For several decades, intensivists have debated the utility of corticosteroids as adjunctive treatment for septic shock. The 2016 Surviving Sepsis Campaign guidelines issued a weak recommendation to use intravenous hydrocortisone if and only if fluid resuscitation and vasopressor therapy were unable to restore hemodynamic stability.1

Since the 2016 guidelines, 2 large randomized trials of adjunctive hydrocortisone in septic shock have been published. The APROCCHSS trial2 enrolled 1241 patients with septic shock requiring high-dose vasopressors for at least 6 hours. Patients randomized to hydrocortisone plus fludrocortisone had lower 90-day mortality.2 Meanwhile, the ADRENAL trial3 enrolled 3658 patients with septic shock receiving any vasopressors for at least 4 hours. Patients randomized to hydrocortisone infusion had similar 90-day mortality as the placebo group, but spent fewer days on mechanical ventilation and had faster resolution of shock.3

Because of the inconsistent mortality benefit across trials, intensivists have mixed opinions regarding the utility of corticosteroids in septic shock. Proponents of corticosteroids argue that they consistently improve nonmortality outcomes. They result in faster shock resolution, shorter intensive care unit (ICU) stays, and fewer days on the ventilator—outcomes of heightened importance during the COVID-19 pandemic. For this reason, proponents may opt to prescribe hydrocortisone to all patients with septic shock meeting trial inclusions.

Meanwhile, skeptics of corticosteroids argue that less is more—and absent a clear mortality benefit, we shouldn’t subject our patients to additional therapies. Corticosteroids have a multitude of side effects (eg, hyperglycemia, hypernatremia, delirium, fluid retention, secondary infection) that may be incompletely measured in clinical trials. For this reason, skeptics may opt to prescribe hydrocortisone to few or no patients with septic shock.

Of course, between these opposing approaches of treating all or treating no patients with corticosteroids lies a vast middle ground of prescribing hydrocortisone to some patients with septic shock. This middle-road approach recognizes that the average treatment effects reported in clinical trials may not be a good estimate of the likely benefit for each and every patient. Rather, the actual benefit experienced by individual patients in trials and in our ICUs can vary dramatically.

The reasons for the variation in benefit (also known as heterogeneity of treatment effect4) are twofold. First, the relative risk reduction of a therapy may vary as a result of specific patient characteristics related to the therapy’s mechanism of action, such as a targeted chemotherapy that works on only certain cancers with a specific genetic mutation. Second, even in situations where the relative risk reduction is constant, the absolute risk reduction will vary based on patients’ risk for the outcome without treatment (eg, the higher a specific patient’s risk of death, the greater the benefit of a 50% reduction in risk of death).

Pirracchio et al5 analyzed 5 clinical trials to: (1) estimate individual patients’ benefit from adjunctive corticosteroids and (2) assess whether treatment decisions informed by these individualized estimates of benefit are superior to treating everyone or treating no one with corticosteroids.5

The authors used 2 different approaches to estimating patients’ individual benefit from corticosteroids. First, they estimated individual benefit according to the pooled relative risk reduction of corticosteroids and each patient’s personalized risk of mortality based on their severity of critical illness (as measured by the Simplified Acute Physiology [SAPS II] score). Second, they directly estimated the absolute risk reduction expected for each patient using an ensemble machine learning algorithm, called the SuperLearner, that incorporated patient characteristics, treatment,
and outcomes. This second approach was fundamentally different from the first approach because it
did not assume that treatment effect increased linearly according to patients' risk of death.

These 2 approaches to using individual benefit to guide corticosteroid prescribing were compared
with the existing strategies of treating everyone or treating no one with corticosteroids. A nice feature
of the analysis was that the approaches were compared across a range of thresholds for tolerating harm
from corticosteroids. Harm was operationalized in the number willing to treat, or the number of pa-
tients that one is willing to treat (and therefore expose to potential steroid-related harms) in order to
save one life. The baseline risk of death varied markedly across patients from 0% to 100% (eFigure 1 in
the supplement5), as did the expected change in mortality with corticosteroids ranging from an ap-
proximately 1% increase to an approximately 12% reduction (eFigure 2 in the supplement5).

Across all scenarios with plausible risk tolerance (ie, willingness to treat 15 or more patients with
steroids to save one life), the individualized approaches were associated with greater benefit, and
the machine learning approach consistently outperformed the risk-based approach to estimating
individual benefit. Interestingly, the machine learning model estimated that the maximal benefit
occurred when treating 20% of patients with corticosteroids (eFigure 4 in the supplement5)—far
lower than would receive corticosteroids in a treat-all approach.

How reliable are these findings? The methods used by Pirracchio et al5 are advanced and
thoughtful. The SuperLearner algorithm is an established machine learning tool. The results were
validated both internally using cross-validation and externally in a fifth trial. However, there is
potential for bias from pooling data across studies such that the comparison of corticosteroid vs
placebo was not fully randomized (because both groups of the COITTS trial received
corticosteroids5). Also, although the findings were validated in a separate clinical trial, it was small (75
patients7). Additional external validation, such as in the ADRENAL trial, would provide greater
confirmation. Finally, it is important to recognize that expected individual benefit may change over
time as outcomes improve, as has been shown in cardiovascular disease.8

This study by Pirracchio et al5 highlights the limitations of applying the average trial result to
each and every patient who would have been eligible for the trial, and the need to incorporate
individual patients' likelihood of benefit into our bedside clinical decision-making. In our clinical
practice, we should also consider that the threshold for tolerating treatment-related harm (ie, the
number willing to treat) likely varies across patients. For a patient with labile diabetes, diastolic heart
failure, and hypoactive delirium, the potential harms of corticosteroids are greater, and therefore,
the individual benefit necessary to prompt hydrocortisone prescription should be higher.

Can these findings by Pirracchio et al5 direct our corticosteroid use in septic shock? Tools to
estimate personalized benefit are already used to guide care for cancer and cardiovascular disease.
By contrast, although intensivists may ponder the benefit of therapies for individual patients, tools to
estimate individual benefit have not been formally incorporated into ICU clinical workflow. The
SuperLearner decision tree, while interpretable, is likely still too complex to guide care without a
readily available app or integration into the electronic health record.

As machine learning techniques continue to advance, they offer the promise of refining our
clinical decision-making—both for corticosteroids, as in this study by Pirracchio et al,5 but also for
other common treatments.9 However, for such models to improve decisions in practice, they must
be integrated within clinical workflow, trusted by clinicians, and tested prospectively. In the
meantime, this study highlights the challenge and nuance of applying clinical trial data to decision-
making for individual patients.

ARTICLE INFORMATION
Open Access: This is an open access article distributed under the terms of the CC-BY License. © 2020 Prescott HC
et al. JAMA Network Open.
REFERENCES


