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

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The 2019-nCoV outbreak

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

Corticosteroids were widely used during the SARS-CoV[1] and MERS-CoV[2] outbreaks, and are presently being used in patients with 2019-nCoV.[3] However, current guidance from WHO 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.

Rationale for corticosteroid therapy

Acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) are, in part, driven by host immune responses. Corticosteroids suppress lung inflammation, but also inhibit immune responses and pathogen clearance. In severe acute respiratory syndrome coronavirus (SARS-CoV) infection, as with influenza, systemic inflammation is associated with adverse outcomes.[5] In SARS, inflammation persisted after viral clearance.[6,7] Pulmonary histology in both SARS and Middle Eastern respiratory syndrome (MERS-CoV) infection reveals inflammation and diffuse alveolar damage[8] with one report suggesting haemophagocytosis.[9] There is a theoretical role for corticosteroid treatment to suppress lung inflammation.

Clinical evidence in respiratory viral infection

Emerging coronaviruses (SARS-CoV and MERS-CoV)

In a retrospective observational study reporting on 309 critically-ill adults with MERS,[2] almost half of patients (49%) received corticosteroids (median hydrocortisone equivalent dose*= 300mg/day). Patients receiving corticosteroids were more likely to require mechanical ventilation, vasopressors, and renal replacement therapy. After statistical correction for immortal time and indication biases, the authors concluded that corticosteroid administration was not associated with a difference in 90-day mortality (adjusted OR 0.8, 95% CI 0.5-1.1, p=0.1) but was associated with delayed clearance of viral RNA from respiratory tract secretions (adjusted HR 0.4, 95% CI 0.2-0.7, p=0.0005). However, these effect estimates carry a high risk of error due to the likely 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] In a case-control study of SARS

patients with (n=15) and without (n=30) SARS-related psychosis, all received corticosteroid treatment but those developing psychosis received a higher cumulative dose (10,975mg hydrocortisone equivalent vs. 6780mg, p=0.02).[10] In a randomised controlled trial of 16 patients with SARS, who were not critically ill, the nine patients receiving hydrocortisone (mean 4.8 days from fever onset) had greater viraemia in the second and third week post-infection.[11] The remaining two studies, from the Chinese literature, reported diabetes and avascular necrosis as complications associated with corticosteroid treatment.[12,13]

Influenza virus

A recent systematic review and meta-analysis[14] identified 10 observational studies in influenza, with a total of 6548 patients. There was a signal for increased mortality in patients receiving corticosteroids (RR 1.75, 95% CI 1.3-2.4, p=0.0002). Among other outcomes, ICU length of stay was increased (MD 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).

Respiratory syncytial virus

Corticosteroids have been investigated for RSV in clinical trials, with no conclusive evidence of benefit, and are therefore not recommended.[15] An observational study of 50 adults with RSV infection, in which 66% received corticosteroids, found a trend towards impaired antibody responses at 28 days in those given corticosteroids.[16]

Table 1: Summary of clinical evidence

Virus	Outcome of corticosteroid therapy	Reference
MERS-CoV	Delayed clearance of viral RNA from respiratory tract	[2]
SARS-CoV	Delayed clearance of viral RNA from blood	[11]
SARS-CoV	Complication: psychosis	[10]
SARS-CoV	Complication: diabetes	[12]
SARS-CoV	Complication: avascular necrosis in survivors	[13]
Influenza	Increased mortality	[14]
RSV	No immunological benefit in adults	[16]
RSV	No clinical benefit in children	[15]

Clinical evidence in critical illness

ARDS

Life-threatening ARDS occurs in 2019-nCoV infection.[17] However, because trials in ARDS typically include a majority of patients with ARDS of nonpulmonary or sterile aetiology, generalising evidence from ARDS studies to viral lung injury is problematic. A recent review of treatments for ARDS of any aetiology, based on 6 studies with a total of 574 patients,[18] concluded that there is insufficient evidence to recommend their use.[19]

Septic shock

Septic shock has been reported in 4% of patients with 2019-nCoV.[17] Corticosteroids are widely used in septic shock despite uncertainty over efficacy. The vast majority of patients in septic shock trials have bacterial infection, leading to vasoplegic shock and myocardial insufficiency.[20,21] In this group, there is a trend towards benefit from steroid treatment in severe shock.[20,21] However, shock in severe hypoxaemic respiratory failure is often a consequence of raised intrathoracic pressure (during invasive ventilation) impeding cardiac filling, and not vasoplegia.[22] In this context it is unlikely that steroid treatment will provide benefit.

Conclusions

There is no clinical data to indicate that net benefit is derived from corticosteroids in the treatment of respiratory infection due to RSV, influenza, SARS-, or MERS-CoV. The available observational data suggest increased mortality and secondary infection rates in influenza, impaired clearance of SARS- and MERS-CoV, and complications of corticosteroid therapy in survivors. If it is present, the effect of steroids on mortality in septic shock is small, and is unlikely to be generalisable to shock in the context of severe respiratory failure due to 2019-nCoV.

Overall, there is no unique reason to expect that patients with 2019-nCoV infection will benefit from corticosteroids, and they may be more likely to suffer harm. We conclude that corticosteroids should not be used in 2019-nCoV outside of a clinical trial, unless there is another clinical reason for corticosteroid treatment.

* *Hydrocortisone-equivalent doses (methylprednisolone 1:5, dexamethasone 1:25, prednisolone 1:4)*

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