WHO Therapeutic Guidance:
Review of current recommendations and application in pregnancy

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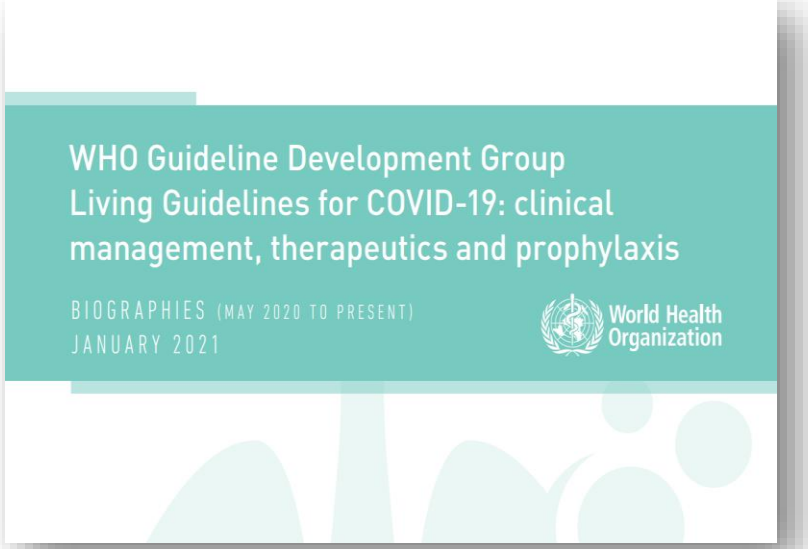
World Health Organization

HEALTH EMERGENCIES programme

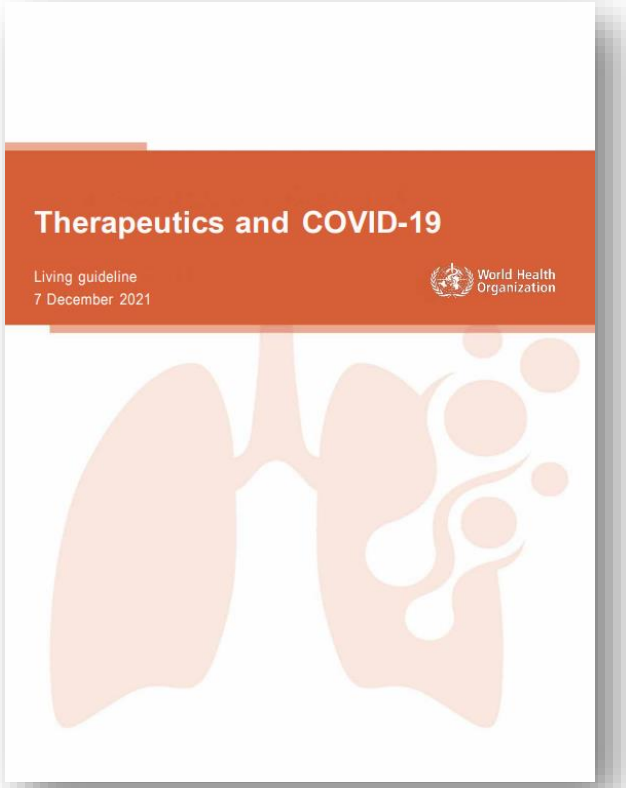
WHO Guideline Development Group Living Guidelines for COVID-19

- For the development of the WHO Living Guideline on Therapeutics for COVID-19, WHO Living Guidance for Clinical Management of COVID-19 and the new WHO Living Guideline for Prophylaxis for COVID-19, a formal Guideline Development Group (GDG) comprising individuals with broad expertise spanning multiple specialties and all regions was convened.
- This group includes patient panel members.
- Confidentiality and declarations of interest are regularly collevcted and reviewed - no conflict of interest identified.



Living Guidelines for Therapeutics and COVID-19

- Downloadable and online publishing platform
- First version, published 2 September 2020
- Seventh version, published 7 December 2021
  - 40 Clinical Questions
  - 22 Recommendations
- Eighth version to be published 14 January 2022



MAGIC Evidence Ecosystem Foundation

Therapeutic Guideline Development

Step 1
WHO Therapeutic Steering Committee
Scanning and prioritization

Step 2
Meta Analysis

Step 3
Guideline Development Group Meetings

Step 4
Recommendation Writing
GRC, PRC, external review

Step 5
Publication
Dissemination and development of tools

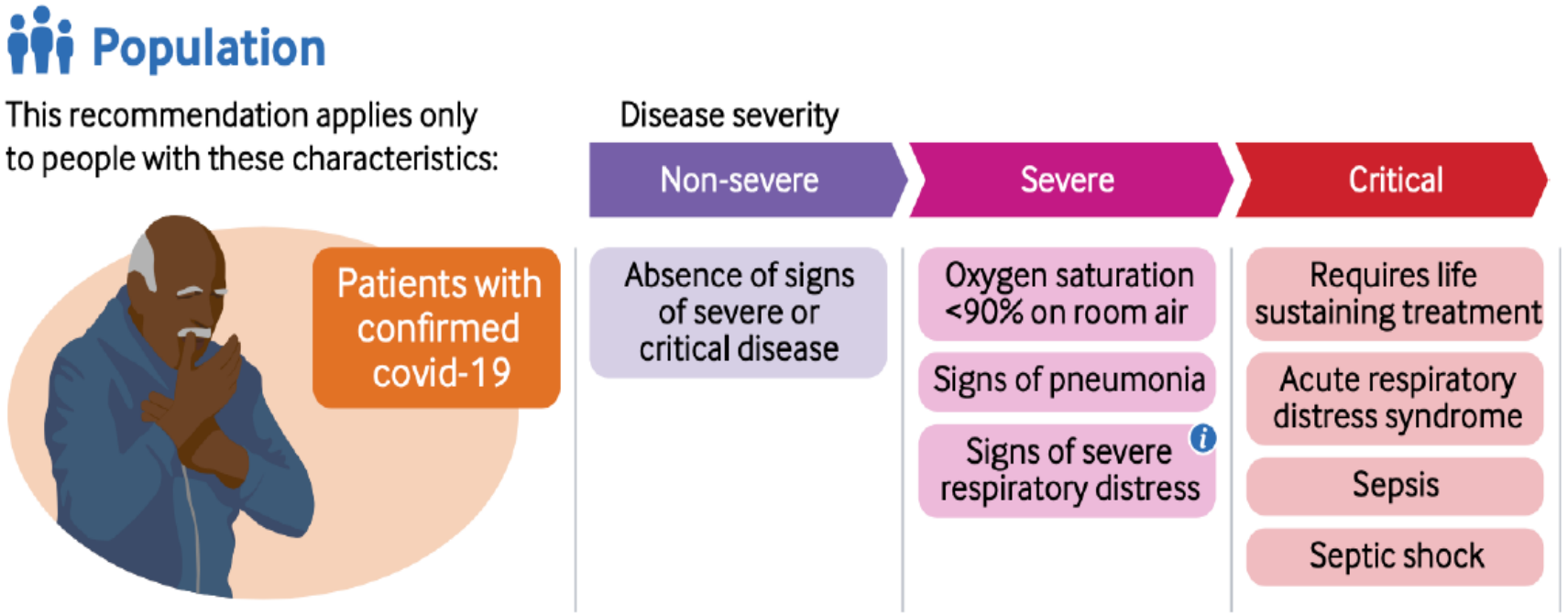
World Health Organization

Session objectives

At the end of this session, you will be able to relate the WHO recommendation for various therapeutics in the treatment of patients with COVID-19 and their application in pregnancy:

- **Systemic corticosteroids**
- **IL-6 receptor blockers**
  - tocilizumab or sarilumab
- **Neutralizing monoclonal antibodies**
  - casirivimab and imdevimab or sotrovimab
- **Janus Kinase Inhibitors**
  - baricitinib
- **Antivirals**
  - molnupiravir, nirmatrelvir/ritonavir

Characterizing COVID-19 by severity



Infographic co-produced by the BMJ and MAGIC; designer Will Stahl-Timmins (see BMJ Rapid Recommendations).

Risk factors:

Older age (> 60 years), hypertension, diabetes, cardiac disease, chronic lung disease, cerebrovascular disease, dementia, mental disorders, chronic kidney disease, immunosuppression (including HIV), obesity, cancer, pregnancy or in the post-partum period (6 weeks).

Corticosteroids in COVID-19: summary of recommendations

- In September 2020, the following recommendations regarding systemic corticosteroids for patients with COVID-19 were released by WHO:

Strong recommendation: We recommend systemic corticosteroids rather than no corticosteroids for the treatment of patients with **severe and critical COVID-19.**

Conditional recommendation: We suggest **not to use** corticosteroids in the treatment of patients with **non-severe COVID-19.**

Corticosteroids in COVID-19: women and pregnancy

- WHO recommends antenatal corticosteroid therapy for women at risk of preterm birth from 24 to 34 weeks of gestation when there is no clinical evidence of maternal infection, and adequate childbirth and newborn care is available.
- For women with mild or moderate COVID-19, the benefits of antenatal corticosteroid might outweigh the risks of potential harm to the mother.
- The balance of benefits and harms for the woman and the preterm newborn should be discussed with the woman and may vary depending on the woman's clinical condition, her wishes and that of her family, and available health care resources.

Which steroids to use in pregnancy?

- **Prednisolone, hydrocortisone, methylprednisolone to treat COVID-19 in the mother**
- **Dexamethasone for fetal lung maturity**
- NB pred/hydro/methylprednisolone are converted extensively by 11betaHSD2 into inactive metabolites reducing passage across the placenta
- BUT dexamethasone is converted less extensively by 11betaHSD2 into inactive metabolites thus passing into the placenta
- Don’t use dexamethasone please unless also want to improve fetal lung maturity

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 had 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: women and pregnancy

- Women of childbearing potential should use effective contraception during and up to 3 months after treatment.
- Can be used in pregnancy if potential benefit justifies the potential risk to mother and fetus.
- The balance of benefits and harms for the woman and fetus should be discussed with the woman which may vary depending on the woman's clinical condition, her wishes and that of her family, and available health care resources.

Casirivimab and imdevimab in COVID-19: summary of recommendations

- In September 2021, the following WHO recommendations regarding casirivimab and imdevimab for patients with COVID-19 were released:

Conditional recommendation: We recommend treatment with casirivimab and imdevimab for patients with non-severe COVID-19 at highest risk for hospitalization and those with severe and critical COVID-19 who are seronegative for SARS-CoV-2.

- Oxygen, corticosteroids and IL-6 receptor blockers have previously been recommended in patients with severe and critical COVID-19. We recommend severe and critical patients with seronegative status should now also receive casirivimab and imdevimab.

* Casirivimab and Imdevimab is active against alpha, beta, gamma, and delta variants of concern. Consider local epidemiological data since emerging evidence predicts decreased efficacy against Omicron.

Casirivimab and imdevimab in COVID-19: women and pregnancy

- Limited data regarding use in pregnant and lactating women with COVID-19 and it is not sufficient to inform drug associated risks for major birth defects, miscarriage or adverse maternal or fetal outcome.
- Can be used in pregnancy if potential benefit justifies the potential risk to mother and fetus
- The balance of benefits and harms for the woman and fetus should be discussed with the woman which may vary depending on the woman's clinical condition, her wishes and that of her family, and available health care resources.
- No available data on the presence in human or animal milk, the effects on the breastfed infant, or the effect of the drug on milk production

Sotrovimab in COVID-19: summary of recommendations

NEW RECOMMENDATION

- In January 2022, the following WHO recommendations regarding sotrovimab for patients with COVID-19 will be released:

  Conditional recommendation: We recommend treatment with sotrovimab for patients with non-severe COVID-19 at highest risk for hospitalization with COVID-19.

- Based on current evidence the benefit of sotrovimab in seronegative patients with severe or critical COVID-19 remains unclear. Careful clinical judgement needs to be applied if casirivimab and imdevimab is unavailable and sotrovimab is considered.

* Sotrovimab is active against alpha, beta, gamma, and delta variants of concern. Emerging evidence suggests continued neutralization against Omicron.

Sotrovimab in COVID-19: women and pregnancy

- Limited data regarding use in pregnant and lactating women with COVID-19 and it is not sufficient to inform drug associated risks for major birth defects, miscarriage or adverse maternal or fetal outcome.
- Can be used in pregnancy if potential benefit justifies the potential risk to mother and fetus.
- The balance of benefits and harms for the woman and fetus should be discussed with the woman which may vary depending on the woman's clinical condition, her wishes and that of her family, and available health care resources.
- No available data on the presence in human or animal milk, the effects on the breastfed infant, or the effect of the drug on milk production.

Janus Kinase Inhibitors in COVID-19: summary of recommendations

NEW RECOMMENDATION

- In January 2022, the following WHO recommendations regarding the Janus Kinase Inhibitor (JAK-Inhibitor) baricitinib for patients with COVID-19 will be released:

Strong recommendation: We recommend treatment with the JAK-Inhibitor IL-6 (baricitinib) for patients with severe and critical COVID-19

- Along with baricitinib, corticosteroids should also be administered in patients with severe and critical COVID-19.
- IL-6 receptor blockers had previously been strongly recommended in patients with severe and critical COVID-19. An IL-6 receptor blocker and baricitinib should **NOT** be given together and should be viewed as alternatives. The choice of which to use depends on availability as well as clinical and contextual factors.

Janus Kinase Inhibitors in COVID-19: women and pregnancy

- Limited data regarding use in pregnant women with COVID-19.
- Can be used in pregnancy if potential benefit justifies the potential risk to mother and fetus.
- The balance of benefits and harms for the woman and fetus should be discussed with the woman which may vary depending on the woman's clinical condition, her wishes and that of her family, and available health care resources.

Molnupiravir in COVID-19: summary of recommendations

Guideline under development – publication date to be announced

- The WHO Guideline Development Committee met 16 and 22 December 2021 to review Molnupiravir.

- The updated guidelines with Molnupiravir are currently being drafted and the WHO recommendations for patients with COVID-19 will be released in late January 2022.

Molnupiravir in COVID-19: women, pregnancy, and other considerations

- In vitro genetic toxicity
  - Molnupiravir is mutagenic in vitro but there was no evidence of mutagenicity in animal models.
  - Molnupiravir may or may not be carcinogenic in humans (these studies have not been done)
- Growth plate thickness
  - An increase in thickness of growth plate associated with decreased bone formation was observed growing in rats but not mice, rats or dogs
  - **Molnupiravir should not be administered to pediatric patients**
- Developmental and reproductive toxicity
  - Reduced fetal body weights in rats and rabbits, as well as embryo-fetal lethality and teratogenicity was observed
  - **Molnupiravir should not be administered during pregnancy**
  - **If a woman of child-bearing age is given Molnupiravir she should also be given barrier contraception**

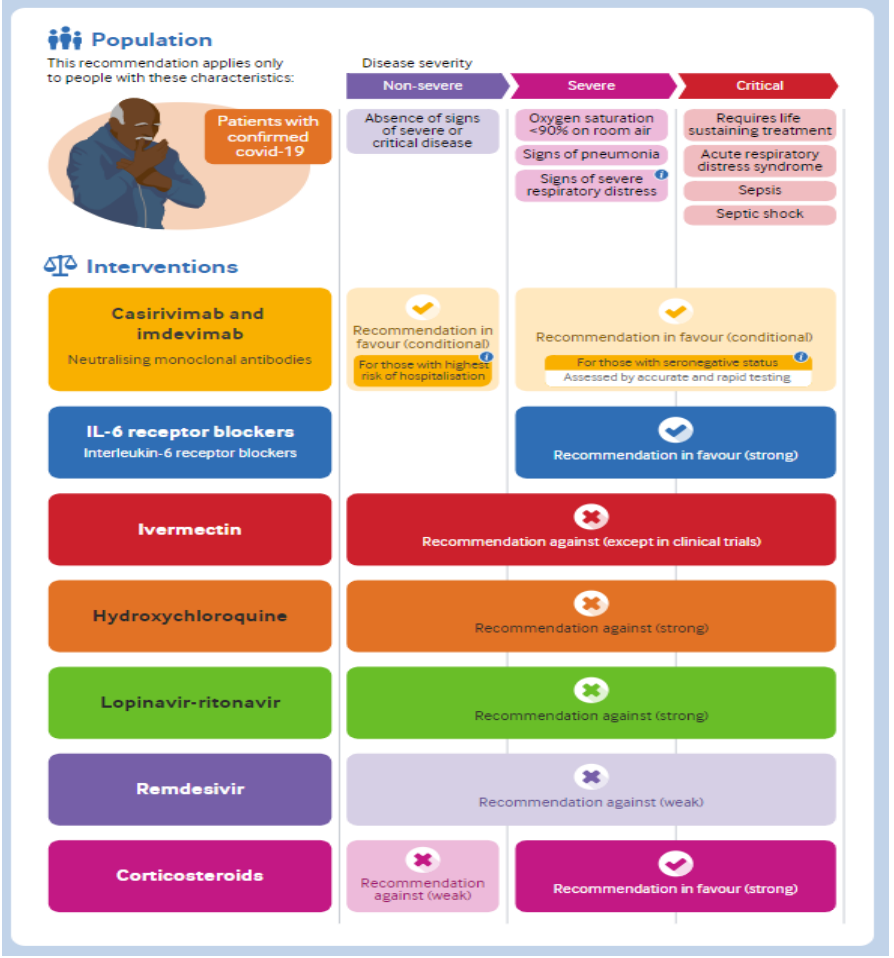
Nirmatrelvir/Ritonavir in COVID-19: women, pregnancy, and other considerations

- WHO Guideline Development Committee will meet 10th February 2022 to review Nirmatrelvir/Ritonavir
- Combination antiviral pill that blocks the SARS-CoV-2-3CL protease, administered with low-dose ritonavir with helps slow metabolism so the active molecule can remain in body longer at higher concentrations
- There is no experience treating pregnant or breastfeeding mothers with this therapeutic
- Numerous drug interactions

- Alfuzosin
- Pethidine, piroxicam, propoxyphene
- Ranolazine
- Amiodarone, dronedarone, flecainide, propafenone, quinidine
- Colchicine
- Lurasidone, pimozide, clozapine
- Dihydroergotamine, ergotamine, methylergonovine
- Lovastatin, simvastatin
- Sildenafil
- Triazolam, oral midazolam
- Apalutamide
- Carbamazepine, phenobarbital, phenytoin
- Rifampin
- St. John's Wort

Visual summary

- For further detail regarding guideline development process, see WHO Living Guideline, available at:
  - The BMJ: https://doi.org/10.1136/bmj.m3379
  - MAGICApp: https://app.magicapp.org/#/guidelines
  - WHO Therapeutics and COVID-19: Living Guideline: https://www.who.int/teams/health-care-readiness-clinical-unit/covid-19/therapeutics

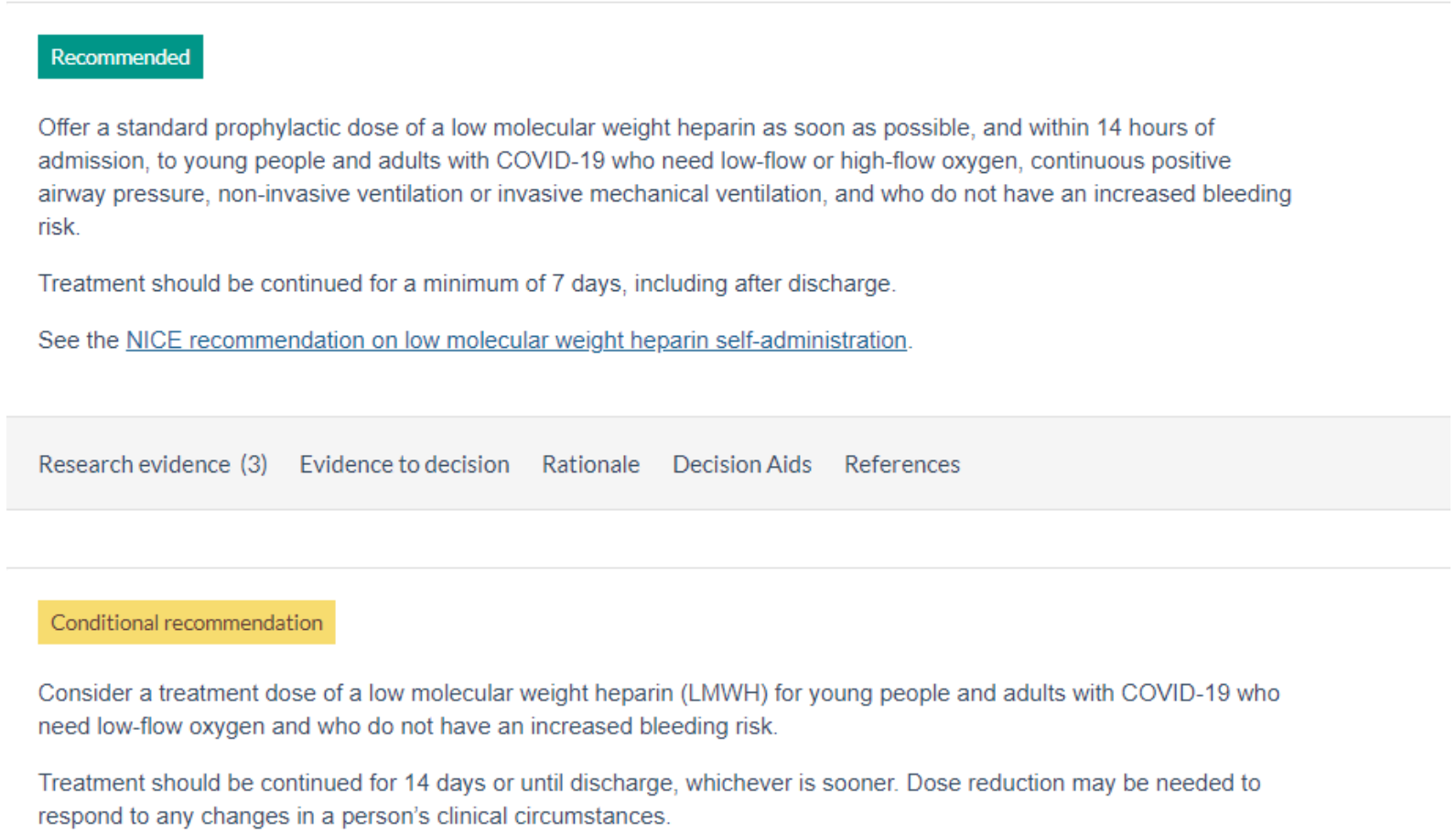


The use of heparins in hospitalised COVID-19 patients should be part of therapeutics – awaiting review by WHO COVID-19 GDG

NICE guidance in the UK

NIHR and ASH guidelines also recommending therapeutic anticoagulation in moderate disease

Pragmatically: At our centre
Give therapeutic anticoagulation to pregnant women with low bleeding risk, revert to standard thromboprophylaxis 2/52 prior to delivery



Recommended

Offer a standard prophylactic dose of a low molecular weight heparin as soon as possible, and within 14 hours of admission, to young people and adults with COVID-19 who need low-flow or high-flow oxygen, continuous positive airway pressure, non-invasive ventilation or invasive mechanical ventilation, and who do not have an increased bleeding risk.

Treatment should be continued for a minimum of 7 days, including after discharge.

See the NICE recommendation on low molecular weight heparin self-administration.

Research evidence (3) Evidence to decision Rationale Decision Aids References

Conditional recommendation

Consider a treatment dose of a low molecular weight heparin (LMWH) for young people and adults with COVID-19 who need low-flow oxygen and who do not have an increased bleeding risk.

Treatment should be continued for 14 days or until discharge, whichever is sooner. Dose reduction may be needed to respond to any changes in a person's clinical circumstances.

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