Corticosteroids for COVID-19-Associated ARDS

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Abstract: Systemic corticosteroids have emerged as a possible therapy to mitigate lung injury in severe COVID-19 infection. Here, we provide historical context for corticosteroid administration in acute respiratory failure due to viral infection and review existing data for the use of systemic corticosteroids for SARS-CoV-2 infection. The results of these limited data consistently suggest a mortality benefit for patients with COVID-19-associated acute respiratory distress syndrome with no existing evidence to suggest harm.

Key Words: corticosteroids, COVID-19, SARS-CoV-2, ARDS, respiratory failure

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STATE OF THE ART: STEROIDS FOR RESPIRATORY FAILURE IN COVID-19 INFECTION

Systemic corticosteroids have emerged as a possible therapy to mitigate lung injury in severe COVID-19 infection. The pandemic from SARS-Co-V2, a viral respiratory tract infection,[1] has posed several challenges to medical providers and health care systems alike: disease severity has been highly variable,[2] the volume of patients needing care has at times outstripped resources available at community and tertiary referral hospitals,[3] and, most concerningly, few treatment options exist that mitigate the disease course.[4] While waiting for a greater supply of antiviral agents like remdesivir and a possible preventative vaccine, providers are in a position of identifying therapies that may at least attenuate the morbidity associated with severe COVID-19 infection.[5,6] Here, we provide the historical context for corticosteroid administration in acute respiratory failure due to viral infection and review the existing data for the use of systemic corticosteroids for SARS-CoV-2 infection.

HISTORICAL PERSPECTIVE: SYSTEMIC CORTICOSTEROIDS IN ACUTE RESPIRATORY DISTRESS SYNDROME AND RESPIRATORY VIRAL ILLNESSES

The potential role of corticosteroids in the treatment of acute respiratory distress syndrome (ARDS) has been widely investigated and debated since ARDS was first described in 1967.[7] ARDS is characterized by acute, diffuse, heterogenous pulmonary inflammation from a variety of different infectious and inflammatory etiologies, carrying with it a high burden of morbidity and mortality.[8] Because of the widespread inflammatory response seen in the lungs of ARDS patients, glucocorticoids naturally emerged as a potential therapy to reverse pulmonary inflammation. To date, however, studies of the potential benefit of corticosteroids for ARDS have been contradictory, and their use remains controversial. Select populations of ARDS patients with moderate to severe lung injury who are early in their disease course may benefit from steroid administration pointing toward the potential benefit in inflammatory phenotypes, but universal use of steroids in ARDS patients has not proven beneficial.[9–15]

The use of systemic steroids in patients with ARDS due to viral infections is especially fraught. Studies of patients with ARDS due to influenza or due to the severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) coronavirus strains have failed to show consistent benefit. Influenza infection remains one of the most common etiologies of ARDS worldwide,[16] and accordingly, identifying the optimal strategy of supportive care for influenza ARDS remains a priority. Studies of glucocorticoids in influenza ARDS patients have been associated with worse clinical outcomes,[17] and for this reason, glucocorticoids are generally avoided for patients with severe influenza pneumonia infection. Notably, however, these data are sourced largely from observational studies with little randomized controlled data to guide therapeutic decision-making.

Studies evaluating systemic steroids in historic novel coronavirus outbreaks have been similarly disappointing. In 2003, the World Health Organization reported a worldwide outbreak of a rapidly progressive novel coronavirus infection in 2003: SARS.[18] SARS infection was associated with ARDS and a fatality rate of 10% from respiratory failure.[19] There are limited data regarding the use of corticosteroids for patients affected by SARS, but among a small critically ill cohort, early administration of steroids was associated with a higher plasma viral load.[20] A 2012 outbreak of the Middle East Respiratory Syndrome novel coronavirus (MERS-CoV)[21] resulted in ARDS in more than half of individuals infected with the virus.[22] Retrospective analysis of critically ill patients who received glucocorticoids for their MERS infection found that glucocorticoid use did not impact mortality even when given early in the patient's presentation. Steroid administration was instead associated with delayed clearance of the RNA virus and prolonged mechanical ventilation and hospitalization.[23,24]

SYSTEMIC CORTICOSTEROIDS IN COVID-19 INFECTION: DATA AND CURRENT PRACTICES

In the age of the novel coronavirus 2019 pandemic, there has been a reemerging interest in systemic glucocorticoids for persons affected by the virus. Initially, a retrospective study of patients with COVID-19 infection complicated by ARDS noted that those who received corticosteroids appeared to have a decreased risk of death, though details of disease severity, timing, and dosing of steroids were not included in the final publication.[25] Subsequently, case series were published suggesting the possible benefits of corticosteroids for those with ARDS, in particular, those with elevated inflammatory markers

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including high ferritin and C-reactive proteins during admission. Early administration of corticosteroids within the first 72 hours of presentation, within 1 week of onset of viral illness, and continued for 3 to 5 days was thought to have allowed this subset of patients to avoid intubation and mechanical ventilation.[26] Another case series of patients with ARDS secondary to COVID-19 infection requiring mechanical ventilation suggested accelerated clinical improvement with the administration of high-dose methylprednisolone, 500 to 1000 mg per day for 3 days starting at the time of intubation, then slowly tapered over a median duration of 13 days.[27] With limited data available, the Society of Critical Care Medicine (SCCM) COVID-19 Therapy Recommendations suggest the use of systemic corticosteroids for mechanically ventilated adults with COVID-19 and ARDS nothing that this recommendation was made on the basis of weak, low-quality evidence.[28] Previously, they had only otherwise recommended steroids for patients with early moderate to severe ARDS,[9] given their association with faster disease resolution in those with sepsis or community-acquired pneumonia.

In June 2020, the RECOVERY trial, a large-scale randomized control trial preliminary report cemented the role of corticosteroids in the care of patients with moderate to severe COVID-19 infection. A multicenter, open-label trial from the United Kingdom released data suggesting a 28-day mortality benefit of low-dose dexamethasone, 6 mg daily, in patients hospitalized with COVID-19 infection.[29] The benefit of corticosteroids was greatest in patients who required mechanical ventilation, with an associated 36% relative mortality reduction and 12% absolute mortality reduction. Among those patients requiring supplemental oxygen, the benefit was less pronounced with a 4% absolute mortality reduction. For those individuals without any oxygen requirement, the use of low-dose corticosteroids was not associated with a mortality benefit and suggested a trend toward harm.

Data continue to emerge that the critically ill subset of patients infected with COVID-19 derives the greatest benefit from corticosteroids. A prospective meta-analysis of 7 randomized clinical trials which included a total of 1703 critically ill patients with COVID-19 infection found that the use of systemic corticosteroids was associated with reduced 28-day mortality (summary odds ratio of 0.66; 95% confidence interval, 0.53-0.82) without increased risk for adverse events.[30] There was no statistical difference between dexamethasone and hydrocortisone treatment response, with doses of dexamethasone ranging from 6 to 20 mg daily for 10 days and hydrocortisone 200 mg either daily or in divided doses for 7 to 14 days. Subgroup analysis suggested that the greatest mortality benefit was among patients who were not receiving mechanical ventilation at the time of randomization. However, one of the studies included for meta-analysis, the CoDEX trial that studied 299 patients with moderate to severe ARDS from COVID-19 infection, did show a difference in ventilator-free days between groups at 28 days, with 6.6 ventilator-free days compared with 4.0 in the control group ($P = 0.04$), suggesting that dexamethasone 20 mg per day for 5 days and then 10 mg daily for another 5 days may impact other important patient-centered outcomes.[31] On the basis of the consistent finding of mortality benefit without evidence of harm within this dataset, it has been increasingly argued that corticosteroids in ARDS secondary to COVID-19 infection should be considered the standard of care.

CORTICOSTEROIDS FOR COVID-19 INFECTION: WHERE DO WE GO FROM HERE?

In the age of a pandemic with widespread illness and limited therapeutic options, findings from these studies give some hope that glucocorticoids may help to lessen lung injury and decrease mortality. The results of these limited data also seem to consistently suggest that the sickest patients with COVID-19 infection appear to benefit the most from corticosteroids. However, numerous questions remain unanswered. If the sickest patients receive the greatest benefit and the least sick do not, where exactly is the tipping point between those who would benefit and those who would not? At what time point along the course of a patient's COVID-19 infection are they likely to receive the greatest benefit from corticosteroids? Can corticosteroids prevent intubation in a subset of patients? Are there subsets of critically ill patients with COVID-19 where the benefits of corticosteroids are perhaps less pronounced and caution in their administration should be exercised? The RECOVERY trial administered low-dose steroids for 10 days or until hospital discharge, but is this truly the optimal duration of therapy for all patients? Were mortality rates for the RECOVERY trial impacted by surge conditions and would similar benefits from corticosteroids be seen in regions with low incidence and prevalence? Why, after years of conflicting data both for and

TABLE 1. Summary of Systemic Corticosteroid Clinical Trials for COVID-19

Corticosteroid Studied	Relevant Study	Reported Dose	Mode of Administration	Reported Duration of Therapy	Duration of Action (h)
Dexamethasone	DEXA-COVID-19	20 mg/d, then	IV	5 d, then	
		10 mg/d	IV	5 d	
	CoDEX	20 mg/d, then	IV	5 d, then	36-72
		10 mg/d	IV	5 d	
	RECOVERY	6 mg/d	IV or PO	10 d, or until discharge if sooner	
Hydrocortisone	CAPE COVID	200 mg/d, continuous infusion, then	IV	7 d, then	
		100 mg daily, then	IV	4 d, then	
		50 mg daily*		3 d	8-12
	COVID STEROID	200 mg daily (continuous or every 6 h)	IV	7 d	
	REMAP-CAP	50 mg every 6 h	IV	7 d	
Methylprednisolone	Steroids-SARI	40 mg every 12 h	IV	5 d	12-26

*If the patient was clinically improving within the first 4 days of systemic corticosteroids, steroids were tapered more quickly: 200 mg/day for 4 days, then 100 mg/day for 2 days, then 50 mg/day for 2 days, ending treatment after 8 days.

d indicates days; h, hours; IV, intravenous; PO, per os.

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against the use of corticosteroids for ARDS, do we see consistent findings favoring their use for this specific illness?

Although studies have not historically supported a role for corticosteroid use in respiratory failure due to viral etiologies, in the midst of a pandemic, researchers are rapidly presenting data that strongly recommends their use for COVID-19-associated ARDS with little evidence of harm. At this point, providers will need to justify the choice not to use corticosteroids while also acknowledging what is not known including safety with coadministration of remdesivir or safety among those with poorly controlled diabetes. As we learn more about the uniquely steroid-responsive nature of COVID-19-associated lung injury, identifying other subgroups of patients with ARDS who would benefit from corticosteroids is a future area for investigation (Table 1).

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