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: 20 OCTOBER 2020 *(second update of the initial 23 June 2020 rapid review report)*

Key findings

- We conducted an updated search of two electronic databases (Epistemonikos and the Cochrane COVID Register) on 10 September 2020.
- A meta-analysis of eight controlled trials of the use of systemic corticosteroids (dexamethasone, hydrocortisone or methylprednisolone) in 1844 hospitalised patients with confirmed or suspected COVID-19 found that 28-day mortality was lower amongst patients receiving corticosteroids (37.4%) versus usual care or placebo (44.3%). The absolute risk of death was reduced by 6.9% (95% CI: 2.4% to 11.5%). 15 (95% CI: 9 to 43) critically ill patients with COVID-19 would need to be treated with systemic corticosteroids to avert 1 additional death.
- In this meta-analysis, based on data from the 6 trials that reported on serious adverse events (SAEs), 18.1% (64/354) of those treated with corticosteroids had an SAE compared to 29.2% (80/342) of the patients randomised to placebo or usual care. However, as SAE definitions varied between the trials, formal meta-analysis of these data was not performed.
- The question of when to initiate corticosteroid therapy remains undecided. The RECOVERY trial showed 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 corticosteroids and doses used varied between RCTs.
- No studies have as yet reported on the use of corticosteroids in children with severe COVID-19.
- There is insufficient evidence in HIV-infected patients and the role of corticosteroids in this group is unclear.

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: The use of 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) is recommended. 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 diagnosed with septic shock.

Rationale: A meta-analysis of 8 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 7 trials, with some concerns raised in respect of 1 trial. Although the results were dominated by the RECOVERY trial, the results of all included trials were consistent.

Level of Evidence: meta-analysis of RCTs of moderate quality

Review indicator: New evidence of safety and/or efficacy that is sufficient to change the recommendation.

(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 19 October 2020, 23 clinical trials investigating the role of corticosteroids (parenteral, oral or inhalation) treatment of COVID-19 were registered on https://clinicaltrials.gov/. Completed studies include NCT04273321; NCT04551781 and NCT04484493. NCT04327401 was terminated by the Data Monitoring Committee based on the RECOVERY Trial results.

BACKGROUND

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] Cytokine elevations have been described in COVID-19 patients with severe pneumonia[2] and manifestations of septic shock.[3, 4] 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.[5] However, corticosteroids are also associated with harms: previous studies in patients with severe acute respiratory syndrome (SARS)[6] and Middle East respiratory syndrome coronavirus (MERS-CoV),[5] due to novel coronaviruses, and with severe influenza[7] have shown that viral clearance is delayed, with no survival benefit and possible harms (e.g. psychosis, hyperglycaemia and hypokalemia[8]). Corticosteroids can also cause host immune suppression, resulting in an increased risk of secondary nosocomial infections.

Children generally present with milder disease compared with adults.[9] To date there has been little data for the use of corticosteroids for multisystem inflammatory condition, which would require further review as more relevant evidence becomes available.

Since the last update of this review, a number of new trials of corticosteroids have been published, and corticosteroids have been included in many treatment guidelines for COVID-19[10, 11]. On 2 September 2020, WHO rapid guidance was issued on the use of corticosteroids for COVID-19,[12] and the following was recommended:

- Systemic corticosteroids rather than no corticosteroids for the treatment of patients with severe and critical COVID-19 (strong recommendation, based on moderate certainty evidence)
- Not to use corticosteroids in the treatment of patients with non-severe COVID-19 (conditional recommendation, based on low certainty evidence)

And, on the 18 September 2020, the European Medicine Agency's (EMA's) human medicines committee had also recommended the use of dexamethasone in COVID-19 patients on oxygen or mechanical ventilation.[13]

RESEARCH QUESTION:

Research question: Should corticosteroids be used for managing severe COVID-19 in hospitalised patients?

Eligibility criteria for review

Population: Patients with confirmed COVID-19 with severe disease requiring hospitalisation (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 (RCTs), and systematic reviews of randomised controlled studies in humans.

METHODS

We conducted an initial 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. Following the publication of the corticosteroid arm of the Randomised Evaluation of COVid-19 thERapY (RECOVERY) Trial,[14] the rapid review was updated on 2 August 2020.

A further updated search of two electronic databases (Epistemonikos and the Cochrane COVID Register) was conducted on 10 September 2020. Records were screened independently and in duplicate (TL and KC), with resolution

by a third party (TK) as required, using COVIDENCE systematic review software. See PRISMA flow diagram below. Living map www.covid-nma.com was also screened to identify additional records. Search strategy is shown in Appendix 1.

For living systematic reviews of RCTs on www.covid-nma.com, the quality of randomised controlled trials was assessed using the Risk of Bias 2.0 tool[15], and the AMSTAR tool[16] was used to assess systematic reviews and meta-analyses. Summary of finding table(s) were generated using GRADEPro software[17] was used to develop summary of finding table(s). Relevant study data were extracted for narrative synthesis (TL), with results reviewed and checked by AG. KC reviewed the overall report.

RESULTS

Results of search

152 records were imported for screening. 22 duplicates were removed and two reviewers screened 130 records, of which 109 were not relevant. 21 full text studies were assessed for eligibility and five potentially eligible studies were identified. Further review produced one relevant record for data extraction, a systematic review and meta-analysis of RCT data. See Figure 1 for the PRISMA flow diagram.

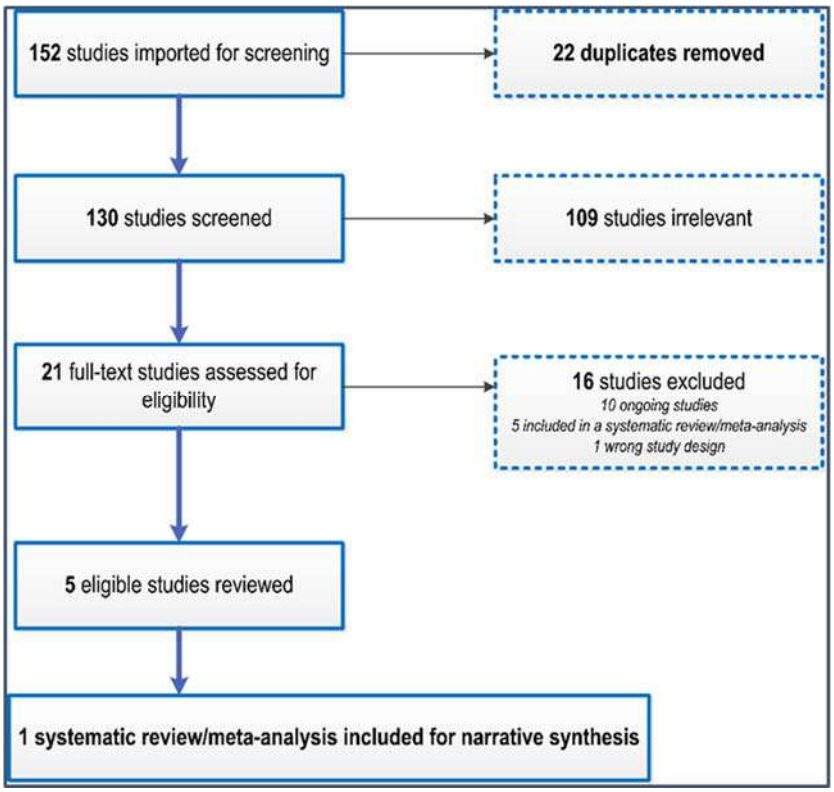


Figure 1: PRISMA flow diagram for review

Two more additional records were identified from the living map, www.covid-nma.com, but these were excluded.

Description of included study:

The main characteristics and outcomes (Table 1) and summary of findings (Table 3) are described for the prospective systematic review and meta-analysis ((PROSPERO CRD42020197242) conducted by the World Health Organization,[18] whilst the excluded studies are summarised in Table 2.

A single-blind trial of pulse (3-day) methylprednisolone, reported by Edalatifard et al., was not included in the WHO meta-analysis, as mortality was only reported at 60-days. [19] This study, conducted in Iran, recruited only 68 participants. It was considered to be at high risk of bias as clinicians were not blinded to treatment allocation. Despite being reported as an intention-to-treat analysis, data from 6 patients in the control group were excluded from the analyses because of deviations from the protocol. Similarly, a pre-print report of a double blind phase 2 trial in Iran, which compared pulse methylprednisolone (1000mg/day for three days; followed by oral prednisolone 1mg/kg with tapering of dose within ten days) in only 29 participants, was not included.[20]

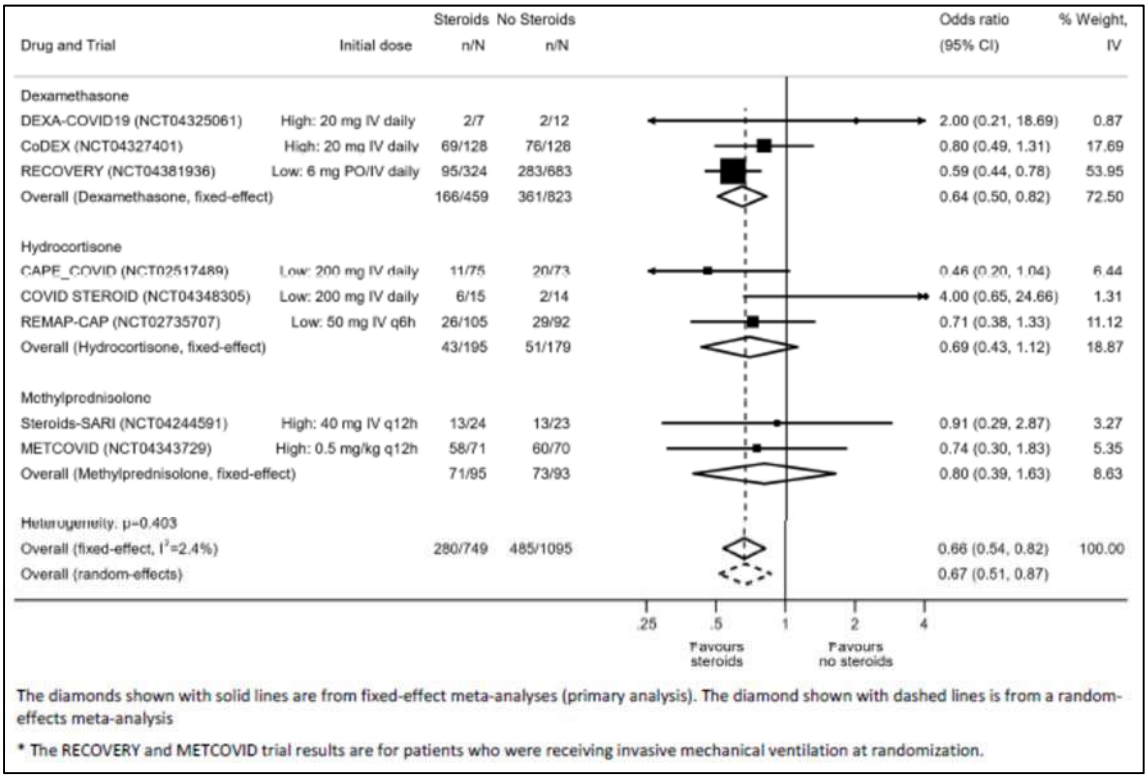
Data were pooled from 8 RCTs, which enrolled a total of 1844 hospitalised adult patients with COVID-19 (749 randomized to corticosteroids and 1095 to usual care or placebo). The majority of participants (55%) were provided by the RECOVERY trial. Only data from patients on invasive mechanical ventilation in the RECOVERY and METCOVID RCTs were analysed. Three included studies (DEXA-COVID 19[21], COVID STEROID[22] and Steroids-SARI[23]) had not been published at the time of inclusion in the meta-analysis. Standard care included antivirals, remdesivir, lopinavir-ritonavir, favipiravir, hydroxychloroquine, azithromycin and convalescent plasma. The systemic corticosteroids studied included dexamethasone, hydrocortisone and methylprednisolone, up to a maximum of 15mg/day, 400mg/day, and 1mg/kg/day, respectively. The primary outcome was mortality 28 days post-randomisation. Subgroup analysis of the primary outcome (mortality) were performed in five subgroups, based on status at time of randomisation: invasive mechanical ventilation, concomitant vasoactive medication at time of randomisation, age, sex and days since symptom onset. The secondary outcome was investigator-defined serious adverse events (SAEs).

Primary outcome:
Overall, 28-day mortality was lower amongst patients receiving corticosteroids (37.4%; 280/749) compared to patients allocated to usual care or placebo (44.3%; 485/1095; summary Odds Ratio 0.67; 95%CI: 0.51 to 0.87; I^2=2.4% (fixed-effect meta-analysis)). The absolute risk reduction (ARR) was 6.9% (95% CI: 2.4% to 11.5%), corresponding to a number needed to treat (NNT) of 15 (95% CI: 9 to 43). The reduction in mortality was similar for dexamethasone, hydrocortisone and methylprednisolone, suggesting a therapeutic class effect of corticosteroids. Similarly, mortality estimates were generally similar for low- and higher-dose corticosteroids, though the estimates were imprecise causing some uncertainty. The forest plot for the primary outcome is shown in Figure 1.

The sub-group analyses showed no additional effect on death at 28 days associated with age and gender, duration of symptoms, or use of vasoactive medicines at randomisation. Corticosteroids were associated with benefit among critically ill patients with COVID-19 receiving either invasive mechanical ventilation (ARR 7.5%; 95% CI: 2.6% to 12.4%; NNT 14; 95% CI 8 to 38) or non-invasive oxygen (ARR 17.8%; 95% CI: 3.4% to 32.3%, NNT 6; 95% CI: 4 to 30). There is imprecision in the estimate of benefit for those patients receiving non-invasive oxygen arm due to the relatively small numbers that were enrolled (144). Accordingly, the higher mortality benefit amongst this group should be interpreted with caution. In this analysis, data from the RECOVERY trial were excluded, as it was unclear which of the patients who received supplemental oxygen were critically ill. The forest plots are shown in Figure 2.

The meta-analysis did not report on hospitalised patients who did not require respiratory support. However, as previously reported, the RECOVERY trial showed that there was no evidence of benefit in such patient, and a possibility of harms (age-adjusted RR 1.19; 95% CI: 0.91 to 1.55), as shown in Figure 3.

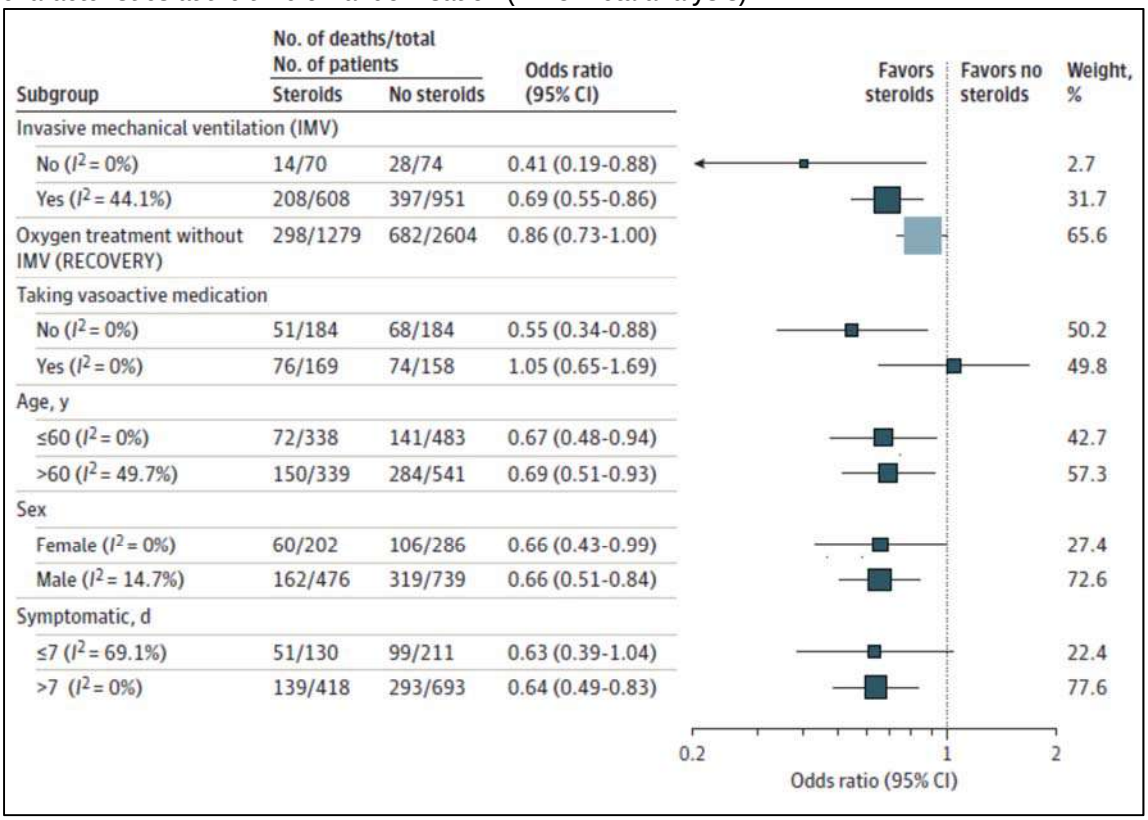
Figure 1: Forest plot showing the association of corticosteroids with all-cause 28-day mortality in each trial, overall and per corticosteroid (WHO meta-analysis)



The diamonds shown with solid lines are from fixed-effect meta-analyses (primary analysis). The diamond shown with dashed lines is from a random-effects meta-analysis

* The RECOVERY and METCOVID trial results are for patients who were receiving invasive mechanical ventilation at randomization.

Figure 2: Association between corticosteroids and 28-day all-cause mortality within subgroups defined by patient characteristics at the time of randomisation (WHO meta-analysis)



The area of the data markers is proportional to their weight in the meta-analysis. The estimated odds ratios were derived using fixed-effect meta-analyses across all trials for which data on the specified subgroup were available. The results for patients in the Randomized Evaluation of COVID-19 Therapy (RECOVERY) trial who required oxygen with or without noninvasive ventilation but were not receiving invasive mechanical ventilation at randomization is shown in a light blue box because these data were not otherwise included in this prospective meta-analysis.

Figure 3: Mortality at day 28 by level of respiratory support received at randomisation (RECOVERY trial)

Subgroup	Treatment allocation: Dexamethasone (n=2104)	Treatment allocation: Usual care (n=4321)	Age-adjusted Cox regression* RR (95% CI)	One-step estimate† RR (95% CI)
No oxygen received	89/501 (17.8%)	145/1034 (14.0%)	1.19 (0.91-1.55)	1.30 (0.99-1.71)
Oxygen only	298/1279 (23.3%)	682/2604 (26.2%)	0.82 (0.72-0.94)	0.86 (0.75-0.99)
Invasive mechanical ventilation	95/324 (29.3%)	283/683 (41.4%)	0.64 (0.51-0.81)	0.67 (0.54-0.84)
All participants	**482/2104 (22.9%)**	**1110/4321 (25.7%)**	**0.83 (0.75-0.93)**	**0.87 (0.78-0.97)**

RR=age−adjusted rate ratio. CI=confidence interval.
* Main analysis shown in Figures 2 and 3, in which the 28-day age-adjusted (ie, conditional) mortality rate ratio is estimated by the hazard ratio from a Cox regression analysis adjusted for age in three categories (<70 years, 70-79 years, and 80 years or older). There was a clear trend towards greater benefit among patients requiring higher levels of respiratory support (chi-squared trend statistic = 11.5).
† Original pre-specified analysis without adjustment for the 1.1-year age-imbalance between the randomised groups. With this method the 'one-step' method is used to estimate the average unadjusted (i.e. marginal) mortality rate ratio from the log-rank 'observed minus expected' statistic (O –E) and its variance (V), through the formula exp([O – E] ÷ V). Its 95% CI is then given by exp([O – E] ÷ V ± 1.96 ÷ √V). There was a clear trend towards greater benefit among patients requiring higher levels of respiratory support (chi-squared trend statistic = 13.1).

The mortality benefit associated with dexamethasone use in patients with severe COVID-19 who required respiratory support, was generally seen after 7 days, suggesting that at this stage viral replication is secondary and pathology is dominated by an immune response. Further analyses from the RECOVERY trial are forthcoming, including cause-specific mortality, need for renal dialysis or haemofiltration and duration of ventilation.

Secondary outcome:
Only 6 RCTs recorded serious adverse events (SAEs). The Recovery RCT did not report SAEs, whilst the Steroids-SARI trial recorded AEs, bit did not differentiate between serious or non-serious AEs. In the corticosteroid group, 64/354 (18.1%) SAEs were reported compared to 80/342 (29.2%) amongst patients randomised to placebo or usual care – see figure 5 below. A meta-analysis of the SAEs was not conducted as the definitions for SAEs differed between the RCTs. Furthermore, participants with missing outcome data was excluded from the analysis.

Quality of the evidence:
We reviewed the WHO meta-analysis using the AMSTAR tool and assessed the study as moderate quality. The following points were noted:

- For the primary outcome of all-cause mortality at 28 days, the risk of bias was assessed as low risk, noting possible risk of bias with allocation concealment in the Steroids-SARI RCT.
- For the secondary outcome of SAEs associated with corticosteroids, the risk of bias was assessed as moderate risk. In 4 of the 6 available RCTs, there were concerns regarding unblinded outcome assessment for SAEs, as classification of SAEs could differ between intervention groups.
- Patient data was pooled from 6 RCTs, of which 4 were published in peer reviewed format; whilst individual patient data was requested from the other 2 trials.
- There was some inconsistency between trial results – whilst most trials reported mortality at 28-days, one trial reported mortality at 21 days and another at 30 days after randomisation (with RECOVERY contributing 57% of the weight).

Few outcome data were missing (1 patient each in the corticosteroid groups of the RECOVERY and CAPE COVID trials; 5 patients in the corticosteroid group and 6 patients in the usual care group of the REMAP-CAP trial).

PRAGMATIC CONSIDERATIONS FOR THE SOUTH AFRICAN CONTEXT:

The WHO meta-analysis reported consistent findings of a mortality benefit from corticosteroid use in critically ill COVID-19 patients. However, the question of the specific doses of dexamethasone, prednisone, hydrocortisone, or methylprednisolone was not definitively answered. In the RECOVERY trial 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 is available on the South African market. Dexamethasone IV is registered in South Africa, but the oral solid dosage form is only accessible via section 21. Oral and IV forms of betamethasone are marketed, as is an

immediate release IV methylprednisolone. Oral solid dosage forms of prednisone are registered and widely accessible. Comparisons of the available corticosteroids are provided in Appendix 2 (Tables 3 and 4).

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 WHO prospective meta-analysis have strengthened the recommendation for use of corticosteroids amongst critically ill COVID-19 patients (requiring either non-invasive oxygen therapy, or mechanical ventilation), although the exact timing of corticosteroid administration remains unclear. Nonetheless, the RECOVERY trial showed some evidence of harm (a trend towards increased mortality) amongst hospitalised patients who did not require oxygen or ventilatory assistance and who were administered systemic corticosteroids. The question of dose has been less definitively answered and it is uncertain whether treatment should be individualized, guided by clinical response or biomarkers; or whether dose tapering would be required or if inflammation rebounds once corticosteroid therapy is stopped din some patients[24]. Adult patients were recruited, and thus the effect of corticosteroids amongst children remains unclear. All the included trials were conducted in high-income countries, and the role of corticosteroids in persons living with HIV is as yet unclear.

Reviewers: Trudy Leong, Andy Gray, Karen Cohen.

Declaration of interests: TL (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.

Acknowledgements: The reviewers would like to thank the South African Cochrane centre (Joy Oliver and Tamara Kredo) for assistance with the initial search and loading of studies for review into the COVIDENCE database for review. TK also assisted with resolution of screening COVIDENCE records.

Table 1. Characteristics of included meta-analyses

Citation	Study design	Population (n)	Treatment	Outcomes	Effect sizes	Comments
WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group[31] *JAMA, 2 September 2020*	Prospective meta-analysis that pooled data from 7 RCTs. *1)DEXA-COVID 19: NCT04325061[33]; 2)CoDEX: NCT04327401[25]; 3)RECOVERY: NCT04381936[29]; 4)CAPE COVID[26]: NCT02517489; 5)COVID STEROID: NCT04348305[34]; 6)REMAP-CAP: NCT02735707[39]; 7)Steroids-SARI: NCT04244591[35]* METCOVID RCT[32] (n=141) was identified after the initial search, and was included in the 28-day all-cause mortality meta-analysis	n=1844 (8 RCTs) Critically ill patients with suspected or confirmed COVID-19. <u>*Eligibility criteria:*</u> *At randomisation* • Critically ill patients with confirmed or suspected COVID-19. • Oxygen supplementation with/ without mechanical ventilation (*Note:* For RECOVERY & METCOVID RCTs - only patients on mechanical ventilation at randomisation were included); • 521 (28%) female patients vs 1323 (72%) male patients; • Median age, 60 years [interquartile range, 52 to 68 years] - *(excl METCOVID RCT data, n=141)*.	Corticosteroid administered systemically (dexamethasone, hydrocortisone, or methylprednisolone) (n=748) ***vs*** usual care/ placebo (n=1095) <u>*Corticosteroids (high*/ low dose**):*</u> • Dexamethasone, IV, 20mg daily x5d; then 10mg daily x5d* • Dexamethasone, IV/oral, 6mg daily** • Hydrocortisone, IV 8d or 14d (200 mg/d × 4d or 7d; 100 mg/d × 2d or 4d; 50mg/d × 2d or 3d)** • Hydrocortisone, IV 200 mg/d × 7d (continuous or bolus dosing every 6h)** • Hydrocortisone, IV, 50 mg every 6h × 7d • Methylprednisolone, IV 40 mg 12hly × 5d*Methylprednisolone, IV 0.5mg/kg 12 hrly<u>*</u> <u>*Usual care (treatment at randomisation):*</u> Any antiviral, remdesivir, LPV/r, favipravir, HCQ, azithromycin, convalescent plasma	<u>*Primary:*</u> • Mortality at 30-days after randomisation (shorter term mortality of 21- and 28-day was acceptable if longer-term mortality was not available) <u>*Secondary outcome:*</u> • Serious adverse events	<u>*Primary outcome:*</u> **28-day all-cause mortality, 8 RCTs:** *Corticosteroid vs none (usual care/ placebo):* • *All participants* (n=1844): 280/749 (37.4%) vs 485/1095 (44.3%), ARR 6.9% (95% CI 2.4% to 11.5%), NNT 15 (9 to 43); OR, 0.67 (95%CI, 0.51 to 0.87), I2=2.4% - fixed-effect meta-analysis **28-day all-cause mortality – subgroup analysis, 7 RCTs (excl METCOVID):** *Corticosteroid vs none (usual care/ placebo):* • <u>*Invasive mechanical ventilation (IMV)*</u> (n=1559): 34.2% *vs* 41.7%; ARR 7.5% (95% CI 2.6% to 12.4%); NNT 14 (8 to 38); OR 0.69 (95% CI 0.55 to 0.86), I2=44.1% • <u>*Oxygen -no IMV*</u> <u>(n=144) – excl RECOVERY:</u> 20% *vs* 37.8%, ARR 17.8% (95% CI 3.4% to 32.3%), NNT=6 (4 to 30); OR 0.41 (95% CI 0.19 to 0.88) • <u>*Oxygen -no IMV*</u> <u>(n=3883) – RECOVERY</u> only: 23.3% *vs* 26.2%, ARR 2.9% (95% CI 0.02% to 5.8%), NNT=35 (18 to 4150); OR 0.86 (95% CI 0.73 to 1.00) <u>*Secondary outcomes:*</u> **Serious adverse events (SAEs), 6 RCTs:** *Corticosteroid vs none (usual care/ placebo):* • 64/354 (18.1%) vs 80/342 (29.2%); -SAEs varied, and a meta-analysis was not done, but there was no suggestion that the risk of SAEs was higher in patients assigned to corticosteroids (*Note*: No SAEs recorded in RECOVERY; Steroids-SARI RCT did not categorize AEs as serious or non-serious, but latter was included in analysis)	AMSTAR assessment of the meta-analysis: **Moderate quality.** • Research questions and inclusion criteria for the review included the components of PICO? Yes • Report of the review contained an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol? Yes • Review authors explained selection of the study designs for inclusion in the review? No • Review authors used a comprehensive literature search strategy? Partial yes • Review authors perform study selection and data extraction in duplicate? Yes Review authors provided a list of excluded studies and justify the exclusions? Yes • Review authors described the included studies in adequate detail? Yes • Review authors used a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review? Yes • Review authors reported on the sources of funding for the studies included in the review? Yes • For meta-analyses, review authors used appropriate methods for statistical combination of results? Yes • For meta-analyses, review authors assessed the potential impact of RoB in individual RCTs on the results of the meta-analysis or other evidence synthesis? Yes • Review authors accounted for RoB in individual RCTs when interpreting/ discussing the results of the review? Yes • Review authors provided a satisfactory explanation for, and discussion of, any

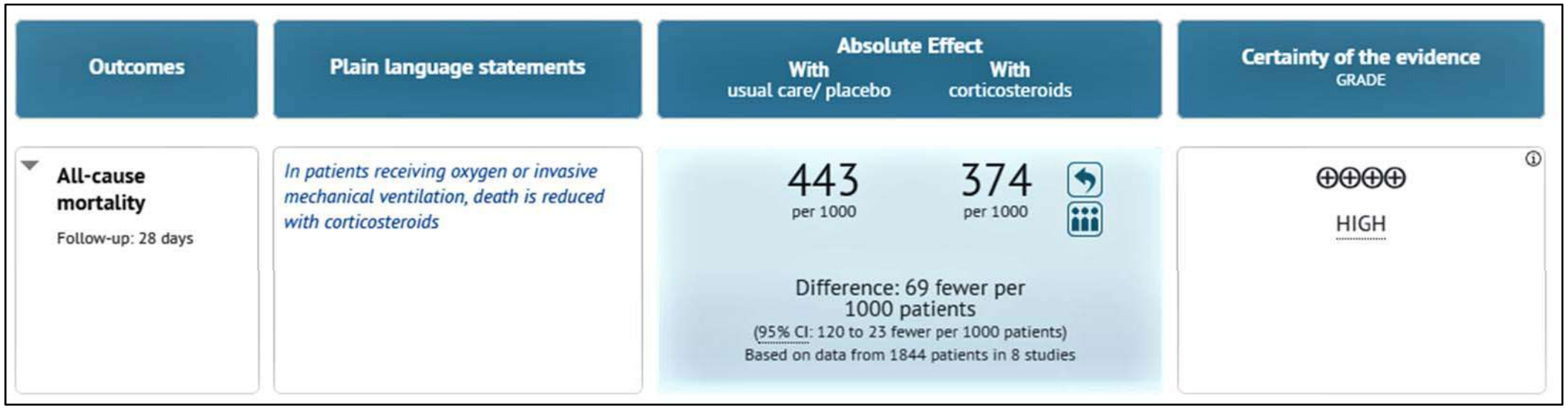
						heterogeneity observed in the results of the review? Yes • For quantitative synthesis, review authors carried out an adequate investigation of publication bias (small study bias) and discussed its likely impact on the results of the review? No • Review authors reported any potential sources of conflict of interest, including any funding they received for conducting the review? Yes **Overall judgement with regards to risk of bias judged as "*LOW RISK*"** **A: Primary outcome: 28-day all-cause mortality, 8 RCTs:** The overall RoB was assessed as ***LOW RISK*** for 7 RCTs (domains assessed included i. Randomisation process; 2. Deviations from the intended interventions; 3. Missing outcome data; 4. Measurement of the outcome; 5. Selection of the reported result). However, some concerns were raised with 1 RCT - the Steroids-SARI RCT regarding the randomisation process: i) the fixed block size within centres (which it might have been easy to deduce, despite the blinding) and (ii) the rather informal use of text messages to implement allocations. ***MODERATE RISK*** **B: Secondary outcomes: Serious adverse events (SAEs), 6 RCTs: *MODERATE RISK*** RoB was assessed as "low" in 2 of the 6 available RCT results for SAEs - the study personnel were blinded to the intervention group. The other 4 RCTs had unblinded outcome assessment, and RoB was assessed as "*some concerns*" based on subjectivity as classification of SAEs could differ between intervention groups.

Table 2. Characteristics of excluded studies

Citation	Type of record	Reason for exclusion
ClynAmygate. NCT04530409, registered 28 August 2020	Trial registry	Ongoing study
Writing Committee for the REMAP-CAP Investigators, Angus et al. REMAP-CAP COVID-19 Study. JAMA. 2020 Sep 2;324(13):1317–29.	Journal article	RCT included in systematic review/meta-analysis
COVID STEROID team. Unpublished data from COVID STEROID study.	Unpublished data	RCT included in systematic review/meta-analysis
Instituto de Seguridad y Servicios Sociales de los Trabajadores del Estado. NCT04540926	Trial registry	Ongoing study
IIS BIODONOSTIA, EudraCT Number: 2020-001707-16	Trial registry	Ongoing study
Hospital Universitari Vall d'Hebron Research Institute, NCT04534478	Trial registry	Ongoing study
Dequin et al. CAPE COVID Trial Group and the CRICS-TriGGERSep Network. JAMA. 2020 Sep 2;324(13):1–9.	Unpublished data	RCT included in systematic review/meta-analysis
Busani et al Trials. 2020 Aug 17;21(1):724.	Journal article	Study protocol
South Valley University. NCT04519385	Trial registry	Ongoing study
Scandinavian Critical Care Trials Group. NCT04509973	Trial registry	Ongoing study
South Valley University. NCT04551781	Trial registry	Study completed, but results not published
Steroids-SARI team. Unpublished data from Steroids-SARI study	Unpublished data	RCT included in systematic review/meta-analysis
DEXA-COVID19 team. Unpublished data from DEXA-COVID19 study	Unpublished data	RCT included in systematic review/meta-analysis
Lee et al. J Clin Med. 2020 Jul 27;9(8):2392.	Journal article	Wrong study design
Villar et al, DEXA-COVID19 Network. Trials 2020;21(1):717	Journal article	Study protocol
Lahore General Hospital. NCT04559113	Trial registry	Ongoing study
Edalatifard et al. Eur Respir J. 2020 Sep 17:2002808.	Journal article	Wrong outcomes
Hoekstra et al. Research Square, Preprint, 5 August 2020	Preprint	Wrong study design
Hasan et al. Expert Rev Respir Med. 2020 Sep 29:1-15.	Journal article	Wrong study design
Tlayjeh et al. MedRxiv Preprint, 14 August 2020	Preprint	Wrong study design
Corral-Gudino et al. MedRxiv Preprint, 18 June 2020	Preprint	Wrong outcomes (composite endpoint)
Farhani et al. Research Square, Preprint, September 2020	Preprint	Wrong study design (Phase 2 controlled trial)

Table 3: Summary of findings for use of corticosteroids in hospitalised patients with COVID-19

Corticosteroids compared to usual care/ placebo for treating hospitalised COVID-19 patients
Patient or population: Hospitalised COVID-19 adult patients Setting: Hospital Intervention: corticosteroids Comparison: usual care/ placebo



Outcomes	Plain language statements	Absolute Effect: With usual care/ placebo	Absolute Effect: With corticosteroids	Certainty of the evidence (GRADE)
All-cause mortality Follow-up: 28 days	*In patients receiving oxygen or invasive mechanical ventilation, death is reduced with corticosteroids*	443 per 1000	374 per 1000 Difference: 69 fewer per 1000 patients (95% CI: 120 to 23 fewer per 1000 patients) Based on data from 1844 patients in 8 studies	⊕⊕⊕⊕ HIGH

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Certainty of the evidence:
a. Some trials did not respond to the requests for data. Some concerns with the Steroids-SARI RCT regarding the randomisation process: i) the fixed block size within centres (which it might have been easy to deduce, despite the blinding) and (ii) the rather informal use of text messages to implement allocations
b. Small amount of heterogeneity across RCTs; I2=2.4%
c. Imprecision noted in the smaller RCTs: Steroids-SARI (n=47), COVID STEROID (n=29), DEXA-COVID 19 (n=19)

Appendix 1: Search strategy

Epistemonikos – 10 September 2020

Search strategy: (title:(Coronavirus* OR covid OR covid-19 OR covid19 OR 2019-ncov OR 2019ncov OR sars-cov-2 OR sars-cov2) OR abstract:(Coronavirus* OR covid OR covid-19 OR covid19 OR 2019-ncov OR 2019ncov OR sars-cov-2 OR sars-cov2)) AND (title:(corticosteroid*) OR abstract:(corticosteroid*))

Output: 52 records (1 study relevant to PICO)

Cochrane COVID Study Register – 10 September 2020

https://covid-19.cochrane.org/

corticosteroid OR corticosteroids

Output: 48 records (1 study relevant to PICO, already identified in Epistemonikos database)

Living mapping and living network meta-analysis of COVID-19 studies – 2 August 2020

https://covid-nma.com/

Corticosteroids

RCTs: 8 records retrieved (6 duplicates, 2 studies excluded as not relevant to PICO)

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:

1. Gonzalez FJ, Coughtrie M, Tukey RH. Drug Metabolism. In: Brunton LL, Chabner BA, Knollmann BC, editors. Goodman and Gilman's pharmacological basis of therapeutics. 12th ed. New York: McGraw-Hill Medical; 2011.
2. DiPiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey LM, editors. Pharmacotherapy: a pathophysiologic approach. 8th ed. Columbus (OH): McGraw-Hill; 2012.
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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 METHYLPREDNISOLONE FORMULATION. THE DEPOT FORMULATION IS FOR INTRAMUSCULAR ADMINISTRATION ONLY AND SHOULD NEVER BE ADMINISTERED INTRAVENOUSLY.**	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 [X] Low [ ] 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	Meta-analysis of mortality data from 8 RCTs (RECOVERY RCT contributed 57% of weight). Low risk of bias.
EVIDENCE OF BENEFIT	**What is the size of the overall effect for beneficial outcomes?** Large [X] Moderate [ ] Small [ ] None [ ] Uncertain [ ] **Note:** The overall effect was judged as moderate; however, in the ventilated cohort the effect was substantial.	*Primary outcome:***28-day mortality:** *Corticosteroids vs none (usual care/ placebo):* • *All participants* (n=1844): 280/749 (37.4%) vs 485/1095 (44.3%), ARR 6.9% (95% CI 2.4% to 11.5%), NNT 15 (9 to 43); OR, 0.67 (95%CI, 0.51 to 0.87), I2=2.4% - fixed-effect meta-analysis *Meta-analysis only pooled data of critically ill patient – RECOVER RCT showed that for 28-day mortality (dexamethasone vs none):* • *No oxygen received* (n=1535): 17.8% *vs* 14%; age-adjusted RR 1.19 (95% CI 0.91 to 1.55)
EVIDENCE OF HARMS	**What is the size of the effect for harmful outcomes?** Large [ ] Moderate [ ] Small [ ] None [ ] Uncertain [X]	No meta-analysis of SAE data was performed, as definitions and reporting varied between included studies.
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.

<table>
<tr>
<td>RESOURCE USE</td>
<td>How large are the resource requirements?
More intensive: X
Less intensive:
Uncertain:</td>
<td>Price of medicines/ treatment course of 10 days (10d)
<table>
<tr><th>Medicine</th><th>Tender Price (R)</th><th>Single Exit Price (R)*</th></tr>
<tr><td>Dexamethasone, IV, 6mg daily x10d**</td><td>126.07</td><td>1720.80</td></tr>
<tr><td>Dexamethasone, oral, 6mg daily x10d</td><td>n/a</td><td>n/a</td></tr>
<tr><td>Hydrocortisone, IV 160mg daily x10d**</td><td>274.68</td><td>477.00</td></tr>
<tr><td>Prednisone, oral, 40 mg daily x 10d</td><td>15.43</td><td>12.31</td></tr>
<tr><td>Betamethasone, IV, 6mg daily x10d**</td><td>93.60</td><td>622.84</td></tr>
<tr><td>Betamethasone, oral, 6mg daily x10d***</td><td>97.26</td><td>453.00</td></tr>
<tr><td>Methylprednisolone, IV, 32mg daily x10d
CAUTION: This is not the depot formulation</td><td>n/a</td><td>231.00</td></tr>
<tr><td>Methylprednisolone, oral, 32mg daily x10d</td><td>n/a</td><td>21.00</td></tr>
<tr><td>Prednisolone, oral, 40 mg daily x 10d</td><td>n/a</td><td>R12.95</td></tr>
</table>
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</td>
</tr>
<tr>
<td>VALUES, PREFERENCES, ACCEPTABILITY</td>
<td>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:</td>
<td>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.</td>
</tr>
<tr>
<td>EQUITY</td>
<td>Would there be an impact on health inequity?
Yes:
No: X
Uncertain:</td>
<td></td>
</tr>
</table>

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.
Second	6 August 2020	TL, KC, AG	Estimates updated to align with peer-reviewed published journal article. Evidence to decision framework and strength of recommendation updated.
Third	20 October 2020	TL, AG, KC	Evidence updated to include results from a meta-analysis of 8 RCTs, strengthening the recommendation for systemic corticosteroids amongst critically ill adult patients with COVID-19.

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acquired infection, OR 2.74; 95% CI, 1.51 to 4.95; 7 studies; but studies are heterogeneous and the evidence relates mainly to high corticosteroid doses and is of low quality with potential confounding by indication a major concern)
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