EVIDENCE SUMMARY

Should corticosteroids be used in the treatment of children with COVID-19 infection?

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Recommendation

We suggest the use of systemic corticosteroids (dexamethasone) among children with severe and critical COVID-19 infection.

Certainty of Evidence: Very Low
Strength of Recommendation: Weak

Consensus Issues
The recommendation was based on the findings from 20 randomized controlled trials done in hospitalized adult patients with COVID-19. Despite the very low certainty of evidence, the panel agreed that the benefit of significantly reducing all-cause mortality in COVID-19 patients as well as the availability and low cost of dexamethasone is enough to justify its use among pediatric patients with severe and critical COVID-19.

Key Findings

There were no direct studies that enrolled pediatric patients with COVID-19, which compared the use of corticosteroids (CS) with standard care or placebo. Twenty randomized controlled trials (RCTs) on the use of systemic CS as treatment for COVID-19 were included in this review, and all of them included adult COVID-19 patients. These studies used any of the following agents in their experimental arm: Dexamethasone (DEX), Hydrocortisone (HCT), Methylprednisolone (MP), or Prednisolone (PRDL). One study compared inhaled plus intranasal Ciclesonide (CIC) with standard care or placebo.

Pooled estimates for all-cause mortality showed that it was significantly reduced in the systemic CS group; subgroup analysis showed DEX to be the only CS showing significant benefitover standard care or placebo. The results were inconclusive for COVID-19-related mortality. One study showed a significant increase in length of intensive care unit (ICU) stay; another study showed more ventilator-free days in the systemic CS group. However, the studies which used DEX had very low overall certainty of evidence which is partly due to the indirectness caused by the predominantly adult population included.

Comparing MP with DEX, there was a significant decrease in World Health Organization Ordinal Scale (WHO OS) scores and length of hospital stay for the MP group. Mortality and need for mechanical ventilation (MV) were similar for both drugs. For the different doses of DEX, there were conflicting results on mortality rates, length of ICU stay, AEs and other outcomes.

Comparing the systemic CS group and the control group, the results were inconclusive for clinical improvement at 28 days, length of hospital stay, ICU admission rate, intubation rate, extracorporeal membrane oxygenation (ECMO) rate, life support-free days, Sequential Organ Failure Assessment (SOFA) score, and adverse events (Aes).

Inhaled plus intranasal CIC did not show significantly different results for respiratory symptom resolution, overall symptom resolution, hospital admission rate, mortality, or Aes.

The included RCTs had very low to moderate certainty due to issues with blinding, selective reporting, indirectness, imprecision, and heterogeneity. One cost-effectiveness study showed that the use of 6 mg DEX per day was more cost-effective than standard care for COVID-19.

Introduction

In the Philippines, 9.6% of total confirmed cases of COVID-19 are 19 years old or younger [1]. Once infected, the body initiates a systemic inflammatory response which could lead to excessive release of cytokines and inflammatory markers. This process may cause severe organ damage manifesting as acute respiratory distress syndrome (ARDS), renal failure, shock, or multisystem inflammatory syndrome in children (MIS-C) [2]. Corticosteroids are widely used drugs with potent anti-inflammatory effects which have been used to treat other severe viral infections (e.g., SARS, MERS). While CS have reputable efficacy and safety profiles, they may still cause several adverse effects such as immunosuppression, hyperglycemia, and fungal infection. As COVID-19 persists in both out-patient and in-patient settings, the potential effects of CS must be further investigated [2].

Review Methods

We searched Cochrane Library, PubMed, MEDLINE, Google Scholar, JSTOR, HERDIN, WHO ICTRP and ClinicalTrials.gov using a combined MeSH and free text search with the terms “SARS-CoV-2”, “COVID-19”, “dexamethasone”, “hydrocortisone”, “methylprednisolone”, “prednisone”, “prednisolone”, “mortality”, “hospitalization”, “recovery”, “clinical improvement”, “need for mechanical ventilation”, “duration of hospital stay”, “duration of ICU stay”, “adverse events”, “negative viral conversion”. Table 1 illustrates our PICO. Randomized controlled trials were prioritized in the search; and if none were found, non-randomized and observational studies were screened as well. When systematic reviews or meta-analyses were found, the individual studies were assessed for possible inclusion.

Table 1. PICO criteria for corticosteroids and COVID-19.

Population	Pediatric patients with COVID-19
Intervention	Corticosteroids
Comparison	Standard of care, placebo
Outcome	Mortality, hospital admission rate, length of hospital stay, length of ICU stay, mechanical ventilator rate, adverse events

Results

We found 20 RCTs done on adult populations which used different CS as treatment for COVID-19. A total of 10,031 COVID-19 patients with all levels of disease severity were analyzed in this review. The included studies compared either systemic CS with standard care or placebo [4][17], two different systemic CS [18], different doses of the same systemic CS [19][21], or inhaled plus intranasal CS with standard care or placebo [22]. The CS used were dexamethasone (8 RCTs) [5][7][11][13][18][21], hydrocortisone (3 RCTs) [4][6][14], methylprednisolone (8 RCTs) [7][8][10][12][15][18], prednisolone (1 RCT) [9], and ciclesonide (1 RCT) [22].

Systemic Corticosteroids

We found indirect evidence from 15 RCTs that compared systemic CS with standard care or placebo in adult COVID-19 patients [4-17] with only one study including patients aged 15-18 years old [13]. All-cause mortality from the pooled estimate of 14 studies was significantly reduced in the systemic CS group (RR 0.90, 95% CI 0.82 to 0.98, I2 = 7%, 13 studies) [4-17]; among the individual CS, only DEX was able to show the same significant benefit (RR 0.90, 95% CI 0.83 to 0.98, I2 = 0%, 4 studies) [5,7,11,13]. COVID-19-related mortality in particular did not differ significantly between the groups (RR 1.04, 95% CI 0.29 to 3.73, 1 study) [15].

For the other outcomes, the results were inconclusive: time to death (all-cause) (HR 0.80, 95% CI 0.24 to 2.61, 1 study) [15], time to death (COVID-19-related) (HR 0.96, 95% CI 0.24 to 3.84, 1 study) [15], time to clinical improvement (HR 0.93, 95% CI 0.65 to1.33, 2 studies) [15,16], length of hospital stay (MD 0.80, 95% CI -0.81 to 2.41, 4 studies) [9,11,12,15], ICU admission rate (RR 0.78, 95% CI 0.32 to 1.90, 2 studies) [9,16], intubation rate (RR 0.69, 95% CI 0.40 to 1.18, 2 studies) [4,9], ECMO rate (RR 0.96, 95% CI 0.14 to 6.64, 1 study) [4], life support-free days (MD -12.68, 95% CI -40.28 to 14.92, 2 studies) [6,14], and SOFA score (MD -0.49, 95% CI -2.18 to 1.20, 2 studies) [5,11]. The rest of the outcomes showed a significant increase for the systemic CS group: length of ICU stay (MD 4.2, 95% CI -3.26 to 5.14, 1 study) [11] and ventilator-free days (MD 2.26, 95% CI 0.2 to 2.38, 1 study) [5].

Another outcome which was increased for the systemic CS group was Glasgow Coma Scale (GCS) score (CS: 15, Control: 10), however, the article did not include specific statistical figures [17]. One study by Ranjbar et al. compared MP with DEX. The MP group had significantly lower WHO OS scores (MD -1.81, 95% CI -2.8 to -0.82) and shorter hospital stay (MD -3.09, 95% CI -5.06 to -1.12) while mortality (RR 0.51, 95% CI 0.24 to 1.07) and need for MV (RR 0.48, 95% CI 0.23 to 1.00) were similar for both groups [18].

Regarding AEs, there was no significant difference found between the systemic CS group and the control group (RR 0.95, 95% CI 0.86 to 1.05, 7 studies) [4,6-10,14]. Likewise, the specific AEs did not show a significant difference: nosocomial infection (RR 0.91, 95% CI 0.61 to 1.36, 2 studies) [4,8], shock (RR 0.17, 95% CI 0.01 to 3.32, 1 study) [8], need for insulin therapy (RR 1.20, 95% CI 0.99 to 1.46, 1 study) [12], and GI symptoms (RR 0.91, 95% CI 0.47 to 1.78, 2 studies) [8,9].

Across the outcomes, the certainty of evidence was very low to moderate; downgrading was done for risk of bias (due to issues of blinding and selective reporting), indirectness, and imprecision (Appendix D). Eleven RCTs were either open-label trials or lacked blinding of the personnel and the outcome assessors [5,7-10,13-16].

Dexamethasone Doses

We found indirect evidence from three RCTs that compared different doses of DEX on adult patients with COVID-19 [19-21]. The included studies varied in the doses used: COVID STEROID 2 – 6 mg DEX OD or 12 mg DEX OD for 10 days [19]; Toroghi et al. – 8 mg OD, BID, or TID for 10 days [20]; Taboada et al. – 6 mg OD for 10 days (low-dose) or 20 mg OD for 5 days then 10 mg OD for 5 days (high-dose) [21].

The COVID STEROID 2 trial showed significantly fewer ventilator-free days (MD -1, 95% CI -1.79 to -0.21), cardiovascular support-free days (MD -1.5, 95% CI -2.12 to -0.88), and renal replacement therapy-free days (MD -1.1, 95% CI -1.54 to -0.66) in the 6 mg/day DEX group. The rest of the outcomes did not show a significant difference between the two doses: mortality (RR 1.18, 95% CI 0.99 to 1.40), life support-free days (MD -2.8, 95% CI -5.8 to 0.2). Adverse events did not significantly differ between the doses: patients who experienced ≥1 AE (RR 1.19, 95% CI 0.85 to 1.66), septic shock (RR 1.22, 95% CI 0.83 to 1.80), invasive fungal infection (RR 1.43, 95% CI 0.75 to 2.75), GI bleeding (RR 0.57, 95% CI 0.19 to 1.69) [19].

For the three-arm study done by Toroghi et al., the BID and TID groups' results were analyzed with the OD group results as the common comparator. Mortality rate was significantly higher (RR 0.41, 95% CI 0.20 to 0.85) and length of ICU stay was significantly longer (MD -2.00, 95% CI -3.07 to -0.93) in the TID group. Time to clinical response was significantly longer for both BID and TID groups (BID: MD -1.00, 95% CI -1.82 to -0.18; TID: MD -1.80, 95% CI -2.90 to -0.70). The rest of the outcomes did not differ significantly: duration of MV (BID: MD 0, 95% CI -0.84 to 0.84; TID: MD -1.00, 95% CI -2.04 to 0.04), length of hospital stay (BID: MD -0.80, 95% CI -2.16 to 0.56; TID: MD -1.30, 95% CI -2.65 to 0.05), need for MV (BID: RR 0.51, 95% CI 0.13 to 2.01; TID: RR 0.49, 95% CI 0.13 to 1.84), ICU admission rate (BID: RR 0.85, 95% CI 0.27 to 2.73; TID: RR 0.54, 95% CI 0.20 to 1.50), hospital readmission rate (BID: RR 0.85, 95% CI 0.05 to 13.17; TID: RR 0.98, 95% CI 0.06 to 15.19). Similarly, Aes did not show significant difference between the groups: acute kidney injury (BID: RR 5.98, 95% CI 0.32 to 112.39; TID: RR 2.94, 95% CI 0.32 to 27.21), acute hepatic injury (BID: RR 1.42, 95% CI 0.36 to 5.57; TID: RR 1.22, 95% CI 0.35 to 4.27), arrythmia (BID: RR 1.28, 95% CI 0.39 to 4.21; TID: RR 0.53, 95% CI 0.22 to 1.32), myocardial infarction (BID: RR 4.27, 95% CI 0.21 to 86.44; TID: RR 1.96, 95% CI 0.18 to 20.85), hyperglycemia (BID: RR 0.79, 95% CI 0.44 to 1.44; TID: RR 0.62, 95% CI 0.37 to 1.06), secondary infection (BID: RR 0.85, 95% CI 0.05 to 13.17; TID: RR 0.24, 95% CI 0.03 to 2.11) [20].

The study done by Taboada et al. showed that the low-dose DEX group had significantly more patients who worsened clinically within 11 days (RR 1.92, 95% CI 1.13 to 3.27). It was also observed that length of ICU stay (MD 1.63, 95% CI 1.00 to 2.26) and duration of MV (MD 4.02, 95% CI 3.44 to 4.60) were prolonged in the low-dose DEX group. In contrast, length of hospital stay was significantly shorter for this group (MD -0.63, 95% CI -1.21 to -0.05). Other outcomes did not differ significantly: mortality (RR 1, 95% CI 0.98 to 1.02), recovery (RR 1, 95% CI 0.37 to 2.71), time to recovery (MD -0.05, 95% CI -0.54 to 0.44), ICU admission rate (RR 1, 95% CI 0.98 to 1.02), need for MV (RR 1, 95% CI 0.98 to 1.02). Complications and Aes were also similar for the two groups: nosocomial infection (RR 1.08, 95% CI 0.43 to 2.75), need for insulin (RR 1, 95% CI 0.57 to 1.74), thrombosis (RR 0.17, 95% CI 0.02 to 1.43) [21].

Altogether, the studies did not show results which consistently favor either lower or higher doses of DEX. The certainty of evidence from these studies were very low to moderate due to risk of bias (lack of blinding), indirectness and imprecision (Appendix 4). All studies used adult COVID-19 patients and most outcomes had confidence intervals which crossed the null value.

Inhaled plus Intranasal Corticosteroids

From the search, one study was found which compared inhaled plus intranasal CIC with placebo. The results were inconclusive for the outcomes of respiratory symptom resolution at Day 7 (RR 0.87, 95% CI 0.61 to 1.24), respiratory symptom resolution at Day 14 (RR 0.89, 95% CI 0.71 to 1.10), overall feeling of improvement at Day 7 (RR 1.03, 95% CI 0.88 to 1.21), overall feeling of improvement at Day 14 (RR 1.03, 95% CI 0.94 to 1.11), symptom resolution at Day 7 (RR 0.94, 95% CI 0.57 to 1.56), symptom resolution at Day 14 (RR 0.83, 95% CI 0.62 to 1.10), hospital admission rate (RR 0.54, 95% CI 0.14 to 2.08), improvement in cough at Day 7) (RR 0.98, 95% CI 0.78 to 1.23), improvement in cough at Day 14 (RR 1.01, 95% CI 0.88 to 1.15), resolution of dyspnea at Day 7 (RR 0.77, 95% CI 0.57 to 1.04), and resolution of dyspnea at Day 14 (RR 0.96, 95% CI 0.81 to 1.14). There were no deaths observed during the study. Adverse events did not significantly differ between the groups (RR 0.70, 95% CI 0.39 to 1.26) [22].

Overall certainty of evidence was low due to indirectness and imprecision (Appendix 4). The study only included adult COVID-19 patients and all outcomes had confidence intervals which crossed the null value.

Other Considerations (Evidence to Decision)

From our literature search, we found one cost-effectiveness analysis done in South Africa on the use of DEX (6 mg oral or intravenous). The study showed that while there is a cost increase with the addition of DEX to standard care, its cost still falls below willingness-to-pay thresholds and approaches 100% cost-effectiveness for thresholds beyond $500 [23]. Locally, CS are considered to be affordable drugs as the daily cost of medication is below the average daily wage in the Philippines (₱263.77) [24,25].

Table 2. Corticosteroid Prices in the Philippines [25-27]

Drug	Unit Price
Dexamethasone	₱39.88 per ampule (5 mg/mL,1 mL ampule)
Hydrocortisone	₱21.06 per vial (100 mg powder, vial)
Methylprednisolone	₱289.93 per vial (40 mg, single dose vial)
Prednisolone	₱200 per bottle (20 mg/5 ml syrup, 60 ml bottle)
Ciclesonide	₱835 per nasal spray bottle (120 actuation bottle)

Recommendations from Other Groups

The Pediatric Infectious Disease Society of the Philippines guidelines updated last January 8, 2022 recommends the use of DEX 0.15 mg/kg IV once daily (maximum dose of 6mg) up to 10 days or until discharge for pediatric patients classified as severe or critical. Alternatives include IV MP, IV HCT, oral DEX, and oral PRDL [28]. Treatment guidelines published by the US NIH specifically recommend using DEX for children with COVID-19 who require high-flow oxygen, noninvasive ventilation, invasive MV, or ECMO [29]. The World Health Organization Guidelines for COVID-19 Therapeutics currently do not have recommendations on the use of CS for pediatric COVID-19 patients. For adult patients, they recommend the use of intravenous (IV) CS for severe or critical COVID-19. As their safety profiles are more familiar and more predictable, these can be

monitored adequately by competent healthcare providers. For non-severe COVID-19, however, their use is not recommended as it was deemed unreasonable to obtain IV access just for CS [30].

Research Gaps

At present we need more randomized controlled trials enrolling children across all ages and severity of COVID-19 to investigate the efficacy and safety of CS, as well as the optimal dosing and frequency. As of January 21, 2022, there are 15 ongoing RCTs on CS use for COVID-19 registered on ClinicalTrials.gov: one of these trials seeks to compare MP vs. DEX in pediatric (15-18 years old) and adult participants.

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Appendix 1. Evidence to Decision Framework

Table 1. Summary of initial judgements prior to the panel discussion (N = 11)

FACTORS	JUDGEMENT (N = 11)							RESEARCH EVIDENCE/ADDITIONAL CONSIDERATIONS
Problem	No	Yes (11)		Varies		Uncertain		
Benefits	Large (6)	Moderate (5)	Small	Trivial	Varies	Uncertain		• Dexamethasone significantly decreased all-cause mortality in COVID-19 patients.
Harm	Large	Moderate (1)	Small (8)	Trivial (1)	Varies	Uncertain (1)		• Adverse events are comparable between the intervention and control groups and among the different doses of dexamethasone.
Certainty of evidence	High	Moderate		Low (2)		Very low (9)		
Balance of effects	Favors drug (5)	Probably favors drug (6)	Does not favor drug or no drug	Probably favors no drug	Favors no drug	Varies	Uncertain	
Values	Important uncertainty or variability (1)	Possibly important uncertainty or variability (3)		Probably no important uncertainty or variability (6)		No important uncertainty or variability (1)		
Resources required	Uncertain	Varies	Large costs	Moderate costs (6)	Negligible costs or savings (4)	Moderate savings (1)	Large savings	
Certainty of evidence of resources required	No included studies		Very low (1)	Low (5)	Moderate (5)	High		
Cost-effectiveness	No included studies	Varies	Favors the comparison (2)	Probably favors the comparison	Does not favor the comparison or the intervention	Probably favors the intervention (2)	Favors the intervention (7)	• Cost-effectiveness study done in South Africa using local currency converted to US dollars favors the addition of dexamethasone to standard of care.
Equity	Uncertain	Varies (1)	Reduced (1)	Probably reduced (2)	Probably no impact (2)	Probably increased (4)	Increased (1)	
Acceptability	Uncertain (5)	Varies	No (1)	Probably no (1)	Probably yes (4)	Yes (1)		
Feasibility	Uncertain (5)	Varies	No	Probably no	Probably yes (3)	Yes (3)		

Additional Comments

- More randomized controlled trials on the use of corticosteroids in children is needed.
- Supply may be limited in far-flung areas but the drug is relatively inexpensive.

Appendix 2. Search Yield & Results

(Cochrane, PubMed, MEDLINE, Google Scholar, JSTOR, HERDIN, WHO ICTRP)

#	Query	Results
1	"steroids" OR "corticosteroids"	2,051,262
2	"dexamethasone" OR "hydrocortisone" OR "methylprednisolone" OR "prednisone" OR "prednisolone"	1,045,360
3	"SARS-CoV-2" OR "COVID-19"	215,638
4	"children" OR "pediatric"	7,699,280
5	"mortality"	4,842,015
6	"hospitalization" OR "recovery" OR "clinical improvement" OR "need for mechanical ventilation" OR "duration of hospital stay" OR "duration of ICU stay" OR "adverse events" OR "negative viral conversion"	582,688
7	#1 OR #2	1,594,434
8	#5 OR #6	2,704,236
9	#7 AND #8	11,709
10	#4 AND #9	**4,775**

Appendix 3. Characteristics of Included Studies

Study ID	Patients (n)	Intervention	Comparator	Outcomes	Method
CAPE COVID 2020	Critically-ill COVID-19 patients (n = 149)	Hydrocortisone (200 mg/day until day 7, then 100 mg/day x 4 days, then 50 mg/day x 3 days)	Saline	All-cause Mortality, Intubation Rate, ECMO Rate, Adverse Events, Nosocomial Infection	Multicenter Randomized Double-blind Trial
CoDEX 2020	COVID-19 patients with moderate to severe ARDS (n = 299)	Dexamethasone (20 mg/day x 5 days, then 10 mg/day x 5 days)	Standard Care	All-cause Mortality, Ventilator-free Days, SOFA Score	Multicenter Randomized Open-label Trial
COVID STEROID 2021	COVID-19 patients with severe hypoxia (n = 30)	Hydrocortisone (200 mg/day)	Saline	All-cause Mortality, Life Support-free Days, Adverse Events	Multicenter Randomized Blinded Trial
COVID STEROID 2 2021	COVID-19 patients with severe hypoxemia (n = 982)	Dexamethasone (6 or 12 mg/day x 10 days)		All-cause Mortality, Life Support-free Days, Ventilator-free Days, Cardiovascular Support-free Days, Renal Replacement Therapy-free Days, Adverse Events	Multicenter Randomized Blinded Trial
DEXA-COVID 19 2020	COVID-19 patients with moderate to severe ARDS (n = 19)	Dexamethasone (20 mg/day × 5 days, then 10 mg/day × 5 days)	Standard Care	All-cause Mortality, Adverse Events	Multicenter Randomized Open-label Trial

Edalatifard 2020	patients with severe COVID-19 (n = 62)	Methylprednisolone (250 mg/day x 3 days)	Standard Care	All-cause Mortality, Adverse Events, Nosocomial Infection, Shock, GI Symptoms	Multicenter Randomized Single-blind Trial
Ezer 2021	patients with polymerase chain reaction confirmed COVID-19, presenting with fever, cough, or dyspnea (n = 203)	Inhaled Ciclesonide (600 µg twice daily) and Intranasal Ciclesonide (200 µg daily)	Saline	Respiratory Symptom Resolution, Overall Feeling of Improvement, Symptom Resolution, Hospital Admission Rate, Improvement in Cough, Resolution of Dyspnea, Mortality, Adverse Events	Multicenter Randomized Double-blind Trial
Farahani 2020	COVID-19 patients with severe respiratory failure (n = 29)	Methylprednisolone (1000 mg/day x 3 days)	Standard Care	GCS	Single-center Randomized Double-blind Trial
Ghanei 2021	patients with severe COVID-19 (n = 336)	Prednisolone (25 mg/day)	Standard Care	All-cause Mortality, Length of Hospital Stay, Admission to ICU, Intubation Rate, Adverse Events, GI Symptoms	Multicenter Randomized Open-label Trial
GLUCOCOVID 2021	patients with severe COVID-19 (n = 64)	Methylprednisolone (40 mg BID x 3 days, then 20 mg TID x 3 days)	Standard Care	All-cause Mortality	Multicenter Randomized Open-label Trial
Jamaati 2021	COVID-19 patients with mild to moderate ARDS (n = 50)	Dexamethasone (20 mg/day x 5 days, then 10 mg/day x 5 days)	Standard Care	All-cause Mortality, Length of Hospital Stay, Length of ICU Stay, SOFA Score	Single-center Randomized Trial

Jeronimo 2021	patients with severe COVID-19 (n = 393)	Methylprednisolone (0.5 mg/kg/day)	Saline	All-cause Mortality, Length of Hospital Stay, Need for Insulin Therapy	Single-center Randomized Double-blind Trial
Ranjbar 2021	COVID-19 patients severe (n = 90)	Dexamethasone (6 mg/day) Methylprednisolone (2 mg/kg/day)		WHO Ordinal Scale	Single-center Randomized Triple-blind Trial
RECOVERY 2021	COVID-19 patients (n = 6,425)	Dexamethasone (6 mg/day x 10 days)	Standard Care	All-cause Mortality	Multicenter Randomized Open-label Trial
REMAP-CAP 2020	patients with severe COVID-19 (n = 379)	Hydrocortisone Fixed 7-day Course (50 mg or 100 mg every 6 hours) Hydrocortisone Shock-Dependent Course (50 mg or 100 mg every 6 hours when in shock)	Standard Care	All-cause Mortality, Life Support-free Days, Adverse Events	Multicenter Randomized Open-label Trial
Solanich 2021	patients with severe COVID-19 (n = 55)	Methylprednisolone (120 mg/day x 3 days)	Standard Care	All-cause Mortality, COVID-19-related Mortality, Time to Death (All-cause), Time to Death (COVID-19-related), Time to Clinical Improvement, Length of Hospital Stay	Single-center Randomized Open-label Trial
Steroids-SARI 2020	ICU-admitted COVID-19 patients (n = 47)	Methylprednisolone (40 mg every 12 hours × 5 days)	Standard Care	All-cause Mortality, Adverse Events	Single-center Randomized Open-label Trial
Taboada 2021	hospitalised patients with moderate or severe COVID-	Dexamethasone (6 mg OD x 10 days or 20 mg OD x 5 days then 10 mg OD x 5 days)		Clinical Worsening, Recovery, Time to Recovery, ICU Admission, Length of	Single-center Randomized Open-label Trial

	19 pneumonia (n = 200)			ICU Stay, Need for MV, Duration of MV, Length of Hospital Stay, Nosocomial Infection, Need for Insulin, Thrombosis, Mortality	
Tang 2021	COVID-19 patients with CT-confirmed pneumonia (n = 86)	Methylprednisolone (1 mg/kg/day)	Saline	All-cause Mortality, Time to Clinical Improvement, Admission to ICU	Multicenter Randomized Single-blind Trial
Toroghi 2021	patients with moderate to severe COVID-19 (n = 87)	Dexamethasone (8 mg OD, BID, or TID x 10 days)		Time to Clinical Response, Need for MV, Duration of MV, Length of Hospital Stay, ICU Admission Rate, Length of ICU Stay, Hospital Readmission Rate, 60-day Mortality	Single-center Randomized Single-blind Trial

Appendix 4A. GRADE Evidence Profile: Systemic corticosteroids vs. Standard of care or placebo

Authors: Grazielle S. Verzosa, MD, DPPS; Maria Teresa S. Tolosa, MD, D Clin Epi, FPDS; Ma. Lucila M. Perez, MD, MSc, FPPS
Question: Should systemic corticosteroids be used in the treatment of children with COVID-19 infection?
Setting: In-patient and Out-patient
Bibliography:

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Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Vit C with standard treatment	standard treatment alone	Relative (95% CI)	Absolute (95% CI)		
All-cause mortality (all corticosteroids)												
14	randomized trials	not serious	not serious	seriousa	not serious	none	791/3130 (25.3%)	1408/5264 (26.7%)	**RR 0.90** (0.82 to 0.98)	**27 fewer per 1,000** (from 48 fewer to 5 fewer)	⊕⊕⊕◯ MODERATE	
All-cause mortality (dexamethasone)												
4	randomized trials	not serious	not serious	seriousa	not serious	none	585/2287 (25.6%)	1218/4506 (27.0%)	**RR 0.90** (0.83 to 0.98)	**27 fewer per 1,000** (from 46 fewer to 5 fewer)	⊕⊕⊕◯ MODERATE	
All-cause mortality (hydrocortisone)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Vit C with standard treatment	standard treatment alone	Relative (95% CI)	Absolute (95% CI)		
3	randomized trials	not serious	not serious	seriousa	seriousb,c	none	96/369 (26.0%)	56/188 (29.8%)	**RR 0.85** (0.50 to 1.44)	**45 fewer per 1,000** (from 149 fewer to 131 more)	⊕⊕◯◯ LOW	
All-cause mortality (methylprednisone)												
4	randomized trials	not serious	not serious	seriousa	seriousb	none	106/357 (29.7%)	122/350 (34.9%)	**RR 0.82** (0.59 to 1.16)	**63 fewer per 1,000** (from 143 fewer to 56 more)	⊕⊕◯◯ LOW	
All-cause mortality (prednisolone)												
1	randomized trials	not serious	not serious	seriousa	seriousb	none	4/116 (3.4%)	12/220 (5.5%)	**RR 0.63** (0.21 to 1.92)	**20 fewer per 1,000** (from 43 fewer to 50 more)	⊕⊕◯◯ LOW	
COVID-19-related mortality												
1	randomized trials	not serious	not serious	seriousa	seriousb,d,e	none	4/27 (14.8%)	4/28 (14.3%)	**RR 1.04** (0.29 to 3.73)	**6 more per 1,000** (from 101 fewer to 390 more)	⊕⊕◯◯ LOW	
Time to death (all-cause)												
1	randomized trials	seriousf	not serious	seriousa	seriousb	none	27 participants	28 participants	**HR 0.80** (0.24 to 2.61)	--	⊕◯◯◯ VERY LOW	
Time to death (COVID-19 related)												
1	randomized trials	seriousf	not serious	seriousa	seriousb	none	27 participants	28 participants	**HR 0.96** (0.24 to 3.84)	--	⊕◯◯◯ VERY LOW	
Time to clinical improvement												
2	randomized trials	seriousf	not serious	seriousa	seriousb	none	70 participants	71 participants	**HR 0.93** (0.65 to 1.33)	--	⊕◯◯◯ VERY LOW	
Lengt of hospital stay (days)												
4	randomized trials	seriousf	not serious	seriousa	seriousb,c	none	362	441	--	MD **0.8 days more** (0.81 fewer to 2.41 more)	⊕◯◯◯ VERY LOW	
ICU admission												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Vit C with standard treatment	standard treatment alone	Relative (95% CI)	Absolute (95% CI)		
2	randomized trials	seriousf	not serious	seriousa	seriousb	none	7/159 (4.4%)	15/263 (5.7%)	**RR 0.78** (0.32 to 1.90)	**13 fewer per 1,000** (from 39 fewer to 51 more)	⊕◯◯◯ VERY LOW	
Length of ICU stay (days)												
1	randomized trials	not serious	not serious	seriousa	not serious	none	25	25	--	**MD 4.2 days more** (3.26 more to 5.14 more)	⊕⊕⊕◯ MODERATE	
Intubation rate												
2	randomized trials	seriousf	not serious	seriousa	seriousb	none	10/132 (7.6%)	16/236 (6.8%)	**RR 0.69** (0.40 to 1.18)	**21 fewer per 1,000** (from 41 fewer to 12 more)	⊕◯◯◯ VERY LOW	
ECMO Rate												
1	randomized trials	not serious	not serious	seriousa	seriousb,e	none	2/76 (2.6%)	2/73 (2.7%)	**RR 0.96** (0.14 to 6.64)	**1 fewer per 1,000** (from 24 fewer to 155 more)	⊕⊕◯◯ LOW	
Life Support-free Days												
2	randomized trials	seriousf	not serious	seriousa	seriousb,c	none	294	115	--	**MD 12.68 days fewer** (40.28 fewer to 14.92 more)	⊕◯◯◯ VERY LOW	
Ventilator-free Days												
1	randomized trials	seriousf	not serious	seriousa	not serious	none	151	148	--	**MD 2.26 days more** (0.2 more to 4.38 more)	⊕⊕◯◯ LOW	
SOFA Score												
2	randomized trials	seriousf	not serious	seriousa	seriousb	none	152	145	--	**MD 0.49 points lower** (2.18 lower to 1.2 higher)	⊕◯◯◯ VERY LOW	

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Vit C with standard treatment	standard treatment alone	Relative (95% CI)	Absolute (95% CI)		
GCS Score												
1	randomized trials	seriousg	not serious	seriousa	seriousb	none	Methylprednisolone Group: GCS 15 Control Group: GCS 10				⊕◯◯◯ VERY LOW	
Adverse events												
7	randomized trials	seriousf,i	not serious	seriousa	seriousb	none	113/538 (21.0%)	168/461 (36.4%)	**RR 0.95** (0.86 to 1.05)	**18 fewer per 1,000** (from 51 fewer to 18 more)	⊕◯◯◯ VERY LOW	
Nosocomial Infection												
2	randomized trials	seriousf	not serious	seriousa	seriousb	none	29/110 (26.4%)	30/101 (29.7%)	**RR 0.91** (0.61 to 1.36)	**27 fewer per 1,000** (from 116 fewer to 107 more)	⊕◯◯◯ VERY LOW	
Shock												
1	randomized trials	seriousf	not serious	seriousa	seriousb,d,e	none	0/34 (0.0%)	2/28 (7.1%)	**RR 0.17** (0.01 to 3.32)	**59 fewer per 1,000** (from 71 fewer to 166 more)	⊕◯◯◯ VERY LOW	
Need for Insulin Therapy												
1	randomized trials	not serious	not serious	seriousa	seriousb	none	103/173 (59.5%)	86/174 (49.4%)	**RR 1.20** (0.99 to 1.46)	**99 more per 1,000** (from 5 fewer to 227 more)	⊕⊕◯◯ LOW	
Gastrointestinal Symptoms												
2	randomized trials	seriousf	not serious	seriousa	seriousb	none	12/148 (8.1%)	23/236 (9.7%)	**RR 0.91** (0.47 to 1.78)	**9 fewer per 1,000** (from 52 fewer to 76 more)	⊕◯◯◯ VERY LOW	

CI: Confidence interval; **HR**: hazard Ratio; **MD**: mean difference; **RR**: relative risk

Explanations

a. The studies used adult subjects.
b. CI crossed the null value.
c. The pooled results were heterogenous.
d. The study had low event rates within a small sample size.
e. The result had a wide CI.
f. Some studies were open-label.
g. Specific figures are not reported.

h. No available data for MD computation.
i. Data was extracted from a secondary source.

Appendix 4B. GRADE Evidence Profile: Methylprednisolone vs. Dexamethasone

Authors: Grazielle S. Verzosa, MD, DPPS; Maria Teresa S. Tolosa, MD, D Clin Epi, FPDS; Ma. Lucila M. Perez, MD, MSc, FPPS
Question: Should Methylprednisolone or Dexamethasone be used in the treatment of children with COVID-19 infection?
Setting: In-patient
Bibliography:
Ranjbar K, Moghadami M, Mirahmadizadeh A, Fallahi MJ, Khaloo V, Shahriarirad R, et al. Methylprednisolone or dexamethasone, which one is superior corticosteroid in the treatment of hospitalized COVID-19 patients: A triple-blinded randomized controlled trial. BMC Infectious Diseases. 2021Apr10;21(1).

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Vit C with standard treatment	standard treatment alone	Relative (95% CI)	Absolute (95% CI)		
Mortality												
1	randomized trials	not serious	not serious	seriousa	seriousb	none	8/44 (18.2%)	15/46 (32.6%)	**RR 0.51** (0.24 to 1.07)	**160 fewer per 1,000** (from 248 fewer to 23 more)	⊕⊕◯◯ LOW	
WHO Ordinal Scale												
1	randomized trials	not serious	not serious	seriousa	seriousb	none	44	46	--	**MD 1.81 points lower** (2.8 lower to 0.82 lower)	⊕⊕◯◯ LOW	
Length of Hospital Stay												
1	randomized trials	not serious	not serious	seriousa	seriousb	none	44	46	--	**MD 3.09 days fewer** (5.06 fewer to 1.12 fewer)	⊕⊕◯◯ LOW	
Need for MV												
1	randomized trials	not serious	not serious	seriousa	seriousb	none	8/44 (18.2%)	18/46 (39.1%)	**RR 0.48** (0.23 to 1.00)	**203 fewer per 1,000** (from 301 fewer to 0 fewer)	⊕⊕◯◯ LOW	

CI: Confidence interval; **MD**: mean difference

Explanations

a. The study used adult subjects.
b. The subject population was small.

Appendix 4C. GRADE Evidence Profile: Dexamethasone 6 mg OD vs. 12 mg OD

Authors: Grazielle S. Verzosa, MD, DPPS; Maria Teresa S. Tolosa, MD, D Clin Epi, FPDS; Ma. Lucila M. Perez, MD, MSc, FPPS

Question: Should Dexamethasone 6 mg OD or Dexamethasone 12 mg OD be used in the treatment of children with COVID-19 infection?

Setting: In-patient

Bibliography:

Munch MW, Russell L, Uhre KR, Lindgaard AL, Degn JF, Wetterslev M, et al. Effect of 12 mg vs 6 mg of dexamethasone on the number of days alive without life support in adults with COVID-19 and severe hypoxemia. JAMA. 2021Nov9;326(18).

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Vit C with standard treatment	standard treatment alone	Relative (95% CI)	Absolute (95% CI)		
Mortality												
1	randomized trials	not serious	not serious	seriousa	seriousb	none	180/478 (37.7%)	157/490 (32.0%)	**RR 1.18** (0.99 to 1.40)	**58 more per 1,000** (from 3 fewer to 128 more)	⊕⊕◯◯ LOW	
Life Support-free Days												
1	randomized trials	not serious	not serious	seriousa	seriousb	none	478	489	--	**MD 2.8 days fewer** (5.8 fewer to 0.2 more)	⊕⊕◯◯ LOW	
Ventilator-free Days												
1	randomized trials	not serious	not serious	seriousa	not serious	none	480	491	--	**MD 1 days fewer** (1.79 fewer to 0.21 fewer)	⊕⊕⊕◯ MODERATE	
Cardiovascular Support-free Days												
1	randomized trials	not serious	not serious	seriousa	not serious	none	480	491	--	**MD 1.5 days fewer** (2.12 fewer to 0.88 fewer)	⊕⊕⊕◯ MODERATE	
Renal Replacement Therapy-free Days												
1	randomized trials	not serious	not serious	seriousa	not serious	none	480	491	-	**MD 1.1 days fewer** (1.54 fewer to 0.66 fewer)	⊕⊕⊕◯ MODERATE	
Adverse Events												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Vit C with standard treatment	standard treatment alone	Relative (95% CI)	Absolute (95% CI)		
1	randomized trials	not serious	not serious	seriousa	seriousb	none	65/485 (13.4%)	56/497 (11.3%)	**RR 1.19** (0.85 to 1.66)	**21 more per 1,000** (from 17 fewer to 74 more)	⊕⊕◯◯ LOW	
Septic Shock												
1	randomized trials	not serious	not serious	seriousa	seriousb	none	50/485 (10.3%)	42/497 (8.5%)	**RR 1.22** (0.83 to 1.80)	**19 more per 1,000** (from 14 fewer to 68 more)	⊕⊕◯◯ LOW	
Invasive Fungal Infection												
1	randomized trials	not serious	not serious	seriousa	seriousb	none	21/485 (4.3%)	15/497 (3.0%)	**RR 1.43** (0.75 to 2.75)	**13 more per 1,000** (from 8 fewer to 53 more)	⊕⊕◯◯ LOW	
Gastrointestinal Bleeding												
1	randomized trials	not serious	not serious	seriousa	seriousb	none	5/485 (1.0%)	9/497 (1.8%)	**RR 0.57** (0.19 to 1.69)	**8 fewer per 1,000** (from 15 fewer to 12 more)	⊕⊕◯◯ LOW	

CI: Confidence interval; **MD**: mean difference; **RR**: relative risk

Explanations

a. The study used adult subjects.
b. CI crossed the null value.

Appendix 4D. GRADE Evidence Profile: Dexamethasone 8 mg OD vs. 8 mg BID

Authors: Grazielle S. Verzosa, MD, DPPS; Maria Teresa S. Tolosa, MD, D Clin Epi, FPDS; Ma. Lucila M. Perez, MD, MSc, FPPS

Question: Should Dexamethasone 8 mg OD or Dexamethasone 8 mg BID be used in the treatment of children with COVID-19 infection?

Setting: In-patient

Bibliography:

Toroghi N, Abbasian L, Nourian A, Davoudi-Monfared E, Khalili H, Hasannezhad M, et al. Comparing efficacy and safety of different doses of dexamethasone in the treatment of COVID-19: A three-arm randomized clinical trial. Pharmacological Reports. 2021;

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Vit C with standard treatment	standard treatment alone	Relative (95% CI)	Absolute (95% CI)		
Mortality												
1	randomized trials	not serious	not serious	seriousa	seriousb,c	none	8/47 (17.0%)	12/40 (30.0%)	**RR 0.57** (0.26 to 1.25)	**129 fewer per 1,000** (from 222 fewer to 75 more)	⊕⊕◯◯ LOW	
Time to Clinical Response (Days)												
1	randomized trials	not serious	not serious	seriousa	seriousb	none	47	40	--	**MD 1 days fewer** (1.82 fewer to 0.18 fewer)	⊕⊕◯◯ LOW	
Need for Mechanical Ventilation												
1	randomized trials	not serious	not serious	seriousa	seriousb,c	none	3/47 (6.4%)	5/40 (12.5%)	**RR 0.51** (0.13 to 2.01)	**61 fewer per 1,000** (from 109 fewer to 126 more)	⊕⊕◯◯ LOW	
Duration of Mechanical Ventilation (Days)												
1	randomized trials	not serious	not serious	seriousa	seriousb,c	none	47	40	--	**MD 0 days** (0.84 fewer to 0.84 more)	⊕⊕◯◯ LOW	
Length of Hospital Stay (Days)												
1	randomized trials	not serious	not serious	seriousa	seriousb,c	none	47	40	--	**MD 0.8 days fewer** (2.16 fewer to 0.46 more)	⊕⊕◯◯ LOW	
ICU Admission Rate												
1	randomized trials	not serious	not serious	seriousa	seriousb,c	none	5/47 (10.6%)	5/40 (12.5%)	**RR 0.85** (0.27 to 2.73)	**19 fewer per 1,000** (from 91 fewer to 216 more)	⊕⊕◯◯ LOW	

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Vit C with standard treatment	standard treatment alone	Relative (95% CI)	Absolute (95% CI)		
Length of ICU-stay (Days)												
1	randomized trials	not serious	not serious	seriousa	seriousb,c	none	47	40	--	**MD 0.2 days fewer** (0.79 fewer to 0.39 more)	⊕⊕◯◯ LOW	
Hospital Readmission												
1	randomized trials	not serious	not serious	seriousa	seriousb,c	none	1/47 (2.1%)	1/40 (2.5%)	**RR 0.85** (0.05 to 13.17)	**4 fewer per 1,000** (from 24 fewer to 304 more)	⊕⊕◯◯ LOW	
Acute Kidney Injury												
1	randomized trials	not serious	not serious	seriousa	seriousb,c	none	3/47 (6.4%)	0/40 (0.0%)	**RR 5.98** (0.32 to 112.39)	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	⊕⊕◯◯ LOW	
Acute Hepatic Injury												
1	randomized trials	not serious	not serious	seriousa	seriousb,c	none	5/47 (10.6%)	3/40 (7.5%)	**RR 1.42** (0.36 to 5.57)	**31 more per 1,000** (from 48 fewer to 343 more)	⊕⊕◯◯ LOW	
Arrhythmia												
1	randomized trials	not serious	not serious	seriousa	seriousb,c	none	5/47 (10.6%)	3/40 (7.5%)	**RR 1.42** (0.36 to 5.57)	**31 more per 1,000** (from 48 fewer to 343 more)	⊕⊕◯◯ LOW	
Myocardial Infarction												
1	randomized trials	not serious	not serious	seriousa	seriousb,c	none	2/47 (4.3%)	0/40 (0.0%)	**RR 4.27** (0.21 to 86.44)	**0 fewer per 1,000** (from 0 fewer to 0 fewer)	⊕⊕◯◯ LOW	
Hyperglycemia												
1	randomized trials	not serious	not serious	seriousa	seriousb,c	none	14/47 (29.8%)	15/40 (37.5%)	**RR 0.79** (0.44 to 1.44)	**79 fewer per 1,000** (from 210 fewer to 165 more)	⊕⊕◯◯ LOW	

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Vit C with standard treatment	standard treatment alone	Relative (95% CI)	Absolute (95% CI)		
Secondary infection												
1	randomized trials	not serious	not serious	seriousa	seriousb,c	none	1/47 (2.1%)	1/40 (2.5%)	**RR 0.85** (0.05 to 13.17)	**4 fewer per 1,000** (from 24 fewer to 304 more)	⊕⊕◯◯ LOW	

CI: Confidence interval; **MD**: mean difference; **RR**: relative risk

Explanations

a. The study used adult subjects.
b. The subject population was small.
c. CI crossed the null value.

Appendix 4E. GRADE Evidence Profile: Dexamethasone 8 mg OD vs. 8 mg TID

Authors: Grazielle S. Verzosa, MD, DPPS; Maria Teresa S. Tolosa, MD, D Clin Epi, FPDS; Ma. Lucila M. Perez, MD, MSc, FPPS
Question: Should Dexamethasone 8 mg OD or Dexamethasone 8 mg TID be used in the treatment of children with COVID-19 infection?
Setting: In-patient
Bibliography:
Toroghi N, Abbasian L, Nourian A, Davoudi-Monfared E, Khalili H, Hasannezhad M, et al. Comparing efficacy and safety of different doses of dexamethasone in the treatment of COVID-19: A three-arm randomized clinical trial. Pharmacological Reports. 2021;

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Vit C with standard treatment	standard treatment alone	Relative (95% CI)	Absolute (95% CI)		
Mortality												
1	randomized trials	not serious	not serious	seriousa	seriousb	none	8/47 (17.0%)	19/46 (41.3%)	**RR 0.41** (0.20 to 0.85)	**244 fewer per 1,000** (from 330 fewer to 62 fewer)	⊕⊕◯◯ LOW	
Time to Clinical Response (Days)												
1	randomized trials	not serious	not serious	seriousa	seriousb	none	47	46	--	**MD 1.8 days fewer** (2.9 fewer to 0.7 fewer)	⊕⊕◯◯ LOW	
Need for Mechanical Ventilation												
1	randomized trials	not serious	not serious	seriousa	seriousb,c	none	3/47 (6.4%)	6/46 (13.0%)	**RR 0.49** (0.13 to 1.84)	**67 fewer per 1,000** (from 113 fewer to 110 more)	⊕⊕◯◯ LOW	
Duration of Mechanical Ventilation (Days)												
1	randomized trials	not serious	not serious	seriousa	seriousb,c	none	47	46	--	**MD 1 days fewer** (2.04 fewer to 0.04 more)	⊕⊕◯◯ LOW	
Length of Hospital Stay (Days)												
1	randomized trials	not serious	not serious	seriousa	seriousb,c	none	47	46	--	**MD 1.3 days fewer** (2.65 fewer to 0.05 more)	⊕⊕◯◯ LOW	
ICU Admission Rate												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Vit C with standard treatment	standard treatment alone	Relative (95% CI)	Absolute (95% CI)		
1	randomized trials	not serious	not serious	seriousa	seriousb,c	none	5/47 (10.6%)	9/46 (19.6%)	**RR 0.54** (0.20 to 1.50)	**90 fewer per 1,000** (from 157 fewer to 98 more)	⊕⊕◯◯ LOW	
Length of ICU-stay (Days)												
1	randomized trials	not serious	not serious	seriousa	seriousb	none	47	46	--	**MD 2 days fewer** (3.07 fewer to 0.93 fewer)	⊕⊕◯◯ LOW	
Hospital Readmission												
1	randomized trials	not serious	not serious	seriousa	seriousb,c	none	1/47 (2.1%)	1/46 (2.2%)	**RR 0.98** (0.06 to 15.19)	**0 fewer per 1,000** (from 20 fewer to 308 more)	⊕⊕◯◯ LOW	
Acute Kidney Injury												
1	randomized trials	not serious	not serious	seriousa	seriousb,c	none	3/47 (6.4%)	1/46 (2.2%)	**RR 2.94** (0.32 to 27.21)	**42 more per 1,000** (from 15 fewer to 570 more)	⊕⊕◯◯ LOW	
Acute Hepatic Injury												
1	randomized trials	not serious	not serious	seriousa	seriousb,c	none	5/47 (10.6%)	4/46 (8.7%)	**RR 1.22** (0.35 to 4.27)	**19 more per 1,000** (from 57 fewer to 284 more)	⊕⊕◯◯ LOW	
Arrhythmia												
1	randomized trials	not serious	not serious	seriousa	seriousb,c	none	6/47 (12.8%)	11/46 (23.9%)	**RR 0.53** (0.22 to 1.32)	**112 fewer per 1,000** (from 187 fewer to 77 more)	⊕⊕◯◯ LOW	
Myocardial Infarction												
1	randomized trials	not serious	not serious	seriousa	seriousb,c	none	2/47 (4.3%)	1/46 (2.2%)	**RR 1.96** (0.18 to 20.85)	**21 more per 1,000** (from 18 fewer to 432 more)	⊕⊕◯◯ LOW	
Hyperglycemia												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Vit C with standard treatment	standard treatment alone	Relative (95% CI)	Absolute (95% CI)		
1	randomized trials	not serious	not serious	seriousa	seriousb,c	none	14/47 (29.8%)	22/46 (47.8%)	**RR 0.62** (0.37 to 1.06)	**182 fewer per 1,000** (from 301 fewer to 29 more)	⊕⊕◯◯ LOW	
Secondary infection												
1	randomized trials	not serious	not serious	seriousa	seriousb,c	none	1/47 (2.1%)	4/46 (8.7%)	**RR 0.24** (0.03 to 2.11)	**66 fewer per 1,000** (from 84 fewer to 97 more)	⊕⊕◯◯ LOW	

CI: Confidence interval; **MD**: mean difference; **RR**: relative risk

Explanations

a. The study used adult subjects.
b. The subject population was small.
c. CI crossed the null value

Appendix 4F. GRADE Evidence Profile: Dexamethasone low-dose vs. high-dose

Authors: Grazielle S. Verzosa, MD, DPPS; Maria Teresa S. Tolosa, MD, D Clin Epi, FPDS; Ma. Lucila M. Perez, MD, MSc, FPPS

Question: Should Low-Dose or High-Dose Dexamethasone be used in the treatment of children with COVID-19 infection?
Setting: In-patient
Bibliography:

Taboada M, Rodríguez N, Varela PM, Rodríguez MT, Abelleira R, González A, et al. Effect of high versus low dose of dexamethasone on clinical worsening in patients hospitalised with moderate or severe COVID-19 pneumonia: An open-label, Randomised Clinical Trial. European Respiratory Journal. 2021Dec16;

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Vit C with standard treatment	standard treatment alone	Relative (95% CI)	Absolute (95% CI)		
Mortality												
1	randomized trials	not serious	not serious	seriousa	seriousb	none	6/102 (5.9%)	4/98 (4.1%)	**RR 1.00** (0.98 to 1.02)	**0 fewer per 1,000** (from 1 fewer to 1 more)	⊕⊕◯◯ LOW	
Clinical Worsening within 11 days												
1	randomized trials	seriousc	not serious	seriousa	not serious	none	32/102 (31.4%)	16/98 (16.3%)	**RR 1.92** (1.13 to 3.27)	**150 more per 1,000** (from 21 more to 371 more)	⊕⊕◯◯ LOW	
Time to Recovery (Days)												
1	randomized trials	seriousc	not serious	seriousa	seriousb	none	102	98	--	**MD 0.05 days fewer** (0.54 fewer to 0.44 more)	⊕◯◯◯ VERY LOW	
ICU Admission Rate												
1	randomized trials	not serious	not serious	seriousa	seriousb	none	13/102 (12.7%)	15/98 (15.3%)	**RR 1.00** (0.98 to 1.02)	**0 fewer per 1,000** (from 3 fewer to 3 more)	⊕⊕◯◯ LOW	
Length of ICU Stay (Days)												
1	randomized trials	seriousc	not serious	seriousa	not serious	none	102	98	--	**MD 1.63 days more** (1 more to 2.26 more)	⊕⊕◯◯ LOW	
Need for Mechanical Ventilation												
1	randomized trials	not serious	not serious	seriousa	seriousb	none	9/102 (8.8%)	10/98 (10.2%)	**RR 1.00** (0.98 to 1.02)	**0 fewer per 1,000** (from 2 fewer to 2 more)	⊕⊕◯◯ LOW	

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Vit C with standard treatment	standard treatment alone	Relative (95% CI)	Absolute (95% CI)		
Duration of Mechanical Ventilation (Days)												
1	randomized trials	seriousc	not serious	seriousa	not serious	none	102	98	--	**MD 4.02 days more** (3.44 more to 4.6 more)	⊕⊕◯◯ LOW	
Length of Hospital Stay (Days)												
1	randomized trials	seriousc	not serious	seriousa	not serious	none	102	98	--	**MD 0.63 days fewer** (1.21 fewer to 0.05 fewer)	⊕⊕◯◯ LOW	
Nosocomial Infection												
1	randomized trials	not serious	not serious	seriousa	seriousb	none	10/102 (9.8%)	10/98 (10.2%)	**RR 1.08** (0.43 to 2.75)	**8 more per 1,000** (from 58 fewer to 179 more)	⊕⊕◯◯ LOW	
Need for Insulin												
1	randomized trials	not serious	not serious	seriousa	seriousb	none	49/102 (48.0%)	47/98 (48.0%)	**RR 1.00** (0.57 to 1.74)	**0 fewer per 1,000** (from 206 fewer to 355 more)	⊕⊕◯◯ LOW	
Thrombosis												
1	randomized trials	not serious	not serious	seriousa	seriousb	none	6/102 (5.9%)	1/98 (1.0%)	**RR 0.17** (0.02 to 1.43)	**8 fewer per 1,000** (from 10 fewer to 4 more)	⊕⊕◯◯ LOW	

CI: Confidence interval; **MD**: mean difference; **RR**: relative risk

Explanations

a. The study used adult subjects.
b. CI crossed the null value.
c. The study was open-label.

Appendix 4G. GRADE Evidence Profile: Inhaled plus intranasal ciclesonide vs. placebo

Authors: Grazielle S. Verzosa, MD, DPPS; Maria Teresa S. Tolosa, MD, D Clin Epi, FPDS; Ma. Lucila M. Perez, MD, MSc, FPPS
Question: Should Inhaled plus Intranasal Ciclesonide be used in the treatment of children with COVID-19 infection?
Setting: Out-patient
Bibliography:
Ezer N, Belga S, Daneman N, Chan A, Smith BM, Daniels S-A, et al. Inhaled and intranasal ciclesonide for the treatment of covid-19 in adult outpatients: Contain phase ii randomised controlled trial. BMJ. 2021;

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Vit C with standard treatment	standard treatment alone	Relative (95% CI)	Absolute (95% CI)		
Respiratory Symptom Resolution (Day 7)												
1	randomised trials	not serious	not serious	seriousa	seriousb	none	34/98 (34.7%)	42/105 (40.0%)	**RR 0.87** (0.61 to 1.24)	**52 fewer per 1,000** (from 156 fewer to 96 more)	⊕⊕◯◯ LOW	
Respiratory Symptom Resolution (Day 14)												
1	randomised trials	not serious	not serious	seriousa	seriousb	none	57/98 (58.2%)	69/105 (65.7%)	**RR 0.89** (0.71 to 1.10)	**72 fewer per 1,000** (from 191 fewer to 66 more)	⊕⊕◯◯ LOW	
Overall Feeling of Improvement (Day 7)												
1	randomised trials	not serious	not serious	seriousa	seriousb	none	74/98 (75.5%)	77/105 (73.3%)	**RR 1.03** (0.88 to 1.21)	**22 more per 1,000** (from 88 fewer to 154 more)	⊕⊕◯◯ LOW	
Overall Feeling of Improvement (Day 14)												
1	randomised trials	not serious	not serious	seriousa	seriousb	none	91/98 (92.9%)	95/105 (90.5%)	**RR 1.03** (0.94 to 1.11)	**27 more per 1,000** (from 54 fewer to 100 more)	⊕⊕◯◯ LOW	
Symptom Resolution (Day 7)												
1	randomised trials	not serious	not serious	seriousa	seriousb	none	22/98 (22.4%)	25/105 (23.8%)	**RR 0.94** (0.57 to 1.56)	**14 fewer per 1,000** (from 102 fewer to 133 more)	⊕⊕◯◯ LOW	
Symptom Resolution (Day 14)												
1	randomised trials	not serious	not serious	seriousa	seriousb	none	44/98 (44.9%)	57/105 (54.3%)	**RR 0.83** (0.62 to 1.10)	**92 fewer per 1,000** (from 206 fewer to 54 more)	⊕⊕◯◯ LOW	

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Vit C with standard treatment	standard treatment alone	Relative (95% CI)	Absolute (95% CI)		
Hospital Admission (Day 14)												
1	randomised trials	not serious	not serious	seriousa	seriousb	none	3/98 (3.1%)	6/105 (5.7%)	**RR 0.54** (0.14 to 2.08)	**26 fewer per 1,000** (from 49 fewer to 62 more)	⊕⊕◯◯ LOW	
Mortality												
1	randomised trials	not serious	not serious	seriousa	seriousb	none	0/98 (0.0%)	0/105 (0.0%)	not estimable	--	⊕⊕◯◯ LOW	
Improvement in Cough (Day 7)												
1	randomised trials	not serious	not serious	seriousa	seriousb	none	54/86 (62.8%)	57/89 (64.0%)	**RR 0.98** (0.78 to 1.23)	**13 fewer per 1,000** (from 141 fewer to 147 more)	⊕⊕◯◯ LOW	
Improvement in Cough (Day 14)												
1	randomised trials	not serious	not serious	seriousa	seriousb	none	72/86 (83.7%)	74/89 (83.1%)	**RR 1.01** (0.88 to 1.15)	**8 more per 1,000** (from 100 fewer to 125 more)	⊕⊕◯◯ LOW	
Resolution of Dyspnea (Day 7)												
1	randomised trials	not serious	not serious	seriousa	seriousb	none	27/49 (55.1%)	38/53 (71.7%)	**RR 0.77** (0.57 to 1.04)	**165 fewer per 1,000** (from 308 fewer to 29 more)	⊕⊕◯◯ LOW	
Resolution of Dyspnea (Day 14)												
1	randomised trials	not serious	not serious	seriousa	seriousb	none	40/49 (81.6%)	45/53 (84.9%)	**RR 0.96** (0.81 to 1.14)	**34 fewer per 1,000** (from 161 fewer to 119 more)	⊕⊕◯◯ LOW	
Adverse Events												
1	randomised trials	not serious	not serious	seriousa	seriousb	none	15/98 (15.3%)	23/105 (21.9%)	**RR 0.70** (0.39 to 1.26)	**66 fewer per 1,000** (from 134 fewer to 57 more)	⊕⊕◯◯ LOW	

Appendix 5. Forest Plots

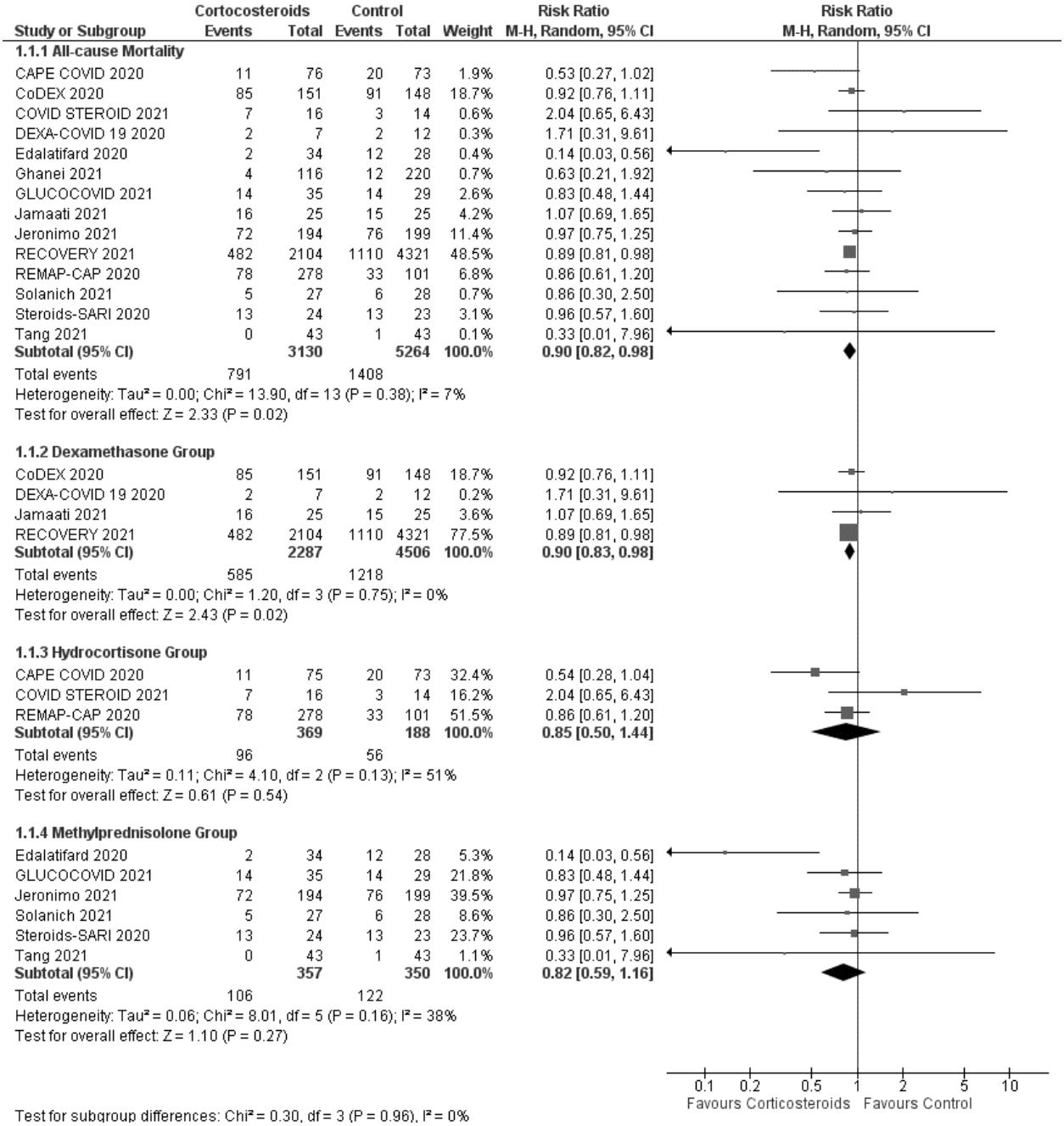

Figure 1. All-Cause Mortality

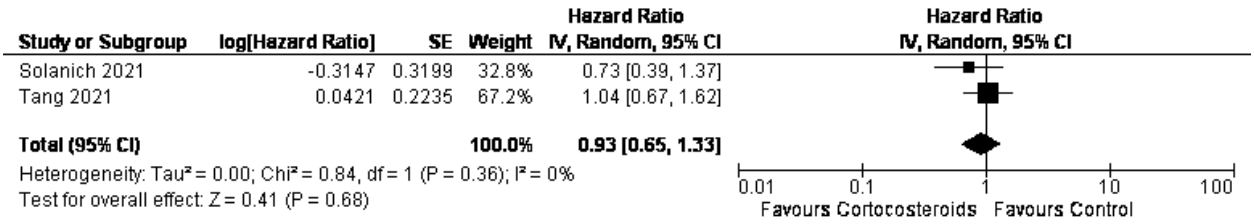

Figure 2. Time to Clinical Improvement

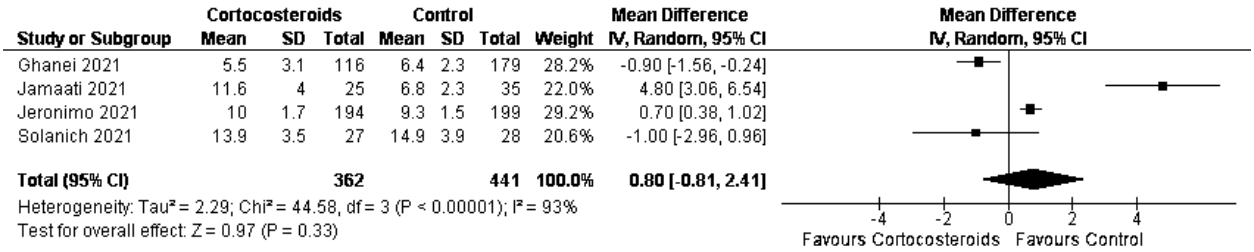

Figure 3. Length of Hospital Stay

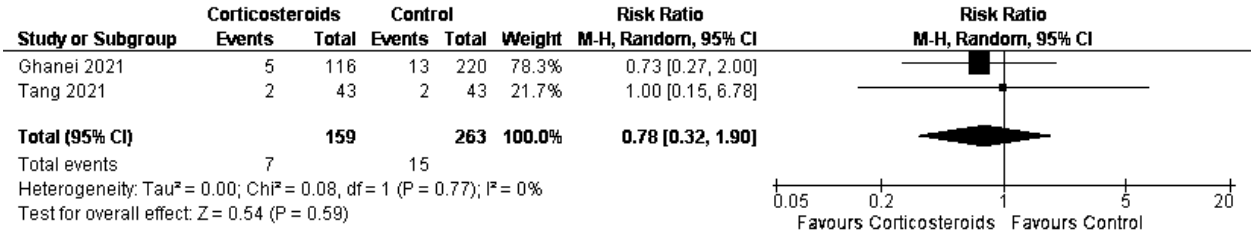

Figure 4. ICU Admission

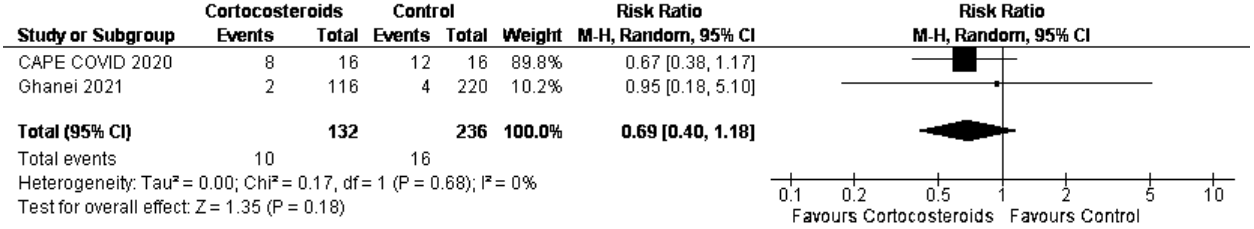

Figure 5. Intubation Rate

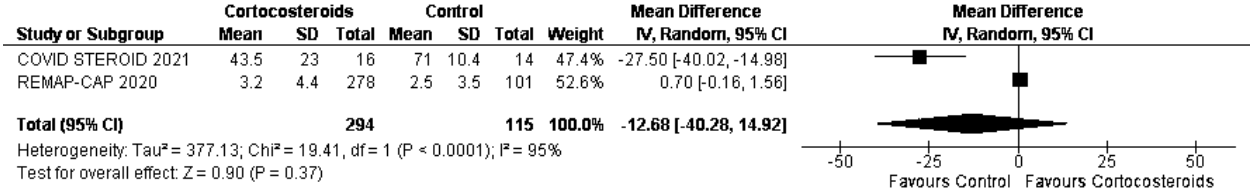

Figure 6. Life Support-free Days

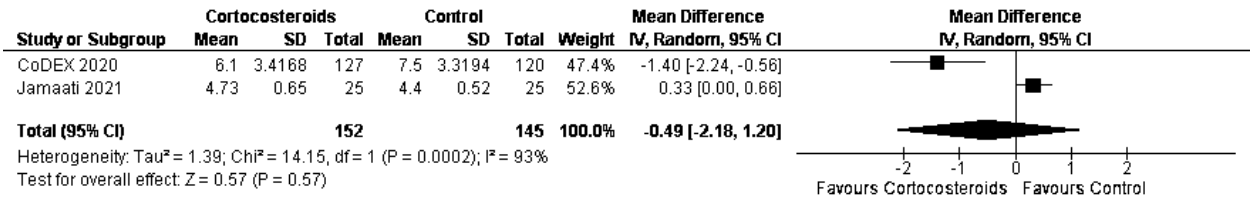

Figure 7. SOFA Score

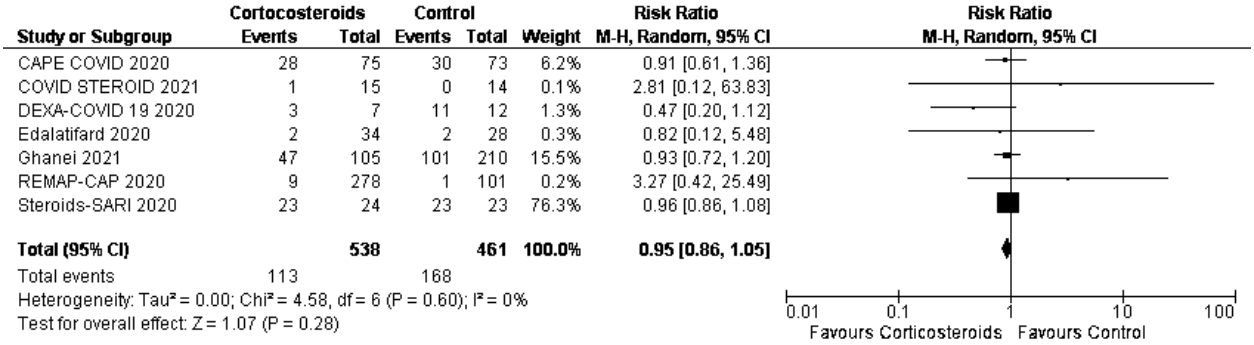

Figure 8. Adverse Events

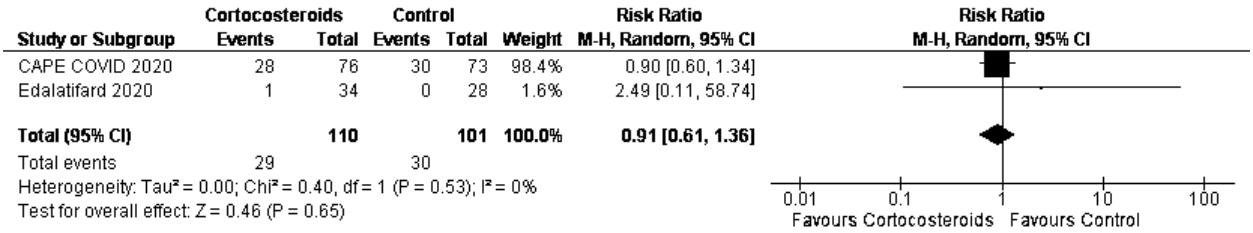

Figure 9. Nosocomial Infection

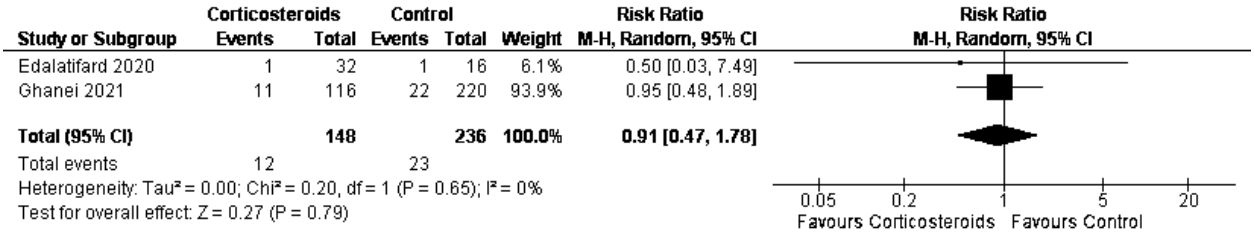

Figure 10. Gastrointestinal Symptoms

Appendix 6. Table of Ongoing Studies

Title (IRCT/NCT Number)	Interventions	Characteristics	Population	Dates/ Location(s)
Comparison between Intravenous Dexamethasone and Methylprednisolone in the Treatment of Hospitalized Patients with COVID-19 (IRCT20210223050466N1)	Dexamethasone Methylprednisolone	Single-center Randomized Single-blind Trial	15 to 80 years old with RT-PCR-confirmed COVID-19	April 26, 2021 – ongoing recruitment Iran
Dexamethasone vs. Methylprednisolone for the Treatment of Patients with ARDS Caused by COVID-19 (NCT04499313)	Dexamethasone Methylprednisolone	Multicenter Randomized Open-label Trial	20 to 80 years old with moderate to severe COVID-19 requiring hospitalization	August 5, 2020 – ongoing recruitment Bangladesh
Methylprednisolone vs. Dexamethasone in COVID-19 Pneumonia (MEDEAS RCT) (NCT04636671)	Methylprednisolone Dexamethasone	Single-center Randomized Open-label Trial	18 years and older with COVID-19 on oxygen support, CPAP, or NPPV	April 14, 2021 – ongoing recruitment Italy
Comparison Between Prednisolone and Dexamethasone on Mortality in Patients on Oxygen Therapy, With CoViD-19 (COPreDex) (NCT04765371)	Dexamethasone Prednisolone	Multicenter Randomized Open-label Trial	18 years and older with COVID-19 requiring oxygen therapy	March 3, 2021 – October 2023 France
Glucocorticoid Therapy in Coronavirus Disease COVID-19 Patients (NCT04780581)	Dexamethasone Methylprednisolone	Multicenter Randomized Open-label Trial	18 years and older with CT-confirmed COVID-19 requiring oxygen therapy	February 1, 2021 – December 31, 2021 Spain
RCT on the Efficacy of Dexamethasone Versus Methyl Prednisolone in Covid-19 Infected Patients with High Oxygen Flow (NCT05062681)	Dexamethasone Methylprednisolone	Single-center Randomized Single-blind Trial	18 years and older with COVID-19 on high oxygen flow therapy or positive pressure ventilation	September 15, 2021 – March 15, 2022 Egypt
Effect of Two Different Doses of Dexamethasone in Patients with ARDS and COVID-19 (REMED) (NCT04663555)	Dexamethasone (20 or 6 mg/day)	Phase II Single-center Randomized Open-label Trial	18 years and older with moderate or severe COVID-19	February 2, 2021 – March 31, 2023 Czech Republic
Higher vs. Lower Doses of Dexamethasone for COVID-19 and Severe	Dexamethasone (12 or 6 mg/day)	Multicenter Randomized	18 years and older COVID-19	August 27, 2020 –

Hypoxia (COVIDSTEROID2) (NCT04509973)		Quadruple-blind Trial	patients with severe hypoxia	November 17, 2021 Denmark India Sweden Switzerland
Randomized Open Investigation Determining Steroid Dose (ROIDS-Dose) (NCT04834375)	Dexamethasone (0.2 mg/kg/day or 6 mg/day)	Single-center Randomized Open-label Trial	18 years and older COVID-19 patients with hypoxemia	March 19, 2021 – April 19, 2022 USA
The Efficacy of Different Hormone Doses in 2019-nCoV Severe Pneumonia (NCT04263402)	Methylprednisolone (< 40 or 40-80 mg/day)	Single-center Randomized Single-blind Trial	18 years and older COVID-19 patients with severe pneumonia	February 1, 2020 – ongoing recruitment China
Efficacy of DEXamethasone in Patients with Acute Hypoxemic REspiratory Failure Caused by INfEctions (DEXA-REFINE) (NCT04545242)	Dexamethasone (6 mg/day or 20 mg/day x 5 days + 10 mg/day x 5 days)	Phase IV Multicenter Randomized Open-label Trial	18 years and older intubated and mechanically ventilated COVID-19 patients	February 8, 2021 – December 30, 2023 Spain
Timing of Corticosteroids in COVID-19 (NCT04530409)	Early-Dexamethasone Late-Dexamethasone	Phase IV Single-center Randomized Open-label Trial	18 years and older with mild or moderate severity COVID-19	February 10, 2021 – ongoing recruitment Egypt
DEXamethasone EARLY Administration in Hospitalized Patients with Covid-19 Pneumonia (EARLYDEXCoV2) (NCT04836780)	Early-Dexamethasone Late-Dexamethasone	Multicenter Randomized Open-label Trial	18 years and older COVID-19 patients with infiltrates on chest radiography or CT	June 10, 2021 – March 30, 2022 Spain
Evaluation of the Efficacy of High Doses of Methylprednisolone in SARS-CoV2 (COVID-19) Pneumonia Patients (NCT04673162)	Methylprednisolone + Dexamethasone Dexamethasone	Multicenter Randomized Quadruple-blind Trial	18 years and older with COVID-19 on non-invasive oxygen support	December 2020 (not yet recruiting) Italy
Randomized, Embedded, Multifactorial Adaptive Platform Trial for Community- Acquired Pneumonia (REMAP-CAP)	Hydrocortisone (fixed duration vs. shock-dependent)	Multicenter Randomized Open-label Trial	18 years and older COVID-19 patients admitted to an ICU for severe community	October 12, 2020 – December 2023 USA

(NCT02735707)			acquired pneumonia	Australia Belgium Canada Croatia Germany Hungary Ireland Netherlands New Zealand Portugal Romania Spain UK