Drug therapy

Version 5 – what's new?

- Recommendations relating to the use of dexamethasone, heparin and remdesivir.
- Recommendation against the use of chloroquine, hydroxychloroquine, or lopinavir/ritonavir outside of a clinical trial.

Dexamethasone is recommended for patients requiring supplemental oxygen or mechanical ventilation.

Heparin venous thromboembolism prophylaxis is recommended for all hospitalised patients. Therapeutic dosing is suggested for patients requiring ≥60% supplemental oxygen, or those with a D-dimer >6 times the upper limit of normal.

Due to remdesivir's high cost and marginal benefit, routine use of the drug in hospitalised patients with COVID-19 is not recommended in the public sector outside of clinical trials.

Corticosteroids

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 who 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 drugs them, oral corticosteroid formulations may reduce the need for intravenous access. Dexamethasone tablets are available via the section 21 application process.

Rationale: The Recovery trial, a large-scale randomised controlled open label multi-center adaptive trial recently reported preliminary results for its dexamethasone arm.[1] Patients on invasive ventilation had an absolute reduction in mortality of 12% (95% CI 5.5-17.9%), with 9 ventilated patients needing to be treated to avert 1 death. There was a smaller benefit seen in those patients requiring supplemental oxygen, with a 3% reduction in mortality (95% CI 0.89-5.25%). 33 such patients would need to be treated to prevent 1 death.

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

We **recommend against** using dexamethasone 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.

Rationale: In the Recovery trial, there was evidence of potential harm when dexamethasone was given to patients not requiring supplemental oxygen. Those receiving dexamethasone had a 4% absolute increase in mortality (relative risk 1.22, 95% CI 0.93-1.61), though the result did not reach statistical significance.[1] In addition, glucocorticoids given to patients with other viral pneumonias such as SARS, MERS and influenza glucocorticoids, showed delayed viral clearance, no survival benefit and possible harms, such as hyperglycaemia and an increased risk of secondary nosocomial infections.[2-4]

Venous thromboembolism prophylaxis and pre-emptive therapy

We **recommend** that all hospitalised patients with COVID-19 receive prophylaxis against venous thromboembolic disease (VTE), in the absence of any contraindications.

We **suggest** that patients hospitalised with COVID-19 be considered for unfractionated or low molecular weight heparin at therapeutic doses (e.g. enoxaparin 1mg/kg 12-hourly based on actual weight) in the following scenarios:

- The patient requires supplemental oxygen at ≥60% oxygen concentration, or requires mechanical ventilation.
- The patient's serum D-dimers are greater than 6-times the upper limit of normal (i.e. above 1.5 mg/L).

Rationale: A recent evidence review concluded that there was insufficient evidence for therapeutic-intensity doses of either unfractionated or low molecular weight heparin in patients with COVID-19 in the absence of proven VTE disease. However, the high incidence of VTE disease seen in several cohorts of patients with severe COVID-19 was noted.[5, 6] In one cohort, therapeutic-intensity anticoagulation amongst COVID-19 patients in ICU was associated with a lower incidence of VTE.[6] Local experience has also seen a number of concerning cases of severe venous and arterial thromboembolic disease. Based on expert opinion, the panel therefore suggested that a severely ill subset of hospitalised COVID-19 patients be given therapeutic intensity heparin. The weakness of the evidence for this practice was acknowledged however, and guidance will be updated once further evidence is available.

Note:

1. The risks of therapeutic anticoagulation need to be considered on a case-by-case basis for each patient.
2. Where available, factor Xa monitoring may be beneficial, since heparin resistance has been described in severely-ill COVID-19 patients.[7]
3. We do not recommend continuing anticoagulation therapy after discharge, as the risks of a major bleed outside a hospital may outweigh any potential benefits.
4. In patients on chronic antiplatelet therapy who are given therapeutic-intensity anticoagulation, consider temporarily withholding the antiplatelet therapy unless there is a compelling indication for it to be continued.
5. The possibility of pulmonary embolism, stroke, or myocardial infarction should be considered in any hospitalised patient with COVID-19 whose condition rapidly deteriorates.

Remdesivir

Owing to remdesivir's anticipated high cost and marginal benefit, we **suggest** that remdesivir **not** be used in patients with COVID-19 within the public sector, outside of a clinical trial.
Remdesivir may be accessed via the section 21 application process for patients in the private sector, or for individual patients within the state sector, in accordance with the MEURI framework.

Rationale: One randomised control trial (RCT) showed that remdesivir shortened median time to recovery from 15 to 11 days, while an earlier RCT (which was underpowered as it could not complete recruitment) demonstrated no statistically significant benefits in any outcomes.[8, 9] A meta-analysis of the two RCTs showed that remdesivir decreased the risk of disease progression to requiring ventilation.[10] However, there were no statistically significant differences in mortality.

Other drugs

The National Essential Medicines List (NEMLC) COVID-19 subcommittee has produced rapid evidence reviews of a large number of potential therapeutic and prophylactic agents. These are updated regularly, and are available at: http://www.health.gov.za/index.php/national-essential-medicine-list-committee-nemlc/category/633-covid-19-rapid-reviews

There is insufficient evidence to recommend any of the following drugs for the treatment of COVID-19 outside of a clinical trial:

- Interferon beta
- Intravenous immunoglobulin
- Tocilizumab
- Azithromycin
- Convalescent plasma
- Favipiravir

Due to evidence of futility from large-scale randomised control trials, we **recommend against** using the following drugs to treat patients with COVID-19 outside of a clinical trial:

- Chloroquine or hydroxychloroquine
- Lopinavir/ritonavir

The guideline group are aware that many medicines are being used based on *in vitro* and observational data, such as vitamin D, vitamin C, beta-2-agonists and statins. None of these are currently recommended for the prevention or treatment of COVID-19, and some may do more harm than good. In addition, the evidence for the use of colchicine is currently undergoing review, and caution is advised until this review is complete. The evidence for all potential pharmacological interventions is constantly being monitored and the guidelines will be updated accordingly.

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 provide 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 the therapeutics' use.
- The patient's informed consent is obtained.
- Adequate resources are devoted to minimizing the risk of administering the therapeutic agent.
- The results of the intervention are documented and shared with the wider medical and scientific community.

Prophylaxis

There is currently **insufficient evidence to recommend** any drug as prophylaxis for COVID-19 other than in a clinical trial. The evidence for chloroquine or favipiravir as prophylaxis has specifically been reviewed by the NEMLC COVID-19 subcommittee and found to be insufficient to warrant a recommendation for their use.

References

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