Steroids in Sepsis – Where Has the Pendulum Swung?

Background

- Experimental and clinical evidence suggests that sepsis is associated with a dysregulated response of the hypothalamic-pituitary-adrenal axis - may involve steps from cortisol production to cortisol use by cells
- 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 - 33% believe steroids improve survival in septic shock, 33% believe they do not, and 33% are unsure

Venkatesh B, et al. Adjunctive glucocorticoid therapy in patients with septic shock. N Engl J Med. 2018; 378:797-808.

- 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
  - 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 in 69 medical-surgical ICUs
        - 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
        - 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**

Annane D, et al. Hydrocortisone plus fludrocortisone for adults with septic shock. N Engl J Med. 2018; 378:809-18. APROCCHSS Trial (Activated Protein C and Corticosteroids for Human Septic Shock)

- Objective
  - Test the hypothesis that hydrocortisone plus fludrocortisone therapy or drotrecogin alfa would improve the clinical outcomes of patients with septic shock
- Study
  - Placebo-controlled trial with four parallel groups organized in a 2x2 factorial design
    - After withdrawal of Xigris from the market - trial continued with 2 parallel groups
  - 34 centers: September 2008 to June 2015
  - Patients
    - Admitted to the ICU
    - Indisputable or probable septic shock for less than 24 hours
    - SOFA score of 3 or 4 for at least 2 organs for at least 6 hours
    - Vasopressor therapy for at least 6 hours to maintain SBP of at least 90 or MAP of at least 65 mm Hg
  - Randomization
    - Assigned in permuted blocks of eight to receive hydrocortisone plus fludrocortisone, drotrecogin alfa, the combination of the 3 drugs, or their respective placebos
    - Hydrocortisone given in 50 mg IV boluses every 6 hours; fludrocortisone given as 50 mcg tablet once a day
    - Treatment for 7 days
  - Measurements
    - Plasma total cortisol levels measured before, 30 min, and 60 min after corticotropin test
  - Treatment according to the 2008 SSC Guidelines
  - Primary Outcome: 90-day all cause mortality
  - Secondary outcomes
    - All cause mortality at ICU DC, hospital DC, day 28, and day 180
    - % of patients weaned from vasopressors at day 28 and 90
    - Time to weaning from vasopressors
    - % of patients weaned from mechanical ventilation at day 28 and day 90
    - Time to weaning from MV
    - Ventilator free days up to day 28 and day 90
    - Others
  - Safety outcomes
    - Superinfection up to day 180
    - GIB up to day 28
    - Hyperglycemia up to day 7

- Results
    - Trial suspended twice
    - Sponsor terminated trial when expiration dates of meds were reached - 1241 patients
    - **90-day all cause mortality**
        - **Hydrocortisone plus fludrocortisone: 43%**
        - **Placebo: 49.1%**
        - **P=0.03; RR of death 0.88**
    - Secondary outcomes
        - ICU DC mortality
            - Hydrocortisone plus fludrocortisone: 35.4%
            - Placebo: 41%
            - P=0.04
        - Hospital DC mortality
            - Hydrocortisone plus fludrocortisone: 39%
            - Placebo: 45.3%
            - P=0.02
        - 180-day mortality
            - Hydrocortisone plus fludrocortisone: 46.6%
            - Placebo: 52.5%
            - P=0.04
    - Hydrocortisone plus fludrocortisone group
        - Shorter time to weaning from mechanical ventilation
        - Shorter time to weaning from vasopressor therapy
        - More vasopressor free days
        - More organ failure free days
    - Serious Adverse Events
        - Hydrocortisone plus fludrocortisone: 53.1%
        - Placebo: 58%
        - P=0.08
        - Risk of GIB or superinfection not higher
- Limitations
    - Some imbalance between groups - slightly more viral pathogens in the hydrocortisone plus fludrocortisone group
    - Drotrecogin alfa removed from market and impacted statistical power calculation
    - Used 2008 SSC Guidelines
    - Did not report all secondary outcomes included in original trial
- **Take Home Point**
    - **7-day treatment course of hydrocortisone plus fludrocortisone resulted in lower mortality at day 90, ICU DC, and hospital DC compared with placebo**

- Differences between ADRENAL and APROCCHSS
    - Landmark trials describing the largest comprehensive analyses of hydrocortisone effects in critically ill medical and surgical patients
    - Patient populations not directly comparable
        - APROCCHSS
            - More seriously ill patients

            - Oral fludrocortisone used
        - ADRENAL
            - Higher rate of surgical admissions
            - Lower RRT rate
            - Lower rates of blood infection, pulmonary infection, and UTI
            - Higher rate of abdominal infection
    - Both showed beneficial effects on secondary outcomes of shock reversal and duration of MV

Rochwerg B, et al. Corticosteroids in sepsis: An updated systematic review and meta-analysis. Crit Care Med. 2018; epub ahead of print.

- Objective
    - Update prior meta-analysis from 2015
    - Respond to new potentially practice changing evidence and provide trustworthy practice guidelines in a timely manner
- Study
    - Included all RCTs comparing the use of steroids with a steroid-free comparator group in critically ill patients with sepsis
    - Both adults and children diagnosed with sepsis, severe sepsis, or septic shock
    - Excluded case reports, case series, and observational studies
    - Outcomes
        - Short-term mortality up to 31 days
        - Long-term mortality (60d to 1 year)
        - Shock reversal at 7 days
        - Organ dysfunction at day 7
        - ICU LOS
        - Hospital LOS
        - Stroke
        - Myocardial infarction
        - Neuromuscular weakness
        - GI bleeding
        - Hypernatremia
        - Superinfection
- Results
    - 2015 Cochrane review included 30 studies
    - 12 new RCTs eligible for a total of **42 articles**
        - 24 examined septic shock
        - 5 were for patients with both CAP and sepsis
        - 4 with ARDS and sepsis
        - 3 studies enrolled only children
        - 1 enrolled both adults and children
    - Most studies used hydrocortisone and most used a low dose (<400 mg/day)
    - Short-term mortality up to 31 days
        - RR 0.93 (CI 0.84-1.03)
        - "Steroids may achieve a small or no reduction in short-term mortality"
    - Long-term mortality (60d to 1 year)
        - RR 0.94 (CI 0.89-1.0)
        - "Steroids possibly achieve a small reduction in long-term mortality"

- Shock reversal at 7 days
  - RR 1.26 (CI 1.12-1.42)
  - "Steroids increase shock reversal in the first week"
- Organ dysfunction at day 7
  - "Steroids decrease organ dysfunction at day 7"
- ICU LOS
  - "Steroids probably achieve a small reduction in the duration of initial ICU LOS"
- Hospital LOS
  - "Steroids probably achieve a small reduction in the duration of hospitalization"
- Stroke
  - RR 2.07 (CI 0.45-9.61)
  - Risk is uncertain
- Myocardial infarction
  - RR 0.91 (CI 0.45-1.82)
  - Risk is uncertain
- Neuromuscular weakness
  - RR 1.21 (CI 1.01-1.45)
  - "Steroids may result in a small increase in neuromuscular weakness"
- GI bleeding
  - RR 1.09 (CI 0.86-1.38)
  - "Steroids may have little or no difference on GIB"
- Hypernatremia
  - RR 1.64 (CI 1.32-2.03)
  - "Steroids probably increase the risk of hypernatremia"
- Superinfection
  - RR 1.02 (CI 0.89-1.18)
  - "Steroids may have little or no impact on superinfection"

- **Take Home Points**
  - **Best estimates suggest a small absolute reduction in mortality in sepsis based on low-to-moderate certainty evidence; however, the confidence interval around the estimate includes no effect.**
  - **Point estimate suggest a reduction in ICU and hospital LOS, but effects are small (less than a day).**
  - **Harms seem minimal.**