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The Uncertain Role of Corticosteroids in the Treatment of COVID-19

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To the Editor

Infection with coronavirus disease 2019 (COVID-19) causes exuberant lung inflammation leading to respiratory failure, acute respiratory distress syndrome (ARDS), and death. Wu et al[1] present early experience and retrospective analysis highlighting potential mortality reduction of COVID-19-associated ARDS using corticosteroids to reduce inflammation. However, despite a novel cause, the clinical syndrome resembles that of older diseases, and the analysis faces statistical challenges that have been encountered previously.

Prior studies in ARDS reveal variable steroid effects potentially related to different causes and resulting pathophysiologies in visible at the bedside.[2] Different studies have found corticosteroid effects ranging from harmful to beneficial. Within 3 cohort studies of influenza A (H1N1) during the 2009 pandemic, as cited,[2] steroid use appeared either ineffective or harmful. Other cohort studies and randomized clinical trials for treatment of ARDS wrestled with artifacts due to indication and survivor bias. The former bias is a familiar issue[3] created when unblended clinician streat individuals with more serious illness more aggressively, in this case using steroids to prevent or mitigate ARDS. The latter bias

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arises in 2 ways, either by missing patients unable to survive long enough to receive steroids or failing to follow up with patients long enough to record late deaths due to secondary infections or other steroid-associated complications.

Wu et al[1] found that steroid therapy had a low hazard ratio for death for patients receiving steroids for ARDS. However, the result is at odds with results suggesting harm caused by steroids used to prevent ARDS[1] and is at odds with an other recent report[4] using a potentially overlapping patient cohort that found no steroid association with mortality. Wu et al[1] suggest that because indication bias usually erroneously suggests harm from a therapy, a beneficial hazard ratio for steroid treatment of ARDS should be believed. However, this assumes that other biases are in consequential, such as survivor bias due to rapid disease progression compounded by health care resource exhaustion. We note that the Kaplan-Meier curves presented in the original article[1] show that substantial numbers of patients were censored, follow-up was substantially shorter than needed to observe steroid adverse reactions, the last observed Kaplan-Meier survival data points of the 2 groups were not statistically different, and, finally, use of steroids was not statistically different between survivors and nonsurvivors of ARDS (Table 3).[1]

Thus, we urge caution before using steroids for ARDS due to COVID-19. Meticulous observation as performed by Wu et al[1] should continue; however, a rigorous blinded randomized clinical trial is needed to discover the benefit or harm of this therapy with confidence.[5]

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