Interim COVID-19 Treatment Protocol

3/19/2020

DISCLOSURE:

This document was developed by members of the ID divisions at Tulane University, LSU, and Ochsner in conjunction with pharmacy and other medicine divisions at Tulane University Medical Center, University Medical Center, Ochsner Health System and Touro Infirmary Hospital to provide guidance to clinicians caring for patients with suspected/confirmed COVID-19 infection.

Please note, this document covers potential off-label and/or experimental use of medications and immunosuppression management for transplant patients as well as a suggested laboratory work up. It does NOT cover recommendations for infection control, PPE, management of hypoxemia/ARDs or other complications in patients with COVID-19.

Further, this is a living document that will be updated in real time as more data becomes available.

The above information is adapted from the MGH treatment and management protocol.

INITIAL CONSIDERATIONS

- *Patient with suspected or confirmed COVID-19:*
    a. Consider discontinuation of ACEi, ARB and NSAID therapies. At the moment this is controversial (http://www.nephjc.com/news/covidace2).
    b. Determine need to treat for community acquired pneumonia. Caution with azithromycin and fluoroquinolone if administering treatment for COVID (I.e. re: QTc monitoring).
    c. Assess severity per Table 1 and initiate immediate treatment according to Figure 1
    d. Consult ID for assistance if starting medication per algorithm.

Figure 1. Treatment Algorithm

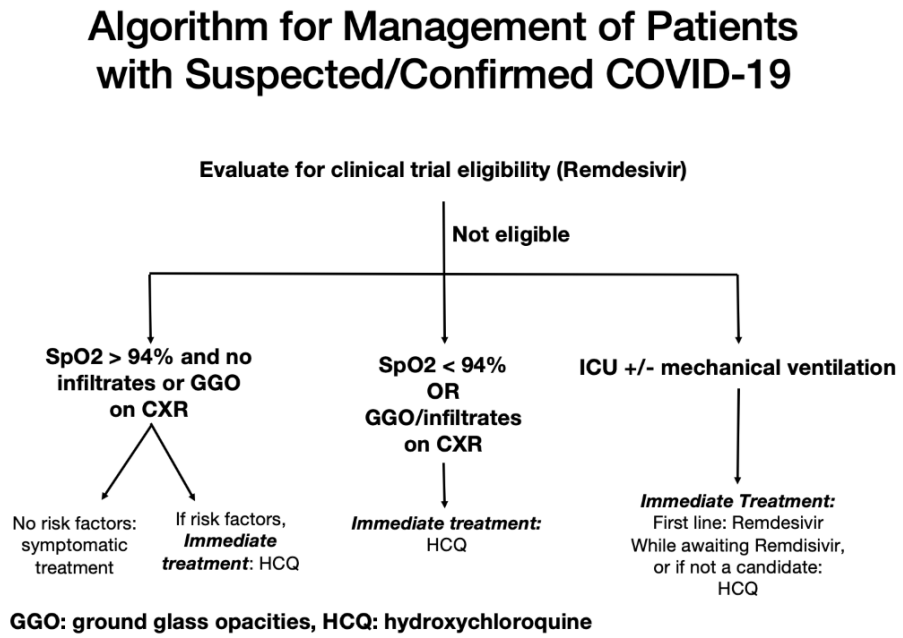

Table 1. Risk Factors

Risk Factors
Age >/= 60
Heart Disease (Hypertension, Coronary Artery Disease, Heart Failure)
End Stage Renal Diseases
Chronic lung disease (e.g. COPD or Asthma)
Smoking History
Cirrhosis
Diabetes
Immune deficiency (SOT/HSCT recipients, malignancy, chronic corticosteroids >20 mg prednisone or equivalent daily, biologics, chronic immunomodulator use, uncontrolled HIV with VL>200 or CD4 count <200 cells/mm3, congenital/acquired immunodeficiency)
Obesity with BMI >/= 40
Healthcare Worker

Table 2. Medication Regimens and Dosing

Drug-drug interactions link: www.covid19-druginteractions.org

Drug	Dose	Duration	Contraindications
Hydroxychloroquine	400 mg BID loading dose, then 200mg BID	5 days and re-evaluate	Pregnancy; retinopathy; **Caution/careful monitoring** if QTc prolongation (440 ms for men and 460 for women), diabetes, G6PD deficiency
Remdesivir Compassionate use (patients must be mechanically ventilated): https://rdvcu.gilead.com	200 mg IV load, then 100 mg IV q24h	Per Protocol	Multi-organ failure, Vasopressor requirement, ALT >5x ULN, CrCl <30 mL/min, dialysis, or CVVH, Concomitant use of other experimental antiviral agents (e.g., lopinavir/ritonavir)

INITIAL CONSIDERATIONS

- *Clinical Severity Index:*
    a. Mild Disease:
        i. SpO2 >/= 94%
        ii. No ground-glass opacities (GGO) or infiltrates on CXR
    b. Moderate Disease:
        i. SpO2 <94% OR GGO/infiltrates on CXR
    c. Critical Disease:
        i. ICU admission +/- mechanical ventilation
- *Key Considerations:*
    a. Laboratory Data:
        i. Initial Laboratory and Radiologic Data:
            - G6PD (if not on file)
                - Do not need to wait for results prior to initiating therapy
            - HIV (if not on file)
                - Do not need to wait for results prior to initiating therapy
            - Troponin
            - NT-proBNP

- Influenza/Respiratory BioFire
- Pregnancy test in women of childbearing age
- CXR OR CT Chest

ii. Daily Laboratory Data
- CBC with differential
- CMP
- CRP
- LDH
- Ferritin
- D-dimer
- CK
- CKMB

iii. Laboratory Data to obtain in the Decompensating Patient
- Repeat Troponin and NT-proBNP
- Consider HLH labs (DIC panel with fibrinogen, triglycerides, ?soluble CD25 (soluble IL-2 receptor alpha [sIL-2R]) and NK cell activity)

iv. ***PRIOR TO INITIATING THERAPY, COUNSEL patients on toxicity risks/experimental therapy and document accordingly***

v. **Patients warrant re-evaluation at day 5 of therapy. If the patient has improved, the treatment should be discontinued.**

SUPPORTING DATA

- Remdesivir:

    - NEJM case – one pt given remdisivir day before clinical improvement, conclusion: further studies needed.[2]
    - “highly effective” in the control of SARS-CoV2 in vitro[3]
    - Prior macaque MERS data: Remdesivir reduced the severity of disease, virus replication, and damage to the lungs when administered either before or after animals were infected with MERS-CoV.[4]
- Lopinavir/r (Kaletra):
    - Singapore data: 5 patients treated, 2 died, for the other three, fever resolved and supplemental oxygen requirement was reduced within 3 days.[5]
    - VL “significantly” decreased and no or little coronavirus titers were observed[6]
    - PEP for MERS: pts received Kaletra + ribavirin, treatment was associated with a 40% decrease in the risk of infection. There were no severe adverse events during PEP therapy.
    - 41 patients treated with lopinavir/r plus ribavirin were compared to 111 historical control patients treated with ribavirin alone. Baseline imbalances did exist between groups (patients treated with lopinavir/ritonavir had lower initial LDH levels – so they weren't as sick), Poor clinical outcomes (ARDS or death) were lower in treatment group (2.4% vs. 29%), and use of L/r correlated with large reduction in viral load.[7]
- Hydroxychloroquine:
    - Hydroxychloroquine was found to be more potent than chloroquine to inhibit SARS-CoV-2 in vitro.[1]
    - “highly effective” in the control of SARS-CoV2 in vitro[3]
    - “Thus far, results from more than 100 patients have demonstrated that chloroquine phosphate is superior to the control treatment in inhibiting the exacerbation of pneumonia, improving lung imaging findings, promoting a virus-negative conversion, and shortening the disease course according to the news briefing.”[8]
    - Dose with loading dose as above, which was shown to reach three times the potency of chloroquine phosphate when given 500 mg twice daily 5 days in advance.[1]
- Steroids:
    - “Overall, no unique reason exists to expect that patients with 2019-nCoV infection will benefit from corticosteroids, and they might be more likely to be harmed with such treatment. We conclude that corticosteroid treatment should not be used for the treatment of 2019-nCoV-induced lung injury or shock outside of a clinical trial.”[9]
    - Studies in SARS/MERS suggest either no benefit from steroids[10] or have shown potential harms[11]
    - Nevertheless, consider steroids if there is another concurrent disease process that has proven benefit from steriods
- Tocilizumab:
    - Tocilizumab is a monoclonal anti-IL-6 receptor antibody used to inhibit IL-6 mediated inflammatory responses.

- Little clinical data for use in the treatment of COVID-19 outside an open-label study of 21 patients in China with diagnosed COVID-19 with clinically defined severe/critical disease where Tocilizumab reduced fever, supplemental oxygen requirements (including patients on high-flow O2 and mechanical ventilation), CRP, and hospital stay (19 of 20 patients were discharged).[12]
- Routine use not recommended. Future clinical trials needed to evaluate efficacy and toxicities (clinical trials in China are ongoing).

REFERENCES

1. Yao X, Ye F, Zhang M, et al. In Vitro Antiviral Activity and Projection of Optimized Dosing Design of Hydroxychloroquine for the Treatment of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). *Clin Infect Dis*. doi:10.1093/cid/ciaa237

2. First Case of 2019 Novel Coronavirus in the United States | NEJM. *N Engl J Med*. http://www.nejm.org/doi/10.1056/NEJMoa2001191. Accessed March 16, 2020.

3. Wang M, Cao R, Zhang L, et al. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. *Cell Res*. 2020;30(3):269-271. doi:10.1038/s41422-020-0282-0

4. Wit E de, Feldmann F, Cronin J, et al. Prophylactic and therapeutic remdesivir (GS-5734) treatment in the rhesus macaque model of MERS-CoV infection. *Proc Natl Acad Sci*. February 2020. doi:10.1073/pnas.1922083117

5. Young BE, Ong SWX, Kalimuddin S, et al. Epidemiologic Features and Clinical Course of Patients Infected With SARS-CoV-2 in Singapore. *JAMA*. March 2020. doi:10.1001/jama.2020.3204

6. Lim J, Jeon S, Shin HY, et al. Case of the Index Patient Who Caused Tertiary Transmission of COVID-19 Infection in Korea: the Application of Lopinavir/Ritonavir for the Treatment of COVID-19 Infected Pneumonia Monitored by Quantitative RT-PCR. *J Korean Med Sci*. 2020;35(6):e79. doi:10.3346/jkms.2020.35.e79

7. Chu CM, Cheng VCC, Hung IFN, et al. Role of lopinavir/ritonavir in the treatment of SARS: initial virological and clinical findings. *Thorax*. 2004;59(3):252-256. doi:10.1136/thorax.2003.012658

8. Gao J, Tian Z, Yang X. Breakthrough: Chloroquine phosphate has shown apparent efficacy in treatment of COVID-19 associated pneumonia in clinical studies. *Biosci Trends*. 2020;14(1):72-73. doi:10.5582/bst.2020.01047

9. Russell CD, Millar JE, Baillie JK. Clinical evidence does not support corticosteroid treatment for 2019-nCoV lung injury. *The Lancet*. 2020;395(10223):473-475. doi:10.1016/S0140-6736(20)30317-2

10. Arabi, Yaseen M. et al. Corticosteroid Therapy For Critically Ill Patients With Middle East Respiratory Syndrome. *American Journal Of Respiratory And Critical Care Medicine*. 2018;197(6):757-767. doi:10.1164/rccm.201706-1172oc

11. Stockman, Lauren J et al. SARS: Systematic Review Of Treatment Effects. *PLoS Medicine*. 2006;3(9):e343. doi:10.1371/journal.pmed.0030343.

12. Xu X, Han, Mingfeng,Li, Tiantian,Sun, Wei,Wang, Dongsheng,Fu, Binqing,Zhou, Yonggang,Zheng, Xiaohu,Yang, Yun,Li, Xiuyong,Zhang, Xiaohua,Pan, Aijun,Wei, Haiming.(2020).Effective Treatment of Severe COVID-19 Patients with Tocilizumab.[ChinaXiv:202003.00026]