 500, history of ventricular arrhythmias, retinal disease; may cause cardiomyopathy
  - Patients on hydroxychloroquine should have ECG prior to initiation and daily thereafter
- G6PD deficiency: can see hemolysis in patients with G6PD deficiency. Would not withhold drug pending testing but would obtain and monitor closely if continue to use in patient with deficiency.

Additional information

- There are open clinical trials in the U.S. on the use of hydroxychloroquine in adults post-exposure and for treatment of symptomatic disease. Consider trying to enroll patients in studies who are **≥ 18 years old** if you can (list of open trials at the end of the document)

- Some other centers are planning on using hydroxychloroquine empirically for hypoxic children and adults outside the ICU. We will consider this on a case by case basis given our current limited supply
- We are not recommending use of hydroxychloroquine and azithromycin currently

2. Remedesivir

Efficacy

- Mechanism of Action: nucleotide analogue, initially developed for treatment of Ebola. Works by inhibiting RNA-dependent RNA polymerase (RdRp)
- *In-vitro* activity against MERS and SARS and has shown efficacy in animal models. (Gordon et al, 2020, de Wit et al 2020, Sheahan et al 2017). It has been shown to inhibit SARS-CoV-2 *in vitro*. (Wang et al, 2020)
- Very limited availability, Gilead currently restricting compassionate release to children <18 y.o. and pregnant women. Must have documented infection and receiving invasive mechanical ventilation without severe organ failure. **ID will facilitate*.**

Dosing

- ≥ 40 kg: 200mg IV loading dose (over 30 min) on day 1 then 100mg IV daily (over 30 min) x 5-10 days (US study protocols, Belgian guidelines)
- <40 kg: 5mg/kg IV loading dose (over 30 min) on day 1 then 2.5 mg/kg/day IV daily (over 30 min) for 5-10 days

Indications

- Severe, documented SARS CoV-2 infection, in consultation with ID

Contraindications (to compassionate use program)

- Multi-organ failure
- Pressors to maintain BP
- ALT > 5 X ULN
- Creatinine Cl < 30 mL/min, dialysis or CVVH
- Use of other experimental agent (unlikely)

* **Obtaining remdesivir**

1. Physician to complete Gilead Request form (https://rdvcu.gilead.com/)
2. Physician should request eIND approval from FDA (https://www.fda.gov/news-events/expanded-access/expanded-access-how-submit-request-forms #Physician Emergency-sbs)
3. Physician to contact Pharmacy Administration on call to inform them that remdesivir has been approved.
4. Pharmacy Administrator will advise on any next steps.
5. Physician must consent (both IRB & Gilead consents) patient to receive remdesivir.

3. Other

a. Lopinavir ritonavir (Kaletra)

- RCT in NEJM shows no efficacy in COVID-19 (Young et al, Cao et al) but single study with relatively small sample size and patients enrolled at different points in disease
- known increased activity in SARS-CoV-1 when used in conjunction with ribavirin (Chu et al)
- Dosing:
  - neonatal: lopinavir 300 mg/m2 per dose PO q12h (or 16 mg/kg/dose)
  - pediatric: lopinavir 230 mg/m2 per dose q12h (max 400 mg/dose)

- adult: lopinavir-ritonavir 400mg/100mg PO q12h
- *Contraindications*: QTC > 500, caution in liver & cardiac disease

b. *Tocilizumab*
- may help cytokine storm (check IL-6 level), case series of 21 patients in China with clinical improvement and no known adverse events (Xu et al)
- should obtain IL-6 level to determine need for use. Controversy over how elevated this value should be to initiate therapy.

c. *Nitazoxanide*
- In vitro inhibition of virus (Wang et al), no in vivo data
- Dosing:
  - Age 1-3 years: 100 mg PO twice daily
  - Age 4-11 years: 200 mg PO twice daily
  - Age ≥12 years: 500 mg PO twice daily

d. *Convalescent sera*: theoretically beneficial (Casadevall & Pirofski), FDA now allowing use of convalescent plasma for critically ill patients (3/24/20)

4. Not currently available in the U.S.

a. *Umifenovir (Arbidol)*: fusion inhibitor, approved in China and Russia

b. *Favipiravir:* approved in China, not available in US

5. Controversial

a. *Corticosteroids*
- may have reduced mortality in COVID-related ARDS (HR 0.38) in single, small, uncontrolled trial (Wu et al) but not recommended due to prior SARS data indicating increased viral shedding (Lee et al); WHO & CDC guidelines currently recommend against use but SCCM guidelines recommend use in patients with ARDS (not in patients without ARDS)

b. *Azithromcyin*

Efficacy
- No in vitro data. Efficacy information limited to 6 patients who happened to be prescribed azithromycin by their treating physician along with hydroxychloroquine in French study (Gautret et al)
- Although all patients receiving both medications cleared virus from upper respiratory tract within 6 days, study subject to many limitations including very small, non-randomized study, potentially misleading endpoint (nasopharyngeal viral clearance, not clinical outcome)

Dosing
- Loading dose 10 mg/kg day 1 (max 500 mg) followed by 5 mg/kg/day (max 250 mg) for 4 days

Indications
- Only use with hydroxychloroquine, discuss with ID before using both medications

Contraindications
- QTc > 500, history of ventricular arrhythmias, retinal disease; may cause cardiomyopathy
  - Patients on hydroxychloroquine (especially combination with azithromycin) should have ECG prior to initiation and daily