### **COVID-19 Pharmacotherapy Weekly Updates: Week of April 20, 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**

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| **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](https://www.ashp.org/Drug-Shortages/Current-Shortages)\*[**FDA Emergency Use Authorization:**](https://www.fda.gov/media/136534/download) allows distribution from national stockpile for use **only** in adults/adolescents ≥50 kg and **hospitalized** with COVID-19[**IDSA**](https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/) recommend use only in the context of clinical trials  |
| Chloroquine phosphate |
| Azithromycin | **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 prolongationMore data needed to assess safety and efficacy for adding azithromycin to hydroxychloroquine for treating COVID-19[**IDSA**](https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/) recommend use only in the context of clinical trials |
| Corticosteroids | **Inconclusive evidence for treating of COVID-19 patients.**[**WHO**](https://www.who.int/publications-detail/clinical-management-of-severe-acute-respiratory-infection-when-novel-coronavirus-%28ncov%29-infection-is-suspected) **& the** [**CDC**](https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-guidance-management-patients.html#Medications) **recommend NOT using corticosteroids solely for COVID-19 patients without other indications**[**IDSA**](https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/) 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**](https://www.esicm.org/wp-content/uploads/2020/03/SSC-COVID19-GUIDELINES.pdf) **suggest against use in critically ill adults with COVID-19**[**IDSA**](https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/) 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[**IDSA**](https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/) recommend use only in the context of clinical trials |
| IVIG – **Updated 4/19/20** | [**ESICM & SCCM**](https://www.esicm.org/wp-content/uploads/2020/03/SSC-COVID19-GUIDELINES.pdf) **suggest against routine use in critically ill adults with COVID-19** |
| Anticoagulation, t-PA– **Updated 4/19/20** | [**ISTH**](https://onlinelibrary.wiley.com/doi/epdf/10.1111/jth.14810) **&** [**ASH**](https://www.hematology.org/covid-19/covid-19-and-coagulopathy) **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 |
| 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, 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](https://www.escardio.org/Councils/Council-on-Hypertension-%28CHT%29/News/position-statement-of-the-esc-council-on-hypertension-on-ace-inhibitors-and-ang?fbclid=IwAR3MelOVecv-vT_64DPAM2BH9LO_Xv9jRLKHGqKLwFOq6Ym1GXPacP1he4A) & [HFSA/ACC/AHA](https://professional.heart.org/professional/ScienceNews/UCM_505836_HFSAACCAHA-statement-addresses-concerns-re-using-RAAS-antagonists-in-COVID-19.jsp) 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**

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| **Potential Treatments for COVID-191-5** |
| **Drugs** | **Rationale & Proposed Mechanism** | **Summary of Clinical Evidence or Experience** | **Bottom Line & Considerations** |
| Chloroquine phosphate | 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:**](https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/)* 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**](https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/) **recommends use only in the context of clinical trials**\*\*Hydroxychloroquine on national [drug shortage list](https://www.ashp.org/Drug-Shortages/Current-Shortages)\*\*[**FDA Emergency Use Authorization:**](https://www.fda.gov/media/136534/download)Allows distribution of both agents from national stockpile for use **only** in adults/adolescents ≥50 kg and hospitalized with COVID-19 |
| Hydroxychloroquine (HCQ) (Plaquenil) |
| Azithromycin (AZ) | 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 guidelines:**](https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/)* 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**](https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/) **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. |

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| **Speculative Treatments with Some Recommendations AGAINST Use for COVID-191-5** |
| **Drugs** | **Rationale & Proposed Mechanism** | **Summary of Clinical Evidence or Experience** | **Bottom Line & Considerations** |
| Corticosteroids | 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**](https://www.who.int/publications-detail/clinical-management-of-severe-acute-respiratory-infection-when-novel-coronavirus-%28ncov%29-infection-is-suspected) **&** [**CDC**](https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-guidance-management-patients.html#Medications)**:*** 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:**](https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/)* **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**](https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/) **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) | 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**](https://www.esicm.org/wp-content/uploads/2020/03/SSC-COVID19-GUIDELINES.pdf) **Surviving Sepsis Campaign:** * Suggest **against** use of LPV/RTV in critically ill adults with COVID-19 (weak recommendation, low quality evidence)

[**IDSA guidelines:**](https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/)* **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**](https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/) **recommends use only in the context of clinical trials** |
| 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 O2
* Case studies/case series describe use in various countries

No other clinical trial evidence supporting safety/efficacy[**IDSA guidelines:**](https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/)* **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**](https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/) **recommends use only in the context of clinical trials** |

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| **Speculative Treatments with Some Recommendations AGAINST Use for COVID-19 (cont.)1-5** |
| **Drugs** | **Rationale & Proposed Mechanism** | **Summary of Clinical Evidence or Experience** | **Bottom Line & Considerations** |
| Immune globulin (IVIG)**Updated 4/19/20** | May modulate response to infectionsMay 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**](https://www.esicm.org/wp-content/uploads/2020/03/SSC-COVID19-GUIDELINES.pdf) **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**](https://www.esicm.org/wp-content/uploads/2020/03/SSC-COVID19-GUIDELINES.pdf) **Surviving Sepsis Campaign** suggest **AGAINST** routine use in critically ill COVID-19 patients |

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| **Medication with ongoing trials but not yet commercially available1** | **Medications with no data to date to support treatment of COVID-191** |
| * 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](https://link.springer.com/content/pdf/10.1007/s00134-020-06022-5.pdf), no adequate studies so cannot recommend for or against use in COVID-10 patients with severe ARDS
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| **Related Medication Concerns1-7** |
| **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](https://www.escardio.org/Councils/Council-on-Hypertension-%28CHT%29/News/position-statement-of-the-esc-council-on-hypertension-on-ace-inhibitors-and-ang?fbclid=IwAR3MelOVecv-vT_64DPAM2BH9LO_Xv9jRLKHGqKLwFOq6Ym1GXPacP1he4A) | [HFSA/ACC/AHA Statement](https://professional.heart.org/professional/ScienceNews/UCM_505836_HFSAACCAHA-statement-addresses-concerns-re-using-RAAS-antagonists-in-COVID-19.jsp)
 | **No sound scientific basis for concern for using ACEi, ARB, or other RAAS blockers in patients with COVID-19.**Continue treatment per standard practice |

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| **Related Medication Concerns (cont.)1-7** |
| **Drugs** | **Rationale & Proposed Mechanism** | **Summary of Clinical Evidence or Experience** | **Bottom Line & Considerations** |
| Ibuprofen / NSAIDs | French health minister suggested anti-inflammatory agents could aggravate COVID-19 infectionSpeculation that ibuprofen increases ACE2NSAID 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](https://www.thelancet.com/journals/lanres/article/PIIS2213-2600%2820%2930116-8/fulltext) 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**](https://www.fda.gov/drugs/drug-safety-and-availability/fda-advises-patients-use-non-steroidal-anti-inflammatory-drugs-nsaids-covid-19) **and** [**WHO**](https://twitter.com/WHO/status/1240409217997189128)**:**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 4/19/20** | 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
* Ongoing compassionate use protocols evaluating t-PA use at CU Anschutz Medical Campus and Denver Health

[**ISTH**](https://onlinelibrary.wiley.com/doi/epdf/10.1111/jth.14810) **&** [**ASH**](https://www.hematology.org/covid-19/covid-19-and-coagulopathy)**:*** 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 patientsNo clinical trial data and general lack of experience with t-PA for ARDS [**ISTH**](https://onlinelibrary.wiley.com/doi/epdf/10.1111/jth.14810) **&** [**ASH**](https://www.hematology.org/covid-19/covid-19-and-coagulopathy) **recommend all hospitalized COVID-19 patients receive prophylactic-dose LMWH unless contraindicated** |
| Nebulized drugs | Concern that nebulizer may distribute COVID-19 virus into air and expose close contacts | **American College of Allergy, Asthma & Immunology (**[**ACAAI**](https://acaai.org/news/important-covid-19-information-those-asthma-andor-allergies)):* 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 conflictingCytokine 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)](https://www.ashp.org/-/media/assets/pharmacy-practice/resource-centers/Coronavirus/docs/ASHP-COVID-19-Evidence-Table.ashx)
* [ESICM & SCCM Surviving Sepsis Campaign: Guidelines on the Management of Critically Ill Adults with Coronavirus Disease 2019 (COVID-19)](https://www.esicm.org/wp-content/uploads/2020/03/SSC-COVID19-GUIDELINES.pdf)
* [CDC COVID-19 Therapeutic Options](https://www.cdc.gov/coronavirus/2019-ncov/hcp/therapeutic-options.html)
* [Renin-Angiotensin-Aldosterone System Inhibitors in Patients with COVID-10 – NEJM Article March 30, 2020.](https://www.nejm.org/doi/pdf/10.1056/NEJMsr2005760?articleTools=true)
* [IDSA COVID-19 Guidelines](https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/)
* [TRC/Natural Medicines: COVID-19 Natural/Alternative Medicines Advisory](https://naturalmedicines.therapeuticresearch.com/tools/covid-19-advisory.aspx?_ga=2.262638282.770002860.1586723958-2080995874.1586530483)

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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](https://www.who.int/publications-detail/clinical-management-of-severe-acute-respiratory-infection-when-novel-coronavirus-%28ncov%29-infection-is-suspected)
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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>

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