COVID-19 Pharmacotherapy Update

Week of April 27, 2020

The information in this document is emerging and rapidly evolving due to the nature of the COVID-19 pandemic and related ongoing research. For more references on COVID-19-related pharmacotherapy, please see "Additional Resources" section at end of document. Updates indicated with date of update.

Summary Table

Drug	Bottom Line & Considerations
Hydroxychloroquine (Plaquenil) **Updated 4/26/20**	**Efficacy/safety for treatment or prevention of COVID-19 is NOT established. More data is needed.** **Hydroxychloroquine on national* drug shortage list. ***FDA Emergency Use Authorization:** allows distribution from national stockpile for use **only** in adults/adolescents ≥50 kg and **hospitalized** with COVID-19. **IDSA** recommend use only in the context of clinical trials. ****FDA caution AGAINST use** outside of hospital/clinical trial settings. *****NIH Guidelines** recommend **AGAINST** use as pre- or post-exposure prophylaxis to prevent of SARS-CoV2. They do **NOT** recommend use of hydroxychloroquine + azithromycin for treatment except in context of clinical trial.
Chloroquine phosphate	
Azithromycin **Updated 4/26/20**	**Insufficient data to establish benefit of use as adjunctive treatment for COVID-19.** Drug-drug interaction between azithromycin and hydroxychloroquine increases risk of QTc interval prolongation. More data needed to assess safety and efficacy for adding azithromycin to hydroxychloroquine for treating COVID-19. **IDSA** recommend use only in the context of clinical trials. *****NIH Guidelines** recommend **AGAINST** using hydroxychloroquine + azithromycin for treatment except in context of clinical trial.
Corticosteroids **Updated 4/26/20**	**Inconclusive evidence for treating of COVID-19 patients.** **WHO** & the **CDC** recommend **NOT** using corticosteroids solely for COVID-19 patients without other indications. **IDSA** recommend **AGAINST** use for patients with COVID-19 pneumonia, but for patients with ARDS due to COVID-19, IDSA recommends use of corticosteroids in context of a clinical trial. *****NIH Guidelines** recommend **AGAINST** use of steroids in mechanically ventilated COVID-19 pts without ARDS.

Lopinavir (LPV) / ritonavir (RTV) (Kaletra) – **Updated 4/26/20**	**Efficacy for treatment of COVID-19 is NOT definitely established.** **ESICM & SCCM suggest against use in critically ill adults with COVID-19.** **IDSA** and **NIH** recommend use only in the context of clinical trials.
Tocilizumab (Actemra)	**Very limited data to support use.** Allowed in China to treat critically ill COVID-19 patients with extensive lung lesions and high IL-6 levels. **IDSA** and **NIH** recommend use only in the context of clinical trials.
IVIG	**ESICM & SCCM suggest against routine use in critically ill adults with COVID-19.**
Anticoagulation, t-PA **Updated 4/26/20**	**ISTH & ASH recommend all hospitalized COVID-19 patients receive prophylactic-dose LMWH unless contraindicated.** No clinical data regarding t-PA use as salvage therapy for patients with declining respiratory function and where ECMO or mechanical ventilators not available. ****University of Colorado Hospital/UCHealth Anticoagulation Subcommittee guidelines.
Remdesivir	Not yet commercially available, but potentially most promising antiviral being studied, with multiple ongoing clinical trials.
Baloxavir, oseltamivir, anakinra, IV ascorbic acid, sirolimus, sarilumab, herbal supplements	No data to support treatment for COVID-19.
Ace inhibitor (ACEi) Angiotensin Receptor Blocker (ARB)	**No sound scientific basis for concern for using ACEi, ARB, or other RAAS blockers in patients with COVID-19.** ESC & HFSA/ACC/AHA recommend continuing treatment per standard practice.
Ibuprofen and other NSAIDs	**No sound scientific basis for concern for using ibuprofen for pain/fever in patients with COVID-19.** Continue use per standard practice. However, acetaminophen is an acceptable alternative, if preferred.

Detailed Information Tables

Potential Treatments for COVID-19[1-8]			
Drugs	**Rationale & Proposed Mechanism**	**Summary of Clinical Evidence or Experience**	**Bottom Line & Considerations**
Chloroquine phosphate Hydroxychloroquine (HCQ) (Plaquenil) **Updated 4/26/20**	*Mechanism:* potential activity against SARS-CoV2 and immunomodulating properties. Hydroxychloroquine may be more potent than chloroquine based on *in vitro* data.	**Limited clinical trial data for treatment/prevention:** • Conflicting results on HCQ from small studies, some with serious methodological flaws. **Clinical experience**: • Possible decreased viral load and duration of illness. **Known toxicities:** • Cardiac toxicity (e.g. QT prolongation), retinal toxicity, significant drug interactions. • **FDA caution AGAINST use** outside of hospital/clinical trial settings due to cardiac toxicity risk. **IDSA** and **NIH guidelines:** • Do **NOT** recommend use of HCQ + azithromycin except in clinical trial. • NIH recommends **AGAINST** use as pre- or post-exposure prophylaxis to prevent of SARS-CoV2.	**Efficacy/safety for treatment or prevention of COVID-19 is NOT established. More data is needed.** **IDSA and FDA recommend use only in the context of clinical trials.** **NIH recommends AGAINST use as prevention, and AGAINST use with azithromycin outside of clinical trial.** ***Hydroxychloroquine on national drug shortage list.* ****FDA Emergency Use Authorization:** Allows distribution of both agents from national stockpile for use **only** in adults/adolescents ≥50 kg and hospitalized with COVID-19.
Azithromycin (AZ) **Updated 4/26/20**	*In vitro* activity against viruses in general, but **no *in vitro* data against coronaviruses;** does have immunomodulatory properties.	**Limited clinical trial data for treatment/prevention:** • Small French studies with HCQ + AZ demonstrated benefit but had serious methodological flaws. **Clinical experience**: • Used for antibacterial coverage in hospitalized COVID-19 patients. • Used as adjunct in respiratory conditions (e.g. COPD, ARDS, bronchiectasis, etc.), and viral infections (e.g. influenza). **IDSA** and **NIH guidelines:** • Do **NOT** recommend use of HCQ + azithromycin except in clinical trial.	**Insufficient data to establish benefit of use as adjunctive treatment agent for COVID-19.** **IDSA recommends use only in the context of clinical trials.** **NIH recommends AGAINST use with HCQ outside of clinical trial.** Drug-drug interaction between azithromycin + HCQ increases risk of QTc interval prolongation. More data needed to assess safety/efficacy.

Speculative Treatments with Some Recommendations AGAINST Use for COVID-19[1-8]			
Drugs	**Rationale & Proposed Mechanism**	**Summary of Clinical Evidence or Experience**	**Bottom Line & Considerations**
Corticosteroids **Updated 4/26/20**	Anti-inflammatory properties; may improve dysregulated immune response caused by sepsis.	**Observational studies:** • Showed **no survival benefit and possible harm** (delayed viral clearance, psychosis, diabetes). **WHO & CDC:** • Recommend steroids **NOT** be routinely used in COVID-19 patients for viral pneumonia or ARDS unless there is another indication (e.g. asthma, COPD, septic shock). **IDSA guidelines:** • Suggests **AGAINST** use for COVID-19 pneumonia (very low certainty of evidence). • For ARDS related to COVID-19, IDSA recommends use of corticosteroids in context of clinical trial. **NIH guidelines:** • Recommend **AGAINST** use in mechanically ventilated COVID-19 pts without ARDS.	**Inconclusive evidence for treating of COVID-19 patients.** **WHO & CDC** recommend **NOT** using corticosteroids solely for COVID-19 without other indications. **IDSA** recommends **AGAINST** use for COVID-19 pneumonia. **NIH r**ecommend **AGAINST** use in mechanically ventilated COVID-19 pts without ARDS.
Lopinavir (LPV) /ritonavir (RTV) (Kaletra) **Updated 4/26/20**	*In vitro* activity against SARS-CoV and MERS-CoV, but **no *in vitro* data against SARS-CoV2 specifically.**	**Limited clinical trial data for treatment** (ongoing trials): • 1 study found **no differences** in clinical outcomes. **ESICM & SCCM Surviving Sepsis campaign:** • Suggest **against** use of LPV/RTV in critically ill adults with COVID-19 (weak recommendation, low quality evidence). **IDSA** and **NIH:** recommend use only in context of clinical trial.	**Efficacy for treatment of COVID-19 is NOT definitely established.** ESICM & SCCM suggest **against** use in critically ill adults with COVID-19.
Tocilizumab (Actemra)	Monoclonal antibody specific for IL-6 receptor to combat cytokine release syndrome in severely ill patients.	**Limited clinical trial data for treatment:** • Preliminary data from China found rapid fever reduction/reduced need for supplemental O_2 • Case studies/case series describe use in various countries. **IDSA** and **NIH** recommends use only in context of clinical trial.	**Very limited data to support use.** Allowed in China to treat critically ill OVID-19 patients with extensive lung lesions and high IL-6 levels.

Speculative Treatments with Some Recommendations AGAINST Use for COVID-19 (cont'd)[1-8]			
Drugs	**Rationale & Proposed Mechanism**	**Summary of Clinical Evidence or Experience**	**Bottom Line & Considerations**
Immune globulin (IVIG)	May modulate response to infections. May contain antibodies against some previously circulating coronaviruses, but antibodies against SARS-CoV-2 depends on time of donor plasma collection.	**Clinical experience:** • IVIG has been used in some patients to treat SARS, but benefits unclear. • Case reports and ongoing clinical trials of use in China. **ESICM & SCCM Surviving Sepsis campaign:** • Suggest **against** use of IVIG in critically ill adults with COVID-19 (weak recommendation, very-low quality evidence).	**No efficacy data to date.** **ESICM & SCCM Surviving Sepsis campaign** suggest **AGAINST** routine use in critically ill COVID-19 patients.

Medication with ongoing trials but not yet commercially available[1]	Medications with no data to date to support treatment of COVID-19[1]	
• Remdesivir – potentially most promising antiviral currently being studied for COVID-19, with multiple ongoing clinical trials. • Favipravir – licensed in Japan and China for treatment for influenza, efficacy and safety for treatment of COVID-19 not established. • Umifenovir – licensed in China and Russia for prophylaxis and treatment for influenza, with ongoing COVID-19 trials.	• Baloxavir. • Oseltamivir (Tamiflu). • Anakinra (Kineret). • Ascorbic acid (vitamin C) – ongoing RCT in China, IV only (no data on PO). • Sirolimus – *in vitro* activity against MERS-CoV, but no data for SARS-CoV2. • Sarilumab (Kefzara) – ongoing RCT in US (similar to tocilizumab).	• All herbal/dietary supplements. • Ruxolitinib (Jakafi) – ongoing trials. • Ivermectin. • Inhaled epoprostenol (Flolan) – per Surviving Sepsis Campaign, no adequate studies so cannot recommend for or against use in COVID-10 patients with severe ARDS.

Related Medication Concerns[1-8]			
Drugs	**Rationale & Proposed Mechanism**	**Summary of Clinical Evidence or Experience**	**Bottom Line & Considerations**
ACEi & ARBs	ACE2 receptor identified as a human cell entry point for SARS-CoV2. In animal studies, ACEi and ARBs increased ACE2 levels.	**To date, there are no clinical trials or recent data detailing additional risks of ACEi/ARBs related to COVID-19.** • Animal studies found increased ACE2 in heart/brain tissue after treatment with ARBs. Little evidence of changes in serum/lung ACE2 levels. • Cardiology societies recommend **against** stopping ACEi/ARBs/other RAAS blockers in COVID-19 patients due to lack of evidence supporting their harmful effects: ESC Position Statement | HFSA/ACC/AHA Statement.	**No sound scientific basis for concern for using ACEi, ARB, or other RAAS blockers in patients with COVID-19.** Continue treatment per standard practice.
Ibuprofen / NSAIDs	French health minister suggested anti-inflammatory agents could aggravate COVID-19 infection. Speculation that ibuprofen increases ACE2. NSAID anti-inflammatory properties may blunt immune response, but data is mixed.	**To date, there are no clinical trials or recent data detailing additional risks of NSAIDS related to COVID-19.** • Article states ibuprofen can increase ACE2, but no sources were cited. • Unsubstantiated reports of young/healthy patients who took ibuprofen and had severe COVID-19 outcomes, but no official case reports. **The FDA and WHO:** Both released statements saying they are unaware of scientific evidence supporting concerns for NSAIDs in COVID-19 patients, and do **not** recommend against the use of ibuprofen.	**No sound scientific basis for concern for using ibuprofen for pain/fever in patients with COVID-19.** Continue use per standard practice. However, acetaminophen is acceptable alternative if preferred.
Anticoagulants (LMWH, UFH) & Tissue Plasminogen Activator (t-PA, Alteplase) **Updated 4/26/20**	Current evidence indicates that patients with severe COVID-19 may develop coagulation abnormalities (e.g. DIC, VTE, elevated D-dimer levels, high fibrinogen levels).	Ongoing clinical trials evaluating prophylactic and therapeutic-dose anticoagulation in hospitalized patients with severe COVID-19 infection. **Clinical Experience for t-PA:** • Small study found possible benefit of t-PA for treatment of ARDS. • Proposed as salvage treatment for COVID-19 patients with decompensating respiratory function when mechanical ventilation or ECMO not available. • **University of Colorado Hospital/UCHealth Anticoagulation Subcommittee guidelines.** **ISTH & ASH:** • Recommend all hospitalized COVID-19 patients, including non-ICU patients, receive prophylactic-dose LMWH unless contraindicated ASH states that therapeutic anticoagulation not required unless there is documented VTE or atrial fibrillation.	More data needed to understand anticoagulant needs of COVID-19 patients. No clinical trial data and general lack of experience with t-PA for ARDS. **ISTH & ASH recommend all hospitalized COVID-19 patients receive prophylactic-dose LMWH unless contraindicated.**

Related Medication Concerns (cont'd)[1-8]			
Drugs	**Rationale & Proposed Mechanism**	**Summary of Clinical Evidence or Experience**	**Bottom Line & Considerations**
Nebulized drugs	Concern that nebulizer may distribute COVID-19 virus into air and expose close contacts.	**American College of Allergy, Asthma & Immunology (ACAAI)**: • Recommends nebulized albuterol be administered in a location that minimizes exposure to close contacts. In hospitals, clinicians are being encouraged to switch to use of metered-dose inhalers (MDI) if possible. **FDA has approved generic inhaler for Proventil (albuterol).**	In hospitals, consider switching nebulizers to MDI when possible. **Proventil (albuterol) now available as generic.**
Elderberry	*In vitro* study shows elderberry extract may be pro-cytokine, but data are conflicting. Cytokine storm syndrome may be a severe complication of COVID-19.	**To date, no clinical trials or data detailing elderberry causing cytokine storm in humans. However, also no evidence for use in treatment or prevention of COVID-19.** **Clinical Experience**: • Elderberry commonly taken for colds/influenza.	No sound scientific basis for concern for elderberry causing increased cytokines in humans, but ALSO no evidence for treatment or prevention of COVID-19.

Additional Resources (Hyperlinks):

- ASHP Assessment of Evidence for COVID-19 Related Treatments (updated regularly)
- ESICM & SCCM Surviving Sepsis Campaign: Guidelines on the Management of Critically Ill Adults with Coronavirus Disease 2019 (COVID-19)
- CDC COVID-19 Therapeutic Options
- Renin-Angiotensin-Aldosterone System Inhibitors in Patients with COVID-10 – NEJM Article March 30, 2020.
- IDSA COVID-19 Guidelines
- TRC/Natural Medicines: COVID-19 Natural/Alternative Medicines Advisory
- University of Colorado Hospital & University of Colorado Health Anticoagulation Subcommittee Guidelines
- NIH COVID-19 Guidelines

References:

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2. Smith T, Bushek J, Prosser T. COVID-19 Drug Therapy – Potential Options. Clinical Drug Information, Clinical Solutions. Elsevier. March 26, 2020. https://www.elsevier.com/__data/assets/pdf_file/0007/988648/COVID-19-Drug-Therapy_Mar-2020.pdf

3. WHO. Clinical management of severe acute respiratory infection (SARI) when COVID-19 disease is suspected. Interim guidance. 2020 Mar 13. From WHO website. Accessed April 2, 2020. https://www.who.int/publications-detail/clinical-management-of-severe-acute-respiratory-infection-when-novel-coronavirus-(ncov)-infection-is-suspected
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5. Pharmacists Letter. Coronavirus (COVID-19) Resource Hub. Accessed April 12, 2020. https://pharmacist.therapeuticresearch.com/Content/Topic/all/covid-19-Resource-Hub
6. 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. https://onlinelibrary.wiley.com/doi/epdf/10.1111/jth.14810
7. American Society of Hematology. COVID-19 and coagulopathy: frequently asked questions. From the ASH website. Accessed 2020 Apr 15. https://www.hematology.org/covid19/covid-19-and-coagulopathy
8. NIH. COVID-19 Treatment Guidelines. April 21, 2020. Last Accessed April 26, 2020. https://www.covid19treatmentguidelines.nih.gov/

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