COVID-19 Drug Therapy

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

Clinical Drug Information | Clinical Solutions

Highlights:

- There are no specific therapies approved by the U.S. Food and Drug Administration (FDA) for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus that causes coronavirus disease 2019 COVID-19. Several agents are being used under clinical trial and compassionate use protocols based on *in vitro* activity (against SARS-CoV-2 or related viruses) and on limited clinical experience. Efficacy has not been established for any drug therapy.
- Antimicrobials with potential activity against SARS-CoV-2:
    - Chloroquine – *In vitro* and limited clinical data suggest potential benefit.
    - Hydroxychloroquine – *In vitro* and limited clinical data suggest potential benefit.
    - Lopinavir; Ritonavir - Role in the treatment of COVID-19 is unclear. Preclinical data suggested potential benefit; however, more recent data has failed to confirm.
    - Remdesivir – Investigational and available only through expanded access and study protocols; several large clinical trials are underway.
    - Favipiravir – Investigational use is being studied.
- Adjunctive / supportive care:
    - Azithromycin – Used in some protocols based on theoretical mechanism and limited preliminary data as adjunct therapy.
    - Immunomodulating agents - Used in some protocols based on theoretical mechanisms and limited preliminary data as adjunct therapy.
    - COVID-19 convalescent plasma – Investigational use is being studied.
    - Corticosteroids - Not recommended for viral pneumonia; use may be considered for patients with refractory shock or acute respiratory distress syndrome.
    - Inhaled pulmonary vasodilators - No evidence for routine in acute respiratory failure; use may be considered in specific patients with ARDS as a temporizing measure.
    - Anticoagulation – Venous thromboembolism prophylaxis with low molecular weight heparin (LMWH) recommended for all hospitalized patients.
    - 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.

- 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.

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

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

Antimicrobials with potential activity against SARS-CoV-2:

Chloroquine:

- Classification: Antimalarial
- Rationale for Use: Chloroquine has *in vitro* activity against SARS-CoV-2 and may have immunomodulating properties.(13) (14) (15) (17)
- Mechanism of Action: Mechanisms may include inhibition of viral enzymes or processes such as viral DNA and RNA polymerase, viral protein glycosylation, virus assembly, new virus particle transport, and virus release. Other mechanisms may also involve ACE2 cellular receptor inhibition, acidification at the surface of the cell membrane inhibiting fusion of the virus, and immunomodulation of cytokine release.(14) (15) (29) (30) (31) (32) (33)
- FDA Emergency Use Authorization (EUA) (66) (67)
    - Chloroquine is not FDA-approved for the treatment of COVID-19.
    - EUA is to facilitate the availability of chloroquine during the COVID-19 pandemic to treat patients for whom a clinical trial is not available, or participation is not feasible.
    - The EUA states treatment is for adult and adolescent patients weighing 50 kg or more who are hospitalized with COVID-19.
    - Authorized chloroquine is limited to product supplied from the Strategic National Stockpile (SNS) and will be distributed to authorized heath care systems and providers.
- Evidence / Experience:
    - Pre-clinical data *in vitro* suggest chloroquine has activity has activity against SARS-CoV-2.(13) (14) (15)
    - There have been reports of potential benefit in inhibiting the exacerbation of pneumonia patients with SARS-CoV-2 infection; however, specific data are not available.(13)
    - Some protocols include recommendations for use.(12) (21) (22)
    - Additional data regarding clinical efficacy for COVID-19 are being evaluated.(16) (31)

- Safety Concerns: (46) (49)
    - Risk of cardiac arrhythmias (e.g., QT prolongation)
    - Risk of retinal damage, especially with long term use
    - Caution in patients with G6PD deficiency
    - Caution in diabetics
    - Significant drug interactions

Hydroxychloroquine:

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

    - A parallel-group, randomized trial (n = 62) of hospitalized patients with non-severe COVID-19 compared 5 days for hydroxychloroquine to standard treatment.(69)
        - Fever recovery time was shortened in the hydroxychloroquine group (2.2 days) compared to standard therapy (3.2 days).
        - Cough recovery time was shortened in the hydroxychloroquine group (2 days) compared to standard therapy (3.1 days).
    - A prospective review assessed virologic and clinical outcomes of 11 hospitalized patients who received hydroxychloroquine and azithromycin.(88)
        - Within 5 days, 1 patient died, 2 were transferred to the ICU, and 1 patient had therapy discontinued due to QT prolongation.
        - Nasopharyngeal swabs were still positive for SARS-CoV-2 in 8 of 10 patients 5 to 6 days after treatment initiation.
    - Some protocols have recommendations for use.(12) (21)
    - Additional data regarding clinical efficacy for COVID-19 are being evaluated.(16) (31)
- Safety Concerns: (47) (49)
    - Risk of cardiac arrhythmias (e.g., QT prolongation)
    - Risk of retinal damage, especially with long term use
    - Caution in patients with G6PD deficiency
    - Caution in diabetics
    - Significant drug interactions

Lopinavir; Ritonavir:

- Classification: HIV Protease Inhibitor
- Rationale for Use: *In vitro* and animal model studies show potential activity for other coronaviruses (SARS-CoV and MERS-CoV).(4) (52) (53) (54)
- Mechanism of Action: Lopinavir and ritonavir may bind to M^{pro}, a key enzyme for coronavirus replication. This may suppress coronavirus activity.(55)
- Evidence / Experience:
    - Pre-clinical data show activity for other coronaviruses.(4) (52) (53) (54)
    - A randomized, controlled, open-label trial involving hospitalized patients with confirmed SARS-CoV-2 infection (n = 199), analyzed treatment with lopinavir; ritonavir.(23)
        - Treatment with lopinavir; ritonavir for 14 days was not associated with a difference from standard of care in the time to clinical improvement (hazard ratio 1.24; 95% CI, 0.9 to 1.72).
        - Mortality at 28 days was similar between groups (19.2% vs. 25%, respectively).
        - The percentages of patients with detectable viral RNA were similar. In a modified ITT analysis, lopinavir; ritonavir had a median time to clinical improvement that was shorter by 1 day (hazard ratio, 1.39%; 95% CI, 1 to 1.91).
    - 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.
- Comment: ESICM and SCCM Surviving Sepsis Campaign recommendations suggest against the routine use of lopinavir; ritonavir in critically ill adults with COVID-19.(26)
- Safety Concerns: (45) (49)
    - Risk of cardiac arrhythmias (e.g., QT prolongation)
    - Caution in patients with hepatic disease or hepatitis
    - Significant drug interactions

Remdesivir (GS-5734):

- Classification: Investigational Nucleoside Analogue
- Rationale for Use: Remdesivir is a broad-spectrum antiviral with *in vitro* activity against coronaviruses.(10) (14) (38) (39) (41) (42) (43) (44)
- Mechanism of Action: Remdesivir is a monophosphoramidate prodrug of remdesivir-triphosphate (RDV-TP), an adenosine analog that acts as an inhibitor of RNA-dependent RNA polymerases (RdRps). Remdesivir-TP competes with adenosine-triphosphate for incorporation into nascent viral RNA chains. Once incorporated into the viral RNA at position i, RDV-TP terminates RNA synthesis at position i+3. Because RDV-TP does not cause immediate chain termination (i.e., 3 additional nucleotides are incorporated after RDV-TP), the drug appears to evade proofreading by viral exoribonuclease (an enzyme thought to excise nucleotide analog inhibitors).(10) (14) (38) (39) (41) (42) (43) (44) (45)
- Evidence / Experience:
    - Remdesivir has been administered to several hundred patients with confirmed, severe SARS-CoV-2 infections in the United States, Europe, and Japan through Expanded Access or Compassionate Use programs. (9)
    - In preclinical trials, remdesivir has demonstrated significant activity against coronavirus and a high genetic barrier to resistance.(10) (14)
        - *In vitro* data found remdesivir exerts potent antiviral activity against a clinical isolate of SARS-CoV-2; [half-maximal effective concentration (EC50) = 0.77 mcgM, half-cytotoxic concentration (CC50) greater than 100 mcgM, selective index (SI) greater than 129.87].
        - Data suggest remdesivir (GS-5735) inhibits activity of 2002 SARS-CoV, MERS-CoV, and bat CoV strains that have the ability to replicate in human epithelial cells and mediate entry via human CoV receptors.
        - Remdesivir has shown prophylactic and therapeutic efficacy against 2002 SARS-CoV in a mouse model.
        - Resistance mutations have not been identified.
    - Several clinical trials evaluating the efficacy of remdesivir in patients infected with SARS-CoV-2 are currently being conducted. Data from some trials are expected by April 2020.(9)

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:
    - Data regarding clinical efficacy for COVID-19 are being evaluated.(73) (74)

Adjunctive/Supportive therapy:

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:
    - In an open-label, non-randomized clinical trial of hydroxychloroquine (n = 26), azithromycin was administered in combination with hydroxychloroquine to prevent bacterial superinfection in 6 patients.(27)
        - Preliminary data suggest the potential for benefit as adjunct therapy.
        - On day 6, all patients treated with the combination (hydroxychloroquine and azithromycin) were virologically cured compared to 57.1% of patients treated with hydroxychloroquine alone (n= 20).
    - In a retrospective analysis of a multicenter cohort study (n = 349) in patients with MERS-CoV, 136 patients received macrolide therapy in combination with antiviral treatment.(28)
        - Macrolide therapy was not associated with a reduction in 90-day mortality compared to the control group (adjusted OR: 0.84; 95% CI: 0.47 to 1.51; p = 0.56).
        - Sensitivity analysis excluding patients who received macrolides after day 3 showed similar results (adjusted OR: 0.7; 95% CI: 0.39 to 1.28; p = 0.25).
    - A prospective review assessed virologic and clinical outcomes of 11 hospitalized patients who received hydroxychloroquine and azithromycin.(88)
        - Within 5 days, 1 patient died, 2 were transferred to the ICU, and 1 patient had therapy discontinued due to QT prolongation.
        - Nasopharyngeal swabs were still positive for SARS-CoV-2 in 8 of 10 patients 5 to 6 days after treatment initiation.

- Safety Concerns: (48) (49)
    - Risk of cardiac arrhythmias (e.g., QT prolongation)
    - Significant drug interactions

Tocilizumab:

- Classification: Interleukin-6 (IL-6) Receptor-Inhibiting Monoclonal Antibody
- Rationale for Use: Cytokine release syndrome may be a component of severe disease in COVID-19 patients.(24) (25) (89) (90)
- Mechanism of Action: Tocilizumab inhibits IL-6-mediated signaling by competitively binding to both soluble and membrane-bound IL-6 receptors. 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)
- Evidence / Experience:
    - 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 C-reactive protein levels all improved in these patients; however, no comparators were reported.
    - Some protocols include recommendations for use.(21)
    - Additional data regarding clinical efficacy for COVID-19 are being evaluated.(51) (84) (86) (87)
- Safety Concerns: (52)
    - Risk of GI perforation
    - Risk of hepatotoxicity
    - Caution in patients with thrombocytopenia and neutropenia
    - Infusion-related reactions

Leronlimab:

- Classification: Investigational Humanized Monoclonal Antibody to the Chemokine Receptor CCR5.(70)
- Rationale for Use: Cytokine release syndrome may be a component of severe disease in COVID-19 patients.(24) (89) (90)
- Mechanism of Action: Leronlimab may enhance immune response while mitigating cytokine storm.(71)
- Evidence / Experience:
    - An Emergency Investigational New Drug Application (eIND) has been granted by the FDA for treatment of patients experiencing respiratory complications due to SARS-CoV-2.(71)

- Use currently being evaluated in a small number of patients with severe COVID-19 via the FDA eIND.(71)

Sarilumab:

- Classification: Interleukin-6 (IL-6) Receptor-Inhibiting Monoclonal Antibody
- Rationale for Use: Cytokine release syndrome may be a component of severe disease in COVID-19 patients.(24) (89) (90)
- Mechanism of Action: Sarilumab binds to both soluble and membrane-bound interleukin-6 (IL-6) receptors (sIL-6R and mIL-6R) and has been shown to inhibit IL-6-mediated signaling through these receptors. IL-6 is a pleiotropic pro-inflammatory cytokine produced by a variety of cell types including T-cells and B-cells, lymphocytes, monocytes, and fibroblasts. IL-6 has been shown to be involved in diverse physiological processes such as T-cell activation, induction of immunoglobulin secretion, initiation of hepatic acute phase protein synthesis, and stimulation of hematopoietic precursor cell proliferation and differentiation.(72) (78)
- Evidence / Experience:
  - Data regarding clinical efficacy for COVID-19 are being evaluated.(72) (76) (77) (82) (83) (84) (85)
- Safety Concerns: (78)
  - Risk of GI perforation
  - Risk of hepatotoxicity
  - Caution in patients with thrombocytopenia and neutropenia

Baricitinib:

- Classification: Janus kinase (JAK) inhibitor
- 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 cytokine or growth factor receptor interactions on the cellular membrane to influence cellular processes of immune cell function and hematopoiesis. JAK-mediated signaling is pivotal in immune activation, as cytokine receptors are expressed on most immune cells. Within the signaling pathway, JAKs phosphorylate and activate signal transducers and activators of transcription proteins (STATs), which modulate intracellular activity including gene expression. Baricitinib modulates the signaling pathway at the point of JAKs, preventing the phosphorylation and activation of STATs. Cytokine signaling is transmitted through pairing of JAKs. Baricitinib has greater affinity for JAK1, JAK2, and TYK2, relative to JAK3. In human leukocytes, baricitinib inhibits cytokine induced STAT phosphorylation mediated by JAK1/JAK2, JAK1/JAK3, JAK1/TYK2, or JAK2/TYK2 with comparable potencies.(92)
- Evidence / Experience:
  - Data regarding clinical efficacy for COVID-19 are being evaluated.(93) (96)
- Safety Concerns: (92)
  - 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)

COVID-19 Convalescent Plasma: (22)

- Classification: Plasma collected from persons who have recovered from COVID-19 that may contain antibodies to SARS-CoV-2
- Rationale for Use: Clinical trials are being conducted to evaluate the use of COVID-19 convalescent plasma to treat patients with severe or immediately life-threatening COVID-19 infections. COVID-19 convalescent plasma is not intended for prevention of the infection.
  - To participate in these trials, investigators should submit requests to the FDA for investigational use under the traditional IND regulatory pathway.
  - In addition to clinical trials, licensed physicians may obtain COVID-19 convalescent plasma for an individual patient through the process of single patient eINDs.
- Evidence / Experience:
  - In a case series of 5 critically ill patients with confirmed COVID-19 and acute respiratory distress syndrome (ARDS), patients received convalescent plasma.(65)
    - Treatment: 2 consecutive transfusions of 200 mL to 250 mL of convalescent plasma (total dose: 400 mL) with a SARS-CoV-2-specific antibody (IgG) titer greater than 1:1,000 on the same day it was obtained from the donor.
    - Patient criteria included:
      - Severe pneumonia with rapid progression and continuously high viral load despite antiviral treatment
      - PAO_2/FIO_2 less than 300
      - Mechanical ventilation
    - After plasma infusion, body temperature normalized within 3 days in 4 of 5 patients, Sequential Organ Failure Assess (SOFA) score decreased and PAO_2/FIO_2 increased within 12 days.
    - Viral loads decreased and became negative within 12 days after the transfusion with the SARS-CoV-2-specific ELISA and neutralizing antibody titers increased after the transfusion.
    - ARDS resolved in 4 patients by day 12 after the transfusion and 3 patients were weaned from mechanical ventilation within 2 weeks of treatment.

Corticosteroids:

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

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)
- 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 nitric oxide is used, a short trial with preestablished criteria for ongoing use or discontinuation is recommended.(26) (61)
- Additional data regarding clinical efficacy for COVID-19 are being evaluated.(58) (59)

Anticoagulation:

- Venous thromboembolism (VTE) prophylaxis with LMWH is recommended for all hospitalized patients with COVID-19 infection in the absence of contraindications, which include active bleeding or platelet count less than 25 x 10^9/L. Use fondaparinux in patients with a history of heparin-induced thrombocytopenia and mechanical thromboprophylaxis in patients where anticoagulants are contraindicated or unavailable.(80) (81) (91) (95)
- Therapeutic-intensity anticoagulation is not recommended in the management of COVID-19 in the absence of confirmed VTE.(95)
- Elevated D-dimer has been noted in COVID-19 patients requiring hospitalization and has been associated with increased mortality.(80) (81) (91)

NSAIDs:

- 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)
- Acetaminophen may be considered for temperature control.(20) (26)
- ESICM and SCCM Surviving Sepsis Campaign recommendations suggest acetaminophen for temperature control in critically ill adults with COVID-19 who develop fever.(26)

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)

- Metered-dose inhalers (MDI) are preferred due to the potential for generation of aerosols that may increase the risk of viral transmission with nebulized therapy. (57) (61)
- Due to concerns about supply chain interruption, some institutions are developing an MDI canister reassignment protocol to address potential shortages. An MDI canister reassignment protocol should emphasize hand hygiene and dual canister disinfection and avoid inadvertent sources of transmission.(57) (79)

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.

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.
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 website: https://www.clinicaltrials.gov/ct2/results?cond=Coronavirus&term=&type=&rslt=&age_v=&gndr=&intr=remdesivir&titles=&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 Februrary 2020. Accessed 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.
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.
23. Cao B, Wang Y, Wen D, et al. A trial of lopinavir-ritonavir in adults hospitalized with severe Covid-19. NEJM 2020 Mar 18. [Epub ahead of print] 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 rapid guidelines of the management of critically ill adults with coronavirus disease 2019 (pre-publication). Available on the World Wide Web at: https://www.esicm.org/ssc-covid19-guidelines/.

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-cytodyns-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 Daikouku 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-kevzarar-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 (TOCIVID). 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 1.0. Accessed April 6, 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). Accessed April 6, 2020. Available on the World Wide Web at: https://clinicaltrials.gov/ct2/show/NCT04320277?cond=COVID&intr=Baricitinib&draw=2&rank=1