SARS-CoV-2 Treatment

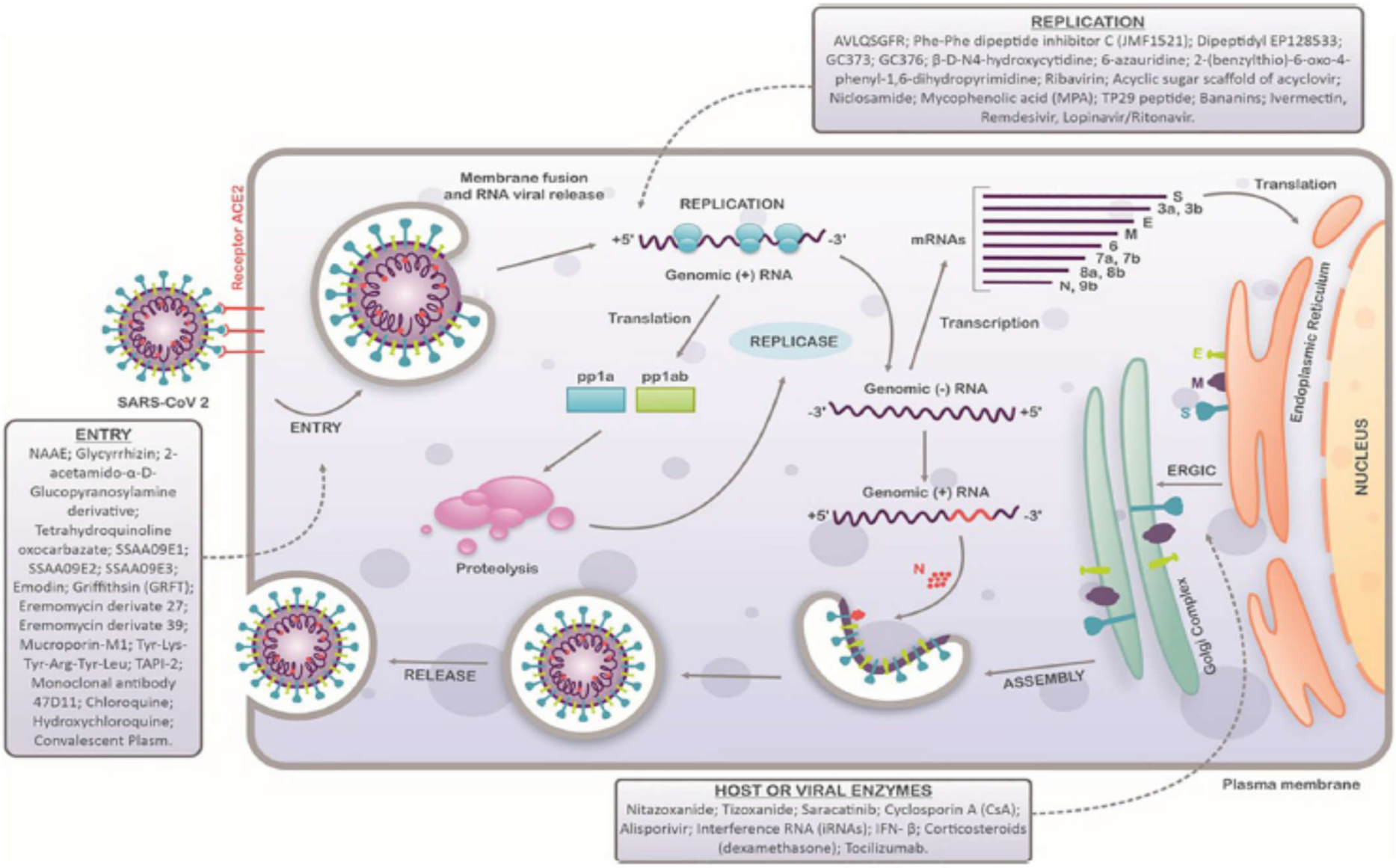
MD.S.KALANTARI

- Because severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) replication leads to many of the clinical manifestations of COVID-19, antiviral therapies are being investigated for the treatment of COVID-19.

- These drugs inhibit viral entry (via the angiotensin-converting enzyme 2 [ACE2] receptor and transmembrane serine protease 2 [TMPRSS2]), viral membrane fusion and endocytosis, or the activity of the SARS-CoV-2 3-chymotrypsin-like protease (3CLpro) and the RNA-dependent RNA polymerase.

- Because viral replication may be particularly active early in the course of COVID-19, antiviral therapy may have the greatest impact before the illness progresses into the hyperinflammatory state that can characterize the later stages of disease, including critical illness

- For this reason, it is necessary to understand the role of antivirals in treating mild, moderate, severe, and critical illness in order to optimize treatment for people with COVID-19.


REPLICATION
AVLQSGFR; Phe-Phe dipeptide inhibitor C (JMF1521); Dipeptidyl EP128533; GC373; GC376; β-D-N4-hydroxycytidine; 6-azauridine; 2-(benzylthio)-6-oxo-4-phenyl-1,6-dihydropyrimidine; Ribavirin; Acyclic sugar scaffold of acyclovir; Niclosamide; Mycophenolic acid (MPA); TP29 peptide; Bananins; Ivermectin, Remdesivir, Lopinavir/Ritonavir.
Membrane fusion and RNA viral release
Receptor ACE2
SARS-CoV 2
ENTRY
REPLICATION
+5'
-3'
Genomic (+) RNA
Translation
pp1a
pp1ab
REPLICASE
Proteolysis
Genomic (-) RNA
-3'
+5'
Genomic (+) RNA
+5'
-3'
Transcription
mRNAs
S
3a, 3b
E
M
6
7a, 7b
8a, 8b
N, 9b
Translation
E
M
S
Endoplasmic Reticulum
NUCLEUS
ERGIC
Golgi Complex
N
ASSEMBLY
RELEASE
Plasma membrane
ENTRY
NAAE; Glycyrrhizin; 2-acetamido-α-D-Glucopyranosylamine derivative; Tetrahydroquinoline oxocarbazate; SSAA09E1; SSAA09E2; SSAA09E3; Emodin; Griffithsin (GRFT); Eremomycin derivate 27; Eremomycin derivate 39; Mucroporin-M1; Tyr-Lys-Tyr-Arg-Tyr-Leu; TAPI-2; Monoclonal antibody 47D11; Chloroquine; Hydroxychloroquine; Convalescent Plasm.
HOST OR VIRAL ENZYMES
Nitazoxanide; Tizoxanide; Saracatinib; Cyclosporin A (CsA); Alisporivir; Interference RNA (iRNAs); IFN- β; Corticosteroids (dexamethasone); Tocilizumab.

Antiviral Drugs That Are Approved for the Treatment of COVID-19

Remdesivir

- Remdesivir is a nucleotide prodrug of an adenosine analog. It binds to the viral RNA-dependent RNA polymerase and inhibits viral replication by terminating RNA transcription prematurely.

- Intravenous remdesivir is approved by the Food and Drug Administration (FDA) for the treatment of COVID-19 in hospitalized adult and pediatric patients

Considerations in Pregnancy

- Remdesivir should not be withheld from pregnant patients if it is otherwise indicated. Pregnant patients were excluded from the clinical trials that evaluated the safety and efficacy of remdesivir for the treatment of COVID-19, but preliminary reports of remdesivir use in pregnant patients from small studies and case reports are reassuring.

Ritonavir-Boosted Nirmatrelvir (Paxlovid)

- Nirmatrelvir (PF-07321332) is an orally bioavailable protease inhibitor that is active against MPRO, a viral protease that plays an essential role in viral replication by cleaving the 2 viral polyproteins. It has demonstrated antiviral activity against all coronaviruses that are known to infect humans.

Molnupiravir

- Molnupiravir is the oral prodrug of beta-D-N4-hydroxycytidine (NHC), a ribonucleoside that has broad antiviral activity against RNA viruses. NHC uptake by viral RNA-dependent RNA-polymerases results in viral mutations and lethal mutagenesis

- Molnupiravir has potent antiviral activity against SARS-CoV-2. As a mutagenic ribonucleoside antiviral agent, there is a theoretical risk that molnupiravir will be metabolized by the human host cell and incorporated into the host DNA, leading to mutations.

- Molnupiravir has been evaluated in 2 in vivo rodent mutagenicity assays. One study produced results that were equivocal; in the other study, there was no evidence for mutagenicity.

- **Recommendations**
- Nirmatrelvir 300 mg with ritonavir 100 mg (Paxlovid) orally twice daily for 5 days, initiated as soon as possible and within 5 days of symptom onset in those aged ≥12 years and weighing ≥40 kg (AIIa).

- Molnupiravir 800 mg orally twice daily for 5 days, initiated as soon as possible and within 5 days of symptom onset in those aged ≥18 years **ONLY** when none of the above options can be used (CIIa).

Considerations in Pregnancy

- The FDA EUA states that molnupiravir is not recommended for use in pregnant patients due to concerns about the instances of fetal toxicity observed during animal studies. However, when other therapies are not available, pregnant people with COVID-19 who are at high risk of progressing to severe disease may reasonably choose molnupiravir therapy after being fully informed of the risks, particularly those who are beyond the time of embryogenesis

Anti-SARS-CoV-2 Antibody Products

- Anti-SARS-CoV-2 monoclonal antibodies (mAbs) that target the spike protein have been shown to have a clinical benefit in treating SARS-CoV-2 infection.
- Some anti-SARS-CoV-2 mAbs have been found to be effective in preventing SARS-CoV-2 infection in household contacts of infected patients and during SARS-CoV-2 outbreaks in skilled nursing and assisted living facilities

Anti-SARS-CoV-2 Monoclonal Antibodies That Have Received Emergency Use Authorizations From the Food and Drug Administration

- Currently, 3 anti-SARS-CoV-2 mAb products have received Emergency Use Authorizations (EUAs) from the Food and Drug Administration (FDA) for the treatment of mild to moderate COVID-19 in nonhospitalized patients with laboratory-confirmed SARS-CoV-2 infection who are at high risk for progressing to severe disease and/or hospitalization.

- • **Bamlanivimab plus etesevimab**: These are neutralizing mAbs that bind to different, but overlapping, epitopes in the spike protein RBD of SARS-CoV-2.
- • The distribution of bamlanivimab plus etesevimab was paused in the United States because both the Gamma (P.1) and Beta (B.1.351) variants have reduced susceptibility to bamlanivimab and etesevimab.

- **Casirivimab plus imdevimab**: These are recombinant human mAbs that bind to non overlapping epitopes of the spike protein RBD of SARS-CoV-2.

- **Sotrovimab**: This mAb was originally identified in 2003 from a SARS-CoV survivor. It targets an epitope in the RBD of the spike protein that is conserved between SARS-CoV and SARS-CoV-2.

- **Recommendations**
- • The COVID-19 Treatment Guidelines Panel (the Panel) recommends using 1 of the following anti- SARS-CoV-2 mAb products to treat nonhospitalized patients with mild to moderate COVID-19 who are at high risk of clinical progression

Considerations in Pregnancy

- monoclonal antibodies should not be withheld from pregnant patients when otherwise appropriate. Pregnancy is one of the medical conditions listed in the EUA eligibility criteria for bamlanivimab in combination with etesevimab, and this is one combination recommended for pregnant patients, particularly those with ≥1 additional risk factor

Immunomodulators Under Evaluation for the Treatment of COVID-19

Corticosteroids

- Multiple randomized trials indicate that systemic corticosteroid therapy improves clinical outcomes and reduces mortality in hospitalized patients with COVID-19 who require supplemental oxygen

- There is no observed benefit of systemic corticosteroids in hospitalized patients with COVID-19 who do not require supplemental oxygen

Interleukin-6 Inhibitors

- Interleukin (IL)-6 is a pleiotropic, **proinflamatory** cytokine produced by a variety of cell types, including lymphocytes, monocytes, and fibroblasts. Infection by SARS-CoV induces a dose-dependent production of IL-6 from bronchial epithelial cells

- There are 2 classes of Food and Drug Administration (FDA)-approved IL-6 inhibitors: anti-IL-6 receptor monoclonal antibodies (mAbs) (e.g., sarilumab, tocilizumab) and anti-IL-6 mAbs (i.e., siltuximab). These drugs have been evaluated in patients with COVID-19 who have systemic inflammation.

- **Recommendations**
- • See Therapeutic Management of Hospitalized Adults With COVID-19 for the COVID-19 Treatment Guidelines Panel's (the Panel) recommendations on the use of IL-6 inhibitors (e.g., sarilumab, tocilizumab) in hospitalized patients who require supplemental oxygen, high-flow oxygen, noninvasive ventilation (NIV), or mechanical ventilation

- • The Panel recommends against the use of anti-IL-6 mAb therapy (i.e., siltuximab) for the treatment of COVID-19, except in a clinical trial (BIII).

Considerations in Pregnancy

- There are insufficient data to determine whether there is a tocilizumab-associated risk for major birth defects or miscarriage. mAbs are actively transported across the placenta as pregnancy progresses (with the greatest transfer occurring during the third trimester), and this may affect immune responses in the exposed fetus.

- Given the paucity of data, current recommendations advise against the use of tocilizumab during pregnancy. Whether to use tocilizumab during pregnancy should be a joint decision between the pregnant individual and their health care provider, and the decision-making process should include a discussion of the potential risks and benefits.

Kinase Inhibitors: Janus Kinase Inhibitors and Bruton's Tyrosine Kinase Inhibitors

- Janus kinase (JAK) inhibitors interfere with phosphorylation of signal transducer and activator of transcription (STAT) proteins that are involved in vital cellular functions, including signaling, growth, and survival

- These kinase inhibitors are proposed as treatments for COVID-19 because they can prevent phosphorylation of key proteins involved in the signal transduction that leads to immune activation and inflammation (e.g., the cellular response to proinflammatory cytokines such as interleukin [IL]-6).

- JAK inhibitors, particularly baricitinib, have theoretical direct antiviral activity through interference with viral endocytosis, potentially preventing SARS-CoV-2 from entering and infecting susceptible cells.

- **Recommendations**
- • See Therapeutic Management of Hospitalized Adults With COVID-19 for the COVID-19 Treatment Guidelines Panel's (the Panel) recommendations on the use of baricitinib and tofacitinib for certain hospitalized patients who require oxygen supplementation.

Considerations in Pregnancy

- There is a paucity of data on the use of JAK inhibitors in pregnancy. As small molecule-drugs, JAK inhibitors are likely to pass through the placenta, and therefore fetal risk cannot be ruled out. Decisions regarding the administration of JAK inhibitors must include shared decision-making between the pregnant individual and their health care provider, considering potential maternal benefit and fetal risks

- Pregnancy registries provide some outcome data on tofacitinib use during pregnancy for other conditions (e.g., ulcerative colitis, rheumatoid arthritis, psoriasis). Among the 33 cases reported, pregnancy outcomes were similar to those among the general population

Antithrombotic Therapy in Patients with COVID-19

- COVID-19 has been associated with inflammation and a prothrombotic state accompanied by increases in fibrinogen and D-dimer. In some studies, elevations in these markers have been associated with worse clinical outcomes. Hospitalized patients with COVID-19 are at high risk for venous thromboembolism (VTE).

- At a minimum, hospitalized COVID-19 patients should receive prophylactic doses of anticoagulants, such as low molecular weight heparin (LMWH) or unfractionated heparin, for the duration of their hospitalization

- The Panel recommends using prophylactic-dose anticoagulation for pregnant patients hospitalized for manifestations of COVID-19 unless otherwise contraindicated

- Because pregnant patients have not been included in most clinical trials evaluating therapeutic anticoagulation in the setting of COVID-19, there is currently insufficient evidence to recommend either for or against therapeutic anticoagulation for pregnant patients with COVID-19 in the absence of a known VTE

Supplements

- **Vitamin C**

• There is insufficient evidence for the COVID-19 Treatment Guidelines Panel (the Panel) to recommend either for or against the use of vitamin C for the treatment of COVID-19.

- **Vitamin D**

• There is insufficient evidence for the Panel to recommend either for or against the use of vitamin D for the treatment of COVID-19.

- **Zinc**

• There is insufficient evidence for the Panel to recommend either for or against the use of zinc for the treatment of COVID-19

Therapeutic Management of Nonhospitalized Adults With COVID-19

PATIENT DISPOSITION	PANEL'S RECOMMENDATIONS
Not Requiring Hospitalization or Supplemental Oxygen, As Determined by a Health Care Provider During an ED, In-Person, or Telehealth Visit	Provide symptomatic management for patients who are not at high risk of disease progression. For patients who are at high risk of progressing to severe COVID-19 (treatments are listed in order of preference, based on efficacy and convenience of use): • **Ritonavir-boosted nirmatrelvir (Paxlovid)**; *or* • **Sotrovimab**; *or* • **Remdesivir**; *or* • **Molnupiravir** The Panel **recommends against** the use of **dexamethasone** or **other systemic glucocorticoids** in the absence of another indication **(AIII)**.[a]

Discharged From Hospital Inpatient Setting in Stable Condition and Does Not Require Supplemental Oxygen	The Panel **recommends against** continuing the use of **remdesivir (AIIa)**, **dexamethasone (AIIa)**, or **baricitinib (AIIa)** after hospital discharge.
Discharged From Hospital Inpatient Setting and Requires Supplemental Oxygen *For those who are stable enough for discharge but who still require oxygen*[b]	There is insufficient evidence to recommend either for or against the continued use of remdesivir, dexamethasone, and/or baricitinib. Review the text below when considering the use of any of these agents after hospital discharge.

Discharged From ED Despite New or Increasing Need for Supplemental Oxygen

When hospital resources are limited, inpatient admission is not possible, and close follow-up is ensured[c]

The Panel recommends using **dexamethasone** 6 mg PO once daily for the duration of supplemental oxygen (dexamethasone use **should not** exceed 10 days) with careful monitoring for AEs **(BIII)**.

There is insufficient evidence to recommend either for or against the use of remdesivir. When considering the use of remdesivir, review the text below for more information.

The Panel **recommends against** the use of **baricitinib** in this setting, except in a clinical trial **(AIII)**.

Patient Risk Scoring Tool

A risk score of ≥ 7 is prioritized.

Factor	Score
Age *(e.g. 50 years old = 5)*	1 point for every 10 years
BMI ≥ 35	1
Diabetes	1
Hypertension	1
Unvaccinated or partially vaccinated (not boosted)	2
Pregnancy	4
Immunocompromised status (see below for defintion)	4

Rank	Agent	Timing of Administration from Symptom Onset	Efficacy *Note: Studies were performed prior to omicron variant*
1	**Nirmatrelvir/ritonavir (Paxlovid)** 300mg/100mg BID PO x 5 days	≤5 days	EPIC-HR study (n = 2,246): Paxlovid **reduced** risk of hospitalization or death by **89%** (within 3 days of symptom onset) and **88%** (within 5 days of symptom onset) vs. placebo.[1]
2	**Sotrovimab (Xevudy)** 500mg IV x 1	≤5 days	COMET-ICE study interim analysis: **relative risk reduction of 85%** in hospitalization or death vs. placebo.[2]
3	**Remdesivir (Veklury)** 200mg IV x 1, then 100mg daily on days 2 and 3	≤7 days	PINETREE study (n = 562): Three day outpatient remdesivir course had a **87% lower risk** of hospitalization or death than placebo.[3]
4	**Molnupiravir (Lagevrio)** 800mg PO BID x 5 days	≤5 days	MOVe-OUT study (n = 1,433): Molnupiravir **~ 31% lower** rate of hospitalization or death through day 29 vs. placebo (hazard ratio, 0.69; 95% CI, 0.48 to 1.01).[4]

Therapeutic Management of Hospitalized Adults With COVID-19 Based on Disease Severity

Hospitalized but Does Not Require Supplemental Oxygen	The Panel **recommends against** the use of **dexamethasone (AIIa)** or **other corticosteroids (AIII)**.[a] There is insufficient evidence to recommend either for or against the routine use of remdesivir. For patients at high risk of disease progression, remdesivir may be appropriate.
Hospitalized and Requires Supplemental Oxygen	Use 1 of the following options: • **Remdesivir**[b,c] (e.g., for patients who require minimal supplemental oxygen) **(BIIa)** • **Dexamethasone plus remdesivir**[b,c] **(BIIb)** • **Dexamethasone (BI)** For patients on dexamethasone with rapidly increasing oxygen needs and systemic inflammation, add a second immunomodulatory drug[d] (e.g., baricitinib[e] or tocilizumab[e]) **(CIIa)**.

Hospitalized and Requires Oxygen Through a High-Flow Device or NIV	Use 1 of the following options: • **Dexamethasone (AI)** • **Dexamethasone plus remdesivir**[b] **(BIII)** For patients with rapidly increasing oxygen needs and systemic inflammation, add either **baricitinib**[e] **(BIIa)** or **IV tocilizumab**[e] **(BIIa)** to 1 of the 2 options above.[d,f]
Hospitalized and Requires MV or ECMO	• **Dexamethasone (AI)**[g] For patients who are within 24 hours of admission to the ICU: • **Dexamethasone plus IV tocilizumab (BIIa)** If IV tocilizumab is not available or not feasible to use, IV **sarilumab** can be used **(BIIa)**.

Drug Name	Dosing Regimen	Comments
Remdesivir	RDV 200 mg IV once, then RDV 100 mg IV once daily for 4 days or until hospital discharge.	• If the patient progresses to more severe illness, complete the course of RDV. • For a discussion on using RDV in patients with renal insufficiency, see Remdesivir.
Dexamethasone	DEX 6 mg IV or PO once daily for up to 10 days or until hospital discharge.	• If DEX is not available, an equivalent dose of another corticosteroid may be used. • For more information, see Corticosteroids.
Baricitinib	Baricitinib dose is dependent on eGFR; duration of therapy is up to 14 days or until hospital discharge.	• eGFR ≥60 mL/min/1.73 m^2: Baricitinib 4 mg PO once daily • eGFR 30 to <60 mL/min/1.73 m^2: Baricitinib 2 mg PO once daily • eGFR 15 to <30 mL/min/1.73 m^2: Baricitinib 1 mg PO once daily • eGFR <15 mL/min/1.73 m^2: Baricitinib **is not recommended**.
Tofacitinib	Tofacitinib 10 mg PO twice daily for up to 14 days or until hospital discharge.	• Use as an alternative immunomodulatory drug if baricitinib is not available or not feasible to use **(BIIa)**. • eGFR <60 mL/min/1.73 m^2: Tofacitinib 5 mg PO twice daily
Tocilizumab	Tocilizumab 8 mg/kg actual body weight (up to 800 mg) administered as a single IV dose.	• In clinical trials, a third of the participants received a second dose of tocilizumab 8 hours after the first dose if no clinical improvement was observed.

thanks for your attention

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)**[f] 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)**[f] *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)**[f]