



## COVID-19 Drug Therapy – Potential Options

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Clinical Drug Information | Clinical Solutions

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### Highlights:

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- There are no specific therapies approved by the U.S. Food and Drug Administration (FDA) for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus that causes coronavirus disease 2019 COVID-19. Several agents are being used under clinical trial and compassionate use protocols based on *in vitro* activity (against SARS-CoV-2 or related viruses) and on limited clinical experience. Efficacy has not been established for any drug therapy.
  - 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.
  - Azithromycin – Used in some protocols based on theoretical mechanism and limited preliminary data as adjunct therapy.
  - Tocilizumab – Immunomodulating agent used in some protocols based on theoretical mechanism and limited preliminary data as adjunct therapy.
  - COVID-19 convalescent plasma – Investigational use is being studied.
- Corticosteroid therapy is not recommended for viral pneumonia; however, use may be considered for patients with refractory shock or acute respiratory distress syndrome.
- The FDA continues to investigate the use of NSAIDs in patients with COVID-19 symptoms. Concern for potential worsening of COVID-19 symptoms has been suggested, but confirmatory clinical data is lacking at this time.

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)

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

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### 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)
- Evidence / Experience:
  - Pre-clinical data *in vitro* suggest chloroquine has activity against SARS-CoV-2.(13) (14) (15)
  - There have been reports of potential benefit in inhibiting the exacerbation of pneumonia patients with SARS-CoV-2 infection; however, specific data are not available.(13)
  - Some protocols include recommendations for use.(12) (21) (22)
  - Additional data regarding clinical efficacy for COVID-19 are being evaluated.(16) (31)
- Safety Concerns: (46) (49)
  - 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)
- Evidence / Experience:
  - Pre-clinical *in vitro* data suggest hydroxychloroquine has activity against SARS-CoV-2.(12) (15) (17) (18) (21)
  - One *in vitro* study suggests that hydroxychloroquine may be more potent than chloroquine.(15)

- Hydroxychloroquine exhibited a higher *in vitro* antiviral effect compared to chloroquine when drug was added prior to the viral challenge.
      - The EC50 values for chloroquine were greater than 100 microM at 24 hours and 18.01 microM at 48 hours.
      - The EC50 values for hydroxychloroquine were 6.25 microM at 24 hours and 5.85 microM at 48 hours.
    - An open-label, non-randomized clinical trial compared hydroxychloroquine treatment (n = 26) to an untreated negative control group.(27)
      - Preliminary data showed the proportion of patients that had negative PCR results significantly differed between treated patients and untreated controls.
      - On day 6, 70% of hydroxychloroquine-treated patients were virologically cured compared to 12.5% in the untreated control group.
    - 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<sup>pro</sup>, 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)

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## Adjunctive/Supportive therapy:

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### 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).
- 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.(25)
- 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)
- Safety Concerns: (52)
  - Risk of GI perforation
  - Risk of hepatotoxicity
  - Caution in patients with thrombocytopenia and neutropenia
  - Infusion-related reactions

## **Other Immunomodulators:**

- Other immunomodulating agents (e.g., alfa-interferon, sarilumab) are being evaluated as adjunctive therapy.(7) (40)

## **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 emergency Investigational New Drug Applications (eINDs).

- Patients eligible under the eIND:
  - Must have laboratory confirmed COVID-19
  - Must have severe or immediate life-threatening COVID-19
    - Severe disease defined as:
      - Dyspnea,
      - Respiratory rate 30 breaths/minute or greater,
      - Blood oxygen saturation 93% or less,
      - Partial pressure of arterial oxygen to fraction of inspired oxygen ratio less than 300, and/or
      - Lung infiltration greater than 50% within 24 to 48 hours
    - Life-threatening disease defined as:
      - Respiratory failure,
      - Septic shock, and/or
      - Multiple organ dysfunction or failure
  - Must provide informed consent
- To obtain authorization for use of COVID-19 convalescent plasma:
  - For emergency situations (response required in less than 4 hours) or extenuating circumstances precluding submission of the expanded access application form 3926.
    - Provider may obtain verbal authorization by contacting the FDA's Office of Emergency Operations at 1-866-300-4374.
    - If verbal authorization is given, the requestor must agree to submit form 3926 within 15 working days.
  - For requests that are not highly time sensitive (response provided within 4 to 8 hours).
    - Provider must complete form 3926 (<https://www.fda.gov/media/98616/download>) and submit the form by email to CBER\_eIND\_Covid-19@FDA.HHS.gov.
    - Completed form should include a brief clinical history of the patient, including diagnosis, current therapy, and rationale for requesting COVID-19 convalescent plasma.
    - Form should include information regarding where the COVID-19 convalescent plasma will be obtained.
    - FDA will review the request and, if approved, send requesting provider a confirmatory email that includes the eIND number.
- Collection of COVID-19 convalescent plasma:
  - Plasma must only be collected from recovered individuals if they are eligible to donate blood. Required testing must be performed and donation must be suitable.
  - Additional considerations for donor eligibility
    - Prior diagnosis of COVID-19 documented by a laboratory test
    - Complete resolution of symptoms at least 14 days prior to donation
    - Female donors negative for HLA antibodies or male donors
    - Negative results for COVID-19 either from:
      - 1 or more nasopharyngeal swab specimens
      - Molecular diagnostic test from blood



- SARS-CoV-2 neutralizing antibody titers may be conducted (optimally greater than 1:320)
- Container label must include the following statement, “Caution: New Drug— Limited by Federal (or United States) law to investigational use.”

#### **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)

#### **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)

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



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