Health Services
LOS ANGELES COUNTY

Expected Practices

Specialty: Infectious Disease, Adult Critical Care

Subject: Use of Medications in Patients with COVID-19 Disease

Date: September 22, 2020

Purpose:
To evaluate the available data and treatment options for COVID-19 Disease and provide guidance on appropriate use of medications in this patient population.

Target Audience:
Inpatient Medicine, Critical Care, Infectious Disease teams managing COVID-19 disease.

Background:

Since the novel coronavirus SARS-CoV-2, the causative agent of COVID-19, began spreading in China in December 2019, this pandemic has rapidly spread around the world. Clinical observations are mounting as more published data becomes available. Since data is still emerging for COVID-19 and there is high mortality rate for those with severe disease (66% in the latest UK ICNARC data[1]), unproven and/or investigational therapies are often considered.

There are currently no FDA-approved therapeutics for the treatment of SARS-CoV-2 infection. However, there are therapeutics available for off-label use and through FDA Emergency-Use-Authorization (EUA). Decisions regarding use of therapeutic agents should consider available guidelines and other available data for the optimal treatment of those with different severity of SARS-CoV-2 infection. Any use of medications for COVID-19 outside of these guidelines should consider inclusion of the following: a) documentation of informed consent and shared decision-making between both the clinical team and the patient and/or surrogate, including discussion of the risks, potential benefits and alternatives, as well as the rationale for its use in light of the available data, b) ensuring that all other evidence-based medical interventions have been evaluated first; c) the patient's clinical condition is severe enough to warrant use of therapeutics not recommended by guidelines, and d) there is sufficient drug supply.

This *Expected Practice* was developed by a DHS Specialty-Primary Care Work Group to fulfill the DHS mission to ensure access to high-quality, patient-centered, and cost-effective health care. SPC Work Groups, composed of specialist and primary care provider representatives from across LA County DHS, are guided by 1) real-life practice conditions at our facilities, 2) available clinical evidence, and 3) the principle that we must provide equitable care for the entire population that LA County DHS is responsible for, not just those that appear in front of us. It is recognized that in individual situations a provider's clinical judgment may vary from this *Expected Practice*, but in such cases compelling documentation for the exception should be provided in the medical record.

The below recommendations are developed with consideration of various society guidelines, including NIH COVID-19 Treatment Guidelines which are updated on regular basis and referred to for select recommendations in this EP.[2–5]

Only remdesivir and dexamethasone have been shown to have efficacy in SARS-CoV-2-infected individuals. For the use of other medications, a note in ORCHID must be documented by the attending physician of record that:

Patient, family or proxy consents to administration of the medication. Conversation must include 1) there is limited evidence to support use of the medication in this context and is not FDA approved for this use, and 2) the drugs can have side effects, including risk of adverse events including in rare cases death.

Expected Practice:

- For outpatients with COVID-19 not requiring admission, no therapies directed at COVID-19 are recommended unless part of a clinical trial.

- Corticosteroids are the preferred option for those receiving supplemental oxygen by high flow device, mechanical ventilation or extracorporeal mechanical oxygenation (ECMO), as recommended by NIH COVID-19 Guidelines,
    - Use of steroids should be for up to 10 days or until stable for discharge, whichever comes first.

- Remdesivir is a preferred option for those with $SpO_2 \leq 94\%$ on ambient air (at sea level) or requiring supplemental oxygen via low flow device. There is insufficient data to recommend for or against use in patients using high flow oxygen, mechanical ventilation or ECMO (NIH COVID-19 Guidelines).
    - Remdesivir should typically be given for 5 days, or until the time of hospital discharge, whichever comes first. FDA EUA for remdesivir does not allow for home IV therapy.
    - Remdesivir should not be used in those with alanine transaminase or aspartate transaminase >5 times the upper limit of normal or calculated creatinine clearance of <30 mL/minute.
    - When the supply of remdesivir is readily available (see your local facility dashboard) broader use can be considered.
        - Providers should consider using in combination with primary use of corticosteroids in those requiring supplemental oxygen via high flow device.
        - There is uncertainty as to whether remdesivir improves outcome mechanical ventilation or ECMO. If sufficient supply exists (reported as green by DHS pharmacy on local dashboards) teams can consider adding to corticosteroids in consultation with ID and/or Critical Care, with theoretical benefits most likely to be present in those just recently intubated.
        - Remdesivir may be more effective early in disease process (~10 days after symptoms onset) as after this time point host inflammatory response may be the driving factor for progression of disease.[6,7]

  If there is a remdesivir shortage, DHS will follow the recommended strategies provided by NIH COVID-19 Guidelines. This includes avoiding use in those on high flow oxygen, mechanically ventilation or ECMO where benefits have not been definitively established. Providers will be

notified of shortages by remdesivir stop light chart which will be posted and updated weekly on facility dash boards.

- COVID-19 convalescent plasma was given an EUA by the FDA. The current recommendations for NIH COVID-19 Guidelines state that there is insufficient data to recommend for or against COVID-19 convalescent plasma at this time. As a result, it should not be used instead of treatments that have been shown to be effective, as outlined above (remdesivir and dexamethasone).
    - There is insufficient data to demonstrate whether adding this treatment to corticosteroids or remdesivir is of any clinical value
    - Consideration of this therapy is at the discretion of the primary attending physician. If potential benefit outweighs risk, enrollment criteria include:
        - Age at least 18 years
        - Laboratory confirmed diagnosis of infection with SARS-CoV-2
        - Admitted to an acute care facility for the treatment of COVID-19 complications
        - Severe or life threatening COVID-19, or judged by the treating provider to be at high risk of progression to severe or life-threatening disease despite standard therapy
        - Informed consent provided by the patient or healthcare proxy
        - There are no exclusion criteria

- For hospitalized patients with COVID-19, hydroxychloroquine or chloroquine should not be used unless as part of a well-designed clinical trial.[8,9]

- For hospitalized patients with COVID-19, lopinavir-ritonavir should not be used unless as part of a well-designed clinical trial or being given for chronic HIV infection.[10,11]

- For hospitalized patients with COVID-19 tocilizumab is not recommended outside of a well-designed clinical trial.

  There may be instances, with written justification, individual clinicians may consider use of the drug for hospitalized patients with COVID-19 who have evidence of pneumonia and clinical indicators of cytokine release syndrome.

- For hospitalized patients with COVID-19 who require mechanical ventilation, the DHS Adult Critical Care Committee supports the use of oral medications for sedation and analgesia when DHS is experiencing drug shortages. Pharmacy can assist with IV to oral conversions. Quetiapine, phenobarbital, morphine sulfate, lorazepam, diazepam, per NGT should be considered to preserve IV medication stock.

- Clinicians may opt for increased dosages of anticoagulation therapy in patients with COVID-19. Anticoagulation dosing should be consistent with the COVID anticoagulation EP.

- Other treatments and supplements not discussed in this document without well described data to support efficacy for off label use should not be used unless conditions are met in the DHS Off-Label Medication Use Policy.

References:

1. House, N., Holborn, H. & Wc, L. ICNARC report on COVID-19 in critical care. 17 (2020).

2. NIH COVID-10 Treatment Guidelines. https://www.covid19treatmentguidelines.nih.gov/whats-new/.

3. Bhimraj A, et. al. Infectious Diseases Society of America Guidelines on the Treatment and Management of Patients with COVID-19. Last updated April 13, 2020 at 9:06AM EDT and posted online at.

4. Willson, K., Chotmirmall, S., Bai, C. & Rello, J. COVID-19: Interim Guidance on Management Pending Empirical Evidence.

5. Alhazzani, W. *et al.* Surviving Sepsis Campaign: Guidelines on the Management of Critically Ill Adults with Coronavirus Disease 2019 (COVID-19). *Critical Care Medicine* **48**, e440–e469 (2020).

6. Siddiqi, H. K. & Mehra, M. R. COVID-19 illness in native and immunosuppressed states: A clinical–therapeutic staging proposal. *The Journal of Heart and Lung Transplantation* **39**, 405–407 (2020).

7. Akhmerov, A. & Marbán, E. COVID-19 and the Heart. *Circ Res* **126**, 1443–1455 (2020).

8. *Statement from the Chief Investigators of the Randomised Evaluation of COVid-19 thERapY (RECOVERY) Trial on hydroxychloroquine, 5 June2020 No clinical benefit from use of hydroxychloroquinein hospitalised patients with COVID-19*. https://www.recoverytrial.net/files/hcq-recovery-statement-050620-final-002.pdf.

9. Tang, W. *et al.* Hydroxychloroquine in patients mainly with mild to moderate COVID-19: an open-label, randomized, controlled trial. *medRxiv* 2020.04.10.20060558 (2020) doi:10.1101/2020.04.10.20060558.

10. Cao, B. *et al.* A Trial of Lopinavir–Ritonavir in Adults Hospitalized with Severe Covid-19. *N Engl J Med* **382**, 1787–1799 (2020).

11. *No clinical benefit from use of lopinavir-ritonavir in hospitalised COVID-19 patients studied in RECOVERY*. https://www.recoverytrial.net/news/no-clinical-benefit-from-use-of-lopinavir-ritonavir-in-hospitalised-covid-19-patients-studied-in-recovery.

12. Mehta, P. *et al.* COVID-19: consider cytokine storm syndromes and immunosuppression. *The Lancet* **395**, 1033–1034 (2020).

13. Ruan, Q., Yang, K., Wang, W., Jiang, L. & Song, J. Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. *Intensive Care Med* (2020) doi:10.1007/s00134-020-05991-x.

14. Le, R. Q. *et al.* FDA Approval Summary: Tocilizumab for Treatment of Chimeric Antigen Receptor T Cell-Induced Severe or Life-Threatening Cytokine Release Syndrome. *The Oncol* **23**, 943–947 (2018).

15. Xu X, Han M, Li T et al. Effective treatment of severe COVID-19 patients with Tocilizumab. *ChinaXiv*.

16. Luo, P. *et al.* Tocilizumab treatment in COVID-19: A single center experience. *J Med Virol* (2020) doi:10.1002/jmv.25801.

17. Day, C. W. *et al.* A new mouse-adapted strain of SARS-CoV as a lethal model for evaluating antiviral agents in vitro and in vivo. *Virology* **395**, 210–222 (2009).

18. *Roche's Actemra falls short in Italian study in early-stage COVID-19 pneumonia*. https://www.aifa.gov.it/web/guest/-/covid-19-studio-randomizzato-italiano-nessun-beneficio-dal-tocilizumab https://www.fiercepharma.com/pharma/roche-s-actemra-fails-italian-study-early-stage-covid-19-pneumonia.

19. Price, C. C. *et al.* Tocilizumab Treatment for Cytokine Release Syndrome in Hospitalized COVID-19 Patients. *Chest* S0012369220316706 (2020) doi:10.1016/j.chest.2020.06.006.