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DRUG THERAPY

VERSION 6 | SEPTEMBER 2021

health

Department:
Health
REPUBLIC OF SOUTH AFRICA

NDP
2030

MODULE 5: DRUG THERAPY

KEY RECOMMENDATIONS

> ▶ **Dexamethasone is recommended for patients requiring supplemental oxygen or mechanical ventilation.**
>
> ▶ **Heparin venous thromboembolism prophylaxis dosing is recommended for all hospitalised patients.** Therapeutic dosing of anticoagulation is no longer recommended for any subset of COVID-19 patients, unless there is a non-COVID indication.

There are many experimental medicines being tested for the treatment or prevention of COVID-19, and some may do more harm than good. The evidence for all potential pharmacological interventions is constantly being monitored and the guidelines will be updated accordingly.

The National Essential Medicines List (NEMLC) COVID-19 subcommittee has produced rapid evidence reviews and evidence-to-decision tables for potential therapeutic and prophylactic agents. These are updated regularly, and are available at: http://www.health.gov.za/covid-19-rapid-reviews/

The NEMLC decision process takes a clinical public-health perspective with consideration of affordability, equity, feasibility and acceptability in addition to considering the balance of benefits and harms.

Summary of COVID-19 treatments *Click on the name of the medicine to see the full evidence review.*
We recommend for treatment of COVID-19: • Corticosteroids for hospitalised patients with COVID-19 requiring oxygen support. • Heparin at prophylactic doses for hospitalised patients with COVID-19.
We recommend against the following medicines for COVID-19: • Chloroquine or hydroxychloroquine for treatment or prevention • Lopinavir/ritonavir • Interferon-beta-1a (subcutaneous or intravenous) • Azithromycin
We suggest against use the following medicines for COVID-19: • Tocilizumab (due to concerns about cost-effectiveness in the state sector) • Remdesivir • Mucolytics • BCG vaccination • Inhaled beta-2-agonists • Colchicine • Convalescent plasma

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- [Favipiravir](#)
- Heparin (or other anticoagulants) at therapeutic doses
- [Intravenous immunoglobulin](#)
- [Ivermectin for treatment](#)
- [Ivermectin for prevention](#)
- Statins
- Vitamin D
- [Vitamin C](#)
- Zinc
- [Inhaled corticosteroids](#)

1. TREATMENTS TO MANAGE COVID-19

1.1. Corticosteroids

Recommendation

We **recommend** a short course of low-dose systemic corticosteroids in hospitalised severe COVID-19 patients receiving respiratory support (as either invasive mechanical ventilation or non-invasive oxygen supplementation) **(strong recommendation, high-certainty evidence)**.

We **recommend** dexamethasone (6mg per day for 10 days) for the following indications:
- Patients with COVID-19 who are mechanically ventilated.
- Patients with COVID-19 who require supplemental oxygen but are not mechanically ventilated.

If dexamethasone is not available, an alternative corticosteroid may be used, such as:
- Betamethasone 6mg daily p.o. or intravenous, for 10 days.
- Prednisone 40 mg daily p.o. for 10 days.

For patients able to tolerate them, oral corticosteroid formulations may reduce the need for intravenous access. Dexamethasone tablets are available via the Section 21 application process

We **recommend against** using corticosteroids for the treatment of COVID-19 in patients who do not require supplemental oxygen or mechanical ventilation.
- Note: systemic corticosteroids should not be withheld from patients who require them for another reason such as an acute exacerbation of asthma or chronic obstructive pulmonary disease. Systemic corticosteroids may also be considered in patients with COVID-19 diagnosed with septic shock.

> **Rationale:** A meta-analysis of eight randomised-controlled trials (RCTs) showed that systemic corticosteroids reduced 28-day mortality in critically ill COVID-19 patients. However, in one RCT of hospitalised patients not requiring respiratory support, there was no evidence of benefit, and a possibility of harms, associated with corticosteroid use. Risk of bias was assessed as low in seven trials, with some concerns raised in respect of one trial. Although the results were dominated by the RECOVERY trial, the results of all included trials were consistent.

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Note: it is unclear whether these benefits can be extrapolated to the HIV population. In HIV-positive patients, particular care should be taken to exclude tuberculosis and *Pneumocystis jirovecii* pneumonia co-infection.

See evidence (20 October 2020): Corticosteroids

1.2. Anticoagulants

We **suggest** that hospitalised COVID-19 patients be prescribed prophylactic doses of anticoagulants rather intermediate- or therapeutic intensity doses in hospitalised immobilised patients meeting the criteria for prevention of thrombosis **(conditional recommendation, low-certainty evidence).**

- e.g. enoxaparin 0.5 mg/kg daily subcutaneously

Rationale: The balance of benefits and harms supports the use of prophylactic rather than therapeutic doses, unless specifically indicated for the management of thrombosis.

Remarks:

1. We do not recommend continuing anticoagulation therapy after discharge, as the risks of a major bleed outside a hospital may outweigh any potential benefits. In addition, in the above trials, therapeutic anticoagulation was continued for a maximum of 14 days as an inpatient.
2. The possibility of pulmonary embolism, stroke, or myocardial infarction should be considered in any hospitalised patient with COVID-19 whose condition rapidly deteriorates.
3. If a patient requires therapeutic doses of anticoagulants for a non-COVID reason (e.g. chronic atrial fibrillation, or pulmonary embolism), we recommend that they continue to receive their anticoagulants at therapeutic doses.
4. Heparin resistance has been described in severely-ill COVID-19 patients.[1]

We **recommend against** using anticoagulants (including low-molecular-weight heparin or direct-acting novel oral anticoagulants, such as rivaroxaban) or antiplatelet agents for outpatients with COVID-19.

Rationale: There is no evidence to support anticoagulants or antiplatelet agents in non-hospitalised patients. The overwhelming majority of such patients will recover fully from COVID-19 without any intervention, and therefore anticoagulants or antiplatelet agents are likely to be associated with risks that exceed any possible benefit.

See evidence (30 July 2021): anticoagulation

1.3. Azithromycin

We **do not recommend** routine use of azithromycin for the treatment of COVID-19 in either ambulatory or hospital settings **(strong recommendation, moderate to high-certainty evidence).** Azithromycin use should be restricted to patients in whom there is a clear antibacterial indication.

Rationale*:* There is no evidence of benefit for routine use of azithromycin for the treatment of COVID-19.

See evidence (9 April 2021): Azithromycin

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1.4. Tocilizumab

We **suggest not** to use tocilizumab **(Conditional recommendation, moderate to high-certainty evidence)**. Despite the reduction in death in the included trials, tocilizumab is not cost effective at the current offered price. However, outside of the state sector, it could be considered on a case-by-case basis, if costs allow.

> **Rationale:** A meta-analysis of 11 RCTs reporting mortality showed that tocilizumab, used in combination with corticosteroids, reduced all-cause mortality at day 28 from 29.2% to 25.7% amongst adult patients with COVID-19 with hypoxia and evidence of systemic inflammation (CRP ≥ 75mg/L), without an increase in clinically significant adverse events. However, the sub-committee expressed concerns regarding the budget impact and national supply of tocilizumab.

See evidence (26 May 2021): Tocilizumab

1.5. Convalescent plasma

We **suggest not** to use convalescent plasma for severe COVID-19 outside of a clinical trial setting **(conditional recommendation, very low-certainty evidence)**.

> **Rationale:** There is currently insufficient evidence to recommend routine use of convalescent plasma in children or adult patients with severe COVID-19. Eligible patients with COVID-19 in South Africa should be considered for enrolment in relevant therapeutic trials. Although additional studies have been published, their generalisability is limited by the variability in convalescent plasma utilised in different settings. In the absence of a standardised and well-characterised product, with proven neutralising ability against emergent variants of concern, further reviews of the literature are not considered to be useful at this time. There is also very limited access to convalescent plasma, outside of clinical trials.

See evidence (9 April 2021): Convalescent plasma

1.6. Ivermectin

We **suggest** that ivermectin **not be used** in the management of COVID-19, except in the context of a clinical trial **(conditional recommendation, very low-certainty evidence).**

> **Rationale:** There is currently insufficient evidence to recommend ivermectin for the treatment of COVID-19. Much of the RCT evidence consists of trials of low methodological quality, for the most part with small sample sizes and disparate interventions and controls, limiting the confidence in any conclusions with respect to ivermectin. What evidence does exist does not suggest any clear clinical or virological benefits.

See evidence (30 July 2021): Ivermectin for treatment

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1.7. Vitamin C

We **suggest that** vitamin C **not** be used for the treatment of COVID-19 in either ambulatory or hospital settings **(conditional recommendation, low to very low-certainty evidence).**

> **Rationale:** The current evidence is insufficient to support the inclusion of vitamin C to treat confirmed SARS-CoV-2 infection.

See evidence (28 May 2021): Vitamin C

1.8. Remdesivir

We **suggest** that remdesivir **not** be used in patients hospitalised with COVID-19 **(conditional recommendation, low-moderate certainty evidence).**

> **Rationale**. Remdesivir has not demonstrated a significant effect on pre-specified clinically important outcomes such as mortality or need for ventilation. Feasibility may be an issue as the medicine is not currently SAHPRA registered.
> In addition, access to the medicine is limited and it remains expensive.

See evidence (15 December 2020): Remdesivir

1.9. Inhaled corticosteroids

We **suggest against** the use of inhaled corticosteroids routinely in ambulant or hospitalised patients with COVID-19, not requiring oxygen therapy, unless indicated for other reasons **(conditional recommendation, very low-certainty evidence).**

> **Rationale:** There is low-certainty evidence of a modest reduction in the time to self-reported resolution of symptoms, based on two open-label studies. Whether this benefit justifies the cost of providing every ambulant patient with COVID-19, or even those in higher risk groups, with inhaled corticosteroids, and the potential adverse events associated with use of these agents, is unclear. There are also concerns of national supply constraints and the negative impact on availability of inhaled corticosteroids for use by patients with asthma or chronic obstructive pulmonary disease.

See evidence (9 July 2021): Inhaled steroids

1.10.   Interferon

We recommend against the use of type-1 interferon for the treatment of COVID-19 in hospitalised Patients **(strong recommendation, very low-certainty evidence).**

> **Rationale:** No mortality benefit, and type-1 interferons are unaffordable.

See evidence **(9 April 2021):** Interferon

1.11.   Chloroquine

Chloroquine or hydroxychloroquine **should not be used** to treat patients with COVID-19.

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Rationale: There is no evidence of benefit (moderate to high-certainty evidence) but increased risk of harm (moderate-certainty evidence).

See evidence (5 March 2021): Chloroquine

1.12. Colchicine

We **suggest not** to use colchicine for the treatment of COVID-19 in hospitalised and non-hospitalised patients, except in the context of an approved clinical trial **(conditional recommendation, very low-certainty evidence)**.

Rationale: The evidence of efficacy and safety is uncertain at this point, with insufficient evidence of clinically relevant benefits, an increased risk of adverse effects, and an uncertain risk of serious adverse effects.

See evidence (12 February 2021): Colchicine

1.13. Lopinavir/ritonavir

We **recommend against** the use of lopinavir-ritonavir for the management of mild to critical COVID-19 (strong recommendation, high-certainty evidence).

Rationale: Randomised controlled trial evidence indicates that lopinavir-ritonavir is no more effective than standard care in treating patients with COVID-19.

See evidence (21 December 2020): Lopinavir-ritonavir

1.14. Mucolytics

We **suggest** that bromhexine **not be used** for adults with COVID-19 **(conditional recommendation, very low-certainty evidence)**. Eligible patients with COVID-19 in South Africa should be considered for enrolment in relevant therapeutic trials.

Rationale: The evidence of efficacy and safety is very uncertain at this point. Studies were underpowered to detect clinically relevant outcomes of mortality or improvement in clinical outcomes; and there is an uncertain risk of serious adverse effects.

See evidence (23 November 2020): Mucolytics

1.15. Favipiravir

We **suggest** that favipiravir **should not** be used for the treatment of COVID-19. It should only be considered in the context of an approved clinical trial **(conditional recommendation, low-certainty evidence)**.

Rationale: There is insufficient evidence of the balance of benefits and harms at this time. Favipiravir is not yet registered by SAHPRA.

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See evidence (25 June 2020): <u>Favipiravir</u>

1.16. Intravenous (IV) immunoglobulins

We **suggest not to use** IV immunoglobulin in the treatment of COVID-19. There is currently insufficient evidence to support inclusion of IV immonoglobulins in treatment guidelines for COVID- 19 in South Africa until further data become available. Eligible patients with COVID-19 in South Africa should be considered for enrolment in relevant therapeutic trials.
See evidence (8 April 2020): <u>IV immunoglobulins</u>

2. PREVENTION OF COVID-19

We **do not suggest use of** any medicine as prophylaxis for COVID-19. The evidence for several medicines as prophylaxis has specifically been reviewed by the NEMLC COVID-19 subcommittee and found to be insufficient to warrant recommending their use.

See evidence:
2.2 <u>Hydroxychloroquine</u> (19 March 2021)
2.3 <u>BCG vaccination</u> (27 May 2020)
2.4 <u>Ivermectin</u> (25 January 2021)

Treatment given within a trial setting

Where investigational therapeutics are given outside of a clinical trial, this should be done under the Monitored Emergency Use of Unregistered Interventions (MEURI) framework, which provides an appropriate structure to offer individuals investigational interventions on an emergency basis in the context of an outbreak with a high mortality.[11] The principles of this include:
- Data providing preliminary support for the intervention's efficacy and safety are available, at least from laboratory or animal studies.
- The relevant human research ethics committee has approved use of the therapeutic.
- The patient's informed consent is obtained.
- Adequate resources are devoted to minimising the risk of administering the therapeutic agent.
- The results of the intervention are documented and shared with the wider medical and scientific community.

REFERENCE

1.   Beun R, Kusadasi N, Sikma M, Westerink J, Huisman A. Thromboembolic events and apparent heparin resistance in patients infected with SARS-CoV-2. *Int J Lab Hematol.* 2020;**42** (Suppl 1):19-20.

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