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Use of Hydrocortisone Based on Plasma Biomarkers in Patients with Septic Shock: Another One Bites the Dust?

In 2018, the ADRENAL (Adjunctive Glucocorticoid Therapy in Patients with Septic Shock) and the APROCCHSS (Hydrocortisone Plus Fludrocortisone for Adults with Septic Shock) trials were published (1, 2). Both trials compared the use of hydrocortisone versus placebo in adults with septic shock and found that hydrocortisone reduced time on mechanical ventilation, time to resolution of shock, and time in the ICU. Although the APROCCHSS trial showed a reduction in mortality with hydrocortisone use, this was not confirmed in the ADRENAL trial. Data from APROCCHSS and ADRENAL were subsequently included in updated systematic reviews and meta-analyses, which confirmed the findings from the two large trials (3, 4). Based on this, an international clinical practice guideline proposed a weak recommendation in favor of corticosteroids in patients with sepsis, including septic shock (5). Although most clinicians—based on the results of the trials and systematic reviews and on the proposed weak recommendation in the clinical practice guideline—may consider using hydrocortisone in patients with septic shock, especially in those with refractory shock, there is more uncertainty about the value of treatment with hydrocortisone based on plasma biomarker levels.

In this issue of the *Journal*, Cohen and colleagues (pp. 700–707) report the results of a cohort study nested within the ADRENAL trial (6). The authors assessed whether prerandomization baseline levels of the plasma biomarkers cortisol, aldosterone, and

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ascorbic acid modified the effect of hydrocortisone among 529 patients with septic shock from 22 ICUs in Australia and New Zealand. The authors observed no statistically significant interaction between plasma concentrations of the biomarkers and adjunctive hydrocortisone on 90-day mortality (primary outcome measure), shock reversal, or any other of the clinically relevant secondary outcomes, suggesting that the treatment effect of hydrocortisone is not dependent on the baseline plasma concentrations of cortisol, aldosterone, or ascorbic acid. There was an indication of interaction for free and total plasma concentrations of cortisol for some secondary outcomes and analyses; however, those analyses were not adjusted for multiple testing and therefore should be interpreted with caution, as acknowledged by the authors.

There are many strengths of the study. Embedding the study in a high-quality randomized clinical trial ensured prospective valid data collection with few missing data, including few patients lost to follow-up. The internal and external validity is high, and the results are applicable to other ICUs with a similar case mix. The comprehensive and prespecified statistical analysis plan, including the heterogeneity of treatment effect analysis, increases the transparency and robustness of the results. The sample size was large with resulting precise estimates. The use of reliable techniques to measure the biomarkers increases the validity of the measurements.

Despite the many strengths, the study holds some limitations. Sampling 14% (529/3,800) of the ADRENAL trial participants and limiting the sampling to baseline-only measurements may have introduced bias. Although robust, prespecified, and comprehensive, the statistical analyses were not adjusted for multiplicity, which may have resulted in false positives (type 1 error). Finally, patients included in the ADRENAL trial did not receive fludrocortisone along with hydrocortisone, therefore limiting the applicability to clinical settings with similar practice.

The clinical implications from this important, well-planned, and reported ADRENAL substudy are multiple. First and foremost, the finding that patients with lower or higher concentrations of baseline total or free cortisol concentrations did not receive any greater or lesser clinical effect from hydrocortisone treatment suggests that initial plasma cortisol is not a useful biomarker to identify patients who may benefit from this treatment. Owing to the known undesirable effects of hydrocortisone (3, 4, 7), use of hydrocortisone outside the pragmatic clinical criteria used in the APROCCHSS or in the ADRENAL trials is discouraged. Second, there is no indication of any clinically relevant association between baseline aldosterone concentrations and patient-important outcomes, which may suggest that mineralocorticoid deficiency plays a limited role in the pathophysiology in septic shock. Finally, there is evidence that low levels of ascorbic acid (hypovitaminosis C) plays a limited role in patients with septic shock, which indirectly questions the proposed combination therapy with ascorbic acid, hydrocortisone, and thiamine as an effective treatment strategy in septic shock (8). This is further supported by the recently published CITRIS-ALI (Effect of Vitamin C Infusion on Organ Failure and Biomarkers of Inflammation and Vascular Injury in Patients with Sepsis and Severe Acute Respiratory Failure) and VITAMINS (Effect of Vitamin C, Hydrocortisone, and Thiamine versus Hydrocortisone Alone on Time Alive and Free of Vasopressor Support among Patients with Septic Shock) trials, which could not confirm any benefit from use of this combination therapy (9, 10).

An important inference is that baseline levels of cortisol, aldosterone, and ascorbic acid do not seem to influence the treatment response of hydrocortisone, which may question the proposed treatment effect heterogeneity in patients with sepsis (11). However, differences in treatment effect to corticosteroids could be influenced by sepsis subtypes (12). These results, along with the fact that corticosteroids are a commonly used low-cost intervention, are an argument for finding patient characteristics that are associated with increased risk of harm with this intervention, rather than focusing on treatment response and efficacy.

In summary, there is no suggestion of heterogeneity in the effect of adjunctive hydrocortisone on mortality, shock resolution, or other clinical outcomes based on cortisol, aldosterone, or ascorbic acid concentrations in patients with septic shock. Consequently, there is no value in measuring these biomarkers at baseline to determine the treatment response of hydrocortisone in patients with septic shock. At best, it makes no difference and is a waste of resources; at worst, it is associated with undesirable effects, including hypernatremia, hyperglycemia, and neuromuscular weakness (5). ■

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Invasive *Aspergillus* Tracheobronchitis Emerging as a Highly Lethal Complication of Severe Influenza

Invasive aspergillosis is increasingly being recognized as a secondary infection in hospitalized patients with influenza. A recent cohort study from Belgium and the Netherlands showed that in ICU patients, influenza was an independent risk factor for invasive pulmonary aspergillosis (1). Influenza-associated pulmonary aspergillosis was associated with a 33% mortality rate in previously healthy individuals and 71% ICU mortality in the subgroup of patients with underlying host factors according to the European Organization for Research and Treatment of Cancer/Mycosis Study Group Education and Research Consortium consensus definitions for invasive mycoses. Fatal outcome may further be associated with delayed initiation of antifungal therapy (2) if an aggressive diagnostic approach is not pursued.

In this issue of the *Journal*, Nyga and colleagues (pp. 708–716) (3) report 10 cases of invasive *Aspergillus* tracheobronchitis in a cohort of 35 (28.6%) patients with severe influenza and invasive pulmonary aspergillosis. The mortality rate of patients with invasive tracheobronchitis was significantly higher compared with those without tracheobronchitis (90% vs. 44%; $P = 0.02$) (3). Although invasive *Aspergillus* tracheobronchitis is a recognized *Aspergillus* disease entity, it is considered a rare manifestation of pulmonary aspergillosis or confined to specific host groups such as patients with chronic obstructive pulmonary disease and lung transplantation recipients. Invasive *Aspergillus* tracheobronchitis has been reported in rare cases in association with influenza (2, 4), but this study shows that invasive tracheobronchitis is a more common manifestation of influenza-associated pulmonary aspergillosis and carries a very high mortality rate in comparison with other pulmonary forms of influenza-associated pulmonary aspergillosis.

Histopathological studies show that influenza causes focal or extensive tracheitis and bronchitis, in addition to diffuse alveolar damage (5). Disruption of the epithelial barrier of the airways is likely to facilitate fungal colonization and infection. Furthermore, influenza virus can exhibit a direct immunomodulatory effect through suppression of the NADP oxidase complex, which might cause a temporary disease status resembling chronic granulomatous disease with impaired host defense against *Staphylococcus aureus* and *Aspergillus* species and excessive innate inflammation. Indeed, influenza viral antigen was found in the tracheobronchial epithelium and submucosal glands, and to a lesser extent in bronchiolar epithelium, alveolar epithelial cells, and macrophages (5), supporting a link between cellular tropism of influenza virus and *Aspergillus* tracheobronchitis. In addition, other factors such as active smoking could further increase the risk for airway disease (3). Invasive *Aspergillus* tracheobronchitis may be a less common disease manifestation in other severe viral infections. Now with the coronavirus disease (COVID-19) pandemic, it is a very timely question whether invasive tracheobronchitis is a frequent *Aspergillus* disease manifestation, similar to influenza. Unlike influenza, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) enters the cell via ACE2 (angiotensin-converting enzyme 2), a receptor that is present in type 2 pneumocytes and ciliated cells but not in the epithelial layer of the larger airways (6). Although invasive pulmonary aspergillosis is increasingly reported in patients with severe COVID-19 (7, 8), cases of invasive *Aspergillus* tracheobronchitis have not yet been reported, which

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