UCHealth Integrated Network

COVID-19 Pharmacotherapy Update

COVID-19 Pharmacotherapy Weekly Updates: Week of April 13, 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)	**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 of both agents from national stockpile for use **only** in adults/adolescents ≥50 kg and **hospitalized** with COVID-19 ****Updated 4/12/20**: **IDSA** recommend use only in the context of clinical trials
Chloroquine phosphate	
Azithromycin	**Insufficient data to establish benefit of use as adjunctive treatment agent 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 ****Updated 4/12/20**: **IDSA** recommend use only in the context of clinical trials
Corticosteroids	**Inconclusive evidence for treating of COVID-19 patients.** **WHO & the CDC recommend NOT using corticosteroids solely for COVID-19 patients without other indications** ****Updated 4/12/20**: **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
Lopinavir (LPV) /ritonavir (RTV) (Kaletra)	**Efficacy for treatment of COVID-19 is NOT definitely established.** **ESICM & SCCM suggest against use in critically ill adults with COVID-19** ****Updated 4/12/20**: **IDSA** recommend use only in the context of clinical trials

Tocilizumab (Actemra)	**Very limited data to support use.** Allowed in China to treat severely/critically ill COVID-19 patients with extensive lung lesions and high IL-6 levels ****Updated 4/12/20**: **IDSA** recommend use only in the context of clinical trials
Remdesivir	Not yet commercially available, but potentially most promising antiviral being studied, with multiple ongoing clinical trials
Baloxavir, Oseltamivir (Tamiflu), Anakinra (Kineret), IV ascorbic acid (vitamin C) Sirolimus, Sarilumab (Kefzara), 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[1-5]			
Drugs	**Rationale & Proposed Mechanism**	**Summary of Clinical Evidence or Experience**	**Bottom Line & Considerations**
Chloroquine phosphate Hydroxychloroquine (HCQ) (Plaquenil) **Updated 4/12/20**	*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 **IDSA guidelines:** • Recommends HCQ/chloroquine only be used in the context of a clinical trial (remains a knowledge gap) • Overall certainty of evidence very low, due to concerns for major flaws in current literature	**Efficacy/safety for treatment or prevention of COVID-19 is NOT established. More data is needed.** **IDSA recommends use only in the context of clinical trials** ***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 4/12/20**	*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 adjunctive therapy in respiratory conditions (e.g. COPD, ARDS, bronchiectasis, etc.), and viral infections (e.g. influenza) **IDSA guidelines:** • Recommends HCQ + AZ only be used in the context of a clinical trial (remains a knowledge gap) • Overall certainty of evidence very low • Does not address use of AZ for secondary bacterial pneumonia in COVID-19 patients	**Insufficient data to establish benefit of use as adjunctive treatment agent for COVID-19.** **IDSA recommends use only in the context of clinical trials** Drug-drug interaction between azithromycin and hydroxychloroquine increases risk of QTc interval prolongation. More data needed to assess safety/efficacy for adding azithromycin to hydroxychloroquine for treating COVID-19.

Speculative Treatments with Some Recommendations AGAINST Use for COVID-19[1-5]			
Drugs	**Rationale & Proposed Mechanism**	**Summary of Clinical Evidence or Experience**	**Bottom Line & Considerations**
Corticosteroids **Updated 4/12/20**	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 exacerbation, septic shock) **IDSA guidelines:** • Suggests AGAINST use for COVID-19 pneumonia (conditional recommendation, very low certainty of evidence) • For ARDS related to COVID-19, IDSA recommends use of corticosteroids in context of clinical trial (knowledge gap)	**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**
Lopinavir (LPV) /ritonavir (RTV) (Kaletra) **Updated 4/12/20**	*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 with LPV/RTV **ESICM & SCCM Surviving Sepsis Campaign:** • Suggest **against** use of LPV/RTV in critically ill adults with COVID-19 (weak recommendation, low quality evidence) **IDSA guidelines:** • Recommends 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** **IDSA recommends use only in the context of clinical trials**
Tocilizumab (Actemra) **Updated 4/12/20**	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 No other clinical trial evidence supporting safety/efficacy **IDSA guidelines:** • Recommends use only in context of clinical trial	**Very limited data to support use.** Allowed in China to treat severely/critically ill COVID-19 patients with extensive lung lesions and high IL-6 levels **IDSA recommends use only in the context of clinical trials**

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 • **Updated 4/12/20:** Favipravir – licensed in Japan and China for treatment for influenza, efficacy and safety for treatment of COVID-19 not established • **Updated 4/12/20:** 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)	• **Updated 4/12/20: all herbal/dietary supplements** • **Updated 4/12/20:** ruxolitinib (Jakafi) – ongoing trials • **Updated 4/12/20:** ivermectin • **Updated 4/12/20:** 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[1-5]			
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
Nebulized drugs **Updated 4/12/20**	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 **Updated 4/12/20**	*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, there are no clinical trials or recent 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

References:

1. ASHP. Assessment of Evidence for COVID-19 Related Treatments. ASHP Coronavirus Disease (COVID-19) Resource Center. From ASHP website. April 1, 2020. Last accessed April 2, 2020. https://www.ashp.org/Pharmacy-Practice/Resource-Centers/Coronavirus
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
4. Bhimraj A, et al. Infectious Diseases Society of America Guidelines on the Treatment and Management of Patients with COVID-19 Infection. April 11, 2020. Accessed April 12, 2020. https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/
5. Pharmacists Letter. Coronavirus (COVID-19) Resource Hub. Accessed April 12, 2020. https://pharmacist.therapeuticresearch.com/Content/Topic/all/covid-19-Resource-Hub

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