Hydrocortisone in septic shock: is it worth it?

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In patients with septic shock, adjunctive corticosteroid therapy appears to speed up resolution of shock, decrease time to extubation and time to intensive care unit (ICU) discharge, and increase the number of days spent alive and outside the ICU from randomisation to 90 days.[1] Given that drug acquisition costs are low, and ICU costs are a substantial contributor to overall health care costs, one might reasonably expect that adjunctive corticosteroid therapy would be cost-effective for patients with septic shock. In this context, the findings of a cost-effectiveness analysis reported in this issue of *Critical Care and Resuscitation* are surprising.[2]

Investigators used total hospital-related costs and quality-adjusted life-years gained at 6 months to calculate incremental cost-effectiveness ratios that provide the cost per quality-adjusted life-year gained. These were compared for hydrocortisone and placebo patients enrolled in the Adjunctive Glucocorticoid Therapy in Patients with Septic Shock (ADRENAL) trial[1] in New South Wales and Queensland (the cost-effectiveness cohort). Adjunctive hydrocortisone therapy did not significantly affect longer term mortality, health-related quality of life, or health care resource use or costs in this cohort. In an estimate of the precision of the calculated incremental cost-effectiveness ratios based on random sampling, most sampling suggested that hydrocortisone was more effective in terms of quality-adjusted life-years gained and more costly than placebo. Moreover, the best estimate was that the incremental cost of hydrocortisone was an astronomical A$1 254 078 per quality-adjusted life-year gained.

As an intensivist who, following the publication of the ADRENAL trial, now gives hydrocortisone routinely in order to try and make more efficient use of ICU resources by endeavouring to make patients potentially ward-ready sooner, these findings are troubling. They are a prompt to consider whether or not adjunctive corticosteroid therapy is really worth it. This is not a simple question and there are many issues to consider.

The first issue is the representativeness of the cost-effectiveness cohort. The between-group differences in 6-month mortality and quality of life data in the cost-effectiveness cohort and the patients not included in the cost-effectiveness cohort are similar. However, the reported between-group differences in health care resource use in the cost-effectiveness cohort differ from those in the other patients in important ways that are likely to have influenced costs. Overall, it appears likely that incremental costs associated with hydrocortisone treatment were higher in the cost-effectiveness cohort than in the cohort of patients not included in the cost-effectiveness analysis. Importantly, the median ICU length of stay for hydrocortisone- and placebo-treated patients was similar in the cost-effectiveness cohort, but patients who were not included in the cost-effectiveness analysis who were allocated to hydrocortisone stayed in the ICU for more than a day less than those who were allocated to placebo. It is implausible that the biological effect of steroids in patients with septic shock in NSW and Queensland differs from the effect of steroids in patients elsewhere. As expected, steroids consistently hastened resolution of shock.[2] Thus, the likely explanations for the apparent inconsistencies in the findings in relation to ICU length of stay are the play of chance, or differences in ICU discharge practices. Such differences might include a greater degree of ICU exit block due to a relative shortage of ward beds in NSW and Queensland, a lesser degree of ICU constraint in these states compared with elsewhere allowing for greater periods of observation before ICU discharge, or both. Cost-effectiveness analyses conducted in ADRENAL trial participants from other jurisdictions would be informative.

The second issue relates to the accuracy of the cost estimates. With a small difference between groups in quality-adjusted life-years, small absolute differences in costs per patient equate to very large differences in incremental cost per quality-adjusted life-year gained. In this setting, minor inaccuracy in estimated costs will translate into substantial inaccuracy in calculated incremental cost per quality-adjusted life-year gained. Moreover, non-hospital associated costs, such as pharmacy costs and costs of primary care, which were not included in this analysis, might be important.

The third issue is that clinically important changes in mortality from adjunctive corticosteroid therapy are not ruled out by the ADRENAL trial data.[1] In the Activated Protein C

and Corticosteroids for Human Septic Shock (APROCCHSS) trial,[3] 90-day all-cause mortality was statistically significantly lower among patients who received hydrocortisone plus fludrocortisone than among those who received placebo. While there are important differences between these two trials and many potential explanations for the apparent variance between their findings, even identical experiments would not be expected to provide identical results. It is possible that the true effect of adjunctive corticosteroid therapy on mortality might lie somewhere between the effects suggested by the ADRENAL[1] and the APROCCHSS trials.[3] If there truly is a benefit of adjunctive corticosteroid therapy on mortality that is larger than the ADRENAL trial data suggest, this would affect estimates of quality-adjusted life-years gained at 6 months with this therapy and cost-effectiveness estimates.

The fourth issue is that cost-effectiveness framed in terms of quality-adjusted life-years gained at 6 months is only one way of considering cost-effectiveness. We have strong evidence that adjunctive corticosteroid therapy reduces the amount of time taken to achieve physiological stability. In all jurisdictions this should equate to patients being physiologically ready for ward discharge and provides the potential to free up ICU bed-days allowing for more efficient use of health care resources. One might reasonably ask the question, based on total health care costs within 6 months of randomisation, what is the incremental cost per potential ICU bed-day gained for hydrocortisone-treated patients compared with placebo-treated patients? While the ability to convert potential ICU bed-days into actual bed-days will depend on local logistic factors, using hydrocortisone in patients with septic shock should provide a pathway to use ICU resources more efficiently. Even if hydrocortisone therapy is not a cost-effective therapy to increase quality-adjusted life-years at 6 months, it might still be a cost-effective way to free up ICU beds to care for other patients.

Competing interests

None declared.

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