COVID-19 Drug Therapy

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Clinical Drug Information | Clinical Solutions

What’s been updated:

- Remdesivir updated with:
  - final data from the Adaptive COVID-19 Treatment Trial (ACTT-1).
  - new data regarding compassionate use in pregnant and immediately postpartum women.
  - new recommendations from the National Institutes of Health (NIH) COVID-19 treatment guidelines.
- Corticosteroids updated with new recommendations from the NIH COVID-19 treatment guidelines.
- COVID-19 convalescent plasma updated with new data from a clinical trial.
- Hydroxychloroquine updated with new data from the Randomised Evaluation of COVid-19 thERapY (RECOVERY) trial.

Highlights:

- 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. Multiple agents are under investigation 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); data from several large clinical trials suggest clinical benefit.
  - Chloroquine – In vitro and limited early clinical data suggested potential benefit; FDA EUA revoked due to lack of data to support efficacy.
  - Hydroxychloroquine – In vitro and limited early clinical data suggest potential benefit; FDA EUA revoked due to lack of data to support efficacy.
Lopinavir; Ritonavir – Preclinical data suggested potential benefit; however, more recent data failed to confirm.

Ivermectin – *In vitro* data suggest activity; however, clinical data are limited and potential doses may far exceed those approved in humans.

Favipiravir – Broad spectrum investigational antiviral; licensed in other countries for treatment of influenza.

**Adjunctive / supportive care:**

- Anticoagulation – Venous thromboembolism prophylaxis with low molecular weight heparin (LMWH) recommended for all hospitalized patients.
- Azithromycin – Early use based on theoretical mechanism and limited preliminary data as adjunct therapy; safety concerns and lack of efficacy data limits current use.
- 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 – Dexamethasone reduces death in COVID-19 patients with severe respiratory complications; NIH recommends dexamethasone (or an alternative corticosteroid if dexamethasone is unavailable) for patients who are mechanically ventilated or require supplemental oxygen; WHO recommends systemic corticosteroids for patients with severe or critical COVID-19.
- Colchicine – Limited data suggest potential benefit; use based on theoretical mechanism as adjunct therapy.
- Fibrinolytics – Severe COVID-19 infection is associated with coagulopathy; fibrin deposition in the pulmonary microvasculature is a causative factor in the development of acute respiratory distress syndrome (ARDS).
- Immunomodulating agents [Interleukin Receptor Antagonists, Janus Kinase (JAK) Inhibitors, Bruton’s Tyrosine Kinase (BTK) 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 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, the National Institutes of Health (NIH), and the Infectious Diseases Society of America (IDSA) there are currently no medications or vaccines proven to be effective for the treatment or prevention of SARS-CoV-2. (1) (2) (3) (133) (161)

The NIH COVID-19 treatment guidelines recommend against the use of any agents for SARS-CoV-2 pre-exposure prophylaxis (PrEP) or post-exposure prophylaxis (PEP), except in a clinical trial.(133)

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

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

**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; however, the drug has been made available through an EUA. Similar restricted market authorizations have been issued by other nations.(168) (169)
  - Under the EUA, remdesivir can be used to treat hospitalized adults and children with suspected or laboratory confirmed COVID-19, irrespective of disease severity. The initial EUA limited use to patients with severe disease but was expanded to include all hospitalized patients in August 2020.
- **Evidence / Experience:**
  - The NIH COVID-19 treatment guidelines recommend the following regarding use of remdesivir: (133)
    - There is insufficient evidence to recommend for or against treating patients with mild to moderate COVID-19 (i.e., non-hospitalized patients or hospitalized patients that do not require supplemental oxygen).
    - For hospitalized patients who require supplemental oxygen BUT NOT high-flow oxygen, noninvasive ventilation, mechanical ventilation, or ECMO, remdesivir either alone or in combination with a corticosteroid is recommended.
    - For hospitalized patients who require oxygen through a high-flow device or noninvasive ventilation, remdesivir may be given in combination with a corticosteroid; however, due to questionable clinical benefit, treatment with remdesivir alone is not recommended.
    - For hospitalized patients who require invasive mechanical ventilation or ECMO and who have recently been intubated, remdesivir may be given in combination with a corticosteroid.
For patients who initially started on remdesivir monotherapy and then progressed to requiring high-flow oxygen, noninvasive ventilation, mechanical ventilation, or ECMO, the NIH add a corticosteroid and continue remdesivir until the treatment course is completed.

Remdesivir therapy may be stopped early if patient is discharged from hospital or may be extended up to 10 days if no improvement is observed at day 5.

- Data from a Phase 3 trial [Adaptive COVID-19 Treatment Trial (ACTT-1)] found remdesivir to be superior to placebo in shortening the time to recovery in hospitalized adults with COVID-19 and lower respiratory tract infection.(145) (211)
  - The median time to recovery was 10 days in the remdesivir group compared to 15 days in the placebo group (rate ratio for recovery 1.29; 95% CI, 1.12 to 1.49, p less than 0.001).
  - Benefit of remdesivir was greater when administered early in the illness.
    - Patients with treatment initiation within 10 days of symptom onset had a rate ratio for recovery of 1.37 (95% CI, 1.14 to 1.64).
    - Patients with treatment initiation more than 10 days after symptom onset had a rate ratio for recovery of 1.2 (95% CI, 0.94 to 1.52).
  - Kaplan-Meier estimates of mortality by day 29 were 11.4% for remdesivir vs. 15.2% for placebo (HR 0.73; 95% CI, 0.52 to 1.03).

- 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; HR 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 were reported in 66% of remdesivir patients and 64% of placebo patients. Remdesivir was stopped early in 12% of patients due to adverse events.

- Randomized, open-label, Phase 3 trial comparing 5-day (n = 200) and 10-day (n = 197) courses of remdesivir in hospitalized patients with severe COVID-19 pneumonia (i.e., lung infiltrates and either receiving supplemental oxygen or an oxygen saturation of 94% or less on room air).(154)
  - No significant difference between the 5-day and 10-day courses was observed in patients with severe COVID-19 not requiring mechanical ventilation.
    - At day 14, clinical improvement of at least 2 points on the 7-point ordinal scale was achieved by 65% in the 5-day group and 54% in the 10-day group.
    - Numerically, more patients were discharged from the hospital in the 5-day group than in the 10-day group (60% vs. 52%, respectively), and mortality was lower (8% vs. 11%, respectively).
  - Of note, patients randomly assigned to the 10-day group had significantly worse clinical status at baseline (p = 0.02).

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.

A multicenter study compared efficacy of remdesivir vs. standard of care alone in adults with severe COVID-19 using data from ongoing phase 3 trials (n = 312) and a retrospective cohort of patients (n = 818). \( ^{184} \)

- Patients had confirmed SARS-CoV-2 infection, were hospitalized, had oxygen saturation 94% or lower on room air or required supplemental oxygen, and had pulmonary infiltrates.
- At day 14, 74.4% of remdesivir patients had recovered vs. 59% of patients receiving standard of care (aOR, 2.03; 95% CI, 1.34 to 3.09; p less than 0.01).
- At day 14, a clinical status of at least 2-points (or being discharged alive) was noted in 71.9% of remdesivir patients compared to 58.8% of patients receiving standard of care (aOR, 1.64; 95% CI, 1.10 to 2.43; p = 0.001).
- At day 14, 7.6% of remdesivir patients had died vs. 12.5% of patients receiving standard of care (aOR, 0.38; 95% CI, 0.22 to 0.68; p = 0.001).

A randomized, open-label, multicenter study compared efficacy of remdesivir 5-day (n = 191) and 10-day (n = 193) therapy vs. standard care alone (n = 200) in patients hospitalized with moderate COVID-19 pneumonia. \( ^{194} \)

- The primary end point was clinical status at day 11 on a 7-point ordinal scale.
  - The 5-day remdesivir group had statistically significant higher odds of a better clinical status compared to standard care (OR, 1.65; 95% CI, 1.09 to 2.48; p = 0.02).
  - The clinical status at day 11 was not significantly different between the 10-day remdesivir group and standard care (p = 0.18).
- The secondary end point was proportion of patients with adverse events throughout the study duration.
  - Adverse events occurred in 51% of the 5-day group, 59% of the 10-day group, and 47% of the standard care group.
  - The difference between the 5-day group and standard care was not statistically significant (4.8%; 95% CI, -5.2% to 14.7%; p = 0.36), but was significant between the 10-day group and standard care (12%; 95% CI, 1.6% to 21.8%; p = 0.02).

An observational study of remdesivir use in 86 hospitalized pregnant women with severe COVID-19. \( ^{213} \)

- All women were pregnant at the time remdesivir use was approved; with 67 initiating remdesivir while pregnant and 19 initiating immediately postpartum (median postpartum day = 1; range 0 to 3 days).
  - For the pregnant group, 93% of those mechanically ventilated were extubated, 93% experienced a 2-point improvement on the ordinal scale, and 90% were discharged by day 28.
  - For the postpartum group, 89% were extubated, 89% recovered, and 84% were discharged by day 28.
- 45 deliveries were observed; 26 among women receiving remdesivir while pregnant and 19 among women who delivered before receiving remdesivir.
  - No neonatal deaths occurred during the 28-day observation period.
  - 1 spontaneous miscarriage at 17 weeks gestation occurred in a mother with concurrent *S. aureus* bacteremia, endocarditis, and septic arthritis.
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 (SBECO)
- Hypersensitivity and 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) (158)
  - Chloroquine is not FDA-approved for the treatment of COVID-19.
  - On June 15, 2020, the FDA revoked the EUA for chloroquine stating that it is unlikely to be effective in treating COVID-19. Also, in light of ongoing serious cardiac adverse events and other serious side effects, the known and potential benefits of chloroquine no longer outweigh the known and potential risks for the authorized use.
  - The EUA was issued in March 2020 and previously stated that treatment was for adult and adolescent patients weighing 50 kg or more who were hospitalized with COVID-19.
- **Evidence / Experience:**
  - The NIH COVID-19 treatment guidelines recommend against the use of chloroquine (with or without azithromycin) for the treatment of COVID-19 in hospitalized patients. In nonhospitalized patients, guidelines recommend against the use of chloroquine (with or without azithromycin) for the treatment of COVID-19 outside of clinical trials. 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)
  - Additional data regarding clinical efficacy for COVID-19 are being evaluated.(132)
- **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)
  o Risk of retinal damage, especially with long term use
  o Caution in patients with G6PD deficiency
  o Caution in diabetics
  o 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) (158)
  o Hydroxychloroquine is not FDA-approved for the treatment of COVID-19.
  o On June 15, 2020, the FDA revoked the EUA for hydroxychloroquine stating that it is unlikely to be effective in treating COVID-19. Also, in light of ongoing serious cardiac adverse events and other serious side effects, the known and potential benefits of hydroxychloroquine no longer outweigh the known and potential risks for the authorized use.
  o The EUA was issued in March 2020 and previously stated that treatment was for adult and adolescent patients weighing 50 kg or more who were hospitalized with COVID-19.
- **Evidence / Experience:**
  o The NIH COVID-19 treatment guidelines recommend against the use of hydroxychloroquine (with or without azithromycin) for the treatment of COVID-19 in hospitalized patients. In nonhospitalized patients, guidelines recommend against the use of hydroxychloroquine (with or without azithromycin) for the treatment of COVID-19 outside of clinical trials.(133)
  o Early *in vitro* data and data from small trials are limited and inconclusive.(12) (15) (17) (18) (21) (27) (69) (88)
  o In a multicenter, parallel, open-label, randomized trial in 150 adult hospitalized patients, hydroxychloroquine (n = 75) was added to standard therapy.(127)
    o The majority of patients (n = 148) had mild to moderate disease.
    o The overall 28-day negative viral conversion rate was not different between the two groups (85.4% hydroxychloroquine vs. 81.3% control).
    o The median time to negative conversion was also similar between groups (8 days hydroxychloroquine vs. 7 days control; HR 0.85; 95% CI, 0.58 to 1.23; p = 0.34).
    o Negative conversion rates on days 4, 7, 10, 14, and 21 were similar between the groups.
    o There was no difference in the 28-day symptom alleviation rate (59.9% hydroxychloroquine vs. 66.6% control) and the median time to alleviation of...
clinical symptoms was similar between the groups (19 days hydroxychloroquine vs. 21 days control; HR 1.01; 95% CI 0.59 to 1.74; p = 0.97).

- Adverse events were reported in 9% of the control group and 30% of the hydroxychloroquine group.

- 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).(151)
  - 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.

- A randomized, multicenter, double-blind, placebo-controlled trial (n = 423) studied symptomatic, nonhospitalized adults with laboratory-confirmed COVID-19 or probably COVID-19 and high-risk exposure; patients received either hydroxychloroquine (n = 201) or masked placebo for 5 days.(176)
  - Change in symptom severity over 14 days did not differ between the groups (difference in symptom severity: relative, 12%; absolute, -0.27 points [95% CI, -0.61 to 0.07 points]; p = 0.117) based on self-assessment.
  - At 14 days, 24% of hydroxychloroquine-treated patients had ongoing symptoms compared with 30% of patients that received placebo (n = 194) (p = 0.21).
  - Medication-related adverse events were reported in 43% of hydroxychloroquine-treated patients compared with 22% of patients that received placebo (p less than 0.001).
  - Ten patients were hospitalized in the placebo group (1 hospitalized death) compared to 4 patients hospitalized in the hydroxychloroquine-treated group (1 nonhospitalized death) (p = 0.29).

- A multicenter, open-label, randomized controlled trial (n = 270) studied nonhospitalized adult patients with recently confirmed SARS-CoV-2 infection with less than 4 days of symptoms; patients received either hydroxychloroquine for 7 days or no antiviral treatment (non-placebo controlled).(177)
No significant differences were found in the mean reduction of viral load at day 3 or day 7.

- There was no reduction in the risk of hospitalization (7.1% control vs. 4.9% hydroxychloroquine; RR 0.75 [0.32:1.77]) nor was the time to complete resolution of symptoms shortened (12 days control vs 10 days hydroxychloroquine; p = 0.38).

- No major treatment-related adverse events were reported.

- A multicenter, randomized, open-label, three-group, controlled trial (n = 504) studied adult hospitalized patients with suspected or confirmed COVID-19 who were not on supplemental oxygen or were receiving a maximum of 4 L/minute of supplemental oxygen. Patients received either standard care, standard care plus hydroxychloroquine for 7 days, or standard care plus hydroxychloroquine and azithromycin for 7 days. (182)

  - As compared to standard care, the proportional odds of having a higher (worse) score on the seven-point ordinal scale to assess clinical status at 15 days was not affected by either hydroxychloroquine alone (OR 1.21; 95% CI, 0.69 to 2.11; p = 1) or hydroxychloroquine plus azithromycin (OR 0.99; 95% CI, 0.57 to 1.73; p = 1).

  - QT prolongation was more common in the hydroxychloroquine plus azithromycin (14.7%) and the hydroxychloroquine alone (14.6%) groups compared to those receiving only standard care (1.7%); however, fewer patients in the control group had serial electrocardiographic studies performed during follow-up. Doses of hydroxychloroquine were higher than those recommended in the FDA Emergency Use Authorization (EUA).

  - Elevation in hepatic enzymes was more common in patients receiving hydroxychloroquine plus azithromycin (10.9%) and hydroxychloroquine alone (8.5%) than in the control group (3.4%).

- A multicenter retrospective cohort study (n = 2,541) evaluated adult hospitalized patients with COVID-19 treated with hydroxychloroquine alone, hydroxychloroquine plus azithromycin, azithromycin alone, or neither agent. (197)

  - In-hospital mortality was 18.1% overall, 13.5% for hydroxychloroquine alone group, 20.1% for hydroxychloroquine plus azithromycin group, 22.4% for azithromycin alone group, and 26.4% for neither agent (p less than 0.001).

  - Steroids were administered to 68.2% of patients overall, 78.9% of patients in the hydroxychloroquine alone group, 74.3% of patients in the hydroxychloroquine plus azithromycin group, 38.8% of patients in the azithromycin alone group, and 35.7% of patients receiving neither agent (p less than 0.001).

  - Patients in the hydroxychloroquine alone group had a 66% hazard ratio reduction and patients in the hydroxychloroquine plus azithromycin group had a 71% hazard ratio reduction compared to patients in the neither agent group (p less than 0.001).

- A multicenter retrospective observational cohort study (n = 2,512) in hospitalized patients with COVID-19 analyzed the effect of hydroxychloroquine. (198)

  - There was no significant association between survival and any use of hydroxychloroquine during hospitalization (HR, 0.99; 95% CI 0.8 to 1.22), hydroxychloroquine alone (HR, 1.02; 95% CI, 0.83 to 1.27), or hydroxychloroquine with azithromycin (HR, 0.98; 95% CI, 0.75 to 1.28).
The unadjusted 30-day mortality for patients was 25% in patients receiving hydroxychloroquine alone, 18% in patients receiving hydroxychloroquine plus azithromycin, and 20% in patients receiving neither drug.

- A multicenter randomized study in hospitalized patients with suspected and confirmed COVID-19 compared patients receiving hydroxychloroquine plus standard of care (n = 97) to standard of care alone (n = 97).(205)
  - After 28 days, there was no significant difference between the two groups regarding clinical outcome (p = 0.07).
  - By logistic regression, the overall mortality risk was not significantly different between the 2 groups (p = 0.757; OR 0.824; 95% CI, 0.243 to 2.797).

- A randomized, controlled, open-label platform trial [i.e., Randomised Evaluation of COVid-19 thERapY (RECOVERY)] in hospitalized patients compared patients receiving hydroxychloroquine (n = 1,561) to usual care (n = 3,155).(214)
  - The primary outcome of 28-day mortality was 27% in the hydroxychloroquine group and 25% in the usual care group (rate ratio 1.09; 95% CI, 0.97 to 1.23).
  - Discharge from the hospital by 28 days occurred in 59.6% of the hydroxychloroquine patients and 62.9% of the patients receiving usual care (rate ratio 0.9; 95% CI, 0.83 to 0.98).
  - For patients not undergoing mechanical ventilation at baseline, the frequency of invasive mechanical ventilation was 9.8% of patients in the hydroxychloroquine group and 8.6% of patients in the usual care group (risk ratio 1.15; 95% CI, 0.93 to 1.41). The frequency of death for these patients was 23.9% in the hydroxychloroquine group and 21.9% in the usual care group (risk ratio 1.09; 95% CI, 0.97 to 1.23).

- Post-exposure and pre-exposure studies with hydroxychloroquine have not reported benefit.(156) (209)
- Additional data regarding clinical efficacy for COVID-19 are being evaluated.(132)

**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\(^{pro}\), 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 trial [i.e., Randomised Evaluation of COVid-19 thERapY (RECOVERY)] compared efficacy of lopinavir; ritonavir plus usual care (n = 1,616) against usual care alone (n = 3,424) in hospitalized patients with COVID-19. (163) (210)
    - The 28-day mortality of patients in the lopinavir; ritonavir group was not significantly different from patients who received usual care alone (23% vs. 22%; RR 1.03; 95% CI, 0.91 to 1.17; p = 0.6).
    - Similarly, no significant differences were observed in the secondary outcomes of time until hospital discharge alive (median 11 days in both groups), proportion of patients discharged alive within 28 days (RR 0.98; 95% CI, 0.91 to 1.05; p = 0.53), or the proportion of patients who met the composite endpoint of invasive mechanical ventilation or death (RR 1.09; 95% CI, 0.99 to 1.20; p = 0.092).
  - 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 vs. 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) (125) (133) (172)
  - Risk of cardiac arrhythmias (e.g., QT prolongation)
    - Seriously ill patients with comorbidities have an increased risk of serious arrhythmias.
    - Avoid other QT prolonging agents whenever feasible.
  - Bradycardia
  - Caution in patients with hepatic disease or hepatitis
  - Significant drug interactions
Ivermectin:

- **Classification:** Antiparasitic
- **Rationale for Use:** Inhibits the replication of SARS-CoV-2 in cell cultures; however, pharmacokinetic and pharmacodynamic studies suggest that doses up to 100-fold higher than those approved in humans would be necessary to achieve the plasma concentrations necessary for the antiviral effect detected *in vitro*. (133)
- **Mechanism of Action:** Ivermectin inhibits the host alpha/beta-1 nuclear transport proteins, which are a part of a key intracellular transport process that viruses use to enhance infection by suppressing the host antiviral response. (133)
- **Evidence / Experience:** (133)
  - The NIH COVID-19 treatment guidelines recommend against the use of ivermectin, except in a clinical trial.
  - The available clinical data on the use of ivermectin to treat COVID-19 are limited.
- **Safety Concerns:** (133) (199) (200)
  - The FDA issued a warning that ivermectin intended for animal use should not be used to treat COVID-19 in humans.
  - Caution in patients with hepatic disease or asthma.

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 less than 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).
  - A multicenter, randomized, Phase II/III trial comparing efficacy of favipiravir to standard care in 60 adults hospitalized with moderate COVID-19 pneumonia. (189)
    - On day 5, viral clearance was achieved in 62.5% of patients on favipiravir (n = 25/40) and 30% of patients on standard care (n = 6/20), p = 0.018.
On day 10, viral clearance was achieved in 92.5% of patients on favipiravir (n = 37/40) and 80% of patients on standard care (n = 16/20), p = 0.155.

Standard care patients (n = 20) were allowed to use other antivirals or antimalarials, however, those receiving favipiravir were not; of the standard care patients, 15 received hydroxychloroquine/chloroquine, 1 received lopinavir; ritonavir, and 4 received no additional antiviral or antimalarial treatment.

17.5% (n = 7/40) of favipiravir recipients experienced adverse events, including diarrhea, nausea, chest pain, and increased hepatic enzymes.

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.

Adjunctive/Supportive therapy:

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 x 10^9/L, or fibrinogen less than 0.5 g/L.(80) (81) (91) (95) (102) (160)
  - In acutely ill hospitalized COVID-19 patients, anticoagulant prophylaxis with LMWH or fondaparinux is recommended over unfractionated heparin (UFH); LMWH, fondaparinux, or UFH is recommended over a direct oral anticoagulant (DOAC).(160)
  - In critically ill COVID-19 patients, anticoagulant prophylaxis with LMWH is recommended over UFH; LMWH or UFH is recommended over fondaparinux or DOAC.(160)
  - Use fondaparinux in patients with a history of heparin-induced thrombocytopenia.(95)
  - Use UFH 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) (160)
  - Standard dose anticoagulant thromboprophylaxis is recommended over intermediate (LMWH twice daily or increased weight-based dosing) or full treatment dosing.(160)
    - Data are insufficient to recommend the use of increasing anticoagulant doses for VTE prophylaxis in hospitalized COVID-19 patients outside of a clinical trial.(95) (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, may consider extended thromboprophylaxis after discharge.(95) (133) (160)
  - 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 outside of a clinical trial.\(^{(95)}\)\(^{(128)}\)
  - In patients already anticoagulated for VTE or atrial fibrillation, continue therapeutic anticoagulation. Consider withholding therapeutic anticoagulation in these patients for platelet count less than 30-50 \(\times 10^9/L\) or fibrinogen less than 1 g/L.\(^{(102)}\)
  - In outpatient COVID-19 patients with proximal deep vein thrombosis (DVT) or pulmonary embolism (PE) and no drug-drug interactions, apixaban, dabigatran, rivaroxaban, or edoxaban are recommended; initial parenteral anticoagulation is necessary for dabigatran and edoxaban.\(^{(160)}\)
    - If DOAC is not used, warfarin (overlapped with parenteral anticoagulation) is recommended over LMWH for patient convenience.\(^{(160)}\)
  - In acutely ill hospitalized COVID-19 patients with proximal DVT or PE, therapeutic LMWH or UFH is favored over oral anticoagulation; LMWH use will limit staff exposure.
    - In the absence of drug-drug interactions, initial oral anticoagulation with apixaban or rivaroxaban is recommended; dabigatran or edoxaban can be used after initial parenteral anticoagulation, and warfarin may be used after overlap with parenteral anticoagulation.\(^{(160)}\)
  - In critically ill COVID-19 patients with proximal DVT or PE, parenteral anticoagulant therapy is recommended over oral anticoagulation; LMWH or fondaparinux is recommended over UFH.\(^{(160)}\)
  - In COVID-19 patients with recurrent VTE despite anticoagulation with therapeutic LMWH (and documented compliance), increase the LMWH dose by 25% to 30%. If recurrent VTE occurs in a patient compliant with DOAC or therapeutic warfarin, switch treatment to therapeutic LMWH.\(^{(160)}\)
  - 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.\(^{(128)}\)\(^{(160)}\)

- 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)
  - Early data from small trials and trials outside of COVID-19 are limited and inconclusive. (27) (28) (88)
  - Two observational trials (n = 1,438 and n = 504) of hospitalized patients compared outcomes in patients receiving azithromycin plus hydroxychloroquine vs. standard care. (151) (182)
    - In both studies, treatment outcomes in patients receiving azithromycin plus hydroxychloroquine did not differ compared to those receiving standard care.
    - Both studies suggested increased cardiac adverse events in patients receiving azithromycin plus hydroxychloroquine compared to those receiving standard care.
  - A multicenter open-label, randomized study in hospitalized patients with suspected or confirmed COVID-19 with at least one additional severity criteria analyzed azithromycin plus standard of care (n = 214) to standard of care without macrolides (n = 183). (206)
    - Clinical status was not significantly different between the groups at day 15 (OR 1.36; 95% CI 0.94 to 1.97, p = 0.11).
    - Rates of adverse events, including cardiac events, were not significantly different between the groups.

- **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)

**Bruton’s Tyrosine Kinase (BTK) Inhibitors:**

- **Rationale for Use:** Cytokine release syndrome may be a component of severe disease in COVID-19 patients. (24) (89) (90) (178)
- **Mechanism of Action:** Bruton’s tyrosine kinases are macrophage signaling molecule. When stimulated by viruses such as SAR-CoV-2, BTK activates NF-kB, resulting in production of inflammatory cytokines and chemokines as well as phagocytosis. BTK also activates NLRP3
BTK inhibitors form a covalent bond with a cysteine residue in the BTK active site, leading to inhibition of BTK enzymatic activity. Evidence / Experience:
- Due to the broad immunosuppressive effect, the NIH COVID-19 treatment guidelines recommend against the use of BTK inhibitors outside of clinical trials.

Safety Concerns:
- Caution in patients with neutropenia, thrombocytopenia, and anemia
- Bleeding risk (intracranial bleeding, GI bleeding, hematuria, hemothorax)
- Monitor for elevated liver function tests (LFTs)
- Cardiac arrhythmias (atrial fibrillation, atrial flutter, ventricular arrhythmias)
- Avoid use during pregnancy

Colchicine:
- Classification: Anti-inflammatory Agent
- Rationale for Use: Cytokine release syndrome may be a component of severe disease in COVID-19 patients.
- Mechanism of Action: Colchicine downregulates multiple pro-inflammatory pathways and increases levels of anti-inflammatory mediators. It also prevents microtubule assembly and thereby disrupts inflammasome activation, microtubule-based inflammatory cell chemotaxis, phagocytosis, and generation of leukotrienes and cytokines (including interleukin-1 beta). Consequently, colchicine prevents the activation, degranulation, and migration of neutrophils.
- Evidence / Experience:
  - A prospective, open-label, multicenter, randomized trial compared the efficacy of colchicine plus standard care (n = 55) against standard care alone (n = 50) in hospitalized patients with COVID-19.
    - The primary clinical end point was time to clinical deterioration by 2 points on a 7-grade clinical status scale which ranged from resumption of normal activities to death. This clinical end point occurred in 1 patient in the colchicine group and in 7 patients who received standard care alone (1.8% vs. 14%; OR 0.11; 95% CI, 0.01 to 0.96; p = 0.046). Compared to the colchicine group, the rate of clinical deterioration was higher and the time to clinical deterioration was shorter in the standard care group. The patient in the colchicine group who met the end point needed mechanical ventilation and subsequently died. Of the 7 standard care patients meeting the clinical endpoint, 1 required noninvasive mechanical ventilation, 5 were intubated and mechanically ventilated (3 died shortly after intubation), and 1 died suddenly of cardiorespiratory arrest in the ward.
    - The mean event-free survival time for colchicine was 20.7 days in the colchicine group and 18.6 days in the standard care alone group (p = 0.03).
    - Standard care treatments included chloroquine, hydroxychloroquine, azithromycin, lopinavir; ritonavir, and tocilizumab. Remdesivir was not used in any patient.
A single-center cohort comparing the efficacy of colchicine plus standard care (n = 122) against standard care alone (n = 140) in hospitalized adults with COVID-19 pneumonia and acute respiratory distress syndrome.(186)

- Survival at day 21 was achieved by 84.2% of patients in the colchicine group and 63.6% of patients in the control group (p = 0.001).
- The Cox proportional hazards regression survival analysis suggest colchicine is independently associated with a lower risk of death (HR = 0.151; 95% CI, 0.062 to 0.368; p less than 0.0001).
- Standard care treatments included hydroxychloroquine, intravenous dexamethasone, and lopinavir; ritonavir.
  - A significantly higher percentage of patients in the colchicine group received concurrent treatment with dexamethasone.
  - Significantly more patients in the control group received treatment with lopinavir; ritonavir.

- Safety Concerns: (165) (166)
  - Gastrointestinal reactions (abdominal pain, diarrhea, nausea, and vomiting)
  - Neuromuscular toxicity and rhabdomyolysis
  - Caution in patients with bone marrow suppression
  - Caution in patients with renal or hepatic impairment

Corticosteroids:

- The NIH COVID-19 treatment guidelines recommend the following regarding use of corticosteroids: (133)
  - For patients with mild to moderate COVID-19 (i.e., non-hospitalized patients or hospitalized patients that do not require supplemental oxygen), corticosteroids are not recommended unless the patient has another clinical indication for steroid therapy.
  - For hospitalized patients who require supplemental oxygen BUT NOT on high-flow oxygen, noninvasive ventilation, mechanical ventilation, or ECMO, dexamethasone in combination with remdesivir is recommended. If remdesivir cannot be used, dexamethasone may be given as monotherapy.
  - For hospitalized patients who require oxygen through a high-flow device, noninvasive ventilation, mechanical ventilation, or ECMO, dexamethasone may be given alone or in combination with a remdesivir.
  - If dexamethasone is not available, it is recommended to use an alternative corticosteroid such as prednisone, methylprednisolone, or hydrocortisone; however, it is unclear if these alternatives will provide the same benefit as dexamethasone.
  - Clinicians are advised to review the patient’s medical history and assess the potential risks and benefits before initiating dexamethasone.
  - Oral and inhaled corticosteroids that were used prior to COVID-19 diagnosis for another underlying condition should not be discontinued.

- The World Health Organization (WHO) strongly recommends use of systemic corticosteroids (for 7 to 10 days) to treat patients with severe or critical COVID-19; but suggests against use of corticosteroids in patients with non-severe COVID-19.(201)
  - Critical COVID-19 is defined by the criteria for ARDS, sepsis, septic shock, or other conditions that require life-sustaining therapies.
Severe COVID-19 is defined as oxygen saturation less than 90% on room air, increased respiratory rate, or signs of severe respiratory distress.

**Evidence / Experience:**

- Preliminary data from a randomized controlled trial (i.e., RECOVERY trial) of hospitalized patients with COVID-19 found dexamethasone reduced deaths in patients with severe respiratory complications.\(^{(159)}\)
  - Overall mortality at 28 days was significantly lower in the dexamethasone group (22.9%; \(n = 482\) of 2,104) than in the usual care group (25.7%; \(n = 1,110\) of 4,321) (rate ratio 0.83; 95% CI, 0.75 to 0.93; \(p < 0.001\)).
  - In patients receiving mechanical ventilation, the incidences of death for dexamethasone and the usual care group were 29.3% and 41.4%, respectively (rate ratio 0.64; 95% CI, 0.51 to 0.81).
  - In patients receiving oxygen without mechanical ventilation, the incidences of death for dexamethasone and the usual care group were 23.3% and 26.2%, respectively (rate ratio, 0.82; 95% CI, 0.72 to 0.94).
  - No benefit was observed in patients not requiring respiratory support (17.8% vs. 14%; rate ratio 1.19; 95% CI, 0.91 to 1.55).

- Data from a single-center, retrospective cohort showed higher survival rates in hospitalized patients with COVID-19 pneumonia who received treatment with a glucocorticoid.\(^{(162)}\)
  - The in-hospital mortality was lower in patients treated with steroids (\(n = 396\)) than in patients who were not (\(n = 67\)) (13.9% vs. 23.9%; HR 0.51; [0.27 to 0.96]; \(p = 0.044\)); overall mortality was reduced by 41.8% relative to no steroid treatment (RRR 0.42 [0.048 to 0.65]).

- An observational study of 72 patients diagnosed with SARS-CoV-2 pneumonia who received tocilizumab (in addition to antiviral therapy) evaluated the efficacy of adding methylprednisolone (\(n = 56\)) vs. no steroid (\(n = 16\)).\(^{(170)}\)
  - Overall death occurred in 21 of 72 patients (29.2%), 10 of 16 non-steroid patients (62.5%), 11 of 56 methylprednisolone-treated patients (19.6%).
  - The primary outcome of in-hospital, all-cause mortality was lower in patients receiving methylprednisolone plus tocilizumab (RR 0.2; 95% CI, 0.08 to 0.47; \(p < 0.01\)).

- A study (\(n = 172\)) compared patients with COVID-19-associated cytokine storm syndrome (CSS) who received steroids with or without tocilizumab to historical controls.\(^{(183)}\)
  - Patients received high-dose IV methylprednisolone for 5 consecutive days (optional 2-day extension). If the respiratory condition had not improved sufficiently, tocilizumab was administered between day 2 and 5 as a single infusion.
  - Of the 86 treated patients, 37 (43%) received tocilizumab. Two patients received a second dose of tocilizumab.
  - Patients in the treatment group had 79% higher likelihood of reaching 2-stage improvement in respiratory status (HR: 1.79; 95% CI, 1.2 to 2.67) and they reached, on average, 7 days (median) earlier than the control group.
  - WHO-endorsed 7-point ordinal scores were better in the treatment group at days 7 and 14 (\(p < 0.0001\)).
Hospital mortality was 65% lower in the treatment group compared to the control group (HR: 0.35; 95% CI, 0.19 to 0.65). At hospital day 14, 10 patients had died in the treatment group compared with 33 in the control group (p less than 0.0001).

The likelihood to require mechanical ventilation was 71% lower in the treatment group compared to the control group (HR: 0.29; 95% CI, 0.14 to 0.6). Among patients not mechanically ventilated at baseline, the daily incidence of mechanical ventilation (new start) was 1.3% in the treatment group compared to 5.4% in the control group (p = 0.0003).

In the sensitivity analysis that excluded patients who received tocilizumab, the treatment effects for all outcomes increased and maintained statistical significance with the steroid alone.

An observational study (n = 1,806) reviewed the effects of early steroid use (n = 140) compared to no steroid use in hospitalized patients with COVID-19.(185)

Patients in the treatment group received steroids within 48 hours of admission.

Overall, early use of steroids was not associated with in-hospital mortality or mechanical ventilation.

Early steroid use in patients with an initial C-reactive protein (CRP) of 20 mg/dL or higher was associated with a significantly reduced risk of mortality or mechanical ventilation in unadjusted (OR, 0.23; 95% CI, 0.08 to 0.7) and adjusted (aOR, 0.2; 95% CI, 0.06 to 0.67) analyses.

Early steroid use in patients with an initial CRP of less than 10 mg/dL was associated with a significantly increased risk of mortality or mechanical ventilation in unadjusted (OR, 2.64; 95% CI, 1.39 to 5.03) and adjusted (aOR, 3.14; 95% CI 1.52 to 6.5) analyses.

A randomized, double-blind, placebo-controlled, Phase IIb study evaluated efficacy of methylprednisolone in patients hospitalized with suspected COVID-19.(190)

Overall mortality at day 28 was not significantly different in patients receiving methylprednisolone (n = 72/194, 37.1%) as compared to placebo (n = 76/199, 38.2%); HR, 0.924; 95% CI, 0.669 to 1.275, p = 0.629.

A post-hoc subgroup analysis of patients older than 60 years found the 28 mortality rate to be lower in the methylprednisolone group (n = 34/73, 46.6%) than in the placebo group (n = 52/84, 61.9%); HR, 0.634; 95% CI, 0.411 to 0.978; p = 0.039.

No patient received concurrent treatment with remdesivir, convalescent plasma, interleukin-1 (IL-1) antagonist, or interleukin-6 (IL-6) receptor antagonist.

A single-center, retrospective study evaluated the efficacy of methylprednisolone in adults with COVID-19 pneumonia requiring intubation and mechanical ventilation.(191)

The primary outcome of ventilator-free days at hospital day 28 was significantly higher in patients receiving methylprednisolone than in the controlled group (6.21 +/- 7.45 days vs. 3.14 +/- 7.45 days, respectively; p = 0.044). Ventilator-free days defined as days after extubation.

The probability of extubation by day 28 was significantly higher in the methylprednisolone group (45% vs. 21%; p = 0.021). Also, there was a trend towards reduced mortality with the use of methylprednisolone (19% vs. 36%; p = 0.087).
A randomized, open-label, multicenter study evaluated the efficacy of dexamethasone plus standard care (n = 151) versus standard care alone (n = 148) in adults on mechanical ventilation for COVID-19 induced ARDS.\(^{(202)}\)

- The primary outcome of ventilator-free days during the first 28 days was significantly higher in the dexamethasone group (6.6 days vs. 4 days; difference, 2.26; 95% CI, 0.2 to 4.38; \(p = 0.4\)).
- A secondary outcome of the mean Sequential Organ Failure Assessment (SOFA) score at day 7 was significantly lower in the dexamethasone group (6.1 vs. 7.5; difference, -1.16; 95% CI, -1.94 to -0.38; \(p = 0.004\)).
- There was no difference in the other secondary outcomes of 28-day all-cause mortality, clinical status at day 15, ICU-free days during the first 28 days, and mechanical ventilation duration at day 28.

A randomized, double-blind, multicenter study evaluated the efficacy of hydrocortisone (n = 76) versus placebo (n = 73) in adults admitted to the ICU with COVID-19-related acute respiratory failure.\(^{(203)}\)

- There was no difference in the primary outcome of treatment failure (i.e., death or persistent mechanical ventilation or high-flow oxygen) on day 21 (42.1% for hydrocortisone vs. 50.7% for placebo; difference, -8.6%; 95% CI, -24.9% to 7.7%; \(p = 0.29\)).
- There was no significant difference in the 4 secondary outcomes.
- This study was terminated early following release of data from the RECOVERY trial; the maximum required sample size was 290 patients.

Additional studies evaluating the efficacy of corticosteroids in treating COVID-19 have been published. Some of these studies were terminated early upon mortality benefit observed in the RECOVERY trial.\(^{(204)}\)

- **Safety Concerns:** \(^{(133)}\) \(^{(173)}\) \(^{(187)}\) \(^{(192)}\)
  - Hyperglycemia
  - Secondary infections/reactivation of latent infections
  - Psychiatric effects

**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:** Administration of plasma from persons who have recovered from COVID-19 provides antibodies to the recipient, which may neutralize the virus and reduce disease progression. Potential benefits include improvement in symptoms, reduced need for supplemental oxygen or mechanical ventilation, and reduced mortality.\(^{(195)}\) \(^{(196)}\) COVID-19 convalescent plasma is not intended for prevention of the infection.
- **FDA Emergency Use Authorization (EUA):** \(^{(195)}\) \(^{(196)}\)
  - COVID-19 convalescent plasma is not an FDA-approved medication; however, it has been made available through an EUA to treat hospitalized patients with COVID-19.
  - According to the EUA, clinical benefit is most likely when treatment is initiated early (e.g., prior to intubation) and when plasma with higher antibody concentrations or neutralizing activity is used (i.e., high titer COVID-19 convalescent plasma).
Plasma containing SARS-CoV-2 antibodies that do not qualify as high titer (i.e., COVID-19 convalescent plasma of low titer) are also authorized for use; however, health care providers are advised to consider the potential risks vs. benefits prior to use.

Evidence / Experience:
- The NIH COVID-19 treatment guidelines do not recommend for or against use to treat COVID-19; however, convalescent plasma should not be considered standard of care. Well-controlled, randomized trials are needed to determine safety and efficacy. Available data suggest serious adverse reactions are infrequent; however, the long-term risks of treatment have not been evaluated.(133)
- A randomized, open-label, multicenter trial evaluating efficacy and safety of convalescent plasma in hospitalized patients with severe or life-threatening COVID-19.(157)
  - No significant difference in time to clinical improvement within 28 days between convalescent plasma plus standard treatment (51.9%, n = 27/52) and standard treatment alone (43.1%, n = 22/51) (difference, 8.8% [95% CI, -10.4% to 28%]; HR 1.40 [95% CI, 0.79 to 2.49]; p = 0.26).
  - No significant difference in 28-day mortality (15.7% vs. 24%; OR, 0.59; 95% CI, 0.22 to 1.59; p = 0.3).
  - Two convalescent plasma recipients experienced transfusion-related adverse events.
- A prospective, propensity score-matched study evaluating efficacy of convalescent plasma (n = 136) against standard care (n = 251) in hospitalized patients with severe or life-threatening COVID-19.(208)
  - Mortality within 28 days (as compared to propensity score-matched controls) was reduced in patients who received transfusion within 72 hours of hospital admission but was not reduced in those transfused after 72 hours.
    - 28-day mortality in all transfused patients vs. matched controls (3.7% vs. 7.6%; p = 0.13).
    - 28-day mortality in patents transfused within 72 hours vs. matched controls (1.8% vs. 6.3%; p = 0.09).
    - 28-day mortality in patients transfused within 72 hours with high titer plasma vs. matched controls (1.2% vs. 7%; p = 0.047).
    - 28-day mortality in patients transfused after 72 hours vs. matched controls (12.9% vs. 11.5%; p = 0.83).
- A randomized, open-label, multicenter trial compared the efficacy of convalescent plasma plus standard care (n = 235) to standard care alone (n = 229) in adults hospitalized with moderate COVID-19.(212)
  - The primary outcome (i.e., composite of progression to severe disease or all-cause 28-day mortality) occurred in 18.7% of patients in the convalescent plasma group and 17.9% of patients in the standard care group (adjusted OR, 1.09; 95% CI, 0.67 to 1.77).
  - Death occurred in 14.5% of convalescent plasma patients and 13.5% of standard care patients (adjusted OR, 1.06; 95% CI, 0.61 to 1.83).
  - Progression to severe disease occurred in 7.2% of convalescent patients and 7.4% of standard care patients (aOR, 1.04; 95% CI, 0.51 to 2.11).
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
  - \( \text{PAO}_2/\text{FIO}_2 \) 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 \( \text{PAO}_2/\text{FIO}_2 \) 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.

**Safety Concerns:**

- Known side effects associated with plasma transfusion include transmitting infection, allergic or anaphylactic reaction, febrile nonhemolytic reactions, hemolytic reactions, transfusion-associated circulatory overload (TACO), transfusion-related acute lung injury (TRALI), posttransfusion purpura, hypothermia, and metabolic complications.(196)
- Safety data from 5,000 hospitalized adults with severe or life-threatening COVID-19 who received convalescent plasma (range: 200 to 500 mL).(152)
  - 36 serious adverse events (SAEs) within 4 hours of transfusion (less than 1% of all transfusions)
    - 15 deaths (0.3% of all transfusions); 4 were attributed to treatment (possibly \( n = 3 \); probably \( n = 1 \); definitely \( n = 0 \))
    - 21 non-lethal SAEs
      - 7 TACO and 11 TRALI; all were attributed to treatment (possibly \( n = 9 \); probably \( n = 7 \); definitely \( n = 2 \))
      - 3 severe allergic transfusion reactions
    - Seven-day mortality rate was 14.9%
- Safety data from 20,000 hospitalized adults who received COVID-19 convalescent plasma (range: 200 to 500 mL) through a national expanded access program.(207)
  - 146 SAEs within 4 hours of transfusion (less than 1% of all transfusions)
    - 63 deaths; 13 were deemed possibly or probably related to treatment
    - 83 non-lethal SAEs
37 TACO and 20 TRALI
- 26 severe allergic transfusion reactions
- 1,136 other SAEs within 7 days of transfusion
  - 643 cardiac events, 74 deemed potentially related to transfusion
  - 406 sustained hypotension, 54 deemed potentially related to transfusion
  - 87 thrombotic or thromboembolic complications, 32 deemed potentially related to transfusion
- Overall 7-day mortality rate was 8.56% (95% CI, 8.18% to 8.95%)

Fibrinolytics:
- In COVID-19 patients with acute, objectively confirmed PE and hypotension or signs of obstructive shock who are not at high risk of bleeding, systemically administered thrombolytics are recommended. Thrombolytic therapy is also recommended for COVID-19 patients with acute PE experiencing cardiopulmonary deterioration due to PE after initiation of anticoagulant therapy who have not yet developed hypotension and who are at low risk for bleeding.(160)
  o Systemic thrombolysis using a peripheral vein is recommended over catheter-directed thrombolysis.(160)

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.
  - Single-center study comparing anakinra plus standard therapy ($n = 52$) to a historical control group of standard therapy plus supportive care ($n = 44$) in adults with severe COVID-19-related bilateral pneumonia. (174)
    - The primary outcome of admission to intensive care for mechanical ventilation or death occurred in 25% of patients receiving anakinra and 73% of patients in the control group (HR 0.22; 95% CI, 0.11 to 0.41; $p < 0.001$).
  - 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:**
  - The NIH COVID-19 treatment guidelines recommend against the use of IL-6 receptor antagonists outside of clinical trials. (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 single-center, observational study of mechanically ventilated patients with COVID-19 comparing tocilizumab treatment (n = 78) with tocilizumab-untreated controls (n = 76).(171)
    - Tocilizumab was associated with a reduction in the hazard of death (adjusted HR 0.54; 95% CI, 0.29 to 1), and a lower 28-day case fatality rate (18% vs. 36%; p= 0.01).
    - Tocilizumab was associated with an increased risk for superinfections (overall, 54% vs. 26%; p less than 0.001; ventilator-associated pneumonia, 45% vs. 20%; p less than 0.001); however, there was no difference in the 28-day case fatality rate in tocilizumab recipients with vs. without superinfection (22% vs. 15%; p = 0.42).
  - A single-arm, multicenter, prospective, open-label study to evaluate the efficacy of intravenous and subcutaneous tocilizumab in 63 hospitalized adults with severe COVID-19.(175)
    - The overall mortality rate at day 14 was 11% (n = 7 of 63); no difference in mortality was observed based on route of administration (12.9%, intravenous; 10.3% subcutaneous).
    - Treatment was associated with improvement in levels of ferritin, C-reactive protein, D-dimer, and lymphocytes.
  - 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.
  - A study (n = 172) compared patients with COVID-19-associated cytokine storm syndrome (CSS) who received steroids with or without tocilizumab to historical controls.(183)
    - Patients received high-dose IV methylprednisolone for 5 consecutive days (optional 2-day extension). If the respiratory condition had not improved sufficiently, tocilizumab was administered between day 2 and 5 as a single infusion.
    - Of the 86 treated patients, 37 (43%) received tocilizumab. Two patients received a second dose of tocilizumab.
    - Patients in the treatment group had 79% higher likelihood of reaching 2-stage improvement in respiratory status (HR: 1.79; 95% CI, 1.2 to 2.67) and they reached, on average, 7 days (median) earlier than the control group.
WHO-endorsed 7-point ordinal scores were better in the treatment group at days 7 and 14 (p less than 0.0001).

Hospital mortality was 65% lower in the treatment group compared to the control group (HR: 0.35; 95% CI, 0.19 to 0.65). At hospital day 14, 10 patients had died in the treatment group compared with 33 in the control group (p less than 0.0001).

The likelihood to require mechanical ventilation was 71% lower in the treatment group compared to the control group (HR: 0.29; 95% CI, 0.14 to 0.6). Among patients not mechanically ventilated at baseline, the daily incidence of mechanical ventilation (new start) was 1.3% in the treatment group compared to 5.4% in the control group (p = 0.0003).

- A single-center, retrospective, case-controlled study evaluating efficacy of tocilizumab plus standard treatment (n = 30) against standard treatment alone (n = 176) in hospitalized patients with COVID-19 and general status deterioration.(193)
  - The combined primary endpoint of mortality and/or need for invasive mechanical ventilation was lower in the tocilizumab group than in standard therapy group (27% vs. 52%; p = 0.009). However, taken separately, the difference in mortality was not significantly different (27% vs. 38%; p = 0.253), but the rate of mechanical ventilation was (0% vs. 22%; p = 0.004).
  - Standard treatment included hydroxychloroquine, lopinavir; ritonavir; or corticosteroids.

- Single-center, retrospective, observational cohort study evaluating efficacy of subcutaneous tocilizumab plus standard care in 12 adults with severe COVID-19-related cytokine release syndrome (CRS).(188)
  - The primary assessment was incidence of grade 4 CRS after administration of tocilizumab
    - Within 2 days of drug administration, 5 of 12 patients (42%) had grade 4 CRS.
    - Within 1 week of drug administration, no cases were observed.
  - No adverse events or new safety concerns were attributed to tocilizumab.

- 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:**
    - An observational, retrospective, longitudinal, multicenter trial of hospitalized patients with moderate COVID-19 pneumonia was conducted to compared safety and efficacy of baricitinib plus lopinavir; ritonavir (n = 113) against standard of care (n = 78, hydroxychloroquine plus lopinavir; ritonavir). (144)
      - The 2-week case fatality rate was significantly lower in the baricitinib group than in patients treated with standard of care (0% vs. 6.4%; 95% CI, 0 to 0.4569; p = 0.01).
      - In the baricitinib group, 7 adverse events were reported. None required treatment discontinuation.
      - The median time to initiation of baricitinib therapy was 7 days from symptom onset.
    - Additional data regarding clinical efficacy for COVID-19 are being evaluated. (132)
  - **Ruxolitinib**
    - A randomized, multicenter, placebo-controlled, Phase 2 trial evaluated the efficacy and safety of ruxolitinib in hospitalized patients with severe COVID-19. (155)
      - No statistical differences in clinical improvement were detected between ruxolitinib (n = 20) and placebo (n = 21); however, the median time to clinical improvement was numerically faster for ruxolitinib (12 vs. 15 days; p = 0.147; HR 1.669; 95% CI, 0.836 to 3.335).
      - 80% of ruxolitinib (n = 16/20) and 71.4% of placebo (n = 15/21) developed adverse events by day 28. The 28-day mortality was 14.3% for placebo (n = 3/21), while no patients died in the ruxolitinib group.
  - Other JAK inhibitors for which COVID-19 efficacy data are being evaluated include 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)
- Due to insufficient data, the NIH COVID-19 treatment guidelines do not recommend for or against the use of vitamin C for the treatment of COVID-19.(133)
- Due to insufficient data, the NIH COVID-19 treatment guidelines do not recommend for or against the use of vitamin D for the prevention or treatment of COVID-19.(133)
- Due to insufficient data, the NIH COVID-19 treatment guidelines do not recommend for or against the use of zinc for the treatment of COVID-19. Guidelines recommend against the use of zinc supplementation above the recommended dietary allowance for the prevention of COVID-19, except in a clinical trial.(133)
- Safety concerns include adverse events from large doses and the potential for drug interactions.(108) (109) (110)
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