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April 2020 ~ Resource #360423

COVID-19 and Pharmacotherapy

The **first chart below** provides information or resources on pharmacotherapy of interest for COVID-19, the disease caused by the SARS-CoV-2 virus. Hyperimmune plasma from recovered donors is also being tried in some centers. An additional resource on pharmacotherapy, which is frequently updated, is:

- The **American Society of Health-System Pharmacists** evidence table of COVID-19 treatments (https://www.ashp.org/-/media/assets/pharmacy-practice/resource-centers/Coronavirus/docs/ASHP-COVID-19-Evidence-Table).

At this point, no pharmacotherapy has been proven effective for COVID-19, so treatment is largely supportive. Resources pertinent to supportive therapy include:

- The **World Health Organization** guidance for the treatment of suspected COVID-19 severe acute respiratory infection (https://www.who.int/publications-detail/clinical-management-of-severe-acute-respiratory-infection-when-novel-coronavirus-(ncov)-infection-is-suspected).
- The **Surviving Sepsis Campaign** COVID-19 guidelines (https://sccm.org/SurvivingSepsisCampaign/Guidelines/COVID-19).

The **second chart below** addresses common questions about pharmacotherapy as it relates to COVID-19.

Search **www.clinicaltrials.gov** for the latest information on COVID-19 clinical trials.

Abbreviations: ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; ARDS = acute respiratory distress syndrome; COPD = chronic obstructive pulmonary disease; CT = computed tomography; EUA = Emergency Use Authorization; IL = interleukin; NSAIDs = nonsteroidal anti-inflammatory drugs; SARS = severe acute respiratory syndrome; SARS-CoV-2 = the virus that causes COVID-19 disease; tPA = tissue plasminogen activator; TNF = tumor necrosis factor

TREATMENTS OF INTEREST

Drug	**Pertinent Information or Resources** Note that **DOSES** provided are examples only for **ADULTS**; the optimal dose has not been determined for any treatment.
Azithromycin	• Macrolides have *in vitro* antiviral (e.g., Zika, Ebola), anti-inflammatory, and immunomodulatory activity.[2,7] • Insufficient evidence to support widespread use [Evidence level C].[2,28] • Was used in a small, widely publicized study with hydroxychloroquine in six patients to prevent bacterial superinfection in COVID-19 patients (See hydroxychloroquine, below).[2] Subsequent observational data including 74 additional patients suggests that the combination can reduce viral load and perhaps improve the clinical course, but there was no comparator group.[28] • Planned studies for COVID-19 treatment include various dosing regimens (e.g., azithromycin 500 mg x 1 then 250 mg for four days; 500 mg once daily for seven to ten days) **WITH** chloroquine or hydroxychloroquine. See clinicaltrials.gov for the latest information on these studies. • When used with hydroxychloroquine or chloroquine (and other QT-prolonging medications), QT prolongation is of increased concern.[2,4,6]

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Drug	**Pertinent Information or Resources** Note that **DOSES** provided are examples only for **ADULTS**; the optimal dose has not been determined for any treatment.
Aviptadil	• **Investigational** synthetic form of vasoactive intestinal polypeptide. Has anti-IL-6 and anti-TNF activity. Phase I trial suggests benefit in ARDS. No COVID-19 data. • Clinical trial is planned for COVID-19-associated ARDS. See www.clinicaltrials.gov for more information.
Baloxavir (*Xofluza*)	• No COVID-19 data.

Chloroquine phosphate*
 	
*Chloroquine phosphate 500 mg = chloroquine base 300 mg[6]
	Efficacy
	• Inhibits SARS-CoV-2 *in vitro*,[2] but clinical trials have not shown benefit against other viruses.[18] Also has immunomodulating effects.[26]
	• Insufficient evidence to support widespread use [Evidence level C].[3]
	• For COVID-19 pneumonia, reportedly speeds clinical improvement and viral clearance.[3]
	• Clinical trials are planned on the use of chloroquine to prevent COVID-19 in healthcare workers.
	• See www.clinicaltrials.gov for regimens being studied.
	Dosing
	• The FDA is suggesting, for patients weighing ≥50 kg, a chloroquine phosphate dose of 1 g on day one, followed by 500 mg once daily for four to seven days.[4] **U.S. providers can request chloroquine** through their local health department **(EUA)** for hospitalized patients unable to participate in a clinical trial.[4]
	• Additional dosing regimens from International consensus documents from around the world include:
	  • chloroquine phosphate 500 mg twice daily for ten days for COVID-19 pneumonia.[6]
	  • chloroquine phosphate 500 mg twice daily for ten days for patients with mild symptoms plus comorbidities, or more severe disease. The duration can be reduced to five days or extended to 20 days, depending on clinical severity.[6]
	  • chloroquine **base** 600 mg x 1, then 300 mg 12 hours later, then 300 mg twice daily on days two through five for intensive care patients or patients requiring hospital admission and oxygen.[6] (The five-day duration was chosen to minimize adverse effects, giving consideration to chloroquine's long half-life [~30 hours]).[6]
	Safety
	• A **fact sheet** on chloroquine for COVID-19 is available from the FDA (https://www.fda.gov/media/136535/download).
	• **Adverse effects** are not well-characterized at the doses studied for COVID-19. In general, potential adverse effects include: gastrointestinal side effects (take with food or milk), headache, hypoglycemia, QT prolongation and other conduction disturbances (especially with hypokalemia, hypomagnesemia, or heart disease), cardiomyopathy, myopathy, movement disorders, neurotoxicity, ocular toxicity, ototoxicity, anemia, thrombocytopenia, neutropenia, bone marrow suppression, serious dermatologic reactions, and psoriasis flare.[4,27] **Monitor** electrolytes, glucose, complete blood count, electrocardiogram, baseline renal and hepatic function, knee and ankle reflexes, vision, and mental status.[4,6,27]
	• When used with azithromycin (and other QT-prolonging medications), QT prolongation is of increased concern.[2,6]

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Drug	**Pertinent Information or Resources** Note that **DOSES** provided are examples only for **ADULTS**; the optimal dose has not been determined for any treatment.
Colchicine	• Based on its anti-inflammatory effect, there is interest in using colchicine to alter the clinical course of COVID-19 in both inpatients and higher-risk outpatients. • Clinical trials are underway. See www.clinicaltrials.gov for more information.
Corticosteroids	• The World Health Organization Guidelines recommends that at this time, **outside of clinical trials**, corticosteroids should be reserved for patients with specific indications for them (e.g., sepsis, COPD, asthma), with consideration to risk vs benefit.[10] • The CDC recommends that corticosteroids be avoided because of the potential for prolonging viral replication, increasing need for mechanical intubation, or increasing mortality, as observed in MERS-CoV patients, unless indicated for other reasons.[11] • Corticosteroids appeared to be ineffective and possibly harmful for SARS, but are being studied for COVID-19.[9,10] In one institution in China, methylprednisolone use in patients with COVID-19 ARDS was associated with reduced mortality.[16]
Hydroxy-chloroquine *Continued…*	Efficacy • Is a more potent inhibitor of SARS-CoV-2 than chloroquine *in vitro*.[2] Also has immunomodulating effects.[27] • Insufficient evidence to support widespread use [Evidence level C].[2,29] • Hydroxychloroquine 200 mg three times daily for ten days was used in a widely publicized open-label, randomized study in hospitalized patients testing positive for SARS-CoV-2.[2] Six of 26 hydroxychloroquine patients were lost to follow-up: one due to death, three due to intensive care admission, one due to side effects (nausea), and one who left the hospital. Viral clearance at day six was 70% in the 20 remaining hydroxychloroquine patients vs 12.5% of the control patients (n = 16).[2] Six treated patients also received azithromycin 500 mg on day one, then 250 mg on days two through five to prevent bacterial infection.[2] In the combination group, viral clearance was 100% at day six vs 57.1% in the hydroxychloroquine-alone group.[2] Also see subsequent observational data under "Azithromycin," above. • In a pilot study in China 30 patients were randomized to hydroxychloroquine 400 mg/day (it is unclear if this was divided) for five days, or usual care. There was no difference between groups in viral clearance at day seven, length of stay, or time to defervescence.[29] In a study of 62 hospitalized patients with mild disease, 31 patients were randomized to hydroxychloroquine 200 mg twice daily. Time to recovery (defervescence and cough remission) was shortened by about one day in the treatment group. On day six, pneumonia was improved per CT in more patients in the treatment group. Four patients progressed to severe disease, all in the control group.[39] Other Dosing Regimens • The FDA is suggesting, for hospitalized patients weighing ≥50 kg, a dose of 800 mg on day one, followed by 400 mg once daily for four to seven days.[31] **U.S. providers can request hydroxychloroquine** through their local health department **(EUA)** for hospitalized patients unable to participate in a clinical trial.[31] • Some U.S. clinicians have reported anecdotally using 400 mg twice daily on day one, then 400 mg once daily for five days or 200 mg twice daily for four days; or 600 mg twice daily on day one, then 400 mg once daily on days two through five.[32]

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Drug	**Pertinent Information or Resources** Note that **DOSES** provided are examples only for **ADULTS**; the optimal dose has not been determined for any treatment.
Hydroxy-chloroquine, continued	• An Italian guideline suggests 200 mg twice daily for ten days for patients with mild symptoms plus comorbidities, or more severe disease.[6] The duration can be reduced to five days or extended to 20 days, depending on clinical severity.[6] • Other investigators are using a 14-day course,[6] and at least one study is using a total daily dose of 800 mg.[26] • Clinical trials are planned on the use of hydroxychloroquine to prevent COVID-19 in healthcare workers. • See www.clinicaltrials.gov for regimens being studied. Safety • Fewer adverse effects and drug interactions than chloroquine.[2] • A **fact sheet** on hydroxychloroquine for COVID-19 is available from the FDA (https://www.fda.gov/media/136537/download). • **Adverse effects** are not well-characterized at the doses studied for COVID-19. In general, potential adverse effects include: gastrointestinal side effects (take with food or milk), headache, hypoglycemia, QT prolongation and other conduction disturbances (especially with hypokalemia, hypomagnesemia, or heart disease), cardiomyopathy, myopathy, movement disorders, neurotoxicity, ocular toxicity, ototoxicity, anemia, thrombocytopenia, neutropenia, bone marrow suppression, serious dermatologic reactions, and psoriasis flare.[27,31] **Monitor** electrolytes, glucose, complete blood count, electrocardiogram, baseline renal and hepatic function, knee and ankle reflexes, vision, and mental status.[6,27,31] When used with azithromycin (and other QT-prolonging medications), QT prolongation is of increased concern.[2,6] • A **hydroxychloroquine suspension** can be made by triturating 15 hydroxychloroquine sulfate 200 mg tablets to a fine power with a mortar and pestle. Levigate to a paste with a small amount of base (*Oral Mix* or *Oral Mix SF*). Add base by geometric dilution. Transfer to a graduated cylinder. Rinse mortar and pestle with base. QS with base to 120 mL. Transfer to an amber polyethylene terephthalate bottle. Shake well. Stable for 112 days at room temperature or under refrigeration.[33]
IL-6 antagonist Tocilizumab (*Actemra*); sarilumab (*Kevzara*); siltuximab (*Sylvant*).	• Anti-IL-6 monoclonal antibody. • Some, but not all, data from China suggests an association between elevated IL-6 and severe COVID-19 disease.[18] • Anecdotal reports and case series suggest benefit for tocilizumab (*Actemra*).[18] A single dose of 400 mg has been used.[18] Other regimens are being studied. • May cause increased infections, neutropenia, thrombocytopenia, and elevated liver enzymes.[1,34-38] • Not for routine use. Clinical trials are planned or underway for treatment of pneumonia or cytokine storm. See www.clinicaltrials.gov for more information.

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Drug	**Pertinent Information or Resources** Note that **DOSES** provided are examples only for **ADULTS**; the optimal dose has not been determined for any treatment.
Lopinavir/ ritonavir (*Kaletra*)	• Lopinavir/ritonavir has not demonstrated anti-SARS-CoV-2 activity in humans.[15] Small study suggested benefit (reduced composite endpoint of ARDS or death) for 2003 SARS vs historical control.[17] • Best current evidence (e.g., randomized, open-label study [n=199]) suggests it might reduce complications such as acute kidney injury, secondary infections, or need for mechanical ventilation in patients with COVID-19 pneumonia.[15] However, time to clinical improvement was not reduced (main outcome measure).[15] Gastrointestinal adverse effects may limit use.[15,30] • There is interest in studying lopinavir/ritonavir earlier in the disease course, or in combination with other medications.[15] • Additional clinical trials are planned or underway. See www.clinicaltrials.gov for more information.
Losartan	• Studies in mice suggest that ARBs can reduce lung damage caused by SARS-CoV.[13] • Clinical trials are planned for treatment of COVID-19. See www.clinicaltrials.gov for more information.
Oseltamivir	• Not expected to be effective against SARS-CoV-2 because SARS-CoV-2 does not use neuraminidase.[26] • Has been used for COVID-19 pneumonia, but there is no efficacy data.[12]
Remdesivir	• In a case report, use was associated with clinical and virologic improvement in a patient with COVID-19 pneumonia.[8] • Well-tolerated.[8] • Investigational only. Phase III trials underway.[8] Contact Gilead at https://rdvcu.gilead.com regarding availability.
Ribavirin	• Not potent enough to be effective at safe doses; hematologic toxicity precludes use.[26]
tPA (alteplase)	• No data. • Interest based on reports of hypercoagulability in COVID-19 patients.[19] • Studies underway to treat ARDS in COVID-19 patients.[19]

—Continue to the next page for FAQs about meds and supplements for COVID-19—

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FAQs ABOUT COVID-19 AND PHARMACOTHERAPY

There is lots of misinformation regarding COVID-19 on the internet. Use this table to help answer patient questions and correct misconceptions.

Clinical question	Pertinent information or resource

Do ACE inhibitors or ARBs make COVID-19 worse?	• The SARS-CoV-2 virus uses ACE2 to enter cells.[13] ACE inhibitors and ARBs may upregulate ACE2.[13] In theory, these drugs could thereby facilitate virus entry into cells.[13] But on the other hand, blocking angiotensin could reduce lung injury.[13]
	• There is currently no clinical evidence that patients taking an ACEI or ARB are more susceptible to COVID-19 or infection, or that these medications worsen outcomes.[14] But we do know that these drugs benefit patients with diabetic nephropathy and cardiovascular disease, populations at risk of severe COVID-19 disease.[13,22]
	• Patients should continue these medications. See statements from:
	  • the **American Heart Association**, the **Heart Failure Society of America**, and the **American College of Cardiology** at https://newsroom.heart.org/news/patients-taking-ace-i-and-arbs-who-contract-covid-19-should-continue-treatment-unless-otherwise-advised-by-their-physician.
	  • the **Canadian Cardiovascular Society** at https://www.ccs.ca/images/Images_2020/CCS_CHFS_Update_COVID__CV_medications_Mar20.pdf.
	  • the **European Society of Cardiology** at https://www.escardio.org/Councils/Council-on-Hypertension-(CHT)/News/position-statement-of-the-esc-council-on-hypertension-on-ace-inhibitors-and-ang.

Can NSAIDs be used in COVID-19-infected patients?	• Anecdotal reports regarding worse COVID-19 outcomes in patients taking NSAIDs have spread in the media and on social media, including via a tweet from a French health official.[14,23] In 2019, a French report suggested that NSAIDs could worsen infections, mainly Strep, perhaps by masking symptoms.[24,25] However, there is currently no reliable clinical data supporting worse outcomes in patients taking NSAIDs or aspirin.[14,20] Preclinical data is mixed on the potential effects of NSAIDs on COVID-19 (increased expression of ACE2, which the virus uses to enter cells, vs potential antiviral activity of NSAIDs).[14] • Patients taking low-dose aspirin should not stop taking it because of COVID-19 concerns.[14] • Neither the FDA nor Health Canada is advising changes to NSAID use due to COVID-19.[20,21]
Are any supplements effective for prevention or treatment of COVID-19?	• There is no scientific evidence that any alternative remedies can prevent or treat COVID-19, and some products may not be safe.[5] There is false information circulating that vitamin D is recommended by health officials. See our *Natural Medicines* database (www.naturaldatabase.com) for information on efficacy and safety of specific alternative medicines. • A study using honey as an adjunct to standard care for treatment of COVID-19 is planned, and intravenous vitamin C is being studied for treatment of severe COVID-19 disease (e.g., pneumonia, sepsis). Several studies are looking at multivitamin/mineral combos as adjuncts for treatment or prevention. See www.clinicaltrials.gov for more information.

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Users of this resource are cautioned to use their own professional judgment and consult any other necessary or appropriate sources prior to making clinical judgments based on the content of this document. Our editors have researched the information with input from experts, government agencies, and national organizations. Information and internet links in this article were current as of the date of publication.

Levels of Evidence

In accordance with our goal of providing Evidence-Based information, we are citing the **LEVEL OF EVIDENCE** for the clinical recommendations we publish.

Level	Definition	Study Quality
A	Good-quality patient-oriented evidence.*	1. High-quality RCT 2. SR/Meta-analysis of RCTs with consistent findings 3. All-or-none study
B	Inconsistent or limited-quality patient-oriented evidence.*	1. Lower-quality RCT 2. SR/Meta-analysis with low-quality clinical trials or of studies with inconsistent findings 3. Cohort study 4. Case control study
C	Consensus; usual practice; expert opinion; disease-oriented evidence (e.g., physiologic or surrogate endpoints); case series for studies of diagnosis, treatment, prevention, or screening.	

***Outcomes that matter to patients** (e.g., morbidity, mortality, symptom improvement, quality of life).
RCT = randomized controlled trial; **SR** = systematic review
[Adapted from Ebell MH, Siwek J, Weiss BD, et al. Strength of Recommendation Taxonomy (SORT): a patient-centered approach to grading evidence in the medical literature. *Am Fam Physician* 2004;69:548-56. http://www.aafp.org/afp/2004/0201/p548.pdf.]

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