COVID-19 Scientific Advisory Group

Rapid Evidence Report

Dose and duration of dexamethasone treatment in hospitalized COVID-19 patients

May 27, 2022

8 July 2022

The research evidence around COVID-19 is constantly evolving. Since completion of this report, additional potentially relevant papers has come to attention to be reviewed for inclusion in any possible future update of this literature synthesis, with the following a notable example:

Bouadma, L., Mekontso-Dessap, A., Burdet, C., Merdji, H., Poissy, J., Dupuis, C., Guitton, C., Schwebel, C., Cohen, Y., Bruel, C., Marzouk, M., Geri, G., Cerf, C., Mégarbane, B., Garçon, P., Kipnis, E., Visseaux, B., Beldjoudi, N., Chevret, S., Timsit, J. F., … COVIDICUS Study Group (2022). High-Dose Dexamethasone and Oxygen Support Strategies in Intensive Care Unit Patients With Severe COVID-19 Acute Hypoxemic Respiratory Failure: The COVIDICUS Randomized Clinical Trial. JAMA internal medicine, 10.1001/jamainternmed.2022.2168. Advance online publication. https://doi.org/10.1001/jamainternmed.2022.2168”

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Lay Summary

CONTEXT

- Current treatment for people in hospital with severe COVID-19 is a daily dose of dexamethasone, a medication that has been clearly shown to reduce mortality
- Dexamethasone treatment may have unpleasant side effects such as high blood pressure, high blood sugar, increased risk of infection, and sleep alteration.
- People who have weaker immune systems (“immunocompromised”) are at high risk of severe COVID-19, but there is very little evidence that describes the best dose and length of time to treat them with dexamethasone
- This review is intended to help doctors determine the best care options for their immunocompromised patients.

KEY MESSAGES

- No studies were found that included immunocompromised individuals
- Studies that used different doses and timing of dexamethasone were too small to show an effect or were ended early because no clinical effect was seen.
- In patients who are not immunocompromised, dexamethasone at 6 mg/day for 10 days is as effective as higher doses and less likely to have side effects than other steroid regimens.

RECOMMENDATIONS

- Dexamethasone at 6 mg/day is sufficient to treat most patients hospitalized for severe COVID-19 who require supplemental oxygen (e.g. for COVID pneumonia or ARDS).
- For patients that tolerate dexamethasone treatment, ten days of therapy is recommended, as this primary duration that has been studied to date
- In the absence of evidence, doctors should use their clinical judgement to determine the dose of dexamethasone or other steroids to be administered to COVID-19 patients who are immunocompromised or are recipients of solid organ transplants
- Immunocompromised patients receiving dexamethasone for COVID-19 should be monitored for bacterial or fungal infections that may arise due to immune suppression.

Authorship and Committee Members

Name	Contribution
Meenakshi Nandagiri	Writing (Evidence screening and extraction, draft preparation, revisions)
Susanne King-Jones	Librarian (Database search)
Elizabeth Mackay	Primary scientific reviewer
Brandie Laurel Walker, Jeremy Slobodan, Mitesh Thakrar, Karen Doucette	Secondary scientific reviewers
Braden Manns, Lynora Saxinger & Scott Klarenbach	Scientific Advisory Group chairs (oversight and leadership responsibility)
John Conly, Alexander Doroshenko, Shelley Duggan, Grant Innes, Elizabeth MacKay, Rosana Salvaterra, Lynora Saxinger, Jeremy Slobodan, Brandie Walker, Nathan Zelyas	Discussion, revision, and approval of document

Topic: Dose and duration of dexamethasone administration in hospitalized COVID-19 patients with acute respiratory illness

1. **What should be the dose and duration of dexamethasone administration in hospitalized COVID-19 patients in respiratory illness who require supplemental oxygen (e.g. COVID pneumonia or Acute Respiratory Distress Syndrome (ARDS))?**
    a. **Should the dose and duration of dexamethasone administration differ for individuals who are immunocompromised or are recipients of solid organ transplants?**

Context

- Findings from the landmark RECOVERY trial have firmly established the role of dexamethasone at a dose of 6 mg once daily for up to 10 days in reducing mortality in hospitalized patients with COVID-19 and respiratory failure who require supplemental oxygen or mechanical ventilation (RECOVERY Collaborative Group 2020). This dose is currently recommended by AHS.
- Results from the DEXA-ARDS trial in non-COVID patients with established moderate to severe ARDS report lower 60-day all-cause mortality and more ventilator-free days with dexamethasone 20 mg once daily from day 1 to day 5, reduced to 10 mg once daily from day 6 to day 10 (Villar 2020), raising questions as to whether higher dexamethasone doses might further improve outcomes in COVID-19 patients with ARDS
- COVID-19 patients who are immunocompromised or are recipients of solid organ transplants are at increased risk of developing severe and life-threatening conditions due in part because of acquired or inherent immunodeficiency and immunosuppressive treatments. These patient populations were not included in the RECOVERY trial and there is a need to assess the evidence base to inform their treatment, including what is the optimal dose and duration of dexamethasone administration in this patient subgroup
- Usual dosages of dexamethasone have potential significant side effects for patients including hypertension and hyperglycemia as well as increased risk of infection and mood and sleep alteration. Determining the optimal dose and length of therapy is important to improve patient outcomes, both for COVID-19 and other conditions.
- Some studies suggest dexamethasone increases the risk of COVID associated aspergillosis in ICU patients (OR 3.1) on multivariate analysis. The use of corticosteroid on admission was significantly associated but cumulative steroid

dose and days on steroid not significant on univariate analysis, and the investigators suggested further studies on dose and duration. (Leistner 2022)

- Dexamethasone and IL-6 inhibitor is now standard care for severe and critical COVID-19 and the combination is associated with COVID-19-associated pulmonary aspergillosis (CAPA) in another cohort. (Gangneux 2021). It is unclear if lower doses of dexamethasone would have the same benefits for reducing mortality and risk of pneumonia as current standard of care.

Key Messages from the Evidence Summary

- The highest quality data on the efficacy of dexamethasone dosing and duration for the treatment of hospitalized COVID-19 patients who require supplemental oxygen is from the landmark RECOVERY trial. In general, the evidence for dexamethasone doses other than that identified in the RECOVERY trial is preliminary, subject to bias, and estimated to be of low to moderate quality.
- The evidence base for dexamethasone use in COVID-19 patients requiring supplemental oxygen, in a dose different to the one from the RECOVERY trial while evolving quickly is generally still quite preliminary, subject to bias, and of low to very low quality.
- Of the six total clinical trials included in this rapid review:
    - Three published trials (CoDEX, COVID STEROID 2 and the HIGHLOWDEXA-COVID) were underpowered to identify a significant difference for either important primary or secondary outcomes. Two trials were either prematurely terminated due to low enrollment rate or halted early because of lack of significant clinical response. In one published trial, higher doses of dexamethasone not only failed to improve efficacy but also resulted in an increase in the number of adverse events and worsen survival in hospitalized patients with moderate to severe COVID-19 compared to the low-dose dexamethasone
    - None of the six peer reviewed articles were found to include hospitalized COVID-19 patients who were immunocompromised or were recipients of solid organ transplants resulting in an evidence gap with respect to the optimal dexamethasone dose and duration in this population of patients.
    - The impact of steroids on outcomes was highly dependent on the severity of COVID-19 at presentation or randomization.
- In the reviewed trials, moderate dose dexamethasone at 6 mg per day was found to be as effective as higher dosages and were less likely to have side effects than higher dosages of dexamethasone or methylprednisone.
- Additional considerations around transplant patients were raised that were not included in the available trials. Patients with solid organ transplants who contract

COVID-19 and in particular those with lung transplants are usually already on steroids and additional immunosuppressants. Patients who have pre-existing Chronic Lung Allograft Dysfunction, (CLAD), may require a higher dosage of steroid than a standard patient without lung transplant (Kamp 2021). There is also the concern that the withholding of other commonly used immunosuppressants, such as mycophenolate, during COVID-19 infection would require a higher dosage of steroid to prevent acute rejection in addition to treatment of COVID-19 associated ARDS (Saez-Giménez 2020).

- Further observational studies and registries of COVID-19 infection in solid organ transplant patients will need to be conducted in order to gather sufficient numbers to clarify the role of steroid dosage and duration on the outcomes for these patients with specific reference to the type of immunosuppressants and baseline degree of allograft dysfunction, in particular the degree of CLAD that is present at baseline (Kamp 2021).

Committee Discussion

The committee agreed with the findings of this review and supported the recommendations with minor adjustments to phrasing. They also identified additional research gaps regarding the study populations and advances in COVID-19 treatment that were originally overlooked. That said, the writer was commended for their high-quality synthesis of the evidence to generate clear, concise recommendations for the use of dexamethasone in COVID-19.

Recommendations

1. Dexamethasone at 6 mg/day is sufficient to treat most patients hospitalized for severe COVID-19 who require supplemental oxygen (e.g. for COVID pneumonia or ARDS).
   Rationale: There is lack of sufficient evidence to recommend higher dosages of dexamethasone. There may be a greater risk of side effects or complications with higher dosages.
2. For most patients, ten days of dexamethasone therapy is recommended, assuming treatment tolerability.
   Rationale: No evidence was identified to suggest an alternate treatment duration. 10 days is the primary duration studied to date.
3. Clinical judgement should be used to determine the dose of dexamethasone or other steroids to be administered to COVID-19 patients who are immunocompromised or are recipients of solid organ transplants (Sait 2022, National Institutes of Health 2021, American Society of Transplantation 2022).

Rationale: There is a lack of evidence on dexamethasone for treating immunocompromised patients with COVID-19. Clinical decisions will need to incorporate the impact of other immunosuppressants and the degree of baseline allograft dysfunction.

4. The clinician should remain vigilant towards the development of bacterial and fungal infections when dexamethasone or higher dosages of other steroids are required for the management of acute COVID-19 infection and the prevention of allograft rejection.
   Rationale: The role of dexamethasone in promoting secondary bacterial and fungal infections and the risk of such infections arising in the solid organ transplant population remains unclear.

Practical Guidance

- Secondary organizing pneumonia after recovery or partial recovery from severe COVID-19 infection can occur after initial dexamethasone treatment has been completed. Re-initiation of high dose corticosteroids may be required but has not been well studied to date and cannot currently be recommended without expert input. This remains a distinct entity with its own considerations for dose and duration of steroids relative to the acute management of COVID-19 associated with acute respiratory illness.

Research Gaps

- Clinical trials on the use of dexamethasone for the treatment of COVID-19 to date have excluded immunocompromised patients and recipients of solid organ transplants.
- Case studies and transplant registries have reported on some early outcomes for solid organ transplant patients with COVID-19 infections. These have identified a higher morbidity and mortality for these patients and in particular a worse outcome for those with baseline allograft dysfunction.
- Clinical trials of dexamethasone are exclusively from pre-vaccinated populations. The effect of dexamethasone treatment in vaccinated individuals is unclear.
- No articles were identified that described the use of dexamethasone with artificial surfactant or other medications to manage the inflammatory cascade that is implicated in COVID pneumonia or ARDS.
- The interaction between dexamethasone and tociluzimab/baritinib may pose additional risks to immunocompromised patients; however these additional risks are unclear and no articles were identified to answer these questions.
- Future clinical trials will need to include the baseline dosage of steroids and other immunosuppressants and the degree of allograft dysfunction and time from

transplantation as important variables that will interact with steroid dosage and duration and outcomes in these patients.

Strength of Evidence

- The evidence for the use of doses higher than 6 mg/day for the treatment of hospitalized COVID-19 patients with ARDS is currently lacking as is the evidence for the optimal dose and duration of dexamethasone administration in COVID-19 patients who are immunocompromised or are recipients of solid organ transplants.
- The evidence base for dexamethasone use in COVID-19 patients with ARDS, in a dose different to the one used in the RECOVERY trial while evolving quickly is generally still quite preliminary, subject to bias, and of low to moderate quality.
- None of the six peer reviewed articles included in this rapid review included hospitalized COVID-19 patients who were immunocompromised or were recipients of solid organ transplants.

Limitations of this review

The need for a rapid turnaround time for this rapid review did not allow for a thorough search of the peer reviewed literature beyond Medline Ovid, Embase Ovid, CINAHL EBSCO and MedRxiv for articles published in English from 2020-2022 utilizing a search strategy based around the key concepts of dexamethasone dosage and COVID-19. Of six trials included in this review, one trial was prematurely terminated due to low enrollment rate, one was halted early and three were underpowered to identify a significant difference for either important primary or secondary outcomes. None of the clinical trials included immunocompromised or solid organ transplant COVID-19 patients.

Research Question

1. **What should be the dose and duration of dexamethasone administration in hospitalized COVID-19 patients with ARDS?**
    a. **Should the dose and duration of dexamethasone administration differ for individuals who are immunocompromised or are recipients of solid organ transplants?**

Evidence from the primary literature

There is currently no evidence to support a change in the dose of dexamethasone needed to treat hospitalized COVID-19 patients moderate to severe pneumonia or with ARDS. Further, since COVID-19 patients who are either immunocompromised or are

recipients of solid organ transplants were not included in the clinical trials it is best left to the clinical judgement of the treating physician and the transplant team to make a determination on the appropriate treatment for this patient population. This acknowledges the higher risk of severe COVID 19, but also the higher potential risk of adverse events related to dexamethasone in the context of the immunosuppressants that are also required to prevent allograft rejection.

As lymphopenia is a risk factor for severe disease some transplant clinicians hold antimetabolites such as mycophenolate, but calcineurin inhibitors, which inhibit IL-6 pathways are sometimes continued as these pathways are implicated in the pathogenesis of severe COVID-19 disease. All changes in immunosuppressive regimens including the dose or duration of dexamethasone in COVID-19 treatment should be individualized to weigh the risks of severe COVID-19, rejection, and secondary infection.

Synthesis of the information relating to the research question

We describe the results of six eligible trials included in this rapid review all of which were published in peer-reviewed journals in the English language (Table 1).

- The CoDEX trial randomized 299 patients with moderate or severe ARDS and COVID-19 to open-label high-dose dexamethasone (n=151, 20 mg/d for 5 days, then 10 mg/d for 5 days plus standard care) versus standard care alone (n=148) (Tomazini 2020). The primary outcome was ventilator-free days through day 28, which were greater in patients randomized to dexamethasone (6.6 vs 4.0, difference, 2.26; 95% CI, 0.2-4.38; P = 0.04). While 28-day all-cause mortality was not significantly different between patients randomized to dexamethasone versus standard care (56.3% vs 61.5%, HR 0.97: 0.72 to 1.31, P = 0.85), stopping the study early when RECOVERY results were announced resulted in a sample size that was underpowered to adequately evaluate the effect of high dose dexamethasone on mortality.
- In a randomized controlled trial by Jamaati et al, 2021, 50 patients were randomized to either a high dose dexamethasone group (n=25, 20 mg/day from day 1–5 and then 10 mg/day from day 6–10) or a control group (n=25). The primary outcomes were the need for mechanical ventilation and death rate. The study.was halted early because of a lack of significant clinical response in patients with COVID-19-induced mild to moderate ARDS with no differences noted for mortality rates (64% versus 60%, P = 0.500) and the need for noninvasive ventilation (92% versus 96%, P = 0.500) or mechanical ventilation (52% versus 44%, P = 0.389) between the dexamethasone and the no dexamethasone control groups.

- The COVID STEROID 2 trial was an investigator-initiated, international, randomized, stratified, parallel-group, blinded clinical trial (Munch 2021). In this study, among 1000 patients with COVID-19 and severe hypoxemia, 12 mg/day of dexamethasone (n=503),) as compared to 6 mg/day of dexamethasone (n=497) did not result in statistically significant primary outcome of more days alive without life support at 28 days (22.0 days; IQR, 6.0-28.0 days, 12 mg of dexamethasone versus 20.5 days; IQR, 4.0-28.0 days, 6 mg of dexamethasone; adjusted mean difference, 1.3 days [95% CI, 0-2.6 days]; P = 0.07). However, the trial may have been underpowered to identify a significant difference.
- In the HIGHLOWDEXA-COVID randomized, open-label, controlled trial (Taboada 2021) 200 patients were randomized to high dose dexamethasone (n=98, 20 mg once daily for 5 days, followed by 10 mg once daily for additional 5 days) versus low dose of dexamethasone (n=102, 6 mg once daily for 10 days) in only patients hospitalized with COVID-19 pneumonia needing oxygen therapy at the time of randomization. HFNC, NIMV, MV or ICU patients were not included in the trial. The high dose of dexamethasone used in this trial was chosen based on previous trials showing the benefit of this dose in patients with COVID-19 (Tomazini 2020) and non-COVID-19 ARDS (Villar 2020). In this study, high dose of dexamethasone was found to reduce the primary outcome of clinical worsening in a well-defined subset of patients, including those with moderate or severe pneumonia needing oxygen therapy at risk of developing ARDS and potentially requiring MV within 11 days after randomization as compared with low dose of dexamethasone (16.3% in the high dose group versus 31.4% in the low dose group; rate ratio, 0.427; 95% CI, 0.216–0.842; P = 0.014). The trial however had several limitations and was underpowered for important secondary outcomes such as mortality and the study was limited to demonstrate benefits in secondary outcomes.
- In a three arm RCT by Toroghi et al, 2022, 133 patients were randomized 1:1:1 to high dose dexamethasone (n=46, 8 mg thrice daily) intermediate dose dexamethasone (n=40, 8 mg twice daily) and low dose dexamethasone (n=47, 8 mg once daily). The primary outcome of the study was time to a clinical response that was described as improvement of at least two scores in the eight-category ordinal scale of the National Institute of Health. Higher doses of dexamethasone not only failed to improve efficacy but also resulted in an increase in the number of adverse events and worsened survival in hospitalized patients with moderate to severe COVID-19 as compared to the low-dose dexamethasone. In the competing risk survival analysis, patients in the low-dose group had a higher clinical response than the high dose group when considering death as a competing risk (HR=2.03, 95% CI: 1.23–3.33, P = 0.03). Also, the

survival was significantly longer in the low-dose group than the high-dose group (HR=0.36, 95% CI=0.15–0.83, P = 0.02).

- In a multicenter randomized, open-label, clinical trial involving 98 adults ventilated for ARDS due to COVID-19, patients were randomized to either high dose dexamethasone (n=49, 16 mg IV daily for five days followed by 8 mg daily for five days or to low dose dexamethasone (6 mg IV daily for 10 days) (Maskin 2021). The trial was terminated early due to poor recruitment which prevented the investigators from reaching the target sample size. There was no difference between high- and low-dose dexamethasone groups in the primary outcome of ventilator free days during the first 28 days (median, 0 [interquartile range [IQR] 0-14] vs. 0 [IQR 0-1] days; P = 0.231), or in the mean duration of mechanical ventilation (19±18 vs. 25±22 days; P = 0.078). The cumulative hazard of successful discontinuation from mechanical ventilation was increased by the high-dose treatment (adjusted sub-distribution hazard ratio: 1.84; 95% CI: 1.31 to 2.5; P < 0.001) — findings that warrant further investigation.

Clinical trials to determine the efficacy of different doses of dexamethasone as monotherapy or in combination with other drugs for the treatment of patients with COVID-19 are ongoing. Information on 22 such clinical trials of interest registered to clinicaltrials.gov that are either active but not recruiting (n=1), recruiting (n=19) and not yet recruiting (n=2) is listed in Table 2.

Table 1. Randomized controlled trials on dexamethasone in COVID-19 retrieved from peer-reviewed literature.

Reference	Study Design	Patient Population	Sample Size, N	Intervention/Comparator	Primary Outcome	Efficacy Results	Adverse Events	Notes
Tomazini et al 2020 (CoDEX) NCT04327401	RCT, open-label multicenter	Patients at least 18 years old, had confirmed or suspected COVID-19 infection receiving mechanical ventilation within 48 hours of meeting criteria for moderate to severe ARDS	299	Dexamethasone: 20 mg IV dexamethasone daily for 5 days, 10 mg of dexamethasone daily for 5 days or until ICU discharge, plus standard care (n=151) Control: Standard care alone (n=148)	Ventilator-free days during the first 28 days, defined as the number of days alive and free from mechanical ventilation for at least 48 consecutive hours.	The dexamethasone group had a mean 6.6 ventilator-free days (95% CI, 5.0-8.2) during the first 28 days vs 4.0 ventilator-free days (95% CI, 2.9-5.4) in the standard care group (difference, 2.26; 95% CI, 0.2-4.38; P = 0.04). At 7 days, patients in the dexamethasone group had a mean SOFA score of 6.1 (95% CI, 5.5-6.7) vs 7.5 (95% CI, 6.9-8.1) in the standard care group (difference, −1.16; 95% CI, −1.94 to −0.38; P = 0 .004). There was no significant difference in the prespecified secondary outcomes of all-cause mortality at 28 days, ICU-free days during the first 28 days, mechanical ventilation duration at 28 days, or the 6-point ordinal scale at 15 days.	Twelve patients (7.9%) in the dexamethasone group had bacteremia versus 14 (9.5%) in the standard care group. Five patients (3.3%) in the dexamethasone group had serious adverse events versus 9 (6.1%) in the standard care group.	The trial was underpowered for important secondary outcomes like mortality and the study was interrupted before the original sample size was obtained due to external evidence of benefit, and the obtained sample size was limited to demonstrate benefits in secondary outcomes Low-moderate quality study. Moderate risk of bias from open label and small sample size before study stopped.
Jamaati et al 2021	RCT	Patients with mild to moderate ARDS due	50	Dexamethasone: 20 mg/day IV dexamethasone from day 1–5	Need for invasive mechanical	92% and 96% of patients in the dexamethasone	Not reported	The main limitation of the current

IRCT20151227025726N17		to COVID-19		and then at 10 mg/day from day 6–10 (n=25) Control: No dexamethasone (n=25)	ventilation and death rate.	and control groups, respectively, required noninvasive ventilation (P = 0.500). Among them, 52% and 44% of patients in the dexamethasone and control groups, respectively, required invasive mechanical ventilation (P = 0.389). At the end of the study, 64% of patients in the dexamethasone group and 60% of patients in the control group died (P = 0.500); the remaining patients were discharged from the hospital during the 28-day follow-up period. The median length of hospital stay was 11 days in the dexamethasone group and 6 days in the control group (P = 0.036) and the median length of hospital stay was 7 days in the dexamethasone group and 3 days in the control group (P < 0.001). No significant differences were observed in the other outcomes.		study was the small sample size. It was halted because no significant clinical response was seen in the fifty patients. This may be due to relatively mild COVID-19 in this population. Low-moderate quality study. High risk of bias from small sample size and low acuity population
Munch et al 2021 (COVID STEROID 2)	RCT, multicenter	Patients ≥ 18 years hospitalized with confirmed SARS-	1000	High dose dexamethasone: 12 mg IV dexamethasone once daily for up to 10 days from	Number of days alive without life support (invasive	The median number of days alive without life support was 22.0 days	Serious adverse reactions, including septic shock and	The trial may have been underpowered to

NCT04509973		CoV-2 infection, and requiring (1) supplementary oxygen at a flow rate of at least 10 L/min (independent of delivery system), (2) noninvasive ventilation or continuous positive airway pressure for hypoxemia, or (3) invasive mechanical ventilation		randomization (n=503) Low dose dexamethasone: 6 mg dexamethasone IV once daily for up to 10 days from randomization (n-497)	mechanical ventilation, circulatory support, or kidney replacement therapy) at 28 days after randomization.	(IQR, 6.0-28.0 days) in the 12 mg of dexamethasone group and 20.5 days (IQR, 4.0-28.0 days) in the 6 mg of dexamethasone group (adjusted mean difference, 1.3 days [95% CI, 0-2.6 days]; P = 0.07). Mortality at 28 days was 27.1% in the 12 mg of dexamethasone group vs 32.3% in the 6 mg of dexamethasone group (adjusted relative risk, 0.86 [99% CI, 0.68-1.08]). Mortality at 90 days was 32.0% in the 12 mg of dexamethasone group vs 37.7% in the 6 mg of dexamethasone group (adjusted relative risk, 0.87 [99% CI, 0.70-1.07]).	invasive fungal infections, occurred in 11.3% of the 12 mg of dexamethasone group vs 13.4% in the 6 mg of dexamethasone group (adjusted relative risk, 0.83 [99% CI, 0.54-1.29])	identify a significant difference and may have chosen a population that had already reached the severe stage where 12 vs 6 mg would not make a difference. Low-moderate quality study. High risk of bias due to late presentation.
Taboada et al 2021 (HIGHLOWDEXA-COVID) NCT04726098	RCT, open-label	Patients with confirmed SARS-CoV-2 infection receiving supplemental oxygen in order to maintain an oxygen saturation greater than 92% (Level 4 WHO-CIS)	200	Low dose dexamethasone: 6 mg once daily for 10 days (n=102) High dose dexamethasone: 20 mg once daily for 5 days, followed by 10 mg once daily for additional 5 days (n=98)	Clinical worsening within 11 days since randomization defined as worsening of the patient´s condition during treatment (need to increase fraction of inspired oxygen > 0.2, need for	Thirty-two patients of 102 (31.4%) enrolled in the low dose group and 16 of 98 (16.3%) in the high dose group showed clinical worsening within 11 days since randomization (rate ratio, 0.427; 95% CI, 0.216-0.842; P = 0.014). The 28-day mortality was 5.9% in the low dose group and 6.1% in the	Adverse events were comparable in both groups	The trial was underpowered for important secondary outcomes like mortality and the study was limited to demonstrate benefits in secondary outcomes. Fourth, our study did not include critically ill

					fraction of inspired oxygen > 0.5, respiratory rate > 25) or score higher than 4 on the 7-point ordinal scale WHO-CIS.	high dose group (P = 0.844). There was no significant difference in time to recovery, and in the 7-point ordinal scale at day 5, 11, 14 and 28.		patients or patients with mild disease Low-moderate quality study. High risk of bias due to small sample size and low acuity patient study population
Toroghi et al 2022 IRCT20100228003449N31	RCT, three-arm	Hospitalized patients with a diagnosis of moderate to severe COVID-19	133	Low dose dexamethasone: 8 mg IV once daily for up to 10 days or until hospital discharge (n=47) Intermediate dose dexamethasone: 8 mg IV twice daily for up to 10 days or until hospital discharge (n=40) High dose dexamethasone: 8 mg IV thrice daily for up to 10 days or until hospital discharge (n=46)	Time to a clinical response described as improvement of at least two scores in the eight-category ordinal scale of the National Institute of Health (NIH).	In the competing risk survival analysis, patients in the low-dose group had a higher clinical response than the high dose group when considering death as a competing risk (HR=2.03, 95% CI: 1.23–3.33, P = 0.03). Also, the survival was significantly longer in the low-dose group than the high-dose group (HR=0.36, 95% CI=0.15–0.83, P = 0.02).	Leukocytosis and hyperglycemia were the most common side effects of dexamethasone. While there were numerically higher number of adverse events observed with high and moderate dose dexamethasone observed, these differences were not significant	Higher doses of dexamethasone not only failed to improve efficacy but also resulted in an increase in the number of adverse events and worsen survival in hospitalized patients with moderate to severe COVID-19 compared to the low-dose dexamethasone Low-moderate quality study. High risk of bias due to small sample sizes and imbalance of risk factors across groups
Maskin et al 2022	RCT, open-label	Patients with confirmed COVID-19-	100	High-dose dexamethasone: 16 mg IV dexamethasone daily for	Ventilator-free days during the	No difference between high- and low-dose	Incidence of adverse events not	The trial was terminated due to

NCT04395105	multicenter	related ARDS receiving mechanical ventilation for less than 72 h		five days followed by 8 mg daily for five days (n=49) Low-dose dexamethasone: 6 mg IV dexamethasone daily for 10 days (n=51)	first 28 days of randomization.	dexamethasone groups in VFD (median, 0 [interquartile range [IQR] 0-14] vs. 0 [IQR 0-1] days; P = 0.231), or in the mean duration of mechanical ventilation (19±18 vs. 25±22 days; P = 0.078). The cumulative hazard of successful discontinuation from mechanical ventilation was increased by the high-dose treatment (adjusted sub-distribution hazard ratio: 1.84; 95% CI: 1.31 to 2.5; P < 0.001). None of the prespecified secondary and safety outcomes showed a significant difference between treatment arms.	observed to be significantly different between arms.	poor recruitment after nine months which prevented the investigators from reaching their target sample for enrollment. Low-moderate quality study. High risk of bias due to small sample size and severity of illness at presentation.

Exclusion criteria related to possible immunocompromised or organ transplant recipient status
Munch 2021: Use of systemic corticosteroids for indications other than COVID-19 in doses higher than 6 mg dexamethasone equivalents; Taboada 2021: Indication for corticosteroids use for other clinical conditions; Toroghi 2022: History of corticosteroid therapy (for more than two weeks); Tomazini 2020: Clinical indication for corticosteroids use for other diseases, use of immunosuppressive drugs; Jamaati 2021: Not stated; Maskin 2022: Known immunocompromised condition, chronic use of systemic corticosteroids.

Table 2. Clinical trials of dexamethasone in patients with COVID-19 that are ongoing (retrieved from clinicaltrials.gov).

Study Title	Interventions	Phase	Number Enrolled	Trial number	Status	Country
1. Dexamethasone and Oxygen Support Strategies in ICU Patients With Covid-19 Pneumonia COVIDICUS	Drug: Dexamethasone Box of 10, 20 mg / 5 ml, solution for injection in ampoule of 5mL. Each allocated box contains complete treatment from D1 to D10 for one patient. Drug: placebo Procedure: conventional oxygen (and 3 more...)	NA	550	NCT04344730	Active, not recruiting	France
2. Early Treatment Strategy With High-dose Dexamethasone in Patients With SARS-CoV-2	Drug: Dexamethasone 20 mg IV for 3 days, followed by daily 6 mg IV or oral for 7 days Drug: Dexamethasone (standard treatment regimen) 6 mg orally or IV for 10 days (with the possibility of escalation to doses of 20 mg daily of oral or IV for 3 days if clinical criteria of respiratory distress develop despite treatment with doses of dexamethasone 6 mg daily	Phase 3	200	NCT05293210	Not yet recruiting	
3. Factorial Randomized Trial of Rendesivir and Baricitinib plus Dexamethasone for COVID-19 (the AMMURAVID Trial)	Drug: Remdesivir + baricitinib + dexamethasone 6 mg for 10 days Drug: Baricitinib + dexamethasone 6 mg for 10 days Drug: Remdesivir + dexamethasone 6 mg for 10 days Drug: Dexamethasone 6 mg IV for 10 days	Phase 3	4000	NCT04832880	Not yet recruiting	Italy
4. Effect of Two Different Doses of Dexamethasone in Patients With ARDS and COVID-19 (REMED)	Drug: Dexamethasone 20 mg IV once daily on day 1-5, followed by 10 mg IV once daily on day 6-10. Drug: Dexamethasone 6 mg IV once daily on day 1-10,	Phase 4	300	NCT04663555	Recruiting	Czechia
5. RCT on the Efficacy of Dexamethasone Versus Methyl Prednisolone in Covid-19 Infected Patients With High Oxygen Flow	Drug: Dexamethasone 8 mg q12hours Drug: Methylprednisolone 0.5 mg/kg q12 hours	Phase 4	60	NCT05062681	Recruiting	Egypt
6. Randomized Clinical Trial of Intranasal Dexamethasone as an Adjuvant in Patients With COVID-19	Drug: IV Dexamethasone 6 mg from day 1 to 10 after randomization Drug: Nasal Dexamethasone 0.12 mg/kg/daily for 3 days from day 1, followed by 0.06 mg/kg/daily from day 4 to 10 after randomization.	Phase 2	60	NCT04513184	Recruiting	Mexico
7. Dexamethasone vs Methylprednisolone for the Treatment of Patients With ARDS Caused by COVID-19	Drug: Dexamethasone 20 mg/iv/daily/from day 1 of randomization, followed by a tapering dose according to the patient's condition Drug: Methylprednisolone 0.5 mg/kg ?daily	Phase 3	60	NCT04499313	Recruiting	Bangladesh
8. **DEXamethasone EARLY Administration in Hospitalized Patients With Covid-19 Pneumonia (EARLYDEXCoV2)**	Drug: Dexamethasone 6 mg once daily for seven days	Phase 3	126	NCT04836780	Recruiting	Spain
9. **Methylprednisolone vs. Dexamethasone in COVID-19 Pneumonia (MEDEAS RCT) MEDEAS**	Drug: Methylprednisolone 160 mg iv day one followed by 80 mg iv daily x 8 days then taper Drug: Dexamethasone 6 mg IV in 30 minutes or PO from day 1 to day 10 or until hospital discharge (if sooner).	Phase 3	680	NCT04636671	Recruiting	Italy

10. **Baricitinib in Hospitalized Covid-19 Patients With Diabetes Mellitus**	Drug: Baricitinib Drug: Dexamethasone 6 mg IV daily while hospitalized for up to a 10-day total course Drug: Remdesivir	Phase 3	382	NCT04970719	Recruiting	Bangladesh
11. **NA-831, Atazanavir and Dexamethasone Combination Therapy for the Treatment of COVID-19 Infection (NATADEX)**	Drug: Drug: NA-831 Combination Product: NA-831 & Atazanavir Combination Product: NA-831 and dexamethasone 8 mg orally twice a day for one day, followed by 4 mg daily for four consecutive days (five days total). Combination Product: Atazanavir and Dexamethasone 8 mg orally twice a day for one day, followed by 4 mg daily for four consecutive days (five days total).	Phase 2 Phase 3	525	NCT04452565	Recruiting	United States
12. **Human Intravenous Interferon Beta-la Safety and Preliminary Efficacy in Hospitalized Subjects With CoronavirUS (HIBISCUS)**	Drug: IFN beta-1a Drug: Dexamethasone daily IV bolus for 6 days while hospitalised	Phase 2	140	NCT04860518	Recruiting	United States
13. **Comparison Between Prednisolone and Dexamethasone on Mortality in Patients on Oxygen Therapy, With COViD-19 (COPreDex)**	Drug: Dexamethasone 6 mg per day during 10 days Drug: PREDNISOLONE 60 mg daily during 10 days	Phase 3	220	NCT04765371	Recruiting	France
14. **Spironolactone and Dexamethasone in Patients Hospitalized With COVID-19**	Drug: Spironolactone + Dexamethasone 2 mg 2x/day, 12/12h for 20 days Drug: Standard-of-care SARS-CoV-2 treatment	Phase 3	440	NCT04826822	Recruiting	Russian Federation
15. **Comparison of Tocilizumab Plus Dexamethasone vs. Dexamethasone for Patients With Covid-19 (TOCIDEX)**	Drug: Tocilizumab Drug: Dexamethasone 10 mg once daily for the first five days (day 1 to day 5) then 5 mg per day for up to 5 days, 2.5mg per day for up to 4 days (or until oxygen supply independency if sooner	Phase 2	660	NCT04476979	Recruiting	French Guiana
16. **Clinical Trial to Evaluate the Efficacy of Different Treatments in Patients With COVID-19**	Drug: Emtricitabine/Tenofovir Disoproxil Fumarate Drug: Baricitinib + dexamethasone dose not specified Drug: Dexamethasone dose not specified	Phase 3	2193	NCT04890626	Recruiting	Spain
17. **Glucocorticoid Therapy in Coronavirus Disease COVID-19 Patients**	Drug: Dexamethasone 6 mg/24h - 10 days (RECOVERY trial dose) Drug: Methylprednisolone 250 mg iv over 4h x 3 days	Phase 4	290	NCT04780581	Recruiting	Spain
18. **Efficacy of DEXamethasone in Patients With Acute Hypoxemic REspiratory Failure Caused by INfEctions**	Drug: Dexamethasone low dose 6 mg/iv/day during 10 days. Drug: Dexamethasone moderate dose 20 mg/IV/ daily from day of randomization (day 1) during 5 days, followed by 10 mg/iv/ daily from Day 6 to Day 10 of randomization.	Phase 4	980	NCT04545242	Recruiting	Spain
19. **Trial to Determine the Efficacy/Safety of Plitidepsin vs Control in Patients With Moderate COVID-19 Infection**	Drug: Plitidepsin Drug: Dexamethasone 6.6 mg dexamethasone base IV on Days 1 to 3, followed 6 mg/day dexamethasone base from Day 4 and up to a total cumulative dose of 60 mg of dexamethasone base (as per physician judgement according to patient clinical condition and evolution) Drug: Remdesivir Drug: Favipiravir	Phase 3	609	NCT04784559	Recruiting	Argentina

20. **Combination of Inhaled DNase, Baricitinib and Tocilizumab in Severe COVID-19**	Drug: Dexamethasone 6-8 mg once daily Drug: Low molecular weight heparin Drug: Anakinra (and 3 more...)	NA	150	NCT05279391	Recruiting	Greece
21. Treatments for COVID-19: Canadian Arm of the SOLIDARITY Trial 22.	Drug: Dexamethasone 6 mg IV/oral for a further five days, followed by a five day taper of 4 mg x 2 days and 2 mg x 3 days, for a total 20 day steroid course (and 5 more…)	Phase 3	2900	NCT04330690	Recruiting	Calgary,
23. **Randomised Evaluation of COVID-19 Therapy (RECOVERY)**	Drug: Lopinavir-Ritonavir Drug: Low doseCorticosteroid dex 6 mg iv vs prednisolone 40 mg po or 80 mg iv daily x 10 days Drug: Hydroxychloroquine Drug: High dose steroid: Dexamethasone 20 mg once daily for 5 days followed by 10 mg od for 5 days Groups A to L	Phase 2 Phase 3 Phase 4	50000	NCT04381936	Recruiting	Multiple countries

N/a: not applicable

Evolving Evidence

We acknowledge that the evidence regarding the care and management of individuals that are suspect or confirmed COVID-19 is rapidly evolving. Therefore significant changes in clinical guidelines may occur and impact this rapid review.

Appendix

List of Abbreviations

AHS	Alberta Health Services
ARDS	Acute Respiratory Distress Syndrome
CAPA	COVID-19-associated pulmonary aspergillosis
CLAD	Chronic Lung Allograft Dysfunction
COVID-19	CoronaVIrus Disease - 2019
HFNC	High Flow Nasal Cannula
ICU	Intensive Care Unit
IDSA	Infectious Diseases Society Of America
KRS	Knowledge Resources Service
MMAT	Mixed Methods Appraisal Tool
MV	Mechanical Ventilation
NIMV	Non-Invasive Mechanical Ventilation
SARS-CoV-2	Severe Acute Respiratory Syndrome – Coronavirus - 2
SpO2	Optimal Oxygen Saturation
VFD	Ventilator Free Days
WHO-CIS	World Health Organization 7-point Ordinal Scale for clinical improvement

Methods

Literature search

A literature search was conducted by Susanne King-Jones from Knowledge Resources Service (KRS) within the Health Evidence Innovation department of Alberta Health Services. KRS searched databases for articles published in English from 2020-2022, and included: Medline Ovid, Embase Ovid, CINAHL EBSCO and MedRxiv. Briefly, the search strategy was based around the following key concepts: “Dexamethasone; dosage and “COVID-19”. Articles identified by KRS in their search were initially screened by title against the inclusion/exclusion criteria listed in Table 4 below. 83 articles were identified by KRS with references and abstracts provided for further review. 79 articles were excluded from the review in accordance with the inclusion/exclusion criteria stated below. Two articles were added adhoc during a hand search for relevant articles.

Table 4. Inclusion and exclusion criteria for screening of the peer-reviewed literature.

Inclusion Criteria	Exclusion Criteria
– Hospitalised patient population with COVID-19 – Patients are treated with dexamethasone alone – Authors describe an objective, clinically relevant outcome – RCT, large case series (n ≥ 50) – Published 2020-2022 – Any jurisdiction – English	– Article is not from a credible source – Article does not have a clear research question or issue – Presented data/evidence is not sufficient to address the research questions – Non-coronavirus respiratory infection – Not treated with dexamethasone – Non-human study – Editorial, commentary, narrative review, study protocol, observational study, case report or small case series (n < 50)

Critical evaluation of the evidence

Exclusion criteria for study quality were adapted from the Mixed Methods Appraisal Tool (MMAT) (Hong et al., 2018). Potential articles were evaluated on three criteria: 1) Peer reviewed or from a reputable source; 2) Clear research question or issue; 3) Whether the presented data/evidence is appropriate to address the research question. Preprints and non peer-reviewed literature (such as commentaries and letters from credible journals) are not excluded out of hand due to the novelty of COVID-19 and the speed with which new evidence is available. The quality of each included article was estimated based on the experience of the writer and review team.

Search Strategy

Medline Ovid 1946 to April 22, 2020

#	Searches	Results
1	exp Coronavirus/ or Coronavirus Infections/ or COVID-19/ or (covid or coronaviru* or corona viru* or ncov* or n-cov* or novel cov* or COVID-19 or COVID19 or COVID-2019 or COVID2019 or SARS-CoV-2 or SARSCoV-2 or SARSCoV2 or SARSCoV19 or SARS-Cov-19 or SARSCov-19 or SARSCoV2019 or SARS-Cov-2019 or SARSCov-2019 or severe acute respiratory syndrome coronaviru* or severe acute respiratory syndrome cov 2 or 2019 ncov or 2019ncov).mp.	266571
2	exp Dexamethasone/	54216
3	dexamethasone.ti,ab.	61016
4	2 or 3	76873
5	1 and 4	1132
6	dosage*.ti,ab.	169750
7	dose*.ti,ab.	1432063
8	frequenc*.ti,ab.	1031520
9	timing.ti,ab.	151524
10	duration*.ti,ab.	678044
11	6 or 7 or 8 or 9 or 10	3154125
12	5 and 11	311
13	limit 12 to (clinical trial, all or controlled clinical trial or meta analysis or practice guideline or pragmatic clinical trial or randomized controlled trial or "systematic review")	50

Embase Ovid 1974 to April 22, 2022

#	Searches	Results
1	COVID-19/ or SARS-CoV-2/ or coronavirinae/ or betacoronavirus/ or Coronavirus infection/	72921
2	*dexamethasone/	26230
3	1 and 2	119
4	dose*.ti,ab.	1645376
5	dosage.ti,ab.	161716
6	timing.ti,ab.	183360
7	duration.ti,ab.	875345
8	4 or 5 or 6 or 7	2647143
9	3 and 8	48
10	limit 9 to english language	47

11	limit 10 to yr="2020 - 2022"	47
12	11 not conference abstract.pt.	24

CINAHL Complete EBSCO April 22, 2022

#	**Query**	**Results**
S7	S3 AND S4 Publication Type: Clinical Trial, Meta Analysis, Practice Guidelines, Randomized Controlled Trial, Systematic Review	8
S6	S3 AND S4 Narrow by Language: - english	38
S5	S3 AND S4	39
S4	dose or dosage or dosing or timing or duration	663,925
S3	S1 AND S2	112
S2	(MH "Dexamethasone")	6,422
S1	covid-19 or coronavirus or 2019-ncov or sars-cov-2 or cov-19	97,798

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