Comparison of early versus late initiation of low-dose corticosteroids in patients with septic shock in the ICU setting

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Disclosure Statement

• Disclosure Statement: These individuals do not have anything to disclose concerning possible financial or personal relationships with commercial entities (or their competitors) that may be referenced in this presentation

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Presentation Objective

Identify patients that may benefit from low dose corticosteroids when treating septic shock
Septic Shock

- One of the major causes of death in the ICU$^{1,2,3}$
  - Accounts for 40-80% of sepsis-related deaths in the United States
  - Associated with the highest costs among all admissions

- Sepsis-3 definition
  - Sepsis-induced hypotension (SBP < 90 mmHg or MAP < 70 mmHg) despite adequate volume resuscitation
  - Lactic acid > 2 mmol/L within 24 hours of initiation of vasopressors

ICU: Intensive Care Unit
SBP: Systolic Blood Pressure
MAP: Mean Arterial Pressure

Surviving Sepsis Guidelines

- Recommendations to restore hemodynamic stability
  - Initial target MAP 65 mmHg

MAP: Mean Arterial Pressure

Adequate fluid resuscitation  Vasopressor therapy

Hydrocortisone 200 mg/day

## Literature Review

<table>
<thead>
<tr>
<th>Study</th>
<th>Time to initiation</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Annane et al.¹</td>
<td>≤ 8 hours</td>
<td>Adrenal insufficiency receiving hydrocortisone or fludrocortisone:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Increased survival (p=0.02)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Faster resolution of shock (p=0.001)</td>
</tr>
<tr>
<td>Sprung et al.²</td>
<td>≤ 72 hours</td>
<td>Hydrocortisone did not improve survival at 28 days but it did hasten the reversal of shock (p=0.51)</td>
</tr>
<tr>
<td>(CORTICUS)</td>
<td></td>
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</tbody>
</table>

**RCT:** Randomized Controlled Trial

# Literature Review

<table>
<thead>
<tr>
<th>Study</th>
<th>Time to initiation</th>
<th>Outcomes</th>
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<tbody>
<tr>
<td>Park et al.(^1)</td>
<td>≤ 6 hours</td>
<td>Significant reduction in mortality in the early group (p=0.0132)</td>
</tr>
<tr>
<td>Retrospective</td>
<td>&gt; 6 hours</td>
<td></td>
</tr>
<tr>
<td>(n = 178)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Katsenos et al.(^2)</td>
<td>≤ 9 hours</td>
<td>Reduced TDV in early group (p&lt;0.0001)</td>
</tr>
<tr>
<td>Prospective</td>
<td>&gt; 10 hours</td>
<td>Early group had improved survival (p=0.029)</td>
</tr>
<tr>
<td>(n = 170)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Qing-quan et al.(^3)</td>
<td>Simultaneous</td>
<td>No significant difference in reversal of shock or mortality (p=0.602)</td>
</tr>
<tr>
<td>Placebo-controlled, RCT</td>
<td>(n = 118)</td>
<td></td>
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</tbody>
</table>

TDV: Time to Discontinuation of Vasopressors  
RCT: Randomized Controlled Trial

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Benefits of timely discontinuation of vasopressors

- Decreased vasopressor requirements
- Decreased mortality
- Decreased hospital costs

Xue-zhong et al. (2013)

- Multivariate analysis showed vasopressors use is an independent risk factor for mortality ($p<0.001$)
- NE doses < 0.7 mcg/kg/min exhibited 45% improved survival compared to NE doses $\geq 0.7$ mcg/kg/min ($p=0.002$)

NE: Norepinephrine

Study Rationale

Conflicting evidence on impact of time to initiation of low dose hydrocortisone in patients with septic shock

Lack of standard definition of early vs late corticosteroid use
Study Purpose

Evaluate the impact of early versus late initiation of low-dose corticosteroids in patients with septic shock
Research Setting

• Ascension St. Vincent’s
  • Riverside
    • 528 bed non-profit, community teaching hospital
  • Southside
    • 311 bed non-profit, community hospital
  • Clay County
    • 106 bed non-profit, community hospital

• A total of 82 ICU beds

ICU: Intensive Care Unit
Study Design

- IRB-approved
- Multi-centered
- Retrospective
- Propensity-matched
Subject Selection

**Inclusion Criteria**
- 18 years of age or older
- Septic shock diagnosis
  - ICD 9/10 codes
- Vasopressor infusion
- Hydrocortisone ≤ 300 mg/day

**Exclusion Criteria**
- Corticosteroids within 30 days of shock
- Adrenal insufficiency
- Cardiac vasoplegia syndrome
- Cardiac arrest within 30 days of shock
- Pregnant
- Incarcerated

**Propensity-Score Matching Criteria**
- Age
- BMI
- Gender
- SOFA score
- Comorbidities
- Source of infection
- Max NE-equivalent dose
- Number of vasopressors
- Fludrocortisone
- Midodrine

Data was collected from the electronic medical record for subjects between **July 2014 to August 2019**.

**SOFA**: Sequential Organ Failure Assessment
Comparator Groups

Early group
Hydrocortisone ≤ 12 hours from initiation of vasopressors

Late group
Hydrocortisone > 12 hours from initiation of vasopressors
Study Outcomes

Primary Outcome

Time to vasopressor discontinuation (hours)
Study Outcomes

Secondary Outcomes

- In-hospital mortality
- ICU length of stay
- Hospital length of stay
- Number of different vasopressors used
- Need for renal replacement therapy
- Total cumulative fluid (mL) given during first 72 hours of shock
- Maximum NE-equivalent dose administered
- Total units of insulin administered from initiation of vasopressors

ICU: Intensive Care Unit
NE: Norepinephrine
Statistical Analysis

Power Calculation

- 120 subjects in each group
- Power: 80%
- 12 hour difference until discontinuation of vasopressors
- Standard deviation: 33 hours
- Alpha: 0.05

Statistical Tests

- Continuous: Student’s t-test or Wilcoxon rank-sum test
- Nominal: Chi-square test or Fisher’s exact test
- Time-to-event analysis: Wilcoxon log-rank test
- Multiple variable linear regression
Data Collection

Demographics
Comorbidities
Vital signs
ICU LOS
Hospital LOS
IV fluids during first 72h
Insulin requirements
Vasopressor dose
Vasopressor duration
In-hospital mortality
Total hydrocortisone dose
Need for RRT

ICU: Intensive Care Unit
LOS: Length of Stay
RRT: Renal Replacement Therapy
Subject Selection

Initial Screen (n=1136)
- No septic shock diagnosis
- No IV antibiotic use
- HC > 300 mg/day
- Adrenal insufficiency

Excluded (n=65)
- CCS < 30 days prior to admission
- CA < 30 days prior to admission
- Steroid initiation prior to vasopressor infusion
- HC not administered

Initial review (n=1441)

Secondary review (n=305)

Included (n=240)

Propensity-Matching
- Age
- BMI
- Gender
- SOFA score
- Comorbidities
- Source of infection
- Max NE-equivalent dose
- Number of vasopressors
- Fludrocortisone
- Midodrine

Early group (n=99)

Late group (n=99)

CCS: Corticosteroids  BMI: Body Mass Index
CCS: Hydrocortisone  SOFA: Sequential Organ Failure Assessment
CA: Cardiac Arrest  CHF: Congestive Heart Failure
# Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Early (n = 99)</th>
<th>Late (n = 99)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age - years</td>
<td>69.7 (61 - 77.2)</td>
<td>68.4 (60.5 - 77.8)</td>
<td>0.4169</td>
</tr>
<tr>
<td>BMI - kg/m²</td>
<td>28.6 (23.8 - 33.6)</td>
<td>29 (23.5 - 34.2)</td>
<td>0.9437</td>
</tr>
<tr>
<td>Lactic acid - mg/dL</td>
<td>5.1 (3.2 - 9.6)</td>
<td>3.4 (2.1 - 7.7)</td>
<td>0.0146</td>
</tr>
<tr>
<td>SOFA score</td>
<td>12 (10 - 15)</td>
<td>12 (9 - 15)</td>
<td>0.7779</td>
</tr>
<tr>
<td><strong>Comorbidities, no. (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>35 (35.4)</td>
<td>39 (39.4)</td>
<td>0.5568</td>
</tr>
<tr>
<td>Hypertension</td>
<td>73 (73.7)</td>
<td>72 (72.7)</td>
<td>0.8725</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>27 (27.2)</td>
<td>25 (25.3)</td>
<td>0.7467</td>
</tr>
<tr>
<td>COPD</td>
<td>24 (24.2)</td>
<td>17 (17.2)</td>
<td>0.2196</td>
</tr>
<tr>
<td>Other pulmonary</td>
<td>6 (6.1)</td>
<td>11 (11.1)</td>
<td>0.2047</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>24 (24.2)</td>
<td>23 (23.2)</td>
<td>0.8673</td>
</tr>
<tr>
<td>MAP at vasopressor initiation - mmHg</td>
<td>60 (52 - 64)</td>
<td>63 (57 - 68)</td>
<td>0.0099</td>
</tr>
<tr>
<td>NE-equivalent dose at HC initiation - mcg/min</td>
<td>20 (8 - 30)</td>
<td>12 (4.5 - 24)</td>
<td>0.0259</td>
</tr>
</tbody>
</table>

All values are displayed as median (IQR) unless otherwise noted.

**SOFA**: Sequential Organ Failure Assessment  
**MAP**: Mean Arterial Pressure  
**NE**: Norepinephrine  
**HC**: Hydrocortisone
Primary Outcome

Primary endpoint
Time to vasopressor discontinuation (hours)

Early group (n=99)

Late group (n=99)

Every hour HC was delayed increased vasopressor duration by 52 minutes (p<0.0001)

HC: Hydrocortisone
## Secondary Outcomes

<table>
<thead>
<tr>
<th>Variables</th>
<th>Early (n = 99)</th>
<th>Late (n = 99)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>In-hospital mortality - no. (%)</td>
<td>42 (42.4)</td>
<td>48 (48.5)</td>
<td>0.3918</td>
</tr>
<tr>
<td>ICU length of stay - day</td>
<td>3.6 (1.78 - 9.2)</td>
<td>5.1 (3 - 9.9)</td>
<td>0.0147</td>
</tr>
<tr>
<td>Hospital length of stay - day</td>
<td>8.9 (2.6 - 15.2)</td>
<td>10.9 (5.5 - 17.9)</td>
<td>0.0220</td>
</tr>
<tr>
<td>IV fluids given during first 72 hours - ml/kg</td>
<td>81.5 (60 - 115.9)</td>
<td>89.6 (55.6 - 136.7)</td>
<td>0.2808</td>
</tr>
<tr>
<td>Total insulin from initiation of vasopressors - unit</td>
<td>12 (0 - 60)</td>
<td>11 (0 - 76)</td>
<td>0.8384</td>
</tr>
<tr>
<td>Max NE-equivalent dose - mcg/kg/min</td>
<td>0.45 (0.2 - 0.8)</td>
<td>0.4 (0.2 - 0.7)</td>
<td>0.6221</td>
</tr>
<tr>
<td>Need for renal replacement therapy - no. (%)</td>
<td>23 (23.2)</td>
<td>24 (24.2)</td>
<td>0.8673</td>
</tr>
</tbody>
</table>

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ICU: Intensive Care Unit  
NE: Norepinephrine
Subgroup Analyses

Early group associated with a significant reduction in vasopressor duration in all subgroups (p<0.05)
Discussion

“Early” HC initiation associated with significant reductions:

- Vasopressor duration
- ICU length of stay
- Hospital length of stay

Linear regression analysis showed hastened resolution of shock with earlier HC initiation

Potential to reduce serious adverse events associated with prolonged vasopressor exposure

ICU: Intensive Care Unit
HC: Hydrocortisone
# Strengths and Limitations

<table>
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<tr>
<th><strong>Strengths</strong></th>
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</thead>
<tbody>
<tr>
<td>Propensity-score matching</td>
</tr>
<tr>
<td>Consistency in findings across all subgroups</td>
</tr>
<tr>
<td>First study to quantify the impact of hydrocortisone initiation on vasopressor duration</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Limitations</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Selection bias</td>
</tr>
<tr>
<td>Retrospective study design</td>
</tr>
<tr>
<td>Inconsistent hydrocortisone dosing</td>
</tr>
</tbody>
</table>
Conclusion

Early group associated with significantly reduced vasopressor duration and shortened ICU and hospital length of stay.

Study not powered to detect a significant difference in mortality and should be studied in a larger cohort.
Acknowledgements

- Bryan Allen, PharmD, BCCCP, BCIDP
- Chad Cannon, PharmD, MSCR, BCPS, BCCCP, BCIDP
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