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Future directions for corticosteroids in sepsis

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To the Editor:

In their systematic review and meta-analysis of corticosteroids for sepsis, Fang et al. suggest that future studies should address the identification of patients who will derive the most benefit from corticosteroids, to enable a personalized medicine approach.[1] I suggest additional directions for this field.

First, the ability of corticosteroids to increase blood pressure and reverse shock could explain their mortality benefit. Therefore, basic and clinical studies should focus on the mechanism of this effect. Corticosteroids act via two receptors, the glucocorticoid receptor (GR) and mineralocorticoid receptor (MR), which have differing tissue distributions and biologic effects. Even the so-called “low dose” hydrocortisone treatment described in the included trials will result in clinically significant activation of both GR and MR, and three trials included additional MR-directed therapy with fludrocortisone. In contrast, dexamethasone and betamethasone have very little MR activity. Activity at either receptor may increase blood pressure via different mechanisms. Future trials designed to more specifically target one or the other receptor (for example, with dexamethasone vs. fludrocortisone) would improve understanding of the mechanism of corticosteroid effects in sepsis patients. This understanding would enable more targeted treatment that limits adverse effects.

Second, the brain is rich in MR and GR, and activity of corticosteroid treatment in the CNS may affect neuropsychiatric outcomes in survivors. Indeed, several studies have suggested a potential benefit of corticosteroid treatment on symptoms of post-traumatic stress disorder and anxiety in survivors of critical illness, including sepsis.[2,3] Therefore, all future clinical trials examining the effect of corticosteroid therapies in critical illness should include an assessment of neuropsychiatric function in survivors. Because persistent psychiatric symptoms appear early after discharge, useful neuropsychiatric data may be gathered even in short-term follow-up.[4]

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