Pharmacotherapy of Covid-19 in elderly patients

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- The virus (novel coronavirus disease 2019) that causes COVID-19 is designated severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).
- The management of COVID-19 in hospitalized adults is very important. Our approach (**UpToDate**) to hospital management evolves rapidly as clinical data emerge. Clinicians should consult their own local protocols for management, which may differ from our approach.

Symptoms associated with coronavirus disease 2019 (COVID-19)

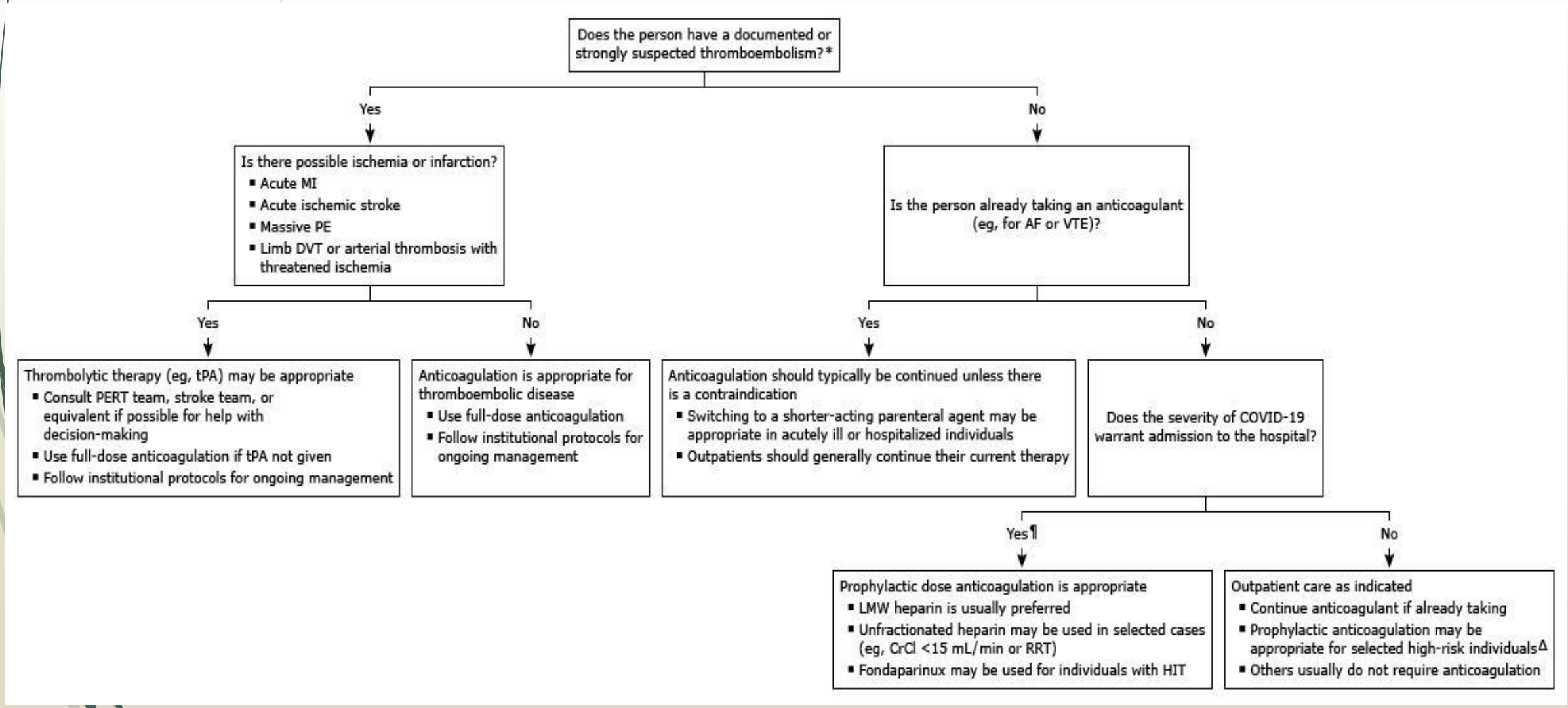
Symptoms that may be seen in patients with COVID-19
■ Cough
■ Fever
■ Myalgias
■ Headache
■ Dyspnea (new or worsening over baseline)
■ Sore throat
■ Diarrhea
■ Nausea/vomiting
■ Anosmia or other smell abnormalities
■ Ageusia or other taste abnormalities
■ Rhinorrhea and/or nasal congestion
■ Chills/rigors
■ Fatigue
■ Confusion
■ Chest pain or pressure

Laboratory features associated with severe COVID-19

Abnormality	Possible threshold
Elevations in:	
▪ D-dimer	>1000 ng/mL (normal range: <500 ng/mL)
▪ CRP	>100 mg/L (normal range: <8.0 mg/L)
▪ LDH	>245 units/L (normal range: 110 to 210 units/L)
▪ Troponin	>2× the upper limit of normal (normal range for troponin T high sensitivity: females 0 to 9 ng/L; males 0 to 14 ng/L)
▪ Ferritin	>500 mcg/L (normal range: females 10 to 200 mcg/L; males 30 to 300 mcg/L)
▪ CPK	>2× the upper limit of normal (normal range: 40 to 150 units/L)
Decrease in:	
▪ Absolute lymphocyte count	<800/microL (normal range for age ≥21 years: 1800 to 7700/microL)

Prevention of and evaluation for venous thromboembolism

We favor pharmacologic prophylaxis of venous thromboembolism for all hospitalized patients with COVID-19, consistent with recommendations from several expert societies (algorithm).



Managing chronic medications

❑ ACE inhibitors/ARBs

Patients receiving angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) should continue treatment with these agents if there is no other reason for discontinuation (eg, hypotension, acute kidney injury).

This approach is supported by multiple guidelines panels. Despite speculation that patients with COVID-19 who are receiving these agents may be at increased risk for adverse outcomes, accumulating evidence does not support an association between renin angiotensin system inhibitor use and more severe disease.

Managing chronic medications

❑ Statins and aspirin

We make a point of continuing statins in hospitalized patients with COVID-19 who are already taking them. We also continue aspirin unless there are concerns about bleeding risk.

We do not initiate statins or aspirin in patients with COVID-19 who do not have pre-existing indications for them. Although observational studies had suggested a potential mortality benefit in hospitalized patients with COVID-19, randomized trials have not confirmed these findings

Managing chronic medications

❑ Immunomodulatory agents

Use of immunosuppressing agents has been associated with increased risk for severe disease with other respiratory viruses, and the decision to discontinue prednisone, biologics, or other immunosuppressive drugs in the setting of COVID-19 must be determined on a case-by-case basis.

❑ COVID-19 Therapy

The optimal approach to treatment of COVID-19 is evolving. Trial data suggest a **mortality benefit** with dexamethasone as well as with adjunctive tocilizumab or baricitinib and a possible clinical benefit with remdesivir. Based on the pathogenesis of COVID-19, approaches that target the virus itself (eg, antivirals, passive immunity, interferons) are more likely to work early in the course of infection, whereas approaches that modulate the immune response may have more impact later in the disease course (figure 1).

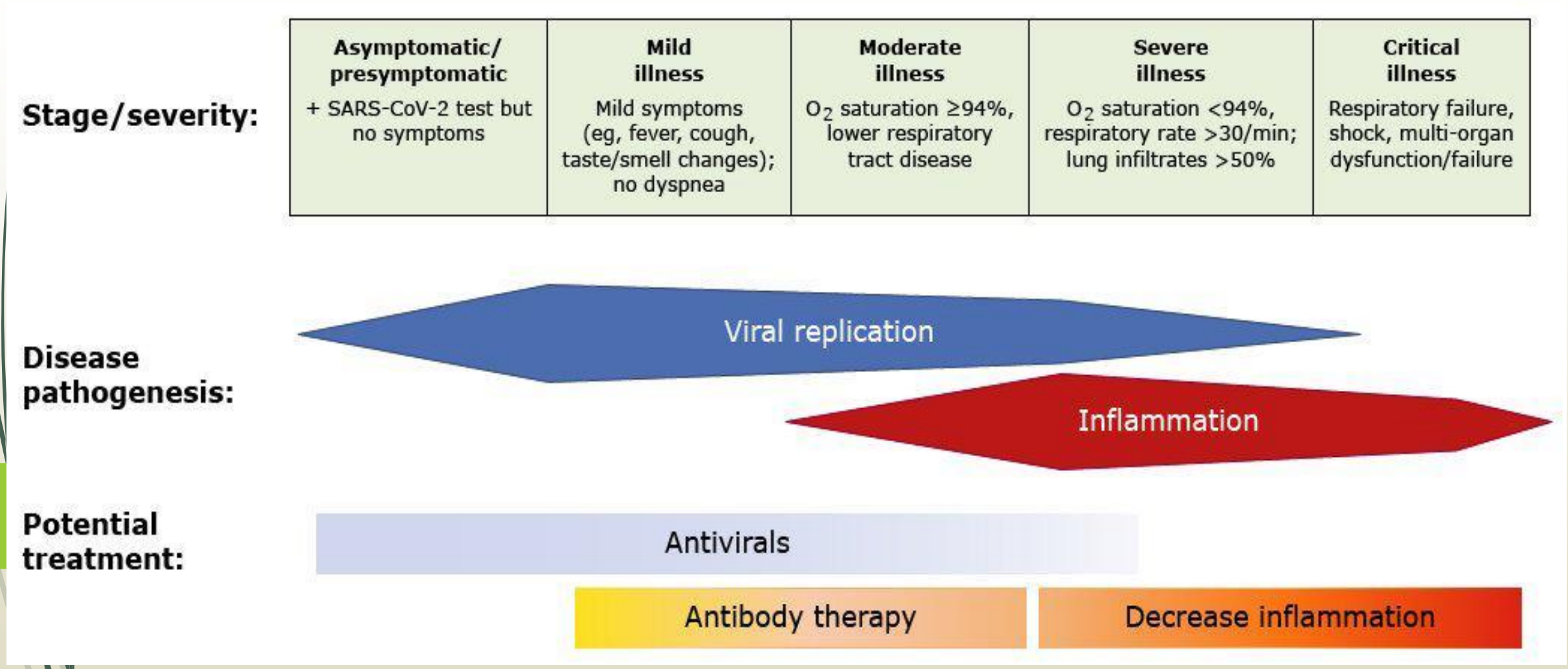


Figure 1. Potential targets of COVID-19 therapies by stage of infection

Patients without oxygen requirement

- For patients who have no oxygen requirement and who have no risk factors for progression to severe disease, we suggest supportive care only.

- For patients with *risk factors for severe disease* who were hospitalized for COVID-19, we suggest remdesivir. Trial data suggest that remdesivir may *improve time to recovery* in such patients, although the magnitude of effect is uncertain.

- We suggest not using dexamethasone, which may be associated with worse outcomes in such patients.

Patients without oxygen requirement

- For patients with risk factors for severe disease who were hospitalized for a non-COVID-19 reason and have incidental SARS-CoV-2 infection (or acquired infection during hospitalization), we evaluate eligibility for therapies authorized for certain high-risk outpatients, specifically monoclonal antibody therapy, nirmatrelvir-ritonavir, and remdesivir. Eligibility criteria entail having nonsevere symptomatic COVID-19 with symptom onset within the prior 5 to 10 days and being high risk for progression (ie, because of age or comorbidities).
- In many locations, supplies of monoclonal antibodies and nirmatrelvir-ritonavir are severely limited, and remdesivir may be the most accessible option for hospitalized patients.

Patients with oxygen requirement/severe disease

- For patients who require oxygen supplementation because of COVID-19, the approach to COVID-19-specific therapy ***depends on the level of support***.
- For patients receiving **low-flow supplemental oxygen**, we suggest **low-dose dexamethasone** and **remdesivir** (Grade 2C). If they have significantly elevated inflammatory markers (eg, C-reactive protein **[CRP] level ≥75 mg/L**), have escalating oxygen requirements (a rapid increase of 6 L/min or more wiyhin 24 hours) despite dexamethasone, and are within 96 hours of hospitalization, we suggest **adding either baricitinib or tocilizumab** on a case-by-case basis (Grade 2C).

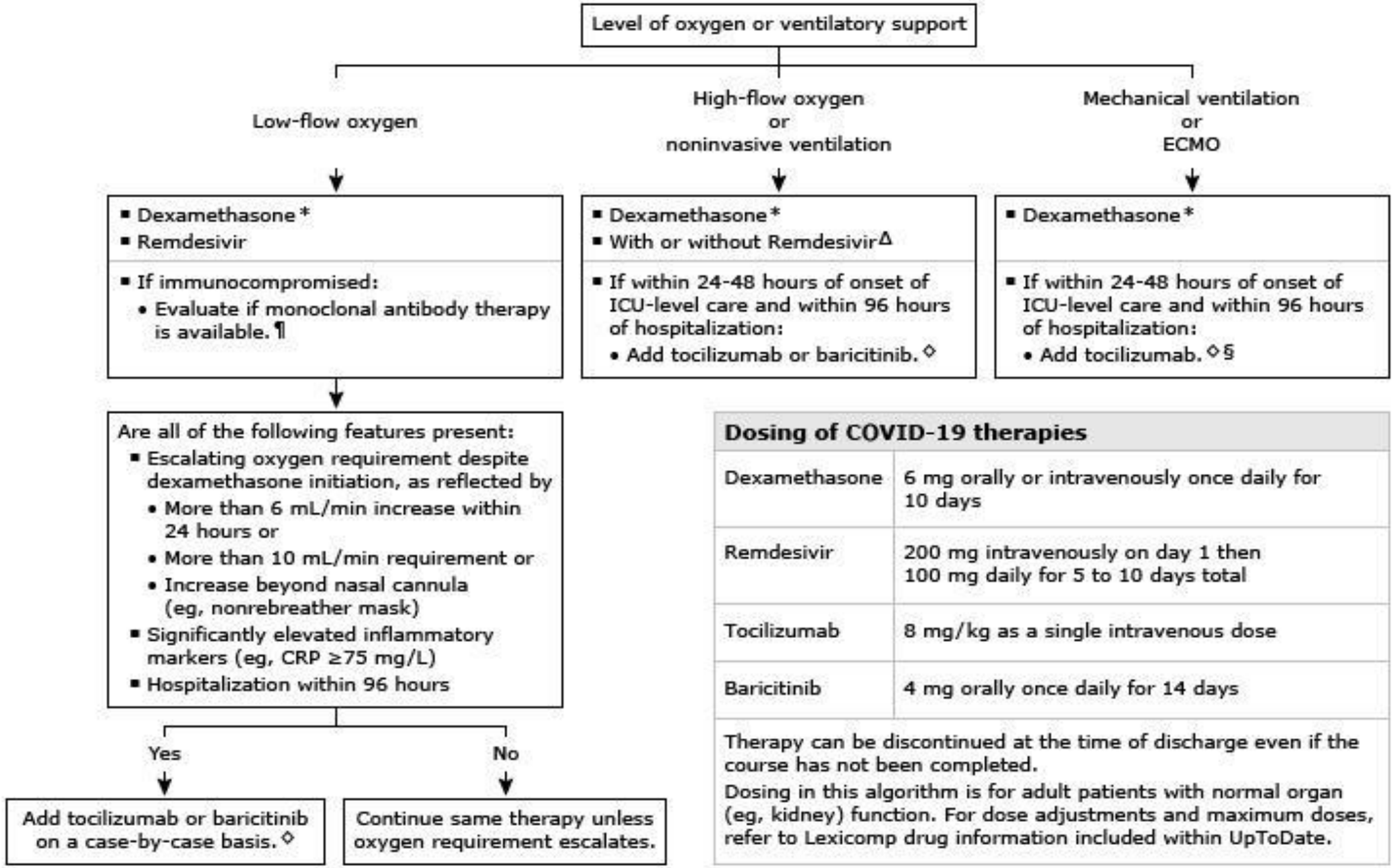
Patients with oxygen requirement/severe disease

- For patients receiving **high-flow supplemental oxygen or non-invasive ventilation**, we suggest **low-dose dexamethasone** (Grade 1B). If they are within 24 to 48 hours of admission to an intensive care unit (ICU) or receipt of ICU-level care (and within 96 hours of hospitalization), we suggest either **baricitinib** or **tocilizumab** in addition to **dexamethasone** (Grade 2B). We also suggest adding **remdesivir** based on the theoretic benefit of adding antiviral therapy to anti-inflammatory treatment (Grade 2C).

Patients with oxygen requirement/severe disease

- For patients who require **mechanical ventilation** or **extracorporeal membrane oxygenation**, we recommend **low-dose dexamethasone** (Grade 1B). For those who are within 24 to 48 hours of admission to an ICU (and within 96 hours of hospitalization), we suggest adding **tocilizumab** to **dexamethasone** (Grade 2B). If tocilizumab is not available, **baricitinib** is a reasonable alternative. We suggest **not routinely** using **remdesivir** in this population (Grade 2C).

- **If dexamethasone is not available, other glucocorticoids at equivalent doses are reasonable alternatives.**



Dosing of COVID-19 therapies	
Dexamethasone	6 mg orally or intravenously once daily for 10 days
Remdesivir	200 mg intravenously on day 1 then 100 mg daily for 5 to 10 days total
Tocilizumab	8 mg/kg as a single intravenous dose
Baricitinib	4 mg orally once daily for 14 days

Therapy can be discontinued at the time of discharge even if the course has not been completed.

Dosing in this algorithm is for adult patients with normal organ (eg, kidney) function. For dose adjustments and maximum doses, refer to Lexicomp drug information included within UpToDate.

Dexamethasone and other glucocorticoids

- We recommend dexamethasone for severely ill patients with COVID-19 who are on supplemental oxygen or ventilatory support (algorithm).
- We use dexamethasone at a dose of 6 mg daily for 10 days or until discharge, whichever is shorter.
- If dexamethasone is not available, it is reasonable to use other glucocorticoids at equivalent doses (eg, total daily doses of hydrocortisone 150 mg, methylprednisolone 32 mg, or prednisone 40 mg).
- In contrast, we recommend that dexamethasone (or other glucocorticoids) not be used for either prevention or treatment of mild to moderate COVID-19 (patients not on oxygen).
- Glucocorticoids may also have a **role in the management** of **refractory shock** in critically ill patients with COVID-19.

Baricitinib

- Baricitinib is a Janus kinase (JAK) inhibitor used for treatment of rheumatoid arthritis. In addition to immunomodulatory effects, it is thought to have potential antiviral effects through interference with viral entry.
- We suggest baricitinib as an option for patients requiring high-flow oxygen or noninvasive ventilation and for select patients who are on low-flow oxygen but are progressing toward needing higher levels of respiratory support despite initiation of dexamethasone (algorithm 2). Baricitinib is also a reasonable alternative to **tocilizumab**, if it is not available.

Baricitinib

- We generally reserve baricitinib for those who are within 96 hours of hospitalization or within 24 to 48 hours of initiation of ICU-level care, similar to the study population in the large trials.
- We do not use baricitinib in patients who have **also received an IL-6 pathway inhibitor**, as these agents have not been studied together and the safety of coadministration is uncertain.
- **Baricitinib** is given at **4 mg orally once daily** for up to 14 days.

Baricitinib

Dosing: Kidney Impairment: Adult

COVID-19 (FDA 2021):

eGFR $\geq$60 mL/minute/1.73 m^2: No dosage adjustment necessary.

eGFR 30 to <60 mL/minute/1.73 m^2: 2 mg once daily.

eGFR 15 to <30 mL/minute/1.73 m^2: 1 mg once daily.

eGFR <15 mL/minute/1.73 m^2: Use is not recommended.

Tocilizumab (IL-6 pathway inhibitor)

- We suggest tocilizumab (**8 mg/kg** as a single intravenous dose) as an option for individuals who require high-flow oxygen or more intensive respiratory support.
- we also suggest tocilizumab on a case-by-case basis as an option for select patients on low-flow oxygen supplementation if they are clinically progressing toward high-flow oxygen despite initiation of dexamethasone and have significantly elevated inflammatory markers (eg, C-reactive protein [CRP] level ≥75 mg/L).

Tocilizumab (IL-6 pathway inhibitor)

- More specifically, we would give tocilizumab to such patients if they have progressively greater oxygen requirements for reasons related to COVID-19 but not if their oxygen requirement is stable or is worsening due to other causes of respiratory decompensation (eg, asthma exacerbation, congestive heart failure).
- We generally reserve tocilizumab for those who are within 96 hours of hospitalization or within 24 to 48 hours of initiation of ICU-level care, similar to the study population in the large trials.
- We only use tocilizumab in patients who are also taking dexamethasone (or another glucocorticoid) and generally limit it to a single dose.

Tocilizumab should be avoided in individuals:

- With hypersensitivity to tocilizumab
- uncontrolled serious infections other than COVID-19
- absolute neutrophil count (ANC) <1000 cells/microL
- platelet counts <50,000
- alanine aminotransferase (ALT) >10 times the upper limit of normal (ULN)
- elevated risk for gastrointestinal perforation.

Tocilizumab should be used with caution in **immunocompromised individuals** as very few were included in randomized trials.

Remdesivir

- Remdesivir is a novel nucleotide analog that has in vitro activity against COVID-19.
- We suggest remdesivir for hospitalized patients with severe COVID-19 who are not on mechanical ventilation because some data suggest it may reduce time to recovery and risk of mechanical ventilation (Guidelines from the IDSA and the NIH recommend remdesivir, whereas other expert organizations (including the WHO) conditionally recommend against remdesivir because a definitive mortality benefit has not been demonstrated.
- In the United States, the Food and Drug Administration (FDA) approved remdesivir for hospitalized children ≥12 years and adults with COVID-19, **regardless of disease severity.**

Remdesivir

- The suggested adult dose is 200 mg intravenously on day 1 followed by 100 mg daily for 5 days total (with extension to 10 days if there is no clinical improvement and in patients on mechanical ventilation or extracorporeal membrance oxygenation).
- If a patient is otherwise ready for discharge prior to completion of the course, remdesivir can be discontinued.
- Remdesivir is prepared in a cyclodextrin vehicle that accumulates in renal impairment and may be toxic; thus, remdesivir is not recommended in patients with GFR <30 mL/min per 1.73 m^2.
- Liver enzymes should be checked before and during remdesivir administration; alanine aminotransferase elevations >10 times the upper limit of normal should prompt consideration of remdesivir discontinuation.

DISCHARGE

- The decision to discharge a patient with COVID-19 is generally the same as that for other conditions and depends on the need for hospital-level care and monitoring.
- Continued need for infection control precautions should not prevent discharge home if the patient can appropriately self-isolate there; long-term care facilities may have specific requirements prior to accepting patients with COVID-19.
- Older age (eg, >65 years), underlying medical comorbidities, and discharge to a skilled nursing facility have been associated with an **increased risk of readmission** following hospitalization for COVID-19.

Thanks for your attention