Steroids in Septic Shock

Key Article

- *Venkatesh B, et al. Adjunctive glucocorticoid therapy in patients with septic shock. N Engl J Med. 2018.*

Background

- Steroids have been used as adjuvant therapy for septic shock for more than 40 years
- Uncertainty remains about their safety and efficacy
- 1980s - RCTs demonstrating harm with high-dose methylprednisolone
- 2 RCTs examining lower-dose hydrocortisone had conflicting results on mortality among patients with septic shock
- Current clinical practice guidelines recommend the use of hydrocortisone in patients with septic shock if adequate fluid resuscitation and vasopressors have not restored hemodynamic stability - Recommendation WEAK based on low quality of evidence
- Much variation in clinical practice

Objective

- Test the hypothesis that hydrocortisone results in lower mortality than placebo among patients with septic shock

Study

- Investigator-initiated, international, pragmatic, double-blind, parallel-group, randomized, controlled trial
- 69 medical-surgical ICUs in Australia, UK, New Zealand, Saudi Arabia, and Denmark
- Patients
    - Included
        - Adults >= 18 years of age
        - Undergoing mechanical ventilation
        - Documented or strong suspicion of infection
        - 2 or more SIRS criteria
        - Treated with vasopressors or inotropic agents for a minimum of 4 hours
    - Excluded
        - Receive treatment with systemic steroids for an indication other than septic shock
        - Received etomidate

        - Were considered likely to die from a pre-existing disease within 90 days after randomization
        - Met all inclusion criteria for more than 24 hours
- Randomized
    - IV infusion of hydrocortisone at a dose of 200 mg per day
    - Placebo
    - Administered over a period of 24 hours for a maximum of 7 days or until ICU discharge or death
    - Patients, treating clinicians, trial personnel unaware of trial-group assignments and sequence
- Outcomes
    - Primary outcome: 90-day mortality
    - Secondary
        - 28-day mortality
        - Time to resolution of shock
        - Recurrence of shock
        - Length of ICU stay
        - Length of hospital stay
        - Frequency and duration of MV
        - Frequency and duration of RRT
        - Incidence of new bacteremia or fungemia between 2-14 days
        - Receipt of blood transfusion

Results

- 3800 patients were enrolled
    - 1898 assigned to hydrocortisone
    - 1902 assigned to placebo
- Ultimately 3658 included in study
    - 1832 to hydrocortisone
    - 1825 to placebo
    - Characteristics of patients similar
- Primary outcome - 90-day mortality
    - 27.9% in hydrocortisone group
    - 28.8% in placebo
    - No difference based on admission type (med vs. surgical), dose of catecholamine infusion, primary site of sepsis, gender, APACHE II score, and duration of shock
- Secondary Outcomes
    - No difference in 28-day mortality
    - Time to resolution of shock shorter in hydrocortisone group
    - Time to ICU DC shorter in hydrocortisone group
    - Shorter duration of initial episode of MV in hydrocortisone group
    - Fewer patients in the hydrocortisone group received a blood transfusion
- Adverse events
    - 33 reported in trial population

        - 1.1% in hydrocortisone group
        - 0.3% in placebo
    - 6 serious adverse events - 4 in hydrocortisone group, 2 in placebo

Limitations

- Only adverse events judged by the treating clinician to be related to trial regimen were recorded
- Did not adjudicate appropriateness of ABX
- Did not collect data regarding all possible secondary infections

Take Home Point

- **A continuous infusion of hydrocortisone did not lower 90-day mortality in septic shock patients undergoing mechanical ventilation**