Pharmacy information regarding treatment of COVID-19 cases

At present, despite much public commentary on what to do about COVID-19, the principal defenses are prevention efforts and supportive care. The researchers' scramble for something definitive has yet to yield any proven therapy or official guidance from regulatory agencies or professional societies.

The information below summarizes what we know at this point. We hope it will help inform conversations and decision making as physicians wrestle with difficult choices, and seek to fully disclose the unknowns to patients and families of very ill patients.

- At present there are no FDA-approved agents for COVID-19
- When deciding on off-label use for COVID-19 be advised supplies are limited
- Please review attached document detailing investigational treatments, agents considered for adjunctive use, agents where risks appear to outweigh benefits and precautions

This document will be updated regularly as more information becomes available.

COVID-19 Treatment Information Review

(Updated 5/5/2020)

Approved Agents for treatment:

At present, there are no FDA-approved agents for treatment of COVID-19. Limited evidence supports possible benefit from several agents. Randomized controlled trials are lacking, and outcomes data are currently unavailable. Risk/benefit must be evaluated before any off-label use. At present time, all therapy is unproven and speculative. IRB approval may be required for some agents.

Investigational Agents for treatment:

Please be advised that these agents are limited in terms of availability. When deciding on off-label use for COVID-19 be advised that supplies are LIMITED. Carefully consider risk vs. benefit, and be aware that if our supply becomes depleted, these drugs may be unavailable for future patients, regardless of diagnosis.

Hydroxychloroquine— off label use, available on UHCS formulary (though affected by shortages/stockpiling). **This agent may increase QT interval, which may be additive in effect with other medications, including azithromycin. Please be aware of possible pro-arrhythmic effects, especially in patients with renal or hepatic dysfunction or immunosuppression. Consider EKG monitoring pre and post-initiation.

FDA has issued an Emergency Use Authorization (EUA) permitting the drug to be distributed from the Strategic National Stockpile (SNS) for use ONLY in adults and adolescents weighing ≥50kg hospitalized with COVID-19 for whom a clinical trial is not available, and with certain mandatory requirements (including adverse event reporting). Contraindicated in the presence of retinal or visual field changes. Hydroxychloroquine should not be used in patients with a prolonged baseline QT interval or patients at increased risk for arrhythmia.

Suggested EUA dosing is 800mg daily on Day #1, then 400mg daily for 4-7 days. This is consistent with study regimens using 400mg BID x 1 day, then 200mg BID x 4 days.

Chloroquine—off label use, commercially available (though affected by shortages/stockpiling). **Cardiotoxicity is a possibility due to QT prolongation, especially in patients with renal or hepatic dysfunction or immunosuppression. Consider EKG monitoring pre and post-initiation. Hydroxychloroquine may have better tolerability.

FDA has issued an Emergency Use Authorization (EUA) permitting the drug to be distributed from the Strategic National Stockpile (SNS) for use ONLY in adults and adolescents weighing ≥50kg hospitalized with COVID-19 for whom a clinical trial is not available, and with certain mandatory requirements

(including adverse event reporting). Contraindicated in the presence of retinal or visual field changes. Chloroquine should not be used in patients with a prolonged baseline QT interval or patients at increased risk for arrhythmia.

Suggested dose per EUA is 1gm PO x 1 on Day #1, followed by 500mg daily x 4-7 days. Dose based on chloroquine phosphate.

Chinese guidelines recommend dose of chloroquine phosphate 500mg BID x 10 days.

Nitazoxanide—an antiprotozoal agent with antiviral potential against coronaviruses, in vitro activity. Various individual hospital guidelines have used doses 500mg-1000mg PO BID.

Remdesivir—Currently not FDA approved for any indication. At present time, this agent is only available via allocation from ASD Healthcare, the sole distributor. ASD will provide health-systems with allocated quantity of remdesivir as instructed by the U.S. government.

FDA has issued an Emergency Use Authorization (EUA) permitting use of the unapproved product remdesivir for treatment of laboratory confirmed or suspected COVID-19 in adults and children with severe disease. Severe disease is defined by O2 saturation ≤94% on room air, or requiring supplemental oxygen, mechanical ventilation or ECMO.

Suggested adult dose per EUA is 200mg IV x 1 then 100mg IV daily x 4-9 days.

Ivermectin—no published data regarding safety or efficacy in COVID-19 patients. In vitro data from a single study show some activity. No human studies, thus no dosing guidelines. No data to support use at present time.

Agents Considered for Adjunctive Use

Tocilizumab—off label use, commercially available, high cost, limited availability. IL-6 inhibitor, has been postulated as potentially helpful for cytokine storm in severe infection. Initial dose 4-8mg/kg (400mg), repeated x 1 additional dose if poor response. No outcomes data.

Corticosteroids—WHO recommends against glucocorticoids due to lack of evidence of benefit and evidence of increased mortality in MERS-CoV, influenza and SARS. Potential to blunt the inflammatory response in SARS, but weigh against the risks of secondary infections and adverse effects. Wide variations in agent, dose and duration from current studies.

Methylprednisolone—May be beneficial in patients with COVID-19 pneumonia progressing to ARDS. RCTs are needed.

Chinese regimens typically 40-80mg IV daily x 3-6 days. Some studies weight-based, so extrapolation to US patients may indicate need for dose adjustment.

Ascorbic Acid—no specific data to COVID-19. Data from sepsis studies have been reviewed. Various dosing regimens have been studied in patients with sepsis and ARDS.

Epoprostenol—has been used off-label by inhalation for sepsis patients with ARDS with evidence of reduced mean pulmonary artery pressure and improved oxygenation. Little data on clinical benefit.

Doses of 20-30ng/kg/minute in adults appear to be safe and effective in sepsis studies. No specific recommendation can be made for use in COVID-19 patients with severe ARDS.

Anticoagulants—Patients with COVID-19 may develop a hypercoagulable state in severe cases. This may be linked to poor outcome. The ISTA and ASH (American Society of Hematology) recommend prophylactic doses of low molecular weight heparin (LMWH) for all hospitalized COVID-19 patients unless contraindicated.

Agents where Risks Appear to Outweigh Benefits

Interferon-alpha—Chinese guidelines mentioned 5million units in sterile water 2ml nebulized BID. Poor in-vitro activity, significant toxicity risk especially in the critically ill.

Interferon beta— Poor in-vitro activity, significant toxicity risk especially in the critically ill.
No current dosing recommendations

Ribavirin—doses and routes vary among studies

Oseltamivir and baloxavir—antiviral activity noted against influenza. No data to suggest in vitro activity against SARS CoV-2.

Lopinavir-ritonavir—off label use, available on UHCS formulary. Latest research shows no improvement in mortality—median time to clinical improvement shortened by one day but this was not statistically significant. Dose used in trials of 400mg-100mg BID x 14 days

NIH guidelines recommend AGAINST use outside the setting of a clinical trial due to pharmacodynamics issues, and negative data from initial clinical trials.

Janus kinase inhibitors (such as baricitinib) have broad immunosuppressive effect and are not recommended for use in COVID-19.

Favipravir—not approved, nor available in the U.S.

Precautions:

NSAIDS—Unclear/ambiguous reports at present. As of March 19, WHO does not recommend against the use of ibuprofen. Indomethacin may have antiviral activity against other coronaviruses (CanineCoV and SARS-CoV) in animal model. No human studies. Acetaminophen remains the preferred agent for fever.

NIH Guidelines recommend that individuals taking NSAIDs for a co-morbid condition should continue therapy as prescribed. NIH recommends no difference in use of antipyretic regimens in terms of acetaminophen or NSAIDS.

ACE/ARBs—Diabetes mellitus and hypertension appear to be risk factors for severe disease. ACE2-increasing drugs may increase binding site for coronaviruses, and increase risk for severe infection Thiazoladinediones and ibuprofen may also increase ACE2. ACE2 polymorphisms linked to DM, cerebral stroke and hypertension in Asian populations may also play a part. Calcium channel blockers do not increase ACE2 expression or activity. **AHA, ACC , HFSA and ESC recommend continuing treatment with ACE/ARBs in patient currently prescribed these agents.**

Azithromycin—updated interim results from a single, small study. No conclusions can be drawn from current data. May have an anti-inflammatory or immunomodulatory effect . **Agent may compound cardiotoxicity from hydroxychloroquine or chloroquine if used concurrently, due to QT prolongation.

Most commonly used dose is 500mg on Day #1, 250mg daily on days 2-5.

NIH Guidelines recommend AGAINST the combination of hydroxychloroquine plus azithromycin except in the context of a clinical trial, due to potential for toxicities.

References:

1. www.thelancet.com/respiratory Published online March 11, 2020 https://doi.org/10.1016/52213-2600(20)30116-8. Accessed 3/19/2020
2. Updated: WHO Now Doesn't Recommend Avoiding Ibuprofen For COVID-19 Symptoms. https://www.sciencealert.com/who-recommends-to-avoid-taking-ibuprofen-for-covid-19-symptoms. Accessed 3/19/2020
3. Coronavirus disease 2019 (COVID-19). https://www.uptodate.com/contents/coronavirus-disease-2019-covid-19?mkt_tok=eyJpIjoiWWpJek5XSTBOV1ptTldFeiIsInQiOiJKZTlIczN3alwvS29xSGQ3QUVOY1pubms4U1BERzVtRzRlZzdFQXI3RVwvNGtDcFhHQkhFZmhoNWYwQnBKMWRwZWdlQ2VjVnpwQ0NJbUppckhGVUVGNng2bitFU294S3oybGUxbW03VUxZQXRYUENmcm4yeEdYVFVqcDhyNmhwbnZXIn0%3D#H1583795407. Accessed 3/19/2020
4. Gautret P, Lagier JC, Parola P et al. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. Int J Antimicrob Agents. 2020; In Press. (DOI 10.1016/jantimicag.2020.105949)
5. Cao et al. A trial of Lopinavir-Ritonavir in Adults Hospitalized with Severe Covid-19. NEJM.org March 18,2020. DOI:10.1056/NEJMoa2001282. Accessed 3/19/2020

6. Letter to the Editor: Remdesivir and chloroquine effectively ihibit the recently emerged novel coronavirus (2019-nCoV) in vitro. Cell Research (2020) 30:269-271; https://doi.org/10.1038/s41422-020-0282-0
7. Novel Coronavirus Pneumonia Diagnosis and Treatment Plan (Provisional 7th Edition) http://kjfy.meetingchina.org/msite/news/show/cn/3337.html. Accessed 3/18/2020
8. Coronavirus (COVID-19) Resources for Pharmacists. https://www.idstewardship.com/coronavirus-covid-19-resources-pharmacists/. Accessed 3/19/2020
9. Inpatient Guidance for Diagnosis and Treatment of COVID-19 in Adults and Children. Michigan Medicine University of Michigan. http://www.med.umich.edu/asp/pdf/adult_guidelines/COVID-19-treatment.pdf. Accessed 3/19/2020
10. Erin K McCreary, PharmD, BCPS, BCIDP, Jason M Pogue, PharmD, BCPS, BCIDP, on behalf of the Society of Infectious Diseases Pharmacists, COVID-19 Treatment: A Review of Early and Emerging Options, *Open Forum Infectious Diseases*, , ofaa105, https://doi.org/10.1093/ofid/ofaa105
11. HFSA/ACC/AHA Statement Addresses Concerns Re: Using RAAS Antagonists in COVID-19 https://www.acc.org/latest-in-cardiology/articles/2020/03/17/08/59/hfsa-acc-aha-statement-addresses-concerns-re-using-raas-antagonists-in-covid-19. Accessed 4/1/2020
12. US Food and Drug Administration. Letter of authorization: Emergency use authorization for use of chloroquine phosphate supplied from the strategic national stockpile for treatment of COVID-19 in certain hospitalized patients. Dated 2020 Mar 28. https://www.fda.gov/media/136535/download
13. US Food and Drug Administration. Letter of authorization: Emergency use authorization for use of hydroxychloroquine sulfate supplied from the strategic national stockpile for treatment of COVID-19 in certain hospitalized patients. Dated 2020 Mar 28. https://www.fda.gov/media/136537/download
14. Farkas J. Internet Book of Critical Care. From EMCrit Project website. https://emcrit.org/ibcc/COVID19/ Accessed 4/1/2020
15. Molina JM, Delaugerre C, Goff JL, et al. No evidence of rapid antiviral clearance or clinical benefit with the combination of hydroxychloroquine and azithromycin in patients with severe COVID19 infection. Médecine et Maladies Infectieuses. 2020. Preprint. https://doi.org/doi:10.1016/j.medmal.2020.03.006 Accessed 4/9/2020.
16. Caly L, Druce JD, Catton MG et al. The FDA-approved drug ivermectin inhibits the replication of SARS-CoV-2 in vitro. Antiviral Res. 2020. Preprint. https://www.sciencedirect.com/science/ article/pii/S0166354220302011?via%3Dihub Accessed 4/9/2020
17. Searcy RJ, Morales JR, Ferreira JA et al. The role of inhaled prostacyclin in treating acute respiratory distress syndrome. Ther Adv Respir Dis. 2015; 9: 302-12. Pubmed: 26294418 DOI: 10.1177/1753465815599345 Accessed 4/9/2020
18. Alhazzani W, Moller MH, Arabi YM et al. Surviving Sepsis Campaign: Guidelines on the Management of Critically Ill Adults with Coronavirus Disease 2019 (COVID-19). Crit Care Med. 2020. PMID: 32224769 DOI: 10.1097/CCM.0000000000004363 Accessed 4/9/2020

19. https://covid19treatmentguidelines.nih.gov/therapeutic-options-under-investigation/ Accessed 4/23/2020.
20. https://covid19treatmentguidelines.nih.gov/concomitant-medications/ Accessed 4/23/2020.
21. American Society of Hematology. COVID-19 and coagulopathy: frequently asked questions. From the ASH website. Accessed 2020 Apr 15. Available from https://www.hematology.org/covid19/covid-19-and-coagulopathy
22. International Society of Thrombosis and Haemostasis Interim Guidance on Recognition and Management of Coagulopathy in COVID-19. From the ISTH website. Accessed 2020 Apr 15. Available from https://onlinelibrary.wiley.com/doi/epdf/10.1111/jth.14810
23. Fact Sheet for Health Care Providers EUA of Remdesivif (GS-5734) https://www.fda.gov/media/137566/download Accessed 5/5/2020.