Jackson HEALTH SYSTEM
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UNIVERSITY OF MIAMI HEALTH HOSPITAL AND CLINICS

Jackson Health System/University of Miami Health System
COVID-19 (confirmed or highly suspected)
Investigational Treatment Protocol
March 20, 2020

ASP Phone Numbers for Therapy Approval:
Jackson Memorial and Holtz: 786-586-0607
Jackson North Medical Center: 305-654-5022; option 1; internal: 20-4022
Jackson South Medical Center: 305-256-5180
UHealth Tower: 786-501-5008
SCCC/BPEI: 786-626-8817

Supportive care is the mainstay of therapy for COVID-19. This includes fluid resuscitation, oxygen supplementation, and antipyretics (acetaminophen preferred). Although not scientifically proven, it is hypothesized that ibuprofen can increase ACE-2, which SARS-CoV-2 uses to bind; therefore ibuprofen may worsen the clinical picture, scientific evidence pending (Fang L et al. Lancet, 2020). **Prior to initiating SARS-CoV-2 targeted therapy, consider baseline functional status, goals of care, and DNR status.** While there are currently no approved treatment options for COVID-19, below are possible treatment options based on ongoing investigational trials, case reports, and *in vitro* data. The known risks and benefits have not yet been evaluated in randomized controlled clinical trials and treatment should be determined on a case-by-case basis. Information is rapidly evolving and this protocol will be updated as more data becomes available.

Criteria (confirmed or highly suspected COVID-19)	Investigational Treatment Options[1]	Clinical Pearls for Treatment Options
Mild: any of the following; *patient does not require hospitalization* • Fever, malaise, cough, headache, sore throat, myalgia, nasal congestion, diarrhea	No drug therapy recommended, supportive care ONLY	• Hydroxychloroquine/Chloroquine ○ Do not crush tablet- hydroxychloroquine and chloroquine can be prepared as a suspension by pharmacy ○ Are QTc prolonging medications. **Baseline EKG is recommended**. Do not use if QTc > 500msec ○ Both are contraindicated in retinal or visual field changes of any etiology • [3]LPV/r ○ Do not crush tablets – reduces exposure 50% Ritonavir is CYP3A4 inhibitor, evaluate for drug-drug interactions (http://www.covid19-druginteractions.org/) ○ LPV/r **solution** is contraindicated in pregnant patients (only use tablets) ○ At JHS, is considered last line • [4]Ribavirin ○ Do not crush, solution can be prepared as a suspension by pharmacy ○ May be used with LPV/r: 10mg/kg LD x1, then 20mg/kg/day PO divided TID (round to nearest 200mg)
Mild with risk factors: • Age≥65, coronary artery disease, diabetes, hypertension, transplant, or immunosuppression	Treat as below for "moderate"	
Moderate: ≥ 2 of the following in non-intubated patients • Any symptom of mild disease • Radiographic imaging (chest x-ray or lung ultrasound) with bilateral ground glass opacities or bilateral consolidations • SpO_2 <90% up to 5L NC • No additional signs or symptoms of severe COVID-19 (see below)	[2]Hydroxychloroquine 400mg PO BID x 2 doses, then 200mg PO BID x 4 days -OR- Chloroquine 500mg PO BID x 5 days If hydroxychloroquine or chloroquine contraindicated [3]Lopinavir/ritonavir (LPV/r) 400mg/100mg PO BID x 10 days ± Ribavirin PO[4]	
Severe: ≥ 2 of the following • Intubated • Radiographic imaging (chest x-ray or lung ultrasound) with bilateral ground glass opacities or consolidations • ARDS with PaO_2/FiO_2 151-300 mmHg • Lymphopenia • [5]IL-6 > 40 pg/mL or CRP > 10 mg/L or elevated D-dimer with no other suspected cause	First Line Remdesivir 200mg IV LD x 1, then 100mg IV daily x 5-10 days If Remdesivir is unavailable or in the process of obtaining [2]Hydroxychloroquine 400mg PO BID x 2 doses, then 200mg PO BID x 4 days If hydroxychloroquine or chloroquine is contraindicated [3]Lopinavir/ritonavir (LPV/r) 400mg/100mg PO BID x 10-14 days ± Ribavirin PO[4] [6]Tocilizumab may be considered; requires ASP approval	• Remdesivir: ○ **See page 28 for criteria** for compassionate use

Critical : ≥ 2 of the following: • Intubated • Radiographic imaging (chest x-ray or lung ultrasound) with bilateral ground glass opacities or consolidations • ARDS with PaO_2/FiO_2 ≤ 150mmHg • *Septic Shock • Altered Consciousness • *Multi-organ failure *Exclusions for Remdesivir compassionate use	First Line Remdesivir 200mg IV LD x 1, then 100mg IV daily x 10 days If Remdesivir is unavailable or in the process of obtaining [2]Hydroxychloroquine 400mg PO BID x 2 doses, then 200mg PO BID x 4 days If hydroxychloroquine is contraindicated [3]Lopinavir/ritonavir 400mg/100mg PO BID x 10-14 days ± Ribavirin PO[4] [6]Tocilizumab has not been studied in critical disease and benefit is unknown	or potential clinical trials • Tocilizumab ○ IL-6 or CRP levels may be used to guide Tocilizumab therapy, current thresholds for treatment are based on clinical practice experience ○ All patients receiving Tocilizumab should be ruled out for latent TB per package insert ○ Tocilizumab should be used with caution in patients with history of GI perforation/diverticulitis or active infection • Pregnant Patients: ○ For detailed information, please visit Table 2: Treatment Options ○ **LPV/r** (**tablets only**, do not crush) is safe in pregnancy ○ Hydroxychloroquine/chloroquine cross the placenta; have been detected in ocular tissues in animal studies; evidence exists that use is safe in pregnant women with lupus ○ **Ribavirin is contraindicated** in pregnant patients ○ Safety of Remdesivir in pregnancy is unknown

[1]Please see table 2 for pediatric dosing

[2]Recent data suggests higher dosing is tolerated and may be considered. However, resource allocation may be a limiting factor. Adults- 600mg PO q12h x 2, followed by 200mg PO q8h x 4 days; Pediatric- 13mg/kg/dose (max dose 600mg) PO q12h x 2, followed by 3mg/kg/dose (max dose 200mg) PO q8h. Additionally one study reports concomitant use with azithromycin (DOI : 10.1016/j.ijantimicag.2020.105949)

[3]A recent student published in the NEJM concluded LPV/r monotherapy did not demonstrate clinical benefit in severe cases (DOI: 10.1056/NEJMoa2001282). Results must be interpreted with caution as it is unclear if earlier therapy would have been beneficial (patients randomized on day 13 of symptoms and unknown if received treatment prior). Of note, power may be limited in the study with a sample size of 199 patients. This is highlighted by the fact that the mITT population had numerically lower 28-day mortality and ICU length of stay. At this point, JHS is reserving LPV/r ± ribavirin as last line.

[5]Recommend obtaining an IL-6 level at time of suspicion (if available) since there may be a delay in turnaround time. CRP and D-dimer can be trended daily.

[6]Tocilizumab is under investigation as supportive therapy for potential cytokine storming in COVID-19 patients. **Current data is not definitive.** Dosing (1h infusion) < 30kg: 12mg/kg (max 400mg) x 1; 30-100kg 400mg IV x1; >100kg: 600mg IV x1

Steps to Apply for Compassionate Use of Remdesivir:

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Gilead is working with government and non-government organizations and regulatory authorities to provide Remdesivir to eligible patients with COVID-19 for emergency treatment in the absence of any approved treatment options. Remdesivir is an investigational agent and is not approved for use in any country. It has not been demonstrated yet to be safe or effective for any use.
Inclusion and exclusion criteria are changing rapidly- please check https://rdvcu.gilead.com/ for any updates

Inclusion Criteria
- Hospitalization
- Confirmed SARS-CoV-2 by PCR
- Invasive Mechanical ventilation

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

Request for Remdesivir for compassionate use (only for confirmed patient)
- Compassionate use requests must be submitted by a patient's lead treating physician. Gilead is currently assessing requests on an individual basis and requires, at a minimum, that the patient be hospitalized with confirmed COVID-19 infection with significant clinical manifestations. Requests for Remdesivir for individual patient use can be made by the treating physician through the following site: https://rdvcu.gilead.com/
- Individual compassionate use requests will only be considered when enrollment in a clinical trial is not a feasible option.
- Minimum criteria for qualification include confirmed COVID-19 infection, hospitalization and substantial clinical symptoms suggesting the benefits of treatment with an experimental agent may outweigh the risks. In addition, the patient must not be too sick to receive an experimental treatment (some exclusion criteria include multi-organ failure, pressor requirement to maintain BP,
- Creatinine clearance <30 mL/min, etc.).
- Importantly, because Remdesivir is an investigational agent that is not approved anywhere for any indication, regulatory approval for each individual use must be granted. Furthermore, patients must provide their consent to receive an experimental treatment, after a thorough explanation of the potential risks and benefits of taking an unapproved product.

Lastly, we need to get the product to the treating hospital. This can be a rate-limiting factor.
Due to high compassionate use demands and requests, Gilead will provide additional information only for an identified infected patient.

Request for Remdesivir on compassionate use process to prepare in the event they receive an infected patient (without confirmed patient)
- For all other compassionate use questions, please contact us at https://www.gilead.com/utility/contact/request-medication-information
- Please see https://www.gilead.com/purpose/advancing-global-health/covid-19 for the most up-to-date information

If patient does not quality for compassionate use, may consider looking into clinical trials:
- NCT04280705, NCT04292730, NCT04292899, NCT04252664, NCT04257656