



## COVID-19 Drug Therapy

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### What's been updated:

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- Remdesivir
  - Recommendation for use from NIH COVID-19 treatment guidelines(133)
  - New randomized, double-blind, placebo-controlled, multicenter trial (150)
  - Safety concerns addition
- Chloroquine
  - Recommendation against the use of high-dose chloroquine from NIH COVID-19 treatment guidelines (133)

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### Highlights:

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- There are no specific therapies approved by the U.S. Food and Drug Administration (FDA) for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus that causes coronavirus disease 2019 COVID-19. Several agents are being used under clinical trial and compassionate use protocols based on *in vitro* activity (against SARS-CoV-2 or related viruses) and on limited clinical experience. Efficacy has not been established for any drug therapy.
- **Antimicrobials with potential activity against SARS-CoV-2:**
  - Remdesivir – Investigational antiviral available under an FDA Emergency Use Authorization (EUA); several large clinical trials are underway with preliminary data suggesting clinical benefit.
  - Chloroquine – *In vitro* and limited clinical data suggest potential benefit; FDA EUA issued to facilitate availability.
  - Hydroxychloroquine – *In vitro* and limited clinical data suggest potential benefit; FDA EUA issued to facilitate availability.
  - Lopinavir; Ritonavir – Role in the treatment of COVID-19 is unclear. Preclinical data suggested potential benefit; however, more recent data has failed to confirm.
  - Favipiravir – Investigational use is being studied.

- **Adjunctive / supportive care:**

- Anticoagulation – Venous thromboembolism prophylaxis with low molecular weight heparin (LMWH) recommended for all hospitalized patients.
- Azithromycin – Used in some protocols based on theoretical mechanism and limited preliminary data as adjunct therapy.
- Bronchodilators – No routine role for inhaled bronchodilators in the management of COVID-19; metered-dose inhalers (MDI) preferred over nebulized therapy due to the risk of viral transmission.
- Corticosteroids – Not recommended for viral pneumonia; use may be considered for patients with refractory shock or acute respiratory distress syndrome.
- COVID-19 convalescent plasma – Investigational use is being studied.
- Fibrinolytics – Severe COVID-19 infection is associated with coagulopathy; fibrin deposition in the pulmonary microvasculature is a causative factor in the development of ARDS.
- Immunomodulating agents [Interleukin Receptor Antagonists, Janus Kinase (JAK) inhibitors] – Used in some protocols based on theoretical mechanisms and limited preliminary data as adjunct therapy.
- Inhaled pulmonary vasodilators – No evidence for routine in acute respiratory failure; use may be considered in specific patients with acute respiratory distress syndrome (ARDS) as a temporizing measure.
- NSAIDs – The FDA continues to investigate the use of NSAIDs; concern for potential worsening of COVID-19 symptoms has been suggested, but confirmatory clinical data is lacking.

According to the World Health Organization (WHO), the Centers for Disease Control and Prevention (CDC), the FDA, and the National Institutes of Health (NIH), there are currently no medications or vaccines proven to be effective for the treatment or prevention of SARS-CoV-2. (1) (2) (3) (133)

Generally, pharmacologic treatment is not recommended for young, healthy patients with mild symptoms and no underlying comorbid conditions.(12) (13)

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## **Antimicrobials with potential activity against SARS-CoV-2:**

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### **Remdesivir (GS-5734):**

- Classification: Investigational Nucleoside Analogue
- Rationale for Use: Remdesivir is a broad-spectrum antiviral with in vitro activity against coronaviruses.(10) (14) (38) (39) (41) (42) (43) (44)
- Mechanism of Action: Remdesivir is a monophosphoramidate prodrug of remdesivir-triphosphate (RDV-TP), an adenosine analog that acts as an inhibitor of RNA-dependent RNA polymerases (RdRps). Remdesivir-TP competes with adenosine-triphosphate for incorporation into nascent viral RNA chains. Once incorporated into the viral RNA at position i, RDV-TP

terminates RNA synthesis at position i+3. Because RDV-TP does not cause immediate chain termination (i.e., 3 additional nucleotides are incorporated after RDV-TP), the drug appears to evade proofreading by viral exoribonuclease (an enzyme thought to excise nucleotide analog inhibitors).(10) (14) (38) (39) (41) (42) (43) (44) (45)

- FDA Emergency Use Authorization (EUA): (146)
  - Remdesivir is not an FDA-approved medication.
  - The EUA allows for the emergency use of remdesivir to treat suspected or laboratory confirmed COVID-19 in adults and children hospitalized with severe disease.
  - The EUA defines severe COVID-19 disease as patients with an oxygen saturation (SpO<sub>2</sub>) of 94% or less on room air, or requiring supplemental oxygen, or requiring mechanical ventilation or extracorporeal membrane oxygenation (ECMO).
- Evidence / Experience:
  - The NIH COVID-19 treatment guidelines recommend the use of remdesivir in hospitalized patients with severe COVID-19; however, its use in patients with mild or moderate COVID-19 is not recommended outside of clinical trials.(133)
  - Preliminary data from a Phase III trial [i.e., Adaptive COVID-19 Treatment Trial (ACTT)] suggest remdesivir may provide clinical benefit in the treatment of hospitalized patients with advanced COVID-19 and lung involvement.(145) (146)
    - The median time to recovery was 11 days in the remdesivir-treated group compared to 15 days in placebo group (hazard ratio: 1.31; 95% CI: 1.12 to 1.54, p < 0.001).
    - Mortality was 8% for the remdesivir group vs. 11.6% for the placebo group (p = 0.059)
  - A randomized, double-blind, placebo-controlled, multicenter trial evaluating efficacy and safety of remdesivir in SARS-CoV-2 infected hospitalized adults (concurrent treatment with corticosteroids, interferons, and lopinavir; ritonavir was permitted).(150)
    - No difference between remdesivir (n = 158) and placebo (n = 79) in the time to clinical improvement (median, 21 vs. 23 days; hazard ratio, 1.23; 95% CI: 0.87 to 1.75). 28-day mortality was similar between remdesivir (14%) and placebo (13%) (95% CI: -8.1 to 10.3).
    - Adverse events reported in 66% of remdesivir patients and 64% of placebo patients. Remdesivir was stopped early in 12% of patients due to adverse events.
  - Preliminary data from open-label compassionate use in patients with severe disease was analyzed.(124)
    - Clinical improvement, as defined by improvement in oxygen support, was reported in 36 of 53 patients (68%).
    - Clinical improvement was less frequent in those receiving invasive ventilation and in patients 70 years or older.
  - Several clinical trials evaluating the efficacy of remdesivir in patients infected with SARS-CoV-2 are currently being conducted.(132)
- Safety Concerns: (133) (146)
  - Caution in patients with renal impairment due to formulation with sulfobutyl ether beta-cyclodextrin sodium (SBECD)
  - Infusion-related reactions
  - Risk for elevated hepatic enzymes

## Chloroquine:

- Classification: Antimalarial
- Rationale for Use: Chloroquine has *in vitro* activity against SARS-CoV-2 and may have immunomodulating properties.(13) (14) (15) (17)
- Mechanism of Action: Mechanisms may include inhibition of viral enzymes or processes such as viral DNA and RNA polymerase, viral protein glycosylation, virus assembly, new virus particle transport, and virus release. Other mechanisms may also involve ACE2 cellular receptor inhibition, acidification at the surface of the cell membrane inhibiting fusion of the virus, and immunomodulation of cytokine release.(14) (15) (29) (30) (31) (32) (33)
- FDA Emergency Use Authorization (EUA): (66) (67)
  - Chloroquine is not FDA-approved for the treatment of COVID-19.
  - EUA is to facilitate the availability of chloroquine during the COVID-19 pandemic to treat patients for whom a clinical trial is not available, or participation is not feasible.
  - The EUA states treatment is for adult and adolescent patients weighing 50 kg or more who are hospitalized with COVID-19.
  - Authorized chloroquine is limited to product supplied from the Strategic National Stockpile (SNS) and will be distributed to authorized health care systems and providers.
- Evidence / Experience:
  - Due to a lack of clinical data, the NIH COVID-19 treatment guidelines do not give recommendations for or against the use of chloroquine; however, if used, guidelines advise monitoring for adverse events, including QT interval prolongation. The NIH recommends against the use of high-dose, twice-daily chloroquine due to a higher risk of toxicities.(133)
  - Pre-clinical data *in vitro* suggest chloroquine has activity against SARS-CoV-2.(13) (14) (15)
  - There have been reports of potential benefit in inhibiting the exacerbation of pneumonia patients with SARS-CoV-2 infection; however, specific data are not available.(13)
  - Some protocols include recommendations for use.(12) (21) (22)
  - Additional data regarding clinical efficacy for COVID-19 are being evaluated.(16) (31)
- Safety Concerns: (46) (49)
  - Use in COVID-19 patients outside of clinical trials or in a nonhospital setting is not recommended due to the potential for serious adverse events and drug interactions.(141)
  - Risk of cardiac arrhythmias (e.g., QT prolongation)
    - Seriously ill patients with comorbidities have an increased risk of serious arrhythmias.(125)
    - Avoid other QT prolonging agents whenever feasible.(125)
    - In a parallel, double-masked, randomized clinical trial (n = 81), two doses of chloroquine were analyzed (600 mg PO twice daily for 10 days vs. 450 mg PO twice daily on day 1 then 450 mg PO once daily for 4 days).(126)
      - The high-dose group had a higher incidence of QT interval greater than 500 milliseconds (18.9%) compared with the low-dose group (11.1%); therefore, the study was unmasked and all patients were reverted to the low-dose group.
  - Risk of retinal damage, especially with long term use

- Caution in patients with G6PD deficiency
- Caution in diabetics
- Significant drug interactions

## Hydroxychloroquine:

- Classification: Antimalarial
- Rationale for Use: Hydroxychloroquine has *in vitro* activity against SARS-CoV-2 and may have immunomodulating properties.(13) (14) (15) (17)
- Mechanism of Action: Mechanisms may include inhibition of viral enzymes or processes such as viral DNA and RNA polymerase, viral protein glycosylation, virus assembly, new virus particle transport, and virus release. Other mechanisms may also involve ACE2 cellular receptor inhibition, acidification at the surface of the cell membrane inhibiting fusion of the virus, and immunomodulation of cytokine release.(14) (15) (29) (30) (31) (32) (33)
- FDA Emergency Use Authorization (EUA): (66) (68)
  - Hydroxychloroquine is not FDA-approved for the treatment of COVID-19.
  - EUA is to facilitate the availability of hydroxychloroquine during the COVID-19 pandemic to treat patients for whom a clinical trial is not available, or participation is not feasible.
  - The EUA states treatment is for adult and adolescent patients weighing 50 kg or more who are hospitalized with COVID-19.
  - Authorized hydroxychloroquine is limited to product supplied from the Strategic National Stockpile (SNS) and will be distributed to authorized health care systems and providers.
- Evidence / Experience:
  - Due to a lack of clinical data, the NIH COVID-19 treatment guidelines do not give recommendations for or against the use of hydroxychloroquine; however, if used, guidelines advise monitoring for adverse events including QT interval prolongation (133)
  - Pre-clinical *in vitro* data suggest hydroxychloroquine has activity against SARS-CoV-2.(12) (15) (17) (18) (21)
  - One *in vitro* study suggests that hydroxychloroquine may be more potent than chloroquine.(15)
    - Hydroxychloroquine exhibited a higher *in vitro* antiviral effect compared to chloroquine when drug was added prior to the viral challenge.
      - The EC50 values for chloroquine were greater than 100 microM at 24 hours and 18.01 microM at 48 hours.
      - The EC50 values for hydroxychloroquine were 6.25 microM at 24 hours and 5.85 microM at 48 hours.
  - An open-label, non-randomized clinical trial compared hydroxychloroquine treatment (n = 26) to an untreated negative control group.(27)
    - Preliminary data showed the proportion of patients that had negative PCR results significantly differed between treated patients and untreated controls.
    - On day 6, 70% of hydroxychloroquine-treated patients were virologically cured compared to 12.5% in the untreated control group.

- A parallel-group, randomized trial (n = 62) of hospitalized patients with non-severe COVID-19 compared 5 days of hydroxychloroquine to standard treatment.(69)
  - Fever recovery time was shortened in the hydroxychloroquine group (2.2 days) compared to standard therapy (3.2 days).
  - Cough recovery time was shortened in the hydroxychloroquine group (2 days) compared to standard therapy (3.1 days).
- A prospective review assessed virologic and clinical outcomes of 11 hospitalized patients who received hydroxychloroquine and azithromycin.(88)
  - Within 5 days, 1 patient died, 2 were transferred to the ICU, and 1 patient had therapy discontinued due to QT prolongation.
  - Nasopharyngeal swabs were still positive for SARS-CoV-2 in 8 of 10 patients 5 to 6 days after treatment initiation.
- In a preliminary report of a multicenter, parallel, open-label, randomized trial in 150 adult hospitalized patients, hydroxychloroquine (n = 75) was added to standard therapy.(127)
  - The overall 28-day negative viral conversion rate was not different between the two groups (85.4% hydroxychloroquine vs 81.3% control, p = 0.341).
  - Negative conversion rates on days 4, 7, 10, and 21 were also similar between the groups.
  - There was no difference in the 28-day symptom alleviation rate; however, a significant efficacy on symptom alleviation was observed when the confounding effects of antiviral agents were removed in the post-hoc analysis.
  - Additionally, there was a greater reduction in C-reactive protein (CRP) (6.986 mg/L hydroxychloroquine vs 2.723 mg/L control, p = 0.045) and a nonsignificant increase in recovery of lymphopenia in the hydroxychloroquine group.
  - Adverse events were reported in 8.8% of the control group and 30% of the hydroxychloroquine group.
- Preliminary data from a retrospective analysis (n = 368) assessed the use of either hydroxychloroquine (n = 97) or hydroxychloroquine plus azithromycin (n = 133) in addition to standard of care compared to standard of care alone (n = 158).(134)
  - The cohort consisted of only men in the Veterans Health Administration medical centers with a median age older than 65 years, the majority of whom were black.
  - The primary outcomes were death and the need for mechanical ventilation.
    - Rates of death in the hydroxychloroquine group, the hydroxychloroquine plus azithromycin group, and the standard treatment group were 27.8%, 22.1%, and 11.4%, respectively. Compared to standard therapy, the risk of death from any cause was higher in the hydroxychloroquine group (adjusted HR 2.61; 95% CI, 1.10 to 6.17; p = 0.03), but not in the hydroxychloroquine plus azithromycin group (adjusted HR 1.14; 95% CI, 0.56 to 2.32; p = 0.72).
    - Rates of ventilation in the hydroxychloroquine group, the hydroxychloroquine plus azithromycin group, and the standard treatment group were 13.3%, 6.9%, and 14.1%, respectively. Compared to standard therapy, the risk of ventilation was similar in both the hydroxychloroquine group (adjusted HR 1.43; 95% CI, 0.53 to 3.79; p =

- 0.48) and the hydroxychloroquine plus azithromycin group (adjusted HR 0.43; 95% CI, 0.16 to 1.12; p = 0.09).
- An observational trial (n = 1,376) examined the association between hydroxychloroquine use and intubation or death at a large medical center.(149)
    - Hydroxychloroquine was not associated with a significantly higher or lower risk of intubation or death (HR 1.04; 95% CI, 0.82 to 1.32); similar results were noted when adjusted for propensity score.
    - Hydroxychloroquine-treated patients were more severely ill at baseline.
    - Due to wide confidence intervals and the observational nature of the trial, the authors stated that the results should not be utilized to rule out either benefit or harm of hydroxychloroquine and suggested further randomized clinical trials to test efficacy.
  - An observational study of 1,438 hospitalized patients assessed mortality in patients receiving hydroxychloroquine (n = 271), azithromycin (n = 211), or both (n = 735) compared to patients who received neither of these agents (n = 221).(155)
    - There was no difference in mortality in patients treated with hydroxychloroquine (HR 1.08; 95% CI, 0.63 to 1.85), azithromycin (HR 0.56; 95% CI, 0.26 to 1.21), or both (HR 1.35; 95% CI, 0.76 to 2.4) compared with no use of these agents.
    - In logistic models, cardiac arrest was significantly more likely in patients receiving hydroxychloroquine plus azithromycin (OR 2.13; 95% CI, 1.12 to 4.05) compared to patients receiving neither drug; however, this was not the case in patients receiving either drug alone.
    - In adjusted logistic regression models, there were no significant differences in the relative likelihood of abnormal electrocardiogram findings.
    - Patient receiving hydroxychloroquine with or without azithromycin were overall sicker on presentation.
  - Some protocols have recommendations for use.(12) (21)
  - Additional data regarding clinical efficacy for COVID-19 are being evaluated.(16) (31)
  - Safety Concerns: (47) (49)
    - Use in COVID-19 patients outside of clinical trials or in a nonhospital setting is not recommended due to the potential for serious adverse events and drug interactions.(141)
    - Risk of cardiac arrhythmias (e.g., QT prolongation)
      - Seriously ill patients with comorbidities have an increased risk of serious arrhythmias.(125)
      - Avoid other QT prolonging agents whenever feasible.(125)
    - Risk of retinal damage, especially with long term use
    - Caution in patients with G6PD deficiency
    - Caution in diabetics
    - Significant drug interactions

## Lopinavir; Ritonavir:

- Classification: HIV Protease Inhibitor
- Rationale for Use: *In vitro* and animal model studies show potential activity for other coronaviruses (SARS-CoV and MERS-CoV).(4) (52) (53) (54)
- Mechanism of Action: Lopinavir and ritonavir may bind to M<sup>pro</sup>, a key enzyme for coronavirus replication. This may suppress coronavirus activity.(55)
- Evidence / Experience:
  - Due to unfavorable pharmacodynamics and negative clinical trial data, the NIH COVID-19 treatment guidelines recommend against the use of lopinavir; ritonavir or other HIV protease inhibitors outside of clinical trials.(133) Similarly, ESICM and SCCM Surviving Sepsis Campaign recommendations suggest against the routine use of lopinavir; ritonavir in critically ill adults with COVID-19.(26)
  - Pre-clinical data show activity for other coronaviruses.(4) (52) (53) (54)
  - A randomized, controlled, open-label trial involving hospitalized patients with confirmed SARS-CoV-2 infection (n = 199), analyzed treatment with lopinavir; ritonavir.(23)
    - Not associated with a difference from standard of care in the time to clinical improvement (median, 16 days versus 16 days; hazard ratio 1.31; 95% CI, 0.95 to 1.80; p = 0.09); percentages of patients with detectable viral RNA were similar; 28 day mortality was also similar (19.2% vs. 25%, respectively).
  - A retrospective cohort study of hospitalized patients reviewing clinical course and risk factors for mortality included 29 patients who received lopinavir; ritonavir.(24)
    - No difference was noted in the duration of viral shedding after treatment with lopinavir; ritonavir.
- Safety Concerns: (45) (49)
  - Risk of cardiac arrhythmias (e.g., QT prolongation)
    - Seriously ill patients with comorbidities have an increased risk of serious arrhythmias.(125)
    - Avoid other QT prolonging agents whenever feasible.(125)
  - Caution in patients with hepatic disease or hepatitis
  - Significant drug interactions

## Favipiravir:

- Classification: Investigational RNA-Dependent RNA Polymerase Inhibitor
- Rationale for Use: Favipiravir is a broad-spectrum antiviral with *in vitro* activity against RNA viruses.(14) (18) (75)
- Mechanism of Action: Favipiravir is an RNA-dependent RNA polymerase (RdRp) inhibitor that inhibits viral RNA synthesis.(14) (18) (75)
- Evidence / Experience:
  - In a non-randomized, controlled, open-label trial, the efficacy of favipiravir (n = 35) in treating patients with laboratory confirmed COVID-19 was compared against lopinavir; ritonavir (n = 45); both treatments were given in combination with inhaled interferon alpha.(142)



- Time to viral clearance was shorter for favipiravir (median, 4 days; range, 2.5 to 9 days) than for lopinavir; ritonavir (median, 11 days; range 8 to 13 days;  $p < 0.001$ ).
    - Chest imaging improvement rate at treatment day 14 was 91% for favipiravir vs. 62% for lopinavir; ritonavir ( $p = 0.004$ )
  - A prospective, randomized, controlled, open-label multicenter trial compared favipiravir ( $n = 116$ ) against umifenovir [Arbidol] ( $n = 120$ ) in treating patients with COVID-19; both treatments were given in combination with conventional therapy.(143)
    - No difference in clinical recovery rate at treatment Day 7 (61% for favipiravir vs. 52% for umifenovir;  $p = 0.1396$ ; 95% CI: -0.0305 to 0.2213).
  - Additional data regarding clinical efficacy for COVID-19 are being evaluated.(132)
- **Safety Concerns:**
  - Contraindicated in pregnancy due to early embryonic death and teratogenicity observed in animal studies.

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## Adjunctive/Supportive therapy:

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### Anticoagulation:

- Venous thromboembolism (VTE) prophylaxis with LMWH is recommended for all hospitalized patients with COVID-19 infection. Withhold VTE prophylaxis for active bleeding, platelet count less than  $25 \times 10^9/L$ , or fibrinogen less than 0.5 g/L.(80) (81) (91) (95) (102)
  - Use fondaparinux in patients with a history of heparin-induced thrombocytopenia.(95)
  - Use unfractionated heparin or reduced-dose LMWH in patients with creatinine clearance less than 30 mL/minute.(103)
  - Use mechanical thromboprophylaxis in patients where anticoagulants are contraindicated or unavailable.(95)
  - Data are insufficient to recommend for or against the use of increasing anticoagulant doses for VTE prophylaxis in hospitalized COVID-19 patients outside of a clinical trial.(133)
  - Hospitalized patients with COVID-19 should not routinely be discharged on VTE prophylaxis. Weighing the individual patient's VTE risk factors and bleeding risk in addition to feasibility, consider extended thromboprophylaxis with a regulatory-approved regimen (e.g., betrixaban, rivaroxaban) after discharge.(95) (133)
    - Aspirin could be considered for COVID-19 VTE prophylaxis if criteria for post-discharge thromboprophylaxis are met.(95)
  - Elevated D-dimer has been noted in COVID-19 patients requiring hospitalization and has been associated with increased mortality. Limited data suggest a decrease in mortality in patients with severe COVID-19 infection or markedly elevated D-dimer concentrations (more than 6 times the upper limit of normal) who were given LMWH or heparin VTE prophylaxis.(80) (81) (91) (102)
- Therapeutic-intensity anticoagulation is not recommended in the management of COVID-19 in the absence of confirmed or suspected VTE.(95) (128)

- In patients already anticoagulated for VTE or atrial fibrillation, continue therapeutic anticoagulation. Consider withholding therapeutic anticoagulation in these patients for platelet count less than  $50 \times 10^9/L$  or fibrinogen less than 1 g/L.(102)
- Treat all COVID-19 patients with confirmed or suspected VTE with therapeutic anticoagulation for at least 3 months. Therapeutic anticoagulation may be discontinued at 3 months if the patient has recovered from COVID-19 and has no ongoing risk factors for thrombosis or other indications for anticoagulation.(128)
- Increasing the intensity of anticoagulation (i.e., from standard-intensity prophylaxis to intermediate-intensity prophylaxis or from intermediate-intensity prophylaxis to therapeutic-intensity prophylaxis) may be reasonable in COVID-19 patients who experience recurrent clotting of access devices or extracorporeal circuits.(95)

### Azithromycin:

- Classification: Macrolide Antibacterial
- Rationale for Use: Azithromycin may prevent bacterial superinfection, and macrolides may have immunomodulatory properties to work as adjunct therapy.(27) (34) (35) (36) (37)
- Mechanism of Action: Macrolides may have immunomodulatory properties in pulmonary inflammatory disorders. They may downregulate inflammatory responses and reduce the excessive cytokine production associated with respiratory viral infections; however, their direct effects on viral clearance are uncertain. Immunomodulatory mechanisms may include reducing chemotaxis of neutrophils (PMNs) to the lungs by inhibiting cytokines (i.e., IL-8), inhibition of mucus hypersecretion, decreased production of reactive oxygen species, accelerating neutrophil apoptosis, and blocking the activation of nuclear transcription factors.(34) (35) (36) (37)
- Evidence / Experience:
  - Due to the potential for toxicities, the NIH COVID-19 treatment guidelines recommend against the use of azithromycin in combination with hydroxychloroquine outside of clinical trials.(133)
  - In an open-label, non-randomized clinical trial of hydroxychloroquine (n = 26), azithromycin was administered in combination with hydroxychloroquine to prevent bacterial superinfection in 6 patients.(27)
    - Preliminary data suggest the potential for benefit as adjunct therapy.
    - On day 6, all patients treated with the combination (hydroxychloroquine and azithromycin) were virologically cured compared to 57.1% of patients treated with hydroxychloroquine alone (n= 20).
  - In a retrospective analysis of a multicenter cohort study (n = 349) in patients with MERS-CoV, 136 patients received macrolide therapy in combination with antiviral treatment.(28)
    - Macrolide therapy was not associated with a reduction in 90-day mortality compared to the control group (adjusted OR: 0.84; 95% CI: 0.47 to 1.51; p = 0.56).
    - Sensitivity analysis excluding patients who received macrolides after day 3 showed similar results (adjusted OR: 0.7; 95% CI: 0.39 to 1.28; p = 0.25).
  - A prospective review assessed virologic and clinical outcomes of 11 hospitalized patients who received hydroxychloroquine and azithromycin.(88)

- Within 5 days, 1 patient died, 2 were transferred to the ICU, and 1 patient had therapy discontinued due to QT prolongation.
  - Nasopharyngeal swabs were still positive for SARS-CoV-2 in 8 of 10 patients 5 to 6 days after treatment initiation.
- Safety Concerns: (48) (49)
  - Risk of cardiac arrhythmias (e.g., QT prolongation)
    - Seriously ill patients with comorbidities have an increased risk of serious arrhythmias.(125)
    - Avoid other QT prolonging agents whenever feasible.(125)
  - Significant drug interactions

## Bronchodilators

- Most patients with COVID-19 do not need inhaled bronchodilator therapy. There is no role for inhaled bronchodilators in the management of COVID-19 unless the patient has underlying asthma or chronic obstructive pulmonary disease (COPD).(57) (61)
  - MDIs are preferred due to the potential for generation of aerosols that may increase the risk of viral transmission with nebulized therapy.(57) (61)
  - Due to concerns about supply chain interruption, some institutions are developing an MDI canister reassignment protocol to address potential shortages. An MDI canister reassignment protocol should emphasize hand hygiene and dual canister disinfection and avoid inadvertent sources of transmission.(57) (79)

## Corticosteroids:

- Corticosteroid therapy is not recommended for viral pneumonia; however, use may be considered for patients with refractory shock or ARDS.(1) (7) (26) (62) (63) (64) (133)

## COVID-19 Convalescent Plasma: (22)

- Classification: Plasma collected from persons who have recovered from COVID-19 that may contain antibodies to SARS-CoV-2
- Rationale for Use: Clinical trials are being conducted to evaluate the use of COVID-19 convalescent plasma to treat patients with severe or immediately life-threatening COVID-19 infections. COVID-19 convalescent plasma is not intended for prevention of the infection.
  - To participate in these trials, investigators should submit requests to the FDA for investigational use under the traditional IND regulatory pathway.
  - In addition to clinical trials, licensed physicians may obtain COVID-19 convalescent plasma for an individual patient through the process of single patient eINDs.
- Evidence / Experience:
  - Due to a lack of clinical data, the NIH COVID-19 treatment guidelines do not give recommendations for or against the use of convalescent plasma.(133)
  - In a case series of 5 critically ill patients with confirmed COVID-19 and ARDS, patients received convalescent plasma.(65)

- Treatment: 2 consecutive transfusions of 200 mL to 250 mL of convalescent plasma (total dose: 400 mL) with a SARS-CoV-2-specific antibody (IgG) titer greater than 1:1,000 on the same day it was obtained from the donor.
- Patient criteria included:
  - Severe pneumonia with rapid progression and continuously high viral load despite antiviral treatment
  - $PAO_2/FIO_2$  less than 300
  - Mechanical ventilation
- After plasma infusion, body temperature normalized within 3 days in 4 of 5 patients, Sequential Organ Failure Assess (SOFA) score decreased and  $PAO_2/FIO_2$  increased within 12 days.
- Viral loads decreased and became negative within 12 days after the transfusion with the SARS-CoV-2-specific ELISA and neutralizing antibody titers increased after the transfusion.
- ARDS resolved in 4 patients by day 12 after the transfusion and 3 patients were weaned from mechanical ventilation within 2 weeks of treatment.
- In a case series of 6 critically ill patients with confirmed COVID-19 with abnormalities on chest CT (with the exception of 1 patient) who were deteriorating while receiving standard treatment, patients received convalescent plasma.(135)
  - Patients received at least 1 cycle (range, 1 to 3 cycles) of convalescent plasma (200 mL per cycle) over 30 minutes.
  - All patients had improved symptoms and chest CT and were discharged from the hospital.

### Fibrinolytics:

- Rationale for Use: Severe COVID-19 infection is associated with coagulopathy, specifically a prothrombotic disseminated intravascular coagulation (DIC) with high rates of VTE, vascular occlusive events, and central line thrombosis and pulmonary congestion with microvascular thrombosis and occlusion observed on pathology. Fibrin deposition in the pulmonary microvasculature is a causative factor in the development of ARDS.(102) (136)
- Mechanism of Action: Fibrinolytic agents act by converting plasminogen to plasmin on the surface of existing thrombi, thereby initiating local fibrinolysis.(137)
- Evidence / Experience:
  - Alteplase:
    - In a case series of 3 critically ill patients with ARDS and respiratory failure, patients received alteplase followed by intravenous heparin.(136)
      - $PaO_2/FiO_2$  (P/F) ratio improved by 11% to 100% in all 3 patients; however, the improvements were transient.
    - Additional data regarding clinical efficacy for COVID-19 are being evaluated.(138)
  - Other fibrinolytics for which COVID-19 efficacy data are being evaluated include defibrotide.(139) (140)
- Safety Concerns: (136) (137)
  - Bleeding

### Inhaled Pulmonary Vasodilators:

- There is no evidence for routine use of inhaled pulmonary vasodilators (e.g., nitric oxide, prostacyclins) in acute respiratory failure in COVID-19 patients. Avoid aerosolized vasodilators.(26) (60) (61) (133)
- Use may be considered in specific patients with ARDS as a temporizing measure when patients develop refractory hypoxemia despite optimization of ventilation and other rescue strategies.(26) (60)
- If inhaled pulmonary vasodilator therapy is used, a short trial with preestablished criteria for ongoing use or discontinuation is recommended.(26) (61) (133)
- Additional data regarding clinical efficacy for COVID-19 are being evaluated.(58) (59)

### Interleukin-1 (IL-1) Antagonists:

- Rationale for Use: Cytokine release syndrome may be a component of severe disease in COVID-19 patients.(24) (89) (90) (107)
- Mechanism of Action: Interleukin-1 antagonists, such as anakinra and canakinumab, prevent the binding of IL-1 (a pro-inflammatory cytokine that mediates various inflammatory and immunological responses, including activation of IL-6) to interleukin-1 receptors. Anakinra acts similarly to the native interleukin-1 receptor antagonist by competitively inhibiting the binding of both IL-1 alpha and IL-1 beta to the IL-1 type 1 receptor. Canakinumab is a human monoclonal antibody that specifically targets and neutralizes IL-1 beta; thereby preventing its interaction with IL-1 receptors.(89) (106) (147)
- Evidence / Experience:
  - Due to a lack of clinical data, the NIH COVID-19 treatment guidelines do not give recommendations for or against the use of IL-1 antagonists.(133)
  - Anakinra:
    - Retrospective cohort study comparing anakinra plus standard therapy to standard therapy alone in patients with COVID-19, moderate-to-severe ARDS, and hyperinflammation.(148)
      - 21-day survival was 90% in the anakinra group and 56% in standard treatment group (p = 0.009). Respiratory function improved in 72% (n = 21/29) of anakinra patients and 50% (n = 8/16) of patients in the standard treatment group.
    - Additional data regarding clinical efficacy for COVID-19 are being evaluated.(132)
  - Other IL-1 antagonists for which COVID-19 efficacy data are being evaluated include canakinumab.(132)
- Safety Concerns: (106) (147)
  - Caution in patients with thrombocytopenia and neutropenia
  - Infusion-related reactions (anakinra)

## Interleukin-6 (IL-6) Receptor Antagonists:

- Rationale for Use: Cytokine release syndrome may be a component of severe disease in COVID-19 patients.(24) (25) (89) (90)
- Mechanism of Action: IL-6 receptor-inhibiting monoclonal antibodies block IL-6-mediated signaling by competitively binding to both soluble and membrane-bound IL-6 receptors (sIL-6R and mIL-6R). IL-6 is a proinflammatory cytokine that is involved in diverse physiological processes such as T-cell activation, immunoglobulin secretion induction, hepatic acute-phase protein synthesis initiation, and hematopoietic precursor cell proliferation and differentiation stimulation. IL-6 is produced by various cell types, including T- and B-cells, lymphocytes, monocytes, and fibroblasts.(52) (72) (78) (97) (98)
- Evidence / Experience:
  - Due to a lack of clinical data, the NIH COVID-19 treatment guidelines do not recommend for or against the use of IL-6 receptor inhibitors.(133)
  - Siltuximab:
    - A retrospective study of 21 patients with COVID-19 induced pneumonia/ARDS analyzed patients who received treatment with siltuximab.(101)
      - CRP concentrations reduced to within normal range by day 5 and remained stable in all 16 patients with available data; 33% (n = 7/21) condition improved with reduced need for ventilation; 43% (n = 9/21) condition stabilized; 24% (n = 5/21) condition worsened and required intubation.
      - A cohort study of patients treated with standard therapy is ongoing
    - Additional data regarding clinical efficacy for COVID-19 are being evaluated.(132)
  - Tocilizumab:
    - A retrospective review analyzed 21 patients in which tocilizumab was added to standard COVID-19 therapy.(25)
      - Preliminary data suggest tocilizumab may have clinical benefit as adjunctive therapy.
      - Clinical symptoms, CT opacity changes, lymphocyte percentage, and CRP concentrations all improved in these patients; however, no comparators were reported.
    - Some protocols include recommendations for use.(21)
    - Additional data regarding clinical efficacy for COVID-19 are being evaluated.(132)
  - Other IL-6 receptor inhibitors for which COVID-19 efficacy data are being evaluated include clazakizumab and sarilumab.(132)
- Safety Concerns: (52) (78) (97)
  - Risk of GI perforation
  - Risk of hepatotoxicity
  - Caution in patients with thrombocytopenia and neutropenia
  - Infusion-related reactions

## Janus Kinase (JAK) Inhibitors:

- Rationale for Use: Cytokine release syndrome may be a component of severe disease in COVID-19 patients.(24) (89) (90) (94)
- Mechanism of Action: Janus kinases are intracellular enzymes that transmit signals arising from the interaction of cytokines and growth factors with receptors located on the cellular membrane. These enzymes phosphorylate and activate signal transducers and activators of transcription proteins (STATs), which modulate intracellular activity including gene expression. The JAK-mediated signaling pathway is pivotal in influencing immune system activation, as cytokine receptors are expressed on most immune cells. JAK inhibitors modulate the signaling pathway by preventing the phosphorylation and activation of STATs.(92) (130) (131)
- Evidence / Experience:
  - Due to the broad immunosuppressive effect, the NIH COVID-19 treatment guidelines recommend against the use of JAK inhibitors outside of clinical trials.(133)
  - Baricitinib:
    - A non-randomized, open-label trial compared safety and efficacy of baricitinib plus lopinavir; ritonavir in 12 patients with moderate COVID-19 against a control group treated with hydroxychloroquine plus lopinavir; ritonavir.(144)
      - For baricitinib-treated patients, all clinical characteristics and respiratory function parameters [i.e., fever, SpO<sub>2</sub>, PaO<sub>2</sub>/FiO<sub>2</sub>, CRP, Modified Early Warning Score (MEWS)] improved at weeks 1 and 2 compared to baseline. For control group, no significant changes were noted at week 2 compared to baseline.
      - Preliminary results found no serious adverse events reported in the baricitinib-treated patients; however, 1 patient stopped treatment after 10 days due to increased liver function test.
    - Additional data regarding clinical efficacy for COVID-19 are being evaluated.(132)
  - Other JAK inhibitors for which COVID-19 efficacy data are being evaluated include: ruxolitinib and tofacitinib.(132)
- Safety Concerns: (92) (130) (131)
  - Thrombosis, including deep vein thrombosis (DVT) and pulmonary embolism (PE)
  - Risk of GI perforation
  - Caution in patients with neutropenia, lymphopenia, and anemia
  - Monitor for elevated liver function tests (LFTs)

## NSAIDs:

- The NIH COVID-19 treatment guidelines recommend there be no difference in the use of antipyretic treatments (e.g., acetaminophen or NSAIDs) between patients with or without COVID-19. Patients taking NSAIDs for comorbid conditions should continue therapy as previously directed by their prescriber.(133)
- ESICM and SCCM Surviving Sepsis Campaign recommendations suggest acetaminophen for temperature control in critically ill adults with COVID-19 who develop fever.(26)
- The FDA continues to investigate the use of NSAIDs in patients with COVID-19 symptoms.(20)

- Concern for potential worsening of COVID-19 symptoms has been suggested, but confirmatory clinical data is lacking at this time.(5)
- There is an anecdotal published letter that suggests a link between ibuprofen and increased ACE2 expression that may lead to worse outcomes in COVID-19 patients.(50)

### Nutritional Supplements

- The role of nutritional supplements for the treatment or prevention of COVID-19 is unknown. Several supplements are under investigation in combination with other treatment modalities (e.g. zinc, vitamin C, vitamin D) for both treatment and prophylaxis.(111) (112) (113) (114) (115) (116) (117) (118) (119) (120)
- Safety concerns include adverse events from large doses and the potential for drug interactions.(108) (109) (110)

**Understanding of the treatment of patients with COVID-19 is rapidly evolving. Information will continue to emerge regarding pharmacologic therapy for SARS-CoV-2 as clinical data are reported.**

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