Sepsis is life threatening organ dysfunction caused by a dysregulated host response to infection. Septic shock is the most severe form of sepsis. These patients experience profound circulatory, metabolic, and cellular abnormalities. They require vasopressors to maintain perfusion pressure. Worldwide, about 30 million people are hospitalised with sepsis every year and up to six million of them die.

In 1976, William Schumer published the results of a study where over an 8-year period he randomized 172 patients with septic shock to receive either high-dose methylprednisolone, high-dose dexamethasone or placebo. The mortality among the steroid treated group was 14% (24/168) as compared to 42.5% (68/160) in the placebo group ($P<0.001$). The use of corticosteroids as adjunctive treatment for sepsis has still remained a very controversial topic till date.

What's the rationale for using steroids in patients with septic shock?

In critically ill patients, dysfunction of the hypothalamic-pituitary-adrenal axis (HPA) may occur in 10 to 20%; it may be as high as 60% in patients with septic shock .

Critical illness-related corticosteroid insufficiency (CIRCI) is based on the hypothesis that even maximal stimulation of the hypothalamic-pituitary-adrenal axis in disease states such as sepsis results in insufficient corticosteroid levels. This is described as "relative adrenal insufficiency". Besides, there may be tissue resistance to corticosteroids in the presence of sepsis.

The use of corticosteroids may help attenuate the dysregulated host response due to sepsis, with improvement in the hemodynamic parameters related to sepsis.

1. **Is there a way to predict which patients will be steroid-responsive?**

In a previous study by Annane et al., the ACTH stimulation test was performed to evaluated "relative adrenal insufficiency" due to dysfunction of the HPA axis. They performed a conventional-dose short test, using synacthen, a synthetic form of ACTH in a dose of 250 µg, IV to assess the integrity of the pituitary-adrenal axis. Cortisol levels are measured at 30 and 60 min. Response defined as 9 mcg/dl or less to tetracosactrin. Patients who did not respond were defined as "non-responders"

The main end point was the 28-day survival distribution from randomization in non-responders to the short corticotropin test. Improved survival only among non-responders. 73 (63) vs. 60 (53)

However, subsequent studies (CORTICUS, ADRENAL, APROCCHSS) have not performed the short-synacthen test to assess response to synacthen.

2. **Why do we choose Hydrocortisone over other steroids in ICU patients**

The preferred corticosteroid preparation is uncertain. Older studies, from the 1970s and 80s used fairly high doses of methylprednisolone, some of them with poor

outcomes. Hydrocortisone is the most commonly studied corticosteroid in recent RCTs, hence is currently preferred. Differences between different types glucocorticoids may be negligible. The additional administration of a mineralocorticoid such as fludrocortisone, has also been evaluated in some studies; however, it is unclear at this stage if it makes a difference.

3. What's the evidence out there either in favour of or against the use of steroids in patients with Septic shock

Annane et al. conducted the first, adequately powered RCT to evaluate the usefulness of corticosteroids in septic shock. The combination of intravenous hydrocortisone 50 mg every 6 hours and fludrocortisone 50 µg tablet once daily were administered for a week and compared with placebo. A short corticotrophin test was performed in all patients to test adrenal function. Patients with a rise in cortisol level of less than 9 µg/dl in response to corticotrophin were considered as “non-responders”. The 28-d survival, the primary outcome, was significantly higher among non-responders; this suggested that exogenous administration of corticosteroids led to improved survival in patients with relative adrenal insufficiency. The time to cessation of vasopressors was also significantly less among non-responders who were treated with corticosteroids. This was followed by the CORTICUS trial, which included 499 patients; in this study, intravenous hydrocortisone alone was administered as adjunctive therapy (fludrocortisone was not used) and compared with placebo. No difference was observed in the 28-d mortality in this study; however, a reduced time to shock reversal was noted in corticosteroid-treated patients. The patients in the CORTICUS trial were less severely ill, compared to the Annane et al. study, with relatively fewer patients who fulfilled the criteria for septic shock.

The ADRENAL study recruited 3800 patients involving 69 medical-surgical ICUs in Australia, the United Kingdom, New Zealand, Saudi Arabia, and Denmark. Patients were intubated or on non-invasive ventilation and on vasopressor therapy for more than 4 h at randomization. In the intervention arm, hydrocortisone was administered as an intravenous infusion of 200 mg/d for 7 d or until death or discharge from the ICU. No difference was observed in the 90-d mortality, the primary outcome, for which the study was powered. Among the secondary outcomes, the investigators observed a significant difference in the median time to shock resolution, the median time to initial of discontinuation of mechanical ventilation, the median time to ICU discharge, and the number of patients who received a blood transfusion. The 28-d mortality, shock recurrence, use of renal replacement therapy, number of days alive and out of ICU, the median time to hospital discharge, and the number of days alive and out of hospital were not different between groups.

The combination of hydrocortisone, 50 mg/kg intravenously 6 hourly and 50 µg fludrocortisone once daily was evaluated in a recent French multicentric study (APROCCHSS) among patients with septic shock who were on vasopressor therapy for at least 6 hours. The study was originally designed to assess the efficacy of the combination of drotrecogin alfa and corticosteroids. However, during the course of the study, drotrecogin alfa was withdrawn from the market; thereafter, the study was

continued with corticosteroids alone and compared with placebo. In contrast to ADRENAL, a statistically significant difference was observed in the 90-d mortality, which was the primary endpoint. The all-cause mortality at ICU and hospital discharge, and at 180 days were also significantly lower among corticosteroid-treated patients. Earlier shock reversal was observed, with fewer patients alive and off vasopressor support at 28 d with corticosteroids.

- All major randomized controlled studies that evaluated the use of corticosteroids in septic shock have shown earlier shock reversal and more rapid weaning down of vasopressors.
- Corticosteroid administration may lead to a shorter duration of mechanical ventilation and length of stay in the intensive care unit.

Prior to ADRENAL and APPROCHSS, between 1976 and 2017, 21 randomized controlled trials have been published examining the role of short-course high-dose corticosteroid (n=4) and a "low-dose" prolonged course of corticosteroid (usually 200–300 mg hydrocortisone/day for 5–7 days) for patients with sepsis, severe sepsis and septic shock. In all 3,928 patients were enrolled in these 21 studies (average n=357±199). The high-dose regimen was associated with an increased risk of death and increased complications (4). The results of the low-dose regimen were mixed with some studies demonstrating a survival advantage with an improvement in some secondary outcomes while other showed no benefit. Seventeen meta-analyses of these studies have been performed and have similarly shown conflicting results with some demonstrating a survival advantage (4-6) while other have not.
Adrenal and APROCCHSS have confirmed that low dose regimen is safe. And it helps to resolve the shock quickly. Again, this is significant finding as one less day in ICU saves a lot of money and its good for both patient and family.

There was another trial called, Hydrocortisone for Prevention of Septic Shock (HYPRESS) in 2016 study randomized patients with severe sepsis to a continuous infusion of hydrocortisone or placebo for 5 days (17). While treatment with hydrocortisone had no effect on the primary outcome (progression to septic shock) or secondary outcomes, the incidence of delirium was significantly less in the corticosteroid treated group. In this study 11.2% (95% CI, 6.4–19.0) of the corticosteroid treated patients developed delirium as compared to 24.5% (95% CI, 17.2–33.7) of control patients (P=0.01). In addition, much like the ADRENAL study the incidence of side effects (except hyperglycemia) was not increased in the patients treated with hydrocortisone.

This has confirmed again that low dose regimen is safe and does not cause delirium. Also, there is no preventive role for steroids in septic shock.

The meta-analysis by Wang et al in 2013 high-dose corticosteroid administration for <10 days has no clinically important effect on wound healing." – Relevant for surgical cohort of patients.

Also, there is some suggestion that rather than monotherapy with corticosteroids, addition of vitamin C and thiamine might enhance the effect of steroids.

What's fascinating to me is the difference in mortality of patients in 2 trials – ADRENAL 28% Vs APROCCHHS 49&. Intact, Annane study in 2002 had mortality of 70% in control group. Just wonder why there is so much difference in the mortality of the same disease across 2 continents.

4. **What's your current practice**

We initially carry out modest fluid resuscitation and noradrenaline infusion in hypotensive patients who are likely to have sepsis. If the blood pressure does not stabilize (mean arterial pressure of around 70 mm Hg) or if the noradrenaline dose required to maintain the target MAP continues to increase, we would strongly consider hydrocortisone in a dose of 50 mg/6 hourly. We do not use an infusion nor do we add fludrocortisone.

I agree with you. Even though its weak recommendation, 3 major societies (SCCM, ESICM & JSCCM) have said that In favour for steroids in patients with hypotension refractory to fluid resuscitation and vasopressor. However, it's still debatable as how to define refractory shock w.r.t cut-off of vasopressor dose or fluid volume used for resuscitation.

So, I do use steroids in refractory septic shock. The only difference to ADRENAL study, which I follow is to wean steroids as soon as there is resolution of shock.

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