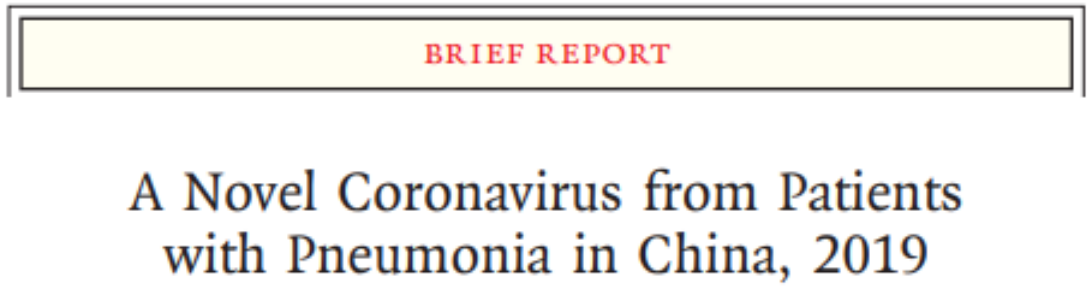
JOURNAL CLUB

DEXAMETHASONE IN HOSPITALIZED PATIENTS WITH COVID-19 – RECOVERY TRIAL

PRELIMINARY REPORT

JACQUELINE TAY | PGY-5 | SEPTEMBER 2, 2020

EMERGENCE OF COVID-19


BRIEF REPORT

A Novel Coronavirus from Patients with Pneumonia in China, 2019

- In December 2019, emergence of a pneumonia of unknown cause linked to a wholesale market in Wuhan, Hubei Province, China
- Agent identified as new beta-coronavirus, SARS coronavirus 2, or SARS-CoV-2
- Officially declared a pandemic on March 11, 2020 by the WHO
  - Carried a mortality rate of approximately 3.7%
  - Had already spread from China to other Asian countries, Europe and the United States

Zhu et al. A Novel Coronavirus from Patients with Pneumonia in China, 2019. *N Engl J Med* 2020. 382(8):727-733.

BURDEN OF DISEASE

Situation by Country, Territory & Area

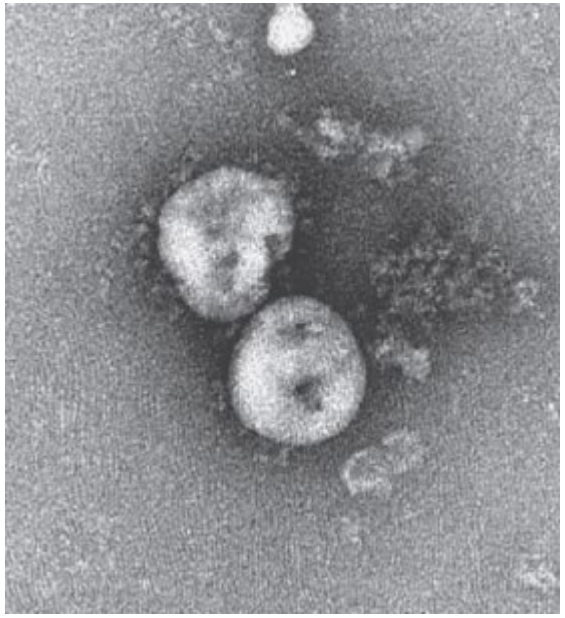
Name	Cases - cumulative total	Cases - newly reported in last 24 hours	Deaths - cumulative total	Deaths - newly reported in last 24 hours	Transmission Classification
Global	**24,854,140**	**265,888**	**838,924**	**5,361**	
United States of Ame…	5,855,521	44,002	180,689	973	Community transmission
Brazil	3,804,803	43,412	119,504	855	Community transmission
India	3,542,733	78,761	63,498	948	Clusters of cases
Mexico	585,738	5,824	63,146	552	Community transmission
The United Kingdom	332,756	1,108	41,498	12	Community transmission
Italy	266,853	1,444	35,473	1	Clusters of cases
France	256,829	5,313	30,465	5	Community transmission
Spain	439,286	0	29,011	0	Clusters of cases
Peru	629,961	7,964	28,471	194	Community transmission
Iran (Islamic Republi…	371,816	1,905	21,359	110	Community transmission

As of August 30, 2020

https://covid19.who.int/table

SARS-COV-2

- β-coronavirus
  - Enveloped non-segmented positive-sense RNA virus
  - Subgenus *sarbecovirus*, *Orthocoronavirinae* subfamily
- Seventh member of the family of coronaviruses that infect humans
  - Third coronavirus to cause severe respiratory illness in humans
- Zoonotic infection that adapted to humans
  - Likely originated in bats with an intermediary host
- Spreads through the respiratory tract by droplets, respiratory secretions, and direct contact
- Uses cell receptor ACE2, found on lung alveolar epithelial cells in lower respiratory tract of humans
  - Same cellular entry receptor as SARS-CoV



Auw aerter PG. Coronavirus COVID-19 (SARS-CoV-2). *Johns Hopkins ABX Guide*, The Johns Hopkins University, 2020. *Johns Hopkins Guide*, www.hopkinsguides.com/hopkins/view/Johns_Hopkins_ABX_Guide/540747/all/Coronavirus_COVID_19__SARS_CoV_2
Zhu et al. A Novel Coronavirus from Patients with Pneumonia in China, 2019. *N Engl J Med* 2020. 382(8):727-733.

BACKGROUND

- Incubation period of 5-6 days, range of 2-12

- Wide range of disease severity of COVID-19
  - Asymptomatic
  - Mild, transient symptoms } most common
  - Severe viral pneumonia with respiratory failure, multiorgan failure, death

- For hospitalized patients with pneumonia, studies suggest:
  - 50% develop hypoxemia by day 8
    - Severe illness and cytokine release syndrome appear to develop mostly within 5-10d after symptom onset in susceptible patients
    - Markers of severe infection include regular high fevers (>39°), RR >30, worsening oxygen requirements (4-6L NC), elevated inflammatory markers (CRP, d-dimer, ferritin, IL-6)
    - ARDS develops in **17-29%**

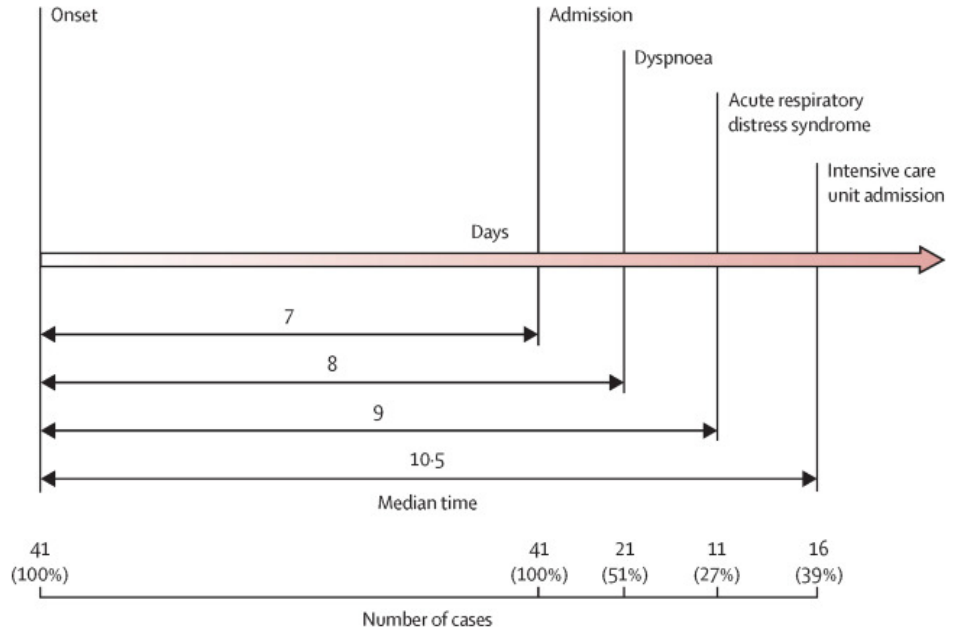
Auw aerter PG. Coronavirus COVID-19 (SARS-CoV-2). *Johns Hopkins ABX Guide*, The Johns Hopkins University, 2020. *Johns Hopkins Guide*, www.hopkinsguides.com/hopkins/view/Johns_Hopkins_ABX_Guide/540747/all/Coronavirus_COVID_19__SARS_CoV_2
World Health Organization, Clinical management of severe acute respiratory infection when COVID-19 disease is suspected. 2020, May 27. https://www.who.int/publications/i/item/clinical-management-of-severe-acute-respiratory-infection-when-novel-coronavirus-(ncov)-infection-is-suspected

BACKGROUND

- An early cohort study of 41 admitted hospital patients with laboratory-confirmed 2019-nCoV infection in China identified median times to development of dyspnea and progression to ARDS and mechanical ventilation
- Noted high amounts of cytokines, suggesting cytokine storm is associated with disease severity

Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China

Chaolin Huang, Yeming Wang*, Xingwang Li*, Lili Ren*, Jianping Zhao*, Yi Hu*, Li Zhang, Guohui Fan, Jiuyang Xu, Xiaoying Gu, Zhenshun Cheng, Ting Yu, Jiaan Xia, Yuan Wei, Wenjuan Wu, Xuelei Xie, Wen Yin, Hui Li, Min Liu, Yan Xiao, Hong Gao, Li Guo, Jungang Xie, Guangfa Wang, Rongmeng Jiang, Zhancheng Gao, Qi Jin, Jianwei Wang†, Bin Cao†*



Huang C, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *The Lancet* 2020. 395(10223): 497-506.

BACKGROUND

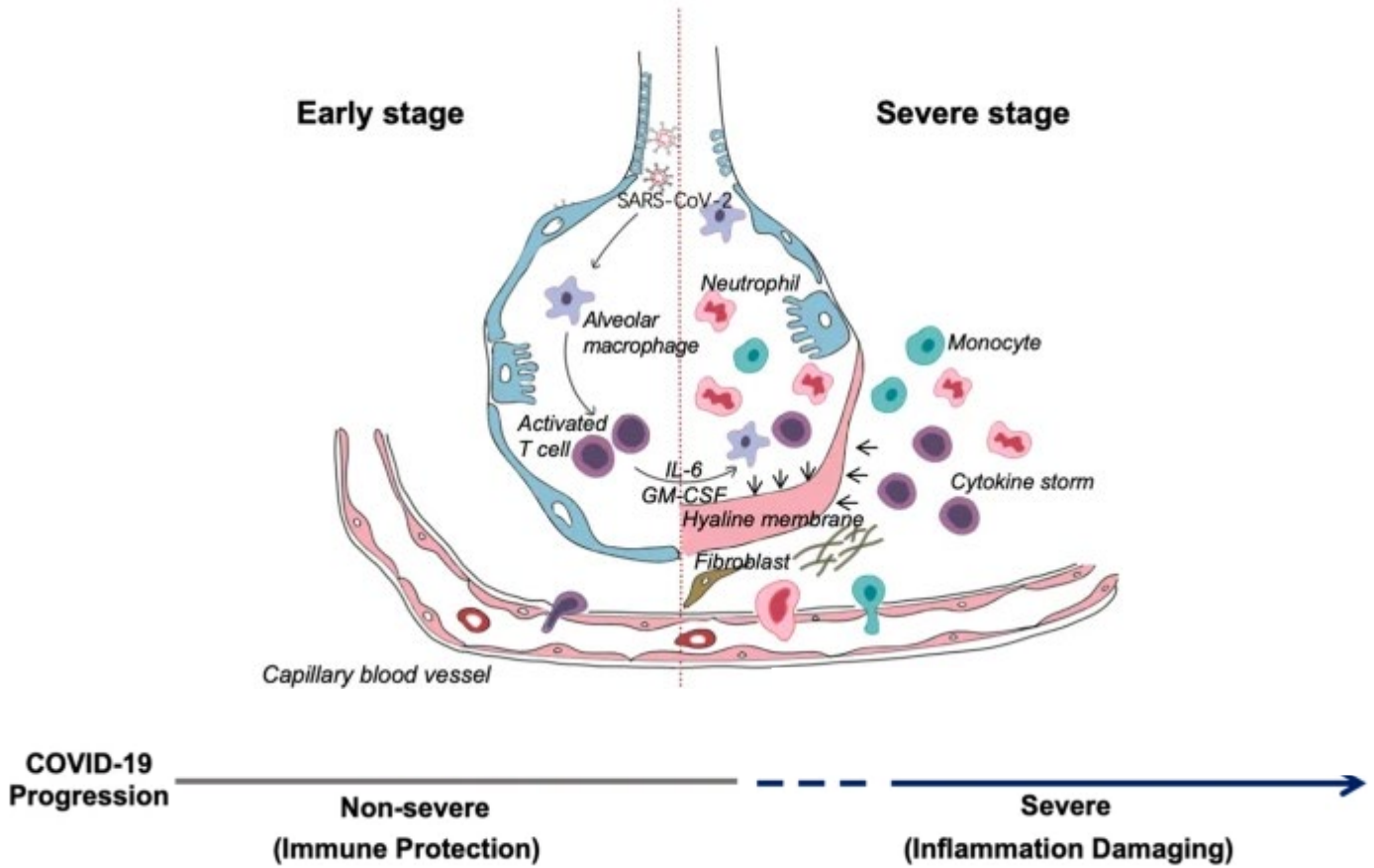


Image adapted from: Shi Y, Wang Y, Shao C, *et al.* COVID-19 infection: the perspectives on immune responses. *Cell Death Differ* 2020. 27:1451–1454.

BACKGROUND

- Risk factors associated with ICU admission
  - Age
  - Comorbidities (COPD, CKD, cardiovascular disease, diabetes)
  - Lymphocytopenia
  - Elevated ALT, d-dimer, CK, high sens cardiac trop I, prothrombin time
  - Disease severity
- Risk factors associated with mortality
  - Older age
  - High Sequential Organ Failure Assessment (SOFA) score
  - D-dimer >1 ug/mL

Auw aerter PG. Coronavirus COVID-19 (SARS-CoV-2). *Johns Hopkins ABX Guide*, The Johns Hopkins University, 2020. *Johns Hopkins Guide*, www.hopkinsguides.com/hopkins/view/Johns_Hopkins_ABX_Guide/540747/all/Coronavirus_COVID_19__SARS_CoV_2
Zhou F, Yu T, Du R, *et al*. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet*, 2020. 395:1054-1062
World Health Organization, Clinical management of severe acute respiratory infection when COVID-19 disease is suspected. 2020, May 27. https://www.who.int/publications/i/item/clinical-management-of-severe-acute-respiratory-infection-when-novel-coronavirus-(ncov)-infection-is-suspected

BACKGROUND

- No therapeutic drugs available that are directly active against SARS-CoV-2
- No standard treatment available and studies ongoing
- Treatment remains supportive
  - Supplemental oxygen
  - Prone positioning
  - Vasopressors to maintain perfusion pressures
  - Mechanical support in end-organ failure
- Antiviral agents, antibiotics, anti-inflammatory, immunomodulatory agents are under investigation

Auw aerter PG. Coronavirus COVID-19 (SARS-CoV-2). *Johns Hopkins ABX Guide*, The Johns Hopkins University, 2020. *Johns Hopkins Guide*, www.hopkinsguides.com/hopkins/view/Johns_Hopkins_ABX_Guide/540747/all/Coronavirus_COVID_19__SARS_CoV_2

BACKGROUND

- The UK New and Emerging Respiratory Virus Threats Advisory Group (NERVTAG) advised evaluation of several possible treatments
  - Lopinavir-Ritonavir
  - Low-dose corticosteroids
  - Hydroxychloroquine
  - Other emerging treatments

- Also advised by the World Health Organization (WHO)

EVIDENCE BEFORE THIS STUDY

- Randomized, controlled, open-label trial involving hospitalized adult patients with confirmed SARS-CoV-2 infection
- 199 patients enrolled, assigned 1:1 to receive either lopinavir-ritonavir (400/100 mg) for 14 days in addition to standard care, or standard care alone
- Primary end point was time to clinical improvement
  - Treatment group for clinical improvement was not associated with a difference from standard care (HR 1.31; 95% CI, 0.95 – 1.80)
- **Bottom line:** No benefit was observed with lopinavir-ritonavir treatment beyond standard care. Future trials may help to assess possibility of treatment benefit.

Cao B, Wang Y, Wen D, et al. A trial of lopinavir–ritonavir in adults hospitalized with severe Covid-19. *N Engl J Med* 2020.382:1787-1799.

EVIDENCE BEFORE THIS STUDY


The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Remdesivir for the Treatment of Covid-19 — Preliminary Report

J.H. Beigel, K.M. Tomashek, L.E. Dodd, A.K. Mehta, B.S. Zingman, A.C. Kalil, E. Hohmann, H.Y. Chu, A. Luetkemeyer, S. Kline, D. Lopez de Castilla, R.W. Finberg, K. Dierberg, V. Tapson, L. Hsieh, T.F. Patterson, R. Paredes, D.A. Sweeney, W.R. Short, G. Touloumi, D.C. Lye, N. Ohmagari, M. Oh, G.M. Ruiz-Palacios, T. Benfield, G. Fätkenheuer, M.G. Kortepeter, R.L. Atmar, C.B. Creech, J. Lundgren, A.G. Babiker, S. Pett, J.D. Neaton, T.H. Burgess, T. Bonnett, M. Green, M. Makowski, A. Osinusi, S. Nayak, and H.C. Lane, for the ACTT-1 Study Group Members*

- Multi-center, double-blind, randomized, placebo-controlled trial of IV remdesivir in adults hospitalized with COVID-19
- Remdesivir showing shorter time to recovery in patients who received remdesivir with median time to recovery 11 days vs. 15 days in placebo group ($p<0.001$)
- Trend towards improved survival at day 14 with Kaplan-Meier estimates of mortality
  - 7.1% with remdesivir
  - 11.9% in placebo
  - HR 0.7 [95% CI 0.47-1.04]
- Awaiting further follow-up data

Beigel JH, Tomashek KM, Dodd LE, et al. Remdesivir for the treatment of Covid-19 — preliminary report. *N Engl J Med* 2020. DOI: 10.1056/NEJMoa2007764.

EVIDENCE BEFORE THIS STUDY

THE LANCET
Respiratory Medicine

Dexamethasone treatment for the acute respiratory distress syndrome: a multicentre, randomised controlled trial

- Multicentre, blinded, randomised controlled trial
- Network of 17 ICUs in Spain
- 277 patients with established moderate-to-severe ARDS
  - 139 patients to dexamethasone group
  - 138 to control group
- Dexamethasone group received IV dose of 20mg once daily from D1 to D5, then 10mg daily from D6 to D10
- Both groups ventilated with lung-protective mechanical ventilation

Villar J, Ferrando C, Martinez D, et al. Dexamethasone treatment for the acute respiratory distress syndrome: a multicentre, randomised controlled trial. *Lancet Respir Med* 2020. 8:267-76.

EVIDENCE BEFORE THIS STUDY

THE LANCET
Respiratory Medicine

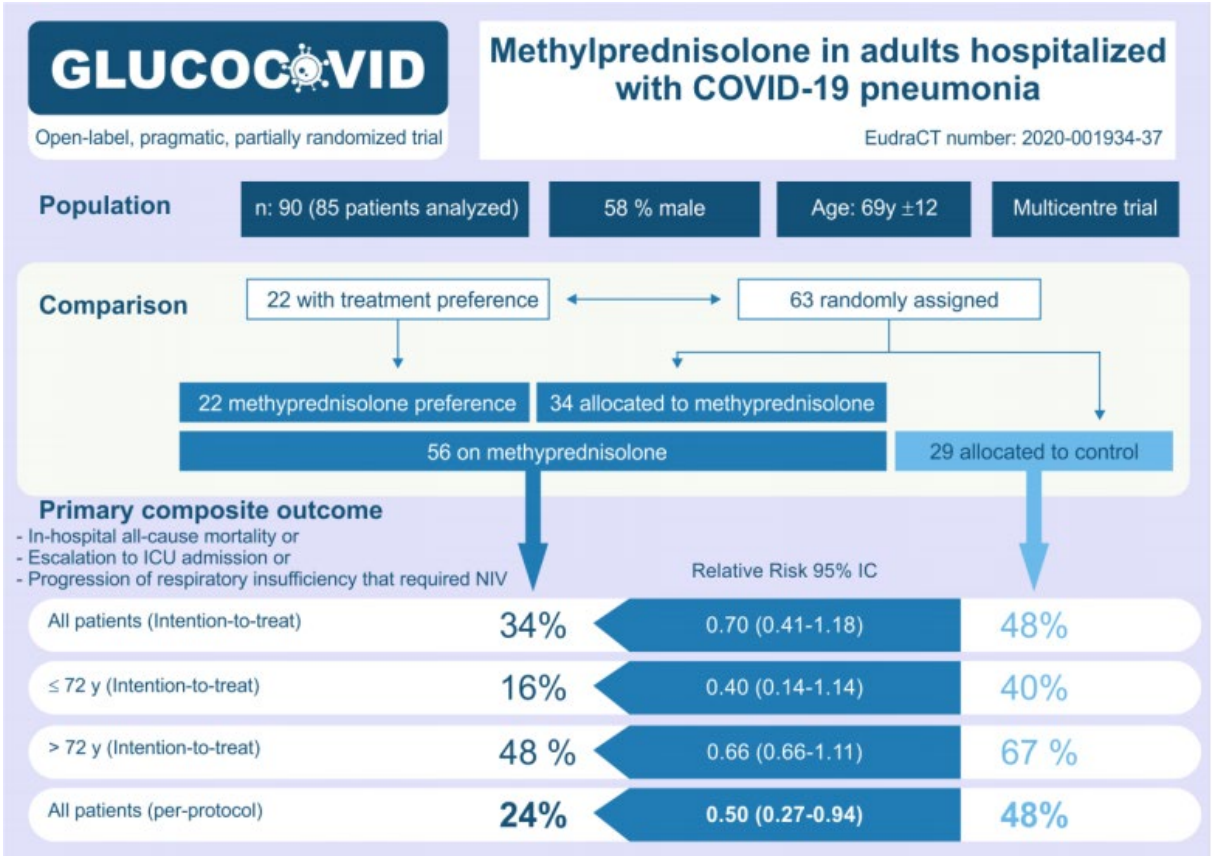
Dexamethasone treatment for the acute respiratory distress syndrome: a multicentre, randomised controlled trial

- Primary outcome: number of ventilator-free days at 28 days
  - Higher in the dexamethasone group than control group with between-group difference of 4.8 days [95% CI 2.57 – 7.03]; p<0.0001
- Secondary outcome: all-cause mortality at 60 days after randomisation
  - Fewer patients in dexamethasone group died than control group with between-group difference of -15.3% [95% CI -25.9 - -4.9]; p=0.0047)
- **Bottom line:** Early administration of dexamethasone could reduce duration of mechanical ventilation and overall mortality in patients with established moderate-to-severe ARDS

Villar J, Ferrando C, Martinez D, et al. Dexamethasone treatment for the acute respiratory distress syndrome: a multicentre, randomised controlled trial. *Lancet Respir Med* 2020. 8:267-76.

GLUCOCOVID: A controlled trial of methylprednisolone in adults hospitalized with COVID-19 pneumonia

Luis Corral-Gudino[1], Alberto Bahamonde[2], Francisco Arnaiz-Revillas[3], Julia Gómez-Barquero[4], Jesica Abadía-Otero[4], Carmen García-Ibarbia[5], Víctor Mora[6], Ana Cerezo-Hernández[7], José L. Hernández[5], Graciela López-Muñiz[7], Fernando Hernández-Blanco [2], Jose M. Cifrián[6], Jose M. Olmos[5], Miguel Carrascosa[8], Luis Nieto[9], María Carmen Fariñas[3], and José A. Riancho[5], for the GLUCOCOVID investigators*



- Multicentric, partially randomized, preference, open-label trial
- Included 85 adults with COVID-19 pneumonia, impaired gas exchange and biochemical evidence of hyperinflammation
- Assigned to standard of care (SOC), or SOC plus intravenous methylprednisolone (40mg/12h x 3d, then 20mg/12h x 3d)
- Primary endpoint was composite of death, admission to the ICU or requirement of non-invasive ventilation
- 34 randomized to MP, 22 assigned to MP by clinician preference, 29 to control group

- **Bottom line:** Use of methylprednisolone was associated with a reduced risk of the composite endpoint in the intention-to-treat, age-stratified analysis (combined risk ratio 0.55 [95% CI 0.33-0.91]; p=0.024)

Corral L, Bahamonde A, Arnaiz delas Revillas F, et al. GLUCOCOVID: A controlled trial of methylprednisolone in adults hospitalized with COVID-19 pneumonia. *medRxiv* 2020. DOI: https://doi.org/10.1101/2020.06.17.20133579

CURRENT GUIDELINES

Surviving Sepsis Campaign®

Society of Critical Care Medicine
The Intensive Care Professionals

GUIDELINES

Surviving Sepsis Campaign: guidelines on the management of critically ill adults with Coronavirus Disease 2019 (COVID-19)

Waleed Alhazzani[1,2], Morten Hylander Møller[3,4], Yaseen M. Arabi[5], Mark Loeb[1,2], Michelle Ng Gong[6], Eddy Fan[7], Simon Oczkowski[1,2], Mitchell M. Levy[8,9], Lennie Derde[10,11], Amy Dzierba[12], Bin Du[13], Michael Aboodi[6], Hannah Wunsch[14,15], Maurizio Cecconi[16,17], Younsuck Koh[18], Daniel S. Chertow[19], Kathryn Maitland[20], Fayez Alshamsi[21], Emilie Belley-Cote[1,22], Massimiliano Greco[16,17], Matthew Laundy[23], Jill S. Morgan[24], Jozef Kesecioglu[10], Allison McGeer[25], Leonard Mermel[8], Manoj J. Mammen[26], Paul E. Alexander[2,27], Amy Arrington[28], John E. Centofanti[29], Giuseppe Citerio[30,31], Bandar Baw[1,32], Ziad A. Memish[33], Naomi Hammond[34,35], Frederick G. Hayden[36], Laura Evans[37] and Andrew Rhodes[38*]

Alhazzani W, Møller MH, Arabi YM, et al. Surviving Sepsis Campaign: guidelines on the management of critically ill adults with Coronavirus Disease 2019 (COVID-19). *Intensive Care Med*. 2020. 46(5):854-887.

Surviving Sepsis Campaign®

Society of Critical Care Medicine
The Intensive Care Professionals

	THERAPY	
41	In mechanically ventilated adults with COVID-19 and respiratory failure (**without ARDS**), we ***suggest against*** the routine use of systemic corticosteroids	Weak
42	In mechanically ventilated adults with COVID-19 **and ARDS**, we ***suggest*** using systemic corticosteroids, over not using corticosteroids *Remark:* The majority of our panel support a weak recommendation (i.e. suggestion) to use steroids in the sickest patients with COVID-19 and ARDS. However, because of the very low-quality evidence, some experts on the panel preferred not to issue a recommendation until higher quality direct evidence is available	Weak
43	In mechanically ventilated patients with COVID-19 and respiratory failure, we ***suggest*** using empiric antimicrobials/antibacterial agents, over no antimicrobials *Remark:* if the treating team initiates empiric antimicrobials, they should assess for de-escalation daily, and re-evaluate the duration of therapy and spectrum of coverage based on the microbiology results and the patient's clinical status	Weak
44	For critically ill adults with COVID-19 who develop fever, we ***suggest*** using acetaminophen/paracetamol for temperature control, over no treatment	Weak
45	In critically ill adults with COVID-19, we ***suggest against*** the routine use of standard intravenous immunoglobulins (IVIG)	Weak
46	In critically ill adults with COVID-19, we ***suggest against*** the routine use of convalescent plasma	Weak
47.1	In critically ill adults with COVID-19: we **suggest against** the routine use of lopinavir/ritonavir	Weak

Alhazzani W, Møller MH, Arabi YM, et al. Surviving Sepsis Campaign: guidelines on the management of critically ill adults with Coronavirus Disease 2019 (COVID-19). *Intensive Care Med*. 2020. 46(5):854-887.

Clinical management of COVID-19

Interim guidance
27 May 2020

World Health Organization

13. Corticosteroid therapy and COVID-19

We recommend against the routine use of systemic corticosteroids for treatment of viral pneumonia.

Remarks:

1. A systematic review and meta-analysis of the impact of corticosteroid therapy on outcomes of persons with SARS-CoV-2, SARS-CoV and MERS-CoV revealed corticosteroids did not significantly reduce the risk of death, did not reduce hospitalization duration, ICU admission rate and/or use of mechanical ventilation, and had several adverse effects *(134)*. A systematic review of observational studies of corticosteroids administered to patients with SARS reported no survival benefit and possible harms (avascular necrosis, psychosis, diabetes and delayed viral clearance) *(135)*. A systematic review of observational studies in influenza found a higher risk of mortality and secondary infections with corticosteroids; the evidence was judged as very low to low quality owing to confounding by indication *(136)*. A subsequent study that addressed this limitation by adjusting for time-varying confounders found no effect on mortality *(137)*. Finally, a study of patients receiving corticosteroids for MERS used a similar statistical approach and found no effect of corticosteroids on mortality but delayed LRT clearance of MERS-CoV *(138)*.

2. Given the lack of effectiveness and possible harm, routine corticosteroids should be avoided unless they are indicated for another reason. Other reasons may include exacerbation of asthma or chronic obstructive pulmonary disease (COPD), septic shock or ARDS, and risk/benefit analysis needs to be conducted for individual patients.

World Health Organization, Clinical management of severe acute respiratory infection when COVID-19 disease is suspected. 2020, May 27. https://www.who.int/publications/i/item/clinical-management-of-severe-acute-respiratory-infection-when-novel-coronavirus-(ncov)-infection-is-suspected

NIH | COVID-19 Treatment Guidelines

Corticosteroids

Recommendations for Patients with COVID-19

- On the basis of the preliminary report from the RECOVERY trial, the COVID-19 Treatment Guidelines Panel (the Panel) recommends using **dexamethasone** 6 mg per day for up to 10 days or until hospital discharge, whichever comes first, for the treatment of COVID-19 in hospitalized patients who are mechanically ventilated **(AI)** and in hospitalized patients who require supplemental oxygen but who are not mechanically ventilated **(BI)**.
- The Panel **recommends against** using **dexamethasone** for the treatment of COVID-19 in patients who do not require supplemental oxygen **(AI)**.
- If **dexamethasone** is not available, the Panel recommends using alternative glucocorticoids such as **prednisone**, **methylprednisolone**, or **hydrocortisone** (see Additional Considerations below for dosing recommendations) **(AIII)**.

National Institutes of Health. Coronavirus Disease 2019 (COVID-19) Treatment Guidelines. 2020, September 1. https://www.covid19treatmentguidelines.nih.gov/immune-based-therapy/immunomodulators/corticosteroids/

Recommendation 4. Among hospitalized patients with severe* COVID-19, the IDSA guideline panel suggests glucocorticoids rather than no glucocorticoids. (Conditional recommendation, Moderate certainty of evidence)

- **Remark:** Dexamethasone 6 mg IV or PO for 10 days (or until discharge if earlier) or equivalent glucocorticoid dose may be substituted if dexamethasone unavailable. Equivalent total daily doses of alternative glucocorticoids to dexamethasone 6 mg daily are methylprednisolone 32 mg and prednisone 40 mg.

Recommendation 5. Among hospitalized patients with COVID-19 without hypoxemia requiring supplemental oxygen, the IDSA guideline panel suggests against the use of glucocorticoids. (Conditional recommendation, Low certainty of evidence)

*Severe illness is defined as patients with SpO_2 ≤94% on room air, and those who require supplemental oxygen, mechanical ventilation, or ECMO.

Adarsh B, Morgan R, Shumaker A, et al. Infectious Diseases Society of America Guidelines on the Treatment and Management of Patients with COVID-19. 2020, April 11. https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/

RECOVERY TRIAL

Randomised Evaluation of COVID-19 Therapy

BACKGROUND

RECOVERY
Randomised Evaluation of COVID-19 Therapy

Randomised Evaluation of COVID-19 Therapy

RECOVERY Trials

The RECOVERY Collaborative Group. Dexamethasone in hospitalized patients with Covid-19 — preliminary report. *N Engl J Med* 2020:1–11. DOI: https://doi.org/10.1056/NEJMoa2021436.

STUDY HYPOTHESIS & ADAPTIVE TRIAL DESIGN

RECOVERY
Randomised Evaluation of COVID-19 Therapy

- **Current study hypothesis as of 21/08/2020:**
  - *Does treatment with either lopinavir + ritonavir, hydroxychloroquine, corticosteroids, azithromycin, intravenous immunoglobulin (children only), convalescent plasma or tocilizumab prevent death in hospitalised patients with COVID-19?*
- Previous study hypothesis from **27/05/2020 to 21/08/2020:**
  - *Does treatment with either lopinavir + ritonavir, hydroxychloroquine, corticosteroids, azithromycin, convalescent plasma or tocilizumab prevent death in hospitalised patients with COVID-19?*
- Previous study hypothesis from **07/05/2020 to 27/05/2020:**
  - *Does treatment with either lopinavir + ritonavir, hydroxychloroquine, corticosteroids, azithromycin or tocilizumab prevent death in hospitalised patients with COVID-19?*
- Original study hypothesis:
  - *Does treatment with either lopinavir + ritonavir, inhaled interferon β1a, hydroxychloroquine or low-dose corticosteroids prevent death in hospitalised patients with COVID-19?*

STUDY OVERVIEW

Patient/population:	Hospitalized with COVID-19
Intervention:	Effects of dexamethasone (and other medications, part of platform trial)
Comparison:	Usual care
Outcome:	All-cause mortality at 28 days

METHOD: PATIENT SELECTION

INCLUSION CRITERIA	EXCLUSION CRITERIA
Admitted to hospital	Condition that might put the patient at substantial risk if they participated* *In the opinion of the attending physician
Proven or Suspected COVID-19	Dexamethasone unavailable
Pregnant women May 9, 2020: Children < 8 years	Dexamethasone definitely indicated or contraindicated

The RECOVERY Collaborative Group. Dexamethasone in hospitalized patients with Covid-19 — preliminary report. *N Engl J Med* 2020:1–11. DOI: https://doi.org/10.1056/NEJMoa2021436.

METHODS: STUDY DESIGN

RANDOMIZATION

- Web-based case-report form including:
  - Demographic data
  - Level of respiratory support
  - Major comorbidities
  - Suitability of trial treatment for the patient
  - Treatment availability
- Randomization performed using web-based system with concealment of the trial-group assignment in a 2:1 ratio:
  - Usual standard of care alone
  - Usual standard of care **plus dexamethasone 6mg PO or IV (up to 10 days or until discharge)**
  - *Other suitable and available treatments that were being evaluated in the trial*
- There was no blinding to the allocated treatment of clinicians, patients, or trial staff
  - All were aware of assigned group

The RECOVERY Collaborative Group. Dexamethasone in hospitalized patients with Covid-19 — preliminary report. *N Engl J Med* 2020:1–11. DOI: https://doi.org/10.1056/NEJMoa2021436.

METHODS: STUDY DESIGN

FOLLOW-UP

- Single online form completed at 28 days, discharge or death
  - Collection of the following information:
    - Adherence to treatment
    - Receipt of other trial treatments
    - Hospital length of stay
    - Respiratory support
      - Type
      - Duration
    - Renal support
    - Vital status (including cause of death)
- Other data collected:
  - Routine health care and registry data
    - Vital status (with date and cause of death)
    - Discharge from the hospital
    - Respiratory and renal support therapy

The RECOVERY Collaborative Group. Dexamethasone in hospitalized patients with Covid-19 — preliminary report. *N Engl J Med* 2020:1–11. DOI: https://doi.org/10.1056/NEJMoa2021436.

METHODS: ENDPOINTS

- Primary
  - All-cause mortality at 28 days after randomization
    - Further analyses were specified at 6 months
- Secondary
  - Time to hospital discharge
  - In patients not receiving mechanical ventilation at time of randomization: mechanical ventilation, ECMO, or death
- Other prespecified outcomes
  - Cause-specific mortality
  - Duration of ventilation
  - Need for renal replacement
  - Major cardiac arrhythmias

The RECOVERY Collaborative Group. Dexamethasone in hospitalized patients with Covid-19 — preliminary report. *N Engl J Med* 2020:1–11. DOI: https://doi.org/10.1056/NEJMoa2021436.

METHODS: STUDY DESIGN

SAMPLE SIZE/POWER CALCULATION

- Could not be estimated at the start of the pandemic
- Trial steering committee determined that if 28-day mortality was 20%, then 2000 patients in the dexamethasone group and 4000 in the usual care group would provide a power of at least 90% at a two-sided P value of 0.01 to detect an absolute risk reduction of 4%
  - Trial steering committee was unaware of the results of trial comparisons
- Enrolment was closed when 2000 patients were recruited to the dexamethasone arm on June 8, 2020

The RECOVERY Collaborative Group. Dexamethasone in hospitalized patients with Covid-19 — preliminary report. *N Engl J Med* 2020:1–11. DOI: https://doi.org/10.1056/NEJMoa2021436.

METHODS: STATISTICAL ANALYSIS

- For primary outcome:
  - Hazard ratio from Cox regression was used to estimate the mortality rate ratio
  - Kaplan-Meier survival curves were constructed to show cumulative mortality over the 28-day period
  - Prespecified analyses performed in five subgroups: age, sex, level of respiratory support, days since symptom onset and predicted 28-day mortality risk

- For secondary outcomes:
  - Cox regression used to analyze the secondary outcome of hospital discharge within 28 days, with censoring of data on day 29 for patients who had died during hospitalization
  - For composite outcome of invasive mechanical ventilation or death within 28 days, log-binomial regression model used to estimate risk ratio

- P-values were all two-sided
- All analyses performed according to the intention-to-treat principle

The RECOVERY Collaborative Group. Dexamethasone in hospitalized patients with Covid-19 — preliminary report. *N Engl J Med* 2020:1–11. DOI: https://doi.org/10.1056/NEJMoa2021436.

RECOVERY TRIAL | RESULTS

RESULTS

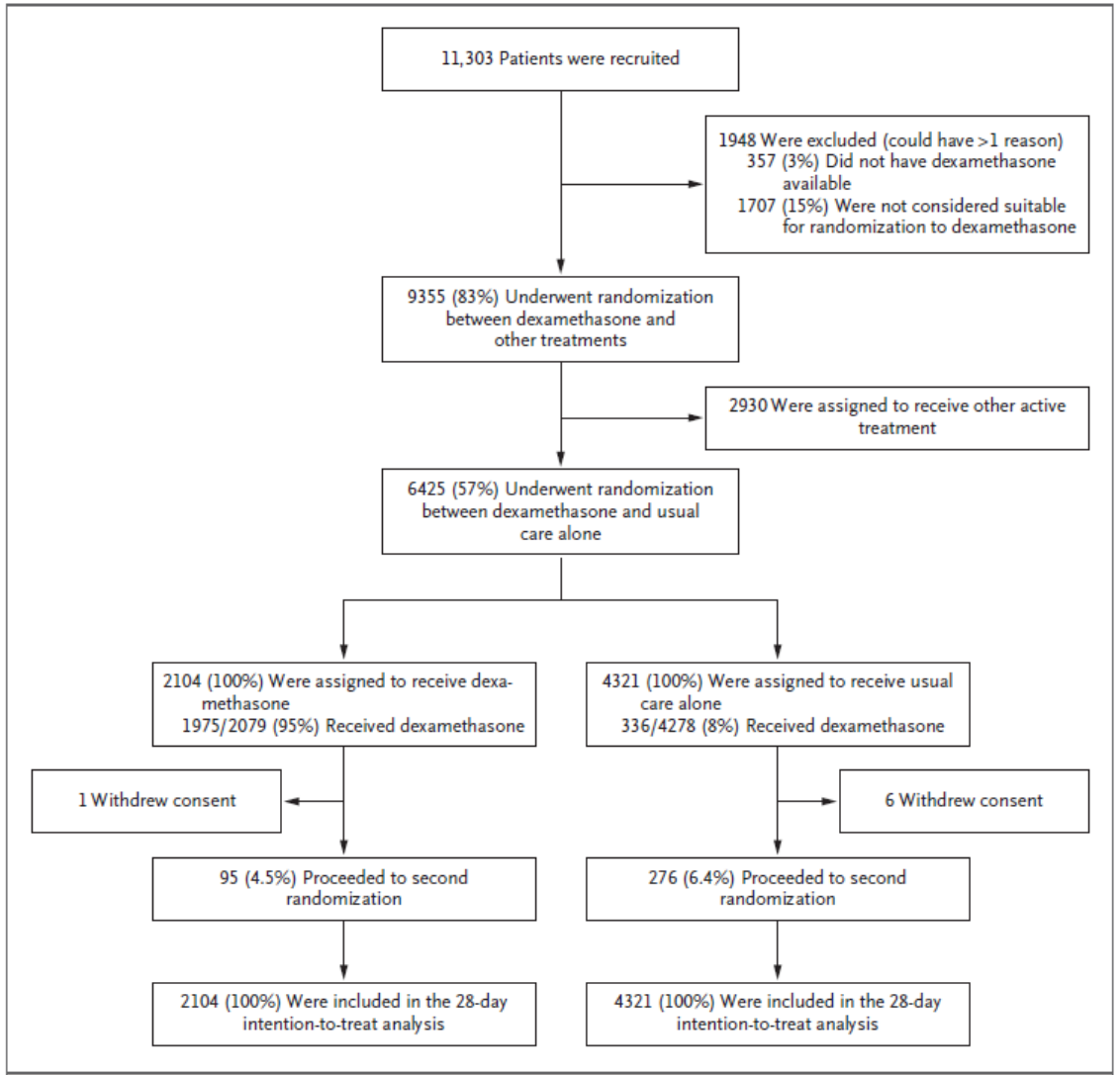


Figure 1. Enrollment, Randomization, and Inclusion in the Primary Analysis.

At the time of this analysis, completed follow-up forms were available for 2079 of 2104 patients (98.8%) in the dexamethasone group and 4278 of 4321 patients (99.0%) in the usual care group. The subgroup of patients who later underwent a second randomization to tocilizumab versus usual care in the RECOVERY trial included 95 of 2104 patients (4.5%) in the dexamethasone group and 276 of 4321 patients (6.4%) in the usual care group. In addition, 13 patients were randomly assigned to receive either convalescent plasma or usual care alone.

The RECOVERY Collaborative Group. Dexamethasone in hospitalized patients with Covid-19 — preliminary report. *N Engl J Med* 2020:1–11. DOI: https://doi.org/10.1056/NEJMoa2021436.

RESULTS

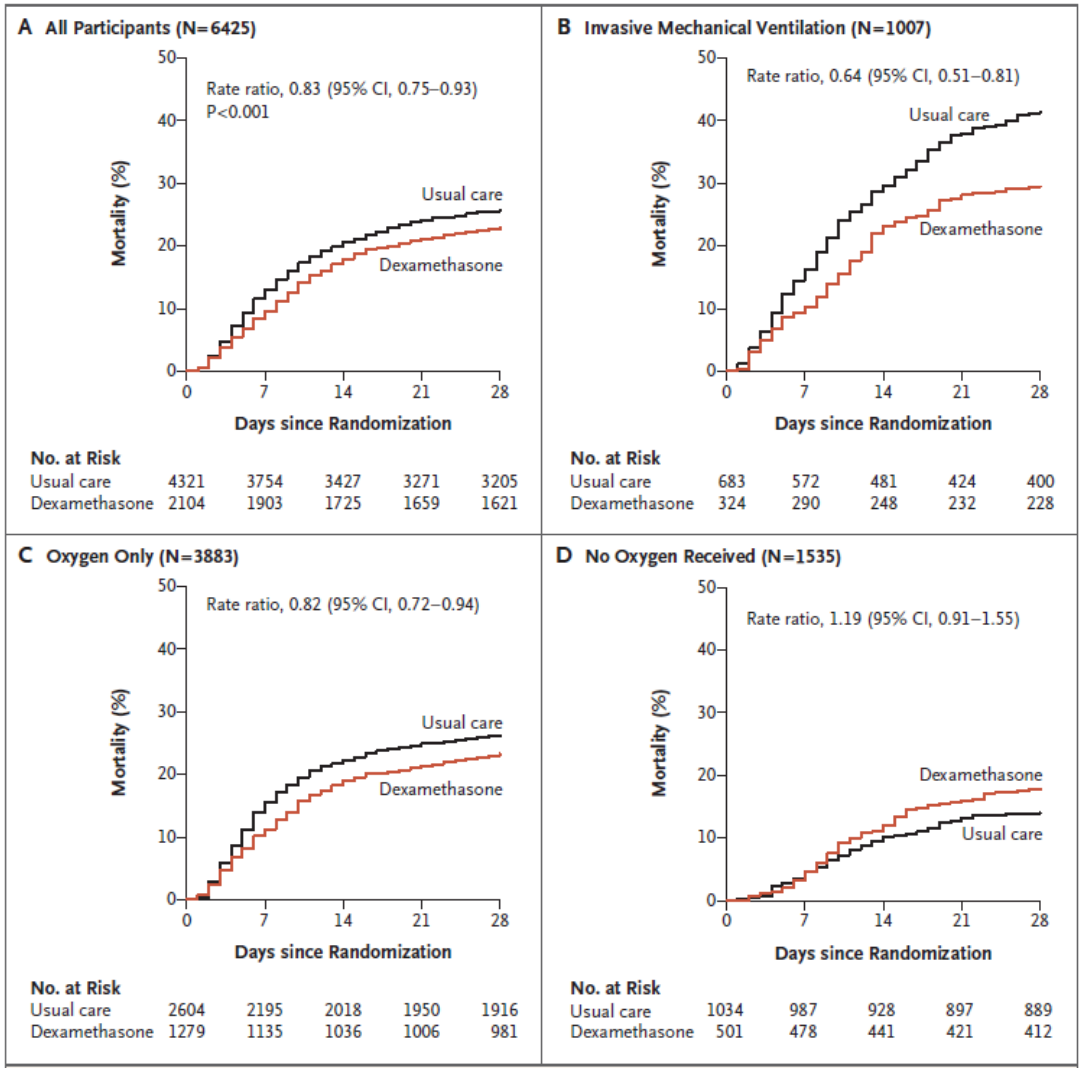
Table 1. Characteristics of the Patients at Baseline, According to Treatment Assignment and Level of Respiratory Support.*

Characteristic	Treatment Assignment		Respiratory Support Received at Randomization		
	Dexamethasone (N=2104)	Usual Care (N=4321)	No Receipt of Oxygen (N=1535)	Oxygen Only (N=3883)	Invasive Mechanical Ventilation (N=1007)
Age†					
Mean — yr	66.9±15.4	65.8±15.8	69.4±17.5	66.7±15.3	59.1±11.4
Distribution — no. (%)					
<70 yr	1141 (54)	2504 (58)	659 (43)	2148 (55)	838 (83)
70 to 79 yr	469 (22)	859 (20)	338 (22)	837 (22)	153 (15)
≥80 yr	494 (23)	958 (22)	538 (35)	898 (23)	16 (2)
Sex — no. (%)					
Male	1338 (64)	2749 (64)	891 (58)	2462 (63)	734 (73)
Female‡	766 (36)	1572 (36)	644 (42)	1421 (37)	273 (27)
Median no. of days since symptom onset (IQR)§	8 (5–13)	9 (5–13)	6 (3–10)	9 (5–12)	13 (8–18)
Median no. of days since hospitalization (IQR)	2 (1–5)	2 (1–5)	2 (1–6)	2 (1–4)	5 (3–9)
Respiratory support received — no. (%)					
No oxygen	501 (24)	1034 (24)	1535 (100)	NA	NA
Oxygen only	1279 (61)	2604 (60)	NA	3883 (100)	NA
Invasive mechanical ventilation	324 (15)	683 (16)	NA	NA	1007 (100)
Previous coexisting disease					
Any	1174 (56)	2417 (56)	911 (59)	2175 (56)	505 (50)
Diabetes	521 (25)	1025 (24)	342 (22)	950 (24)	254 (25)
Heart disease	586 (28)	1171 (27)	519 (34)	1074 (28)	164 (16)
Chronic lung disease	415 (20)	931 (22)	351 (23)	883 (23)	112 (11)
Tuberculosis	6 (<1)	19 (<1)	8 (1)	11 (<1)	6 (1)
HIV infection	12 (1)	20 (<1)	5 (<1)	21 (1)	6 (1)
Severe liver disease¶	37 (2)	82 (2)	32 (2)	72 (2)	15 (1)
Severe kidney impairment‖	166 (8)	358 (8)	119 (8)	253 (7)	152 (15)
SARS-CoV-2 test result					
Positive	1850 (88)	3848 (89)	1333 (87)	3416 (88)	949 (94)
Negative	247 (12)	453 (10)	193 (13)	452 (12)	55 (5)
Test result not yet known	7 (<1)	20 (<1)	9 (1)	15 (<1)	3 (<1)

The RECOVERY Collaborative Group. Dexamethasone in hospitalized patients with Covid-19 — preliminary report. *N Engl J Med* 2020:1–11. DOI: https://doi.org/10.1056/NEJMoa2021436.

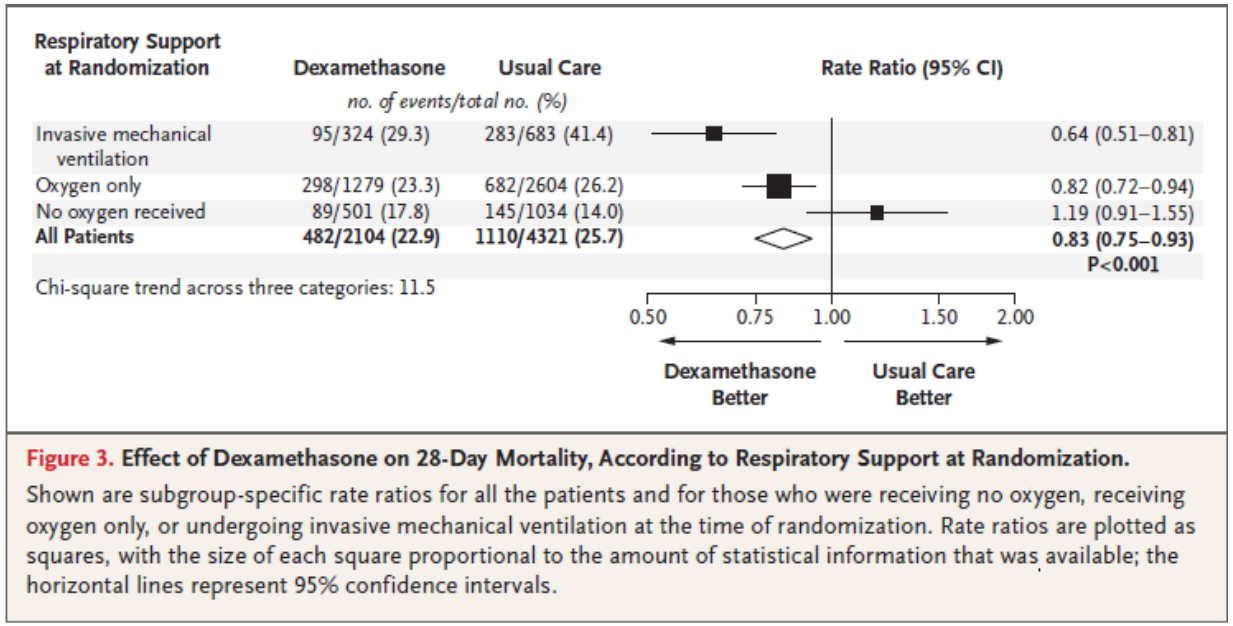
RESULTS

- Mortality at 28 days was significantly lower in the dexamethasone group than in the usual care group (rate ratio, 0.83; 95% CI, 0.75 – 0.93; P<0.001)
  - In patients receiving invasive mechanical ventilation, incidence of death was lower in dexamethasone group than in the usual care group (29.3% vs. 41.4%; rate ratio, 0.64; 95% CI, 0.51 – 0.81)
  - In patients receiving oxygen only, incidence of death was lower in dexamethasone group than in the usual care group (23.3% vs 26.2%; rate ratio, 0.82; 95% CI, 0.72 – 0.94)
  - No clear effect of dexamethasone on patients who were not receiving any respiratory support (trend towards harm)



The RECOVERY Collaborative Group. Dexamethasone in hospitalized patients with Covid-19 — preliminary report. *N Engl J Med* 2020:1–11. DOI: https://doi.org/10.1056/NEJMoa2021436.

RESULTS



Respiratory Support at Randomization	Dexamethasone	Usual Care	Rate Ratio (95% CI)
	no. of events/total no. (%)		
Invasive mechanical ventilation	95/324 (29.3)	283/683 (41.4)	0.64 (0.51–0.81)
Oxygen only	298/1279 (23.3)	682/2604 (26.2)	0.82 (0.72–0.94)
No oxygen received	89/501 (17.8)	145/1034 (14.0)	1.19 (0.91–1.55)
All Patients	**482/2104 (22.9)**	**1110/4321 (25.7)**	**0.83 (0.75–0.93)**
			P<0.001

Chi-square trend across three categories: 11.5

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.

- Prespecified analyses according to level of respiratory support at randomization, *trend* showing greatest absolute and proportional benefit among patients who were receiving invasive mechanical ventilation ($X^2 = 11.5$)

The RECOVERY Collaborative Group. Dexamethasone in hospitalized patients with Covid-19 — preliminary report. *N Engl J Med* 2020:1–11. DOI: https://doi.org/10.1056/NEJMoa2021436.

RESULTS

Table 2. Primary and Secondary Outcomes.

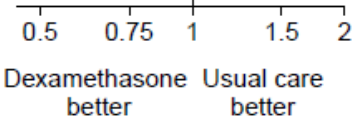
Outcome	Dexamethasone (N=2104)	Usual Care (N=4321)	Rate or Risk Ratio (95% CI)*
	no./total no. of patients (%)		
Primary outcome			
Mortality at 28 days	482/2104 (22.9)	1110/4321 (25.7)	0.83 (0.75–0.93)
Secondary outcomes			
Discharged from hospital within 28 days	1413/2104 (67.2)	2745/4321 (63.5)	1.10 (1.03–1.17)
Invasive mechanical ventilation or death†	456/1780 (25.6)	994/3638 (27.3)	0.92 (0.84–1.01)
Invasive mechanical ventilation	102/1780 (5.7)	285/3638 (7.8)	0.77 (0.62–0.95)
Death	387/1780 (21.7)	827/3638 (22.7)	0.93 (0.84–1.03)

The RECOVERY Collaborative Group. Dexamethasone in hospitalized patients with Covid-19 — preliminary report. *N Engl J Med* 2020:1–11. DOI: https://doi.org/10.1056/NEJMoa2021436.

RESULTS

Figure S1: Effect of allocation to dexamethasone on 28−day mortality by other pre−specified baseline characteristics

Subgroup	Dexamethasone	Usual care	RR (95% CI)	Het/trend
Age, years				
<70	129/1141 (11.3%)	428/2504 (17.1%)	0.64 (0.53−0.78)	χ^2_1=4.9
≥70 <80	155/469 (33.0%)	271/859 (31.5%)	1.03 (0.84−1.25)	
≥80	198/494 (40.1%)	411/958 (42.9%)	0.89 (0.75−1.05)	
Sex				
Men	331/1338 (24.7%)	782/2749 (28.4%)	0.80 (0.71−0.91)	χ^2_1=0.9
Women	151/766 (19.7%)	328/1572 (20.9%)	0.90 (0.74−1.09)	
Days since symptom onset				
≤7	269/916 (29.4%)	500/1801 (27.8%)	1.01 (0.87−1.17)	χ^2_1=12.3
>7	212/1184 (17.9%)	604/2507 (24.1%)	0.69 (0.59−0.80)	
Baseline risk				
<30%	150/1268 (11.8%)	377/2682 (14.1%)	0.83 (0.69−1.00)	χ^2_1=0.4
≥30% <45%	146/464 (31.5%)	334/878 (38.0%)	0.77 (0.63−0.94)	
≥45%	186/372 (50.0%)	399/761 (52.4%)	0.90 (0.76−1.07)	
All participants	**482/2104 (22.9%)**	**1110/4321 (25.7%)**	**0.83 (0.75−0.93) p<0.001**	



The RECOVERY Collaborative Group. Dexamethasone in hospitalized patients with Covid-19 — preliminary report. *N Engl J Med* 2020:1–11. DOI: https://doi.org/10.1056/NEJMoa2021436.

RESULTS: PRIMARY OUTCOMES

- Age-adjusted absolute reductions in 28-day mortality associated with the use of dexamethasone were:
  - **12.3 percentage points (95% CI, 6.3 – 17.6)** among patients who were receiving mechanical ventilation
  - **4.2 percentage points (95% CI, 1.4 – 6.7)** among those receiving oxygen only
- Greater mortality benefit in response to treatment with dexamethasone seen in patients with longer duration of symptoms

The RECOVERY Collaborative Group. Dexamethasone in hospitalized patients with Covid-19 — preliminary report. *N Engl J Med* 2020:1–11. DOI: https://doi.org/10.1056/NEJMoa2021436.

RESULTS: SECONDARY OUTCOMES

- Patients in the dexamethasone group had a shorter duration of hospitalization compared to usual care group (median, 12 days vs. 13 days)
- Greater probability of discharge alive within 28 days (rate ratio 1.10; 95% CI, 1.03 – 1.17)
  - Effect greater among patients who were receiving invasive mechanical ventilation at randomization
- In patients not receiving IMV at randomization, patients who progressed to prespecified composite secondary outcome (IMV or death) was lower in the dexamethasone group than in the usual care group (risk ratio, 0.92; 95% CI, 0.84 – 1.01)
  - Effect greater among patients who were receiving oxygen at randomization
- Risk of progression to invasive mechanical ventilation was lower in the dexamethasone group than in the usual care group (risk ratio, 0.77; 95% CI, 0.62 – 0.95)
- Ongoing analyses regarding cause-specific mortality, the need for renal replacement, duration of ventilation

The RECOVERY Collaborative Group. Dexamethasone in hospitalized patients with Covid-19 — preliminary report. *N Engl J Med* 2020:1–11. DOI: https://doi.org/10.1056/NEJMoa2021436.

SUMMARY OF RESULTS

- Reduction in 28-day mortality with the use of dexamethasone at a dose of 6 mg/day for 10 days in patients with COVID-19 (NNT = 36)
  - Effect most significant in mechanically ventilated patients (NNT = 8)
  - Effect also seen in patients requiring oxygen therapy (NNT = 35)

- No evidence of benefit of dexamethasone in patients who were not receiving respiratory support at randomization
  - May be harmful

- Reduction in 28-day mortality in patients treated more than 7 days after symptom onset
  - They were more likely to be receiving invasive mechanical ventilation at time of randomization
  - Receipt of dexamethasone was associated with a reduction in 28-day mortality among those with symptoms for more than 7 days but not among those with a more recent symptom onset

RECOVERY TRIAL | APPRAISAL

ARE THE RESULTS VALID?

- Was the assignment of patients to treatments randomised?
  - Yes, patients were assigned 2:1 to receive dexamethasone and usual care, or usual care alone (or one of the other suitable treatments in the trial) using Web-based system with concealment

- Were the groups similar at the start of the trial?
  - Yes, they were similar in baseline characteristics *except* age, as the mean age was 1.1 years older in the dexamethasone group than those in the usual care group. This was accounted for by adjusting for the baseline age in three categories (<70 years, 70-79 years, and ≥80 years)

ARE THE RESULTS VALID?

- Aside from allocated treatment, were groups treated equally?
  - Yes, both groups received usual care and any adjunctive treatments were given at comparable rates in both groups

- Were all patients who entered the trial accounted for? And were they analysed in the groups to which they were randomised?
  - Yes, 99% of patients were followed to 28 days – 7 withdrew consent but included in the intention-to-treat analysis.

- Were measures objective or were the patients and clinicians kept "blind" to which treatment was being received?
  - Randomization was done with allocation concealment, but clinicians, staff, and trial staff were all unblinded. Outcome was objective (mortality at 28 days)

WHAT WERE THE RESULTS?

- How large was the treatment effect?
  - 28 day mortality:
    - ARR of 2.8% in all patients (NNT 36)
    - ARR of 12% in the ventilated group (NNT 8)
    - ARR of 2.9% in the oxygen only group (NNT 35)

CAN THE RESULTS BE APPLIED TO MY PATIENTS?

- Were the study patients similar to my patients?
  - Yes, 64% male (36% female), >40% of patients > age of 70
  - Comorbid (chronic lung disease, CV disease, diabetes)

- Is the treatment feasible in my setting?
  - Yes, dexamethasone readily available
  - Objective measures are available to determine if patients require supplemental oxygen or ventilatory support

- Will the potential benefits of treatment outweigh the potential harms of treatment for my patient?
  - Yes, mortality benefit likely outweighs known potential adverse effect of steroid use (e.g. hyperglycemia, increased infection risk, psychiatric effects, avascular necrosis, medication interactions)
  - Short course of dexamethasone may decrease rates of adverse effects
  - Cost of dexamethasone is minimal

STRENGTHS

- Large, pragmatic, randomized controlled trial conducted in setting of global pandemic
  - Preliminary results were announced on June 16, only approximately 3 months after enrolment of first patients
  - 15% of patients hospitalized with COVID-19 in the UK were enrolled
- Use of adaptive platform trial design
- Allocation concealment, intention-to-treat analysis
- Near complete follow-up
- 95% of patients randomized to dexamethasone arm received dexamethasone
- Important, objective and clinically meaningful outcomes

LIMITATIONS

- Randomized, but unblinded
- "Usual care" for COVID-19 was not standardized during the time the study was carried out (March 19 – June 8, 2020)
- Study participants who required oxygen (60%) but not mechanical ventilation are a heterogeneous group of patients with respect to their severity of illness, oxygen requirements
  - No standardized criteria for oxygen supplementation
- Age distribution of participants differed by respiratory status at randomization
  - Those who received mechanical ventilation were more likely to be aged <70 years
  - Survival benefit of dexamethasone for mechanically ventilated patients aged >80 years is unknown

LIMITATIONS

- Mortality rates differ by country, impact of treatment may not be as robust
  - For example, in a retrospective case study of 117 patients admitted to the ICU in Vancouver (February 21 to April 14, 2020), a total of 18 (15.4%) of patients had died
- Hospital practice tendencies (e.g. choice of patients for mechanical ventilation or oxygen supplementation) may have influenced dexamethasone effects
- Limited results in this preliminary study
  - Secondary endpoints
  - Potential adverse events
  - Subgroup analysis

Mitra AR, Fergusson NA, Lloyd-Smith E, et al. Baseline Characteristics and Outcomes of patients with COVID-19 admitted to Intensive Care Units in Vancouver, Canada: a case series. CMAJ June 29, 2020 192 (26) E694-E701; DOI: https://doi.org/10.1503/cmaj.200794

FUTURE DIRECTIONS

Updates to WHO, CCM and other guidelines?

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

An mRNA Vaccine against SARS-CoV-2 — Preliminary Report

nature

https://doi.org/10.1038/s41586-02

Accelerated Article Preview

Phase 1/2 study of COVID-19 RNA vaccine BNT162b1 in adults

cmaj

BEST EVIDENCE • BEST PRACTICE • BEST HEALTH

How Canada can better embed randomized trials into clinical care

Srinivas Murthy, Robert A. Fowler and Andreas Laupacis

CMAJ August 10, 2020 192 (32) E928-E929; DOI: https://doi.org/10.1503/cmaj.201764

REFERENCES

Adarsh B, Morgan R, Shumaker A, et al. Infectious Diseases Society of America Guidelines on the Treatment and Management of Patients with COVID-19. 2020, April 11. https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/

Alhazzani W, Møller MH, Arabi YM, et al. Surviving Sepsis Campaign: guidelines on the management of critically ill adults with Coronavirus Disease 2019 (COVID-19). *Intensive Care Med*. 2020;46(5):854-887

Auwaerter, Paul G. Coronavirus COVID-19 (SARS-CoV-2). *Johns Hopkins ABX Guide*, The Johns Hopkins University, 2020. *Johns Hopkins Guide*, www.hopkinsguides.com/hopkins/view/Johns_Hopkins_ABX_Guide/540747/all/Coronavirus_COVID_19__SARS_CoV_2

Beigel JH, Tomashek KM, Dodd LE, et al. Remdesivir for the treatment of Covid-19 — preliminary report. *N Engl J Med* 2020. DOI: 10.1056/NEJMoa2007764.

Cao B, Wang Y, Wen D, et al. A trial of lopinavir–ritonavir in adults hospitalized with severe Covid-19. *N Engl J Med* 2020;382:1787-1799

Corral L, Bahamonde A, Arnaiz delas Revillas F, et al. GLUCOCOVID: A controlled trial of methylprednisolone in adults hospitalized with COVID-19 pneumonia. *medRxiv* 2020. DOI: https://doi.org/10.1101/2020.06.17.20133579

Huang, Chaolin et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *The Lancet* 2020. 395(10223):497-506

Mitra AR, Fergusson NA, Lloyd-Smith E, et al. Baseline Characteristics and Outcomes of patients with COVID-19 admitted to Intensive Care Units in Vancouver, Canada: a case series. *CMAJ* June 29, 2020 192 (26) E694-E701; DOI: https://doi.org/10.1503/cmaj.200794

National Institutes of Health. Coronavirus Disease 2019 (COVID-19) Treatment Guidelines. 2020, September 1. https://www.covid19treatmentguidelines.nih.gov/immune-based-therapy/immunomodulators/corticosteroids/

Shi Y, Wang Y, Shao C, *et al*. COVID-19 infection: the perspectives on immune responses. *Cell Death Differ* 2020. 27:1451–1454.

The RECOVERY Collaborative Group. Dexamethasone in hospitalized patients with Covid-19 — preliminary report. *N Engl J Med* 2020:1–11. DOI: https://doi.org/10.1056/NEJMoa2021436

Villar J, Ferrando C, Martinez D, et al. Dexamethasone treatment for the acute respiratory distress syndrome: a multicentre, randomised controlled trial. *Lancet Respir Med* 2020; 8:267-76

World Health Organization, Clinical management of severe acute respiratory infection when COVID-19 disease is suspected. 2020, May 27. https://www.who.int/publications/i/item/clinical-management-of-severe-acute-respiratory-infection-when-novel-coronavirus-(ncov)-infection-is-suspected

Zhou F, Yu T, Du R, *et al*. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study *Lancet* 2020. 395:1054-1062

Zhu et al. A Novel Coronavirus from Patients with Pneumonia in China, 2019. *N Engl J Med* 2020. 382(8):727-733