Stressed Over Steroids: Timing Steroids in Sepsis

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Objectives

• Describe historical use and primary literature of steroids in sepsis

• Discuss the outcomes of the HYPRESS trial

• Outline an approach for initiation of steroids in the setting of septic shock
Clinical Controversy

Benefit

Risk
Pathophysiology

ROS = Reactive Oxygen Species

Cytokines, Proteases, ROS, Complement Activation

Inflammation

Image Source: http://combioboilersleeds.com/keywords/body-1.html
Pathophysiology

Inflammation

CO x SVR = BP

Hypoxemia

Tissue Damage


CO = Cardiac Output
SVR = Systemic Vascular Resistance
BP = Blood Pressure
Objective 1

Describe historical use and primary literature of steroids in sepsis
Historical Literature

Bennett and colleagues - 1963

**Population**
- Life-threatening infection (n=194)

**Timing**
- Within 24h of diagnosis

**Intervention**
- Hydrocortisone 300mg (followed by taper x6 days)
- Placebo

**Outcome**
- No difference in mortality

Historical Literature

Schumer - 1976

Population: Septic shock (n=172)

Timing: At the time of diagnosis

Intervention:
- Dexamethasone 3mg/kg
- Methylprednisolone 30mg/kg
- Placebo

Outcome: Early steroids improve mortality

Historical Literature

Sprung and colleagues - 1984

Population: Septic shock (n=59)

Timing: 17.5 ± 5.4 hours after onset

Intervention:
- Dexamethasone 6mg/kg
- Methylprednisolone 30mg/kg
- Placebo

Outcome: Early steroids improve mortality and shock reversal temporarily

Historical Literature

Bone and colleagues - 1987

Population: Severe Sepsis or Septic Shock (n=382)

Timing: Within 2h of diagnosis

Intervention:
- Methylprednisolone 30mg/kg x4 doses
- Placebo

Outcome: No difference in mortality

Pathophysiology

Catecholamines

hydrocortisone

Historical Literature

Annane and colleagues - 2002

Population
Septic Shock (n=299)

Timing
Within 8h of diagnosis

Intervention
- Hydrocortisone 50mg q6h + Fludrocortisone 50mcg daily
- Placebo

Outcome
Early steroids improve mortality and decrease time to shock reversal

Historical Literature

CORTICUS - 2008

Population
- Septic Shock (n=499)

Timing
- Within 72h of diagnosis

Intervention
- Hydrocortisone 50mg q6h
- Placebo

Outcome
- Late steroids do not improve mortality, but decrease time to shock reversal

Question 1

What are the key findings of the Annane and CORTICUS trials regarding steroids in septic shock?

A – The Annane trial found a decrease in mortality, but CORTICUS only found a decrease in vasopressor requirements

B – Both trials found steroids to be ineffective

C – The CORTICUS trial found a decrease in mortality, but Annane only found a decrease in vasopressor requirements

D – Both trials found a decrease in mortality
Objective 2

Discuss the outcomes of the HYPRESS trial
Pathophysiology

Inflammation

Severe Sepsis

Septic Shock
New Definitions

Sepsis    Severe Sepsis    Septic Shock

HYPRESS

Population: Severe Sepsis (n=353)

Timing: Within 48h of diagnosis

Intervention: Hydrocortisone 50mg bolus + 200mg/day continuous infusion x5 days followed by 6 day taper / Placebo

Outcome: Occurrence of septic shock within 14 days

HYPRESS

Percent of Patients (%)

- Septic Shock: p = 0.70
- 28 Day Mortality: p = 0.86
- 90 Day Mortality: p = 0.44
- 180 Day Mortality: p = 0.32
- Mechanical Ventilation: p = 0.21
- RRT: p = 0.98

HYPRESS

- **Secondary Infections**: Placebo vs. Hydrocortisone, p = 0.26
- **Hyperglycemia**: Placebo vs. Hydrocortisone, p = 0.009
- **Muscle Weakness**: Placebo vs. Hydrocortisone, p = 0.18
- **Hypomagnesemia**: Placebo vs. Hydrocortisone, p = 0.97
- **GI bleeding**: Placebo vs. Hydrocortisone, p = 0.68


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**HYPRESS**

**Strengths**
- Multicenter (34 ICUs)
- Blinded well
- Comparable treatment groups

**Limitations**
- Not powered due to low rate of septic shock
- Difficulty obtaining timely consent
- High rates of exclusion

Question 2

- According to the results of the HYPRESS trial, steroids in severe sepsis:
  - A - Decrease mortality
  - B - Decrease incidence of septic shock
  - C - Increase risk of secondary infection
  - D - Decrease vasopressor requirements
  - E - Do not impact the incidence of septic shock
Objective 3

Outline an approach for initiation of steroids in the setting of septic shock

H. CORTICOSTEROIDS

1. We suggest against using IV hydrocortisone to treat septic shock patients if adequate fluid resuscitation and vaso-pressor therapy are able to restore hemodynamic stability. If this is not achievable, we suggest IV hydrocortisone at a dose of 200 mg per day (weak recommendation, low quality of evidence).
Timing

Park and colleagues - 2012

Population

Septic Shock (n=178)

Variable

Hydrocortisone initiation

Groups

< 6 hours

> 6 hours

Timing

28-day Mortality

P = 0.0107

Timing

P = 0.0683
P = 0.0243
P = 0.0026
P = 0.0132
P = 0.0024

Timing

Katsenos and colleagues - 2014

Population

Septic Shock (n=170)

Variable

Hydrocortisone initiation

Groups

< 9 hours

> 9 hours

Timing

Katsenos and colleagues - 2014


Survival (days)

% survival

log-rank: 5.553
p: 0.018

Total days of vasopressors

Cumulative % of patients off vasopressors

log-rank: 18.248
p: 0.000019

### Timing

**Wang and colleagues - 2014**

<table>
<thead>
<tr>
<th>Article</th>
<th>Population Size</th>
<th>Enrollment</th>
<th>Mortality Reduction</th>
<th>Early Shock Reversal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bollaert, et al.</td>
<td>41</td>
<td>After 48 hours</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Briegel, et al.</td>
<td>40</td>
<td>Within 72 hours</td>
<td>-</td>
<td>+</td>
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<tr>
<td>Chawla, et al.</td>
<td>44</td>
<td>After 72 hours</td>
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<td>+</td>
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<tr>
<td>Annane, et al.</td>
<td>299</td>
<td>Within 8 hours</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Oppert, et al.</td>
<td>41</td>
<td>Within 24 hours</td>
<td>-</td>
<td>+</td>
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<tr>
<td>Mussack, et al.</td>
<td>24</td>
<td>Within 72 hours</td>
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<td>+</td>
</tr>
<tr>
<td>Sprung, et al.</td>
<td>499</td>
<td>Within 72 hours</td>
<td>-</td>
<td>+</td>
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<tr>
<td>Arabi, et al.</td>
<td>75</td>
<td>Within 72 hours</td>
<td>-</td>
<td>+</td>
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</tbody>
</table>

Question 3

- Steroids are most beneficial in which patients?
  - Early septic shock
  - Sepsis/severe sepsis
  - Late septic shock
  - Steroids are not beneficial in sepsis/septic shock
Approach

Sepsis

Sepsis

No benefit

Septic Shock

0 – 9 hours
Possible mortality benefit

9 – 72 hours
Reduce pressor requirements

>72 hours
Questionable benefit
Future Research

ADRENAL trial

Population: Septic Shock (n=3,800)

Timing: Within 24 hours of diagnosis

Intervention: Hydrocortisone 200mg/day continuous infusion x7 days

Outcome: All cause mortality at 90 days

Intervention: Placebo
Comments/Questions?

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