Clinical Management of COVID-19

IL-6 RECEPTOR BLOCKERS FOR COVID-19

Learning objectives

At the end of this module, you will be able to:

- Recognize the role for IL-6 receptor blockers in the management of patients with COVID-19.
- Describe key IL-6 receptor blockers dosing and administration considerations for patients with severe and critical COVID-19.

Special note

Drugs and doses stated here are for illustrative purposes only.

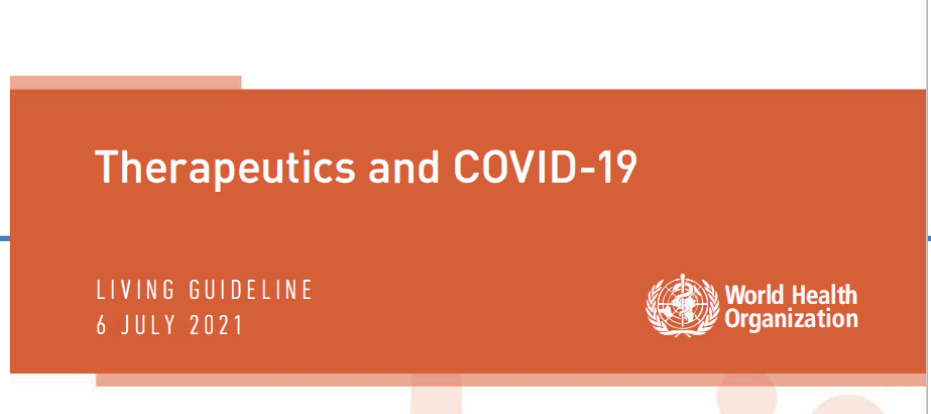
Decisions regarding the use of any medication must be made by a licensed provider and take into account each patient's specific clinical history and other circumstances, and be in accordance with relevant local management and prescribing guidelines.

IL-6 receptor blockers in COVID-19: summary of recommendations

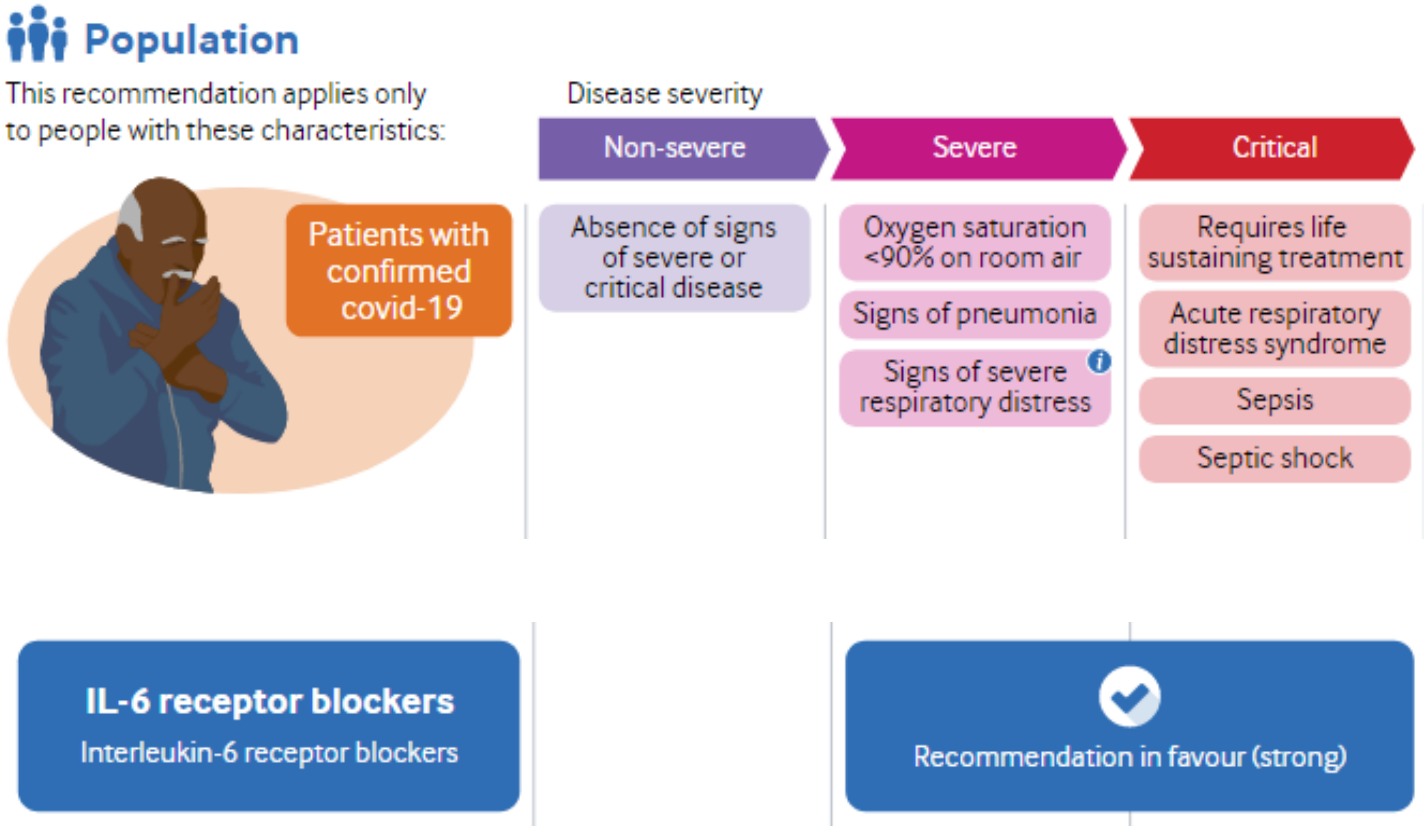
In July 2021, the following WHO recommendations regarding IL-6 receptor blockers for patients with COVID-19 were released:

Strong recommendation: We recommend treatment with IL-6 receptor blockers (tocilizumab or sarilumab) for patients with severe and critical COVID-19.

Corticosteroids have previously been strongly recommended in patients with severe and critical COVID-19, and we recommend **patients meeting these severity criteria should now receive both corticosteroids and IL-6 receptor blockers**.



IL-6 receptor blockers in COVID-19: recommendation



A living WHO guideline on drugs for covid-19. BMJ 2020;370:m3379. https://doi.org/10.1136/bmj.m3379

Review of IL-6 biology and function

What is IL-6 (Interleukin 6)?

- Cytokines refer to a broad group of small proteins important in cell signaling. Categories of cytokines include interferons, **interleukins**, tumor necrosis factors and others.

- **Interleukin (IL) 6 is a strong pro-inflammatory cytokine**. It plays an important role in the body's fight against autoimmune diseases such as Rheumatoid Arthritis.

- IL-6 is important for both systemic and local inflammation and is associated with symptoms such as fever, fatigue and anorexia (decreased appetite).[1]

- Prior to 2020, increased IL-6 levels had been associated with several viral infections, including influenza, hepatitis B, hepatitis C, HIV, Crimean-Congo hemorrhagic fever and Chikungunya. Evidence from clinical studies had shown that increased IL-6 levels worsen clinical outcomes involving viral pathogens.[1] Similar postulations were made for SARS-CoV-2.

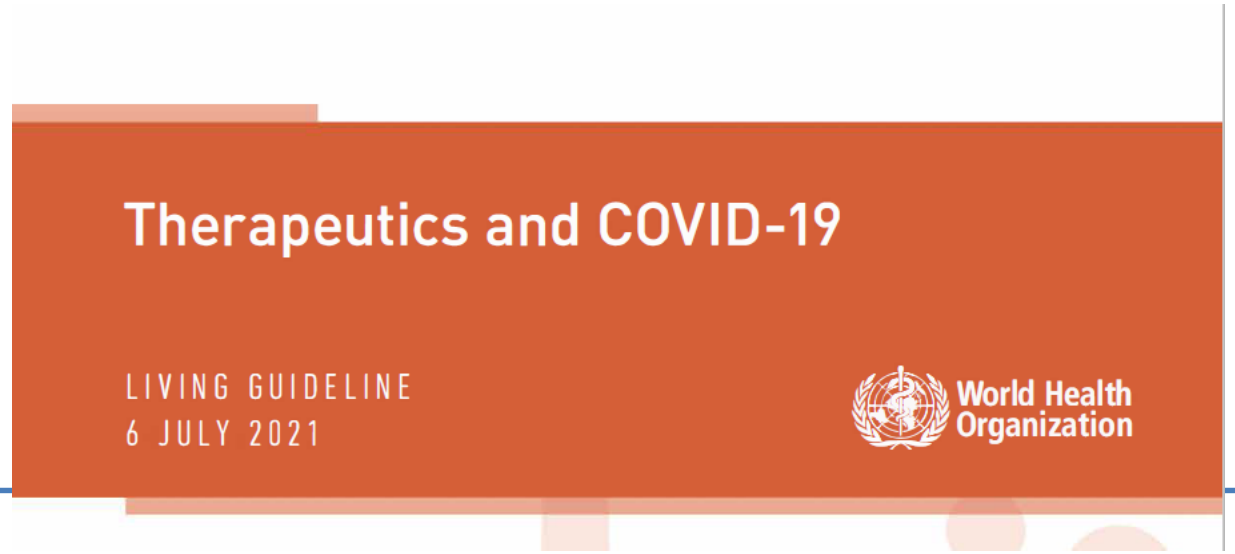
IL-6 receptor and IL-6 receptor blockers

- The interleukin-6 receptor is a protein complex consisting of two parts: an IL-6 receptor (IL6R) subunit and a glycoprotein.
- IL-6 binds to the IL-6 receptor complex. The body's immune system responds through a variety of immune cascades.
- For many years, medicines have been created and tested specifically to target blocking the IL6R and/or glycoprotein subunits for various autoimmune diseases.
- Tocilizumab and Sarilumab are two examples of IL6R blockers. They bind to IL6R and thus prevent IL-6 from binding to IL6R.
- Tocilizumab is humanized (human-generated) antibody to the IL6R. Sarilumab is a human antibody to the IL6R. Other antibodies to IL6R and IL-6 also exist.

Reviewing the evidence and recommendations regarding IL-6 receptor blockers

Strong recommendation for IL-6R blockers and corticosteroids in severe and critical COVID-19

The GDG made a **strong recommendation for IL-6 blockers and corticosteroids in severe and critical COVID-19** based on **high certainty of evidence** which showed **reduction in mortality and decreased need for mechanical ventilation** in patients with COVID-19 who are severely or critically ill.



Understanding the strength of recommendations

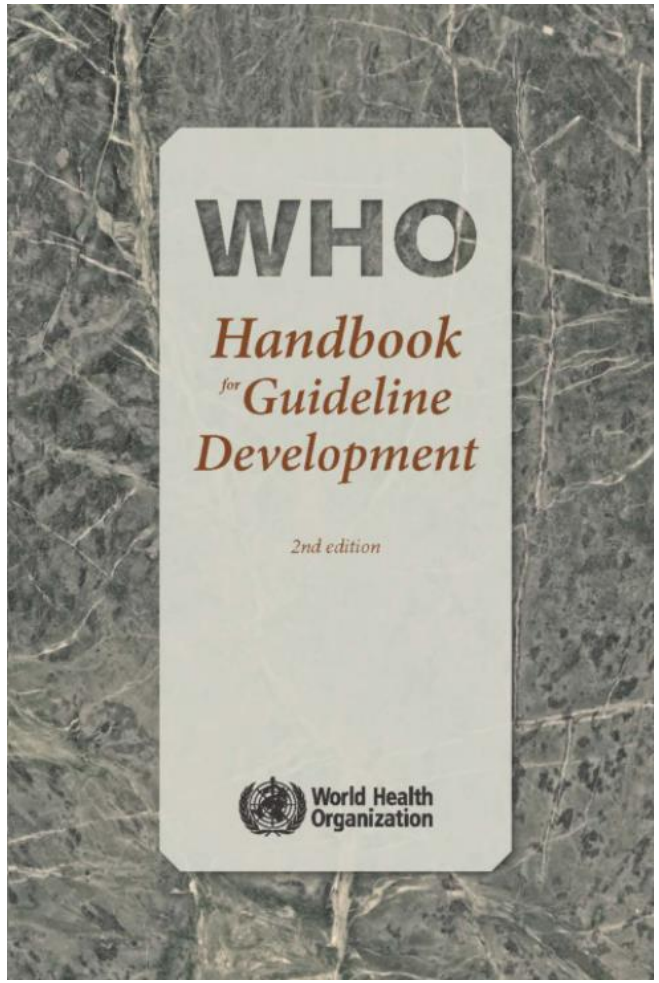
Strong	Conditional
• **For patients:** most individuals in this situation would want the recommended course of action and only a small proportion would not. • **For clinicians:** Most individuals should receive this course of action. • **For policymakers:** The recommendation can be adapted as a policy in most situations including for the use as performance indicators.	• **For patients:** The majority of individuals would want the suggested course of action, but many would not. • **For clinicians:** Different choices are likely to be appropriate for different patients and therapy should be tailored to the individual patient circumstances. • **For policymakers:** Policy making will require substantial debates and involvement of many stakeholders. Policies are also likely to vary between regions.

IL-6R blockers for COVID-19: guideline development process (1/2)

- **The WHO Therapeutics and COVID-19 Guideline Development Group (GDG),** a group of international content experts, patients, clinicians and methodologists with no conflicts of interest and balanced in terms of gender, geography, expertise, and patient representation[3], met in mid 2021 to discuss IL-6R blockers.

- The GDG followed standards for trustworthy guideline development using the **GRADE approach** (Grading of Recommendations Assessment, Development and Evaluation), in full compliance with the WHO Handbook for guideline development, 2nd edition.[2]

- The GDG took an **individual patient perspective to values and preferences** when making decisions. Values considered include:
  - **Applicability of the guideline to various populations of patients;**
  - **Balance of benefits and harms;**
  - **Resource implications, feasibility, equity and human rights;**
  - **Acceptability.**

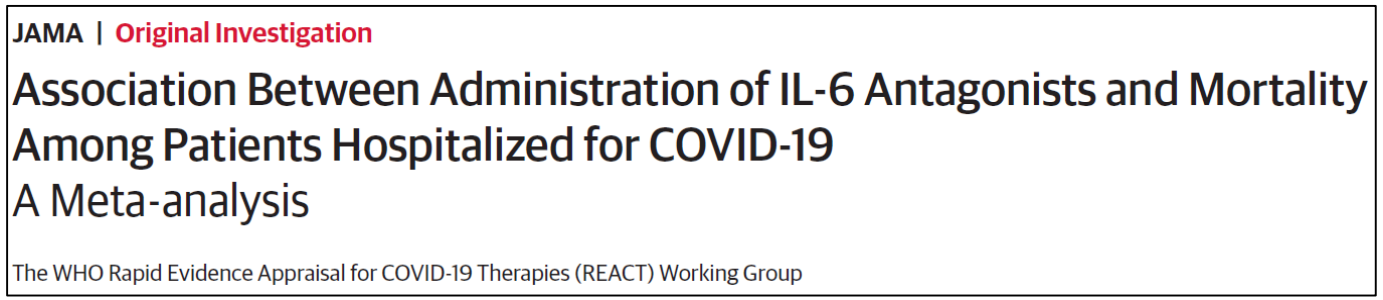


IL-6R blockers in COVID-19: guideline development process (2/2)

- Since 2020, WHO has partnered with principal investigators of several ongoing clinical research trials and formed the Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group.

- WHO REACT conducts prospective meta-analysis (PMA) of randomized trials for therapies such as IL-6R blockers for COVID-19.[4]

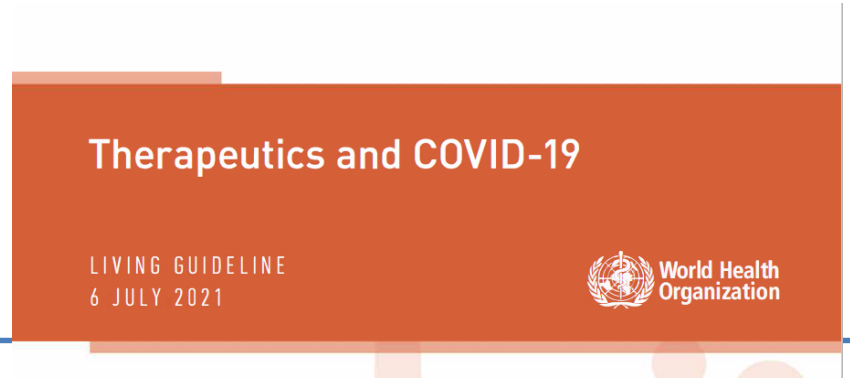
- The GDG is presented with the evidence from the PMA and discusses the values and preferences in order to arrive at a recommendation.[5]


JAMA | Original Investigation

Association Between Administration of IL-6 Antagonists and Mortality Among Patients Hospitalized for COVID-19

A Meta-analysis

The WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group



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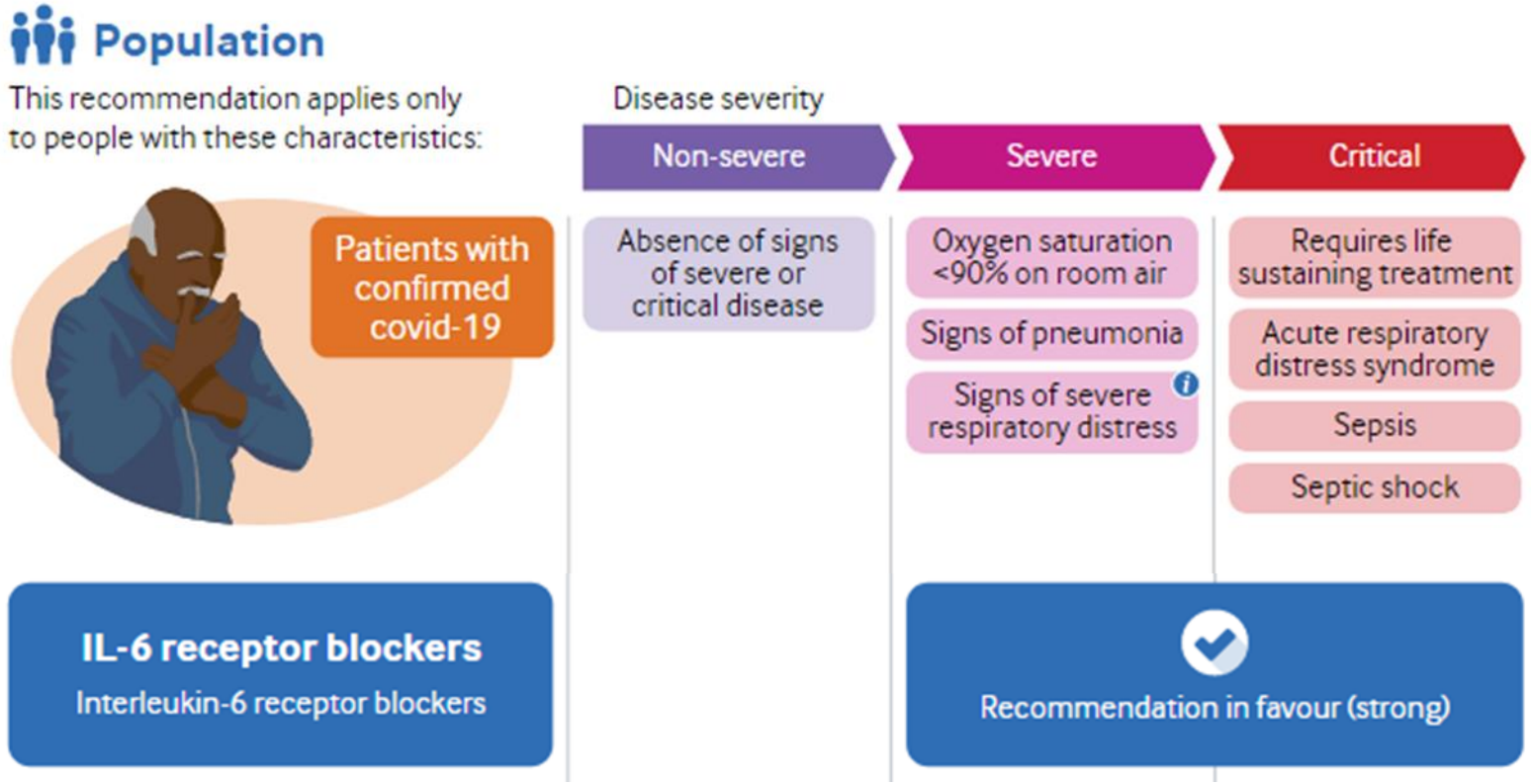
IL-6 receptor blockers in COVID-19: categories of illness severity

The recommendation for IL-6 receptor blocker use applies only to patients who are **severely** or **critically** ill, as per the definitions below. [5]



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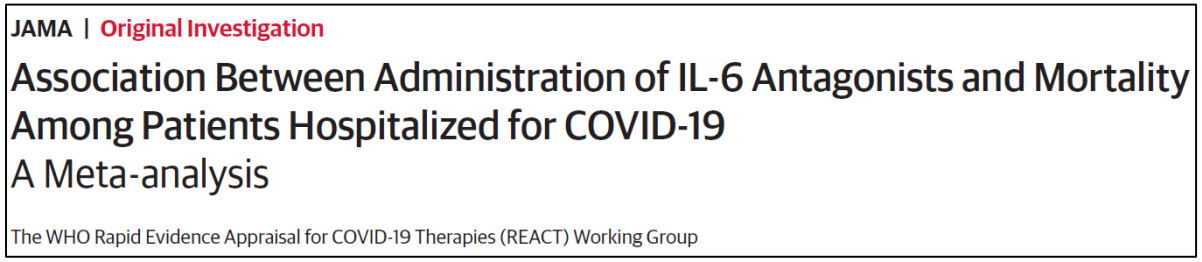
Deeper into the evidence

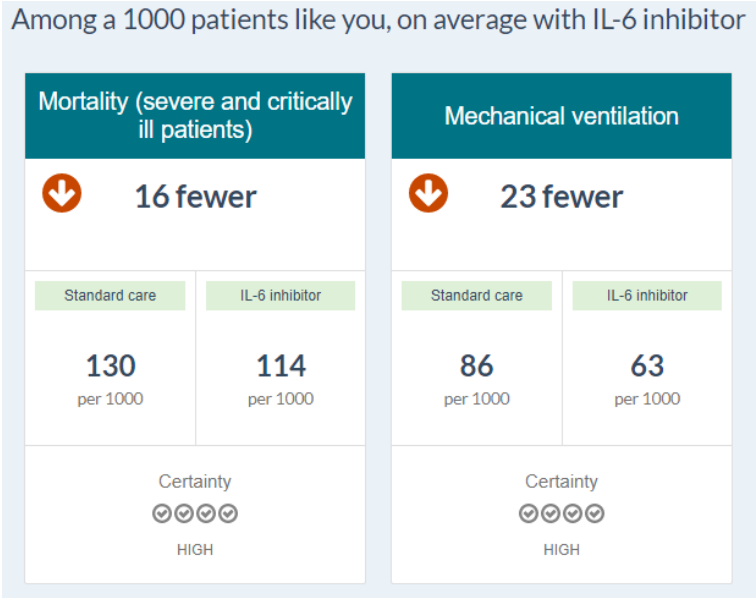
Summary of the prospective meta-analysis

- The prospective meta-analysis for IL-6 receptor blockers brought together data from 27 randomized clinical trials, totaling 10,930 patients (median 61 years age, 33% women).[4]
- Mortality risk at 28-days decreased with IL-6 receptor blockers (22%) compared to usual care or placebo (25%). IL-6 receptor blockers were found to be most effective when administered with corticosteroids (21% mortality risk with IL-6RB and steroids vs 25% with steroids alone).[4]



Evidence: IL-6RB vs. SC

Therapeutics and COVID-19: living guideline (magicapp.org)

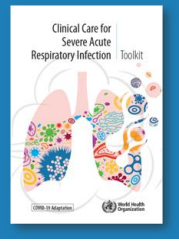


The GDG made a **strong recommendation for IL-6 blockers and corticosteroids in severe and critical COVID-19** based on **high certainty of evidence** which showed **reduction in mortality and decreased need for mechanical ventilation** in patients with COVID-19 who are severely or critically ill (4)

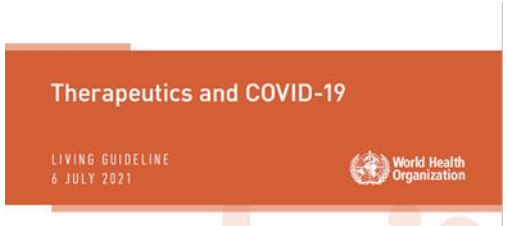
Outcome Timeframe	Study results and measurements	Absolute effect estimates Standard care	 IL-6 inhibitor	Certainty of the Evidence (Quality of evidence)	Plain language summary
Mortality (severe and critically ill patients)	Odds Ratio 0.86 (CI 95% 0.79 — 0.95) Based on data from 10930 patients in 27 studies	130 per 1000	114 per 1000 Difference: **16 fewer per 1000** (CI 95% 24 fewer — 6 fewer)	High	IL-6 inhibitors reduce mortality. Intervention
Mechanical ventilation	Odds Ratio 0.72 (CI 95% 0.57 — 0.90) Based on data from 5686 patients in 9 studies	86 per 1000	63 per 1000 Difference: **23 fewer per 1000** (CI 95% 35 fewer — 8 fewer)	High	IL-6 inhibitors reduce need for mechanical ventilation. Intervention
Adverse events leading to drug discontinuation	Odds Ratio 0.50 (CI 95% 0.03 — 9.08) Based on data from 815 patients in 2 studies	9 per 1000	5 per 1000 Difference: **4 fewer per 1000** (CI 95% 9 fewer — 67 more)	Very low Due to serious risk of bias and very serious imprecision	The effect of IL-6 inhibitors on adverse events leading to discontinuation is uncertain. No imp. diff.
Bacterial infections	Odds Ratio 0.95 (CI 95% 0.72 — 1.29) Based on data from 3548 patients in 18 studies	101 per 1000	96 per 1000 Difference: **5 fewer per 1000** (CI 95% 26 fewer — 26 more)	Low Due to serious risk of bias and serious imprecision	IL-6 inhibitors may not increase secondary bacterial infections. No imp. diff.
Duration of mechanical ventilation	Lower better Based on data from 1189 patients in 10 studies	14.7 (Mean)	13.5 (Mean) Difference: **1.2 lower (MD)** (CI 95% 2.3 lower — 0.1 lower)	Low Due to serious risk of bias and serious imprecision	IL-6 inhibitors may reduce duration of mechanical ventilation. Intervention
Duration of hospitalization	Lower better Based on data from 6665 patients in 9 studies	12.8 (Mean)	8.3 (Mean) Difference: **4.5 lower (MD)** (CI 95% 6.7 lower — 2.3 lower)	Low Due to serious risk of bias and serious inconsistency	IL-6 inhibitors may reduce duration of hospitalization. Intervention

Clinical considerations when administering IL-6 receptor blockers

IL-6 receptor blockers in COVID-19: treatment



- For COVID-19, **only the intravenous formulation of IL-6 receptor blockers should be used**. Subcutaneous injections have not been studied for COVID-19.
- IL-6 receptor blockers should be given as **single dose over 1 hour using a dedicated IV line**.
- Avoid IV push or IV bolus.
- If a clinical response is determined to be inadequate after 12-48 hours, a second dose may be considered.



Indication (patient criteria)

Hospitalized patients with confirmed COVID-19 infection requiring supplemental oxygen and/or mechanical ventilation AND corticosteroid treatment (see *Therapeutics and COVID-19: living guideline*).

Treatment should be started as early as possible in the patient's critical illness.

Dose and route

Tocilizumab 8 mg/kg (maximum dose of 800 mg) intravenous infusion administered over 60 minutes as a single dose.

- Avoid IV push or bolus.
- If clinical response is determined to be inadequate after 12–48 hours, a second dose may be considered.
- Renal dose adjustment is not warranted.

Dose of tocilizumab (mg) to be given:

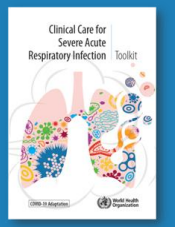
Patient body weight	Band dose
< 41 kg	8 mg/kg, rounded to nearest 20 mg
41–45 kg	360 mg
46–55 kg	400 mg
56–65 kg	480 mg
66–80 kg	600 mg
81–90 kg	680 mg
> 91 kg	800 mg

Available formulations

Volume tocilizumab 20 mg/mL:
80 mg in 4-mL vial
200 mg in 10-mL vial
400 mg in 20-mL vial.

The drugs and doses stated here are for illustrative purposes only. Decisions regarding the use of any medication must be made by a licensed provider and take into account each patient's specific clinical history and other circumstances, and be in accordance with relevant local management and prescribing guidelines.

IL-6 receptor blockers in COVID-19: pre-treatment monitoring

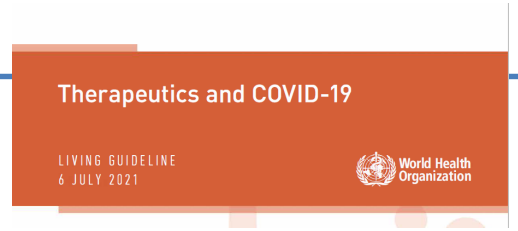


- Prior to initiating IL-6 receptor blocker therapy, routine bloodwork should be checked for the following:
  - **Neutrophil count**
  - **Platelets**
  - **Transaminases**
  - **Total bilirubin**
  - **Lipid profile**

- Additional labs such as screening for HIV, hepatitis B and C and other tests may be considered as per clinician discretion.

- Clinicians may choose to avoid IL-6 receptor blocker therapy in patients with history of autoimmune disease such as Rheumatoid Arthritis or giant cell arteritis, especially those who also have abnormal lab findings on routine bloodwork.

General monitoring	• Please refer to USPI, SmPC or local labelling for important safety issues and warnings. • At baseline and 72 hours after infusion of IL-6 RB: – **Neutrophil count** (it is not recommended to initiate treatment in patients with < 2000/mL). – **Platelets count** (it is not recommended to initiate treatment in patients with < 50 000/mL). – **Transaminases** (it is not recommended to initiate treatment in patients with elevated transaminases ALT or AST above 1.5× ULN. Discontinue infusion or do not give second dose in patients who develop persistent elevated ALT or AST above 3× ULN or who develop ALT or AST above 5× ULN). – **Lipid profile** (LDL, HDL cholesterol, triglycerides) (possibility of elevated lipid profile after treatment). • At baseline: – **Screening for HIV, Hep B (HBsAg, HBcAb) and C (HC Ab)*** (Discuss the results with microbiology or infectious diseases physicians if unsure how to interpret.) Individual clinical assessment of these patients is needed. * *Delays in the result of these tests should not restrain clinicians from starting treatment when indicated.* • Before, during and after IL-6 receptor blockers infusion: patients should be regularly clinically assessed for bacterial infection. Monitor the appearance of sepsis produced by other pathogens different from COVID-19 (caution is recommended when considering the use in patients with a history of recurring or chronic infections or underlying conditions which may predispose patients to infections). • Monitor for presumptive TB infection, mainly if in areas of high prevalence of TB or immunosuppressed patients. (Treatment for latent infection should be initiated prior to tocilizumab use.)
Special populations to monitor closely for complications	• Patients on concomitant immunosuppressive therapy. • Patients with recurring chronic infections or underlying conditions that predispose to infections. • Patients receiving IL-6 RB on long-term regimens for conditions other than COVID-19 (risk of fatal infections such as active TB, bacterial, viral and other opportunistic infections). • Women of childbearing potential must use effective contraception during and up to 3 months after treatment. • Pregnant women – only use in pregnancy only if the potential benefit justifies the potential risk to the fetus.
Examples of possible complications	• Acute severe infections: TB, bacterial, invasive fungal, viral and other opportunistic superinfections. • Immunosuppression. • Elevated liver function tests and lipid profile. • Gastrointestinal perforation. • Hypersensitive reactions, anaphylaxis.



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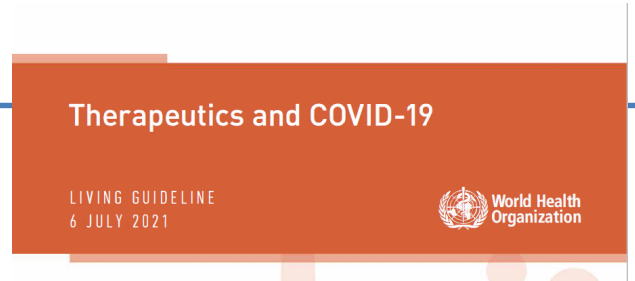
IL-6 receptor blockers in COVID-19: post-treatment monitoring

- The evidence of serious adverse events of IL-6 blocker use in COVID-19 is **uncertain**.
- COVID-19 trials only followed patients for a short interval and cited challenges in accurately capturing adverse events. **Evidence summary may under-represent the risks of treatment with IL-6 receptor blockers**.
- Serious and potentially fatal infections such as active tuberculosis, invasive fungal, bacterial, viral and other opportunistic infections have been reported in patients receiving tocilizumab for conditions other than COVID-19.
- **Use discretion and caution** in using IL-6 receptor blockers in patients on concomitant immunosuppressive therapy. **Closely monitor patients** for signs and symptoms of infection during and after treatment.



Summary

Summary

- Give IL-6 receptor blockers along with oxygen and systemic corticosteroids for patients with severe and critical COVID-19.

- Be aware and monitor for potential adverse events including opportunistic infections, especially due to concomitant corticosteroid administration.

References

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Acknowledgements

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