

Clinical evidence does not support corticosteroid treatment for 2019-nCoV lung injury



Published Online
February 6, 2020
[https://doi.org/10.1016/S0140-6736\(20\)30317-2](https://doi.org/10.1016/S0140-6736(20)30317-2)

The 2019 novel coronavirus (2019-nCoV) outbreak is a major challenge for clinicians. The clinical course of patients remains to be fully characterised, little data are available that describe the disease pathogenesis, and no pharmacological therapies of proven efficacy yet exist.

Corticosteroids were widely used during the outbreaks of severe acute respiratory syndrome (SARS)-CoV¹ and Middle East respiratory syndrome (MERS)-CoV,² and are being used in patients with 2019-nCoV in addition to other therapeutics.³ However, current interim guidance from WHO on clinical management of severe acute respiratory infection when novel coronavirus (2019-nCoV) infection is suspected (released Jan 28, 2020) advises against the use of corticosteroids unless indicated for another reason.⁴ Understanding the evidence for harm or benefit from corticosteroids in 2019-nCoV is of immediate clinical importance. Here we discuss the clinical outcomes of corticosteroid use in coronavirus and similar outbreaks (table).

Acute lung injury and acute respiratory distress syndrome are partly caused by host immune responses. Corticosteroids suppress lung inflammation but also inhibit immune responses and pathogen clearance. In SARS-CoV infection, as with influenza, systemic inflammation is associated with adverse outcomes.¹² In SARS, inflammation persists after viral clearance.^{13,14} Pulmonary histology in both SARS and MERS infections reveals inflammation and diffuse alveolar damage,¹⁵ with one report suggesting haemophagocytosis.¹⁶ Theoretically, corticosteroid treatment could have a role to suppress lung inflammation.

In a retrospective observational study reporting on 309 adults who were critically ill with MERS,² almost half of patients (151 [49%]) were given corticosteroids (median hydrocortisone equivalent dose [ie, methylprednisolone 1:5, dexamethasone 1:25, prednisolone 1:4] of 300 mg/day). Patients who were given corticosteroids were more likely to require mechanical ventilation, vasopressors, and renal replacement therapy. After statistical adjustment for immortal time and indication biases, the authors concluded that administration of corticosteroids was not associated with a difference in 90-day mortality (adjusted odds ratio 0.8, 95% CI 0.5–1.1; p=0.12) but was associated with delayed clearance of viral RNA from respiratory tract secretions (adjusted hazard ratio 0.4, 95% CI 0.2–0.7; p=0.0005). However, these effect estimates have a high risk of error due to the probable presence of unmeasured confounders.

In a meta-analysis of corticosteroid use in patients with SARS, only four studies provided conclusive data, all indicating harm.¹ The first was a case-control study of SARS patients with (n=15) and without (n=30) SARS-related psychosis; all were given corticosteroid treatment, but those who developed psychosis were given a higher cumulative dose than those who did not (10 975 mg hydrocortisone equivalent vs 6780 mg; p=0.017).⁶ The second was a randomised controlled trial of 16 patients with SARS who were not critically ill; the nine patients who were given hydrocortisone (mean 4.8 days [95% CI 4.1–5.5] since fever onset) had greater viraemia in the second and third weeks after infection than those who were given 0.9% saline control.⁵ The

| | Outcomes of corticosteroid therapy* | Comment |
|-----------|--|--|
| MERS-CoV | Delayed clearance of viral RNA from respiratory tract ² | Adjusted hazard ratio 0.4 (95% CI 0.2–0.7) |
| SARS-CoV | Delayed clearance of viral RNA from blood ⁵ | Significant difference but effect size not quantified |
| SARS-CoV | Complication: psychosis ⁶ | Associated with higher cumulative dose, 10 975 mg vs 6780 mg hydrocortisone equivalent |
| SARS-CoV | Complication: diabetes ⁷ | 33 (35%) of 95 patients treated with corticosteroid developed corticosteroid-induced diabetes |
| SARS-CoV | Complication: avascular necrosis in survivors ⁸ | Among 40 patients who survived after corticosteroid treatment, 12 (30%) had avascular necrosis and 30 (75%) had osteoporosis |
| Influenza | Increased mortality ⁹ | Risk ratio for mortality 1.75 (95% CI 1.3–2.4) in a meta-analysis of 6548 patients from ten studies |
| RSV | No clinical benefit in children ^{10,11} | No effect in largest randomised controlled trial of 600 children, of whom 305 (51%) had been treated with corticosteroids |

CoV=coronavirus. MERS=Middle East respiratory syndrome. RSV=respiratory syncytial virus. SARS=severe acute respiratory syndrome. *Hydrocortisone, methylprednisolone, dexamethasone, and prednisolone.

Table: Summary of clinical evidence to date

remaining two studies reported diabetes and avascular necrosis as complications associated with corticosteroid treatment.^{7,8}

A 2019 systematic review and meta-analysis⁹ identified ten observational studies in influenza, with a total of 6548 patients. The investigators found increased mortality in patients who were given corticosteroids (risk ratio [RR] 1.75, 95% CI 1.3–2.4; $p=0.0002$). Among other outcomes, length of stay in an intensive care unit was increased (mean difference 2.1, 95% CI 1.2–3.1; $p<0.0001$), as was the rate of secondary bacterial or fungal infection (RR 2.0, 95% CI 1.0–3.8; $p=0.04$).

Corticosteroids have been investigated for respiratory syncytial virus (RSV) in clinical trials in children, with no conclusive evidence of benefit and are therefore not recommended.¹⁰ An observational study of 50 adults with RSV infection, in which 33 (66%) were given corticosteroids, suggested impaired antibody responses at 28 days in those given corticosteroids.¹⁷

Life-threatening acute respiratory distress syndrome occurs in 2019-nCoV infection.¹⁸ However, generalising evidence from acute respiratory distress syndrome studies to viral lung injury is problematic because these trials typically include a majority of patients with acute respiratory distress syndrome of non-pulmonary or sterile cause. A review of treatments for acute respiratory distress syndrome of any cause, based on six studies with a total of 574 patients,¹⁹ concluded that insufficient evidence exists to recommend corticosteroid treatment.²⁰

Septic shock has been reported in seven (5%) of 140 patients with 2019-nCoV included in published reports as of Jan 29, 2020.^{3,18} Corticosteroids are widely used in septic shock despite uncertainty over their efficacy. Most patients in septic shock trials have bacterial infection, leading to vasoplegic shock and myocardial insufficiency.^{21,22} In this group, there is potential that net benefit might be derived from steroid treatment in severe shock.^{21,22} However, shock in severe hypoxaemic respiratory failure is often a consequence of increased intrathoracic pressure (during invasive ventilation) impeding cardiac filling, and not vasoplegia.²³ In this context, steroid treatment is unlikely to provide a benefit.

No clinical data exist to indicate that net benefit is derived from corticosteroids in the treatment of respiratory infection due to RSV, influenza, SARS-CoV,

or MERS-CoV. The available observational data suggest increased mortality and secondary infection rates in influenza, impaired clearance of SARS-CoV and MERS-CoV, and complications of corticosteroid therapy in survivors. If it is present, the effect of steroids on mortality in those with septic shock is small, and is unlikely to be generalisable to shock in the context of severe respiratory failure due to 2019-nCoV.

Overall, no unique reason exists to expect that patients with 2019-nCoV infection will benefit from corticosteroids, and they might be more likely to be harmed with such treatment. We conclude that corticosteroid treatment should not be used for the treatment of 2019-nCoV-induced lung injury or shock outside of a clinical trial.

JKB is a member of the WHO panel on clinical management for 2019-nCoV. CDR and JEM declare no competing interests.

Clark D Russell, Jonathan E Millar, *J Kenneth Baillie
j.k.baillie@ed.ac.uk

University of Edinburgh Centre for Inflammation Research, The Queen's Medical Research Institute Edinburgh, Edinburgh, UK (CDR); and Genetics and Genomics, Roslin Institute, University of Edinburgh, Edinburgh EH25 9RG, UK (JKB, JEM)

- 1 Stockman LJ, Bellamy R, Garner P. SARS: systematic review of treatment effects. *PLoS Med* 2006; **3**: e343.
- 2 Arabi YM, Mandourah Y, Al-Hameed F, et al. Corticosteroid therapy for critically ill patients with middle east respiratory syndrome. *Am J Respir Crit Care Med* 2018; **197**: 757–67.
- 3 Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet* 2020; published online Jan 24. [https://doi.org/10.1016/S0140-6736\(20\)30183-5](https://doi.org/10.1016/S0140-6736(20)30183-5).
- 4 WHO. Clinical management of severe acute respiratory infection when novel coronavirus (nCoV) infection is suspected. Geneva: World Health Organization, Jan 28, 2020. [https://www.who.int/publications-detail/clinical-management-of-severe-acute-respiratory-infection-when-novel-coronavirus-\(ncov\)-infection-is-suspected](https://www.who.int/publications-detail/clinical-management-of-severe-acute-respiratory-infection-when-novel-coronavirus-(ncov)-infection-is-suspected) (accessed Feb 2, 2020).
- 5 Lee N, Allen Chan KC, Hui DS, et al. Effects of early corticosteroid treatment on plasma SARS-associated Coronavirus RNA concentrations in adult patients. *J Clin Virol* 2004; **31**: 304–09.
- 6 Lee DTS, Wing YK, Leung HCM, et al. Factors associated with psychosis among patients with severe acute respiratory syndrome: a case-control study. *Clin Infect Dis* 2004; **39**: 1247–49.
- 7 Xiao JZ, Ma L, Gao J, et al. Glucocorticoid-induced diabetes in severe acute respiratory syndrome: the impact of high dosage and duration of methylprednisolone therapy. *Zhonghua Nei Ke Za Zhi* 2004; **43**: 179–82 (in Chinese).
- 8 Li YM, Wang SX, Gao HS, et al. Factors of avascular necrosis of femoral head and osteoporosis in SARS patients' convalescence. *Zhonghua Yi Xue Za Zhi* 2004; **84**: 1348–53 (in Chinese).
- 9 Ni Y-N, Chen G, Sun J, Liang B-M, Liang Z-A. The effect of corticosteroids on mortality of patients with influenza pneumonia: a systematic review and meta-analysis. *Crit Care* 2019; **23**: 99.
- 10 McGee S, Hirschmann J. Use of corticosteroids in treating infectious diseases. *Arch Intern Med* 2008; **168**: 1034–46.
- 11 Corneli HM, Zorc JJ, Mahajan P, et al. A multicenter, randomized, controlled trial of dexamethasone for bronchiolitis. *N Engl J Med* 2007; **357**: 331–39.
- 12 Tang NL-S, Chan PK-S, Wong C-K, et al. Early enhanced expression of interferon-inducible protein-10 (CXCL-10) and other chemokines predicts adverse outcome in severe acute respiratory syndrome. *Clin Chem* 2005; **51**: 2333–40.
- 13 Peiris JSM, Chu CM, Cheng VCC, et al. Clinical progression and viral load in a community outbreak of coronavirus-associated SARS pneumonia: a prospective study. *Lancet* 2003; **361**: 1767–72.

- 14 Beijing Group of National Research Project for SARS. Dynamic changes in blood cytokine levels as clinical indicators in severe acute respiratory syndrome. *Chin Med J (Engl)* 2003; **116**: 1283–87.
- 15 Arabi YM, Balkhy HH, Hayden FG, et al. Middle East respiratory syndrome. *N Engl J Med* 2017; **376**: 584–94.
- 16 Nicholls JM, Poon LLM, Lee KC, et al. Lung pathology of fatal severe acute respiratory syndrome. *Lancet* 2003; **361**: 1773–78.
- 17 Lee FE-H, Walsh EE, Falsey AR. The effect of steroid use in hospitalized adults with respiratory syncytial virus-related illness. *Chest* 2011; **140**: 1155–61.
- 18 Chen N, Zhou M, Dong X, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *Lancet* 2020; published online Jan 30. [https://doi.org/10.1016/S0140-6736\(20\)30211-7](https://doi.org/10.1016/S0140-6736(20)30211-7).
- 19 Ashbaugh DG, Bigelow DB, Petty TL, Levine BE. Acute respiratory distress in adults. *Lancet* 1967; **2**: 319–23.
- 20 Lewis SR, Pritchard MW, Thomas CM, Smith AF. Pharmacological agents for adults with acute respiratory distress syndrome. *Cochrane Database Syst Rev* 2019; **7**: CD004477.
- 21 Venkatesh B, Finfer S, Cohen J, et al. Adjunctive glucocorticoid therapy in patients with septic shock. *N Engl J Med* 2018; **378**: 797–808.
- 22 Annane D, Renault A, Brun-Buisson C, et al. Hydrocortisone plus fludrocortisone for adults with septic shock. *N Engl J Med* 2018; **378**: 809–18.
- 23 Fougères E, Teboul J-L, Richard C, Osman D, Chemla D, Monnet X. Hemodynamic impact of a positive end-expiratory pressure setting in acute respiratory distress syndrome: importance of the volume status. *Crit Care Med* 2010; **38**: 802–07.