

## Monotherapy or Combination Therapy for Septic Shock



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International guidelines recommend using corticosteroids for adults with septic shock who require vasopressor therapy, supported by moderate-quality evidence. While corticosteroids may shorten the duration of shock, their impact on mortality remains uncertain. A recent meta-analysis found no significant reduction in mortality among septic shock patients treated with hydrocortisone compared to those given a placebo.

Teja and colleagues conducted a meta-analysis of 17 randomised controlled trials to investigate the impact of corticosteroids on mortality in patients with septic shock. They compared the combination of fludrocortisone plus hydrocortisone to placebo/usual care or hydrocortisone alone.

Their findings revealed that the combination of fludrocortisone plus hydrocortisone significantly lowered the risk of all-cause mortality compared to both placebo/usual care and hydrocortisone alone, with a high posterior probability of superiority. They estimated that this combination could lead to 48 fewer deaths per 1000 septic shock patients compared to placebo/usual care. Safety profiles were similar across treatment regimens, but evidence certainty was low due to limited data availability. Extension of the analysis to include data from non-peer-reviewed RCTs produced consistent results. Overall, the combination of fludrocortisone plus hydrocortisone emerged as the most promising treatment regimen for septic shock patients in terms of mortality reduction.

The authors address the lack of direct data comparing the combination of fludrocortisone plus hydrocortisone to hydrocortisone alone in managing septic shock. With only two trials directly comparing these treatments, they employed sophisticated statistical methods to leverage both the limited direct and more abundant indirect evidence. This approach allowed them to draw meaningful conclusions despite the scarcity of head-to-head comparisons.

The main concern for readers interpreting the results of this meta-analysis lies in the reliance on indirect evidence. Specifically, the conclusion regarding the superiority of the combination of fludrocortisone plus hydrocortisone versus hydrocortisone alone was primarily based on indirect evidence from trials comparing these treatments to placebo/usual care. Ensuring the validity of such indirect comparisons necessitates that the different sets of trials are similar in all important characteristics that could affect treatment outcomes. To address this, the authors pre-specified potential effect modifiers such as age, mechanical ventilation use, and severity of illness.

The authors thus caution that their main finding—that fludrocortisone plus hydrocortisone reduced all-cause mortality more than hydrocortisone alone in septic shock—relies heavily on indirect evidence. In any case, these findings are expected to provoke significant debate among clinicians. While some may find the results robust enough to consider incorporating corticosteroid combinations into septic shock management, others may remain sceptical. It's important to recognise that sepsis is a heterogeneous syndrome with various subphenotypes that may respond differently to corticosteroids. Ongoing precision medicine research aims to identify which patients with septic shock may be harmed by corticosteroids, who may benefit from hydrocortisone alone, and who may gain survival benefits from the combination of fludrocortisone plus hydrocortisone.

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