National Institute for Health and Care Excellence

NICE COVID-19 rapid guideline: managing COVID-19

[A] Evidence review for corticosteroids

NICE guideline NG191

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Guideline version (Final)

Disclaimer

The recommendations in this guideline represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, professionals are expected to take this guideline fully into account, alongside the individual needs, preferences and values of their patients or service users. The recommendations in this guideline are not mandatory and the guideline does not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

Local commissioners and/or providers have a responsibility to enable the guideline to be applied when individual health professionals and their patients or service users wish to use it. They should do so in the context of local and national priorities for funding and developing services, and in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities. Nothing in this guideline should be interpreted in a way that would be inconsistent with compliance with those duties.

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Objective

This evidence review aims to evaluate the clinical effectiveness of corticosteroids in people with COVID-19.

Review question

A description of the relevant population, intervention, comparison and outcomes (PICO) for this review was developed by NICE for the topic (see appendix A for more information). The review question for this evidence review is:

What is the effectiveness and safety of corticosteroids for acute symptoms and complications of COVID-19?

Methodology

Because there was a need for prompt guidance on managing COVID-19, NICE collaborated with other guideline development teams to produce evidence reviews. NICE has reused data from the National Australian COVID-19 clinical evidence taskforce for this review.

Evidence provided by the National Australian COVID-19 clinical evidence taskforce was used through the sharing of RevMan files, which the NICE team used to populate the evidence summary section and GRADE profiles for this review. Data extraction and risk of bias was done in line with NICE's interim process and methods for guidelines developed in response to health and social care emergencies.

Included studies

Evidence comes from a meta-analysis and associated living guidance of seven randomised controlled trials (RCTs) of patients with critical COVID-19, one study of patients with moderate, severe and critical COVID-19, and one study of patients with severe COVID-19. Over 5,700 patients are included in the meta-analysis. All trials compared corticosteroids plus standard care with standard care alone.

In addition, two meta-analyses of corticosteroids for other conditions – other coronavirus infections, influenza, community-acquired pneumonia, acute respiratory distress and sepsis – provided indirect evidence for serious adverse events.

Three RCTs compared dexamethasone with standard care, three compared hydrocortisone with standard care and three compared methylprednisolone with standard care.

Disease severity was reported independently for each trial. Definitions included patients who required mechanical ventilation or non-invasive ventilation, PaO2/FiO2 < 200, positive end-expiratory pressure (PEEP) ≥ 5 cm H2O, and the presence of pneumonia or infiltrates on chest imaging.

Mean or median age ranged from 57 to 67 years in the corticosteroid groups and from 60 to 66 years in the standard care groups. The proportion of women was 32% (range 13% to 43%) in the corticosteroid groups and 29% (range 21% to 36%) in the standard care groups.

See appendix C for study characteristics.

Results

What are the main results?

Compared with standard care, corticosteroids probably reduce death in patients with severe and critical COVID-19. For every 1000 patients given corticosteroids, 51 more are likely to survive compared with those receiving standard care (RR 0.84 CI 95% 0.73 to 0.98; 5789 patients in 9 RCTs). Corticosteroids in patients requiring oxygen also probably reduce the composite outcome of requirement for invasive mechanical ventilation or death, and discharge from hospital within 28 days.

In patients who do not require oxygen, corticosteroids probably increase death (RR 1.27 CI 95% 1.00 to 1.61; 1535 patients in 1 study) and the composite outcome of invasive mechanical ventilation or death.

Indirect evidence of corticosteroid use in patients with other, similar indications showed no difference in the incidence of gastrointestinal bleeding, bacterial co-infections, neuromuscular weakness and neuropsychiatric effects. However, corticosteroid use was associated with an increase in hyperglycaemia (RR 1.16 CI 95% 1.08 to 1.25; 8938 patients in 24 studies).

See appendix E for full GRADE tables.

Our confidence in the results

In patients with COVID-19 requiring oxygen, certainty of the evidence is moderate for all-cause mortality and serious adverse events (due to serious inconsistency in direction of effect) and invasive mechanical ventilation or death (due to only one study), and discharge from hospital (due to serious inconsistency).

In patients with COVID-19 who do not require oxygen, certainty is moderate for all outcomes (all-cause mortality, invasive mechanical ventilation or death and discharge from hospital) due to serious imprecision (reliance on a single study and wide confidence intervals).

For the adverse events (gastrointestinal bleeding, super infections, neuromuscular weakness and neuropsychiatric effects), certainty is low due to serious indirectness (evidence from non-COVID-19 patients) and serious imprecision. For

hyperglycaemia, certainty is moderate due to serious indirectness (evidence from non-COVID-19 patients).

Evidence to decision

Benefits and harms

For adults with COVID-19 needing supplemental oxygen, corticosteroids compared with usual care or placebo lower all-cause mortality, improve discharge from hospital, and may decrease the need for invasive mechanical ventilation (IMV) and death within 28 days of starting treatment.

For adults with COVID-19 not needing supplemental oxygen, corticosteroids may increase the need for IMV and death within 28 days of starting treatment.

Based on indirect evidence from non-COVID-19 populations, hyperglycaemia is the only statistically significant adverse event associated with corticosteroids.

The panel noted the evidence to support using corticosteroids for adults with COVID-19 on supplemental oxygen, or adults with a level of hypoxia that needs supplemental oxygen but who are unable to have or tolerate it. They noted that it is now established standard practice to offer dexamethasone. This is based on the most robust evidence on corticosteroids covering this treatment, and its widespread availability, ease of administration and acceptable safety profile. The panel indicated that, if dexamethasone cannot be used or is unavailable, suitable alternatives are hydrocortisone or prednisolone. The panel noted the evidence that corticosteroids may be harmful for people with COVID-19 not needing supplemental oxygen. Because of the risk of harm, the panel cautioned against using corticosteroids for people with COVID-19 not on oxygen unless there is another medical indication to do so.

The panel noted the need for clear and unambiguous terminology. Therefore, they agreed that reference to COVID-19 severity would not be used. Instead, they agreed that a person's oxygen saturation should be used to determine whether corticosteroid treatment was appropriate. The panel highlighted the need to allow for varying prescribed oxygen saturation levels in different population groups. Because

of this, they agreed that the recommendation should not detail specific oxygen saturation levels.

The course duration recommended, for up to 10 days unless there is a clear indication to stop early (including discharge from hospital or a hospital-supervised virtual COVID ward), is based on that used in the RECOVERY trial. The panel recognised the importance of minimising risk of harm caused by continuing treatment for people whose condition is improving and who are discharged. They agreed that the long pharmacodynamic half-life of dexamethasone would reduce the risk of any rebound effect caused by stopping the course before 10 days in the event of discharge. The panel agreed that, where patients are transferred to a virtual ward environment, the course could be completed safely under clinical supervision.

The panel acknowledged the lack of evidence outside the hospital setting. They also acknowledged that the supply and use of corticosteroids in other settings is based on clinical experience and knowledge of service delivery. It was the panel's opinion that, when corticosteroids are first started in community settings, GPs are suitably qualified to assess oxygen levels with pulse oximetry and the need for corticosteroids. They agreed that it is realistic that treatment with dexamethasone could be started in the community setting. They also agreed that the class effect of corticosteroids would allow for hydrocortisone or prednisolone as suitable alternatives if dexamethasone cannot be used or is unavailable.

Use of corticosteroids in children was considered. The panel decided that the recommendation should not be limited to adults because the evidence included both adults and children. The panel therefore agreed to avoid age-specific wording in the recommendation. Instead, they agreed that the dosing for adults and children should be provided as supplementary advice. Paediatric experts highlighted that the risk of progression for a child with a stable minimal oxygen requirement is not as high as for adults. Therefore, they suggested cross reference to Royal College of Child and Paediatric Health risk criteria markers for assessing corticosteroid use. For preterm babies with a corrected gestational age of less than 44 weeks, specialist advice is considered necessary because evidence is lacking for corticosteroid use in this age group.

The panel noted the indirect evidence about the risk of hyperglycaemia in other non-COVID-19 populations. They agreed that whether to monitor for hyperglycaemia and other adverse effects should be determined by their healthcare professionals, without the need for specific advice in the guideline. They added that potential adverse effects and contraindications would need to be balanced against the risks of depriving a person of a potentially life-saving treatment.

The panel considered that clinical judgement should guide management for people who do not need supplemental oxygen and who are already having corticosteroids for pre-existing or new comorbid conditions, without the need for specific advice in the guideline.

Certainty of the evidence

Certainty of the evidence is moderate for all-cause mortality within 28 days in both subgroups (adults needing oxygen, and adults not needing oxygen) because of serious imprecision (inconsistent direction of effects for studies of adults needing oxygen and only a single study for adults not needing oxygen). The panel noted that, despite serious imprecision, the pooled effect was statistically significantly in favour of corticosteroids for adults needing oxygen, and showed a direction of effect in favour of control for adults not needing oxygen that was only marginally non-significant.

Certainty of the evidence is moderate for invasive mechanical ventilation or death at 28 days in both subgroups because of serious imprecision (only a single study for both subgroups). The panel noted that, despite serious imprecision, the effect was statistically significantly in favour of dexamethasone for adults needing oxygen, and showed a direction of effect in favour of control for adults not needing oxygen that was only marginally non-significant.

Certainty of evidence is moderate for discharge from hospital in both subgroups because of serious imprecision (inconsistent confidence intervals for studies of adults needing oxygen and only a single study for adults not needing oxygen). However, the panel noted that, for adults with COVID-19 needing oxygen, there was a statistically significant effect in favour of corticosteroids for improving discharge from hospital at 28 days.

Certainty of evidence was moderate for serious adverse events of corticosteroids in adults with COVID-19 needing oxygen. The panel noted that corticosteroids probably have little effect on serious adverse events in this group of people, but were aware of indirect systematic review evidence showing a statistically significant risk of hyperglycaemia among people without COVID-19.

Certainty of evidence was low to moderate for other individual adverse effects, none of which showed statistically significant effects estimates.

Values and preferences

The panel were not aware of any systematically collected data on people's preferences and values. The panel inferred that, in view of the probable mortality benefits for people with COVID-19 who need oxygen, most would choose corticosteroids after shared decision making with healthcare professionals. Dexamethasone was considered to be the preferred corticosteroid treatment because of the larger amount of data supporting its use. The panel agreed that the class effect of corticosteroids would allow for hydrocortisone or prednisolone as suitable alternatives if dexamethasone cannot be used or is unavailable.

The panel also inferred that, because of the risk of harm, most fully informed people with COVID-19 who do not need supplemental oxygen would not want to have systemic corticosteroids. However, some people may want to consider having this intervention through shared decision making with their healthcare professional.

Resources

Use of corticosteroids in adults with COVID-19 who are on supplemental oxygen is unlikely to affect the availability of these medicines for other indications.

The panel expressed concern over specifying oxygen therapy as a requirement for corticosteroid treatment in a recommendation. They agreed that this might result in inequalities in access to treatments because of certain groups of people not being able to have oxygen therapy, even though their oxygen saturations may indicate that they should. This may also result in supply issues in the event of oxygen shortages. The panel agreed that the emphasis should be on oxygen saturation targets for

people who need oxygen supplementation.

The panel noted possible supply issues with corticosteroids in community pharmacies where people have treatment outside the hospital setting, such as in residential care. However, they agreed that GP assessment with pulse oximetry and treatment with dexamethasone is realistic in the community setting. The class effect of corticosteroids would allow for suitable alternatives. The panel acknowledged the lack of evidence outside the hospital setting. They also noted that the use and supply of corticosteroids in other settings is based on clinical experience and knowledge of service delivery.

Equity

The panel noted limited evidence on the use of corticosteroids in children with COVID-19 but that children should not be excluded from the recommendations. The panel agreed that all age groups should be encompassed with appropriate age-specific advice on dosage.

The panel also noted the lack of evidence on the use of corticosteroids in community settings and the risk of inequitable treatment if limited to people in hospital. The panel were aware of people with COVID-19 needing supplemental oxygen who are having treatment outside the hospital setting and would benefit from corticosteroids. For this reason, the panel agreed that the recommendation should not specify any treatment setting.

See the Resources section for the panel's concern over potential inequality of access to corticosteroids if oxygen therapy is stated as a requirement for corticosteroid treatment, and the need for this to be reflected in the wording of the recommendation.

Acceptability

The panel considered that acceptability of corticosteroids would be high given the widespread availability, ease of oral ingestion in any setting and established safety profile. They anticipated that, when considering the risks and benefits of treatment through shared decision making, most people with COVID-19 who:

- need supplemental oxygen would choose to have corticosteroids
- do not need supplemental oxygen would choose not to have corticosteroids.

Feasibility

Although there is no systematically collected evidence about feasibility, the panel noted that the established distribution, supply and use of corticosteroids in clinical practice is an indicator of feasibility.

Appendices

Appendix A: PICO table

PICO table

What is the effectiveness and safety of pharmacological and non-pharmacological treatments for acute symptoms and complications of COVID-19?

Criteria	Notes
Population	Adults, young people and children with suspected or confirmed COVID-19.
Interventions	Pharmacological and non-pharmacological treatments that has the potential to be used to treat COVID-19
Comparators	• Standard care alone, standard care plus placebo, placebo or active comparator Note: Standard care comprises best supportive care and in certain circumstances the use of additional drugs (such as dexamethasone, remdesivir).
Outcomes	Those marked with an * are critical outcomes • All-cause mortality (n/N)* • Duration of invasive mechanical ventilation (IMV) (days)* • IMV or death (composite) (n/N)* • IMV (number of patients requiring IMV who were not already receiving IMV at randomisation) (n/N)* • Number of patients experiencing one or more serious adverse events (n/N)* • Reduction in hospitalisation* • Duration of supplemental oxygen (days) • NIC/HFNO (number of patients requiring NIV/HFNO who were not already receiving NIV/HFNO at randomisation) (n/N) • Supplemental oxygen (number of patients requiring supplemental oxygen who were not already receiving supplemental oxygen at randomisation) (n/N) • Number of patients experiencing one or more adverse events (n/N)

	• Number of patients who discontinued treatment due to an adverse event (n/N) • Number of patients experiencing septic shock (n/N) • Number of patients experiencing resolution of dyspnoea/breathlessness (n/N) • Number of patients requiring hospitalization (n/N) • Number of patients requiring admission to intensive care (n/N) • Duration of hospital stay (days) • Number of patients discharged from hospital (n/N) • Virological clearance (number of patients returning a negative PCR) (n/N) • Number of patients who experienced clinical recovery (resolution of symptoms or number of patients within category 1 of an ordinal scale [non-hospitalised and returned to normal life]) • Time to recovery (days) • Number of patients who experienced clinical improvement (measured by a one or two point decrease on a 6-8 point ordinal scale, or defined as a reduction in disease severity [e.g. 'severe' to 'mild' illness]) (n/N) • Time to improvement (days) • Number of patients who experienced clinical deterioration (measured by a one or two point increase on a 6-8 point ordinal scale, or defined as an increase in disease severity [e.g. 'mild' to 'severe' illness]) (n/N) • Time to deterioration (days) • Longer-term outcomes reported in the study such as functional independence The definitions of mechanical ventilation, non-invasive ventilation and other forms of respiratory support such as high flow nasal oxygen (HFNO) therapy or continuous positive airway pressure or non-invasive bilevel ventilation may differ across the studies. In the context of UK practice the following definitions should be considered: **Advanced respiratory support:** Invasive mechanical ventilation, bilevel positive airway pressure (BiPAP) via translaryngeal tube or

	tracheostomy, continuous positive airway pressure (CPAP) via translaryngeal tube, or extracorporeal respiratory support) **Non-invasive ventilation:** includes HFNO, CPAP, CPAP via tracheostomy, and non-invasive bilevel ventilation. Note: oxygen via (low flow) nasal cannulae or face mask does not fall within the categories above.
Settings	All settings
Subgroups	• Adults > 50 years • Children <12 years of age • Disease severity (moderate/severe/critical) • Gender • Ethnic background • Pregnant women • Comorbidities (chronic obstructive pulmonary disease, hypertension, diabetes, coronary heart disease, chronic kidney disease, cancer, cerebral vascular disease, obesity) • Time from symptom onset • Treatment with other therapeutics used for COVID-19
Study types	The search will look for: • Systematic review of randomised controlled trials (RCTs) • RCTs If no systematic reviews or RCT evidence is available progress to: • non-randomised controlled trials • systematic reviews of non-randomised controlled trials • cohort studies • before and after studies • interrupted time series studies Preprints will be considered as part of the evidence review.
Countries	Any
Timepoints	From 2020 onwards

Other exclusions	The scope sets out what the guidelines will and will not include (exclusions). Further exclusions specific to this guideline include: • non-English language papers, studies that are only available as abstracts, and narrative reviews • animal studies • editorials, letters, news items, case reports and commentaries, conference abstracts and posters • theses and dissertations
Equality issues	Sex, age, ethnicity, religion or beliefs, people with a learning disability and disabled people, socioeconomic status, people who are pregnant or breastfeeding, people whose first language isn't English, people who are homeless, refugees, asylum seekers, migrant workers and people who are homeless.

Appendix B: Included studies

Angus, D. C., Derde, L., Al-Beidh, F. et al. (2020) Effect of Hydrocortisone on Mortality and Organ Support in Patients With Severe COVID-19: The REMAP-CAP COVID-19 Corticosteroid Domain Randomized Clinical Trial. Jama 324(13): 1317-1329

Dequin, P. F., Heming, N., Meziani, F. et al. (2020) Effect of Hydrocortisone on 21-Day Mortality or Respiratory Support Among Critically Ill Patients With COVID-19: A Randomized Clinical Trial. Jama 324(13): 1298-1306

Du B WL (2020) Glucocorticoid therapy for COVID-19 critically ill patients with severe acute respiratory failure. ClinicalTrials.gov

Edalatifard, M., Akhtari, M., Salehi, M. et al. (2020) Intravenous methylprednisolone pulse as a treatment for hospitalised severe COVID-19 patients: results from a randomised controlled clinical trial. Eur Respir J

Horby, P., Lim, W. S., Emberson, J. R. et al. (2020) Dexamethasone in Hospitalized Patients with Covid-19 - Preliminary Report. N Engl J Med

Jeronimo, C. M. P., Farias, M. E. L., Val, F. F. A. et al. (2020) Methylprednisolone as Adjunctive Therapy for Patients Hospitalized With COVID-19 (Metcovid): A Randomised, Double-Blind, Phase IIb, Placebo-Controlled Trial. Clin Infect Dis

Petersen, M. W., Meyhoff, T. S., Helleberg, M. et al. (2020) Low-dose hydrocortisone in patients with COVID-19 and severe hypoxia (COVID STEROID) trial - protocol and statistical analysis plan. Acta Anaesthesiol Scand

Rochwerg B, Oczkowski SJ, Siemieniuk RAC et al. (2018) Corticosteroids in Sepsis: An Updated Systematic Review and Meta-Analysis. Critical care medicine 46(9): 1411-1420

Tomazini, B. M., Maia, I. S., Cavalcanti, A. B. et al. (2020) Effect of Dexamethasone on Days Alive and Ventilator-Free in Patients With Moderate or Severe Acute Respiratory Distress Syndrome and COVID-19: The CoDEX Randomized Clinical Trial. Jama 324(13): 1307-1316

Villar, J., Añón, J. M., Ferrando, C. et al. (2020) Efficacy of dexamethasone treatment for patients with the acute respiratory distress syndrome caused by COVID-19: study protocol for a randomized controlled superiority trial. Trials 21(1): 717

WHO (2020) Corticosteroids for COVID-19 - Living Guidance. World Health Organization

Ye Z, Wang Y, Colunga-Lozano LE et al. Efficacy and safety of corticosteroids in COVID-19 based on evidence for COVID-19, other coronavirus infections, influenza, community-acquired pneumonia and acute respiratory distress syndrome: a systematic review and meta-analysis. CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne 192(27): E756-E767

Appendix C: Study characteristics

Summary of corticosteroids administered in the studies

Study	Corticosteroid
CAPE COVID (Dequin 2020)	Hydrocortisone IV continuous infusion x 8 or 14 days (200 mg daily x 4 or 7 days, 100 mg daily x 2 or 4 days, 50 mg daily x 2 or 3 days)
CoDEX (Tomazini 2020)	Dexamethasone 20 mg IV daily x 5 days, then 10 mg IV daily x 5 days
COVID STEROID (Perner 2020)	Hydrocortisone 200 mg IV daily x 7 days (continuous or bolus in q6h dosing)
DEXA-COVID 19 (Villar 2020)	Dexamethasone 20 mg IV daily x 5 days, then 10 mg IV daily x 5 days
Edalatifard 2020	methylprednisolone pulse (intravenous injection, 250 mg/day for 3 days)
METCOVID 2020 (Jeronimo 2020)	Methylprednisolone IV 0.5 mg/kg q12h x 5 days
RECOVERY (Horby 2021)	Dexamethasone 6 mg PO/IV daily
REMAP-CAP 2020 (Angus 2020)	Hydrocortisone 50 mg IV q6h daily x 7 days
Steroids-SARI 2020 (Du 2020	Methylprednisolone 40 mg IV q12h x 5 days

Summary of study characteristics

Study	CODEX Tomazini 2020	CODEX Tomazini 2020	RECOVERY Horby 2020	RECOVERY Horby 2020	REMAP-CAP Angus 2020		REMAP-CAP Angus 2020
Setting	Intensive care	Intensive care	Hospital (no further detail)	Hospital (no further detail)	Intensive care		Intensive care
Arm	Dexamethasone	Standard care	Dexamethasone	Usual care	Hydrocortisone		Usual care
					Fixed dose	Shock dependent dose	
Number of patients (N)	151	148	2104	4321	137	146	101
Age, mean (SD)	60.1 (15.8)	62.7 (13.1)	66.9	65.8	60.4(11.6)	59.5(12.7)	59.9(14.6)
Gender (female; %)	40.4%	34.5%	36%	36%	28.5%	29.5%	28.7%
Pregnant patients	Excluded	Excluded	Included (1 pregnant women included)	Included (3 pregnant women included)	NR		NR
Paediatric patients	Excluded	Excluded	Initially excluded but age limit of at least 18 years old was removed on 9th May 2020 (note that	Initially excluded but age limit of at least 18 years old was removed on 9th May 2020 (note that	NR		NR

			randomization took place March-June)	randomization took place March-June)		
Exclusion criteria	pregnancy or active lactation, known history of dexamethasone allergy, corticosteroid use in the past 15 days for non-hospitalized patients, use of corticosteroids during the present hospital stay for more than 1 day, indication for corticosteroid use for other clinical conditions (eg, refractory septic shock), use of immunosuppressive drugs, cytotoxic chemotherapy in the past 21 days, neutropenia due to	pregnancy or active lactation, known history of dexamethasone allergy, corticosteroid use in the past 15 days for non-hospitalized patients, use of corticosteroids during the present hospital stay for more than 1 day, indication for corticosteroid use for other clinical conditions (eg, refractory septic shock), use of immunosuppressive drugs, cytotoxic chemotherapy in the past 21 days, neutropenia due to	Dexamethasone unavailable at the hospital at the time of enrollment, considered to be definitely indicated or definitely contraindicated	Dexamethasone unavailable at the hospital at the time of enrollment, considered to be definitely indicated or definitely contraindicated	known hypersensitivity to hydrocortisone, systemic corticosteroid use, and more than 36 hours elapsed since ICU admission. Presumption that death is imminent with lack of commitment to full support and participation in the trial in the prior 90 days.	Presumption that death is imminent with lack of commitment to full support and participation in the trial in the prior 90 days.

	hematological or solid malignancies with bone marrow invasion, consent refusal, or expected death in the next 24 hours	hematological or solid malignancies with bone marrow invasion, consent refusal, or expected death in the next 24 hours				
Drug and Dose	dexamethasone 20 mg once daily for 5 days, followed by 10 mg once daily for additional 5 days or until ICU discharge, whichever occurred first, plus standard care	NR	Dexamethasone 6mg once daily plus usual care	NR	Fixed dose: intravenous hydrocortisone, 50 mg, every 6 hours Shock-Dose: intravenous hydrocortisone, 50 mg, every 6 hours	No hydrocortisone-no further details on usual care given.
Duration of treatment	10 days	NR	Up to 10 days or until discharge if sooner	NR	Fixed dose: 7 days Shock-dose: while in shock for up to 28 days (Shock was defined as the requirement for intravenous vasopressor infusion for the	NR

					treatment of shock presumed due to COVID-19. This involved restricting hydrocortisone to the period when the patient had overt shock would maximize the risk-benefit ratio).		
Route of administration	IV	NR	PO/IV	NR	IV		NR
Moderate/severe/critical	Moderate to severe ARDS (acute respiratory distress syndrome) according to the Berlin Definition criteria	Moderate to severe ARDS (acute respiratory distress syndrome) according to the Berlin Definition criteria	NR	NR	Severe: defined as presumed or confirmed SARS-CoV-2 infection who were admitted to an intensive care unit (ICU) for provision of respiratory or cardiovascular organ support		Severe: defined as presumed or confirmed SARS-CoV-2 infection who were admitted to an intensive care unit (ICU) for provision of respiratory or cardiovascular organ support
Proportion of patients using oxygen at baseline (%)	NR	NR	61% (Using oxygen only)	60% (using oxygen only)	Fixed dose High-flow nasal cannula 12.4 % Non- invasive ventilation only 24.1%	Shock dependent High-flow nasal cannula 15.8% Non-invasive ventilation only 33.6%	Usual care High-flow nasal cannula 15.8% Non- invasive ventilation only 31.7%

Proportion of patients on mechanical Ventilation (%) at baseline	100%	100%	Invasive mechanical ventilation 15%	Invasive mechanical ventilation 16%	Invasive mechanical ventilation 63.5%	Invasive mechanical ventilation 50%	Invasive mechanical ventilation 52.5%
Other medications	Hydroxychloroquine 23.8% Azithromycin 68.9% Other antibiotics 88.1% Oseltamivir 29.1%	Hydroxychloroquine 18.9% Azithromycin 73.6% Other antibiotics 86.5% Oseltamivir 35.1%	Azithromycin 24% Lopinavir/ritonavir, hydroxychloroquine, sarilumab or tocilizumab 3% or less	Azithromycin 26% Lopinavir/ritonavir, hydroxychloroquine, sarilumab or tocilizumab 3% or less	Chronic immunosuppressive therapy 5.8%	Chronic immunosuppressive therapy 4.9%	Chronic immunosuppressive therapy 6%
Co-morbidities	Hypertension 60.3% Diabetes 37.8% Obesity 30.5% Heart failure 7.3% Chronic kidney failure 4.6% Current smoker 4%	Hypertension 72.3% Diabetes 46.6% Obesity 23.7% Heart failure 8.1% Chronic kidney failure 6.1% Current smoker 4.7%	Any previous coexisting disease 56% Diabetes 25% Heart disease 28% Chronic lung disease 20%	Any previous coexisting disease 56% Diabetes 24% Heart disease 27% Chronic lung disease 22%	Diabetes 38.8% Respiratory disease 21.3% (Asthma,/COPD 15.3%, Other 5.5%) Severe cardiovascular disease 6.6% Immunosuppressive disease 5.5%	Diabetes 27.1% Respiratory disease 19.4% (Asthma,/COPD 17.4%, Other 2.8%) Severe cardiovascular disease 9.3%	Diabetes 30.6% Respiratory disease 20.4% (Asthma,/COPD 16%, Other 4.2%) Severe cardiovascular disease 6.1%

	Corticosteroids before randomisation 4.6%	Corticosteroids before randomisation 2%			Kidney disease 10.2%	Immunosuppressive disease 6.3% Kidney disease 8.7%	Immunosuppressive disease 2.1% Kidney disease 8.7%
Critical outcome(s) (as per PICO)	Duration of non-invasive ventilation or high flow nasal oxygenation (NIV/HFNO) (days)*: described in the paper as 'ventilator-free days during the first 28 days' All-cause mortality at 28 days Mechanical ventilation duration at 28 days	Duration of non-invasive ventilation or high flow nasal oxygenation (NIV/HFNO) (days)*: described in the paper as 'ventilator-free days during the first 28 days' All-cause mortality at 28 days Mechanical ventilation duration at 28 days	All-cause mortality at 28 days	All-cause mortality at 28 days	Mortality (21 days)		Mortality (21 days)
Other information	35% of the patients in the control group			In usual care, 8% of the patients receive			

	received corticosteroids during the study period			glucocorticoid as part of their clinical care.		

Appendix D: Forest Plots

Figure 1: All-cause mortality: moderate severity COVID-19

Study or Subgroup	Corticosteroids Events	Total	Standard care Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
RECOVERY	89	501	145	1034	100.0%	1.27 [1.00, 1.61]
Total (95% CI)		**501**		**1034**	**100.0%**	**1.27 [1.00, 1.61]**
Total events	89		145			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.92 (P = 0.05)

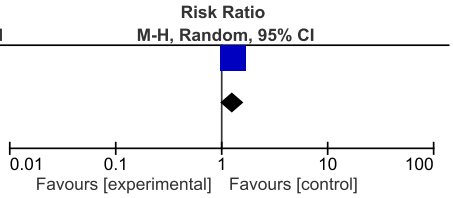


Figure 2: All-cause mortality: severe COVID-19

Study or Subgroup	Corticosteroids Events	Total	Standard care Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
CAPE COVID 2020	11	75	20	73	4.1%	0.54 [0.28, 1.04]
CoDEX 2020	69	128	76	128	17.0%	0.91 [0.73, 1.13]
COVID STEROID 2020	6	15	2	14	1.0%	2.80 [0.67, 11.64]
DEXA-COVID 19 2020	2	7	2	12	0.7%	1.71 [0.31, 9.61]
Edalatifard 2020	2	34	12	28	1.0%	0.14 [0.03, 0.56]
METCOVID 2020	58	71	60	70	21.3%	0.95 [0.82, 1.10]
RECOVERY	95	324	283	683	18.4%	0.71 [0.58, 0.86]
RECOVERY	298	1279	682	2604	22.9%	0.89 [0.79, 1.00]
REMAP-CAP 2020	26	105	29	92	7.5%	0.79 [0.50, 1.23]
Steroids-SARI 2020	13	24	13	23	6.1%	0.96 [0.57, 1.60]
Total (95% CI)		**2062**		**3727**	**100.0%**	**0.84 [0.73, 0.98]**
Total events	580		1179			

Heterogeneity: Tau² = 0.02; Chi² = 19.23, df = 9 (P = 0.02); I² = 53%
Test for overall effect: Z = 2.29 (P = 0.02)

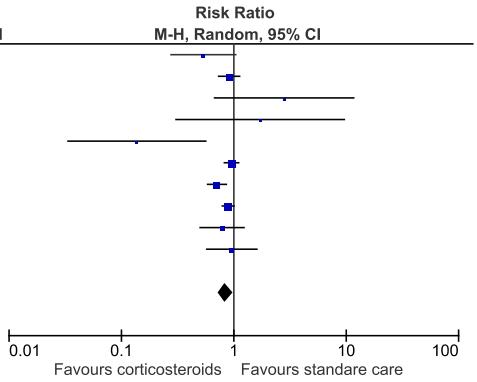


Figure 3: Hospital discharge: moderate severity COVID-19

Study or Subgroup	Corticosteroids Events	Total	Standard care Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
RECOVERY	385	501	831	1034	100.0%	0.96 [0.90, 1.01]
Total (95% CI)		**501**		**1034**	**100.0%**	**0.96 [0.90, 1.01]**
Total events	385		831			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.55 (P = 0.12)

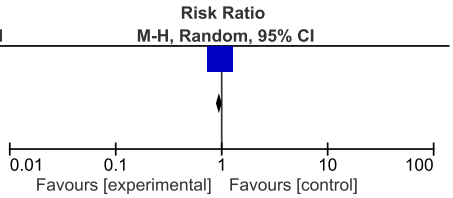


Figure 4: Hospital discharge: severe COVID-19

Study or Subgroup	Corticosteroids Events	Total	Standard care Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Edalatifard 2020	32	34	16	28	1.4%	1.65 [1.18, 2.29]
RECOVERY	921	1279	1755	2604	90.6%	1.07 [1.02, 1.12]
RECOVERY	107	324	159	683	8.0%	1.42 [1.15, 1.74]
Total (95% CI)		**1637**		**3315**	**100.0%**	**1.10 [1.06, 1.15]**
Total events	1060		1930			

Heterogeneity: Chi² = 13.48, df = 2 (P = 0.001); I² = 85%
Test for overall effect: Z = 4.50 (P < 0.00001)

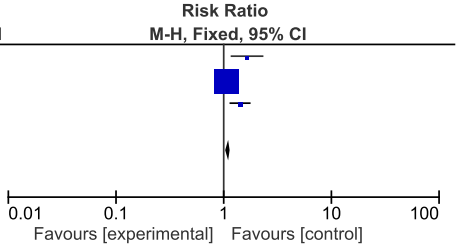


Figure 5: Invasive mechanical ventilation: moderate COVID-19

Study or Subgroup	Corticosteroids Events	Total	Standard care Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
RECOVERY	97	501	160	1034	100.0%	1.25 [1.00, 1.57]
Total (95% CI)		**501**		**1034**	**100.0%**	**1.25 [1.00, 1.57]**
Total events	97		160			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.92 (P = 0.05)

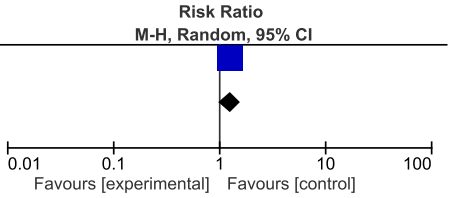


Figure 6: Invasive mechanical ventilation: severe COVID-19

Study or Subgroup	Corticosteroids Events	Total	Standard care Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
RECOVERY	359	1279	834	2604	100.0%	0.88 [0.79, 0.97]
Total (95% CI)		**1279**		**2604**	**100.0%**	**0.88 [0.79, 0.97]**
Total events	359		834			

Heterogeneity: Not applicable
Test for overall effect: Z = 2.49 (P = 0.01)

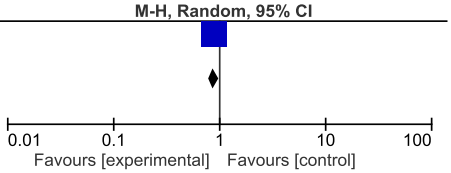
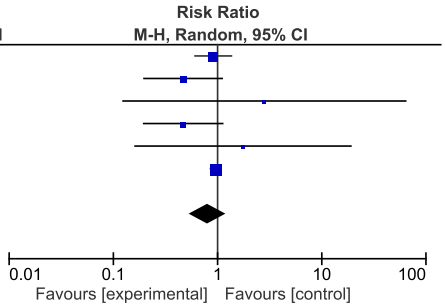


Figure 7: Serious adverse events

Study or Subgroup	Corticosteroids Events	Total	Standard care Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
CAPE COVID 2020	28	75	30	73	28.7%	0.91 [0.61, 1.36]
CoDEX 2020	7	128	15	128	14.2%	0.47 [0.20, 1.11]
COVID STEROID 2020	1	15	0	14	1.6%	2.81 [0.12, 63.83]
DEXA-COVID 19 2020	3	7	11	12	14.0%	0.47 [0.20, 1.12]
REMAP-CAP 2020	2	105	1	92	2.7%	1.75 [0.16, 19.01]
Steroids-SARI 2020	23	24	23	23	38.9%	0.96 [0.86, 1.08]
Total (95% CI)		**354**		**342**	**100.0%**	**0.80 [0.53, 1.19]**
Total events	64		80			

Heterogeneity: $Tau^2 = 0.11$; $Chi^2 = 11.81$, df = 5 (P = 0.04); $I^2 = 58\%$
Test for overall effect: Z = 1.10 (P = 0.27)



Appendix E: GRADE tables

Corticosteroids compared to control for people with COVID-19

Certainty assessment							Summary of findings				
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With control	With corticosteroids		Risk with control	Risk difference with corticosteroids
All-cause mortality [adults requiring oxygen] (follow-up: 28 days)											
5789 (9 RCTs)	not serious	serious[a]	not serious	not serious	none	Moderate	1179/3727 (31.6%)	580/2062 (28.1%)	**RR 0.84** (0.73 to 0.98)	316 per 1,000	**51 fewer per 1,000** (from 85 fewer to 6 fewer)
All-cause mortality [adults not requiring oxygen] (follow-up: 28 days)											
1535 (1 RCT)	not serious	not serious	not serious	serious[b]	none	Moderate	145/1034 (14.0%)	89/501 (17.8%)	**RR 1.27** (1.00 to 1.61)	140 per 1,000	**38 more per 1,000** (from 0 fewer to 86 more)
Invasive mechanical ventilation or death [adults requiring oxygen] (follow-up: 28 days)											
3883 (1 RCT)	not serious	not serious	not serious	serious[b]	none	Moderate	834/2604 (32.0%)	359/1279 (28.1%)	**RR 0.88** (0.79 to 0.97)	320 per 1,000	**38 fewer per 1,000** (from 67 fewer to 10 fewer)
Invasive mechanical ventilation or death [adults not requiring oxygen] (follow-up: 28 days)											
1535 (1 RCT)	not serious	not serious	not serious	serious[b]	none	Moderate	160/1034 (15.5%)	97/501 (19.4%)	**RR 1.25** (1.00 to 1.57)	155 per 1,000	**39 more per 1,000** (from 0 fewer to 88 more)

Certainty assessment							Summary of findings				
Discharge from hospital [adults requiring oxygen] (follow-up: 28 days)											
4952 (1 RCT)	not serious	serious[c]	not serious	not serious	none	Moderate	1930/3315 (58.2%)	1060/1637 (64.8%)	**RR 1.10** (1.06 to 1.15)	582 per 1,000	**58 more per 1,000** (from 35 more to 87 more)
Discharge from hospital [adults not requiring oxygen] (follow-up: 28 days)											
1535 (1 RCT)	not serious	not serious	not serious	serious[b]	none	Moderate	831/1034 (80.4%)	385/501 (76.8%)	**RR 0.96** (0.90 to 1.01)	804 per 1,000	**32 fewer per 1,000** (from 80 fewer to 8 more)
Serious adverse events [adults requiring oxygen] (follow-up: 28 days)											
696 (6 RCTs)	not serious	serious[a]	not serious	not serious	none	Moderate	80/342 (23.4%)	64/354 (18.1%)	**RR 0.80** (0.53 to 1.19)	234 per 1,000	**47 fewer per 1,000** (from 110 fewer to 44 more)
Gastrointestinal bleeding											
5403 (30 RCTs)	not serious	not serious	serious[d]	serious[d]	none	Low	NR	NR	**RR 1.06** (0.82 to 1.33)	48 per 1,000	**3 more per 1,000** (from 9 fewer to 16 more)[d]
Bacterial co-infections											
6027 (32 RCTs)	not serious	not serious	serious[d]	serious[d]	none	Low	NR	NR	**RR 1.01** (0.90 to 1.13)	186 per 1,000	**2 more per 1,000** (from 19 fewer to 24 more)[d]
Hyperglycaemia											
8938 (24 RCTs)	not serious	not serious	serious[d]	not serious	none	Moderate	NR	NR	**RR 1.16** (1.08 to 1.25)	286 per 1,000	**46 more per 1,000** (from 23 more to 72 more)[d]

Certainty assessment							Summary of findings				
Neuromuscular weakness											
6358 (8 RCTs)	not serious	not serious	serious[d]	serious[d]	none	Low	NR	NR	**RR 1.09** (0.86 to 1.39)	69 per 1,000	**6 more per 1,000** (from 10 fewer to 27 more)[d]
Neuropsychiatric effects											
1813 (7 RCTs)	not serious	not serious	serious[d]	serious[d]	none	Low	NR	NR	**RR 0.81** (0.41 to 1.63)	35 per 1,000	**7 fewer per 1,000** (from 21 fewer to 22 more)[d]

Explanations

a. The direction of the effect is not consistent between the included studies
b. Only data from one study, Wide confidence intervals
c. The confidence interval of some of the studies do not overlap with those of most included studies/ the point estimate of some of the included studies.
d. As reported in systematic review