Clinical Management of COVID-19

CORTICOSTEROIDS FOR COVID-19

Learning objectives

At the end of this module, you will be able to:

- Recognize the role for corticosteroid therapy in the management of patients with COVID-19.
- Identify possible corticosteroid dosing regimens for patients with severe and critical COVID-19.
- Identify key considerations in safe administration of corticosteroids.

Special note

Drugs and doses stated here are for illustrative purposes only.

Decisions regarding the use of any medication must be made by a licensed provider and take into account each patient's specific clinical history and other circumstances, and be in accordance with relevant local management and prescribing guidelines.

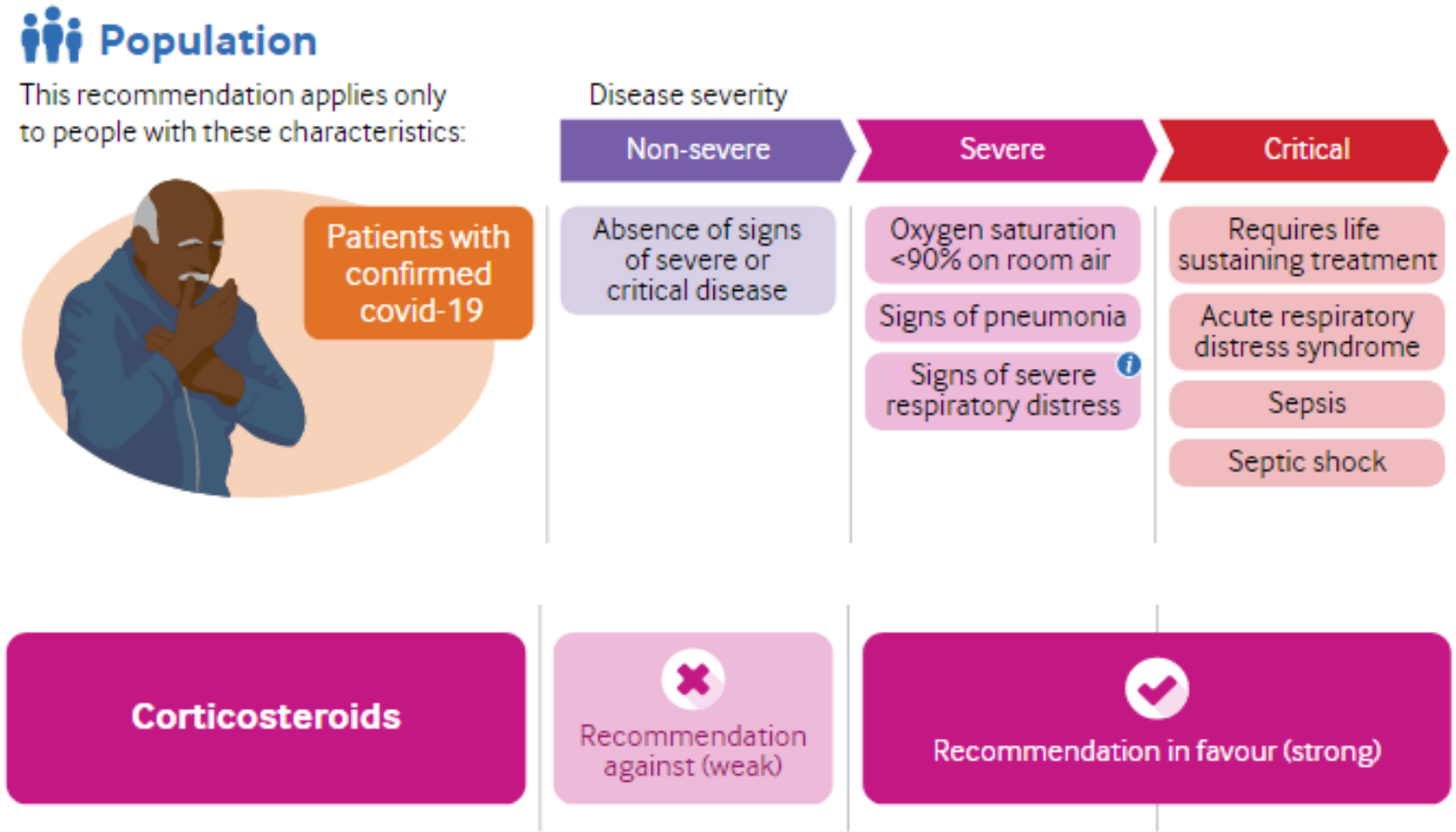
Corticosteroids in COVID-19: summary of recommendations

In September 2020, the following recommendations regarding systemic corticosteroids for patients with COVID-19 were released by WHO:

- **Strong recommendation:** We recommend systemic corticosteroids rather than no corticosteroids for the treatment of patients with **severe and critical COVID-19.**

- **Conditional recommendation:** We suggest **not to use** corticosteroids in the treatment of patients with **non-severe COVID-19.**

Corticosteroids in COVID-19: recommendation



A living WHO guideline on drugs for covid-19. BMJ 2020;370:m3379. https://doi.org/10.1136/bmj.m3379

Overview of drug: corticosteroids

- Systemic corticosteroids are powerful immunomodulators.
- Severe and critical COVID-19 are associated with a severe immune response leading to acute lung injury and acute respiratory distress syndrome (ARDS).
- Corticosteroids are generally low-cost, easy to administer and accessible. Dexamethasone has been listed as a WHO essential medication since 1977, and prednisolone since 1979.[1,2]

Reviewing the evidence and recommendations regarding corticosteroids

Corticosteroids in COVID-19: guideline development process (1/2)

In July 2020, WHO partnered with principal investigators of 7 corticosteroid trials and formed the Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group to conduct a prospective meta-analysis (PMA) of randomized trials for corticosteroid therapy for COVID-19.[3]


JAMA | Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

Association Between Administration of Systemic Corticosteroids and Mortality Among Critically Ill Patients With COVID-19
A Meta-analysis

The WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group

Corticosteroids in COVID-19: guideline development process (2/2)

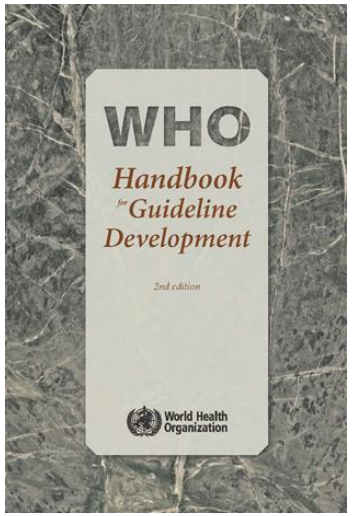
- **The WHO Therapeutics and COVID-19 Guideline Development Group (GDG)**, a group of international content experts, patients, clinicians and methodologists with no conflicts of interest and balanced in terms of gender, geography, expertise, and patient representation, met in July 2020.[4]

- The GDG produced recommendations following standards for trustworthy guideline development using the **GRADE approach** (Grading of Recommendations Assessment, Development and Evaluation), in full compliance with the WHO Handbook for guideline development, 2nd edition.[5]

- The GDG took an **individual patient perspective to values and preferences.**

A high value also was placed on resource allocation, given the burden of the pandemic for health care systems globally. Values considered include:

  - **Applicability**
  - **Balance of benefits and harms**
  - **Resource implications, feasibility, equity and human rights**
  - **Acceptability**



Understanding the strength of recommendations

Strong	Conditional
• **For patients:** most individuals in this situation would want the recommended course of action and only a small proportion would not. • **For clinicians:** Most individuals should receive this course of action. • **For policymakers:** The recommendation can be adapted as a policy in most situations including for the use as performance indicators.	• **For patients:** The majority of individuals would want the suggested course of action, but many would not. • **For clinicians:** Different choices are likely to be appropriate for different patients and therapy should be tailored to the individual patient circumstances. • **For policymakers:** Policy making will require substantial debates and involvement of many stakeholders. Policies are also likely to vary between regions.

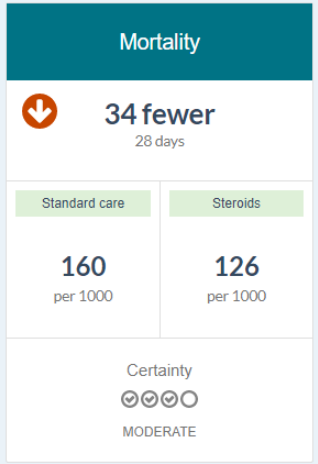
Evidence: Corticosteroids vs standard of care in severe-critical COVID-19

Therapeutics and COVID-19: living guideline (magicapp.org)

Outcome Timeframe	Study results and measurements	Absolute effect estimates Standard care	 Steroids	Certainty of the Evidence (Quality of evidence)	Plain language summary
Mortality 28 days	Relative risk 0.79 (CI 95% 0.70 — 0.90) Based on data from 1703 patients in 7 studies Follow up: 28 days.	160 per 1000	126 per 1000 Difference: **34 fewer per 1000** (CI 95% 48 fewer — 16 fewer)	Moderate Due to serious risk of bias	Systemic corticosteroids probably reduce the risk of 28-day mortality in patients with critical illness due to COVID-19. Intervention

The GDG made a **strong recommendation for systemic corticosteroids in severe and critical COVID-19** based on **moderate certainty of evidence** which showed **reduction in mortality of 3.4%** in patients with COVID-19 who are critically or severely ill.

Among a 1000 patients like you, on average with Steroids



Outcome Timeframe	Study results and measurements	Absolute effect estimates Standard care	 Steroids	Certainty of the Evidence (Quality of evidence)	Plain language summary
Mortality 28 days	Relative risk 0.79 (CI 95% 0.70 — 0.90) Based on data from 1703 patients in 7 studies Follow up: 28 days.	160 per 1000	126 per 1000 Difference: **34 fewer per 1000** (CI 95% 48 fewer — 16 fewer)	Moderate Due to serious risk of bias	Systemic corticosteroids probably reduce the risk of 28-day mortality in patients with critical illness due to COVID-19. Intervention
Need for invasive mechanical ventilation 28 days	Relative risk 0.74 (CI 95% 0.59 — 0.93) Based on data from 5481 patients in 2 studies Follow up: 28 days.	116 per 1000	86 per 1000 Difference: **30 fewer per 1000** (CI 95% 48 fewer — 8 fewer)	Moderate Due to serious risk of bias	Systemic corticosteroids probably reduce the need of mechanical ventilation Intervention
Gastrointestinal bleeding	Relative risk 1.06 (CI 95% 0.85 — 1.33) Based on data from 5403 patients in 30 studies	48 per 1000	51 per 1000 Difference: **3 more per 1000** (CI 95% 7 fewer — 16 more)	Low Due to serious indirectness, Due to serious imprecision	Corticosteroids may not increase the risk of gastrointestinal bleeding. No imp. diff.
Super-infections	Relative risk 1.01 (CI 95% 0.90 — 1.13) Based on data from 6027 patients in 32 studies	186 per 1000	188 per 1000 Difference: **2 more per 1000** (CI 95% 19 fewer — 24 more)	Low Due to serious indirectness, Due to serious imprecision	Corticosteroids may not increase the risk of super-infections. No imp. diff.
Hyperglycaemia	Relative risk 1.16 (CI 95% 1.08 — 1.25) Based on data from 8938 patients in 24 studies	286 per 1000	332 per 1000 Difference: **46 more per 1000** (CI 95% 23 more — 72 more)	Moderate Due to serious indirectness	Corticosteroids probably increase the risk of hyperglycaemia. Comparator
Hypernatremia	Relative risk 1.64 (CI 95% 1.32 — 2.03) Based on data from 5015 patients in 6 studies	40 per 1000	66 per 1000 Difference: **26 more per 1000** (CI 95% 13 more — 41 more)	Moderate Due to serious indirectness	Corticosteroids probably increase the risk of hypernatremia. Comparator
Neuromuscular weakness	Relative risk 1.09 (CI 95% 0.86 — 1.39) Based on data from 6358 patients in 8 studies	69 per 1000	75 per 1000 Difference: **6 more per 1000** (CI 95% 10 fewer — 27 more)	Low Due to serious indirectness, Due to serious imprecision	Corticosteroids may not increase the risk of neuromuscular weakness. No imp. diff.
Neuropsychiatric effects	Relative risk 0.81 (CI 95% 0.41 — 1.63) Based on data from 1813 patients in 7 studies	35 per 1000	28 per 1000 Difference: **7 fewer per 1000** (CI 95% 21 fewer — 22 more)	Low Due to serious indirectness, Due to serious imprecision	Corticosteroids may not increase the risk of neuropsychiatric effects. No imp. diff.
Duration of hospitalization	Measured by: days Lower better Based on data from 6425 patients in 1 study	13 days	12 days	Low Due to serious risk of bias, Due to serious imprecision	Steroids may result in an important reduction in the duration of hospitalizations Intervention

World Health Organization

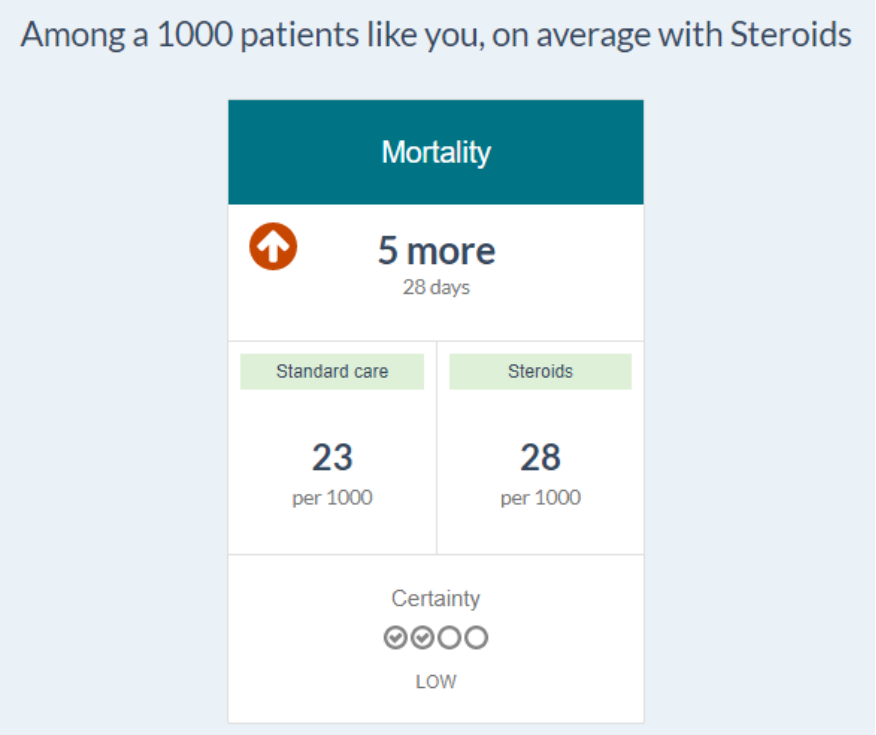
Corticosteroids for COVID-19

LIVING GUIDANCE
2 SEPTEMBER 2020

World Health Organization

Conditional recommendation against systemic corticosteroids in non-severe COVID-19

- The GDG made a **conditional recommendation against corticosteroid therapy for patients with non-severe COVID-19**, based on the following:
  - **Low certainty evidence** which **suggested an increased 28-day mortality** in patients with non-severe COVID-19.
  - Systemic corticosteroid use has potential harms (e.g. hyperglycaemia, neuromuscular weakness, superinfection).
  - Indiscriminate use of the therapy for COVID-19 may potentially rapidly deplete global resources, and deprive patients who may benefit from it most.



Therapeutics and COVID-19: living guideline (magicapp.org)

World Health Organization

HEALTH EMERGENCIES programme

Corticosteroids in COVID-19: categories of illness severity (1/2)

- There are different definitions for severe disease, critical disease and use of respiratory support in COVID-19.
- In the RECOVERY trial,[6] patient populations were divided into those who received **oxygen alone** and those who received **invasive mechanical ventilation**.
- The GDG decided against defining patient populations on the basis of access to health interventions and attributed the effect of intervention in the RECOVERY trial to illness severity.
- Thus, for the purposes of these recommendations, **disease severity categorization was based on the WHO Clinical management of COVID-19 interim guidance** [7] with the following adjustments:

Criteria for oxygen saturation threshold for Severe COVID-19 was adjusted from 94% to 90%

- *The panels noted that this was arbitrary and should be interpreted cautiously in determining which patients should be offered systemic corticosteroids.*
- *Clinicians must use their judgement to determine whether a low oxygen saturation is a sign of severity or is normal (e.g. in a patient with chronic lung disease).*
- *Similarly, a **saturation > 90-94% on room air** may be abnormal if the clinician suspects that this number is downward trending.*

Corticosteroids in COVID-19: categories of illness severity (2/2)

WHO COVID-19 disease severity categorization

Critical COVID-19	Defined by the criteria for acute respiratory distress syndrome (ARDS), sepsis, septic shock or other conditions that would normally require the provision of life-sustaining therapies, such as mechanical ventilation (invasive or non-invasive) or vasopressor therapy.
Severe COVID-19	Defined by any of: • oxygen saturation < 90% on room air. • respiratory rate > 30 breaths per minute in adults and children > 5 years old; ≥ 60 in children less than 2 months; ≥ 50 in children 2–11 months; and ≥ 40 in children 1–5 years old. • signs of severe respiratory distress (i.e. accessory muscle use, inability to complete full sentences; and in children, very severe chest wall indrawing, grunting, central cyanosis, or presence of any other general danger signs).
Non-severe COVID-19	Defined as absence of any signs of severe or critical COVID-19.

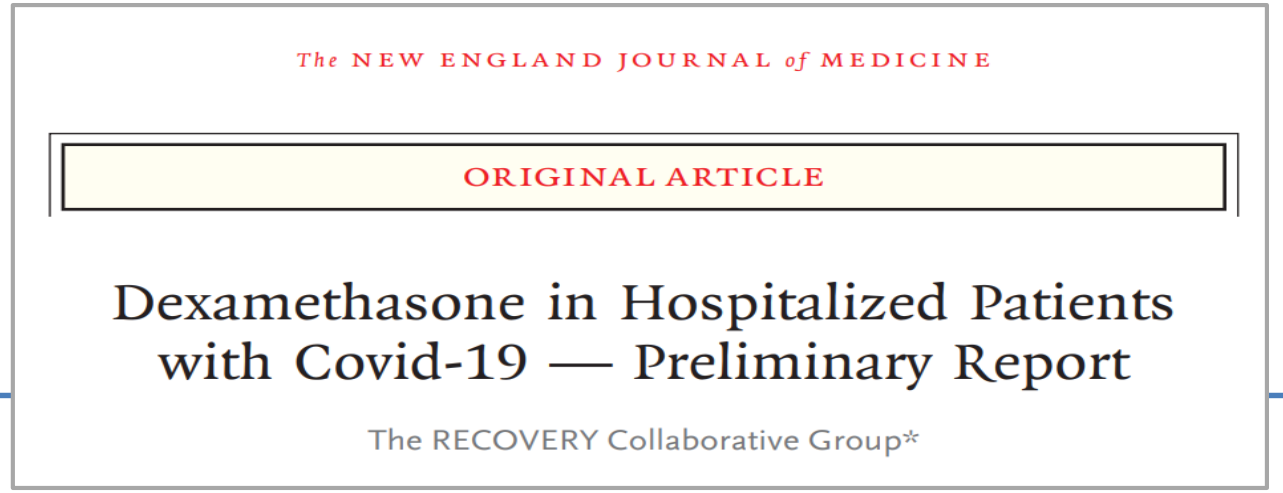
World Health Organization

HEALTH EMERGENCIES programme

Deep dive into the evidence

The RECOVERY trial

- **The RECOVERY trial[6] demonstrated a lower 28-day mortality in patients who received corticosteroids and were either receiving oxygen alone or receiving invasive mechanical ventilation, compared to usual care.**
  - Largest of the 7 trials: enrolled 6425 hospitalized patients
    - At time of randomization: 60% receiving oxygen only (with or without non-invasive ventilation), 16% receiving invasive mechanical ventilation or extracorporeal membrane oxygenation, 24% receiving neither
    - Approximately ⅓ randomized to dexamethasone and ⅔ randomized to usual care
      - Dexamethasone 6mg was given daily for up to ten days



Dexamethasone in hospitalized patients with COVID-19

– Preliminary report. The RECOVERY Collaborative Group. NEJM, 17 July 2020. DOI: 10.1056/NEJMoa2021436.

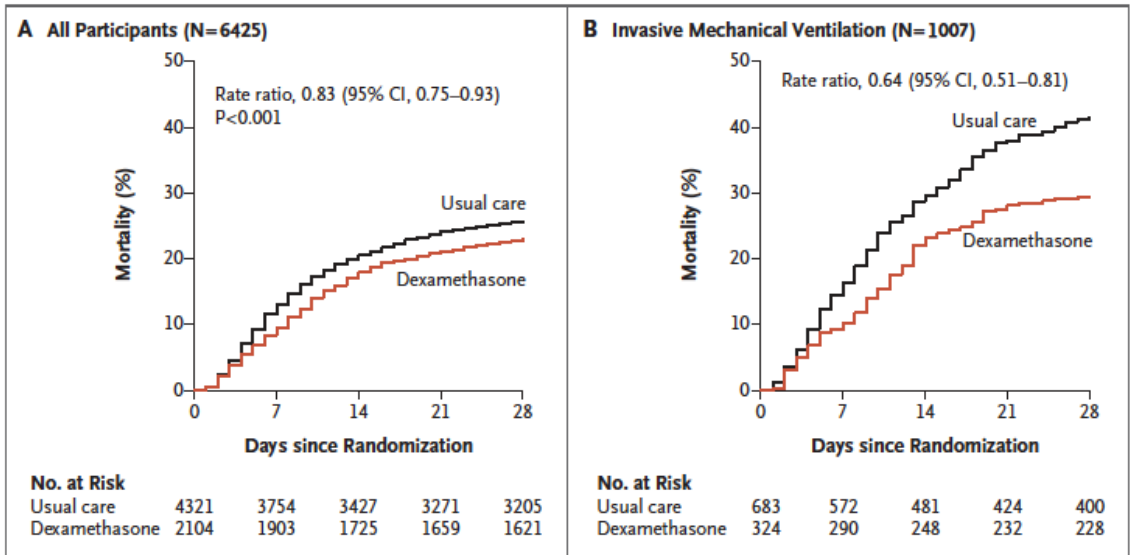


Figure 2. Mortality at 28 Days in All Patients and According to Respiratory Support at Randomization.

Shown are Kaplan–Meier survival curves for 28-day mortality among all the patients in the trial (primary outcome) (Panel A) and in three respiratory-support subgroups according to whether the patients were undergoing invasive mechanical ventilation (Panel B), receiving oxygen only without mechanical ventilation (Panel C), or receiving no supplemental oxygen (Panel D) at the time of randomization. The Kaplan–Meier curves have not been adjusted for age. The rate ratios have been adjusted for the age of the patients in three categories (<70 years, 70 to 79 years, and ≥80 years). Estimates of the rate ratios and 95% confidence intervals in Panels B, C, and D were derived from a single age-adjusted regression model involving an interaction term between treatment assignment and level of respiratory support at randomization.

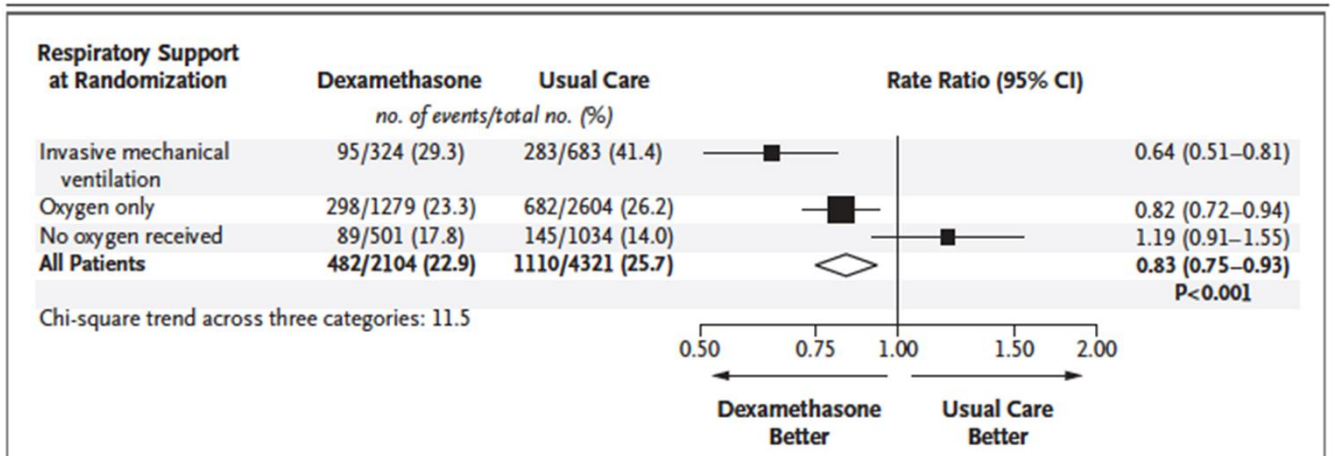


Figure 3. Effect of Dexamethasone on 28-Day Mortality, According to Respiratory Support at Randomization.

Shown are subgroup-specific rate ratios for all the patients and for those who were receiving no oxygen, receiving oxygen only, or undergoing invasive mechanical ventilation at the time of randomization. Rate ratios are plotted as squares, with the size of each square proportional to the amount of statistical information that was available; the horizontal lines represent 95% confidence intervals.

HEALTH EMERGENCIES programme

Prospective meta-analysis (PMA) by the WHO REACT Working Group

- Pooled data on **1703 patients with critical COVID-19** from **seven randomized clinical trials** that evaluated efficacy of corticosteroids across **12 countries on 5 continents.**[8-11]
  - Definition of "critical" varied across studies.

    RECOVERY trial recruited both critically ill and non–critically ill hospitalized patients. Because it was not possible to distinguish whether patients had been critically ill but not receiving invasive mechanical ventilation at the time of randomization, only data on patients who received invasive mechanical ventilation in RECOVERY were included.
  - Corticosteroid preparations and dosing varied across studies.

Corticosteroids in COVID-19: results

As of September 2020, available data across 7 studies suggests corticosteroids offer:

- Reduced 28-day all-cause mortality in patients with critical COVID-19
- Reduced 28-day all-cause mortality in patients with severe COVID-19
- Increased risk of 28-day mortality in patients with non-severe COVID-19
- Reduced risk of need for invasive mechanical ventilation at 28-days from hospitalization
- Reduced duration of hospitalization
- Low likelihood of serious adverse events in patients with critical COVID-19


JAMA | Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

Effect of Hydrocortisone on Mortality and Organ Support in Patients With Severe COVID-19

The REMAP-CAP COVID-19 Corticosteroid Domain Randomized Clinical Trial

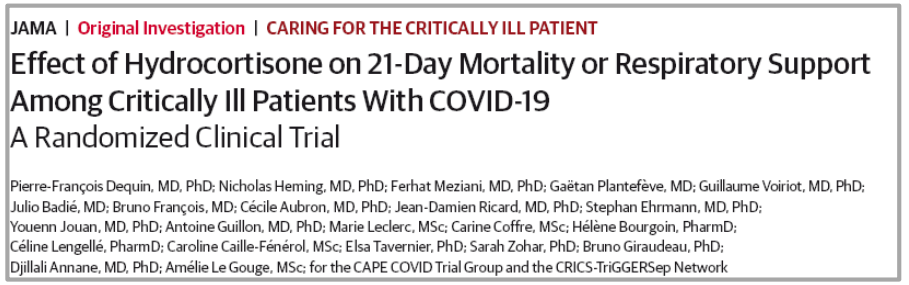
The Writing Committee for the REMAP-CAP Investigators


JAMA | Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

Association Between Administration of Systemic Corticosteroids and Mortality Among Critically Ill Patients With COVID-19

A Meta-analysis

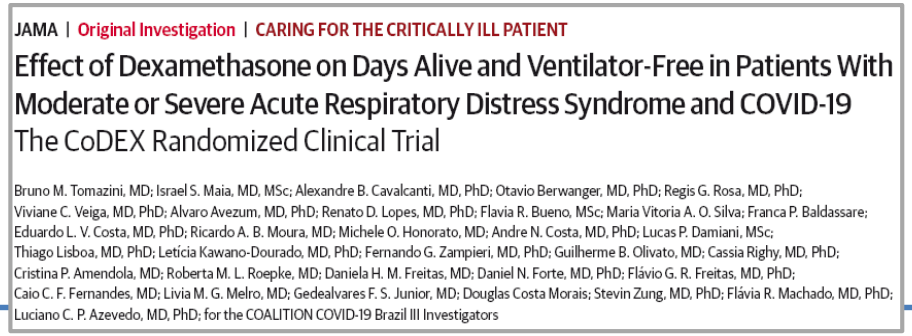
The WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group


JAMA | Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

Effect of Hydrocortisone on 21-Day Mortality or Respiratory Support Among Critically Ill Patients With COVID-19

A Randomized Clinical Trial

Pierre-François Dequin, MD, PhD; Nicholas Heming, MD, PhD; Ferhat Meziani, MD, PhD; Gaëtan Plantefève, MD; Guillaume Voiriot, MD, PhD; Julio Badié, MD; Bruno François, MD; Cécile Aubron, MD, PhD; Jean-Damien Ricard, MD, PhD; Stephan Ehrmann, MD, PhD; Youenn Jouan, MD, PhD; Antoine Guillon, MD, PhD; Marie Leclerc, MSc; Carine Coffre, MSc; Hélène Bourgoin, PharmD; Céline Lengellé, PharmD; Caroline Caille-Fénérol, MSc; Elsa Tavernier, PhD; Sarah Zohar, PhD; Bruno Giraudeau, PhD; Djillali Annane, MD, PhD; Amélie Le Gouge, MSc; for the CAPE COVID Trial Group and the CRICS-TriGGERSep Network


JAMA | Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

Effect of Dexamethasone on Days Alive and Ventilator-Free in Patients With Moderate or Severe Acute Respiratory Distress Syndrome and COVID-19

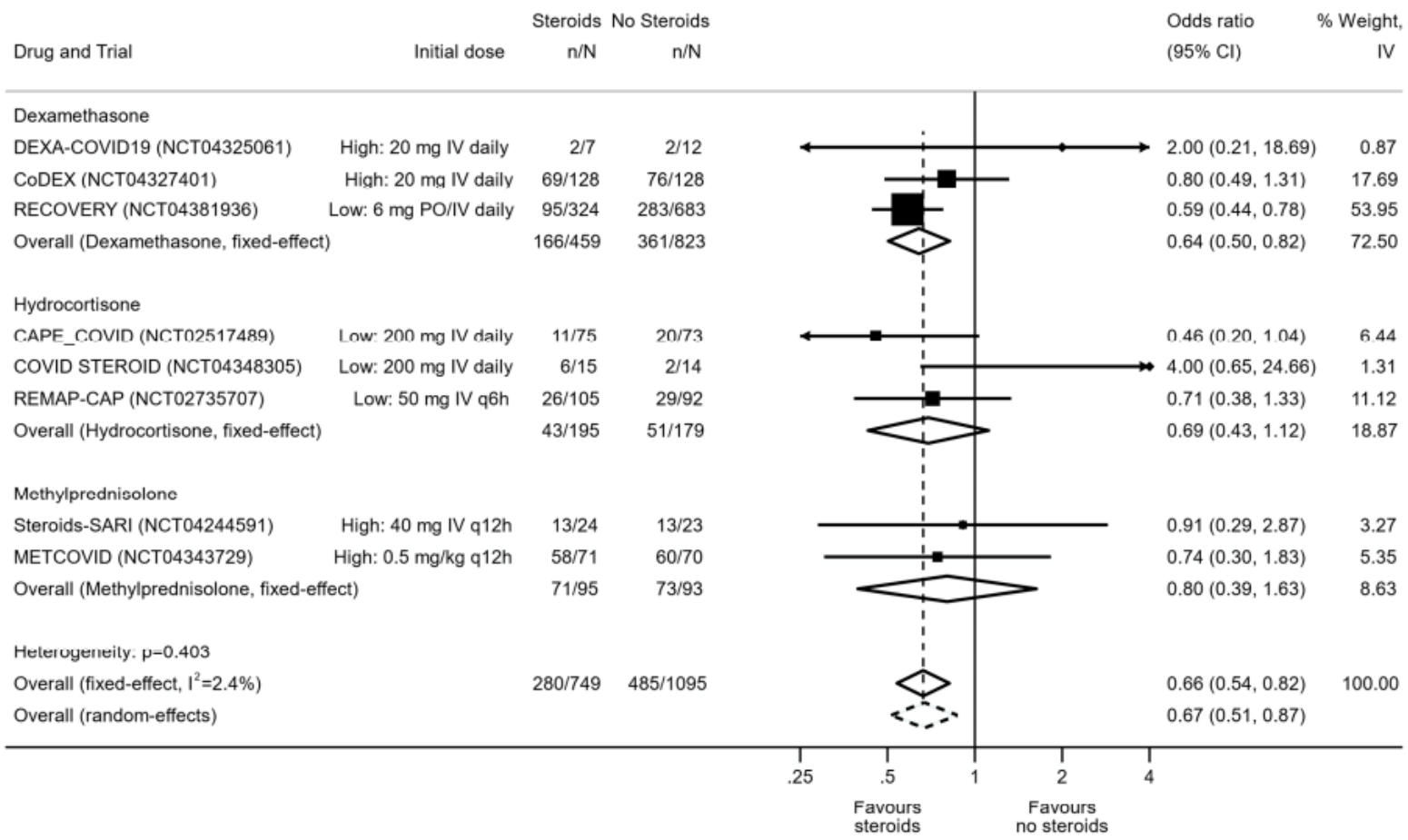
The CoDEX Randomized Clinical Trial

Bruno M. Tomazini, MD; Israel S. Maia, MD, MSc; Alexandre B. Cavalcanti, MD, PhD; Otavio Berwanger, MD, PhD; Regis G. Rosa, MD, PhD; Viviane C. Veiga, MD, PhD; Alvaro Avezum, MD, PhD; Renato D. Lopes, MD, PhD; Flavia R. Bueno, MSc; Maria Vitoria A. O. Silva; Franca P. Baldassare; Eduardo L. V. Costa, MD, PhD; Ricardo A. B. Moura, MD; Michele O. Honorato, MD; Andre N. Costa, MD, PhD; Lucas P. Damiani, MSc; Thiago Lisboa, MD, PhD; Letícia Kawano-Dourado, MD, PhD; Fernando G. Zampieri, MD, PhD; Guilherme B. Olivato, MD; Cassia Righy, MD, PhD; Cristina P. Amendola, MD; Roberta M. L. Roepke, MD; Daniela H. M. Freitas, MD; Daniel N. Forte, MD, PhD; Flávio G. R. Freitas, MD, PhD; Caio C. F. Fernandes, MD; Livia M. G. Melro, MD; Gedealvares F. S. Junior, MD; Douglas Costa Morais; Stevin Zung, MD, PhD; Flávia R. Machado, MD, PhD; Luciano C. P. Azevedo, MD, PhD; for the COALITION COVID-19 Brazil III Investigators

World Health Organization

HEALTH EMERGENCIES programme

eFigure 6. Additional forest plot showing the association of corticosteroids with all-cause 28-day mortality in each trial including the METCOVID trial*, overall and according to corticosteroid drug



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

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

Association between administration of systemic corticosteroids and mortality among critically ill patients with COVID-19: a meta-analysis.

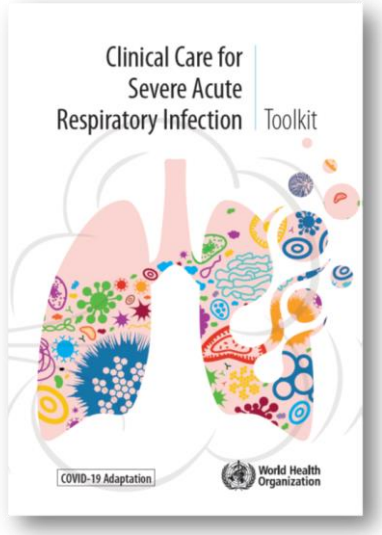
The WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group.

DOI: 10.1001/jama.2020.17023.

Clinical considerations when administering corticosteroids

Corticosteroids in COVID-19: clinical use

Route[a]	Systemic corticosteroids may be administered orally or intravenously.
Type[b]	Daily regimen of **dexamethasone 6 mg once daily** is equivalent to: • **150 mg of hydrocortisone daily** (e.g. 50 mg every 8 hours) *or* • **40 mg of prednisone daily** *or* • **32 mg of methylprednisolone daily** (e.g. 8 mg every 6 hours or 16 mg every 12 hours).
Duration	Up to 7–10 days.
General monitoring	Monitor glucose levels (even if no diabetes diagnosed previously).
Special populations to monitor closely for complications	• Patients receiving other immunosuppressants/immunomodulators. • Patients with these conditions: – diabetes (specially with diabetic ketoacidosis) – severe immunodeficiency disorders – haematological and other malignancies – low number of white blood cells – organ transplantations – iron overload states – severe burns – injection drug use – malnutrition – open wound following trauma.
Examples of possible complications	• Hyperglycaemia or decompensated diabetes • Immunosuppression • Superinfections: bacterial, fungal, viral, parasites • Poor wound healing.



The drugs and doses stated here are for illustrative purposes only. Decisions regarding the use of any medication must be made by a licensed provider and take into account each patient's specific clinical history and other circumstances, and be in accordance with relevant local management and prescribing guidelines.

HEALTH EMERGENCIES programme

Corticosteroids in COVID-19: contraindications

- Relatively few absolute contraindications to corticosteroids exist, and **clinician judgment and shared decision making should be utilized when considering systemic corticosteroids**.
- Patients excluded from randomization in the trials often were those for whom corticosteroids could not be stopped (e.g. patients on chronic steroids prior to entering the trial, who would require a continuing or tapering dose).
- Risks of systemic corticosteroids include:
  - Hyperglycaemia (especially in diabetics)
  - Hypernatremia
  - Gastrointestinal bleeding
  - Neuropsychiatric effects
  - Neuromuscular weakness
  - Superinfection/immunocompromise
  - Stroke or myocardial infarction

Corticosteroids in COVID-19: serious adverse events

- Clinicians should be aware of risks of systemic corticosteroids any time that they are prescribed, and consider the individual risk to each patient.

- From the COVID-19 prospective meta-analysis, serious adverse events noted to be statistically significant were **hyperglycaemia (elevated blood sugar)** and **hypernatremia (elevated blood sodium).**

Corticosteroids in COVID-19: uncertainties

Many things remain unknown about the use of corticosteroids in COVID-19, including:

- Generalizability in resource-limited settings (i.e. low and middle income countries)
- Generalizability among patient populations (e.g. children, immunocompromised, patients with tuberculosis)
- Optimal steroid preparation, dosing and timing of drug initiation
- Long-term effect of systemic corticosteroids on mortality and functional outcomes in those recovering from COVID-19
- Impact of systemic corticosteroids on immunity and the risk of subsequent infection
- Impact on mortality beyond 28 days
- Effect on viral replication

Antenatal corticosteroid therapy

- WHO recommends antenatal corticosteroid therapy for women at risk of preterm birth from 24 to 34 weeks of gestation when there is no clinical evidence of maternal infection, and adequate childbirth and newborn care is available.

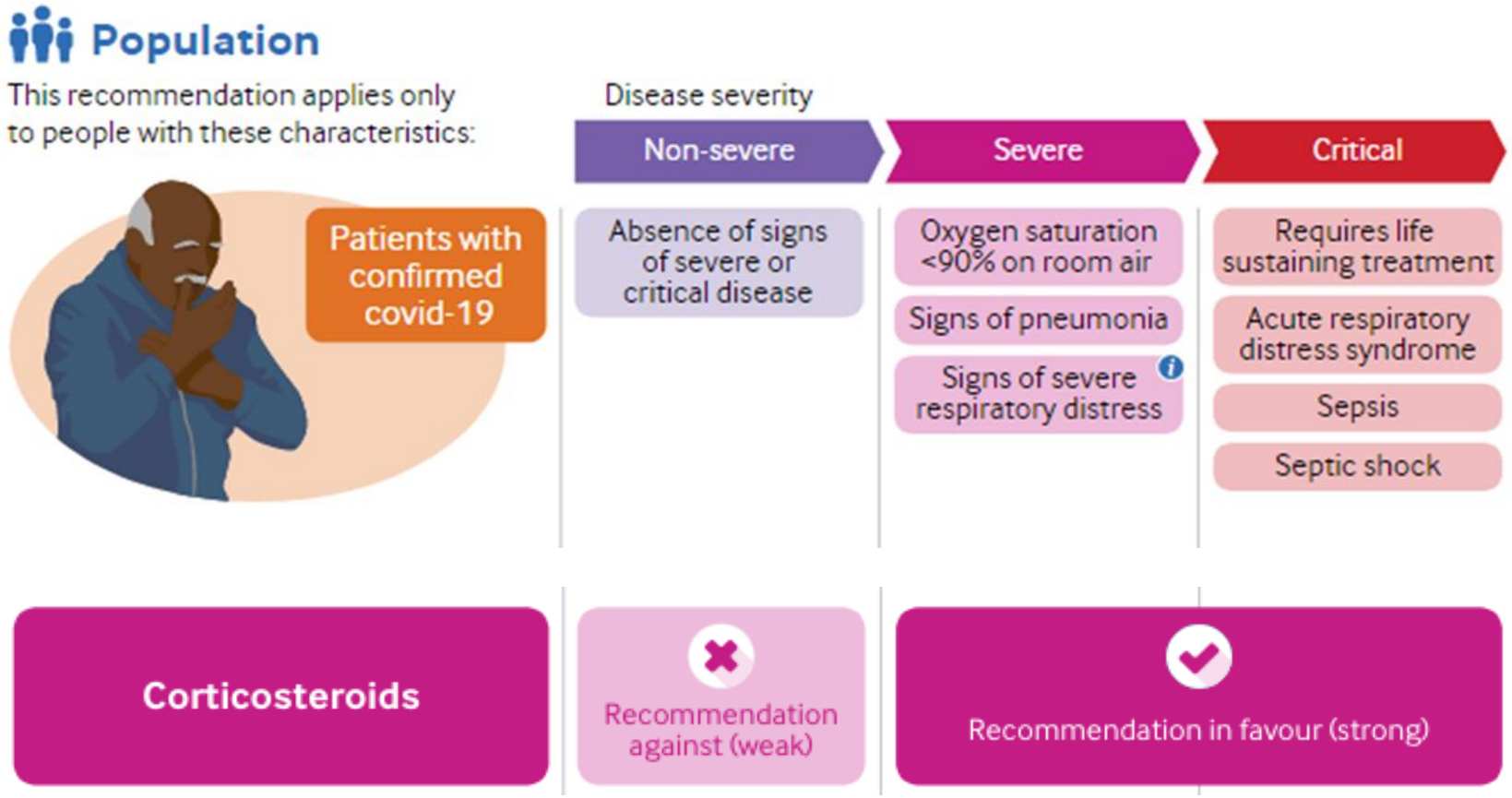
- For women with mild or moderate COVID-19, the benefits of antenatal corticosteroid might outweigh the risks of potential harm to the mother.
  - the balance of benefits and harms for the woman and the preterm newborn should be discussed with the woman and may vary depending on the woman's clinical condition, her wishes and that of her family, and available health care resources.

Summary

Summary

- Give systemic corticosteroids for severe and critical COVID-19.
- Be aware and monitor for potential adverse events due to corticosteroid administration.
- Use shared decision-making in discussing corticosteroids for patients in whom the risks and benefits remain unclear (e.g. immunocompromised, tuberculosis, paediatric, non-severe disease)

Visual summary



A living WHO guideline on drugs for covid-19. BMJ 2020;370:m3379. https://doi.org/10.1136/bmj.m3379

Resources

- WHO: Corticosteroids for COVID-19: living guidance. 2 September 2020. https://apps.who.int/iris/bitstream/handle/10665/334125/WHO-2019-nCoV-Corticosteroids-2020.1-eng.pdf

- WHO: Therapeutics and COVID-19: Living guideline. Published 17 December 2020. https://apps.who.int/iris/bitstream/handle/10665/337876/WHO-2019-nCoV-therapeutics-2020.1-eng.pdf

- MAGICapp, 'WHO Living Guidelines: Therapeutics and COVID-19, v3.1. Published 2 February 2021. https://app.magicapp.org/#/guideline/4717

- A living WHO guideline on drugs for covid-19. BMJ 2020;370:m3379. Published 4 September 2020. https://doi.org/10.1136/bmj.m3379

- WHO: Q&A Dexamethasone and COVID-19. 25 June 2020. https://www.who.int/emergencies/diseases/novel-coronavirus-2019/question-and-answers-hub/q-a-detail/q-a-dexamethasone-and-covid-19

References

1. Comparative Table of Medicines on the WHO Essential Medicines List. Accessed 20 August 2020 http://www.who.int/medicines/publications/essentialmedicines/compar_table_who_edls.xls.
2. Persaud N, Jiang M, Shaikh R, Bali A et al. Comparison of essential medicines lists in 137 countries. Bulletin of the World Health Organization. 2019;97(6):394.
3. Sterne J, Marshall J, Diaz J, Villar J, Murthy S, et al. A prospective meta-analysis of randomized trials of corticosteroid therapy for COVID-19. PROSPERO 2020 CRD42020197242. https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=197242
4. WHO GDG Clinical practice guideline on corticosteroids for COVID-19, Bios. 7 July 2020
5. World Health Organization (2014). WHO Handbook for guidelines development, 2nd edition. World Health Organization. https://apps.who.int/iris/handle/10665/145714
6. The RECOVERY Collaborative Group. Dexamethasone in hospitalized patients with COVID-19 – Report. NEJM, 17 July 2020. doi: 10.1056/NEJMoa2021436
7. World Health Organization : Clinical management of COVID-19. Interim guidance, 27 May 2020. https://www.who.int/publications/i/item/clinical-management-of-covid-19
8. The WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group. Association between administration of systemic corticosteroids and mortality among critically ill patients with COVID-19: a meta-analysis. *JAMA*. Published September 2, 2020. doi: 10.1001/jama.2020.17023
9. Dequin PF, Heming N, Meziani F, et al; for the CAPE COVID Trial Group and the CRICS-TriGGERSep Network. Effect of hydrocortisone on 21-day mortality or respiratory support among critically ill patients with COVID-19: a randomized clinical trial. *JAMA*. Published September 2, 2020. doi:10.1001/jama.2020.16761
10. Tomazini BM, Maia IS, Cavalcanti AB, et al; for the COALITION COVID-19 Brazil III Investigators. Effect of dexamethasone on days alive and ventilator-free in patients with moderate or severe acute respiratory distress syndrome and COVID-19: the CoDEX randomized clinical trial. *JAMA*. Published September 2, 2020. doi:10.1001/jama.2020.17021
11. The Writing Committee for the REMAP-CAP Investigators. Effect of hydrocortisone on mortality and organ support in patients with severe COVID-19: the REMAP-CAP COVID-19 corticosteroid domain randomized clinical trial. *JAMA*. Published September 2, 2020. doi: 10.1001/jama.2020.17022

Acknowledgements

Contributors

Dr Janet Diaz, WHO, Geneva, Switzerland
Dr Pryanka Relan, WHO, Geneva, Switzerland
Dr Teresa Kortz, WHO Consultant, Geneva, Switzerland
Dr Keegan Checkett, WHO Consultant, Geneva, Switzerland
Dr Marta Lado, WHO, Geneva, Switzerland
Vanessa Cramond, WHO, Geneva Switzerland
Dr Krutika Kuppalli, WHO, Geneva Switzerland