Corticosteroids for COVID#19: evidence review of the ckinical benefit and harm

South African National Department of Health
Brief Report of Rapid Review
Component: COVID-19

TITLE: CORTICOSTEROIDS FOR COVID-19: EVIDENCE REVIEW OF THE CLINICAL BENEFIT AND HARM

Date: 23 June 2020

Key findings

- We did not find any systematic reviews of controlled trials for the use of corticosteroids in patients with confirmed or suspected COVID-19.
- Based on a preliminary report, in an open-label, randomised controlled trial, low-dose corticosteroids (dexamethasone 6mg daily, orally or intravenously) reduced mortality at 28 days in hospitalised COVID-19 patients on oxygen supplementation. The absolute reduction in risk of death overall was 3.1% (95% confidence interval (CI) 0.89% to 5.25%). For every 33 hospitalised patients treated with low dose corticosteroids, 1 death would be averted (95% CI 19 to 112 patients to prevent 1 death).
- However, there was no benefit from corticosteroids in the subgroup who did not require oxygen at baseline, and it is possible that corticosteroids caused harm in that group.
- The greatest benefit was seen in patients requiring mechanical ventilation at baseline - the absolute reduction in risk of death was 11.7% (5.5% to 17.9%). For every 9 ventilated patients treated with low dose corticosteroids, 1 death would be averted (95% CI 6 to 18)
- In patients on oxygen without mechanical ventilation at baseline, absolute reduction in risk of death was 3.5% (0.7% to 6.3%). For every 29 patients on oxygen only treated with corticosteroids, 1 death would be averted (95% CI 16 to 151).
- In the same study, dexamethasone shortened duration of hospitalisation (median of 12 days vs. 13 days, respectively) and reduced the risk of progression to mechanical ventilation (absolute risk reduction 1.9%, 95% CI 0.6% to 3.3%).
- The preliminary report did not describe adverse drug reactions of corticosteroids in COVID-19 patients.
- We found no studies of the use of corticosteroids in children with severe COVID-19.

NEMLC THERAPEUTIC GUIDELINES SUB-COMMITTEE RECOMMENDATION:

	We recommend against the option and for the alternative **(strong)**	We suggest not to use the option **(conditional)**	We suggest using either the option or the alternative **(conditional)**	We suggest using the option **(conditional)**	We recommend the option **(strong)**
Type of recommendation					**X**

Recommendation: Based on this evidence review, the NEMLC Subcommittee recommends the use of a short duration of low-dose systemic corticosteroids in hospitalised severe COVID-19 patients receiving respiratory support (as either invasive mechanical ventilation or non-invasive oxygen supplementation). Hospitalised patients not requiring respiratory support should not routinely be administered systemic corticosteroids, unless indicated 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 with septic shock.

Rationale: In one RCT, which has not yet been peer-reviewed, low dose corticosteroids reduced 28-day mortality in hospitalised patients on respiratory support. However, in hospitalised patients on no respiratory support, there was no evidence of benefit, with a possibility of harms associated with corticosteroid use. The recommendation should be reviewed when the RECOVERY trial is published in final, peer-reviewed form.

Level of Evidence: RCT, Standard of care

(Refer to appendix 3 for the evidence to decision framework)

Therapeutic Guidelines Sub-Committee for COVID-19: Marc Blockman, Karen Cohen, Renee De Waal, Andy Gray, Tamara Kredo, Gary Maartens, Jeremy Nel, Andy Parrish *(Chair)*, Helen Rees, Gary Reubenson *(Vice-Chair)*.

Note: Due to the continuous emergence of new evidence, the rapid review will be updated when more relevant evidence becomes available. As of 23 June 2020, 22 clinical trials are investigating the role of corticosteroids (parenteral, oral or inhalation) treatment of COVID-19 are registered on https://clinicaltrials.gov/. Completed studies includes observational study, NCT04374071, and NCT04273321 - a prospective randomised trial (study results yet to be posted).

BACKGROUND

Covid-19 commonly presents as mild illness and may progress within approximately one week to severe illness, with clinical features such as dyspnoea and hypoxemia. Severe COVID-19 is characterised by rapid progression to acute respiratory distress syndrome (ARDS), but may also lead to acute cardiac, kidney, and liver injury, cardiac arrhythmias, rhabdomyolysis, coagulopathy, and shock.[1]

There is much debate on the efficacy and safety of corticosteroids as adjuvant therapy for the treatment of severe COVID-19 patients. Existing guidelines provide conflicting recommendations. Chinese guidelines recommend the short-term use of corticosteroids in seriously ill patients (those with worsening hypoxia, rapid progression of infiltrates on radiological imaging, or excessive immune activation).[2]

The Surviving Sepsis Campaign[3] recommends low dose corticosteroid therapy in adults with COVID-19 and refractory shock (e.g. hydrocortisone 200mg per day as infusion or intermittent doses). This recommendation is based on indirect evidence from critically ill patients in general - a systematic review of 22 randomised controlled trials compared corticosteroids to no corticosteroid in patients with septic shock, and found no impact on mortality, but that steroids shortened time to resolution of shock and length of ICU and hospital stay.[4] The Surviving Sepsis campaign cautions against the routine use of systemic corticosteroids in mechanically ventilated patients with respiratory failure, but without acute respiratory distress syndrome (ARDS), but suggests short-course corticosteroids (such as intravenous methylprednisolone, 1–2 mg/kg/day for 5–7 days) for ARDS in mechanically ventilated COVID-19 patients with ARDS. This recommendation was also based on indirect evidence: a systematic review of systemic corticosteroids in hospitalised patients with community-acquired pneumonia concluded that corticosteroids may decrease need for mechanical ventilation, incidence of ARDS, and duration of hospital stay, but raised concerns about using corticosteroids in viral pneumonias.[5] These guidelines note a shorter duration of supplemental oxygen use (8.2 days vs. 13.5 days; p <0.001) in a published, but not peer-reviewed report of 26 patients with severe COVID-19[6].

A Cochrane systematic review evaluating the use of corticosteroids in influenza found increased mortality in patients with influenza (OR 2.76, 95% CI 2.06 to 3.69), but no impact on mortality for coronaviruses (OR 0.83, 95% CI 0.32 to 2.17).[7] An update of a Cochrane systematic review[8] (that included an additional RCT[9]) of pharmacological agents in the management of ARDS, (7 RCTS and 851 patients) found that corticosteroids reduced mortality (RR 0.75, 95% CI 0.59 to 0.95) and duration of mechanical ventilation (MD −4.93 days, 95% CI −7.81 to −2.06), but these trials did not focus on ARDS due to viral infections and results may not be generalisable to COVID-19.

The Infectious Diseases Society of America does not recommend the use of corticosteroids in patients admitted to hospital with COVID-19 pneumonia, and recommends that corticosteroids should only be given to patients with ARDS due to COVID-19 in the context of a clinical trial[10].

The World Health Organization guidelines currently recommend that routine systemic steroids should only be given in the context of a clinical trial, except in septic shock or ARDS due to COVID-19, and risk/benefit analysis needs to be conducted for individual patients.[11] All of these guidelines acknowledge the limited and low quality evidence guiding recommendations.

It is biologically plausible that corticosteroids may be of benefit in management of severe COVID-19 patients but also that corticosteroids may cause harms. Cytokine elevations have been described in COVID-19 patients with severe pneumonia[12] and manifestations of septic shock.[13, 14] Immunomodulatory therapy may down-regulate the cytokine storm. Corticosteroids have anti-inflammatory properties, and inhibit pro-inflammatory genes that encode cytokines, chemokines, cell adhesion molecules, inflammatory enzymes, and receptors to direct the inflammatory process and restore homeostasis.[15] Previous studies of corticosteroids in patients with severe acute respiratory syndrome (SARS)[16] and Middle East respiratory syndrome coronavirus (MERS-CoV),[5] due to novel coronaviruses, and with severe influenza[17] have shown that viral clearance is delayed, with no survival benefit and possible harms (e.g. psychosis, hyperglycaemia and hypokalemia[18]). Corticosteroids can also cause host immune suppression, resulting in an increased risk of secondary nosocomial infections. [19]

Limited published data reports that children constitute <2% of COVID-19 cases[20, 21, 22] and present with milder disease compared with adults.[23] However, recently, preliminary reports are emerging from Europe and North America clusters of children and adolescents admitted to intensive care units with a multisystem inflammatory condition (MIS-C) similar

to Kawasaki disease and toxic shock syndrome, which has been treated with intravenous immunoglobulin and corticosteroids[24, 25, 26]. As there is an urgent need to collect standardised data on clinical presentations, severity, outcomes, and epidemiology, the WHO has developed a preliminary case definition and case report form for multisystem inflammatory disorder in children and adolescents.[27] As evidence evolves, the use of corticosteroids for MIS-C would require further review.

RESEARCH QUESTION:

Research question: Should corticosteroids be used for managing severe COVID-19 (with or without ARDS, sepsis or septic shock) in patients requiring oxygen or ventilatory assistance?

Eligibility criteria for review

Population: Patients with confirmed COVID-19 with severe disease requiring oxygen, ventilator support and admission to ICU (no restriction to age)

Intervention: Corticosteroid either alone or in combination with other medicines. No restriction on dose, frequency, or timing with respect to onset of symptoms/severity of disease.

Comparators: Any (standard of care/placebo or active comparator).

Outcomes: Mortality; duration of hospitalisation; progression to ICU admission; progression to mechanical ventilation; duration of ICU stay; adverse reactions and adverse events.

Study designs: Randomised controlled trials, and systematic reviews of randomised controlled studies in humans.

METHODS

We conducted a rapid review of the evidence including systematic searching of four electronic databases (PubMed as well as the Epistemonikos, Cochrane COVID Study Register and Living mapping and living network meta-analysis of COVID-19 studies databases). We included randomised controlled trials and systematic reviews and meta-analyses of randomised controlled trials. We excluded observational studies, case reports, case series, case reports and narrative reviews. Publications were restricted to English. One reviewer screened records and extracted data. We summarised included studies in a narrative table of results. Risk of bias was assessed by two reviewers, using the modified Cochrane Collaboration risk of bias tool.[28] The search strategy is shown in Appendix 1.

RESULTS

We searched PubMed, as well as the Epistemonikos, Cochrane COVID Study Register and Living Mapping and Living Network meta-analysis of COVID-19 studies electronic databases on 23 June 2020. Details of each search are provided in Appendix 1. One reviewer screened 86 records and identified 1 potentially eligible article. The main characteristics and outcomes of the included study are reported **Table 1**.

The included study is an arm of the Randomised Evaluation of COVid-19 thERapY (RECOVERY) Trial, conducted in the United Kingdom. Results were presented in a preliminary report which has not been peer-reviewed[29].

The RECOVERY trial is a randomised, controlled, open-label, adaptive trial exploring efficacy and safety of a number of possible treatment options for COVID-19 in hospitalised patients. To date, more than 11 500 participants have been enrolled in more than 175 public sector hospitals in the UK. Of these, 2104 participants were randomised 2:1 to receive either dexamethasone 6 mg once per day (either orally or by intravenous injection) or usual care, for ten days or until discharge. The median duration of dexamethasone was 6 days [IQR 3 to 10 days]. Participants could be switched between oral and IV routes of administration as clinically required. Pregnant or breastfeeding women were treated with prednisolone 40 mg orally once daily or hydrocortisone 80 mg twice daily intravenously. Outcomes in patients receiving corticosteroids were compared with those in 4321 participants randomised to usual care only.
As part of usual care, a quarter of participants in both groups received azithromycin. (It has been suggested that azithromycin may have immunomodulatory effects[30]). A small proportion of participants received hydroxychloroquine, lopinavir-ritonavir, or interleukin-6 antagonists (tocilizumab or sarilumab), though treatments were distributed evenly between the dexamethasone and unusual care groups (see table 1).

The primary outcome of the study was mortality 28 days post-randomisation. Analyses of the primary outcome were performed in five subgroups, based on status at time of randomisation: age, sex, level of respiratory support, days since symptom onset, and predicted 28-day mortality risk.

Other secondary and subsidiary endpoints of relevance to our PICO were discharge from hospital within 28 days, need for ventilation, progression to supportive invasive mechanical ventilation, duration of ventilation, major cardiac arrhythmia, need for renal replacement therapy. Other adverse events and adverse reactions were not prespecified outcomes and were not described in the preliminary report.

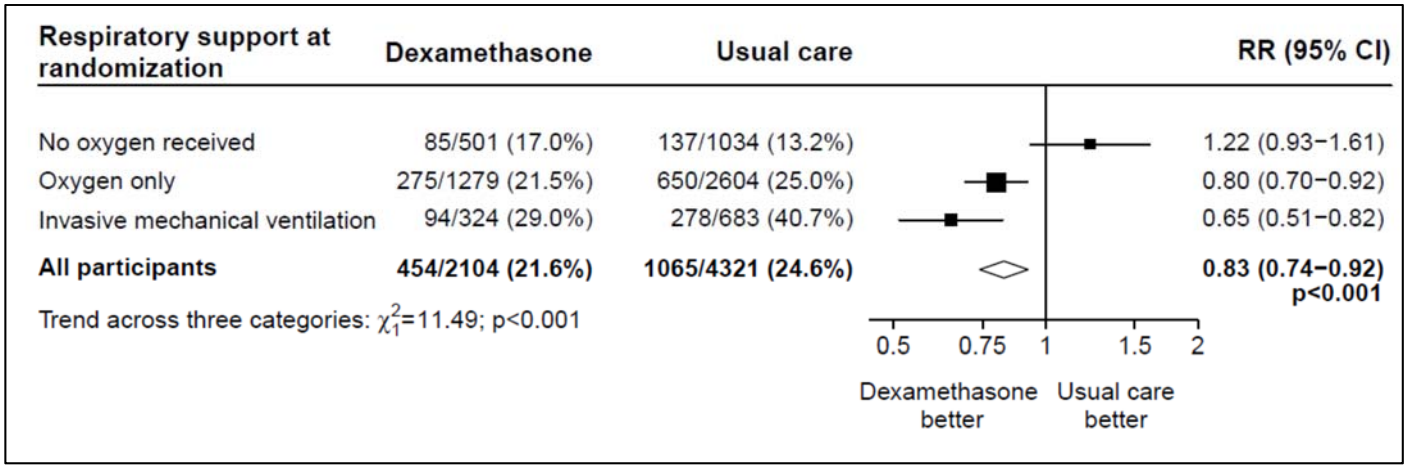
Mean age of study participants was 66.1 years, 36% were female patients and 6 participants were pregnant. The mean age of the dexamethasone cohort was 1.1 years higher than the usual care group. Therefore, the outcome estimates were adjusted for baseline age category (<70 years, 70-79 years, and 80 years or older). Analysis was by intention to treat. 4.8 % of participants were lost to follow up, but the actual number of loss to follow-up, for which outcome or how their data was analysed was not described in the preprint.

Primary outcome:
Overall, 21.6% (454/2104) patients allocated to the dexamethasone arm vs 24.6% (1065/43) patients allocated to usual care died within 28 days (age-adjusted rate ratio (RR) 0.83, 95% CI 0.74 to 0.92; p<0.001; absolute risk reduction (ARR) 3.1%, 95% CI 0.9% to 5.3%; NNT 33 (19to 112)).

28-day mortality differed significantly between the respiratory support subgroup analyses by level of respiratory support received at randomisation. Dexamethasone reduced deaths in ventilated patients (age-adjusted RR 0.65, 95% CI 0.51 to 0.82; p<0.001; ARR 11.7%, (5.5% to 17.9%); NNT 9 (6 to 18)); and in other patients receiving non-invasive oxygen (age-adjusted RR 0.80, 95% CI 0.70 to 0.92; p=0.002; ARR 3.5% (0.7% to 6.3%); NNT 29 (16 to 151)) - see figure 1, below.

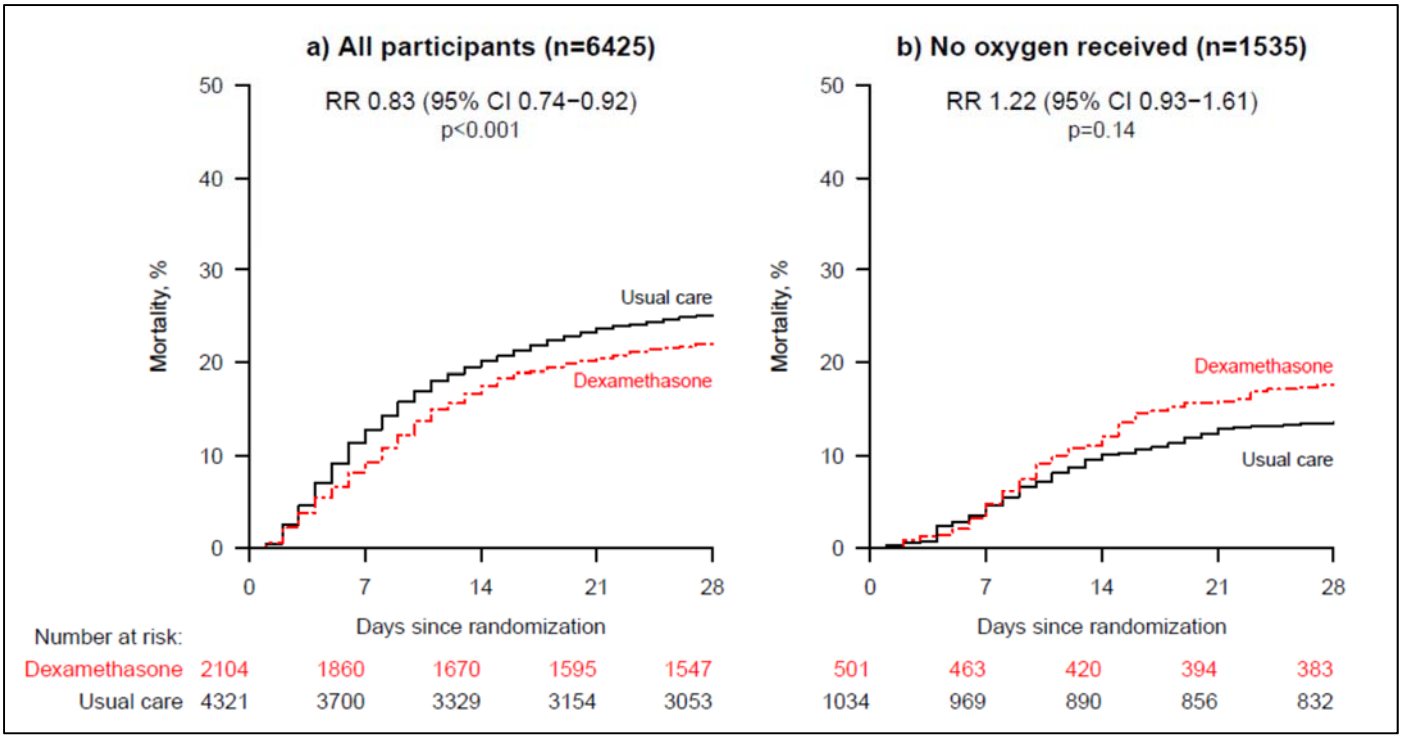
However, amongst hospitalised patients not requiring respiratory support, there was no evidence of benefit with a possibility of harms (RR 1.22, 95% CI 0.93 to 1.61; p=0.14) – see figure 2, below. It is postulated that peak viral shedding in COVID-19 is higher early in the illness and then declines.[31, 32]The mortality benefit of dexamethasone in patients with severe COVID-19 who required respiratory support, was generally seen after 7 days, suggesting that at this stage the viral replication is secondary and pathology is dominated by an immune response – see figure 3, below. In a retrospective single study from Wuhan, radiological abnormalities (compared with baseline) occurred on day 7 following symptom onset[33]. Dexamethasone was of no benefit in patients 70 years or older, where mortality is the highest.[34] Only 17% of this patient group was ventilated compared to 83% in those less than 70 years of age – see figure 3 and 4, below.

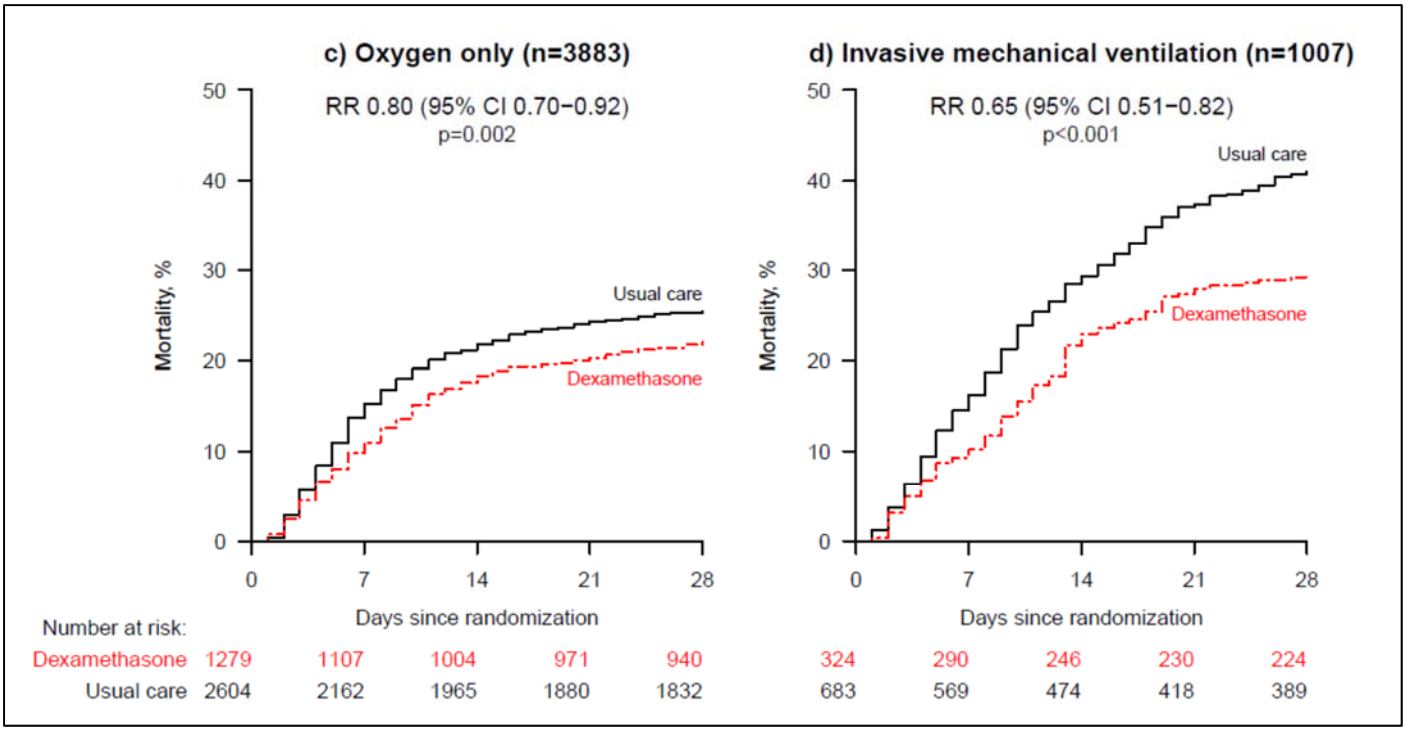
Figure 1: Mortality at day 28 by level of respiratory support received at randomisation



RR=age−adjusted rate ratio. CI=confidence interval. The 'oxygen only' group includes non−invasive ventilation. Note: in the RECOVERY trial press release of 16 June 2020, effects in subgroups of level of respiratory support received were shown with 99% CIs, not 95% CIs as inadvertently stated. The age−adjusted rate ratio and 99% confidence intervals remain unchanged in this analysis: no oxygen required, RR 1.22 (99% CI 0.86−1.75); oxygen only, RR 0.80 (99% CI 0.67−0.96); invasive mechanical ventilation, RR 0.65 (99% CI 0.48−0.88).

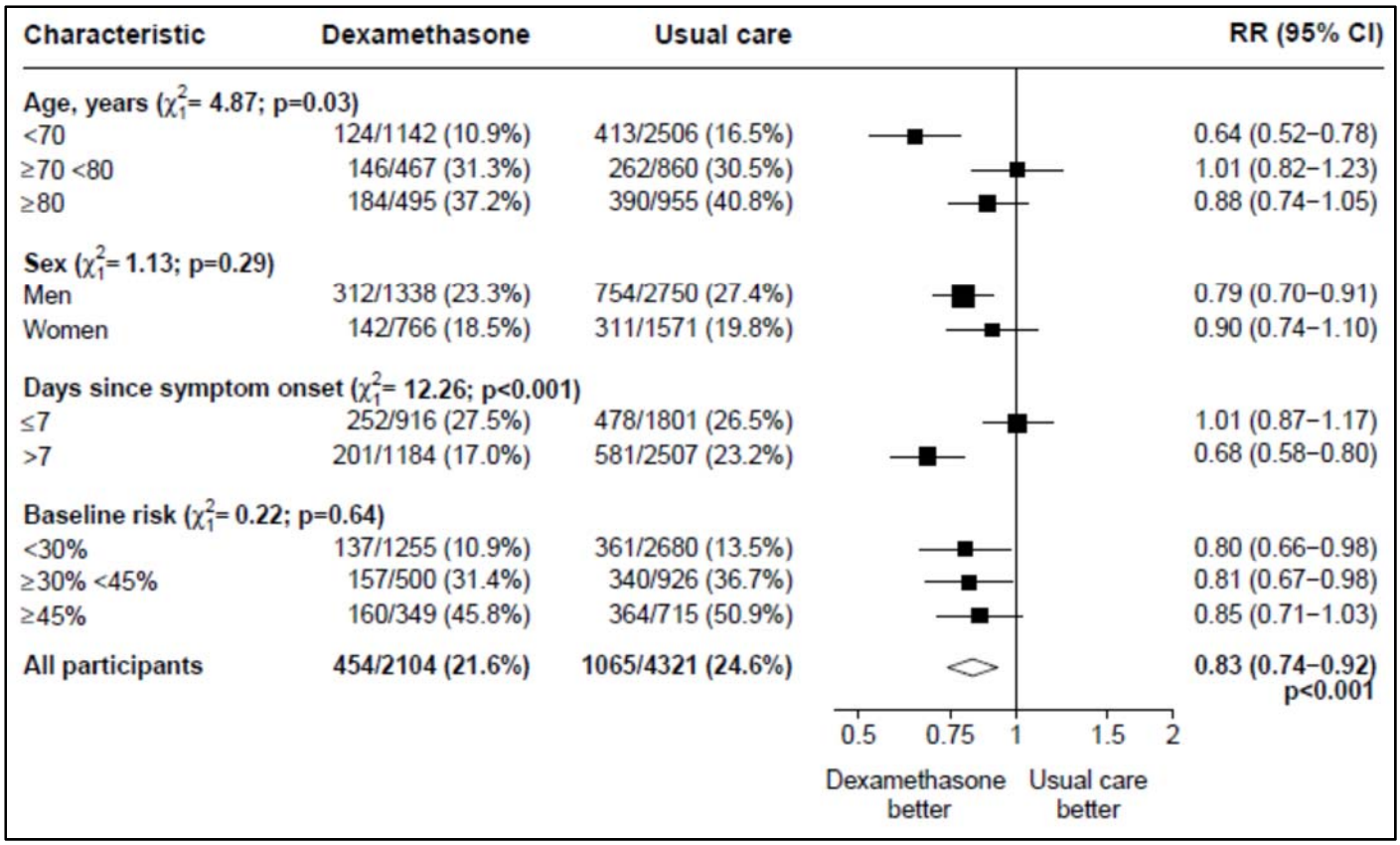
Figure 2: 28−day mortality in all patients (panel a) and separately according to level of respiratory support received at randomization (panels b−d)





RR=age−adjusted rate ratio. CI=confidence interval. The 'oxygen only' group includes non−invasive ventilation. Note: in the RECOVERY trial press release of 16 June 2020, effects in subgroups of level of respiratory support received were shown with 99% CIs, not 95% CIs as inadvertently stated. The age−adjusted rate ratio and 99% confidence intervals remain unchanged in this analysis: no oxygen required, RR 1.22 (99% CI 0.86−1.75); oxygen only, RR 0.80 (99% CI 0.67−0.96); invasive mechanical ventilation, RR 0.65 (99% CI 0.48−0.88)

Figure 3: Mortality at day 28 by other pre−specified baseline characteristics



RR=age−adjusted (or age−specific) rate ratio. CI=confidence interval. Subgroup−specific RR estimates are represented by squares (with areas of the squares proportional to the amount of statistical information) and the lines through them correspond to the 95% confidence intervals.

Figure 4: Baseline characteristics by randomised allocation and level of respiratory support

	Treatment allocation		Respiratory support received at randomization		
	Dexamethasone (n=2104)	Usual care (n=4321)	No oxygen received (n=1535)	Oxygen only (n=3883)	Invasive mechanical ventilation (n=1007)
Age, years	66.9 (15.4)	65.8 (15.8)	69.3 (17.6)	66.7 (15.3)	59.0 (11.5)
<70	1142 (54%)	2506 (58%)	660 (43%)	2149 (55%)	839 (83%)
≥70 to <80	467 (22%)	860 (20%)	338 (22%)	837 (22%)	152 (15%)
≥80	495 (24%)	955 (22%)	537 (35%)	897 (23%)	16 (2%)
Sex					
Male	1338 (64%)	2750 (64%)	892 (58%)	2462 (63%)	734 (73%)
Female*	766 (36%)	1571 (36%)	643 (42%)	1421 (37%)	273 (27%)
Number of days since symptom onset	8 (5-13)	9 (5-13)	6 (3-10)	9 (5-12)	13 (8-18)
Respiratory support received					
No oxygen received	501 (24%)	1034 (24%)	1535 (100%)	0 (0%)	0 (0%)
Oxygen only	1279 (61%)	2604 (60%)	0 (0%)	3883 (100%)	0 (0%)
Invasive mechanical ventilation	324 (15%)	683 (16%)	0 (0%)	0 (0%)	1007 (100%)

Secondary outcome(s):

For the secondary outcome of hospital discharge within 28 days, patients allocated to dexamethasone had a shorter duration of hospitalisation vs patients allocated usual care (median 12 days vs. 13 days, respectively; and at 28 days: 1360/2104 (64.6%) vs 2639/4321 (61.1%), ARR 3.6%, 95% CI 1.1 % to 6.1%; NNT 29, 95% CI 17 to 95; age-adjusted RR 1.11, 95% CI 1.04 to 1.19; p=0.002).

Subsidiary clinical outcomes:
The risk of progression to invasive mechanical ventilation was lower among those allocated to the dexamethasone arm vs. usual care [92/1780 (5.2%) vs 258/3638 (7.1%), ARR 1.9%, 95 % CI 0.6% to 3.3%; NNH 52 (31 to 167); age-adjusted RR 0.76, 95% CI 0.61 to 0.96; p=0.021].
Further analyses of cause-specific mortality, need for renal dialysis or haemofiltration, and duration of ventilation, and are in process.

Safety:
Adverse outcomes and adverse drug reactions associated with corticosteroids, other than mortality, was not reported in the pre-print report.

Data in the paediatric population is currently lacking.

Quality of the evidence:
- We reviewed the RECOVERY study results in preprint, prior to peer-review.
- Risk of bias was assessed as low to moderate risk:
  - The study was open-label, but with randomisation and control to reduce bias. However, performance bias may be present as details of usual standard care in the participating hospital was not reported, and it is uncertain whether usual care was standardised across all 176 National Health Service (NHS) study centre hospitals in the UK. In addition, 7% of usual care group received dexamethasone.
  - Participants and personnel were not blinded to the allocated treatment.
  - Blinding of outcome assessment (detection bias): There was no blinding for the assessment of outcomes, but risk assessed to be "low" for the outcomes of mortality. However, the adjustment for age appears to be a post hoc analysis.
  - Baseline demographics between study groups were generally similar, except that there was greater provision of respiratory support to patients <70 years of age (oxygen 55%; ventilation 83%); whilst less patients ≥80 years of age were ventilated (oxygen 23%; ventilation 2%). The rationale for providing ventilation to younger study participants was not provided. Details of the duration of mechanical ventilation after randomisation has not been described.
  - Details of loss to follow-up has not been provided – actual numbers of study participants, which outcomes were affected and if attrition was differential.
  - The preprint does not provide the complete data, evidence or rationale of the study (e.g. post hoc age adjusted analysis was reported, but the unadjusted results were not provided). Thus, risk of bias may be incomplete and reassessment would be required, once the complete peer-reviewed study results is published
- Concomitant azithromycin (known to have immunomodulatory activity) that was administered to a quarter of study participants in both the dexamethasone and usual care groups, may have contributed to the mortality benefit that has been attributed to low-dose corticosteroids in this study. However, the proportion receiving azithromycin was similar in the intervention and comparator groups.
- This RCT has adequate statistical power and is multi-centred. However, the distribution of study participants' inclusions per centre has not been reported in the preprint. Exclusion criteria were also not reported.
- Baseline comparative laboratory data on inflammatory markers were not reported.

PRAGMATIC CONSIDERATIONS FOR SOUTH AFRICAN CONTEXT:

Availability of corticosteroids in South Africa
Although the intravenous dosage form of dexamethasone is registered in South Africa, the oral solid dosage form is only available under section 21. The supply constraints warrant consideration of alternative corticosteroids (refer to appendix 2 for estimated equivalent doses of corticosteroids which is based on relative anti-inflammatory potency). In the protocol, hydrocortisone IV (80 mg twice daily) and prednisone oral (40 mg daily) were allowed in pregnant or breastfeeding women. A 100 mg hydrocortisone IV dosage form available on the South African market.

It is important to guard against inappropriate use of dexamethasone (or alternative oral corticosteroids) in ambulatory care, where patients do not receive oxygen therapy. Whether a corticosteroid should be administered at primary care level in patients who receive non-invasive oxygen supplementation at that point, remains to be determined – though a pre-referral dose could be considered where hospital transfer is delayed.

CONCLUSION

Data from the RECOVERY trial, conducted in the United Kingdom, provides evidence of mortality benefit, supporting the use of corticosteroids in patients requiring either non-invasive oxygen therapy, or mechanical ventilation. However, hospitalised patients with severe disease not requiring oxygen or ventilatory assistance should not be administered systemic corticosteroids routinely, as there is evidence of harm (a trend towards increased mortality). However, this recommendation should be reviewed when the RECOVERY trial is published in final, peer-reviewed form.

Reviewers: Trudy Leong, Jane Riddin, Andy Gray, Karen Cohen.

Declaration of interests: TL and JR (National Department of Health, Affordable Medicines Directorate, Essential Drugs Programme), AG (Division of Pharmacology, University of KwaZulu-Natal); and KC (Division of Clinical Pharmacology, Department of Medicine, Groote Schuur Hospital, University of Cape Town) have no interests to declare in respect of corticosteroid therapy for COVID-19.

Table 1. Characteristics of included randomised controlled trial

Citation	Study design	Population (n)	Treatment	Outcomes	Effect sizes	Comments
RECOVERY Collaborative Group[29] *Preprint*	Randomised, controlled, open-label, adaptive trial	N=6425 (total) Dexamethasone group(n=2104) ***vs*** usual care (n= 4321) *At randomisation:* • Invasive mechanical ventilation/ECMO: 15% (324/2104) vs 16% (683/4321) • Oxygen only (with/without non-invasive ventilation): 61% (1279/2104) vs 60% (2604/4321) • Neither oxygen or invasive ventilation/ECMO: 24% (501/2104) vs 24% (1034/4321) • Clinically suspected (9%) or confirmed SARS-CoV-2 infection (82%). • Mean age of 66.1 years, 36% female patients (6 pregnant women). • Comorbidities: Diabetes (25% vs 24%), heart disease (28% vs 27%), chronic lung disease (20% vs 22%), at least one comorbidity (56% vs 56%).	Dexamethasone, oral/ IV, 6 mg once daily for 10 days ***vs*** none (usual care) • Pregnancy/ breastfeeding women: prednisolone, oral, 40 mg daily or hydrocortisone, IV, 80 mg twice daily for 10 days. • Protocol permitted switch between oral and IV routes of administration as clinically indicated. • *Concomitant therapy:* - Azithromycin: 449 (23%) vs 970 (24%) - Lopinavir/ritonavir 2 (0%) vs 5 (0%) - HCQ: 16 (1%) vs 20 (1%) - Tocilizumab/ sarilumab 28 (1%) vs 99 (1%) - Not recorded 17 (1%) vs 29 (1%)	<u>*Primary:*</u> • Mortality at 28-days from onset of symptoms <u>*Secondary:*</u> • Discharged from hospital within 28 days • Progression to invasive mechanical ventilation • Subsidiary clinical outcomes: major cardiac arrhythmia, and receipt and duration of ventilation	<u>*Primary outcome:*</u> **28-day mortality:** *Dexamethasone vs none (usual care):* • *All participants* (n=6425): 21.6% *vs* 24.6%, ARR 3.1% (95% CI 0.9% to 5.3%), NNT 33 (19 to 112); age-adjusted RR 0.83 (95% CI 0.74 to 0.92, p<0.001) • *No oxygen received* (n=1535) 17.0% *vs* 13.2%, ARR 3.7% (95% CI, -0.17% to 7.6%), NNH 27; age-adjusted RR 1.22 (95% CI 0.93 to 1.61, p=0.14) • *Oxygen only* (n=3883): 21.5% *vs* 25.0%, ARR 3.5% (95% CI 0.7% to 66.3%), NNT=29 (16 to 151); age-adjusted RR 0.80 (95% CI 0.70 to 0.92, p=0.002) • *Invasive mechanical ventilation* (n=1007): 29.0% *vs* 40.7%, ARR 11.7% (95% CI 5.5% to 17.9%), NNT=9 (6 to 18); age-adjusted RR 0.65 (95% CI 0.51 to 0.82, p<0.001) <u>*Secondary outcomes:*</u> • **Hospital discharge within 28 days:** median 12 days vs. 13 days, respectively; age-adjusted RR 1.11, 95% CI 1.04 to 1.19; p=0.002); ARR 3.6% (95% CI 1.1% to 6.1%), NNT 29 (17 to 95) • **Risk of progression to invasive mechanical ventilation**: age-adjusted RR 0.76, 95% CI 0.61 to 0.96; p=0.021; ARR 1.9% (95% CI 0.6% to 3.3%), NNT 52 (31 to 167).	• Preprint reviewed, prior to peer-reviewed journal publication. • Despite a loss of follow up of 4.8% patents, this is an intention to treat analysis. • Open-label with randomisation, control and blinded outcome assessment (study results not made available to research team, patients, or members of the Steering Committee) to reduce bias. • Details of usual care is not reported and may not be uniform across study sites (176 NHS hospitals). • Concomitant azithromycin (known to have immunomodulatory activity) administered to a quarter of study participants, this was balanced between groups. • Adverse events and adverse drug reactions associated with glucocorticoids not reported. • Study is supported by a grant to the University of Oxford from UK Research and Innovation/National Institute for Health Research (NIHR) and by core funding provided by NIHR Oxford Biomedical Research Centre, the Wellcome Trust, the Bill and Melinda Gates Foundation, Health Data Research UK, and the Medical Research Council Population Health Research Unit, and NIHR Clinical Trials Unit Support Funding. **<u>Overall judgement with regards to risk of bias judged as "*MODERATE RISK*":</u>** **-Random sequence generation (selection bias)**: simple web-based randomisation in a 2:1 ratio of dexamethasone:usual care. ***LOW RISK.*** **-Allocation concealment (selection bias)**: Allocation was concealed. ***LOW RISK***

						-Blinding of participants and personnel (performance bias): There was no blinding. ***HIGH RISK.*** **- Blinding of outcome assessment (detection bias)**: There was no blinding, but risk assessed to be "low" for the outcomes: Mortality. The adjustment for age appears to be a post hoc analysis. ***MODERATE RISK*** **-Incomplete outcome data addressed (attrition bias)**: 4.8% loss to follow up – but details not provided (actual numbers and which outcomes were affected, if attrition was differential). Intention to treat analysis. ***MODERATE RISK*** **-Selective reporting (reporting bias)**: Protocol and statistical analysis plan were available. Risk assessed to be low for the outcomes: Mortality. However, the preprint does not provide for detailed transparent analyses, statistical analysis plans and statistical analysis reports or amendments made to plans during or after the trial. ***LOW RISK***. - **Other bias:** As this is a preprint, and not the full study report published in a peer-reviewed journal, data and rationale may be lacking to determine whether an important risk of bias exists (e.g. baseline laboratory inflammatory markers not reported; rationale for mostly ventilating younger patients <70 years of age, post hoc age adjusted analysis was reported, but the unadjusted results were not provided). Risk of bias requires to be reassessed, once complete peer-reviewed study results is published. ***MODERATE RISK***

Table 2: Summary of findings for use of dexamethasone in hospitalised patients with COVID-19

Note: The preprint only reports age-adjusted rate ratios, and not the unadjusted results. The rate ratios in the table below are not age-adjusted, and had been sourced from a living systematic review (on the 29 June 2020), available at: https://covid-nma.com/living_data/index.php

Outcomes	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	Risk difference with corticosteroids	№ of participants (studies)	Certainty of the evidence (GRADE)
	Risk with standard care	Risk with corticosteroids				
Overall mortality follow up: 28 days	246 per 1,000	**217 per 1,000** (195 to 237)	**RR 0.88** (0.79 to 0.96)	**30 fewer per 1,000** (from 52 fewer to 10 fewer)	6425 (1 RCT)	⊕⊕⊕◯ MODERATE [a]
Mortality - no oxygen received follow up: 28 days	132 per 1,000	**170 per 1,000** (132 to 217)	**RR 1.28** (1.00 to 1.64)	**37 more per 1,000** (from 0 fewer to 85 more)	1535 (1 RCT)	⊕⊕◯◯ LOW [a,b]
Mortality - oxygen only follow up: 28 days	250 per 1,000	**215 per 1,000** (190 to 245)	**RR 0.86** (0.76 to 0.98)	**35 fewer per 1,000** (from 60 fewer to 5 fewer)	3883 (RCTs)	⊕⊕⊕◯ MODERATE [a]
Mortality - mechanical ventilation follow up: 28 days	407 per 1,000	**289 per 1,000** (240 to 350)	**RR 0.71** (0.59 to 0.86)	**118 fewer per 1,000** (from 167 fewer to 57 fewer)	1007 (1 RCT)	⊕⊕⊕◯ MODERATE [a]

a. Blinding of participants and personnel (performance bias): There was no blinding.
Blinding of outcome assessment (detection bias): There was no blinding, but risk assessed to be "low" for the outcomes: Mortality. The adjustment for age was probably a post hoc analysis.
Incomplete outcome data addressed (attrition bias): 4.8% loss to follow up – but details not provided (actual numbers, which outcomes were affected and attrition differential). Intention to treat analysis.

b. The results cross null and there is appreciable harm associated with dexamethasone in this patient cohort.

Appendix 1: Search strategy

Epistemonikos

Search strategy: (title:((title:(coronavirus) OR abstract:(coronavirus)) OR (title:(covid) OR abstract:(covid)) OR (title:(2019-ncov) OR abstract:(2019-ncov)) OR (title:(sars-cov-2) OR abstract:(sars-cov-2)) AND (title:(corticosteroid) OR abstract:(corticosteroid))) OR abstract:((title:(coronavirus) OR abstract:(coronavirus)) OR (title:(covid) OR abstract:(covid)) OR (title:(2019-ncov) OR abstract:(2019-ncov)) OR (title:(sars-cov-2) OR abstract:(sars-cov-2)) AND (title:(corticosteroid) OR abstract:(corticosteroid))))

Output: 11 records (1 duplicate, 4 ongoing studies, none relevant to PICO)

PubMed

Search strategy: (("COVID-19"[All Fields] OR "COVID-2019"[All Fields] OR "severe acute respiratory syndrome coronavirus 2"[Supplementary Concept] OR "severe acute respiratory syndrome coronavirus 2"[All Fields] OR "2019-nCoV"[All Fields] OR "SARS-CoV-2"[All Fields] OR "2019nCoV"[All Fields] OR (("Wuhan"[All Fields] AND ("coronavirus"[MeSH Terms] OR "coronavirus"[All Fields])) AND (2019/12[PDAT] OR 2020[PDAT]))) AND ("adrenal cortex hormones"[MeSH Terms] OR ("adrenal"[All Fields] AND "cortex"[All Fields] AND "hormones"[All Fields]) OR "adrenal cortex hormones"[All Fields] OR "corticosteroid"[All Fields])) AND ("hospitals"[MeSH Terms] OR "hospitals"[All Fields] OR "hospital"[All Fields])

Output: 65 records (2 duplicates, none relevant to the PICO)

Living mapping and living network meta-analysis of COVID-19 studies (https://covid-nma.com/)

Corticosteroids

RCTs: No records retrieved

Cochrane COVID Study Register (https://covid-19.cochrane.org/)

Corticosteroids

Output: 10 records (1 duplicate, all relevant to the PICO, 8 are ongoing studies, 1 preliminary report of completed RCT – Horby et al., 22 June 2020)

Appendix 2: Comparison of systemic corticosteroids

Table 3: Systemic corticosteroids comparisons

Glucocorticoid	Equivalent doses (mg)	Routes of administration	Pregnancy Category	Relative anti-inflammatory potency	Approximate plasma half-life (min)	Biologic half-life (h)
Short-acting						
Cortisone	25	oral, IM	D	0.8	30	8-12
Hydrocortisone	20	oral, IM, IV	C	1	90	8-12
Intermediate-acting						
Methylprednisolone	4	oral, IM, IV		5	180	18-36
Prednisolone	5	oral	B	4	200	18-36
Prednisone	5	oral	B	4	60	18-36
Triamcinolone	4	oral, IM	C	5	300	18-36
Long-acting						
Betamethasone	0.6	oral, IM, slow IV	C	25	100-300	36-54
Dexamethasone	0.75	oral, IM, IV	C	25-30	100-300	36-54

Abbreviations: mg=milligram, IM=intramuscular; IV=intravenous; min=minute; h=hour; B, C, D=FDA assigned pregnancy categories

Data sourced from:

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4. South African Medicines Formulary. 13th Edition. Division of Clinical Pharmacology. University of Cape Town, 2020.

Table 4: Equivalent corticosteroid doses for severe COVID-19 patients on respiratory support

Glucocorticoid	Equivalent dose (mg)
Dexamethasone, oral*, IV	6 mg daily for 10 days
Betamethasone, oral, slow IV	6 mg daily for 10 days
Hydrocortisone, IV	80 mg twice daily for 10 days
Methylprednisolone, oral, IV** **CAUTION: THIS IS NOT THE DEPOT METHYLPREDNISIOLONE FORMULATION**	32 mg daily for 10 days
Prednisone, oral	40 mg daily for 10 days
Prednisolone, oral	40 mg daily for 10 days

**Dexamethasone, oral tablets/capsules can only be obtained on Section 21 application.*

***Formulation is the **methylprednisolone immediate-release** dosage form.*

Note: Switch between IV and oral routes of administration, wherever clinically indicated.

Appendix 3: Evidence to decision framework

	JUDGEMENT	EVIDENCE & ADDITIONAL CONSIDERATIONS
QUALITY OF EVIDENCE OF BENEFIT	**What is the certainty/quality of evidence?** High: [ ] Moderate: [ ] Low: [X] Very low: [ ] *High quality:* confident in the evidence *Moderate quality:* mostly confident, but further research may change the effect *Low quality:* some confidence, further research likely to change the effect *Very low quality:* findings indicate uncertain effect	One randomised, controlled, open-label, adaptive trial by RECOVERY Collaborative Group, UK. The study has adequate statistical power and is multi-centred. Study results available in a preprint report that has not been peer-reviewed as yet. ***Note:*** As the peer-reviewed publication is not currently available, the quality of evidence was judged low and will be reviewed once the peer-reviewed publication is available.
EVIDENCE OF BENEFIT	**What is the size of the overall effect for beneficial outcomes?** Large: [ ] Moderate: [X] Small: [ ] None: [ ] Uncertain: [ ] **Note:** The overall effect was judged as moderate; however, in the ventilated cohort the effect was substantial.	<u>*Primary outcome:*</u>**28-day mortality:** *Dexamethasone vs none (usual care):* • *All participants* (n=6425): 21.6% *vs* 24.6%, ARR 3.1% (95% CI 0.9% to 5.3%), NNT 33 (19 to 112); age-adjusted RR 0.83 (95% CI 0.74 to 0.92, p<0.001) • *No oxygen received* (n=1535) 17.0% *vs* 13.2%, ARR 3.7% (95% CI, -0.17% to 7.6%), NNH 27; age-adjusted RR 1.22 (95% CI 0.93 to 1.61, p=0.14) • *Oxygen only* (n=3883): 21.5% *vs* 25.0%, ARR 3.5% (95% CI 0.7% to 66.3%), NNT=29 (16 to 151); age-adjusted RR 0.80 (95% CI 0.70 to 0.92, p=0.002) • *Invasive mechanical ventilation* (n=1007): 29.0% *vs* 40.7%, ARR 11.7% (95% CI 5.5% to 17.9%), NNT=9 (6 to 18); age-adjusted RR 0.65 (95% CI 0.51 to 0.82, p<0.001)
EVIDENCE OF HARMS	**What is the size of the effect for harmful outcomes?** Large: [ ] Moderate: [ ] Small: [ ] None: [ ] Uncertain: [X]	Adverse outcomes associated with corticosteroids, other than mortality, were not reported in the preliminary report of the RCT of hospitalised patients infected with SarsCoV-2.
BENEFITS & HARMS	**Do the desirable effects outweigh the undesirable harms?** Favours intervention: [X] Favours control: [ ] Intervention = Control *or* Uncertain: [ ]	
FEASABILITY	**Is implementation of this recommendation feasible?** Yes: [X] No: [ ] Uncertain: [ ]	Dexamethasone oral is accessible via section 21. However, therapeutic equivalent corticosteroids are available – see appendix 2.
RESOURCE USE	**How large are the resource requirements?** More intensive: [X] Less intensive: [ ] Uncertain: [ ]	Price of medicines/ treatment course of 10 days (10d)

Medicine	Tender Price (R)	Single Exit Price (R)*
Dexamethasone, IV, 6mg daily x10d**	126.07	1720.80
Dexamethasone, oral, 6mg daily x10d	n/a	n/a
Hydrocortisone, IV 160mg daily x10d**	274.68	477.00
Prednisone, oral, 40 mg daily x 10d	15.43	12.31
Betamethasone, IV, 6mg daily x10d**	93.60	622.84
Betamethasone, oral, 6mg daily x10d***	97.26	453.00
Methylprednisolone, IV, 32mg daily x10d **CAUTION: This is not the depot formulation**	n/a	231.00
Methylprednisolone, oral, 32mg daily x10d **CAUTION: This is not the depot formulation**	n/a	21.00
Prednisolone, oral, 40 mg daily x 10d	n/a	R12.95

Note: S21 access supplication may be done for medicines that are unavailable on the South African market.

*SEP database (price excludes dispensing fee): Cheapest generic price used i.e. Fresenius Dexamethasone 4mg/ml®=R86.04; Macleods Hydrocortisone injection 100mg/2ml®=R23.85; Trolic® 5mg tablets, 1000s=R153.85; Capsoid®5mg tablets, 500=R131.25; Betanoid® 0.5mg tablets, 20=R75.50; Betanoid® 4mg/ml injection, 10's=R311.42; Mylan prednisolone 40mg/2ml®=R23.10 [Accessed 26Jun2020] https://mpr.code4sa.org/

**Contract circular RT297-2019 (1 July 2020) - weighted average price where required

***Contract circular HP09-2019SD/01 (1 July 2020) - weighted average price where required

VALUES, PREFERENCES, ACCEPTABILITY	**Is there important uncertainty or variability about how much people value the options?** Minor [X] Major [ ] Uncertain [ ] **Is the intervention acceptable to key stakeholders?** Yes [X] No [ ] Uncertain [ ]	Patients: No specific research surveying patients' value of this therapeutic agent is currently available, and NEMLC Subcommittee judged this as "minor". Healthcare workers: NEMLC Subcommittee was of the opinion that the intervention was acceptable to clinicians.
EQUITY	**Would there be an impact on health inequity?** Yes [ ] No [X] Uncertain [ ]	

Version	Date	Reviewer(s)	Recommendation and Rationale
First	23 June 2020	TL, JR, KC, AG	Evidence of mortality harms associated with routine use of routine corticosteroids in severe hospitalised COVID-19 patients without ventilatory support, but evidence of mortality benefit in patients on supplemental non-invasive oxygen or mechanical ventilation. Corticosteroids may be considered for COVID-19 with septic shock.

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