There is much to learn about ICU-acquired weakness. Pharmacological therapies will need strong preclinical biological rationale and early phase evidence of safety before large numbers of critically ill patients are included in efficacy trials. Without robust early data, there is a high risk of undertaking "negative" trials or worse exposing patients to a therapy that might cause harm. This research area is still in its infancy, and it is worth reflecting that cancer cachexia has been studied for far longer, but remains incompletely understood and without pharmacologic interventions with proven effectiveness (14).

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Corticosteroids for Influenza Pneumonia: Hold Off for Now!*

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In this issue of *Critical Care Medicine*, Cao et al (1) evaluated their experience with corticosteroid adjuvant therapy in 288 adults with avian-origin influenza A (H7N9) pneumonia. Using propensity score–matched case-control analysis, they showed that the median viral shedding time was longer among patients receiving high-dose corticosteroids. More importantly, patients receiving corticosteroids also had a significantly greater risk of mortality. This same group of investigators showed that the use of corticosteroids was common among patients hospitalized with this form of influenza with 62.2% of patients receiving at least one glucocorticoid (2). Despite the use of corticosteroids, progression to Acute Respiratory Distress Syndrome (ARDS) was high (71.2%) as was mortality (≈ 30%). This experience would suggest that adjuvant corticosteroids should not be routinely used among patients with severe influenza to include patients developing respiratory failure and ARDS. A potential explanation for this is the impact of corticosteroids on the host immune response allowing the viral infection to be unchecked accounting for the prolonged viral shedding and potentially for the greater mortality. It must be recognized that this study is limited by the retrospective nature of the analysis and being performed in a single country experiencing an outbreak with a specific strain of influenza. In addition, the propensity score methodology lowered the number of patients receiving high-dose corticosteroids to 26 potentially limiting the overall power of the analysis to identify

***See also p. e318.**

Key Words: corticosteroids; influenza; mortality

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risk factors for mortality. Nevertheless, other studies would seem to collaborate these findings.

When faced with the alarming 2009 H1N1 pandemic, immunomodulatory agents, such as corticosteroids, macrolides, statins, hyperimmune globulins from survivors, and various ventilatory rescue maneuvers, were tested out along with antivirals and standard ICU care. The majority of patients ended up receiving corticosteroids although at nonstandardized doses and durations (3, 4). The idea of corticosteroid administration stemmed from studies showing hypercytokinemia or "cytokine storm" in patients with H1N1 and H5N1 infections (5–7). High cytokine levels in infected individuals were particularly prominent in those who died, and these levels correlated with pharyngeal viral loads (5). In addition, patients developing post–influenza ARDS seemed to have a slower decline in nasopharyngeal viral loads, had higher plasma levels of proinflammatory cytokines, and had greater bacterial coinfection compared with patients with less severe disease (7). Another potential justification for corticosteroid treatment in severe influenza is the development of adrenal insufficiency that has been described in some patients (8). Initially, the theoretical role for corticosteroid therapy in influenza was partially confirmed by animal studies, suggesting that tissue injury resulting from viral replication could be mitigated with their use (9, 10). Early case reports and case series also suggested a clinical benefit when corticosteroids were added to the treatment of patients with severe influenza (11, 12). Unfortunately randomized controlled trials have failed to enroll enough patients to confirm these findings; so, available evidence relies on observational studies and heterogeneous meta-analyses (13).

Initial observational studies examining corticosteroid administration in influenza H1N1 during the 2009 pandemic failed to describe a benefit. When analyzing 220 critically ill patients with H1N1 infection, Martin-Loeches et al (14) found no improved outcomes after corticosteroid use but a higher likelihood of hospital-acquired pneumonia. Patients who received corticosteroids were significantly older and were more likely to have coexisting asthma, chronic obstructive pulmonary disease, and chronic corticosteroid use. A second Spanish prospective multicenter study performed in 148 ICUs that took into account the indication for corticosteroid treatment similarly did not detect a mortality benefit in patients with H1N1 influenza after adjusting for potential confounders, including severity of illness (4).

Brun-Buisson et al (3) examined patients from the French registry of critically ill patients with influenza A (H1N1) from the 2009 outbreak fulfilling criteria for ARDS. After excluding patients having other indications for corticosteroids or decompensated underlying disease as the primary cause for ICU admission, they evaluated 208 patients with ARDS; of those, 83 (39.9%) received corticosteroids. Steroid therapy was associated with excess death, both in crude analysis and after propensity score–adjusted analysis, controlling for admission severity of illness, initial administration of vasopressors, and immunodepression. Early therapy with corticosteroids (≤ 3 d of mechanical ventilation) seemed more strongly associated with mortality than late administration. Similarly, Han et al (15) assessed 83 patients with H1N1; of those, 46% developed critical illness, 17% died, and 37% recovered and were discharged. Critically ill and other patients did not differ by underlying conditions and severity, median temperature, and other measured risk factors. However, of 17 patients who received early glucocorticoid treatment, 71% subsequently developed critical disease compared with 39% of 66 patients who received late (> 72 hr) or no glucocorticoid treatment. Kim et al (16) evaluated 245 Korean patients with H1N1 admitted to the ICU; of those, 107 (44%) received adjuvant corticosteroid treatment. The 90-day mortality rate of patients given corticosteroids was significantly higher than that of those not given corticosteroids. The corticosteroid group was also more likely to have bacterial superinfection and had more prolonged ICU care. The impact of corticosteroids on mortality was confirmed with multivariate analysis and by case-control study.

Following these observational studies, a meta-analysis including 23 studies with 6,105 H1N1 patients found that corticosteroid use was associated with higher mortality (17). Eighteen of the studies addressed the critically ill patients solely. Cohort studies were less heterogeneous showing a relative risk for increased mortality in the corticosteroid group of 1.85 (95% CI, 1.5–2.3), whereas case-control studies were more heterogeneous but demonstrated a relative risk of 4.2 (95% CI, 3.1–5.8). The main limitations of this meta-analysis—significant heterogeneity among observational studies and more importantly lack of correction for severity of disease as older, sicker patients were prescribed corticosteroids—persisted in a subsequent meta-analysis performed by Rodrigo et al (18). The authors assessed 10 studies in the mortality analysis of 16 eligible studies (3,039 patients). The majority of studies (n = 9) were performed during the 2009 H1N1 pandemic with only one including patients diagnosed with H5N1 influenza. Some studies lacked data on disease severity and the indication for corticosteroid administration. When focusing on the four studies with low heterogeneity, Rodrigo et al (18) found an increased odds of mortality in patients receiving corticosteroids (odds ratio, 2.58; 95% CI, 1.4–4.8).

An important confounding factor for influenza in terms of assessing the response to therapeutic agents is the variability of the viral genotypes. Compared with H5N1, patients with H7N9 are older (median age, 63 vs 26 yr), more likely to be smokers, men, and have chronic conditions according to an observational study (19). The cumulative proportion of hospitalized subjects requiring invasive ventilation was the greatest for H7N9 at 62%, followed by 54% for H5N1, and the lowest for H1N1 at 17%. However, mortality was the highest in the H5N1 group with H5N1-infected patients also having the earliest onset of mortality

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among the three genotypes examined. The identification in patients with H7N9 of known risk factors for severe seasonal influenza and the more protracted clinical course compared with H5N1 patients suggests that host factors may be an important contributor to the severity and outcome of influenza infection. The current study by Cao et al (1) tries to define the role for adjuvant corticosteroids in the treatment of this new avian influenza A, H7N9 subtype recognizing that the findings may not be applicable for other influenza genotypes. Their findings add to the observational data suggesting a lack of impact of corticosteroids in the treatment of influenza.

With the lack of available clinical data showing benefit from corticosteroids for the treatment of influenza, especially severe disease, it seems prudent to hold off on this type of salvage therapy for now. What is needed are robust prospective clinical trials aimed at addressing this important issue. With that in mind, the organization of an "off-the-shelf" trial ready to be carried out during the next influenza pandemic is appropriate and should be supported during the "hibernation" period existing between such pandemics (20).

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