به نام حضرت دوست

Pharmacological therapy for COVID-19

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Pharmacological therapy for COVID-19

- **Antiviral Therapy**
- **Immune-Based Therapy**

1.NIH guideline
2.Uptodate

Antiviral Therapy

- Remdesivir
- **Favipiravir**
- **Chloroquine**
- **Hydroxychloroquine**
- **Lopinavir/Ritonavir**

Remdesivir

- Pharmacologic Category:
- Anitiviral agent

Remdesivir is the only Food and Drug Administration-approved drug for the treatment of COVID-19. (22 October 2020)

Remdesivir-Cont

- Mechanism of Action:
- an inhibitor of the SARS-CoV-2 RNA-dependent RNA polymerase (RdRp), which is essential for viral replication.
- Remdesivir is an adenosine nucleotide prodrug that is metabolized to the pharmacologically active nucleoside triphosphate metabolite after being distributed into cells.
- Remdesivir triphosphate (GS-443902) acts as an adenosine triphosphate analog and competes for incorporation into RNA chains by the SARS-CoV-2 RdRp, resulting in delayed chain termination during viral RNA replication.
- Remdesivir triphosphate can also inhibit viral RNA synthesis due to incorporation into the viral RNA template.

Remdesivir-Cont

- Use: Labeled Indications:
- **Coronavirus disease 2019 (COVID-19):**
- Treatment of COVID-19 in adult and pediatric patients (12 years of age and older weighing at least 40 kg) requiring hospitalization.

- Remdesivir should only be administered in a hospital or in a health care setting capable of providing acute care comparable to inpatient hospital care.

Remdesivir-Cont

- *Dosing:*
- 200 mg as a single dose on day 1, followed by 100 mg once daily for 4 days or until hospital discharge, whichever is first; may extend duration up to 10 days in patients without substantial clinical improvement at day 5
- May give as monotherapy or in combination with dexamethasone (NIH 2020).

Remdesivir-Cont

- *Patients requiring low-flow supplemental oxygen:*
- May give as monotherapy or in combination with dexamethasone (NIH 2020).
- *Patients requiring high-flow supplemental oxygen or noninvasive ventilation:*
- NIH guidelines recommend only using in this population in combination with dexamethasone (NIH 2020).
- *Patients requiring invasive mechanical ventilation or extracorporeal membrane oxygenation:*
- NIH guidelines recommend only using in this population in combination with dexamethasone (NIH 2020).

Dosing: Renal Impairment: Adult

- eGFR ≥30 mL/minute: No dosage adjustment necessary.
- eGFR <30 mL/minute: Manufacturer's labeling does not recommend use; however, significant toxicity with a short duration of therapy (eg, 5 to 10 days) is unlikely
- Benefits may outweigh the risks in select patients

- In 1 observational report, 46 patients with acute kidney injury and/or chronic kidney disease received remdesivir at the usual recommended dosage for an average of 5 days and did not experience severe rises in AST/ALT or changes in kidney function attributable to the drug

Remdesivir-Cont

- Dosing: Hepatic Impairment: Adult
- **Baseline hepatic impairment:** There are no dosage adjustments provided in the manufacturers labeling (has not been studied).
- **Hepatoxicity during therapy:**
- ALT >10 times the ULN: Consider remdesivir discontinuation.
- ALT elevation AND signs or symptoms of liver inflammation: Discontinue remdesivir.

Dosing: Pediatric

- Infants and Children <12 years:
- Lyophilized powder only:
- 3.5 kg to <40 kg: IV: Loading dose: 5 mg/kg/dose on day 1, followed by 2.5 mg/kg/dose once daily
- ≥40 kg: IV: Loading dose: 200 mg on day 1, followed by 100 mg once daily

Dosing: Pediatric-Cont

- Children ≥12 years and Adolescents:
- <40 kg: Lyophilized powder only: IV: Loading dose: 5 mg/kg/dose on day 1, followed by 2.5 mg/kg/dose once daily

- ≥40 kg: Injection solution or lyophilized powder: IV: Loading dose: 200 mg on day 1, followed by 100 mg once daily (Chiotos 2020; manufacturer's labeling).

Dosing: Pediatric-Cont

- Duration:

- In patients not requiring mechanical ventilation or extracorporeal membrane oxygenation (ECMO), recommended treatment duration is 5 days or until hospital discharge, whichever is first
- If patient does not improve clinically, may extend duration to a total of 10 days.
- A 10-day treatment duration is recommended for patients who require mechanical ventilation or ECMO
- however, some experts have suggested starting with a 5-day course and extending to 10 days on a case-by-case basis

Remdesivir-Cont

Administration: Adult **IV:** Administer as an IV infusion over 30 to 120 minutes.

Adverse Reactions:

- 1% to 10%:
- Endocrine & metabolic:
- Hyperglycemia
- increased serum glucose
- Hepatic: Acute hepatic failure
- increased serum alanine aminotransferase
- increased serum aspartate aminotransferase
- Renal: Acute renal failure
- decreased estimated GFR (eGFR
- increased serum creatinine
- Miscellaneous: Fever
- <1%:
- Renal: Decreased creatinine clearance
- Frequency not defined: Miscellaneous:
- Infusion related reaction (including hypotension, nausea, vomiting, diaphoresis, and shivering)

Pregnancy Considerations

Based on preliminary data, maternal treatment with remdesivir during pregnancy had a high rate of recovery (Burwick 2020).

Use should not be withheld if otherwise needed (NIH 2020).

Breast-Feeding Considerations

- It is not known if remdesivir is present in breast milk.

- According to the manufacturer, the decision to breastfeed during therapy should consider the risk of infant exposure, the benefits of breastfeeding to the infant, and the benefits of treatment to the mother.

Remdesivir-Cont

- **Monitoring Parameters:**

✓Baseline and during remdesivir administration when clinically appropriate:

✓ Hepatic function tests (ALT, AST, bilirubin, alkaline phosphatase, prothrombin time);

✓ renal function tests (serum creatinine, CrCl);

✓signs/symptoms of infusion reaction

Antivirals:Favipiravir

- RNA polymerase inhibitor
- Favipiravir may hasten SARS-CoV-2 RNA clearance, although data are limited.

- In a randomized, open-label trial from Russia that included hospitalized patients who were on room air or receiving supplemental oxygen through mask or nasal cannula, the rate of viral RNA clearance from upper respiratory tract specimens at day 5 was higher with favipiravir compared with standard of care, which included hydroxychloroquine or chloroquine (clearance rates of 62 versus 36 percent) [98].

- In a non-randomized study from China of patients with non-severe disease (including oxygen saturation >93 percent), use of favipiravir was associated with faster rates of viral clearance (median time to clearance 4 versus 11 days) and more frequent radiographic improvement (in 91 versus 62 percent by day 14) compared with lopinavir-ritonavir [99].
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Antivirals:Favipiravir

Dosing:

1600 Bid on day 1 then 600 bid

Total duration: 7-14 days

Antiviral Therapy

NIH uptodate

- **Chloroquine or Hydroxychloroquine With or Without Azithromycin:**
- The Panel **recommends against** the use of **chloroquine** or **hydroxychloroquine** with or without **azithromycin** for the treatment of COVID-19 in hospitalized patients **(AI)**.
- In nonhospitalized patients, the Panel **recommends against** the use of **chloroquine** or **hydroxychloroquine** with or without **azithromycin** for the treatment of COVID-19, except in a clinical trial **(AI)**.
- The Panel **recommends against** the use of **high-dose chloroquine** (600 mg twice daily for 10 days) for the treatment of COVID-19 **(AI)**.

Antiviral Therapy

NIH

- **Lopinavir/Ritonavir and Other HIV Protease Inhibitors:**
- The Panel **recommends against** using **lopinavir/ritonavir (AI)** or **other HIV protease inhibitors (AIII)** to treat COVID-19, except in a clinical trial.
- **Ivermectin:**
- The Panel **recommends against** the use of **ivermectin** for the treatment of COVID-19, except in a clinical trial **(AIII)**.

Immune-Based Therapy

- **Blood-derived products:**

✓convalescent plasma

✓ immunoglobulin products

- **Immunomodulators:**

✓**Corticosteroids**

✓Interleukin (IL)-1 inhibitors (e.g., **anakinra**).

✓**Interferon beta**

✓**Interleukin-6 Inhibitors (sarilumab, tocilizumab, siltuximab)**

✓**Kinase Inhibitors**

Immune-Based Therapy

- **Blood-derived products:**

- There are insufficient data for the COVID-19 Treatment Guidelines Panel (the Panel) to recommend either for or against the use of the following blood-derived products for the treatment of COVID-19:

- **COVID-19 convalescent plasma**
- **Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) immunoglobulins**

Immune-Based Therapy

- **Blood-derived products:**

- The Panel **recommends against** the use of the following blood-derived products for the treatment of COVID-19, except in a clinical trial:

✓**Mesenchymal stem cells (AII)**

✓**Non-SARS-CoV-2-specific intravenous immunoglobulin (IVIG) (AIII)**.

Immune-Based Therapy

Immunomodulators

Immune-Based Therapy

Immunomodulators:

Corticosteroids:

- **Dexamethason:**
- Long-acting potent synthetic glucocorticoid with minimal mineralocorticoid activity
- minimal effect on sodium balance and fluid volume.
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- **Glucocorticoid activity includes:**
- anti-inflammatory
- immunosuppressive
- anti-proliferative
- vasoconstrictive effects

- **Potent anti-inflammatory effects may mitigate or prevent the systemic inflammatory response associated with severe COVID-19.**

Immune-Based Therapy

- **Corticosteroids:**
- If dexamethasone is not available, an alternative corticosteroid such as:
- **prednisone, methylprednisolone, or hydrocortisone can be used (BIII).**
- **The approximate total daily dose equivalencies for these glucocorticoids to dexamethasone 6 mg (PO or IV) are:**
- prednisone 40 mg
- methylprednisolone 32 mg
- hydrocortisone 160 mg.

Immune-Based Therapy

Corticosteroids:

- **Long-acting corticosteroid**: dexamethasone; half-life: 36 to 72 hours, administer once daily.
- **Intermediate-acting corticosteroids**: prednisone and methylprednisolone; half-life: 12 to 36 hours, administer once daily or in two divided doses daily.
- **Short-acting corticosteroid**: hydrocortisone; half-life: 8 to 12 hours, administer in two to four divided doses daily.

- **Hydrocortisone is commonly used to manage septic shock in patients with COVID-19**

Immune-Based Therapy

Immunomodulators:

- Interferons **(Alfa, Beta)**
- are a family of cytokines with antiviral properties.
- They have been suggested as a potential treatment for COVID-19 because of their *in vitro* and *in vivo* antiviral properties.

Immune-Based Therapy

Immunomodulators:

- **Interferons:**
- **Recommendation:**
- The COVID-19 Treatment Guidelines Panel **recommends against** the use of **interferons** for the treatment of patients with severe or critical COVID-19, except in a clinical trial **(AIII)**.

- There are insufficient data to recommend either for or against the use of **interferon beta** for the treatment of early (i.e., <7 days from symptom onset) mild and moderate COVID-19.

Immune-Based Therapy

Immunomodulators:

- **Interleukin-1 Inhibitors:**

- There are insufficient data to recommend for or against the use of interleukin (IL)-1 inhibitors, such as **anakinra**, for the treatment of COVID-19.

- **Rationale for Use in Patients with COVID-19:**
- Endogenous IL-1 is elevated in patients with COVID-19 and other conditions, such as severe CAR T-cell-mediated CRS.
- Case reports and case series have described favorable responses to anakinra in patients with these syndromes, including a survival benefit in patients with sepsis and reversal of cytokine storm after tocilizumab failure in adults with MAS

Immune-Based Therapy

Immunomodulators:

- **Interleukin-6 Inhibitors:**

- There are two classes of Food and Drug Administration (FDA)-approved IL-6 inhibitors:
- anti-IL-6 receptor monoclonal antibodies (e.g., sarilumab, tocilizumab) and anti-IL-6 monoclonal antibodies (siltuximab).
- These classes of drugs have been evaluated for the management of patients with COVID-19 who have systemic inflammation.

Immune-Based Therapy

Immunomodulators:

- **Interleukin-6 Inhibitors:**

- The Panel **recommends against** the use of anti-IL-6 receptor monoclonal antibodies (e.g., **sarilumab, tocilizumab**)
- or anti-IL-6 monoclonal antibody (**siltuximab**) for the treatment of COVID-19, except in a clinical trial **(BI)**.
- Preliminary, unpublished data from randomized, controlled trials failed to demonstrate efficacy of sarilumab or tocilizumab in patients with COVID-19.
- There are only limited, unpublished data describing the efficacy of siltuximab in patients with COVID-19

Immune-Based Therapy

Immunomodulators:

- **Kinase Inhibitors: Bruton's Tyrosine Kinase Inhibitors and Janus Kinase Inhibitors:**
- **Recommendation:**
- The COVID-19 Treatment Guidelines Panel **recommends against** the use of **Bruton's tyrosine kinase (BTK) inhibitors**, such as **acalabrutinib, ibrutinib,** and **zanubrutinib;** and **Janus kinase (JAK) inhibitors**, such as **baricitinib, ruxolitinib,** and **tofacitinib;** for the treatment of COVID-19, except in a clinical trial **(AIII)**.

Other agents that have been proposed for COVID-19 therapy

- sofosbuvir plus daclatasvir
- famotidine
- colchicine
- vitamin D
- and zinc
- **Clinical data thus far are insufficient to support a role for these agents, and their use for COVID-19 should be limited to clinical trials.**

Figure 1. Recommendations for Pharmacologic Management of Patients with COVID-19 Based on Disease Severity

DISEASE SEVERITY	PANEL'S RECOMMENDATIONS *(Recommendations are listed in order of preference in each category below; however, all options are considered acceptable.)*
Not Hospitalized ***or*** **Hospitalized but Does Not Require Supplemental Oxygen**	No specific antiviral or immunomodulatory therapy recommended The Panel **recommends against** the use of **dexamethasone (AI)** See the Remdesivir section for a discussion of the data on using this drug in hospitalized patients with moderate COVID-19.[a]
Hospitalized and Requires Supplemental Oxygen **(but Does Not Require Oxygen Delivery Through a High-Flow Device, Noninvasive Ventilation, Invasive Mechanical Ventilation, or ECMO)**	**Remdesivir** 200 mg IV for one day, followed by remdesivir 100 mg IV once daily for 4 days or until hospital discharge, whichever comes first **(AI)**[b,c,d] ***or*** **Remdesivir** (dose and duration as above) plus **dexamethasone**[e] 6 mg IV or PO for up to 10 days or until hospital discharge, whichever comes first **(BIII)**[r] If **remdesivir** cannot be used, **dexamethasone**[e] may be used instead **(BIII)**
Hospitalized and Requires Oxygen Delivery Through a High-Flow Device or Noninvasive Ventilation	**Dexamethasone**[d] plus **remdesivir** at the doses and durations discussed above **(AIII)**[r] ***or*** **Dexamethasone**[d,e] at the dose and duration discussed above **(AI)**
Hospitalized and Requires Invasive Mechanical Ventilation or ECMO	**Dexamethasone**[d,e] at the dose and duration discussed above **(AI)** ***or*** **Dexamethasone**[e] plus **remdesivir** for patients who have recently been intubated at the doses and durations discussed above **(CIII)**[r]