COVID-19 Treatment Guidance

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Version 1.0

Overview

The World Health Organization (WHO) states there is no current evidence to recommend any specific anti-COVID-19 supportive or antiviral treatment for patients with confirmed COVID-19. There are many ongoing clinical trials and data is emerging frequently. Use of investigational anti-COVID-19 therapeutics should be done under approved, randomized, controlled trials whenever feasible.

Antiviral Treatment Algorithm

- **Treatment for COVID-19 positive or suspect patients should be approved by Infectious Diseases and/or a Critical Care Provider/Intensivist at sites with these services prior to dispensing.**
    - Due to demand, intermittent shortages of these agents can be expected.

Patient Subset	Antiviral Therapy	Comments
COVID-19 positive patient asymptomatic < OR > Mild symptoms: (Fever >37.5, cough, age < 60 years without risk factors (COPD, diabetes, heart disease, lung disease, immunosuppressed, pregnancy) < OR > No radiographic evidence of pneumonia	None Clinical observation & supportive care	

COVID-19 positive patient with mild respiratory symptoms
<AND >
Age≥ 60 years
<OR>
Risk factors (COPD, DM, heart disease, lung disease, immunosuppressed)
 	
OR
 	
COVID-19 positive patients symptomatic or with mild to moderate symptoms (Fever > 38°C), cough, dyspnea (mild to moderate)
< AND >
Radiographic evidence of pneumonia
 	
OR
	Supportive Care
	
	<AND >
	
	Consider Hydroxychloroquine 400 mg BID on day 1, then 200 mg BID x 4 days (some have extended duration based on clinical response)
		• Supportive care is standard therapy
		• Hydroxychloroquine tablets may be halved or crushed
		• Hydroxychloroquine is contraindicated in patient with pre-existing maculopathy
		• Hydroxychloroquine drug interactions
		  ○ Amiodarone
		  ○ Azithromycin
		  ○ Digoxin
		  ○ Antacids – separate by 4 hours
		• Pregnancy and nursing mothers – excreted in breast milk and some sources recommend caution. Has been used routinely in pregnant/nursing RA patients.
		• The hydroxychloroquine package insert mentions increased risk of hemolytic anemia in patients with G6PD deficiency. However, no published studies quantify this potential risk. Consider testing for G6PD deficiency.
		• Hydroxychloroquine tolerability/adverse effects
		  ○ Cardiovascular: Prolonged QT interval, Torsades de pointes, AV block, and ventricular arrhythmia

COVID-19 positive non-ventilated patients with severe disease: ≥ 1 of the following: • RR ≥ 30/min • O2 sat ≤ 93%, • Pa02/Fi02 <300 • Radiographic evidence of lung infiltrates		○ Dermatologic: Erythroderma, skin pigmentation disorder ○ Endocrine: Hypoglycemia (Severe) ○ Hematologic: Agranulocytosis, Aplastic anemia, Thrombocytopenia ○ Musculoskeletal: Myopathy/muscle weakness ○ Psychiatric: Anxiety, hallucination ○ Respiratory: Bronchospasm has been reported in post-marketing data ○ Ocular: retinal disorder only with prolonged use of greater than 5 years (7.5%) ○ Monitoring/Labs: CBC, ECG, BMP
COVID-19 positive patient <AND> Mechanical ventilation Exclusion criteria (3/15/20): • Evidence of Multi-organ failure • Pressor requirement to maintain blood pressure • ALT levels > 5 x ULN • CrCl < 30 ml/min or HD or CRRT	Supportive Care <AND> Consider Hydroxychloroquine 400 mg BID on day 1, then 200 mg BID x 4 days (some countries have extended duration based on clinical response) <AND> Consider remdesivir (investigational drug) compassionate use request if inclusion/exclusion criteria met.	• Remdesivir requires obtaining an E-IND (Emergency Investigational New Drug Application) for expanded use (compassionate use) which can take UP TO 72 HOURS. Information on the process for obtaining remdesivir and a patient information/consent form can be found at **http://www.trinity-health.org/covid19-pulse** ○ FDA/IRB approval and informed consent necessary if approved • Collecting the following information as request proceeds may be helpful ○ Attending of reference ○ Institution/ hospital name, address, email, and phone number ▪ Attending on record phone and email ○ Shipping information ○ Patient case information, including previous or current treatments and an extensive clinical status evaluation including laboratory values, HPI, clinical condition. • Remdesivir is a prodrug metabolized via CYP3A4, concomitant CYP3A4 inhibitors should be avoided if possible.* • Remdesivir has been generally well tolerated in preclinical and clinical studies to date. Self-limiting, reversible hepatotoxicity has been observed, which resolved after therapy cessation. Nephrotoxicity has been observed in preclinical studies. • As of 3/22/20 am, Gilead is only releasing compassionate use drugs for specific indications: single patient requests are no longer accepted, except for pregnant woman and children under the age of 18. They are transitioning to an expanded access program and we will provide you with updated guidance as soon as it is available.

* Liverpool COVID-19 Drug Interactions: http://www.covid19-druginteractions.org/

Other Pharmacotherapy Considerations

Other Antivirals

- A recent trial of adults hospitalized with severe COVID-19 treated with Lopinavir–Ritonavir (Kaletra®) has shown no benefit over supportive care and is not recommended (Cao et al.). Darunavir/cobisistat activity against COVID-19 has not been confirmed, activity is extrapolated from other coronaviruses (SARS/MERS).
- Oseltamivir and other neuraminidase inhibitors do not appear to have activity against other coronaviruses (SARS), and should be reserved for treatment of influenza.

Interleulin-6 Inhibitors

Some emerging evidence suggests that some patients may respond to COVID-19 with an exuberant "cytokine storm" reaction. Limited data is available for use of IL-6 receptor antagonists for treatment of COVID. A clinical trial is underway to evaluate the benefit of the IL-6 antagonist sarilumab in COVID patients. A single retrospective review of 20 COVID patients, with known baseline elevated IL-6 levels, treated with a combination of supportive care along with lopinavir, methylprednisolone, and the IL-6 inhibitor tocilizumab which showed promise. Most centers do not have IL-6 levels readily available, making the application of this small report problematic. In consultation with an Infectious Disease or critical care physician, off – label adjunctive IL-6 Tocilizumab (Actemra) could be considered for a patient that meets all of the following criteria: Site cannot enroll patient into sarilumab clinical trial, mechanically ventilated patients with severe disease refractory to supportive care and antiviral treatment, and presence of elevated levels of inflammatory markers. More readily available inflammatory markers that could be used for evaluation include CRP levels (> 60 mg/L) or Ferritin levels (>300 mcg/L).

Corticosteroids: Consider only for select patients with COVID-19 related refractory shock

- The World health organization does not recommend the routine use of systemic corticosteroids for treatment of viral pneumonia outside of clinical trials due to prior studies in patients with closely related viruses (SARS-CoV and MERS-CoV) showing a lack of effectiveness and possible harm. Clinicians considering corticosteroids for a patient with COVID-19 and with sepsis must balance the potential small reduction in mortality with the potential for prolonged shedding of coronavirus.
- Society of Critical Care Medicine recommendation: For adults with COVID-19 and refractory shock, we suggest using low-dose corticosteroid therapy ("shock-reversal"), over no corticosteroid therapy (weak recommendation, low quality evidence).
    - Remark: A typical corticosteroid regimen in septic shock is intravenous hydrocortisone 200 mg per day administered either as an infusion or intermittent doses.
- CDC guidelines also do not recommend corticosteroid therapy unless indicated for other evidence-based reasons (e.g. COPD exacerbation or septic shock).

ACE Inhibitors and ARBs

There is interest in the potential role of ACE-inhibitors and angiotensin receptor blockers (ARBs) in the pathophysiology of this disease since the SARS-CoV-2 virus binds to the ACE2 receptor for cellular entry. However, current guidance from cardiology organizations (i.e. ACC/AHA/HFSA) state that there is not enough evidence to recommend for or against these medications in the setting of the COVID-19 pandemic.

- The HFSA, ACC, and AHA recommend continuation of RAAS antagonists for those patients who are currently prescribed such agents for indications for which these agents are known to be beneficial, such as heart failure, hypertension, or ischemic heart disease.
- In the event patients with cardiovascular disease are diagnosed with COVID-19, individualized treatment decisions should be made according to each patient's hemodynamic status and clinical presentation.

Therefore, be advised not to add or remove any RAAS-related treatments, beyond actions based on standard clinical practice.

NSAIDS

The FDA is aware of news reports stating the use of non-steroidal anti-inflammatory drugs (NSAIDs) could worsen coronavirus disease (COVID-19). However, there is no scientific evidence to support these claims to date. The agency is investigating this issue and currently does not have any specific recommendations to withhold NSAID therapy in these patients. The European Medicines Agency has also issued guidance that there is not enough data to recommend avoiding NSAIDS in COVID patients.

Respiratory Treatments

Inhaled medications can be delivered either by Metered Dose Inhalers (MDIs) or by nebulization; when delivered by nebulization, these can be aerosol generating. For COVID positive or patients suspected to have COVID, the use of MDIs is preferred when / if available. Please refer to the " Patients and Inhaled Respiratory Medications - Changes to Current Processes" document at http://www.trinity-health.org/covid19-pulse.

Other Care Considerations

Patient positioning

Colleagues from Providence St. Joseph, who cared for the first US patient, report that placing patients with shortness of breath in the prone position was helpful in delaying and even avoiding the placement of COVID-19 patients on mechanical ventilation.

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