Health Services
LOS ANGELES COUNTY

Expected Practices

Specialty: Infectious Disease, Adult Critical Care

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

Date: December 28, 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:
Providers who care for patients with 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. New data and therapeutics continue to be developed, and unproven and/or investigational therapies are often considered.

There is currently only a single FDA-approved therapeutic for the treatment of SARS-CoV-2 infection. However, there are many therapeutics that have been considered for therapy and 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 COVID-19. 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.[1–4]

Only remdesivir and dexamethasone have been shown in well conducted randomized-controlled trials 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 states:

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 it 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

- DHS continues to evaluate novel therapies for outpatient COVID-19 disease but does not recommend any specific therapy at this time.

For outpatients with COVID-19 requiring O2 supplementation for home

- Data is limited as to the benefits and risks of discharging a patient to complete a course of dexamethasone (or alternative steroid) for severe COVID-19. In the absence of data, providers should use their discretion as to whether they believe the benefits of such a strategy outweighs the risks for a given patient, such as the concerns for unmonitored blood pressure and blood glucose levels as an outpatient.

Patient hospitalized with COVID-19 not requiring oxygen

- No specific therapy is recommended at this time.

Patient hospitalized with COVID-19 requiring oxygen

- 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, (Figure 1)
    - 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). (Figure 1)
    - Remdesivir should typically be given for 5 days, or until the time of hospital discharge, whichever comes first. Home IV therapy is not recommended.
    - 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
        - There is limited data to suggest that remdesivir can be considered in patients with calculated creatinine clearance of <30 mL/minute and in patients receiving

hemodialysis if the benefits outweigh the risk. At this time, there are no recommended dose adjustments for this patient population.[5–8]
        - Pediatric patients 3.5kg to 12 years of age, Remdesivir should not be given if ALT is >10 times normal (see https://www.fda.gov/media/137566/download)
    - 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 outcomes on 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.[9,10]

  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.

- Baricitinib should not be used unless as part of a well-designed clinical trial.

- 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.

- Hydroxychloroquine or chloroquine should not be used unless as part of a well-designed clinical trial.[11,12]

- Lopinavir-ritonavir should not be used unless as part of a well-designed clinical trial or being given for chronic HIV infection.[13,14]

- Tocilizumab is not recommended outside of a well-designed clinical trial.

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

2. 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.

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

4. 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).

5. Sörgel, F. *et al.* Pharmacokinetics of remdesivir in a COVID-19 patient with end-stage renal disease on intermittent haemodialysis. *Journal of Antimicrobial Chemotherapy* dkaa500 (2020) doi:10.1093/jac/dkaa500.

6. Davis, M. R., Pham, C. U. & Cies, J. J. Remdesivir and GS-441524 plasma concentrations in patients with end-stage renal disease on haemodialysis. *Journal of Antimicrobial Chemotherapy* dkaa472 (2020) doi:10.1093/jac/dkaa472.

7. Ackley, T. W., Mcmanus, D., Topal, J. E., Cicali, B. & Shah, S. A Valid Warning or Clinical Lore: An Evaluation of Safety Outcomes of Remdesivir in Patients with Impaired Renal Function from a Multicenter Matched Cohort. *Antimicrob Agents Chemother* AAC.02290-20, aac;AAC.02290-20v1 (2020) doi:10.1128/AAC.02290-20.

8. Hafner, V. *et al.* Pharmacokinetics of Sulfobutylether-Beta-Cyclodextrin and Voriconazole in Patients with End-Stage Renal Failure during Treatment with Two Hemodialysis Systems and Hemodiafiltration. *AAC* **54**, 2596–2602 (2010).

9. 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).

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

11. *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.

12. 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.

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

14. *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.

Figure 1. Pharmacologic Management of Patients with COVID-19 Based on Disease Severity

Doses and durations are listed in the footnote.

DISEASE SEVERITY	PANEL'S RECOMMENDATIONS
Not Hospitalized, Mild to Moderate COVID-19	There are insufficient data to recommend either for or against any specific antiviral or antibody therapy. SARS-CoV-2 neutralizing antibodies (**bamlanivimab** or **casirivimab plus imdevimab**) are available through EUAs for outpatients who are at high risk of disease progression.[a] These EUAs do not authorize use in hospitalized patients. **Dexamethasone** should not be used **(AIII)**.
Hospitalized[a] But Does Not Require Supplemental Oxygen	**Dexamethasone** should not be used **(AIIa)**. There are insufficient data to recommend either for or against the routine use of **remdesivir**. For patients at high risk of disease progression, the use of remdesivir may be appropriate.
Hospitalized[a] and Requires Supplemental Oxygen (But Does Not Require Oxygen Delivery Through a High-Flow Device, Noninvasive Ventilation, Invasive Mechanical Ventilation, or ECMO)	Use one of the following options: • **Remdesivir**[b,c] (e.g., for patients who require minimal supplemental oxygen) **(BIIa)** • **Dexamethasone**[d] **plus remdesivir**[b,c] (e.g., for patients who require increasing amounts of supplemental oxygen) **(BIII)**[e,f] • **Dexamethasone**[d] (e.g., when combination therapy with remdesivir cannot be used or is not available) **(BI)**
Hospitalized[a] and Requires Oxygen Delivery Through a High-Flow Device or Noninvasive Ventilation	Use one of the following options: • **Dexamethasone**[d,f] **(AI)** • **Dexamethasone**[d] **plus remdesivir**[b,c] **(BIII)**[e,f]
Hospitalized[a] and Requires Invasive Mechanical Ventilation or ECMO	**Dexamethasone**[d] **(AI)**[g]

Rating of Recommendations: A = Strong; B = Moderate; C = Optional
Rating of Evidence: I = One or more randomized trials without major limitations; IIa = Other randomized trials or subgroup analyses of randomized trials; IIb = Nonrandomized trials or observational cohort studies; III = Expert opinion

[a] See the Panel's statements on the FDA EUAs for bamlanivimab and casirivimab plus imdevimab. These EUAs do not authorize use in hospitalized patients.

[b] The remdesivir dose is 200 mg IV for one dose, followed by 100 mg IV once daily for 4 days or until hospital discharge (unless the patient is in a health care setting that can provide acute care that is similar to inpatient hospital care). Treatment duration may be extended to up to 10 days if there is no substantial clinical improvement by Day 5.

[c] For patients who are receiving remdesivir but progress to requiring oxygen through a high-flow device, noninvasive ventilation, invasive mechanical ventilation, or ECMO, remdesivir should be continued until the treatment course is completed.

[d] The dexamethasone dose is 6 mg IV or PO once daily for 10 days or until hospital discharge. If dexamethasone is not available, equivalent doses of other corticosteroids, such as prednisone, methylprednisolone, or hydrocortisone, may be used. See the Corticosteroids section for more information.

[e] The combination of dexamethasone and remdesivir has not been studied in clinical trials.

[f] In the rare circumstances where corticosteroids cannot be used, baricitinib plus remdesivir can be used **(BIIa)**. The FDA has issued an EUA for baricitinib use in combination with remdesivir. The dose for baricitinib is 4 mg PO once daily for 14 days or until hospital discharge.

[g] The combination of dexamethasone and remdesivir may be considered for patients who have recently been intubated **(CIII)**. Remdesivir alone **is not recommended**.

Key: ECMO = extracorporeal membrane oxygenation; EUA = Emergency Use Authorization; FDA = Food and Drug Administration; IV = intravenous; the Panel = the COVID-19 Treatment Guidelines Panel; PO = orally; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2