The Combination of Vasopressin and Corticosteroids in Septic Shock:
Cutting the mustard or a lemon in disguise?

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Learning Objectives

1. Discuss the impact of septic shock on critically ill patients and current use of catecholamines for hemodynamic support.
2. Based on the current Surviving Sepsis Campaign guidelines, explain when the addition of vasopressin and/or corticosteroids is recommended in the management of septic shock.
3. Describe the potential interaction between vasopressin and corticosteroids in patients with septic shock.
4. Evaluate the use of vasopressin and corticosteroids as combination therapy in patients with septic shock.
I. What is sepsis?\textsuperscript{1,2}
   a. Suspected or documented infection with systemic manifestations (Figure 1)
      i. Patient must meet ≥ 2 of systemic inflammatory response syndrome (SIRS) criteria
         1. Temperature > 38°C or < 36°C
         2. Heart rate > 90 beats per minute
         3. Respiratory rate > 20 per minute
         4. White blood cell (WBC) count > 12,000/mm\textsuperscript{3}, < 4,000/mm\textsuperscript{3}, or > 10% bands
   b. Can progress to severe sepsis and septic shock

   \textbf{Figure 1.} Progression of sepsis\textsuperscript{2}

II. Severe sepsis and septic shock\textsuperscript{1,3,4}
   a. Affects millions of people each year
   b. Major health concern
      i. Multi-organ dysfunction
      ii. Major cause of mortality in intensive care unit (ICU) patients
         1. Third most common cause of death in the U.S. after heart disease and malignant neoplasm\textsuperscript{5}
         2. Mortality rates have decreased steadily over last quarter century\textsuperscript{6}
         3. Incidence of in-hospital mortality up to 50%\textsuperscript{4,5}
            a. Mortality rates vary depending on patient-specific factors
               i. Comorbidities, infecting pathogen, site of infection, organ dysfunction
            iii. Estimated annual U.S. healthcare system cost of $24.3 billion\textsuperscript{7}

III. Pathophysiologic changes\textsuperscript{5}
   a. Diffuse endothelial injury and altered microvascular flow
      i. Increased endothelial permeability due to shedding of the endothelial glycocalyx and development of microvascular leak
      ii. Leads to tissue and organ edema, hypotension, and shock
   b. Vasoplegic shock
      i. Distributive shock due to failure of vascular smooth muscle constriction
      ii. Leads to arterial and venodilatation
         1. Decreases venous return and compounds intravascular volume deficit
   c. Myocardial depression
I. Focus on early management\textsuperscript{3,5}
   a. Speed and appropriateness of therapy likely influence outcomes
   b. Early, aggressive administration of intravenous (IV) fluids, antibiotics, and vasoactive agents

II. Initial resuscitation\textsuperscript{1,3}
   a. Sepsis-induced tissue hypoperfusion
      i. Hypotension persisting after initial fluid challenge
      ii. Blood lactate concentration $\geq 4$ mmol/L
   b. Early goal-directed therapy\textsuperscript{3,8}
      i. Goals during the first 6 hours of resuscitation
         1. Central venous pressure (CVP) 8-12 mm Hg
         2. Mean arterial pressure (MAP) $\geq 65$ mm Hg
         3. Urine output $\geq 0.5$ mL/kg/hr
         4. Superior vena cava oxygenation saturation ($\text{ScvO}_2$) $\geq 70\%$ or mixed venous oxygen saturation ($\text{SvO}_2$) $\geq 65\%$
   c. Normalization of elevated serum lactate ($\leq 4$ mmol/L)

III. Fluid therapy\textsuperscript{1}
   a. Adequate fluid resuscitation is a fundamental aspect of hemodynamic support
   b. Crystalloids
      i. Initial fluid of choice for resuscitation
      ii. Fluid challenge should be administered to patients with sepsis-induced tissue hypoperfusion
         1. Minimum of 30 mL/kg of crystalloids
   c. Colloids
      i. May be considered in patients refractory to crystalloids
      ii. Theoretical benefits over crystalloids
         1. Antioxidant and anti-inflammatory effects
         2. Ability to stabilize the endothelial glycocalyx
      iii. No proven mortality difference in septic shock when compared to crystalloids\textsuperscript{9,10}

IV. Antimicrobial therapy\textsuperscript{1}
   a. Cultures should be obtained prior to initiation of antimicrobial therapy
   b. Effective IV antimicrobials within the first hour of severe sepsis and septic shock recognition
      i. Each hour delay in antibiotic administration associated with measurable increase in mortality (Figure 2)$^{11}$

![Figure 2. Survival impact of effective antimicrobial initiation following onset of septic shock$^{11}$](image-url)
c. Initial empiric antimicrobial therapy
   i. Should include ≥ 1 medication with activity against all likely pathogens and provide adequate tissue penetration
   ii. De-escalation should be performed as soon as susceptibility profile is known
d. Imaging studies to confirm potential source of infection
e. Source control, if possible, should be performed as rapidly as possible within the first 12 hours after diagnosis

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**Role of Vasopressors**

I. Vasopressor agents
   a. Used to target an initial MAP of ≥ 65 mm Hg
      i. Goal to maintain perfusion during life-threatening hypotension
         1. When MAP falls below autoregulatory threshold of critical vascular beds, organ blood flow decreases linearly
            a. MAP < 60 mm Hg will likely result in ischemia of brain, heart, and kidney
      ii. Optimal MAP should be individualized
         1. Higher MAP goals may be required in patients with atherosclerosis or chronic hypertension
   b. MAP endpoints should be supplemented with other markers of perfusion
      i. Serum lactate concentrations, mental status, urine output, skin perfusion
   c. Ideally, fluid resuscitation should be achieved before vasopressors and inotropes utilized

II. Choosing a vasopressor
   a. Dopamine (DA) versus norepinephrine (NE)
      i. 2012 meta-analysis
         1. DA use associated with increased risk of death and development of arrhythmias as compared with NE in patients with septic shock
   b. Norepinephrine
      i. First choice vasopressor
      ii. α1-vasoconstrictive effects increase MAP with little change in heart rate or stroke volume
   c. Dopamine
      i. Alternative agent to NE only in select patients
         1. Indicated in absolute or relative bradycardia
      ii. Increases MAP and cardiac output
   d. Epinephrine
      i. Added or substituted for NE when additional agent needed to maintain adequate organ perfusion
      ii. Increases aerobic lactate production: stimulation of β2 receptors on skeletal muscles

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<table>
<thead>
<tr>
<th>Table 1. Vasopressor Receptor Activity</th>
<th>α1</th>
<th>β1</th>
<th>β2</th>
<th>DA</th>
<th>V₁</th>
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<tbody>
<tr>
<td>Epinephrine</td>
<td>+++</td>
<td>+++</td>
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<td>Norepinephrine</td>
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<tr>
<td>Dopamine</td>
<td>&gt; 10a</td>
<td>5-10a</td>
<td>&lt; 5a</td>
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<td>Phenylephrine</td>
<td>+++</td>
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<tr>
<td>Vasopressin</td>
<td>+++</td>
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</table>

*Approximate affects based on dopamine dose in mcg/kg/min
DA=dopamine; V₁=vasopressin-1 receptor
e. Phenylephrine
   i. Pure α-adrenergic effects: least likely to produce arrhythmias
   ii. Not recommended for the treatment of septic shock
       1. Decreases stroke volume, cardiac output, renal and splanchnic blood flow
   iii. May be used in select circumstances
       1. Patients with serious arrhythmias associated with NE
       2. High cardiac output with persistently low blood pressure
       3. Salvage therapy when combined inotrope, vasopressor, and vasopressin therapy have failed to maintain MAP

IV. Vasopressin$^{1,16,17}$
   a. Used as adjunctive therapy to NE
      i. Increase MAP
      ii. Decrease catecholamine requirement
   b. Physiology of endogenous vasopressin
      i. Vasopressin is released into systemic circulation from posterior pituitary gland
         1. Release stimulated by hypotension, hypovolemia, and hypernatremia
      ii. Vasopressin acts on a variety of receptors$^{16}$(Table 2)
         1. At vasopressin concentrations < 10 pg/mL, antidiuretic actions (V₂ receptor) of vasopressin predominate
         2. Little effect on arterial pressure (V₁ receptor) at physiologic concentrations

<table>
<thead>
<tr>
<th>Table 2. Vasopressin Receptors$^{16}$</th>
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<tbody>
<tr>
<td>Receptor</td>
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<tr>
<td>-----------</td>
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<tr>
<td>V₁</td>
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<td>V₃</td>
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c. Physiology of vasopressin in septic shock$^{17}$(Figure 3)
   i. Acts as a stress hormone during hypotension
      1. Vasopressin levels increase to maintain blood pressure via vasoconstriction due to predominate V₁ receptor activity
      2. Minimal antidiuretic effects in shock

Angiotensin II, Sympathetic Stimulation, Hyperosmolarity, Hypovolemia, Hypotension

Figure 3. Physiology of vasopressin$^{17}$
d. Relative vasopressin deficiency in septic shock
   i. Endogenous vasopressin concentrations (Table 3)
      1. Elevated early in septic shock
      2. Decrease to normal ranges within 24 to 48 hours
         a. Initially due to depletion of vasopressin stores in posterior pituitary
         b. Vasopressin levels remain inappropriately low suggesting a sustained impairment of vasopressin synthesis and release
            i. Down-regulation of vasopressin production by excessive nitric oxide release in posterior pituitary
      3. Exogenous vasopressin infusion used to restore vasopressin concentrations

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<thead>
<tr>
<th>Table 3. Serum Vasopressin Concentrations (pg/mL)</th>
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<tbody>
<tr>
<td>Normotensive adult</td>
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<tr>
<td>Cardiogenic shock</td>
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<tr>
<td>Severe hypotensive hemorrhage</td>
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<tr>
<td>Septic shock</td>
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<tr>
<td>Vasopressin infusion 0.01-0.04 units/min</td>
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</table>

e. Exogenous vasopressin administration
   i. Fixed-dose continuous infusion up to 0.04 units/min
f. Level of evidence supporting vasopressin use
   i. Ungraded recommendation in Surviving Sepsis Campaign guidelines
   ii. The Vasopressin and Septic Shock Trial (VASST)
      1. Randomized controlled trial of vasopressin versus NE
      2. Performed to address uncertainties regarding vasopressin in septic shock
      3. Stratified patients by center and severity of septic shock as determined by NE infusion rate the hour before study inclusion
         a. Less severe septic shock: NE 5 to 14 mcg/min
         b. More severe septic shock: NE ≥ 15 mcg/min
      4. No significant difference between vasopressin-treated and NE-treated groups in primary outcome of 28-day mortality
      5. Secondary outcome evaluating effect of vasopressin in more severe septic shock versus less severe septic shock
         a. Less severe septic shock: vasopressin group had decreased 90-day mortality
            i. Suggests that addition of vasopressin may be more beneficial when initiated early in septic shock prior to escalation of catecholamines
      6. Similar serious adverse event rates between groups
g. Benefit of vasopressin over catecholamines
   i. Function preserved in acidosis
   ii. Corrects relative vasopressin deficiency
   iii. Vasopressin-induced vasoconstriction spares cerebral, coronary, pulmonary, and afferent glomerular capillary circulations
I. Endogenous stress response primarily mediated by hypothalamic-pituitary-adrenal (HPA) axis and sympathoadrenal system
   a. Activation of HPA axis causes increased secretion of corticotropin-releasing hormone (CRH) and arginine vasopressin
   b. Ultimately leads to increased production and release of cortisol

II. Critical illness-related corticosteroid insufficiency (CIRCI)
   a. Leads to exaggerated and protracted proinflammatory response
   b. Caused by:
      i. Inadequate cellular glucocorticoid activity
      ii. Adrenal suppression and/or glucocorticoid tissue resistance
   c. Clinical manifestation: hypotension refractory to fluid and vasopressor administration
   d. Low-dose hydrocortisone (HC) supplementation (HC 25-200 mg/day) may be beneficial
      i. Restore balance to altered HPA axis
      ii. Increase adrenergic responsiveness
      iii. Preserve endothelial glycocalyx

III. Replacement of corticosteroids (CCS) during septic shock
   a. Effect of CCS on mortality in patients with septic shock
      i. Placebo-controlled, randomized, double-blind trial
      ii. Designed to assess whether replacement therapy with HC and fludrocortisone (FC) could improve 28-day survival in septic shock patients
      iii. Regimens
         1. CCS group: HC 50 mg IV every six hours, plus FC 50 mcg enteral daily
         2. Placebo
      iv. Primary outcome (Figure 4)
         1. 28-day survival in non-responders to short corticotropin test
            a. Cortisol samples drawn immediately before and at 30 and 60 minutes after short corticotropin test
            b. Non-responders defined as cortisol response < 9 mcg/dL between lowest and highest concentration

*Non-responders to short corticotropin stimulation test
CI=confidence interval; FC=fludrocortisone; HC=hydrocortisone; OR=odds ratio

Figure 4. 28-day survival in non-responders to short corticotropin test

v. Secondary outcomes
   1. 28-day survival in responders to corticotropin test: no significant difference
   2. 28-day survival in all patients: no significant difference
   3. 28-day, ICU, hospital, and 1-year mortality rates
      a. Non-responders: 28-day, ICU, and hospital mortality significantly lower in patients who received CCS
      b. Responders: no significant difference
   4. Time to vasopressor therapy withdrawal
      a. Non-responders: significantly shorter in CCS group (7 vs. 10 days; p=0.001)
      b. Responders: no significant difference
      c. All patients: significantly shorter in CCS group (7 vs. 9 days; p=0.01)

vi. Take-home points
   1. In non-responders, CCS therapy significantly reduced
      a. 28-day, ICU, and hospital mortality (number needed to treat= 7)
      b. Time to vasopressor withdrawal
   2. Responders: no significant effect of CCS
   3. All patients
      a. No significant difference in mortality rates
      b. CCS group had significantly shorter time to vasopressor withdrawal
   4. No significant differences in adverse events
   5. Overall mortality rate much lower (64%) than that expected (95%)
   6. Frequency of non-responders higher than expected (actual 77%, expected 40%)

b. Corticosteroid Therapy of Septic Shock (CORTICUS) study\textsuperscript{21}
   i. Multicenter, randomized, double-blind, placebo-controlled study (Figure 5)
   ii. Evaluated efficacy and safety of HC therapy in septic shock patients

\begin{figure}
\centering
\includegraphics[width=\textwidth]{CORTICUS_study.png}
\caption{Enrollment of patients in CORTICUS study\textsuperscript{21}}
\end{figure}

\textsuperscript{*}Corticotropin results unknown for 8 patients in HC group and 4 patients in placebo group
HC=hydrocortisone; non-responder=serum cortisol response of < 9 mg/dL after cosyntropin 250 mcg IV bolus

iii. Regimens
   1. HC 50 mg IV every 6 hours for 5 days, then 50 mg IV every 12 hours on days 6-10, then 50 mg IV daily on days 9-11
   2. Placebo

iv. Primary endpoint: 28-day mortality in non-responders to corticotropin test
   1. No significant difference between study groups
v. Secondary endpoints
   1. Reversal of organ system failure
      a. Time until shock reversal
         i. Significantly shorter in patients who received HC (p<0.001)
            1. 3.3 days HC group vs. 5.8 days placebo group
         ii. Significantly shorter in responders to corticotropin test (p<0.001)
         iii. No difference in time to shock reversal in non-responders (p=0.06)
   2. No significant difference:
      a. 28-day mortality in responders or in all patients
      b. ICU, hospital, and 1-year mortality
      c. ICU and hospital length of stay
   vi. Safety was assessed by measuring adverse events
   vii. Etomidate use
      1. 60.4% (58/96) of patients who received etomidate prior to study enrollment did not have a response to corticotropin compared to 43.4% (175/403) of patients who did not receive etomidate (p=0.004)
   viii. Take-home points
      1. HC use had no significant effect on 28-day mortality, regardless of response to corticotropin
      2. Patients in HC group had decreased time to shock reversal, regardless of corticotropin response
      3. Increase incidence of new onset septic shock, hyperglycemia, and hypernatremia in HC group
      4. Sample size of 800 patients was not achieved to have statistical power
   c. Comparison of Annane et al. and CORTICUS studies evaluating CCS use in septic shock (Table 4)

<table>
<thead>
<tr>
<th>Table 4. Comparison of Annane et al. and CORTICUS Studies²⁰,²¹</th>
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<tbody>
<tr>
<td><strong>Annane et al.²⁰</strong></td>
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<tr>
<td>Mean SAPS II score</td>
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<tr>
<td>Overall mortality</td>
</tr>
<tr>
<td>CCS regimen</td>
</tr>
<tr>
<td>Administration of CCS</td>
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<tr>
<td>CCS discontinuation</td>
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<tr>
<td>Adverse events</td>
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</table>

CCS=corticosteroid; FC=fludrocortisone; HC=hydrocortisone; SAPS II=Simplified Acute Physiology Score II (Appendix A)

IV. Time-dependent initiation of CCS has not been taken into consideration
   a. Non-randomized prospective longitudinal study²²
      i. First study to investigate the importance of time frame between development of septic shock and CCS initiation
      ii. Enrollment (Table 5)

<table>
<thead>
<tr>
<th>Table 5. 170 Total Enrolled Patients²²</th>
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<tbody>
<tr>
<td><strong>Initiation Group</strong></td>
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<td>Early (46 patients)</td>
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<td>Late (124 patients)</td>
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iii. Primary endpoint: effect of HC time delay after start of vasopressors on final outcome
   1. Proportion of survivors significantly greater in early initiation group (52.2% vs. 30.6%; p=0.012; OR, 0.40 [95% CI, 0.20-0.81]) (Figure 6a)
   2. Univariate analysis determined that only APACHE II score (Appendix A), SOFA score (Appendix A), and the delayed start of HC were linked with unfavorable outcomes
      a. Early initiation of HC in patients with APACHE II score ≥ 19 increased survival rate from 19.8% to 41.2% (p=0.021)
      b. Early initiation of HC in patients with APACHE II score < 19 increased survival rate from 55% to 83.3%
   3. Mean time to withdrawal of vasopressor was 4 days in early initiation versus 15 days for late initiation group (p<0.0001) (Figure 6b)

![Figure 6. a) Impact of early initiation of HC on final outcome; b) Impact of early initiation of HC on total time on vasopressors](image)

iv. Secondary endpoint: effect of HC time delay on cytokine stimulation in vitro (34 patients [9 from early initiation group, 25 from late initiation group])
   1. Cytokine stimulation in vitro was lower in early initiation group

v. Take-home points
   1. Early initiation group:
      a. Survival significantly prolonged
      b. Vasopressor withdrawal occurred sooner
      c. Cytokine response decreased in vitro
   2. Evaluated small sample of patients with severe septic shock
   3. No comparison to a control group not receiving steroid therapy
   4. Adverse event rates not reported

IV. Adverse events associated with CCS
   a. Dependent on dose, dosing strategy, and duration of therapy
   b. Concerns with short-term CCS therapy
      i. Increased risk infection
      ii. Hyperglycemia
      iii. Hypernatremia
      iv. Others: myopathy, impaired wound healing, metabolic acidosis, psychosis, HPA axis and glucocorticoid receptor suppression
I. Interaction of the HPA axis and the hypothalamic-posterior pituitary-vasopressin axis *(Figure 7)*\(^{16,19,23}\)
   a. Arginine vasopressin and CRH stimulate different signaling systems leading to synergistic effects on release of adrenocorticotropic hormone (ACTH)
   b. Vasopressin interacts with the HPA axis in response to hypotension or other stressors
      i. Stimulation of anterior pituitary V\(_3\) receptors by vasopressin increases release of ACTH
         1. ACTH levels are increased even in levels of stress when CCS levels are elevated
         2. This effect is resistant to CCS negative feedback

![Diagram of the HPA axis and vasopressin interaction](image)

ACTH=adrenocorticotropin hormone; CRH=corticotropin-releasing hormone

*Figure 7. Interaction of vasopressin and HPA axis*\(^{16}\)

II. Interaction of exogenously administered vasopressin and CCS is not clearly understood, particularly in the setting of septic shock\(^{16,20,21}\)

III. A significant clinical interaction? *(Table 6)*

<table>
<thead>
<tr>
<th>Significant interaction</th>
<th>No significant interaction</th>
</tr>
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<tbody>
<tr>
<td>• Vasopressin may ↑ adrenal GC production directly and through ↑ ACTH</td>
<td>• CCS do not change vasopressin levels</td>
</tr>
<tr>
<td>• In presence of cortisol, NE inhibits antidiuretic effect of vasopressin in kidney</td>
<td>• CCS may delay vasopressin release</td>
</tr>
<tr>
<td>• CCS may restore hemodynamic responsiveness to vasopressin</td>
<td>• CCS may ↓ vasopressin gene expression</td>
</tr>
<tr>
<td>• CCS have been reported to ↑ vasopressin mRNA</td>
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</table>

ACTH=adrenocorticotropic hormone; CCS=corticosteroid; GC=glucocorticoid; NE=norepinephrine

*Table 6. Interaction Between Vasopressin and Corticosteroids*\(^{16,23,24}\)
IV. Literature Review

a. Effect of CCS on vasopressin-containing regimens for septic shock

i. Retrospective case-control study

ii. To clinically evaluate the effects of CCS on time to vasopressin withdrawal and mortality in septic shock patients

iii. Patient population (Figure 8)

621 patients receiving vasopressin

579 patients excluded

- Vasopressin < 1 hr
- Vasopressin initiated in OR
- CCS for < 5 days
- CCS started after vasopressin stopped
- Study drug indication other than septic shock
- CI or preexisting disease indication for CCS

Inclusion Criteria

- SBP ≤ 90 mm Hg or MAP ≤ 70 mm Hg within 1 hour before start of vasopressin
- Positive fluid balance
- Mechanical ventilation
- At least 2 SIRS criteria
- Positive culture or strong clinical suspicion of infection with the initiation of antimicrobials

42 patients included

Patients matched based on:

- Primary ICU service
- APS component of APACHE II score
- # of vasopressors at initiation of vasopressin
- Sex
- Age

21 patients in CCS arm

HC 50 mg IV q6h + FC 50 mcg PO daily

21 patients in control arm

Did not receive CCS

APS= Acute Physiology Score; APACHE II= Acute Physiology and Chronic Health Evaluation II (Appendix A); CCS=corticosteroids; CI=contraindications; FC=fludrocortisone; HC=hydrocortisone; ICU=intensive care unit; MAP=mean arterial pressure; PO=enteral; q6h=every six hours; SBP=systolic blood pressure; SIRS=systemic inflammatory response syndrome

Figure 8. Patient population
1. Baseline characteristics

<table>
<thead>
<tr>
<th>Table 7. Patient Baseline Characteristics²⁵</th>
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<tbody>
<tr>
<td>CCS</td>
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<tr>
<td>CRRT during vasopressin</td>
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<tr>
<td>Non-responder to corticotropin stimulation test</td>
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<tr>
<td>Vasopressin for initial hemodynamic support</td>
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<tr>
<td>Vasopressin monotherapy</td>
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CCS=corticosteroids; CRRT=continuous renal replacement therapy; non-responder=change in serum cortisol ≤ 9 mcg/dL after 250 mcg cosyntropin test

iv. Outcomes (Figure 9)
1. Primary outcome: effect of CCS on time to withdrawal of vasopressin
2. Secondary outcomes
   a. Proportion of patients alive without vasopressors at day 7
   b. 28-day, ICU, hospital mortality

![Study outcomes](image)

v. Take-home points
1. First study to clinically evaluate the effect of CCS on vasopressin
2. Significantly more patients in CCS group were alive without vasopressor support at 7 days
3. ICU, 28-day, and hospital mortality numerically lower in CCS group
4. Small sample size may have led to study being underpowered
5. Vasopressin used as the initial hemodynamic support agent in about 50% of all patients and remained only hemodynamic agent for 38% of patients
6. Median time from vasopressor to CCS initiation was 22.2 hours

b. Post hoc analysis of VASST trial¹⁸,²⁴
i. To investigate the interaction of vasopressin and CCS treatment in septic shock
   1. Post hoc analysis of multicenter, blinded, randomized controlled trial
   2. VASST patients (N=779) received NE or NE plus vasopressin
   3. Vasopressor infusions were titrated to goal MAP of 65 to 75 mm Hg
      a. If not achieved with study medications, open-label vasopressors were added
   4. Assignment to CCS treatment not randomized nor blinded
ii. Patient population (Figure 10)

Figure 10. Patient population in VASST trial who received corticosteroids\(^{18,24}\)

iii. Outcomes

1. Primary outcome: 28-day mortality (Figure 11)

   a. Vasopressin and CCS treatment were associated with lower 28-day mortality compared to NE and CCS treatment (35.9% vs. 44.7%, \(p=0.03\))

   b. In patients not treated with CCS, vasopressin was associated with a trend toward increased mortality (33.7% vs. 21.3%, \(p=0.06\))

Figure 11. Probability of 28-day survival in corticosteroid versus no corticosteroid treated patients\(^{24}\)
2. Secondary outcomes
   a. 90-day mortality
      i. Lower in vasopressin plus CCS group (45.2% vs. 55.5%, p=0.01)
   b. Days alive and free from organ dysfunction over first 28 days
      i. Trend towards more days free from any organ dysfunction in vasopressin group (p=0.08)
3. Adverse events
   a. Similar in two treatment groups
   b. Significantly higher rate of cardiac arrests in NE patients treated with CCS compared to vasopressin patients treated with CCS (2.4% vs. 0.3%, p=0.04)
4. Plasma vasopressin levels
   a. Vasopressin and CCS patients had significantly higher plasma vasopressin concentrations at 6 hours (p=0.006) and 24 hours (p=0.025)
   b. NE and CCS patients’ plasma vasopressin levels were extremely low and were not altered by CCS
iv. Take-home points
   1. First trial to investigate the interaction of vasopressin and CCS on mortality and organ dysfunction
   2. Vasopressin plus CCS associated with lower 28-day mortality compared to NE plus CCS
   3. Patients treated with vasopressin who did not receive CCS had an increased mortality compared with patients who received NE and no CCS
   4. Due to CCS treatment being at the discretion of treating physician, this group had increased severity of illness compared to those who did not receive CCS
      a. In survival analysis, vasopressin was compared to NE within each CCS subgroup rather than comparing to no CCS group
   5. In patients who received vasopressin, CCS increased vasopressin levels by 67% at 24 hours
   6. Did not address the mechanism of potential benefit from vasopressin plus CCS versus NE plus CCS
c. Pilot randomized controlled trial\textsuperscript{26}
   i. Open-label, randomized, placebo-controlled, parallel-group trial
   ii. To investigate if there is an interaction between vasopressin and CCS and feasibility of vasopressin as initial vasopressor therapy in septic shock
   iii. Patient population and interventions (Figure 12)

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure12}
\caption{Patient population and interventions\textsuperscript{26}}
\end{figure}

1. CCS regimen
   a. Once vasopressin rate of 0.06 units/min reached, patients started on HC 50 mg or placebo IV every 6 hours for 5 days, every 12 hours for 3 days, then once daily for 3 days
   b. 5 patients given rescue CCS for treatment of life-threatening hypotension and considered crossovers
2. Open-label vasopressors
   a. Could be started if patient hypotensive after first dose of HC or placebo
3. Plasma vasopressin samples
   a. Collected once max vasopressin infusion reached (T0), 6-12 hours (T1), and 24-36 hours (T2) after the first dose of HC/placebo

ACS=acute coronary syndrome; ESRD=end-stage renal disease; HC=hydrocortisone; Vaso=vasopressin
iv. Baseline characteristics
   1. Vasopressin used as initial vasopressor in 18 (30%) patients
   2. 43 (70%) patients received another agent as initial vasopressor in the emergency setting to stabilize the patient
      a. NE most commonly used
      b. Median time to starting trial vasopressin was < 4 hours

v. Outcomes
   1. Primary outcome (interaction analysis)
      a. No difference in plasma vasopressin concentrations between groups
   2. Secondary outcome (clinical outcome analysis)
      a. Difference in vasopressin requirements
         i. Patients in HC group received 3.1 day (95% CI, 1.1-5.1 days; p=0.001) shorter duration of vasopressin infusion than placebo group (Figure 13a)
      ii. HC patients used half the total dose (ratio, 0.47; 95% CI, 0.32-0.71; p=0.001) of vasopressin compared to placebo group (Figure 13b)
      iii. Duration of additional NE infusion was 2 days shorter in HC group (95% CI, -7 to 0 days; p=0.015)
   b. No difference in 28-day, ICU, or hospital mortality, organ failure-free days, or onset of new organ failure
   3. 6 HC patients versus 2 placebo patients never received any NE

vi. Adverse events: 14 reported
   1. 4 defined as serious adverse events, one possibly related to study drugs
   2. 5 minor adverse events possibly related to study medications
      a. 3 cool/mottled peripheries, 1 elevated serum lactate, 1 elevated troponin

vii. Take-home points
   1. First randomized controlled trial evaluating the impact of vasopressin and CCS combination therapy in septic shock
   2. Small sample size has limited power to detect differences in clinical outcomes
   3. Vasopressin intended for initial vasopressor for hemodynamic support
      a. Does not follow recommendations from 2012 Surviving Sepsis Campaign guidelines
      b. Only 30% of patients received vasopressin for initial hemodynamic support
4. Patients who received combination vasopressin and CCS had a significantly shorter duration of vasopressin infusion and decreased total dose requirement.

5. Vasopressin 0.06 units/min maximum dose is higher than that recommended in the Surviving Sepsis Campaign guidelines.

### Future Directions

I. Future studies
   a. Adjunctive CCS treatment in critically ill patients with septic shock (ADRENAL)
      i. Randomized, double-blind, placebo-controlled trial to determine if patients admitted to ICU with septic shock given HC versus placebo will have improved 90-day survival (http://clinicaltrials.gov/ct2/show/NCT01448109)
   b. Vasopressin versus NE as initial therapy in septic shock (VANISH)
      i. Randomized, double-blind, controlled trial to investigate if initial therapy with vasopressin is more effective in reducing kidney dysfunction compared to NE and if there is any interaction between vasopressin and CCS in septic shock (http://www.controlledtrials.com/ISRCTN20769191)

### Conclusion

I. Summary
   a. The clinical interaction between vasopressin and CCS in septic shock is poorly understood
   b. Limited number of studies investigating clinical outcomes of septic shock patients treated with vasopressin and CCS combination therapy
   c. Outcomes in available trials suggest a benefit with the combination of vasopressin and CCS for the treatment of septic shock
      i. Decreased vasopressor requirements
      ii. Decreased time to vasopressor withdrawal
      iii. Decreased mortality
      iv. Limited adverse events seen with combination of vasopressin and CCS

II. Recommendations (Figure 14)

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**Figure 14. Recommendations**

CCS=corticosteroids; MAP=mean arterial pressure; NE=norepinephrine
# Appendix A. Severity of Illness Scores

### Acute Physiology and Chronic Health Evaluation (APACHE) II Score
- Severity of disease classification system determined from the worst physiologic value during the initial 24 hours after ICU admission
- Consists of 3 components
  - Acute physiology score (APS) points (0 to 48 points)
    - Sum of 12 individual points: temperature, MAP, heart rate, respiratory rate, oxygenation, arterial pH, serum sodium, serum potassium, serum creatinine, hematocrit, WBC, GCS
  - Age points (0 to 6 points)
  - Chronic health points (2 or 5 points)

### Simplified Acute Physiology Score (SAPS II)
- Severity score and mortality estimation tool calculated from the worst physiologic variables within the first 24 hours of ICU admission
- Consists of 12 physiologic variables and 3 disease-related variables

### Sepsis-related Organ Failure Assessment (SOFA) Score
- Morbidity severity score and mortality estimation tool calculated from worst physiological variable collected serially every 24 hours of a patient’s ICU admission
- Consists of 6 variables, each representing an organ system
  - Each organ system assigned a point value from 0 (normal) to 4 (high degree of dysfunction)

<table>
<thead>
<tr>
<th>SOFA Score</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 to 6</td>
<td>&lt; 10%</td>
</tr>
<tr>
<td>7 to 9</td>
<td>15-20%</td>
</tr>
<tr>
<td>10 to 12</td>
<td>40-50%</td>
</tr>
<tr>
<td>13 to 14</td>
<td>50-60%</td>
</tr>
<tr>
<td>15</td>
<td>&gt; 80%</td>
</tr>
<tr>
<td>15 to 24</td>
<td>&gt; 90%</td>
</tr>
</tbody>
</table>