



## COVID-19 Drug Therapy

Tim Smith, PharmD, BCPS; Jennifer Bushek, PharmD; Aimée LeClaire, PharmD, BCPS;  
Tony Prosser, PharmD

Clinical Drug Information | Clinical Solutions

---

### What's been updated:

---

- Remdesivir
  - Updated with information regarding U.S. Food and Drug Administration (FDA) approval for the treatment of COVID-19 requiring hospitalization.
  - Updated with data from the World Health Organization (WHO) SOLIDARITY trial.
- Lopinavir; ritonavir updated with data from the WHO SOLIDARITY trial.
- Tocilizumab updated with data from 3 randomized trials and a retrospective cohort trial.
- Hydroxychloroquine updated with data from the WHO SOLIDARITY trial.
- Hydroxychloroquine and chloroquine updated with data from a trial assessing ICU admissions.

---

### Highlights:

---

- **Antimicrobials with potential activity against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus that causes coronavirus disease 2019 (COVID-19):**
  - Remdesivir – Antiviral approved by the U.S. Food and Drug Administration (FDA) for use in adults and pediatric patients (12 years and older and weighing at least 40 kg) to treat COVID-19 requiring hospitalization; also available under an FDA Emergency Use Authorization (EUA) to treat hospitalized pediatric patients (3.5 to 39 kg or less than 12 years but at least 3.5 kg).
  - 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; National Institutes of Health (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.
  - COVID-19 convalescent plasma – Investigational; available under an FDA EUA.
  - 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.

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: 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)
- Availability:
  - Remdesivir is FDA-approved for use in adults and pediatric patients (12 years and older and weighing at least 40 kg) to treat COVID-19 requiring hospitalization.(222)
  - Although not FDA-approved for use in patients younger than 12 years or weighing less than 40 kg, the FDA has issued an Emergency Use Authorization (EUA) which allows the drug to be used to treat suspected or laboratory-confirmed COVID-19 in hospitalized pediatric patients weighing 3.5 to 39 kg or hospitalized pediatric patients less than 12 years of age weighing at least 3.5 kg.(146) (223) (224)
  - Similar market approvals and restricted market authorizations have been issued by other nations.(168) (169)
- 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).
- 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.
- Preliminary data from an open-label, randomized, multicenter trial (SOLIDARITY trial) compared remdesivir (n = 2,743) to a controlled group (n = 2,708) in adults hospitalized with COVID-19.(215)

- There was no difference in in-hospital mortality between remdesivir and the control group (10.97% vs. 11.19%; death rate ratio, 0.95; 95% CI, 0.81 to 1.11;  $p = 0.5$ ).
    - Remdesivir did not reduce the initiation of ventilation in those not already ventilated (295 for remdesivir vs. 284 for the control group).
    - Remdesivir did not reduce the duration of hospitalization, with 69% of remdesivir and 59% of the control group still hospitalized at day 7.
  - 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)
  - 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)



- An observational, multicenter, cohort study assessed death on the COVID-19 ward and transfer to the ICU in hospitalized patients with moderate to severe COVID-19 receiving chloroquine (n = 377) compared to no treatment (n = 498).(216)
  - There was no significant difference between groups in regard to mortality (HR 0.99; 95% CI, 0.7 to 1.43).
  - There was no significant difference between groups in regard to transfer to the ICU (HR 0.8; 95% CI, 0.55 to 1.15, p = 0.207) compared to controls.
- 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)
  - 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) (158)
  - Hydroxychloroquine is not FDA-approved for the treatment of COVID-19.
  - 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.
  - 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 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)

- Early *in vitro* data and data from small trials are limited and inconclusive.(12) (15) (17) (18) (21) (27) (69) (88)
- In a multicenter, parallel, open-label, randomized trial in 150 adult hospitalized patients, hydroxychloroquine (n = 75) was added to standard therapy.(127)
  - The majority of patients (n = 148) had mild to moderate disease.
  - The overall 28-day negative viral conversion rate was not different between the two groups (85.4% hydroxychloroquine vs. 81.3% control).
  - 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).
  - Negative conversion rates on days 4, 7, 10, 14, and 21 were similar between the groups.
  - 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).
- Preliminary data from an open-label, randomized, multicenter trial (SOLIDARITY trial) compared hydroxychloroquine (n = 947) to a controlled group (n = 906) in adults hospitalized with COVID-19.(215)
  - There was no difference in in-hospital mortality between hydroxychloroquine and the control group (10.98% vs. 9.27%; death rate ratio, 1.19; 95% CI, 0.89 to 1.59; p = 0.23).
  - Hydroxychloroquine did not reduce the initiation of ventilation in those not already ventilated (75 for hydroxychloroquine vs. 66 for the control group).

- Hydroxychloroquine did not reduce the duration of hospitalization, with 64% of hydroxychloroquine and 54% of the control group still hospitalized at day 7.
  - An observational, multicenter, cohort study assessed death on the COVID-19 ward and transfer to the ICU in hospitalized patients with moderate to severe COVID-19 receiving hydroxychloroquine (n = 189) compared to no treatment (n = 498).(216)
    - There was no significant difference between groups in regard to mortality (HR 0.96; 95% CI, 0.63 to 1.45).
    - Hydroxychloroquine was associated with a significantly decreased risk of transfer to the ICU (HR 0.47; 95% CI, 0.27 to 0.82, p = 0.008) compared to controls.
  - Post-exposure and pre-exposure studies with hydroxychloroquine have not reported benefit.(156) (209) (217)
  - 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<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 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.
  - Preliminary data from an open-label, randomized, multicenter trial (SOLIDARITY trial) compared lopinavir; ritonavir (n = 1,399) to a controlled group (n = 1,372) in adults hospitalized with COVID-19.(215)
    - There was no difference in in-hospital mortality between lopinavir; ritonavir and the control group (10.5% vs. 10.6%; death rate ratio, 1.00; 95% CI, 0.79 to 1.25; p = 0.97).
    - Lopinavir; ritonavir did not reduce the initiation of ventilation in those not already ventilated (124 for lopinavir; ritonavir vs. 119 for the control group).
    - Lopinavir; ritonavir did not reduce the duration of hospitalization, with 68% of lopinavir; ritonavir and 59% of the control group still hospitalized at day 7.
- 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  $25 \times 10^9/L$ , 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 inflammasome, resulting in maturation and secretion of IL-1 beta. BTK inhibitors form a covalent bond with a cysteine residue in the BTK active site, leading to inhibition of BTK enzymatic activity.(178) (179) (180) (181)
- 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.(133)
- Safety Concerns: (179) (180) (181)
  - 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.(24) (89) (90) (107)
- 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.(165) (166) (167)
- 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.(164)
    - 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 less than 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 less than 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 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).
  - 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 patients 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 (PLACID 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
      - PAO<sub>2</sub>/FIO<sub>2</sub> 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<sub>2</sub>/FIO<sub>2</sub> 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)

- 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 less than 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 mL-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.
- A multicenter, retrospective, cohort study evaluating the association between early treatment with tocilizumab and mortality in 3,924 critically ill adults with COVID-19.(218)
  - Patients were categorized by whether they received tocilizumab within the first 2 days of ICU admission (tocilizumab group,  $n = 433$ ) or not (control group,  $n = 3,491$ ).
  - Overall mortality during the 27-day follow-up was 28.9% ( $n = 125$ ) for the tocilizumab group and 40.6% ( $n = 1,419$ ) for the control group (adjusted HR, 0.71; 95% CI, 0.56 to 0.92).
  - The estimated 30-day mortality was 27.5% for tocilizumab and 37.1% for the control group (risk difference, 9.6%; 95% CI, 3.1% to 16%).
- A randomized, double-blind, placebo-controlled trial evaluating the efficacy of tocilizumab to standard care in adults hospitalized with severe acute respiratory COVID-19, hyperinflammatory states, and at least 2 of the following signs: fever, pulmonary infiltrates, or need for supplemental oxygen.(219)
  - The primary outcome of need for intubation or death within 28 days occurred in 10.6% ( $n = 17/161$ ) of patients in tocilizumab group and 12.5% ( $n = 10/81$ ) of patients in the placebo group (adjusted HR, 0.66; 95% CI, 0.28 to 1.52).
  - At day 28, 19.3% of tocilizumab patients and 17.4% of placebo patients had had worsening disease (HR, 1.11; 95% CI, 0.59 to 2.1;  $p = 0.73$ ).
  - At day 28, 82.6% of tocilizumab patients and 84.9% of placebo patients were no longer receiving supplemental oxygen (HR, 0.94, 95% CI, 0.67 to 1.3;  $p = 0.69$ ). The median (IQR) duration of need for supplemental oxygen was 4 days (1.8 to 11.6 days) for tocilizumab and 3.9 days (1.1 to 9.2 days) for placebo.
- A prospective, open-label, randomized, multicenter trial comparing early tocilizumab therapy to standard care in preventing clinical worsening in adults hospitalized with COVID-19 pneumonia.(220)

- Early tocilizumab therapy was defined as administration within 8 hours of randomization.
- The primary outcome of clinical worsening within 14 days (defined as entry into ICU with mechanical ventilation, death, or PaO<sub>2</sub>/FiO<sub>2</sub> ratio less than 150 mm Hg) occurred in 28.3% (n = 17/60) of tocilizumab patients and 27% (n = 17/63) of patients in the standard care group (rate ratio, 1.05; 95% CI, 0.59 to 1.86; p = 0.87).
- A cohort-embedded, multicenter, open-label, randomized trial comparing efficacy of tocilizumab plus usual care against usual care alone in adults hospitalized with moderate or severe COVID-19 pneumonia.(221)
  - The primary outcomes were scores higher than 5 on the World Health Organization 10-point Clinical Progression Scale (WHO-CPS) by day 4 and survival without need of invasive or noninvasive ventilation by day 14.
    - On day 4, 19% (n = 12/63) of patients in the tocilizumab group and 28% (n = 19/67) of patients in the usual care group had a WHO-CPS score greater than 5 (absolute difference, -9%; 90% credible interval, -21 to 3.1).
    - On day 14, 24% of tocilizumab patients and 36% of usual care patients had needed ventilation, high-flow oxygen, or had died (HR, 0.58; 90% credible interval, 0.33 to 1).
  - 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 compare 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)

## References:

1. World Health Organization. Clinical management of severe acute respiratory infection when novel coronavirus (nCoV) infection is suspected [https://www.who.int/publications-detail/clinical-management-of-severe-acute-respiratory-infection-when-novel-coronavirus-\(ncov\)-infection-is-suspected](https://www.who.int/publications-detail/clinical-management-of-severe-acute-respiratory-infection-when-novel-coronavirus-(ncov)-infection-is-suspected).
2. CDC Website: <https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-guidance-management-patients.html>.
3. FDA Website: <https://www.fda.gov/emergency-preparedness-and-response/mcm-issues/coronavirus-disease-2019-covid-19>.
4. Chu CM, Cheng VCC, Hung IFN, et al. Role of lopinavir/ritonavir in the treatment of SARS: Initial virological and clinical findings. *Thorax* 2004;59(3):252–256. PMID: 1498565
5. Loutfy MR, Blatt LM, Siminovitch KA, et al. Interferon Alfacon-1 Plus Corticosteroids in Severe Acute Respiratory Syndrome: A Preliminary Study. *J Am Med Assoc* 2003;290(24):3222–3228. PMID: 14693875
6. Peiris JSM, Chu CM, Cheng VCC, et al. Clinical progression and viral load in a community outbreak of coronavirus-associated SARS pneumonia: A prospective study. *Lancet* 2003;361(9371):1767–1772. PMID: 12781535
7. Jin Y., Cai, L., Cheng, Z. et al. A rapid advice guideline for the diagnosis and treatment of 2019 novel coronavirus (2019-nCoV) infected pneumonia (standard version). *Military Med Res* 7, 4 (2020).
8. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet* Published online January 24, 2020. PMID: 31986264
9. ClinicalTrials.gov. National Institutes of Health (NIH) U.S. National Library of Medicine  
ClinicalTrials.gov website  
[https://www.clinicaltrials.gov/ct2/results?cond=Coronavirus&term=&type=&rslt=&age\\_v=&gndr=&intr=remdesivir&tiles=&outc=&spons=&lead=&id=&cntry=&state=&city=&dist=&locn=&rsub=&strd\\_s=&strd\\_e=&prcd\\_s=&prcd\\_e=&sfpd\\_s=&sfpd\\_e=&rfpd\\_s=&rfpd\\_e=&lupd\\_s=&lupd\\_e=&sort=](https://www.clinicaltrials.gov/ct2/results?cond=Coronavirus&term=&type=&rslt=&age_v=&gndr=&intr=remdesivir&tiles=&outc=&spons=&lead=&id=&cntry=&state=&city=&dist=&locn=&rsub=&strd_s=&strd_e=&prcd_s=&prcd_e=&sfpd_s=&sfpd_e=&rfpd_s=&rfpd_e=&lupd_s=&lupd_e=&sort=)
10. Agostini ML, Andres EL, Sims AC, et al. Coronavirus susceptibility to the antiviral remdesivir (GS-5734) is mediated by the viral polymerase and the proofreading exoribonuclease. *MBio* 2018;9(2):1–15. PMID: 29511076
11. Elfiky AA. Anti-HCV, nucleotide inhibitors, repurposing against COVID-19. *Life Sciences* 2020 May 1;248:117477. PMID: 32119961
12. Korea Biomedical Review website: <http://www.koreabiomed.com/news/articleView.html?idxno=7428>.
13. Gao J, T Zhenxue, Yang X. Breakthrough: Chloroquine phosphate has shown apparent efficacy in treatment of COVID-19 associated pneumonia in clinical studies. *Biosci Trends* 2020;14(1):72-73. PMID: 32074550
14. Wang M, Cao R, Zhang L, et al. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. *Cell Research* 2020;30:269–271. PMID: 32020029
15. Yao X, Ye F, Zhang M, et al. In vitro antiviral activity and projection of optimized dosing design of hydroxychloroquine for the treatment of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). *Clin Infect Dis* 2020 Mar 9. [Epub ahead of print] PMID: 32150618
16. World Health Organization (WHO). Coronavirus: landscape analysis of therapeutics as of 17 February 2020. Retrieved March 16, 2020. Available on the World Wide Web at [https://www.who.int/blueprint/priority-diseases/key-action/Table\\_of\\_therapeutics\\_Appendix\\_17022020.pdf?ua=1](https://www.who.int/blueprint/priority-diseases/key-action/Table_of_therapeutics_Appendix_17022020.pdf?ua=1).
17. Colson P, Rolain J, Lagier J, et al. Chloroquine and hydroxychloroquine as available weapons to fight COVID-19. *Int J Antimicrob Agents* 2020. [Epub ahead of print] PMID: 32145363

18. Dong L, Hu S, Gao J. Discovering drugs to treat coronavirus disease 2019 (COVID-19). *Drug Discov Ther* 2020;14:58-60. PMID: 32147628
19. Multicenter Collaboration Group of Department of Science and Technology of Guangdong Province and Health Commission of Guangdong Province for chloroquine in the treatment of novel coronavirus pneumonia. Expert consensus on chloroquine phosphate for the treatment of novel coronavirus pneumonia. *Zhonghua Jie He Hu Xi Za Zhi* 2020 Mar;43:185-188. PMID: 32164085
20. FDA Website: <https://www.fda.gov/drugs/drug-safety-and-availability/fda-advises-patients-use-non-steroidal-anti-inflammatory-drugs-nsaids-covid-19>.
21. Italian Society of Infectious and Tropical Diseases. Handbook for the care of people with disease-COVI 19. Edition 2.0, March 13, 2020.
22. FDA Website: [https://www.fda.gov/vaccines-blood-biologics/investigational-new-drug-ind-or-device-exemption-ide-process-cber/investigational-covid-19-convalescent-plasma-emergency-inds?utm\\_campaign=What%27sNew2020-03-24&utm\\_medium=email&utm\\_source=Eloqua](https://www.fda.gov/vaccines-blood-biologics/investigational-new-drug-ind-or-device-exemption-ide-process-cber/investigational-covid-19-convalescent-plasma-emergency-inds?utm_campaign=What%27sNew2020-03-24&utm_medium=email&utm_source=Eloqua).
23. Cao B, Wang Y, Wen D, et al. A trial of lopinavir-ritonavir in adults hospitalized with severe Covid-19. *N Engl J Med* 2020;382(19):1787-1799. PMID: 32187464
24. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet* 2020 Mar 11. [Epub ahead of print] PMID: 32171076.
25. Xu X, Han M, LI T, et al. Effect treatment of severe COVID-19 patients with tocilizumab. *ChinaXiv.20200300026.v1*
26. ESICM, SCCM. Surviving Sepsis Campaign: guidelines on the management of critically ill adults with Coronavirus Disease 2019 (COVID-19). *Crit Care Med* 2020;48(6):e440-e469. PMID: 32224769
27. Gautret P, Lagier J, Parola P, et al. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. *Int J Antimicrob Agents* 2020 Mar 20. [Epub ahead of print] PMID: 32205204
28. Arabi YM, Deeb A, Al-Hameed, et al. Macrolides in critically ill patients with Middle East Respiratory Syndrome. *Int J Infect Dis* 2019;81:184-190. PMID: 30690213
29. Fox R. Anti-malarial drugs: possible mechanisms of action in autoimmune disease and prospects for drug development. *Lupus* 1996;5 Suppl 1:S4-10. PMID: 8803903
30. Ben-Zvi H, Kivity S, Langevitz P, et al. Hydroxychloroquine: from malaria to autoimmunity. *Clin Rev Allergy Immunol* 2012;42:145-153. PMID: 21221847
31. Cortegiani A, Ingoglia G, Ippolito M, et al. A systematic review on the efficacy and safety of chloroquine for the treatment of COVID-19. *J Crit Care* 2020 Mar 10. [Epub ahead of print] PMID: 32173110
32. Savarino A, Trani LD, Donatelli I, et al. New insights into the antiviral effects of chloroquine. *The Lancet* 2006;6:67-9. PMID: 16439323
33. Fox RI. Mechanism of action of hydroxychloroquine as an antirheumatic drug. *Semin Arthritis Rheum* 1993; 23(2 Suppl 1):82-91. PMID: 8278823
34. Amsden GW. Anti-inflammatory effects of macrolides - an underappreciated benefit in the treatment of community-acquired respiratory tract infections and chronic inflammatory pulmonary conditions? *J Antimicrob Chemother* 2005;55:10-21. PMID: 15590715
35. Beigelman A, Mikols CL, Gunsten SP, et al. Azithromycin attenuates airway inflammation in a mouse model of viral bronchiolitis. *Respir Res* 2010;11:90. PMID: 20591166
36. Kanoh S, Rubin BK. Mechanisms of action and clinical application of macrolides as immunomodulatory medications. *Clin Microbiol Rev* 2010;23:590-615. PMID: 20610825



37. Zarogoulidis P, Papanas N, Kioumis I, et al. Macrolides: from in vitro anti-inflammatory and immunomodulatory properties to clinical practice in respiratory disease. *Eur J Clin Pharmacol* 2012;68:479-503. PMID: 22105373
38. U.S. Army Medical Research and Development Command. Expanded access remdesivir (RDV; GS-5734). Retrieved March 18, 2020. Available on the World Wide Web at: <https://clinicaltrials.gov/ct2/show/NCT04302766?term=remdesivir&draw=2&rank=3>.
39. Brown AJ, Won JJ, Graham RL, et al. Broad spectrum antiviral remdesivir inhibits human endemic and zoonotic deltacoronaviruses with a highly divergent RNA dependent RNA polymerase. *Antiviral Research* 2019;169:1-10. PMID: 31233808
40. Regeneron Pharmaceuticals. Evaluation of the efficacy and safety of sarilumab in hospitalized patients with COVID-19. Retrieved March 24, 2020. Available on the World Wide Web at: <https://clinicaltrials.gov/ct2/show/NCT04315298?term=sarilumab&draw=3&rank=4>.
41. de Wit, Feldmann F, Cronin J, et al. Prophylactic and therapeutic remdesivir (GS-5734) treatment in the rhesus macaque model of MERS-CoV infection. *Proc Natl Acad Sci U S A*. 2020 Feb 13.[Epub ahead of print] PMID: 32054787
42. Ko W, Rolain J, Lee N, et al. Arguments in favor of remdesivir for treating SARS-CoV-2 infections. *Int J Antimicrob Agents* 2020 Mar 6. [Epub ahead of print] PMID: 32147516
43. Gordon CJ, Tchesnokov EP, Feng JY, et al. The antiviral compound remdesivir potently inhibits RNA-dependent RNA polymerase from Middle East respiratory syndrome coronavirus. *J Biol Chem* 2020 Feb 24. [Epub ahead of print] PMID: 32094225
44. Warren TK, Jordan R, Lo MK, et al. Therapeutic efficacy of the small molecule GS-5734 against Ebola virus in rhesus monkeys. *Nature* 2016;531:381–385. PMID: 26934220
45. Kaletra (lopinavir; ritonavir) tablet and solution package insert. North Chicago, IL: AbbVie Inc; 2019 Dec.
46. Aralen (chloroquine) package insert. Bridgewater, NJ: Sanofi-aventis U.S. LLC.; 2018 Oct.
47. Plaquenil (hydroxychloroquine) package insert. St. Michael, Barbados: Concordia Pharmaceuticals, Inc.; 2017 Jan.
48. Zithromax (azithromycin 250 mg and 500 mg tablets and azithromycin oral suspension) package insert. New York, NY: Pfizer Inc.; 2019 Apr.
49. Credible Meds. COVID-19 experimental therapies and TdP risk. Retrieved March 24, 2020. Available on the World Wide Web at: <https://crediblemeds.org/blog/covid-19-experimental-therapies-and-tdp-risk/>
50. Fang L, Karakiulakis G, Roth M. Are patients with hypertension and diabetes mellitus at increased risk for COVID-19 infection? *Lancet Respir Med* 2020 Mar 11. [Epub ahead of print] PMID:32171062
51. Peking University First Hospital. Favipiravir combined with tocilizumab in the treatment of Corona Virus Disease 2019. Retrieved March 24, 2020. Available on the World Wide Web at: <https://clinicaltrials.gov/ct2/show/NCT04310228?cond=Coronavirus&intr=Tocilizumab&draw=2&rank=1>.
52. Actemra (tocilizumab) injection package insert. South San Francisco, CA: Genentech, Inc.; 2019 Jun.
53. Chen F, Chan KH, Jiang Y et al. In vitro susceptibility of 10 clinical isolates of SARS coronavirus to selected antiviral compounds. *J Clin Virol* 2004; 31:69-75. PMID: 15288617
54. Yao TT, Qian JD, Zhu WY et al. A systematic review of lopinavir therapy for SARS coronavirus and MERS coronavirus-A possible reference for coronavirus disease-19 treatment option. *J Med Virol* 2020 Feb 27. [Epub ahead of print] PMID: 32104907
55. Liu X, Wang XJ. Potential inhibitors for 2019-nCoV coronavirus M protease from clinically proven medicines. *J Genet Genomics* 2020 Feb 13. [Epub ahead of print] PMID: 32173287

56. Chen J, Liu D, Liu L, et al. A pilot study of hydroxychloroquine in treatment of patients with common coronavirus disease-19 (COVID-19). *J Zhejiang Univ (Med Sci)* 2020;49(1).
57. Institute for Safe Medication Practices (ISMP). Acute Care ISMP Medication Safety Alert. Special edition COVID-19. 2020 March;25(6):1-5.
58. Massachusetts General Hospital. Nitric oxide gas inhalation therapy for mild/moderate COVID-19 (NoCovid). Retrieved March 30, 2020. Available on the World Wide Web at: <https://clinicaltrials.gov/ct2/show/NCT04305457?cond=Coronavirus&intr=Nitric+Oxide&draw=2&rank=4>.
59. Massachusetts General Hospital. Nitric oxide gas inhalation for Severe Acute Respiratory Syndrome in COVID-19 (NOSARSCOVID). Retrieved March 30, 2020. Available on the World Wide Web at: <https://clinicaltrials.gov/ct2/show/NCT04306393?cond=Coronavirus&intr=Nitric+Oxide&draw=2&rank=2>.
60. Department of Defense (DoD). DoD COVID-19 practice management guide: clinical management of COVID-19. March 23, 2020. Available on the World Wide Web at: <https://www.health.mil/Reference-Center/Technical-Documents/2020/03/24/DoD-COVID-19-Practice-Management-Guide>
61. American Association for Respiratory Care (AARC). SARS CoV-2 guidance document. Retrieved March 30, 2020. Available on the World Wide Web at: <https://www.aarc.org/wp-content/uploads/2020/03/guidance-document-SARS-COVID19.pdf>.
62. Wu C, Chen X, Cai Y, et al. Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China. *JAMA Intern Med*. 2020 Mar 13. [Epub ahead of print] PMID: 32167524
63. Zhou YH, Qin YY, Lu YQ, et al. Effectiveness of glucocorticoid therapy in patients with severe novel coronavirus pneumonia: protocol of a randomized controlled trial. *Chin Med J (Engl)*. 2020 Mar 5. [Epub ahead of print] PMID: 32149773
64. Lian J, Jin X, Hao S, et al. Analysis of epidemiological and clinical features in older patients with Corona Virus Disease 2019 (COVID-19) out of Wuhan. *Clin Infect Dis*. 2020 Mar 25. [Epub ahead of print] PMID: 32211844
65. Shen C, Wang Z, Zhao F, et al. Treatment of 5 critically ill patients with COVID-19 with convalescent plasma. *JAMA* 2020 Mar 27. [Epub ahead of print] PMID: 32219428
66. Food and Drug Administration (FDA). Chloroquine phosphate or hydroxychloroquine sulfate supplied from the strategic national stockpile for treatment of 2019 coronavirus disease: emergency use authorization letter. Retrieved March 30, 2020. Available on the World Wide Web at: <https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization#2019-ncov>.
67. Food and Drug Administration (FDA). Fact sheet for health care providers: emergency use authorization (EUA) of chloroquine phosphate supplied from the strategic national stockpile for treatment of COVID-19 in certain hospitalized patients. Retrieved March 30, 2020. Available on the World Wide Web at: <https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization#2019-ncov>.
68. Food and Drug Administration (FDA). Fact sheet for health care providers: emergency use authorization (EUA) of hydroxychloroquine sulfate supplied from the strategic national stockpile for treatment of COVID-19 in certain hospitalized patients. Retrieved March 30, 2020. Available on the World Wide Web at: <https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization#2019-ncov>.
69. Chen Z, Hu J, Zhang Z, et al. Efficacy of hydroxychloroquine in patients with COVID-19: results of a randomized clinical trial. 2020 DOI: <https://doi.org/10.1101/2020.03.22.20040758>

70. Miao M, De Clercq E, Li G. Clinical significance of chemokine receptor antagonists. *Expert Opin Drug Metab Toxicol*. 2020 Jan;16(1):11-30. [Epub ahead of print] PMID: 31903790
71. CytoDyn. Press release. Retrieved April 2, 2020. Available on the World Wide Web at: <https://www.cytodyn.com/newsroom/press-releases/detail/405/treatment-with-cytodys-leronlimab-indicates-significant>
72. Assistance Publique – Hopitaux de Paris. Cohort multiple randomized controlled trials open-label of immune modulatory drugs and other treatments in COVID-19 patients – sarilumab trial – CORIMUNO-19-SARI (CORIMUNO-SARI). Retrieved April 2, 2020. Available on the World Wide Web at: <https://clinicaltrials.gov/ct2/show/NCT04324073?term=sarilumab&draw=3&rank=2>
73. Peking University First Hospital. Favipiravir combined with tocilizumab in the treatment of Corona Virus Disease 2019. Retrieved March 24, 2020. Available on the World Wide Web at: <https://clinicaltrials.gov/ct2/show/NCT04310228?cond=Coronavirus&intr=Tocilizumab&draw=2&rank=1>
74. Beijing Chao Yang Hospital. Clinical trial of favipiravir tablets combine with chloroquine phosphate in treatment of novel coronavirus pneumonia. Retrieved April 2, 2020. Available on the World Wide Web at: <https://clinicaltrials.gov/ct2/show/NCT04319900?term=favipiravir&draw=2&rank=9>
75. Shiraki K and Daikoku T. Favipiravir, an anti-influenza drug against life-threatening RNA virus infections. *Pharmacol Ther*. 2020 Feb 22. [Epub ahead of print] PMID: 32097670
76. Regneron. Press release. Retrieved April 2, 2020. Available on the World Wide Web at: <https://newsroom.regeneron.com/news-releases/news-release-details/regeneron-and-sanofi-begin-global-kevzara-sarilumab-clinical>
77. Sanofi. Press release. Retrieved April 2, 2020. Available on the World Wide Web at: <http://www.news.sanofi.us/2020-03-16-Sanofi-and-Regeneron-begin-global-Kevzara-R-sarilumab-clinical-trial-program-in-patients-with-severe-COVID-19>
78. Kevzara (sarilumab) package insert. Bridgewater, NJ: Sanofi-Aventis US. LLC; 2018 Apr.
79. Institute for Safe Medication Practices (ISMP). Acute Care ISMP Medication Safety Alert. 2020 April;25(6 Supplement):1-5.
80. Thachil J, Tang N, Gando S, et al. ISTH interim guidance on recognition and management of coagulopathy in COVID-19. *J Thromb Haemost* 2020 [Epub ahead of print] DOI: doi:10.1111/jth.14810.
81. Tang N, Bai H, Chen X. Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy. *J Thromb Haemost*. 2020. [Epub ahead of print] PMID: 32220112
82. Regeneron Pharmaceuticals. Evaluation of the efficacy and safety of sarilumab in hospitalized patients with COVID-19. Retrieved April 2, 2020: Available on the World Wide Web at: <https://clinicaltrials.gov/ct2/show/study/NCT04315298?term=sarilumab&draw=2>
83. Sanofi. Sarilumab COVID-19. Retrieved April 2, 2020. Available on the World Wide Web at: <https://clinicaltrials.gov/ct2/show/NCT04327388?cond=Coronavirus&intr=sarilumab&draw=2&rank=2>
84. Henriksen M. Anti-il6 treatment of serious COVID-19 disease with threatening respiratory failure (TOCIDVID). Retrieved April 2, 2020. Available on the World Wide Web at: <https://clinicaltrials.gov/ct2/show/NCT04322773?cond=Coronavirus&intr=sarilumab&draw=2&rank=3>
85. Barrett L. Treatment of moderate to severe coronavirus disease (COVID-19) in hospitalized patients. Retrieved April 2, 2020. Available on the World Wide Web at: <https://clinicaltrials.gov/ct2/show/NCT04321993?cond=Coronavirus&intr=sarilumab&draw=2&rank=4>
86. Assistance Publique - Hopitaux de Paris. Cohort multiple randomized controlled trials open-label of immune modulatory drugs and other treatments in COVID-19 patients - tocilizumab trial - CORIMUNO-19 - TOCI (CORIMUNO-TOCI) (CORIMUNO-TOC). Retrieved April 2, 2020. Available

on the World Wide Web at:

<https://clinicaltrials.gov/ct2/show/NCT04331808?cond=Coronavirus&intr=Tocilizumab&draw=2&rank=1>

87. University Hospital Ghent. Treatment of COVID-19 patients with anti-interleukin drugs (COV-AID). Retrieved April 2, 2020. Available on the World Wide Web at:  
<https://clinicaltrials.gov/ct2/show/NCT04330638?cond=Coronavirus&intr=Tocilizumab&draw=2&rank=4>
88. Molina JM, Delaugerre C, Goff JL, et al. No evidence of rapid antiviral clearance or clinical benefit with the combination of hydroxychloroquine and azithromycin in patients with severe COVID-19. *Med Mal Infect* 2020. [Epub ahead of print] DOI:<https://doi.org/10.1016/j.medmal.2020.03.006>. PMID: 32240719
89. Zhang C, Wu Z, Li JW, et al. The cytokine release syndrome (CRS) of severe COVID-19 and Interleukin-6 receptor (IL-6R) antagonist tocilizumab may be the key to reduce the mortality. *Int J Antimicrob Agents*. 2020. [Epub ahead of print] PMID: 32234467
90. Zhang W, Zhao Y, Zhang F, et al. The use of anti-inflammatory drugs in the treatment of people with severe coronavirus disease 2019 (COVID-19): the perspectives of clinical immunologists from China. *Clin Immunol*. 2020. [Epub ahead of print] PMID: 32222466
91. Lin L, Lu L, Cao W, et al. Hypothesis for potential pathogenesis of SARS-CoV-2 infection—a review of immune changes in patients with viral pneumonia. *Emerg Microbes Infect*. 2020;9:727-732. PMID: 32196410
92. Olumiant (baricitinib) tablets package insert. Indianapolis, IN: Lilly USA, LLC; 2019 Oct.
93. Barret L. Treatment of moderate to severe coronavirus disease (COVID-19) in hospitalized patients. Retrieved April 2, 2020. Available on the World Wide Web at:  
<https://clinicaltrials.gov/ct2/show/NCT04321993?cond=Coronavirus&intr=Baricitinib&draw=2&rank=1>
94. Stebbing J, Phelan A, Griffin I, et al. COVID-19: combining antiviral and anti-inflammatory treatments. *Lancet Infect Dis*. 2020. [Epub ahead of print] PMID: 32113509
95. American Society of Hematology (ASH). COVID-19 and VTE/anticoagulation: frequently asked questions Version 4.0. Retrieved August 27, 2020. Available on the World Wide Web at:  
<https://www.hematology.org/covid-19/covid-19-and-vte-anticoagulation>
96. Hospital of Prato. Baricitinib in symptomatic patients infected by COVID-19: an open-label, pilot study (BARI-COVID). Retrieved April 6, 2020. Available on the World Wide Web at:  
<https://clinicaltrials.gov/ct2/show/NCT04320277?cond=COVID&intr=Baricitinib&draw=2&rank=1>
97. Sylvant (siltuximab) package insert. Hemel Hempstead, United Kingdom: EUSA Pharma. Ltd; 2019 Dec.
98. Maston LD, Jones DT, Giermakowska W, et al. Interleukin-6 trans-signalling contributes to chronic hypoxia-induced pulmonary hypertension. *Pulm Circ*. 2018;8(3):1-11. PMID: 29767573
99. Martinez JP. Efficacy and safety of siltuximab vs. corticosteroids in hospitalized patients with COVID19 pneumonia. Retrieved April 8, 2020. Available on the World Wide Web at:  
<https://clinicaltrials.gov/ct2/show/NCT04329650?term=Siltuximab&draw=3&rank=12>
100. A.O. Ospedale Papa Giovanni XXIII. An observational case-control study of the use of siltuximab in ARDS patients diagnosed with COVID-19 infection (SISCO). Retrieved April 8, 2020. Available on the World Wide Web at:  
<https://clinicaltrials.gov/ct2/show/NCT04322188?term=Siltuximab&draw=3&rank=13>
101. Gritti G, Raimondi F, Ripamonti D, et al. Use of siltuximab in patients with COVID-19 pneumonia requiring ventilatory support. Retrieved April 8, 2020. Available on the World Wide Web at:  
<https://www.medrxiv.org/content/10.1101/2020.04.01.20048561v1>



102. American Society of Hematology (ASH). COVID-19 and coagulopathy: frequently asked questions Version 3.0. Retrieved May 20, 2020. Available on the World Wide Web at: <https://www.hematology.org/covid-19/covid-19-and-coagulopathy>
103. Hunt B, Retter A, McClintock C. Practical guidance for the prevention of thrombosis and management of coagulopathy and disseminated intravascular coagulation of patients infected with COVID-19. Retrieved April 9, 2020. Available on the World Wide Web at: <https://thrombosisuk.org/covid-19-thrombosis.php>
104. Swedish Orphan Biovitrum. Efficacy and safety of emapalumab and anakinra in reducing hyperinflammation and respiratory distress in patients with COVID-19 infection. Retrieved April 9, 2020. Available on the World Wide Web at: <https://clinicaltrials.gov/ct2/show/NCT04324021>
105. Hellenic Institute for the study of sepsis. Personalized immunotherapy for SARS-CoV-2 (COVID-19) associated with organ dysfunction (ESCAPE). Retrieved April 9, 2020. Available on the World Wide Web: <https://clinicaltrials.gov/ct2/show/NCT04339712?term=anakinra&cond=covid&draw=2&rank=2>
106. Kineret (anakinra) package insert. Stockholm, Sweden: Swedish Orphan Biovitrum AB; 2018 Jun.
107. Mehta P, McAuley DF, Brown M, et al. COVID-19: consider cytokine storm syndromes and immunosuppression. *Lancet*. 2020;395(10229):1033-1034. PMID: 32192578
108. National Institutes of Health (NIH). Zinc: fact sheet for health professionals. Retrieved April 9, 2020. Available on the World Wide Web at: <https://ods.od.nih.gov/factsheets/Zinc-HealthProfessional/>
109. National Institutes of Health (NIH). Vitamin C: fact sheet for health professionals. Retrieved April 9, 2020. Available on the World Wide Web at: <https://ods.od.nih.gov/factsheets/VitaminC-HealthProfessional/>
110. National Institutes of Health (NIH). Vitamin D: fact sheet for health professionals. Retrieved April 9, 2020. Available on the World Wide Web at: <https://ods.od.nih.gov/factsheets/VitaminD-HealthProfessional/>
111. ProgenaBiome. A study of hydroxychloroquine, vitamin C, vitamin D, and zinc for the prevention of COVID-19 infection (HELPCOVID-19). Retrieved April 9, 2020. Available on the World Wide Web at: <https://clinicaltrials.gov/ct2/show/NCT04335084?cond=COVID&intr=zinc&draw=2&rank=2>
112. Istinye University. Proflaxis using hydroxychloroquine plus vitamins-zinc during COVID-19 pandemic. Retrieved April 9, 2020. Available on the World Wide Web at: <https://clinicaltrials.gov/ct2/show/NCT04326725?cond=COVID&intr=zinc&draw=2&rank=3>
113. ProgenaBione. A study of quintuple therapy to treat COVID-19 infection (HAZCpaC). Retrieved April 9, 2020. Available on the World Wide Web at: <https://clinicaltrials.gov/ct2/show/NCT04334512?cond=COVID&intr=zinc&draw=2&rank=4>
114. University of Melbourne. World-first trial to test benefit of intravenous zinc in COVID-19 fight. Retrieved April 9, 2020. Available on the World Wide Web at: <https://medicalxpress.com/news/2020-04-world-first-trial-benefit-intravenous-zinc.html>
115. University of Palermo. Use of ascorbic acid in patients With COVID 19. Retrieved April 9, 2020. Available on the World Wide Web at: <https://clinicaltrials.gov/ct2/show/NCT04323514?cond=COVID&intr=vitamin+C&draw=2&rank=1>
116. Providence Health and Services. Hydroxychloroquine in patients with newly diagnosed COVID-19 compared to standard of care. Retrieved April 9, 2020. Available on the World Wide Web at: <https://clinicaltrials.gov/ct2/show/NCT04334967?cond=COVID&intr=vitamin+C&draw=2&rank=4>
117. Washington University. Hydroxychloroquine for COVID-19 PEP. Retrieved April 9, 2020. Available on the World Wide Web at: <https://clinicaltrials.gov/ct2/show/NCT04328961?cond=COVID&intr=vitamin+C&draw=2&rank=5>

118. ZhiYong Peng. Vitamin C infusion for the treatment of severe 2019-nCoV infected pneumonia. Retrieved April 9, 2020. Available on the World Wide Web at:  
<https://clinicaltrials.gov/ct2/show/NCT04264533?cond=COVID&intr=vitamin+C&draw=2&rank=6>
119. Universite de Sherbrooke. Lessening organ dysfunction with vitamin C (LOVIT). Retrieved April 9, 2020. Available on the World Wide Web at:  
<https://clinicaltrials.gov/ct2/show/NCT03680274?cond=COVID&intr=vitamin+C&draw=2&rank=8>
120. Universidad de Granada. Vitamin D on Prevention and Treatment of COVID-19 (COVITD-19). Retrieved April 9, 2020. Available on the World Wide Web at:  
<https://clinicaltrials.gov/ct2/show/NCT04334005?cond=COVID&intr=Vitamin+D&draw=2&rank=1>
121. University of Colorado. Safety and efficacy of baricitinib for COVID-19. Retrieved April 14, 2020. Available on the World Wide Web at:  
<https://clinicaltrials.gov/ct2/show/NCT04340232?cond=COVID&intr=Baricitinib&draw=2&rank=1>
122. Benfield T. Efficacy and safety of novel treatment options for adults with COVID-19 pneumonia (CCAP). Retrieved April 14, 2020. Available on the World Wide Web at:  
<https://clinicaltrials.gov/ct2/show/NCT04345289?cond=COVID&intr=Baricitinib&draw=2&rank=4>
123. Assistance Publique – Hopitaux de Paris. Study of Immune Modulatory Drugs and Other Treatments in COVID-19 Patients: Sarilumab, Azithromycin, Hydroxychloroquine Trial - CORIMUNO-19 - VIRO (CORIMUNO-VIRO). Retrieved April 13, 2020. Available on the World Wide Web at:  
<https://clinicaltrials.gov/ct2/show/NCT04341870?term=sarilumab&cond=SARS-CoV+2&draw=2&rank=1>
124. Grein J, Ohmagari N, Shin D, et al. Compassionate use of remdesivir for patients with severe Covid-19. *N Engl J Med* 2020. [Epub ahead of print] PMID: 32275812
125. Roden DM, Harrington RA, Poppas A, et al. Considerations for drug interactions on QTc in exploratory COVID-19 (Coronavirus Disease 2019) treatment. *Circulation* 2020. [Epub ahead of print] PMID: 32267762
126. Borba MGS, Val FFA, Sampaio VS, et al. Effect of high vs low doses of chloroquine diphosphate as adjunctive therapy for patients hospitalized with Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) infection: a randomized clinical trial. *JAMA Netw Open* 2020;3:e208857. PMID: 32330277
127. Tang W, Cao Z, Han M, et al. Hydroxychloroquine in patients with mainly mild to moderate coronavirus disease 2019: open label, randomised controlled trial. *BMJ* 2020;369:m1849. PMID: 32409561
128. American Society of Hematology (ASH). COVID-19 and pulmonary embolism: frequently asked questions Version 2.0. Retrieved May 20, 2020. Available on the World Wide Web at:  
<https://www.hematology.org/covid-19/covid-19-and-pulmonary-embolism>
129. Avigan (favipiravir) tablets package insert [English translation]. Tokyo, Japan: Taisho Toyama Pharmaceutical Co., Ltd.; 2017 Nov. Accessed 2020 Apr 14. Available at:  
[https://www.cdc.gov.tw/File/Get/ht8jUiB\\_MI-aKnlwstzwv](https://www.cdc.gov.tw/File/Get/ht8jUiB_MI-aKnlwstzwv)
130. Jakafi (ruxolitinib) package insert. Wilmington, DE: Incyte Corporation; 2020 Jan.
131. Xeljanz (tofacitinib) package insert. New York, NY: Pfizer, Inc.; 2019 Dec.
132. ClinicalTrials.gov. National Institutes of Health (NIH) U.S. National Library of Medicine ClinicalTrials.gov website <https://clinicaltrials.gov>.
133. COVID-19 Treatment Guidelines Panel. Coronavirus Diseases 2019 (COVID-19) Treatment Guidelines. National Institutes of Health. Accessed October 22, 2020. Available at on the World Wide Web at: <https://covid19treatmentguidelines.nih.gov>



134. Magagnoli J, Narendran S, Pereira F, et al. Outcomes of hydroxychloroquine usage in United States veterans hospitalized with Covid-19. Pre-print. Retrieved April 22, 2020. Available on the World Wide Web at: <https://www.medrxiv.org/content/10.1101/2020.04.16.20065920v1>
135. Ye M, Fu D, Ren Y, et al. Treatment with convalescent plasma for COVID-19 patients in Wuhan, China. *J Med Virol*. 2020. [Epub ahead of print] PMID: 32293713
136. Wang J, Hajizadeh N, Moore EE, et al. Tissue plasminogen activator (tPA) treatment for COVID-19 associated acute respiratory distress syndrome (ARDS): a case series. *J Thromb Haemost*. 2020. [Epub ahead of print] PMID: 32267998
137. Activase (alteplase) package insert. South San Francisco, CA: Genentech, Inc.; 2018 Feb.
138. Beth Israel Deaconess Medical Center. BIDMC launches clinical trial to assess common anti-clotting medication for treatment of COVID-19-related respiratory failure. Retrieved April 22, 2020. Available on the World Wide Web at <https://www.bidmc.org/about-bidmc/news/2020/04/covid-19-anti-clotting-medication>
139. IRCCS San Raffaele. Defibrotide in COVID-19 pneumonia (DEFI-VID19). Retrieved April 17, 2020. Available on the World Wide Web at: <https://clinicaltrials.gov/ct2/show/NCT04335201?term=defibrotide&cond=COVID&draw=2&rank=2>
140. Fundacion para la Formacion e Investigacion Sanitarias de la Region de Murcia. Defibrotide as prevention and treatment of respiratory distress and cytokine release syndrome of COVID 19 (DEFACOVID). Retrieved April 17, 2020. Available on the World Wide Web at: <https://clinicaltrials.gov/ct2/show/NCT04348383?term=defibrotide&cond=COVID&draw=2&rank=1>
141. Food and Drug Administration. FDA Drug Safety Communication: Hydroxychloroquine or chloroquine for COVID-19: FDA cautions against use outside of the hospital setting or a clinical trial due to risk of heart rhythm problems. Retrieved April 23, 2020. Available on the World Wide Web at: [https://www.fda.gov/safety/medical-product-safety-information/hydroxychloroquine-or-chloroquine-covid-19-drug-safety-communication-fda-cautions-against-use?utm\\_campaign=FDA%20MedWatch%20](https://www.fda.gov/safety/medical-product-safety-information/hydroxychloroquine-or-chloroquine-covid-19-drug-safety-communication-fda-cautions-against-use?utm_campaign=FDA%20MedWatch%20)
142. Cai Q, Yang M, Liu D, et al. Experimental treatment with favipiravir for COVID-19: An open-label control study. *Engineering*. <https://doi.org/10.1016/j.eng.2020.03.007>
143. Chen C, Zhang Y, Huang J, et al. Favipiravir versus Arbidol for COVID-19: A Randomized Clinical Trial. Pre-print. Retrieved April 27, 2020. Available on the World Wide Web at: <https://doi.org/10.1101/2020.03.17.20037432>
144. Cantini F, Niccoli L, Nannini C, et al. Retrospective, multicentre study on the impact of baricitinib in COVID-19 moderate pneumonia. *J Infect* 2020 Jun 24;S0163-4453(20)30433-3. PMID: 32592703
145. Beigel JH, Tomashek KM, Dodd LE, et al. Remdesivir for the treatment of Covid-19 - preliminary report. *N Engl J Med*. 2020; DOI:10.1056/NEJMoa2007764. PMID: 32445440
146. Food and Drug Administration (FDA). Fact sheet for health care providers emergency use authorization (EUA) of remdesivir (GS-5734). Retrieved August 28, 2020. Available on the World Wide Web at: <https://www.fda.gov/media/137566/download>
147. Ilaris (canakinumab) package insert. East Hanover, NJ: Novartis Pharmaceuticals Corporation; 2016 Dec.
148. Cavalli G, De Luca G, Campochiaro C, et al. Interleukin-1 blockade with high-dose anakinra in patients with COVID-19, acute respiratory distress syndrome, and hyperinflammation: a retrospective cohort study. *Lancet Rheumatol* 2020 Jun;2(6):e325-e331. [Epub ahead of print] PMID: 32501454
149. Geleris J, Sun Y, Platt J, et al. Observational study of hydroxychloroquine in hospitalized patients with COVID-19. *N Engl J Med* 2020;382:2411-2418. PMID: 32379955
150. Wang Y, Zhang D, Du G, et al. Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial. *Lancet* 2020;395(10236):1569-1578. PMID: 32423584

151. Rosenberg ES, Dufort EM, Udo T, et al. Association of treatment with hydroxychloroquine or azithromycin with in-hospital mortality in patients with COVID-19 in New York state. *JAMA* 2020;323:2493-2502. PMID: 32392282
152. Joyner MJ, Wright RS, Fairweather D, et al. Early safety indicators of COVID-19 convalescent plasma in 5,000 patients. *J Clin Invest*. Retrieved July 20, 2020. Available on the World Wide Web at: <https://doi.org/10.1172/JCI140200>.
153. [Retracted. – Data no longer included.] Mehra MR, Desai SS, Ruschitzka F, et al. Hydroxychloroquine or chloroquine with or without a macrolide for treatment of COVID-19: a multinational registry analysis. *Lancet* 2020 May 22. [Epub ahead of print]
154. Goldman JD, Lye D, Hui DS, et al. Remdesivir for 5 or 10 days in patients with severe Covid-19. *N Engl J Med* 2020 May 27; DOI:10.1056/NEJMoa2015301. [Epub Ahead of Print] PMID: 32459919
155. Cao Y, Wei J, Zou L, et al. Ruxolitinib in treatment of severe coronavirus disease 2019 (COVID-19): A multicenter, single-blind, randomized controlled trial. *J Allergy Clin Immunol* 2020 Jul;146(1):137-146. PMID: 32470486
156. Boulware DR, Pullen MF, Bangdiwala KA, et al. A randomized trial of hydroxychloroquine as postexposure prophylaxis for Covid-19. *N Engl J Med* 2020 Jun 3. [Epub Ahead of Print] PMID: 32492293
157. Li L, Zhang W, Hu Y, et al. Effect of convalescent plasma therapy on time to clinical improvement in patients with severe and life-threatening COVID-19: A randomized clinical trial. *JAMA* 2020 June 3; DOI:10.1001/jama.2020.10044. [Epub Ahead of Print] PMID: 32492084
158. Food and Drug Administration (FDA). Coronavirus (COVID-19) update: FDA revokes emergency use authorization for chloroquine and hydroxychloroquine. Retrieved June 15, 2020. Available on the World Wide Web at: <https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-revokes-emergency-use-authorization-chloroquine-and>
159. Horby P, Lim WS, Ebersone J, et al. Dexamethasone in hospitalized patients with COVID-19: Preliminary Report. *N Engl J Med* 2020 July 17. DOI:10.1056/NEJMoa2021436. [Epub Ahead of Print]
160. Moores LK, Tritschler T, Brosnahan S, et al. Prevention, diagnosis, and treatment of VTE in Patients with COVID-19: CHEST Guideline and Expert Panel Report. *Chest* 2020 June 2. [Epub Ahead of Print] PMID: 32502594
161. Bhimraj A, Morgan RL, Shumaker AH, et al. Infectious Diseases Society of America guidelines on the treatment and management of patients with COVID-19. Infectious Diseases Society of America. Accessed June 29, 2020. Available at on the World Wide Web at: <http://www.idsociety.org/COVID19guidelines>
162. Fernandez Cruz A, Ruiz-Antoran B, Gomez AM, et al. Impact of glucocorticoid treatment in SARS-CoV-2 infection mortality: a retrospective controlled cohort study. *Antimicrob Agents Chemother* 2020 June 22; DOI:10.1128/AAC.01168-20. [Epub Ahead of Print] PMID: 32571831
163. Nuffield Department of Population Health. No clinical benefit from use of lopinavir-ritonavir in hospitalised COVID-19 patients studied in RECOVERY. Retrieved June 30, 2020. Available on the World Wide Web at: <https://www.recoverytrial.net/news/no-clinical-benefit-from-use-of-lopinavir-ritonavir-in-hospitalised-covid-19-patients-studied-in-recovery>
164. Devereux SG, Giannopoulos G, Vrachatis DA, et al. Effect of colchicine vs standard care on cardiac and inflammatory biomarkers and clinical outcomes in patients hospitalized with coronavirus disease 2019: The GRECCO-19 randomized clinical trial. *JAMA* 2020 June 24; DOI:10.1001/jamanetworkopen.2020.13136. PMID: 32579195
165. Colcrys (colchicine) package insert. Deerfield, IL: Takeda Pharmaceuticals America, Inc.; 2020 May.

166. Mitigare (colchicine) capsule package insert. Eatontown, NJ: West-Ward Pharmaceuticals Corp; 2015 Nov.
167. Dalbeth N, Lauterio TJ, Wolfe HR. Mechanism of action of colchicine in the treatment of gout. *Clin Ther.* 2014;36:1465-1479.
168. Gilead Sciences, Inc. Gilead announces approval of Veklury (remdesivir) in Japan for patients with severe COVID-10. Retrieved July 8, 2020. Available on the World Wide Web at: <https://www.gilead.com/news-and-press/press-room/press-releases/2020/5/gilead-announces-approval-of-veklury-remdesivir-in-japan-for-patients-with-severe-covid19>
169. Gilead Sciences, Inc. European commission grants conditional marketing authorization for Gilead's Veklury (remdesivir) for treatment of COVID-19. Retrieved July 8, 2020. Available on the World Wide Web at: <https://www.gilead.com/news-and-press/press-room/press-releases/2020/7/european-commission-grants-conditional-marketing-authorization-for-gileads-veklury-remdesivir-for-the-treatment-of-covid19>
170. Herrero FS, Gimeno FP, Garcia PO, et al. Methylprednisolone added to tocilizumab reduces mortality in SARS-CoV-2 pneumonia: An observational study. *JIM* 2020 June 30. [Epub Ahead of Print] PMID: 32603493
171. Somers EC, Eschenauer GA, Troost JP, et al. Tocilizumab for treatment of mechanically ventilated patients with COVID-19. *CID* 2020 July 11. [Epub Ahead of Print] PMID: 32651997
172. Beyls C, Martin N, Hermida A, et al. Lopinavir-ritonavir treatment for COVID-19 infection in intensive care unit: risk of bradycardia. *Circ Arrhythm Electrophysiol* 2020 July 9. Available on the World Wide Web at: <https://doi.org/10.1161/CIRCEP.120.008798>
173. Decadron (dexamethasone) package insert. Whitehouse Station, NJ: Merck and Co., Inc.; 2019 May.
174. Huet T, Beaussier H, Voisin O, et al. Anakinra for severe forms of COVID-19: a cohort study. *Lancet Rheumatol* 2020;2:e393-e400.
175. Sciascia S, Apra F, Baffa A, et al. Pilot prospective open, single-arm multicentre study on off-label use of tocilizumab in patients with severe COVID-19. *Clin Exp Rheumatol* 2020;38(3):529-532. PMID: 32359035
176. Skipper CP, Pastick KA, engen NW, et al. Hydroxychloroquine in nonhospitalized adults with early COVID-19. *Ann Int Med* 2020. PMID: 32673060
177. Mitja O, Corbacho-Monne M, Ubals M, et al. Hydroxychloroquine for early treatment of adults with mild Covid-19: A randomized-controlled trial. *Clin Infect Dis.* 2020. PMID: 32674123
178. Roschewski M, Lionakis MS, Sharman JP, et al. Inhibition of Bruton tyrosine kinase in patients with severe COVID-19. *Sci Immunol* 2020;5(48):eabd0110. DOI: 10.1126/sciimmunol.abd0110. [Epub Ahead of Print] PMID: 32503877
179. Calquence (acalabrutinib) capsules package insert. Wilmington, DE: AstraZeneca Pharmaceuticals LP; 2019 Nov.
180. Imbruvica (ibrutinib) capsule package insert. Sunnyvale, CA: Pharmacyclics, Inc.; 2019 Nov.
181. Brukinsa (zanubrutinib) capsules package insert. San Mateo, CA: BeiGene USA, Inc.; 2019 Nov.
182. Cavalcanti AB, Zampieri FG, Rosa RG, et al. Hydroxychloroquine with or without azithromycin in mild-to-moderate Covid-19. *New Engl J Med* 2020. [Epub Ahead of Print] PMID: 3270953
183. Ramiro S, Mostard RLM, Magro-Checa C, et al. Historically controlled comparison of glucocorticoids with or without tocilizumab versus supportive care only in patients with COVID-19-associated cytokine storm syndrome: results of the CHIC study. *Ann Rheum Dis* 2020. [Epub Ahead of Print] PMID: 32719045
184. Olender SA, Perez KK, Go AS, et al. Remdesivir for severe COVID-19 versus a cohort receiving standard of care. *Clin Infect Dis* 2020. [Epub Ahead of Print] PMID: 32706859

185. Keller MJ, Kitsis EA, Arora S, et al. Effect of systemic glucocorticoids on mortality or mechanical ventilation in patients with COVID-19. *J Hosp Med* 2020;8:489-493.
186. Scarsi M, Piantoni S, Colombo E, et al. Association between treatment with colchicine and improved survival in a single-centre cohort of adult hospitalized patients with COVID-19 pneumonia and acute respiratory distress syndrome. *Ann Rheum Dis* 2020. [Epub Ahead of Print] Available on the World Wide Web at: <http://dx.doi.org/10.1136/annrheumdis-2020-217712> PMID: 32732245
187. Rayman G, Lumb A, Kennon B, et al. Concise advice on inpatient diabetes (COVID:Diabetes): Dexamethasone therapy in COVID-19 patients: Implications and guidance for the management of blood glucose in people with and without diabetes. Available on the World Wide Web at: [https://www.diabetes.org.uk/resources-s3/public/2020-06/COvID\\_Dex\\_v1.4.pdf](https://www.diabetes.org.uk/resources-s3/public/2020-06/COvID_Dex_v1.4.pdf)
188. Mastroianni A, Greco S, Apuzzo G, et al. Subcutaneous tocilizumab treatment in patients with severe COVID-19-related cytokine release syndrome: An observational cohort study. *Lancet* 2020. Available on the World Wide Web at: <http://doi.org/10.1016/j.eclinm.2020.100410>
189. Ivashchenko AA, Dmitriev KA, Vostokova NV, et al. Avifavir for treatment of patients with moderate COVID-19: Interim results of a Phase II/III multicenter randomized clinical trial. *Clin Infect Dis* 2020. [Epub Ahead of Print] PMID: 32770240
190. Jeronimo CMP, Farias MEL, Val FFA, et al. Methylprednisolone as adjunctive therapy for patients hospitalized with COVID-19 (Metcovid): A randomised, double-blind, Phase IIb, placebo-controlled trial. *Clin Infect Dis* 2020. [Epub Ahead of Print] PMID: 32785710
191. Nelson BC, Laracy J, Shoucri S, et al. Clinical outcomes associated with methylprednisolone in mechanically ventilated patients with COVID-19. *Clin Infect Dis* 2020. [Epub Ahead of Print] PMID: 32772069
192. Stauffer WM, Alpern JD, Walker PF. COVID-19 and dexamethasone: A potential strategy to avoid steroid-related *Strongyloides* hyperinfection. *JAMA* 2020;324(7):623-624. PMID:32761166
193. Klopfenstein T, Zayet S, Lohse A, et al. Impact of tocilizumab on mortality and/or invasive mechanical ventilation requirement in a cohort of 206 COVID-19 patients. *Int J Infect Dis* 2020. Available on the World Wide Web at: <https://doi.org/10.1016/j.ijid.2020.08.024>
194. Spinner CD, Gottlieb RL, Criner GJ, et al. Effect of remdesivir vs standard care on clinical status at 11 days in patients with moderate COVID-19: A randomized clinical trial. *JAMA* 2020. Available on the World Wide Web at: <https://doi:10.1001/jama.2020.16349>
195. Food and Drug Administration (FDA). Clinical memorandum: COVID-19 convalescent plasma emergency use authorization. Retrieved August 24, 2020. Available on the World Wide Web at: <https://www.fda.gov/media/141480/download>
196. Food and Drug Administration (FDA). Fact sheet for health care providers: emergency use authorization (EUA) of COVID-19 convalescent plasma for treatment of COVID-19 in hospitalized patients. Retrieved August 24, 2020. Available on the World Wide Web at: <https://www.fda.gov/media/141478/download>
197. Arshad S, Kilgore P, Chaudhry ZS, et al. Treatment with hydroxychloroquine, azithromycin, and combination in patients hospitalized with COVID-19. *Int J Infect Dis* 2020;97:396-403. PMID: 32623082
198. Ip A, Berry DA, Hansen E, et al. Hydroxychloroquine and tocilizumab therapy in COVID-19 patients – an observational study. *PLoS One* 2020;15:e0237693. PMID: 32790733
199. US Food and Drug Administration (FDA). FDA Medwatch: ivermectin intended for animals: letter to stakeholders - do not use in humans as a treatment for COVID-19. Retrieved April 14, 2020. Available on the World Wide Web at: <https://www.fda.gov/safety/medical-product-safety-information/ivermectin-intended-animals-letter-stakeholders-do-not-use-humans-treatment-covid-19>.
200. Stromectol (ivermectin) package insert. Whitehouse Station, NJ: Merck and Co., Inc.; 2018 Feb.



201. World Health Organization Guideline Panel. Corticosteroids for COVID-19. World Health Organization. Accessed September 3, 2020. Available on the World Wide Web at: <https://www.who.int/publications/i/item/WHO-2019-nCoV-Corticosteroids-2020.1>
202. Tomazini BM, Maia IS, Cavalcanti AB, et al. Effect of dexamethasone on days alive and ventilator-free in patients with moderate or severe acute respiratory distress syndrome and COVID-19: The CoDEX randomized clinical trial. *JAMA* 2020;324(13):1307-1316. PMID: 32876695
203. Dequin PF, Heming N, Meziani F, et al. Effect of hydrocortisone on 21-day mortality or respiratory support among critically ill patients with COVID-19: A randomized clinical trial. *JAMA* 2020;324(13):1298-1306. PMID: 32876689
204. Committee for the REMAP-CAP investigators. Effect of hydrocortisone on mortality and organ support in patients with severe COVID-19: The REMAP-CAP COVID-19 corticosteroid domain randomized clinical trial. *JAMA* 2020;324(13):1317-1329. PMID: 32876697
205. Abd-Elsalam S, Esmail ES, Khalaf M, et al. Hydroxychloroquine in the treatment of COVID-19: a multicenter randomized controlled study. *Am J Trop Med Hyg* 2020 Aug 14; DOI: 10.4269/ajtmh.20-0873. [Epub Ahead of Print] PMID: 32828135
206. Furtado RHM, Berwanger O, Fonseca HA, et al. Azithromycin in addition to standard of care versus standard of care alone in the treatment of patients admitted to the hospital with severe COVID-19 in Brazil (COALITION II): a randomised clinical trial. *Lancet* 2020 Sep 4; DOI: 10.1016/S0140-6736(20)31862-6. [Epub Ahead of Print] PMID: 32896292
207. Joyner MJ, Bruno KA, Klassen SA, et al. Safety Update: COVID-19 convalescent plasma in 20,000 hospitalized patients. *Mayo Clin Proc* 2020;95(9):1888-1897. PMID: 32861333
208. Salazar E, Christensen PA, Graviss EA, et al. Treatment of coronavirus disease 2019 patients with convalescent plasma reveals a signal of significantly decreased mortality. *Am J Pathol* 2020 Aug 11; DOI: 10.1016/j.ajpath.2020.08.001. [Epub Ahead of Print] PMID: 32795424
209. Abella BS, Jolkovsky EL, Biney BT, et al. Efficacy and safety of hydroxychloroquine vs placebo for pre-exposure SARS-CoV-2 prophylaxis among health care workers: a randomized clinical trial. *JAMA Intern Med.* Sep 30, 2020; DOI:10.1001/jamainternmed.2020.6319. [Epub Ahead of Print]
210. RECOVERY Collaborative Group. Lopinavir-ritonavir in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. *Lancet*. Retrieved October 5, 2020. Available on the World Wide Web at: [https://doi.org/10.1016/S0140-6736\(20\)32013-4](https://doi.org/10.1016/S0140-6736(20)32013-4)
211. Beigel JH, Tomashek KM, Dodd LE, et al. Remdesivir for the treatment of Covid-19 - final report. *N Engl J Med.* 2020; DOI:10.1056/NEJMoa2007764. PMID: 32445440
212. Agarwal A, Mukherjee A, Kumar G, et al. Convalescent plasma in the management of moderate COVID-19 in India: An open-label parallel-arm phase II multicentre randomized controlled trial (PLACID Trial). *medRxiv.* 2020. Available on the World Wide Web at: <https://www.medrxiv.org/content/10.1101/2020.09.03.20187252v2>
213. Burwick RM, Yawetz S, Stephenson KE, et al. Compassionate use of remdesivir in pregnant women with severe Covid-19. *Clin Infect Dis.* 2020. Available on the World Wide Web at: <https://doi.org/10.1093/cid/ciaa1466> PMID: 33031500
214. RECOVERY Collaborative Group. Effect of hydroxychloroquine in hospitalized patients with Covid-19. *New Engl J Med* 2020 Oct 8 [Epub ahead of print] PMID: 33031652
215. WHO Solidarity trial consortium. Repurposed antiviral drugs for COVID-19 – interim WHO SOLIDARITY trial results. *medRxiv.* 2020. Available on the World Wide Web at: <https://doi.org/10.1101/2020.10.15.20209817>

216. Lammers AJJ, Brohet RM, Theunissen REP, et al. Early hydroxychloroquine but not chloroquine use reduces ICU admission in COVID-19 patients. *Int J Infect Dis* 2020 Sep 29 [Epub ahead of print] PMID: 33007454
217. Rajasingham R, Bangdiwala AS, Nicol MR, et al. Hydroxychloroquine as pre-exposure prophylaxis for COVID-19 in healthcare workers: a randomized trial. *Clin Infect Dis* 2020 Oct 17 [Epub ahead of print] PMID: 33068425
218. Gupta S, Wang W, Hayek SS, et al. Association between early treatment with tocilizumab and mortality among critically ill patients with COVID-19. *JAMA Intern Med*. 2020 Oct 20; DOI: 10.1001/jamainternmed.2020.6252. [Epub Ahead of Print] PMID: 33080002
219. Stone JH, Frigault MJ, Serling-Boyd NJ, et al. Effect of tocilizumab in patients hospitalized with COVID-19. *New Engl J Med* 2020 Oct 21; DOI: 10.1056/NEJMoa2028836. [Epub Ahead of Print]
220. Salvarani C, Dolci G, Massari M, et al. Effect of tocilizumab vs standard care on clinical worsening in patients hospitalized with COVID-19 pneumonia: A randomized clinical trial. *JAMA Intern Med*. 2020 Oct 20; DOI: 10.1001/jamainternmed.2020.6615. [Epub Ahead of Print] PMID: 33080005
221. Hermine O, Mariette X, Tharaux PL, et al. Effect of tocilizumab vs usual care in adults hospitalized with COVID-19 and moderate or severe pneumonia: A randomized clinical trial. *JAMA Intern Med*. 2020 Oct 20; DOI: 10.1001/jamainternmed.2020.6820. [Epub Ahead of Print] PMID: 33080017
222. Veklury (remdesivir) injection package insert. Foster City, CA: Gilead Sciences, Inc; 2020 Oct.
223. U.S. Food and Drug Administration. FDA communication on remdesivir Emergency Use Authorization. Updated October 22, 2020. Available at: <https://www.fda.gov/media/137564/download>.
224. Food and Drug Administration (FDA). Fact sheet for health care providers: emergency use authorization (EUA) of Veklury (remdesivir) for hospitalized pediatric patients weighing 3.5 kg to less than 40 kg or hospitalized pediatric patients less than 12 years of age weighing at least 3.5 kg. Retrieved October 23, 2020. Available on the World Wide Web at <https://www.fda.gov/media/137566/download>.