Corticosteroids

A Review of Pertinent Drug Information for SARS-CoV-2

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Data as of June 24, 2020

Objectives

- Discuss the mechanism of action and safety of corticosteroids
- Explain the potential benefit and harm of using corticosteroids for COVID-19
- Evaluate relevant literature for role of corticosteroids in COVID-19

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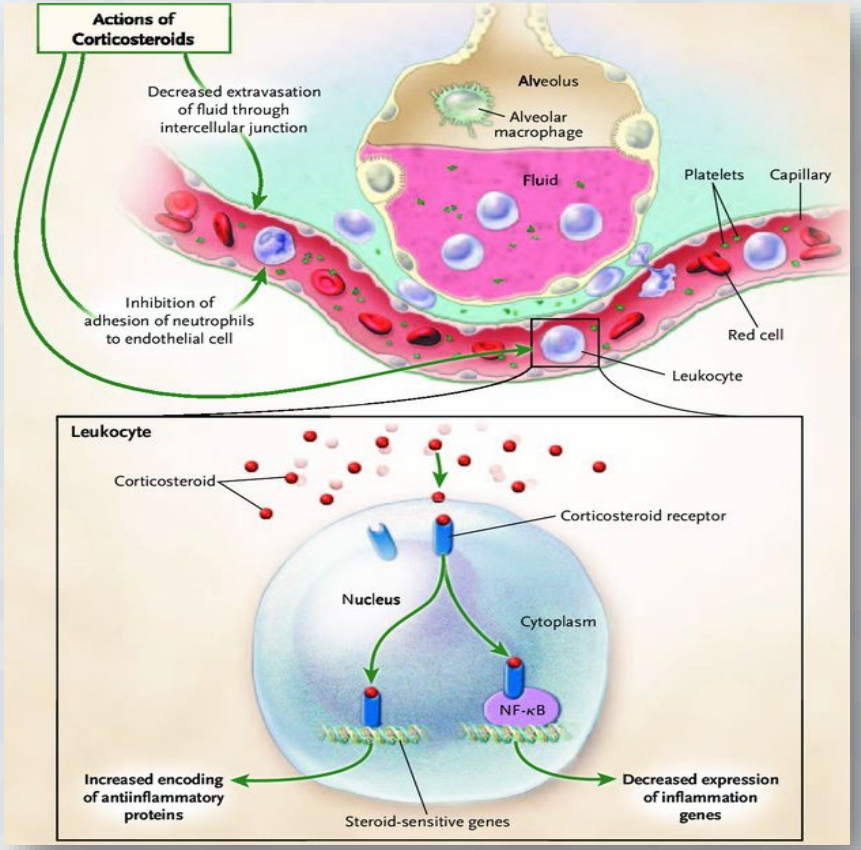
Mechanism of Action

- Anti-inflammatory/Immunomodulatory
  - Effects on gene expression
    - Glucocorticoid receptors (GR) binding to glucocorticoid-responsive elements
    - GR interactions with transcription factors (activator protein 1 & NF-kβ)
  - Effects of GR on 2nd-messenger cascades



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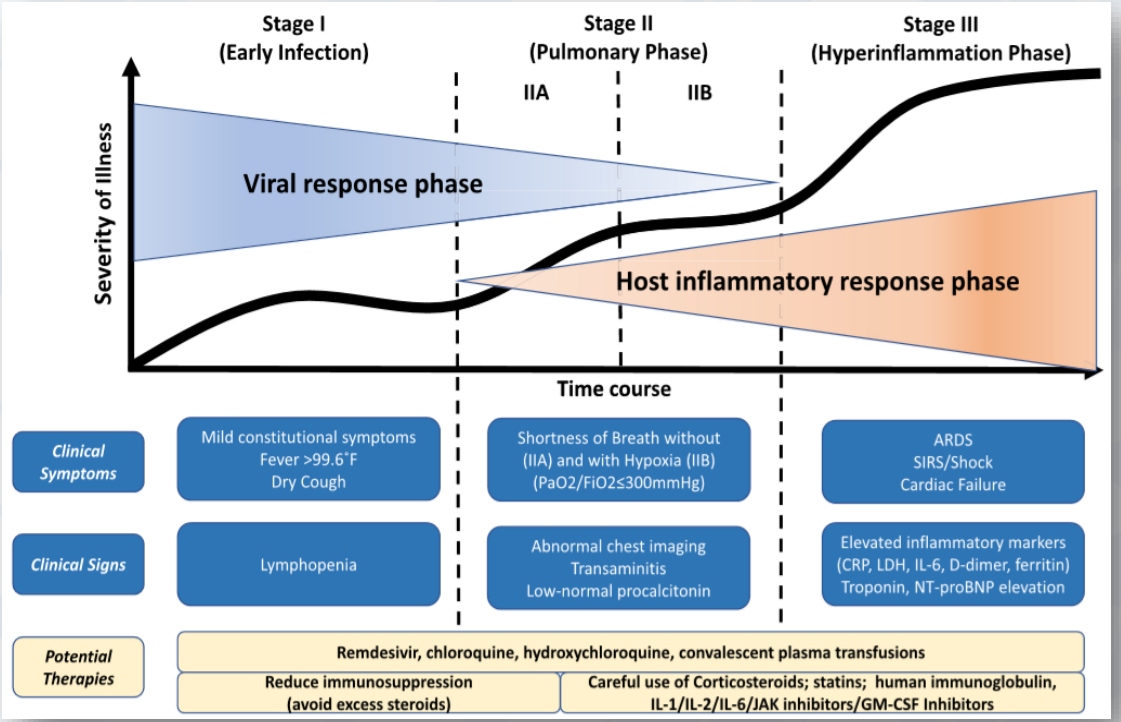
Alijotas-Reig J, et al. Autoimmun Rev. May 2020. https://www.sciencedirect.com/science/article/abs/pii/S1568997220301312?via%3Dihub

Suter PM. NEJM. 2006;354:1739-42. https://www.nejm.org/doi/full/10.1056/NEJMe068033?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%3dpubmed

Stages of COVID-19 Disease Progression

- **Stage I**: might not be beneficial and could even enhance viral replication?
- **Stage II**: potentially in case of worsening hypoxia?
- **Stage III**: greatest benefit?



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Siddiqi HK, et al. J Heart Lung Transplant. 2020;39:405-7. https://linkinghub.elsevier.com/retrieve/pii/S1053-2498(20)31473-X

Dosing

SCCM Guidelines

- Acute Respiratory Distress Syndrome (ARDS)
  - Early ARDS (up to day 7 of onset): 1 mg/kg/day (methylprednisolone or equivalent doses)
  - Late ARDS (after day 6 of onset): 2 mg/kg/day
  - Follow treatment with slow taper over 6-14 days
- Refractory Septic Shock
  - Low-dose (hydrocortisone IV 200 mg/day)

Recovery Trial

- Dexamethasone 6 mg/day X 10 days

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Alhazzani W, et al. CritCare Med 2020 Jun;48(6):e440-e469.
Horby P, et al. https://www.recoverytrial.net/news/low-cost-dexamethasone-reduces-death-by-up-to-one-third-in-hospitalised-patients-with-severe-respiratory-complications-of-covid-19

Adverse Drug Reactions

Infections	Hyperglycemia	Hypernatremia Hypokalemia	Fluid retention
Leukocytosis	Neuropsychiatric	Muscular	Gastrointestinal

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Solu-Medrol Package Insert. Last revised July 24, 2018. http://labeling.pfizer.com/ShowLabeling.aspx?id=873
Adverse Reactions. Lexicomp. Wolters Kluwer Health Inc. Riverwoods, Il. Available at: http://online.lexi.com. Accessed May 10, 2020.

Drug-Drug Interactions

- Additive
- Metabolic
  - CYP450 3A4 inhibitors (including protease inhibitors) and inducers

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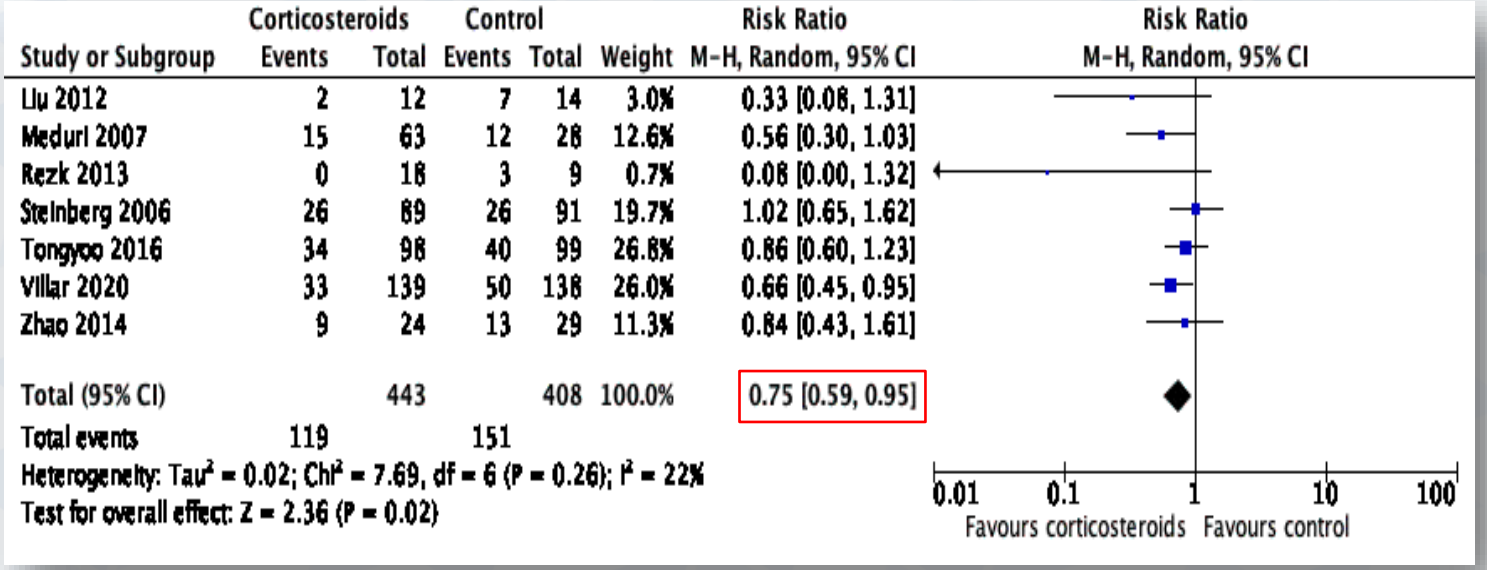
Solu-Medrol Package Insert. Last revised July 24, 2018. http://labeling.pfizer.com/ShowLabeling.aspx?id=873
Drug Interactions. Lexicomp. Wolters Kluwer Health Inc. Riverwoods, Il. Available at: http://online.lexi.com. Accessed May 10, 2020.

Mortality in ARDS: Meta-analysis of RCTs



Study or Subgroup	Corticosteroids Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Liu 2012	2	12	7	14	3.0%	0.33 [0.08, 1.31]
Meduri 2007	15	63	12	28	12.6%	0.56 [0.30, 1.03]
Rezk 2013	0	18	3	9	0.7%	0.08 [0.00, 1.32]
Steinberg 2006	26	89	26	91	19.7%	1.02 [0.65, 1.62]
Tongyoo 2016	34	98	40	99	26.8%	0.86 [0.60, 1.23]
Villar 2020	33	139	50	138	26.0%	0.66 [0.45, 0.95]
Zhao 2014	9	24	13	29	11.3%	0.84 [0.43, 1.61]
Total (95% CI)		443		408	100.0%	0.75 [0.59, 0.95]
Total events	119		151			

Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 7.69$, $df = 6$ ($P = 0.26$); $I^2 = 22\%$

Test for overall effect: $Z = 2.36$ ($P = 0.02$)

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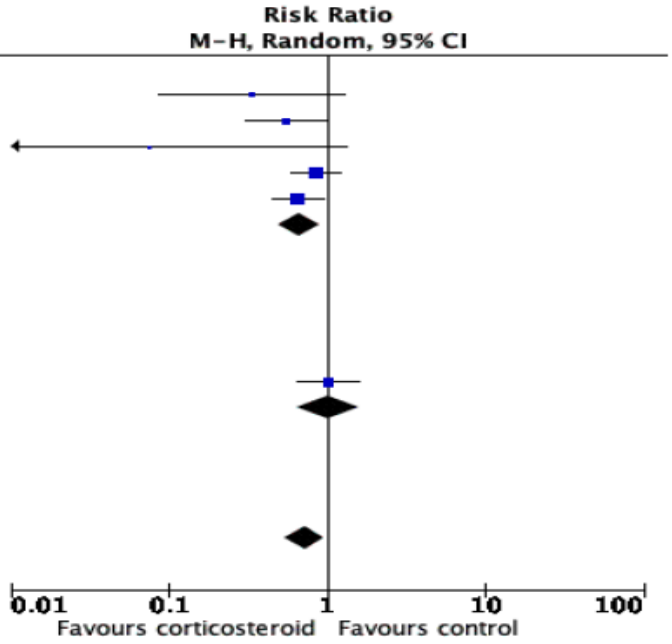
Bhimraj A, et al. Clin Infect Dis. April 27, 2020. [epubahead of print] doi:10.1093/cid/ciaa478

Mortality in ARDS: Meta-analysis of RCTs

Study or Subgroup	Corticosteroids Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
1.8.1 Timing of corticosteroid therapy < 7 days						
Liu 2012	2	12	7	14	4.1%	0.33 [0.08, 1.31]
Meduri 2007	15	63	12	28	15.4%	0.56 [0.30, 1.03]
Rezk 2013	0	18	3	9	1.0%	0.08 [0.00, 1.32]
Tongyoo 2016	34	98	40	99	28.8%	0.86 [0.60, 1.23]
Villar 2020	33	139	50	138	28.1%	0.66 [0.45, 0.95]
Subtotal (95% CI)		330		288	77.4%	0.66 [0.49, 0.91]
Total events	84		112			
Heterogeneity: $Tau^2 = 0.03$; $Chi^2 = 5.42$, df = 4 (P = 0.25); $I^2 = 26\%$						
Test for overall effect: Z = 2.59 (P = 0.010)						
1.8.2 Timing of corticosteroid therapy > 7 days						
Steinberg 2006	26	89	26	91	22.6%	1.02 [0.65, 1.62]
Subtotal (95% CI)		89		91	22.6%	1.02 [0.65, 1.62]
Total events	26		26			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.10 (P = 0.92)						
Total (95% CI)		419		379	100.0%	0.73 [0.55, 0.97]
Total events	110		138			
Heterogeneity: $Tau^2 = 0.04$; $Chi^2 = 7.59$, df = 5 (P = 0.18); $I^2 = 34\%$						
Test for overall effect: Z = 2.18 (P = 0.03)						
Test for subgroup differences: $Chi^2 = 2.34$, df = 1 (P = 0.13), $I^2 = 57.2\%$						



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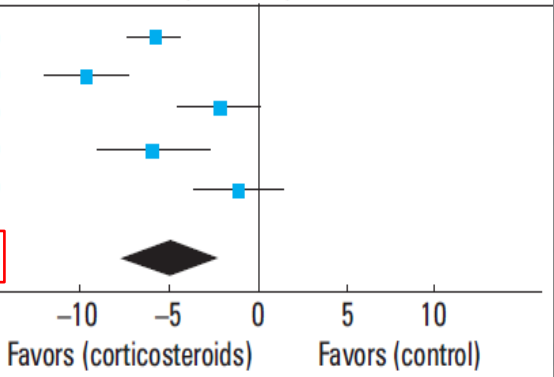
Mammen MJ, et al. Pol Arch Intern Med 2020; 130: 276-286. https://www.mp.pl/paim/issue/article/15239

Duration of MV in ARDS: Meta-analysis of RCTs

Study or subgroup	Corticosteroids Mean	SD	Total	Control Mean	SD	Total	Weight, %	Mean difference IV, Random, 95% CI
Meduri, 2007	5.25	1.46	63	11.1	3.9	28	21.9	–5.85 (–7.34, –4.36)
Rezk, 2013	10.6	4.4	18	20.3	1.9	9	20.1	–9.70 (–12.08, –7.32)
Tongyoo, 2016	11.8	7.8	98	13.9	9	99	20.1	–2.10 (–4.45, 0.25)
Villar, 2020	14.3	13.3	139	20.2	14	138	18.0	–5.90 (–9.12, –2.68)
Zhao, 2014	10.5	4.6	24	11.6	4.6	29	19.8	–1.10 (–3.59, 1.39)
Total (95% CI)			342			303	100	–4.93 (–7.81, –2.06)

Heterogeneity: $T^2 = 9.22$; $\chi^2 = 31.72$; $df = 4$ ($P < 0.00001$); $I^2 = 87\%$

Test for overall effect: $Z = 3.37$ ($P = 0.0008$)



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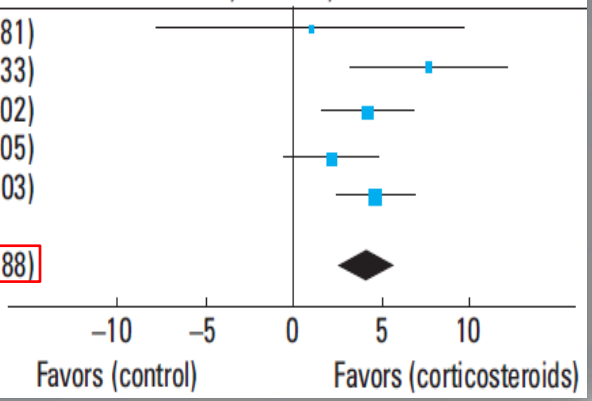
Mammen MJ, et al. Pol Arch Intern Med 2020; 130: 276-286. https://www.mp.pl/paim/issue/article/15239

Ventilator-Free Days in ARDS: Meta-analysis of RCTs

	Corticosteroids			Control				Mean difference
Study or subgroup	Mean	SD	Total	Mean	SD	Total	Weight, %	IV, Random, 95% CI
Liu, 2012	13.9	11.3	12	12.8	11.3	14	3.3	1.10 (–7.61, 9.81)
Meduri, 2007	16.5	10.1	63	8.7	10.2	28	11.1	7.80 (3.27, 12.33)
Steinberg, 2006	11.2	9.4	89	6.8	8.5	91	26.9	4.40 (1.78, 7.02)
Tongyoo, 2016	12	9.7	98	9.7	10	99	25.1	2.30 (–0.45, 5.05)
Villar, 2020	12.3	9.9	139	7.5	9	138	33.6	4.80 (2.57, 7.03)
Total (95% CI)			401			370	100	4.28 (2.67, 5.88)

Heterogeneity: $T^2 = 0.69$; $\chi^2 = 5.04$; $df = 4$ ($P = 0.28$); $I^2 = 21\%$

Test for overall effect: $Z = 5.23$ ($P < 0.00001$)



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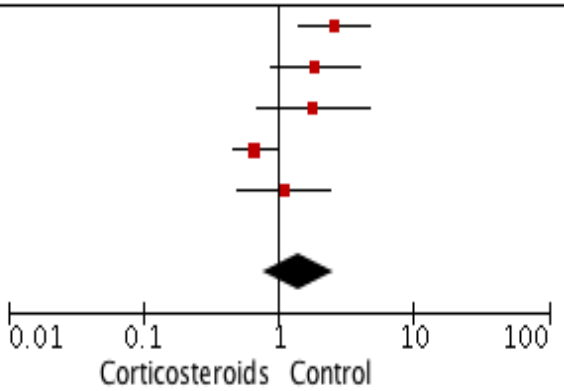
Mammen MJ, et al. Pol Arch Intern Med 2020; 130: 276-286. https://www.mp.pl/paim/issue/article/15239

Mortality in Viral ARDS: Meta-analysis of Observational Studies

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Random, 95% CI
Brun-Buisson 2011	0.9517	0.3066	21.5%	2.59 [1.42, 4.72]
Cao 2016	0.6152	0.3849	19.1%	1.85 [0.87, 3.93]
Kim 2011	0.5878	0.4892	16.2%	1.80 [0.69, 4.70]
Li 2017	-0.4005	0.1919	24.6%	0.67 [0.46, 0.98]
Martin-Loeches 2011	0.0953	0.4023	18.6%	1.10 [0.50, 2.42]
Total (95% CI)			**100.0%**	**1.40 [0.76, 2.57]**

Heterogeneity: $Tau^2 = 0.35$; $Chi^2 = 17.29$, df = 4 (P = 0.002); $I^2 = 77\%$

Test for overall effect: Z = 1.09 (P = 0.28)



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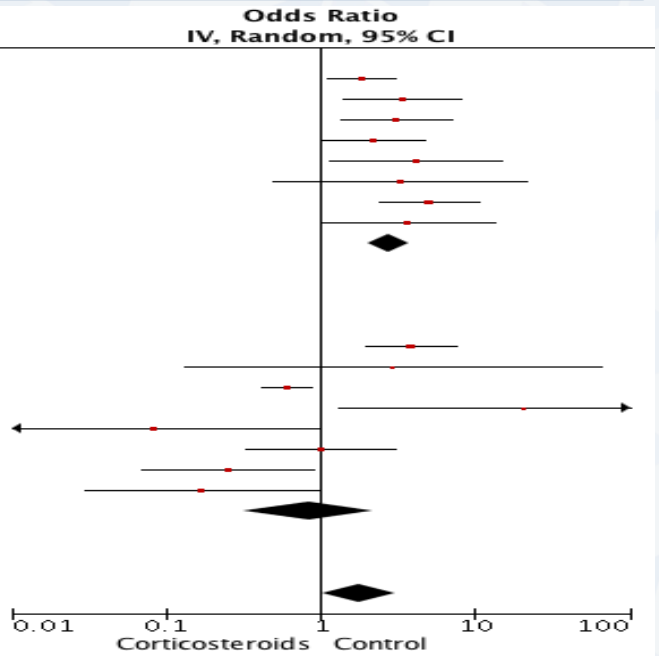
Bhimraj A, et al. Clin Infect Dis. April 27, 2020. [epubahead of print] doi:10.1093/cid/ciaa478

Mortality in Viral Pneumonia: Meta-analysis of Observational Studies

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Random, 95% CI
1.1.1 Influenza				
Delaney 2016	0.6152	0.2561	8.8%	1.85 [1.12, 3.06]
Delgado-Rodtriguez 2012	1.2149	0.4518	7.6%	3.37 [1.39, 8.17]
Jung 2011	1.1282	0.4187	7.8%	3.09 [1.36, 7.02]
Kim 2011	0.7885	0.3872	8.0%	2.20 [1.03, 4.70]
Liem 2009	1.4134	0.6543	6.2%	4.11 [1.14, 14.82]
Linko 2011	1.1939	0.9628	4.4%	3.30 [0.50, 21.78]
Tsai 2020	1.6134	0.3786	8.0%	5.02 [2.39, 10.54]
Xi 2010	1.3002	0.6685	6.1%	3.67 [0.99, 13.60]
Subtotal (95% CI)			**56.7%**	**2.76 [2.06, 3.69]**
Heterogeneity: Tau² = 0.00; Chi² = 6.13, df = 7 (P = 0.52); I² = 0%				
Test for overall effect: Z = 6.81 (P < 0.00001)				
1.1.2 Corona/SARS/MERS				
Alfaraj 2019	1.3455	0.3457	8.2%	3.84 [1.95, 7.56]
Alghamdi 2016	1.0716	1.5877	2.3%	2.92 [0.13, 65.59]
Arabi 2017	-0.4943	0.1904	9.1%	0.61 [0.42, 0.89]
Auyeung 2005	3.0301	1.4122	2.7%	20.70 [1.30, 329.63]
Chen 2006	-2.4889	1.2617	3.2%	0.08 [0.01, 0.98]
Yam 2007 HC	0	0.5657	6.8%	1.00 [0.33, 3.03]
Yam 2007 MP	-1.3863	0.6495	6.2%	0.25 [0.07, 0.89]
Yam 2007 P	-1.772	0.885	4.8%	0.17 [0.03, 0.96]
Subtotal (95% CI)			**43.3%**	**0.83 [0.32, 2.17]**
Heterogeneity: Tau² = 1.24; Chi² = 38.12, df = 7 (P < 0.00001); I² = 82%				
Test for overall effect: Z = 0.37 (P = 0.71)				
Total (95% CI)			**100.0%**	**1.76 [1.03, 3.03]**
Heterogeneity: Tau² = 0.80; Chi² = 75.61, df = 15 (P < 0.00001); I² = 80%				
Test for overall effect: Z = 2.06 (P = 0.04)				
Test for subgroup differences: Chi² = 5.48, df = 1 (P = 0.02), I² = 81.8%				



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Bhimraj A, et al. Clin Infect Dis. April 27, 2020. [epubahead of print] doi:10.1093/cid/ciaa478

Corticosteroids and COVID-19

Trial	Trial Design	N	Corticosteroids	Outcomes
Wu C, et al	Retrospective cohort study in China	N = 84 with ARDS	Methylprednisolone No specific data on dose or duration	Reduced risk of death (HR, 0.38; 95% CI, 0.20-0.72; P=0.003)

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Wu C, et al. JAMA Intern Med 2020. https://jamanetwork.com/journals/jamainternalmedicine/fullarticle/2763184

Corticosteroids and COVID-19

Trial	Trial Design	N	Corticosteroids	Outcomes
Wang Y, et al	Retrospective cohort study in China	N = 46 with severe COVID-19 pneumonia	Methylprednisolone 1-2 mg/kg/day X 5-7 days	SpO2 improvement: 8 days vs. 14 days; P < 0.001. Need for MV: 11.5% vs. 35%; P = 0.05. Hospital LOS: 14 days vs. 22 days; P < 0.001. ICU LOS: 8 days vs. 15 days; P < 0.001. No difference in deaths: 2 vs. 1; P=0.714.

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Wang Y, et al. Signal Transduct Target Ther 2020 Apr 28;5(1):5 2020.
https://www.x-mol.com/paper/1258041365053505536?adv

Corticosteroids and COVID-19

Trial	Trial Design	N	Corticosteroids	Outcomes
Lu X, et al	Retrospective cohort study in China	N = 244 critically ill COVID-19 (ARDS or sepsis with acute organ dysfunction) N = 62 propensity score matched	Methylprednisolone 40 mg/day or equivalent of dexamethasone X 8 days	28-day mortality in multivariate analysis: aOR, 1.05; 95% CI, 0.15-7.46. 28-day mortality in PSM: 39% vs. 16%; P=0.09.

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Lu X, et al. Crit Care 2020 May 19;24(1):241. https://ccforum.biomedcentral.com/articles/10.1186/s13054-020-02963-w

Corticosteroids and COVID-19

Trial	Trial Design	N	Corticosteroids	Outcomes
Cruz AF, et al	Retrospective cohort study in Spain	N = 463 propensity score matched patients with COVID-19 pneumonia with ARDS and/or hyperinflammatory syndrome	1 mg/kg/day (methylprednisolone or equivalent) or pulses (78% vs. 22%) Unclear duration	In-hospital mortality: 13.9% vs. 23.9%; HR 0.51; 95 %CI, 0.27-0.96, p=0.044.

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Cruz AF, et al. AAC 2020; https://aac.asm.org/content/early/2020/06/16/AAC.01168-20.long

Corticosteroids and COVID-19

Trial	Trial Design	N	Corticosteroids	Outcomes
Fadel R, et al	Pre-test, post-test quasi-experimental study in United States	N = 213 with moderate to severe COVID-19 pneumonia requiring respiratory support	Methylprednisolone 0.5-1 mg/kg/day X 3 days	Composite endpoint (escalation to ICU, requiring MV, & mortality): 34.9% vs. 54.3%; p=0.005. After Adj: aOR, 0.41; 95% CI, 0.22 – 0.77. Mortality:13.6% vs. 26.3%; p=0.024 Requiring MV: 21.7% vs. 36.6%; p=0.025 Escalation to ICU: 27.3% vs. 44.3%; p=0.017. ARDS: 26.6% vs. 38.8%; p=0.04. Hospital LOS: 5 days vs. 8 days; p < 0.001.

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Fadel R, et al. Clin Infect Dis 2020. https://academic.oup.com/cid/advance-article/doi/10.1093/cid/ciaa601/5840526

Corticosteroids and COVID-19

Trial	Trial Design	N	Corticosteroids	Outcomes
Sun F, et al	Retrospective cohort study in China	N = 139 with COVID-19 of any severity	Methylprednisolone or dexamethasone ≤0·5-1 mg/kg/day methylprednisolone or equivalent X 7 days	Clinical deterioration during the whole hospital stay: aOR, 3.0; 95% CI, 1.2-7.8. Deterioration within 72h of 1st S/S: aOR, 1; 95% CI, 0.2-6.3.

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Sun F, et al. Lancet 2020. https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3551323

Corticosteroids and COVID-19

Trial	Trial Design	N	Corticosteroids	Outcomes
Yuan M, et al	Retrospective cohort study in China	N = 132 with non-severe COVID-19 pneumonia N = 70 propensity score matched	Methylprednisolone 50 mg/day X 11 days	CT imaging score on day 7: 8.6 days vs. 12.0 days; P=0.046. Others (progression to severe cases, LOS, viral shedding duration, & fever time): no significant differences. All outcomes in PSM: No significant differences

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Yuan M, et al. Shock (Augusta, Ga.) 2020.
https://journals.lww.com/shockjournal/Abstract/9000/Effects_of_Corticosteroid_Treatment_for_Non_Severe.97456.aspx

First RCT: Recovery Trial

Low-cost dexamethasone reduces death by up to one third in hospitalised patients with severe respiratory complications of COVID-19

16 June 2020

Statement from the Chief Investigators of the Randomised Evaluation of COVid-19 thERapY (RECOVERY) Trial on dexamethasone, 16 June 2020

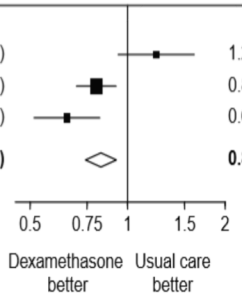
Table 2: Effect of allocation to dexamethasone on main study outcomes

	Treatment allocation			
	Dexamethasone (n=2104)	Usual care (n=4321)	RR (95% CI)	p-value
Primary outcome:				
28-day mortality	454 (21.6%)	1065 (24.6%)	0.83 (0.74-0.92)	<0.001
Secondary outcomes:				
Discharged from hospital within 28 days	1360 (64.6%)	2639 (61.1%)	1.11 (1.04-1.19)	0.002
Receipt of invasive mechanical ventilation or death*	425/1780 (23.9%)	939/3638 (25.8%)	0.91 (0.82-1.00)	0.049
Invasive mechanical ventilation	92/1780 (5.2%)	258/3638 (7.1%)	0.76 (0.61-0.96)	0.021
Death	360/1780 (20.2%)	787/3638 (21.6%)	0.91 (0.82-1.01)	0.07

Figure 2: Effect of allocation to dexamethasone on 28-day mortality by level of respiratory support received at randomization

Respiratory support at randomization	Dexamethasone	Usual care	RR (95% CI)
No oxygen received	85/501 (17.0%)	137/1034 (13.2%)	1.22 (0.93–1.61)
Oxygen only	275/1279 (21.5%)	650/2604 (25.0%)	0.80 (0.70–0.92)
Invasive mechanical ventilation	94/324 (29.0%)	278/683 (40.7%)	0.65 (0.51–0.82)
All participants	**454/2104 (21.6%)**	**1065/4321 (24.6%)**	**0.83 (0.74–0.92) p<0.001**

Trend across three categories: χ^2_1=11.49; p<0.001



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Horby P, et al. https://www.recoverytrial.net/news/low-cost-dexamethasone-reduces-death-by-up-to-one-third-in-hospitalised-patients-with-severe-respiratory-complications-of-covid-19

Summary

- The role of corticosteroids in COVID-19 is controversial
- Low dose dexamethasone was found in one RCT to significantly reduce mortality in COVID-19 patients requiring respiratory support
- No evidence of benefit and concern of potential harm in patients not requiring respiratory support
- Multiple RCTs are ongoing

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A Review of Pertinent Drug Information for SARS-CoV-2

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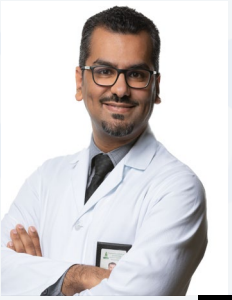

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Data as of June 24, 2020