Cleveland Clinic

Treatment Considerations for Adult and Pediatric Patients with Laboratory Confirmed SARS-CoV-2 (COVID-19)

Updated: 03/18/2020. Key updates include minor changes to Table 1 due to impending medication shortages, considerations for patients with HTN, and new sections on therapy options with insufficient data and chemoprophylaxis

I. PURPOSE

The purpose of this document is to provide guidance for the management of patients with laboratory confirmed novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, aka COVID-19, until further information becomes available from the Centers for Disease Control and Prevention (CDC) and World Health Organization (WHO). Given the rapidly evolving nature of data on COVID-19, this document is subject to change.

Additional up to date information can be found at the following resources:

- CDC[1]: https://www.cdc.gov/coronavirus/2019-nCoV/hcp/index.html
- WHO[2]: https://www.who.int/publications-detail/clinical-management-of-severe-acute-respiratory-infection-when-novel-coronavirus-(ncov)-infection-is-suspected

II. MANAGEMENT CONSIDERATIONS

Disclaimer: The options listed below are **NOT** licensed for the treatment of COVID-19. Use of these agents is based on *in vitro*, animal model data and limited clinical data in related coronaviruses such as the Severe Acute Respiratory Syndrome (SARS) and Middle Eastern Respiratory Syndrome (MERS) CoVs. Therefore, the recommendations below should **NOT** be considered as curative for COVID-19 and clinical judgment should be used when weighing the benefits of these unproven treatment options versus the risks of adverse effects.

Infectious Diseases consultation is **strongly** recommended for management of critically ill patients and/or patients with risk factors for progression to severe COVID-19 disease*.

Table 1: Therapy considerations for management of COVID-19 infection

Severity of illness	Consideration
Outpatients	
Mild illness with or without risk factors for progression*	• Supportive care
Hospitalized patients	
Mild illness • No hypoxia or radiographic evidence of pneumonia	• Supportive care
Moderate illness • Presence of hypoxia or radiographic evidence of pneumonia, but not critically ill	• Supportive care • May consider lopinavir/ritonavir **OR** hydroxychloroquine if risk factors for progression to severe disease are present*
Critical illness • Mechanically ventilated, but **no** extra-pulmonary end organ damage (i.e. ALT < 5x ULN, CrCl > 30 ml/min, no dialysis or pressor requirement)	• Remdesivir (for compassionate use only) for up to 10 days, **OR** • Lopinavir/ritonavir x 10 days, **AND/OR** • Hydroxychloroquine x 5 days

• Severe pneumonia requiring mechanical ventilation and multi-organ damage	• Lopinavir/ritonavir x 10 days, **AND/OR** • Hydroxychloroquine x 5 days
Special Populations	
Immunosuppressed patients	• Reduction of immunosuppression: Consider holding mycophenolate For hospitalized patients, may consider the following options: • Remdesivir (compassionate use only, for patients who meet inclusion/exclusion criteria), **OR** • Hydroxychloroquine x 5 days, **OR** • Lopinavir/ritonavir x 10 days ○ Close TDM of calcineurin inhibitors and mTOR inhibitors required due to interaction with lopinavir/ritonavir
Pregnant or breastfeeding patients[11-17]	***General principles for management of COVID-19 during pregnancy include early isolation, aggressive infection control measures, rapid testing for co-infections, oxygen therapy as needed, fetal and uterine contraction monitoring, early mechanical ventilation for progressive respiratory failure, individualized delivery planning, and a multi-specialty team based approach. For hospitalized patients, may consider the following options: • Lopinavir/ritonavir x 10 days, **AND** • Hydroxychloroquine x 5 days • May consider remdesivir (compassionate use only, for patients who meet inclusion/exclusion criteria, if allowed by program) **Decisions about the use of corticosteroids for fetal lung maturity should be made in consultation with ID specialists and maternal-fetal medicine consultants.

Pediatric patients	• Supportive care recommended for mild to moderate illness
	• In case of severe illness, may consider the following options:
	  ○ Remdesivir x 10 days (for compassionate use only), **OR**
	  ○ Lopinavir/ritonavir x 10 days **AND** hydroxychloroquine x 5 days

Patients with Hypertension[23]	• There is no clinical evidence at this time linking ACE-inhibitors or ARBs to COVID-19 infection or severity • Can continue currently prescribed antihypertensive therapies, including ACE-inhibitors and ARBs. In hospitalized patients, antihypertensive therapy decisions may be made on a case by case basis

*Risk factors for progression to severe disease include age > 60 years, immunocompromised state, underlying structural lung disease, cardiac disease, hypertension or diabetes[1]

**Due to a lack of demonstrable benefit, risk of prolonged viral shedding and toxicities, corticosteroids for the treatment of COVID-19 pneumonia should be avoided unless other indications are present[3]

Table 2: Dosing and additional considerations for experimental or adjunct options for the management of COVID-19

Agent	Dosing	Comments
Remdesivir[4,5] (compassionate use only)	200mg IV on day 1 100mg IV q24h x 9 days **Pediatric:** < 40 kg: 5 mg/kg IV on day 1, then 2.5 mg/kg IV q24h	• Investigational antiviral drug with reported *in vitro* activity against SARS-CoV-2 that is currently being evaluated in multiple phase 3 trials as a possible treatment option for COVID-19. Remdesivir is currently only available either through a clinical trial or via Gilead's compassionate use program • See **Appendix A** for compassionate use process • Remdesivir cannot be used in combination with other experimental antiviral agents • Remdesivir was used in pediatric patients < 40 kg for treatment of Ebola per the WHO R&D Blueprint[17]. Defer to Gilead compassionate use program regarding availability and dosing for pediatric patients with COVID-19 • Pregnancy & Breastfeeding: Pregnancy & breastfeeding are listed as exclusion criteria in some Gilead phase 3 studies. Allowances for compassionate use are unknown. In a randomized controlled trial of Ebola virus therapeutics, 6/175 (3.4%) of patients in the remdesivir cohort were pregnant. However, there is no data on safety of remdesivir in pregnancy
Lopinavir/ritonavir (Kaletra)[6-9]	400/100mg PO Q12h **Pediatric (based on lopinavir):** **Oral solution** < 15kg: 12mg/kg/DOSE q12h 15-40kg: 10mg/kg/DOSE q12h >40kg: 400mg q12h **Oral tablet** ≥15-25kg: 200mg q12h ≥25-35kg: 300mg q12h >35kg: 400mg q12h	• Liquid formulation is preferred for feeding tube administration • Potent CYP3A4 inhibitor – monitor for drug interactions (eg: calcineurin inhibitors, mTOR inhibitors, corticosteroids, statins, azoles) • No renal dose adjustment necessary • Pregnancy: Experience mainly in treatment of HIV infection. Prospective reports from the Antiretroviral Pregnancy Registry of > 3,000 exposures to lopinavir containing regimens (including > 1,000 exposed in the first trimester) showed no difference in overall birth defect rates with lopinavir compared to the background birth defect rate of 2.7% (U.S. reference population of Metropolitan Atlanta Congenital Defects Program) • Breastfeeding: Small amounts of lopinavir are secreted into breast milk. Lopinavir/ritonavir is approved to treat HIV infection in infants and children with a postmenstrual age ≥ 42 weeks and postnatal age ≥ 14 days
Hydroxychloroquine[4,10] (Plaquenil)	400mg PO Q12h x 1 day, 200mg PO Q12h x 4 days **Pediatric:** 6.5mg/kg/DOSE PO q12h x 1 day, then 3.25mg/kg/DOSE PO q12h x 4 days (up to adult maximum dose)	• Liquid formulation can be compounded for administration via feeding tube. Tablets have a film coating • No renal or hepatic dose adjustments necessary • Recommend EKG monitoring as QT prolongation can be an adverse effect of hydroxychloroquine, especially in combination with other QT prolonging agents • Pregnancy: Package insert data states no increase rate of birth defects in exposed mothers. No recommendations for dosage adjustments in pregnancy • Breastfeeding: Small amounts of hydroxychloroquine can be found in breast milk. Recommend avoiding breastfeeding during therapy due to the slow elimination rate and potential for drug accumulation
Oral Ribavirin[4,6-9] *(optional)*	2 grams x 1 dose, then 600mg q8h	• Optional for co-administration WITH lopinavir/ritonavir • *In vitro* studies have demonstrated less potency with ribavirin compared to remdesivir. Clinical studies using ribavirin with lopinavir/ritonavir for SARS CoV utilized significantly higher doses of ribavirin, which raises concerns for adverse effects • Liquid formulation can be compounded for feeding tube administration • Boxed warning for hemolytic anemia

		• Renal dose adjustment recommended. Consider 50% dose reduction if CrCl < 50 ml/min or if anemia develops on therapy • Pregnancy & Breastfeeding: CONTRAINDICATED
Tocilizumab[19-22] *(optional)*	4-8 mg/kg (max 400mg) IV x 1 dose	• IL-6 inhibitors have been proposed to help reduce hyper-inflammatory response and maintain cytokine release associated with COVID-19 • Reports of tocilizumab use in COVID-19 infections have been mostly anecdotal from Italy or case series data from China. There are ongoing randomized controlled trials for this indication in China • AVOID in patients with ALT/AST > 5x ULN, ANC <2000/mm^3 or platelets <100,000/mm^3 • Adverse effects: LFT elevations, infusion/injection-related reactions, increased risk for TB reactivation and invasive fungal infections • Restricted medication. Strongly recommend ID consult. MUST CONTACT DRUG INFORMATION CENTER for approval if tocilizumab is being considered for COVID-19 • Pregnancy & breastfeeding: AVOID use • Serum IL-6 monitoring at CCHS is a send out test to ARUP and may take 5-7 days to return

Therapy options with **insufficient** data and/or not recommended:

- **Darunavir-based regimens[24]** – NOT RECOMMENDED. Based on preliminary, unpublished results from a previously reported *in vitro* experiment, it is not likely DRV will have significant activity against SARS-CoV-2 when administered at the approved doses for treatment of HIV-1 infection. Additionally, structural analyses show very few interactions of DRV with the active site of the SARS-CoV-2 protease
- **NSAIDs[25]** – There is no clinical evidence to suggest that NSAIDs can worsen COVID-19 infection. Clinical judgment recommended when deciding to initiate NSAID therapy. Acetaminophen may be a reasonable alternative antipyretic

III. CHEMOPROPHYLAXIS[1]

CDC does **NOT** endorse post-exposure prophylaxis for people who may have been exposed to COVID-19 at this time.

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Appendix A: Remdesivir Compassionate Use Program

Remdesivir (Gilead Sciences) is an investigational agent that has been evaluated in early clinical trials via IV administration for Ebola virus infection. However, the efficacy and safety of remdesivir has not been established for any indication including COVID-19 infection. Remdesivir is not approved for use in any country and has not been demonstrated to be safe or effective.

Cleveland Clinic is currently not enrolled in any remdesivir clinical trials. However, individual patients may qualify for compassionate use remdesivir depending on severity of illness. This requires an individual IND for each patient who meets the following inclusion criteria.

Key Inclusion Criteria:

- Patient hospitalized with confirmed SARS-CoV-2 by PCR
- On mechanical ventilation
- Unable to participate in existing RDV clinical trial

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 continuous veno-venous hemofiltration
- Remdesivir cannot be used in conjunction with other experimental antiviral agents for COVID-19

If your patient meets the above criteria,

- Contact Gilead and provide Patient and Hospital contacts through the designated portal only: https://rdvcu.gilead.com/
- Select “I am a Healthcare Provider”
- Review the Inclusion/Exclusion criteria and complete the Gilead Contact Information

For assistance with the process, please contact any of the following research staff at Cleveland Clinic: Susan Stein (216-445-0628 pager 23532), Andrea Rice (216-445-1202 pager V2162197088), Bette Maierson (216-444-2901 pager 25654) or Becki Algeri (216-445-3157 pager 82526). Additional information may be available from the company at CompassionateAccess@gilead.com.