Jorge Mera, MD

COVID-19 Update
September 11, 2020

JAMA Network

QUESTION In patients with COVID-19 and moderate or severe ARDS, does intravenous (IV) dexamethasone plus standard care compared with standard care alone increase the number of days patients remained alive and free from mechanical ventilation?

CONCLUSION This clinical trial found that IV dexamethasone plus standard care, compared with standard care alone, resulted in a statistically significant increase in the number of days patients remained alive and free of mechanical ventilation over 28 days.

POPULATION

187 Men
112 Women

Adults with confirmed or suspected COVID-19 and moderate to severe ARDS

Mean age: 61 years

LOCATIONS

41
ICUs in Brazil

INTERVENTION

299 Patients randomized

151
Dexamethasone
IV dexamethasone, 20 mg/d for 5 days, then 10 mg/d for 5 days or to discharge, plus standard care

148
Standard care

PRIMARY OUTCOME

Ventilator-free days during first 28 days

FINDINGS

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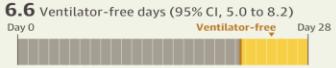
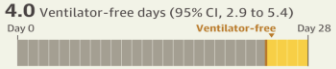
Mean ventilator-free days to day 28

Dexamethasone
6.6 Ventilator-free days (95% CI, 5.0 to 8.2)



Standard care
4.0 Ventilator-free days (95% CI, 2.9 to 5.4)



The between-group difference was significant:
2.26 days (95% CI, 0.2 to 4.4); *P* = .04

Tomazini BM, Maia IS, Cavalcanti AB, et al. 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 online September 2, 2020. doi:10.1001/jama.2020.17021

JAMA Network

QUESTION Does intravenous hydrocortisone, administered either as a 7-day fixed-dose course or restricted to when shock is clinically evident, improve 21-day organ support-free days in patients with severe coronavirus disease 2019 (COVID-19)?

CONCLUSION This randomized clinical trial was stopped early and no treatment strategy met prespecified criteria for statistical superiority, precluding definitive conclusions.

POPULATION

273 Men
111 Women

Adults with suspected or confirmed COVID-19

Mean age: 60 years

LOCATIONS

121 Sites
in 8 countries

INTERVENTION

384 Patients randomized
379 Patients analyzed

143
Fixed-dose hydrocortisone
Intravenous hydrocortisone, 50 mg or 100 mg, every 6 hours

152
Shock-dependent hydrocortisone
Intravenous hydrocortisone, 50 mg, every 6 hours

108
No hydrocortisone
Standard of care with no hydrocortisone (or other corticosteroid) use

PRIMARY OUTCOME

Organ support-free days (days alive and free of intensive care unit-based respiratory or cardiovascular support) within 21 days with death counted as -1 day

FINDINGS

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Median organ support-free days

Fixed-dose hydrocortisone
0 days (interquartile range, -1 to 15)

Shock-dependent hydrocortisone
0 days (interquartile range, -1 to 13)

No hydrocortisone
0 days (interquartile range, -1 to 11)

Median adjusted odds ratio for improvement vs no hydrocortisone (95% credible interval), and probability of superiority:

1.43 (0.91 to 2.27), **93%** in the fixed-dose group

1.22 (0.76 to 1.94), **80%** in the shock-dependent group

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

JAMA Network

QUESTION Does low-dose hydrocortisone decrease treatment failure in patients with COVID-19-related acute respiratory failure?

CONCLUSION This clinical trial found that low-dose hydrocortisone did not significantly reduce treatment failure in patients with COVID-19-related acute respiratory failure; however, the study was stopped early and was therefore likely underpowered.

POPULATION

104 Men 45 Women

Adult ICU patients with COVID-19-related acute respiratory failure

Mean age: 62 years

LOCATIONS

9
ICUs in France

INTERVENTION

149 Patients randomized
148 Patients analyzed

76
Hydrocortisone
IV infusion of hydrocortisone: 200 mg/d until day 4, then adapted to the patient's status evolution, for a total duration of 8 or 14 days, with a progressive reduction of the dose

73
Placebo
IV infusion of saline

PRIMARY OUTCOME

Treatment failure on day 21 (death or persistent dependency on mechanical ventilation or high-flow oxygen)

FINDINGS

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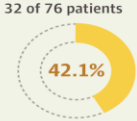
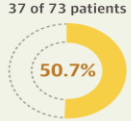
Treatment failure on day 21

Hydrocortisone
32 of 76 patients



Placebo
37 of 73 patients



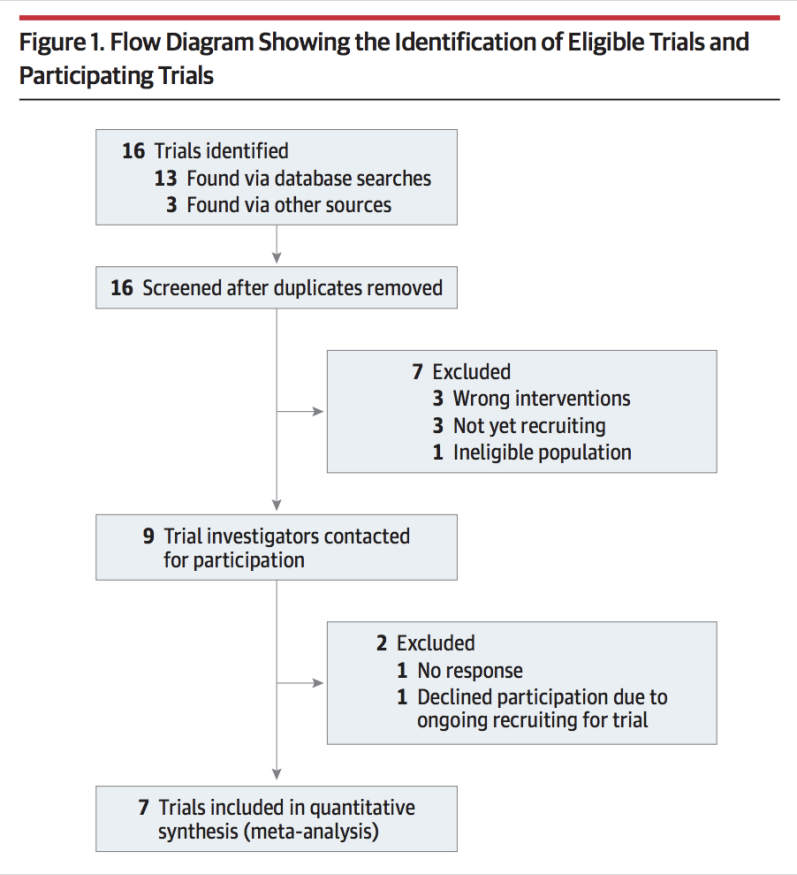
The between-group difference was not significant:
-8.6% (95.48% CI, -24.9% to 7.7%); *P* = .29

However, the study was stopped early and was likely underpowered to find a statistically or clinically important difference in primary outcome.

Dequin P-F, Heming N, Meziani F, et al; CAPE-COVID Trial Group and 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 online September 2, 2020. doi:10.1001/jama.2020.16761

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

- **Objective**
  - To estimate the association between administration of corticosteroids compared with usual care or placebo and 28-day all-cause mortality.
- **Design, Setting, and Participants**
  - Prospective meta-analysis of 7 multinational randomized clinical trials that evaluated the efficacy of corticosteroids in 1703 critically ill patients with COVID-19 from February 26, 2020, to June 9, 2020.
- **Exposures**
  - Patients had been randomized to receive systemic dexamethasone, hydrocortisone, or methylprednisolone (678 patients) or to receive usual care or placebo (1025 patients).
- **Main Outcomes and Measures**
  - The primary outcome measure was all-cause mortality at 28 days after randomization. A secondary outcome was investigator-defined serious adverse events.



The WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group *JAMA.* Published online September 2, 2020. doi:10.1001/jama.2020.17023

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

- 1703 patients included in the analysis, median age, 60 years (52-68 years), 29% women
- Most patients were on mechanical ventilation
- Mortality at 28 days
  - 222 **(32.7%)** deaths among the 678 patients randomized to corticosteroids compared to 425 **(41.4%)** deaths among the 1025 patients randomized to SOC or placebo
  - **Summary OR, 0.66** [95% CI, 0.53-0.82]; *P* < .001)

- **The OR for the association with mortality was**
  - **0.64** (95% CI, 0.50-0.82; ***P* < .001**) for **dexamethasone**
    - (3 trials, 1282 patients, and 527 deaths),
  - **0.69** (95% CI, 0.43-1.12; *P* = .13) for **hydrocortisone**
    - (3 trials, 374 patients, and 94 deaths),
  - **0.91** (95% CI, 0.29-2.87; *P* = .87) for **methylprednisolone**
    - (1 trial, 47 patients, and 26 deaths)
- Among the 6 trials that **reported serious adverse events**
  - 64 (18%) events among 354 patients on corticosteroids
  - 80 (23%) events among 342 patients on SOC or placebo.

The WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group *JAMA.* Published online September 2, 2020. doi:10.1001/jama.2020.17023

Conclusions

- Administration of corticosteroids was associated with lower all-cause mortality at 28 days after randomization.
- There was no suggestion of an increased risk of serious of adverse events.
- The ORs for the association between corticosteroids and mortality were similar for dexamethasone and hydrocortisone.
- Corticosteroids were associated with lower mortality among critically ill patients who were and were not receiving invasive mechanical ventilation at randomization
- The association between corticosteroids and lower mortality was stronger in patients who were not receiving vasoactive medication at randomization than in those who were receiving
- The ORs for the association between corticosteroids and mortality appeared similar for older and younger individuals, men and women, and for longer and shorter durations of symptoms be- fore randomization.

The WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group *JAMA.* Published online September 2, 2020. doi:10.1001/jama.2020.17023

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

- What does this mean?
  - If you treat 100 patients with steroids 68 will survive
  - If you treat 100 patients without steroids 60 will survive
  - The number of patients needed to treat to benefit one patient is 12

Corticosteroids in COVID-19 ARDS
Evidence and Hope During the Pandemic

- “While much work remains on the exact details of implementation into clinical practice, the consistent findings of benefit in these studies provide definitive data that corticosteroids should be first-line treatment for critically ill patients with COVID-19”

- “The COVID-19 pandemic has brought fear and a sea of change to the world. These studies provide evidence and some hope that an effective, inexpensive, and safe treatment has been identified”

Prescott HC, Rice TW, JAMA. Published online September 2, 2020. doi:10.1001/jama.2020.1674

Corticosteroids in COVID-19 ARDS
Evidence and Hope During the Pandemic
QUESTIONS?

- Should corticosteroid administration be individualized, with initiation, dosing, and duration guided by clinical response or biomarkers, such as C-reactive protein?
- Does inflammation rebound after cessation of corticosteroids in some patients and would tapering them improve outcomes?
- What are the true incidence and optimal management of adverse effects, given that most of the randomized trials are open-label pragmatic designs with minimal reporting of adverse effects?
- Should less severely ill or non-hospitalized patients be treated with corticosteroids?
- What is the threshold of illness severity at which corticosteroids are now indicated?
- Do corticosteroids delay clearance of SARS-CoV-2, especially in less ill patients not hospitalized, and if so, does this affect clinical outcomes?
- Should remdesivir or other potentially active therapeutics be administered with corticosteroids?

Prescott HC, Rice TW, JAMA. Published online September 2, 2020.doi:10.1001/jama.2020.1674

Cases of SARS-CoV-2 Reinfection Highlight the Limitations — and the Mysteries — of Our Immune System

- Why does one parent never get sick when their kids start coughing and sneezing and dripping with colds, while the other gets a cold *every single time?*
- Why do some tourists happily dine on delicious street food in Mexico City, while this same cuisine will put others in their hotel bathrooms for the whole trip?
- Why is infection with Epstein Barr virus (nearly 100% in humans by adulthood) most of the time asymptomatic, while a certain unlucky few will be laid up with severe mononucleosis for weeks?
- Why do some people get the flu twice within the same flu season? Or some (rare) people get chicken pox twice?

Paul, E. Sax, MD. ID and HIV Observations. J Watch August 30, 2020

COVID-19 Reinfection Tracker

Reported	Location	Patient	Interval	Symptoms (1st case)	Symptoms (2nd case)	Recovered	Links
August 30	Ecuador	46/M	47 days	Mild	Moderate	Yes	Details
August 28	United States	25/M	31 days	Mild	Serious	N/A	Details
August 26	Netherlands	60s/M	Several days	Mild	Serious	Yes	Details
August 26	Netherlands	80s/M	21 days	Mild	Mild	Yes	Details
August 26	Netherlands	60+	60 days (estimate)	N/A	N/A	Yes	Details
August 24	Netherlands	60+	N/A	N/A	N/A	N/A	Details
August 24	Belgium	51/F	93 days	Mild	Mild (less intense)	Yes	Details

https://bnonews.com/index.php/2020/08/covid-19-reinfection-tracker/

COVID-19 re-infection by a phylogenetically distinct SARS-coronavirus-2 strain confirmed by whole genome sequencing

- Methods
  - Whole genome sequencing was performed during two episodes of COVID-19 in a patient to differentiate re-infection from persistent viral shedding.
- Results
  - The second episode of asymptomatic infection occurred 142 days after the first symptomatic
  - During the second episode, there was serological evidence of SARS-CoV-2 IgG seroconversion.
  - Viral genomes from first and second episodes belong to different clades/lineages.
- Conclusions
  - Epidemiological, clinical, serological and genomic analyses confirmed that the patient had re-infection
  - Our results suggest SARS-CoV-2 may continue to circulate among the human populations despite herd immunity due to natural infection or vaccination

Kai-Wang To K, Fan-Ngai Hung I, Daniel Ip J; et al. *Clinical Infectious Diseases*, https://doi.org/10.1093/cid/ciaa1275

NEVADA SARS-CoV-2 CASE

March 25: Onset of sore throat, cough, headache, nausea, diarrhea.
April 18: Tested positive for SARS-CoV-2 by PCR.
April 27: Symptoms resolved.
May 9 and 26: Tested negative for virus by two methods.
May 28: Onset of fevers, headache, dizziness, cough, nausea, and diarrhea. Chest x-ray negative.
June 5: Symptoms worsened, and now with hypoxia; admitted to the hospital and found to have new infiltrates on chest x-ray. PCR positive for SARS-CoV-2.
June 6: SARS-CoV-2 IgM and IgG antibody positive.

Cases of SARS-CoV-2 Reinfection Highlight the Limitations — and the Mysteries — of Our Immune System

- ***How often does reinfection happen, and why?*** It doesn't appear common, but we must conclude from these cases that it *does* occur. Perhaps with similar frequency to other coronavirus infections in humans?
- ***Will cases be as severe as the first infection?*** Based solely on the Nevada case's household contact, it's possible that severity may be related to intensity of exposure. Maybe he was not taking precautions in the household, believing himself immune? Some believe inoculum is an overlooked aspect of COVID-19 disease severity.
- ***When reinfection happens, will these new cases carry the same risk of transmission as the first infection?*** We will have to assume so, but it is plausible that an immune response will render people less infectious to others.
- ***How do these cases factor into policies about screening people who have already recovered from COVID-19?*** Given the long duration of PCR positivity in some people, some infection control specialists have advocated not retesting people who are admitted with prior disease if they are asymptomatic. Same for preprocedural screening.
    - **Seems we may need to put this policy change on hold until we have further data on reinfection, and how often it occurs.**
- ***What are the implications for vaccine efficacy?*** Will a vaccine even work? If so, for how long? The cases suggest that a vaccine may need to be repeated periodically, but optimists can point to the HPV vaccine as a model of how vaccine immunity can be stronger than natural immunity, so we'll see.

Paul, E. Sax, MD. ID and HIV Observations. J Watch August 30, 2020