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Web Exclusive. Annals for Hospitalists Inpatient Notes - Corticosteroids and COVID-19-Calming the Storm?

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Mounting evidence implicates cytokine storm in the high mortality rate associated with severe respiratory viral infections. *Cytokine storm* is a loosely defined term referring to the hyperactive production of proinflammatory cytokines, which contributes to the development of acute respiratory distress syndrome (ARDS) and multisystem organ dysfunction in affected patients. Corticosteroids are hypothesized to blunt the host immune inflammatory response and attenuate lung injury. However, evidence of a beneficial effect in severe influenza infection is limited. The (mostly observational) data on corticosteroids for the treatment of influenza suggest that the harms (for example, secondary infections and hyperglycemia) outweigh the benefits (1). Similarly, research on the use of corticosteroids in the treatment of many other hyperinflammatory syndromes (for example, sepsis, ARDS, and community-acquired pneumonia) has produced controversial and inconclusive results.

As with influenza, researchers have also investigated the use of corticosteroids and other immunomodulators in the treatment of coronavirus disease 2019 (COVID-19) during the global pandemic. Because corticosteroids have been associated with worse outcomes in influenza and prolonged viral shedding in severe acute respiratory syndrome and Middle East respiratory syndrome, there was initial hesitancy to administer these drugs to patients with COVID-19. However, evidence from more recent clinical trials showed a benefit of corticosteroids in ARDS and septic shock, and in March 2020, the Society of Critical Care Medicine issued a weak recommendation for corticosteroid use only in COVID-19 cases associated with septic shock or ARDS (2).

In June 2020, investigators from the RECOVERY (Randomized Evaluation of COVID-19 Therapy) trial released their results on the effect of low-dose dexamethasone in the treatment of COVID-19 (3). The RECOVERY trial represents the largest randomized controlled trial examining systemic corticosteroids in the treatment of COVID-19 to date. The study included 6425 patients hospitalized with proven or suspected COVID-19, regardless of illness severity. Patients were randomly assigned to receive either 6 mg of dexamethasone once daily for up to 10 days or placebo. Patients in the dexamethasone group had a lower mortality rate at 28 days. A prespecified subgroup analysis showed the largest benefit in patients receiving invasive mechanical ventilation, with a smaller benefit seen in those receiving oxygen or noninvasive ventilation. The group receiving no respiratory support did

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not experience any benefit; rather, the investigators saw a trend toward harm in this group. After the RECOVERY trial's publication, other trials of corticosteroids for treatment of COVID-19 were suspended because of lack of equipoise. Fortunately, the World Health Organization had coordinated an ongoing prospective meta-analysis of these trials, allowing for pooling of data from several trials that had not met their enrollment targets.

The results from the World Health Organization's meta-analysis were recently published and incorporated data from 7 trials involving 1703 critically ill patients with COVID-19 (4). The exact definition of critical illness varied across studies, although most included patients who were admitted to the intensive care unit and receiving advanced respiratory support or vasopressors. Among the patients from the RECOVERY trial, this meta-analysis included only those receiving invasive mechanical ventilation at enrollment. The analysis found a decrease in 28-day all-cause mortality associated with corticosteroids, including in the subgroup of patients not receiving invasive mechanical ventilation, although the number in this group was low. Although the type and dose of corticosteroid varied by trial, most used low-dose corticosteroids with a similar potency to the dose of dexamethasone used in the RECOVERY trial.

On the basis of the available evidence, we recommend prescribing systemic corticosteroids to hospitalized patients with COVID-19 who have a peripheral arterial oxygen saturation less than 90% on room air or are receiving respiratory support of any kind. The regimen best supported by the current evidence is 6 mg of dexamethasone once daily for 7 to 10 days. This regimen has not been directly compared with others, and equivalent doses of alternate corticosteroids, such as prednisone or hydrocortisone, are likely to be equally effective. In noncritically ill, hospitalized patients without hypoxemia, we recommend against prescribing systemic corticosteroids because of the possibility of harm, although the evidence here is less certain. In these patients, the optimal approach is likely to withhold corticosteroids unless other established indications are present, such as an exacerbation of asthma or chronic obstructive pulmonary disease.

To date, systemic corticosteroids are the only treatment shown to decrease mortality in randomized controlled clinical trials of patients with severe COVID-19. Despite this evidence, many questions still exist about the use of immunosuppressants in these patients. The rate of secondary infections with corticosteroids is unknown, although it is a common adverse effect seen in the influenza literature. Observational studies of other immunomodulatory agents, such as tocilizumab, have shown inconsistent results while also suggesting an increased risk for secondary infections (5). Further robust randomized controlled trials on these agents will be forthcoming; however, the current mainstay of treatment of severe COVID-19 is systemic corticosteroids with the goal of calming the cytokine storm.

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