SHADES OF GREY: PHARMACOLOGIC CONTROVERSIES SURROUNDING THE MANAGEMENT OF CRITICALLY ILL SEPTIC PATIENTS

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Disclosure

• No personal conflicts of interest

• However, some off-label use of medications will be discussed

Objectives

• Describe the definitions and epidemiology of severe sepsis and septic shock

• Debate specific pharmacologic controversies surrounding the management of severe sepsis and septic shock

• Identify the role of pharmacists in the management of severe sepsis and septic shock patients

Sepsis...A Serious Matter...

• ~750,000 cases per year
  – ~30% mortality rate
  – Hospital costs = $24 billion (5% of national hospital expenditures)

• In a recent severe sepsis epidemiological series of ~307,000 patients by Page et al...
  – 62.8% community-acquired severe sepsis
  – 25.9% healthcare-associated severe sepsis
  – 11.3% hospital-acquired severe sepsis

Pathophysiology of Sepsis

• Gram-positive bacteria
  – Staphylococcus aureus
  – Streptococcus pneumonia

• Gram-negative bacteria
  – Escherichia Coli
  – Klebsiella species
  – Pseudomonas aeruginosa

Don’t forget about fungi!!!
Pathophysiology of Sepsis

The Sepsis Syndrome

Sepsis

• SIRS + Suspected infection

Severe Sepsis

• Sepsis + Sepsis-induced tissue hypoperfusion or organ dysfunction

Sepsis Shock

• Sepsis + Hypotension (after adequate fluid resuscitation)

Old (Sepsis-2) New (Sepsis-3)

Sepsis

Suspected infection

Sepsis

SIRS + Suspected infection

Sepsis

SIRS + Suspected infection

Sepsis

SIRS + Suspected infection

Suspected/documented infection

2 or 3 on qSOFA:

SIRS + Hypotension (SBP ≤ 100 mmHg)

Altered Mental Status (GCS ≤ 13)

Tachypnea (≥ 22 breaths/min)

Or

Rise in SOFA score by 2 or more

qSOFA

Sepsis

SIRS + Suspected infection

Sepsis

SIRS + Suspected infection

Sepsis

SIRS + Suspected infection

Sepsis

Suspected infection

Septic shock

Hypotension (after adequate fluid resuscitation)

Vasopressors needed for MAP > 65 mmHg

Lactate > 2 mmol/L (after adequate fluid resuscitation)


Sepsis Redefined (Sepsis-3)

Pros

• Reflects up to date pathobiology

• Backed by data

• Simple to use and offers consistency

• Recommendations on ICD-9 and ICD-10 codes to use

• Recommendation on implementation

• Acknowledgement of continual evolution of the definition

Cons

• Adjusting to new definitions after ~15 years with SIRS criteria

• qSOFA recommendations mostly based on retrospective US databases

• Prospective validation warranted and encouraged

• Lactate

• Debate continues...

• Major CMS requirement

Sepsis Redefined (Sepsis-3)

This Just In!!!

New definition of sepsis!!!
(A non-pharmacologic controversy)

Sequential Organ Failure Assessment (SOFA)

<table>
<thead>
<tr>
<th>Sepsis</th>
<th>Old (Sepsis-2)</th>
<th>New (Sepsis-3)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
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</table>

Pros

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• Lactate

• Debate continues...

• Major CMS requirement
Surviving Sepsis: Guidelines, Updated Bundles, and CMS Sepsis Core Measures

First 3 Hours
- Measure lactate
- Pre-antimicrobial blood cultures
- Broad spectrum antimicrobials
- Preferably within 1 hour
- 30 mL/kg crystalloid for hypotension or lactate concentration ≥ 4 mmol/L

First 6 Hours
- Apply vasopressors to maintain a mean arterial pressure (MAP) ≥ 65 if not response to initial fluids
- For persistent hypotension after initial fluid administration (MAP < 65 mmHg) or initial lactate ≥4 mmol/L, re-assess volume status and tissue perfusion
- Re-measure lactate if initial level elevated.

Shades of Grey???
1. Fluid resuscitation
2. Stress-dosed steroids
3. Timing of antimicrobials

Controversies surrounding fluid resuscitation
Which fluid type is right?

Why Fluids?
- IV fluids are used to maintain/increase the intravascular space and ensure optimal organ perfusion
- Surviving Sepsis Guideline
  - Initial fluid challenge in patients with sepsis-induced tissue hypoperfusion with a suspicion of hypovolemia to achieve a minimum of 30 mL/kg (grade 1C)

Fluids Are Drugs!!

<table>
<thead>
<tr>
<th>Fluid</th>
<th>Composition (mmol/L)</th>
<th>Osmolarity (mOsm/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.9% NaCl</td>
<td>154 154 308 308</td>
<td>154 154 308</td>
</tr>
<tr>
<td>Lactated Ringers</td>
<td>131 5.4 2 111 28</td>
<td>308</td>
</tr>
<tr>
<td>Plasma-Lyte</td>
<td>140 5 3 3 88 37 23 20 204</td>
<td></td>
</tr>
<tr>
<td>HES 166-186</td>
<td>0-4 0.5 0.1-0.5 118-154 0.34 0.28</td>
<td>286-308</td>
</tr>
<tr>
<td>Albumin 4% 5% 10%</td>
<td>148 128 250</td>
<td></td>
</tr>
</tbody>
</table>

*To convert the values for potassium to milligrams per deciliter, divide by 0.2558. To convert the values for calcium to milligrams per deciliter, divide by 0.25. To convert the values for magnesium to milligrams per deciliter, divide by 0.4114.
Fluid Recommendations

- Crystalloids as the initial fluid of choice in the resuscitation of severe sepsis and septic shock (grade 1B).


- Albumin in the fluid resuscitation of severe sepsis and septic shock when patients require substantial amounts of crystalloids (grade 2C).


Endothelial Glycocalyx Layer


Albumin vs. Saline in the ICU (SAFE Trial)

<table>
<thead>
<tr>
<th>Table 1: Primary and Secondary Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

Albumin in Severe Sepsis or Septic Shock (ALBIOS Trial)

- Subjects: 1810 adult severe sepsis patients
- Intervention: 20% albumin and crystalloid solution (albumin group, n=903) or crystalloid solution alone (crystalloid group, n=907)
- Primary Outcome: 28-day all cause mortality
- Results: 28 days: 31.8% in the albumin group and 32.0% in the crystalloid group died
- Conclusion: Albumin plus crystalloids vs. crystalloids alone did not improve the rate of survival at 28 and 90 days

Fluid Recommendations

• Against the use of hydroxyethyl starches (HES) for fluid resuscitation of severe sepsis and septic shock (grade 1B).

<table>
<thead>
<tr>
<th>Study</th>
<th>Results</th>
</tr>
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<tbody>
<tr>
<td>CHEST</td>
<td>Primary outcome was all-cause mortality 90 days after randomization (NO DIFFERENCE between HES vs. 0.9% NS, 18% vs. 17%, p=0.26 (RR: 1.10; 95% CI 0.95 to 1.26). Study underpowered.</td>
</tr>
<tr>
<td>6S</td>
<td>Primary outcome was death or dependence on dialysis 90 days after randomization (INCREASED MORTALITY with HES vs. Ringers acetate, 31% vs 43%, p=0.03 (RR: 1.17; 95% CI 1.01 to 1.36).</td>
</tr>
<tr>
<td>CRISTMAS</td>
<td>Primary outcome was 6% difference absolute mortality (NO DIFFERENCE between HES vs. 0.9% NS, 35% vs. 29.3%, p=0.37. Study underpowered.</td>
</tr>
</tbody>
</table>

CRISTAL Trial (JAMA 2013)

• Objective: To test whether use of colloids vs. crystalloids for fluid resuscitation alters mortality in patients admitted to the ICU
• Design: Multicenter, randomized clinical trial
• Subjects: n=2857; not specifically septic patients
• Intervention: Colloids=1414; gelatins, dextrans, hydroxyethyl starches, or 4% or 20% of albumin. Crystalloids=1443; isotonic or hypertonic saline or Ringer lactate solution
• Primary Outcome: 28-day mortality

<table>
<thead>
<tr>
<th>Study</th>
<th>Results</th>
</tr>
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<tbody>
<tr>
<td>Table 1. Study Outcomes by Treatment Group</td>
<td></td>
</tr>
<tr>
<td></td>
<td>COLLOIDS</td>
</tr>
<tr>
<td>Death</td>
<td>796</td>
</tr>
<tr>
<td>Hospital Length of Stay (days)</td>
<td>5.9 (5.5 to 6.2)</td>
</tr>
<tr>
<td>ICU Length of Stay (days)</td>
<td>3.7 (3.2 to 4.2)</td>
</tr>
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</table>

6S and CHEST...Comparing Apples to Oranges

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<tr>
<td>CHEST</td>
<td></td>
</tr>
<tr>
<td>Total patients (n)</td>
<td>796</td>
</tr>
<tr>
<td>Patients with sepsis (n)</td>
<td>796</td>
</tr>
<tr>
<td>Mortality (patients with sepsis)</td>
<td>11%</td>
</tr>
<tr>
<td>Ratio of HES to crystalloids for 24 h</td>
<td>1:1</td>
</tr>
<tr>
<td>Difference in CYP response</td>
<td>No</td>
</tr>
<tr>
<td>Carrier solution</td>
<td>Ringer’s acetate</td>
</tr>
<tr>
<td>Benefit (HR vs control) (CI:RR)</td>
<td>1.04 (0.96-1.12)</td>
</tr>
<tr>
<td>No difference seen in 160 ICU patients.</td>
<td></td>
</tr>
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CRISTAL Trial (JAMA 2013): Outcomes

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</tr>
<tr>
<td>Patients</td>
<td>COLLOIDS</td>
</tr>
<tr>
<td></td>
<td>No. Deaths</td>
</tr>
<tr>
<td>Death</td>
<td>214</td>
</tr>
<tr>
<td>HES vs isotonic saline</td>
<td>645</td>
</tr>
<tr>
<td>HES vs hypertonic saline</td>
<td>645</td>
</tr>
<tr>
<td>Glutamine vs isotonic saline</td>
<td>201</td>
</tr>
<tr>
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<td>Ringer’s acetate vs isotonic saline</td>
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<td>201</td>
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<td>Mortality (HR 95% CI)</td>
<td>1.03 (0.97-1.10)</td>
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### A Different Perspective...

**Table**: Fluid Composition and Osmolarity

<table>
<thead>
<tr>
<th>Fluid</th>
<th>Na (mmol/L)</th>
<th>K (mmol/L)</th>
<th>Ca (mmol/L)</th>
<th>Mg (mmol/L)</th>
<th>Cl (mmol/L)</th>
<th>Acetate (mmol/L)</th>
<th>Lactate (mmol/L)</th>
<th>Gluconate (mmol/L)</th>
<th>Osmolarity (mOsm/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.9% NaCl</td>
<td>154</td>
<td>154</td>
<td></td>
<td></td>
<td>308</td>
<td></td>
<td></td>
<td></td>
<td>280</td>
</tr>
<tr>
<td>Lactated Ringers</td>
<td>155</td>
<td>2</td>
<td></td>
<td>20</td>
<td>155</td>
<td></td>
<td></td>
<td></td>
<td>280</td>
</tr>
<tr>
<td>Plasma-Lyte</td>
<td>140</td>
<td>5</td>
<td>3</td>
<td>27</td>
<td>118-154</td>
<td>0.34</td>
<td>0.28</td>
<td>286-308</td>
<td></td>
</tr>
<tr>
<td>Albumin</td>
<td>148</td>
<td>128</td>
<td></td>
<td></td>
<td>250</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
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### Problems with 0.9% NaCl

- Acid-base disturbances
  - Hyperchloremic metabolic acidosis
- Renal impairment
  - Affenter arteriolar vasocostriction
  - Decreased glomerular filtration rate

**Table 1**: Multivariate Analysis of Hospital Mortality as the Dependent Variable Among Hyperchloremic Patients at the Time of ICU Admission (0Cl ≥ 110 mEq/L) for 1) Serum Chloride at the Time of ICU Admission, 2) Serum Chloride at 72 Hours of ICU Stay, and 3) Within-Subject Time-Related Change in Serum Chloride From ICU Admission to 72 Hours ICU

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds Ratio Hospital Mortality</th>
<th>p</th>
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<th>p</th>
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<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cl₄₈₁₃₂</td>
<td>(0Cl ≥ 110 mEq/L)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cl₄₈₋₁₈₂</td>
<td>1.04 (0.89-1.21)</td>
<td></td>
<td>1.02 (0.86-1.20)</td>
<td></td>
<td>1.02 (0.86-1.20)</td>
<td></td>
</tr>
<tr>
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<td>1.02 (0.86-1.20)</td>
<td></td>
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<td></td>
<td>1.02 (0.86-1.20)</td>
<td></td>
</tr>
</tbody>
</table>

*As a serum chloride of the time of ICU admission, Cl₄₈₋₁₈₂ serum chloride at 72h of ICU stay, Cl₄₈₋₁₈₂ Cl₄₈₋₁₈₂.

---

### Yunos, et al. (JAMA 2012)

- **Objective**
  - Assess the association of a chloride-restrictive (vs chloride-liberal) IV fluid strategy with AKI in critically ill patients

- **Design**
  - Prospective, open-label, sequential period pilot study

- **Subjects**
  - n=1533
    - 760 patients in the control period
    - 773 patients in the intervention period

- **Intervention**
  - During control period, patients received standard intravenous fluids.
  - During intervention period, use of chloride-rich IV fluids (0.9% saline, 4% succinylated gelatin solution, or 4% albumin solution) restricted to MD approval
  - Patients received a lactated solution (Hartmann solution), a balanced solution (Plasma-Lyte 148), and chloride-poor 20% albumin instead

- **Primary Outcomes**
  - Increase from baseline to peak SCr in the ICU and incidence of AKI according to the RIFLE classification

**Yunos, et al. (JAMA 2012): Outcomes**

- Chloride-restrictive strategy associated with a significantly lower increase in serum creatinine level during ICU stay
  - 14.8 μmol/L (95% CI, 9.8 to 19.9 μmol/L) during the intervention period
  - 0.2 mg/dL (95% CI, 0.1 to 0.2 mg/dL) during the control period
  - p=.03; adjusted p=.007

---

### Yunos, et al. (JAMA 2012): Outcomes

**Table 2**: Incidence of Acute Kidney Injury Stratified by Risk, Injury, Failure, Loss, and End-Stage (RIFLE) Serum Creatinine Criteria

<table>
<thead>
<tr>
<th>RIFLE Class</th>
<th>Control Period (n = 700)</th>
<th>Intervention Period (n = 773)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk</td>
<td>71 (9.5) (2-11.0)</td>
<td>57 (7.4) (5.9-9.0)</td>
<td>.18</td>
</tr>
<tr>
<td>Injury</td>
<td>49 (6.9) (5.5-8.1)</td>
<td>23 (3.0) (1.9-4.2)</td>
<td>.002</td>
</tr>
<tr>
<td>Failure</td>
<td>57 (7.9) (6.8-9.1)</td>
<td>42 (5.4) (3.8-7.1)</td>
<td>.15</td>
</tr>
</tbody>
</table>

*Values are presented as N (%) (95% CI). Results were adjusted for age, sex, and APACHE II through data through August 11, 2006, and the intervention period was from February 1 through August 11, 2006.
Association Between Choice of IV Crystalloid and In-Hospital Mortality in Critically Ill Septic Adults

- **Design:**
  - Retrospective cohort study (360 US hospitals)

- **Subjects:**
  - 53,448 adult patients with sepsis
    - Treated with vasoppressors and crystalloids in ICU by hospital day 2
    - 3,396 received balanced fluids

- **Intervention:**
  - None

- **Primary Outcome:**
  - In-hospital mortality after hospital day 2

### Table 1: Association Between Resuscitation With Balanced Fluids and Primary and Secondary Outcomes in Propensity-Matched Cohorts

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Balanced Fluid Matched Cohort (%)</th>
<th>Balanced Fluid Proportion Matched Cohort (%)</th>
<th>Effect Estimate</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absolute in hospital mortality</td>
<td>16.9% (539 of 3,243)</td>
<td>23.9% (750 of 3,205)</td>
<td>Relative risk</td>
<td>0.70</td>
</tr>
<tr>
<td>ARF with diabetes</td>
<td>4.1% (14 of 344)</td>
<td>4.5% (14 of 314)</td>
<td>Relative risk</td>
<td>0.87</td>
</tr>
<tr>
<td>ARF without diabetes</td>
<td>7.5% (24 of 323)</td>
<td>10.1% (16 of 323)</td>
<td>Relative risk</td>
<td>0.70</td>
</tr>
<tr>
<td>Hospital LOS in days</td>
<td>11.29</td>
<td>11.09</td>
<td>Absolute difference</td>
<td>-0.21</td>
</tr>
<tr>
<td>ICU LOS in days</td>
<td>5.00</td>
<td>5.50</td>
<td>Absolute difference</td>
<td>-0.50</td>
</tr>
</tbody>
</table>

ARF = acute renal failure; LOS = length of stay.

SPLIT Trial (JAMA 2015)

- **Objective:**
  - To determine the effect of a buffered crystalloid compared with saline on renal complications in patients admitted to the ICU

- **Design:**
  - Multicenter, double-blind, cluster randomized, double-crossover trial
    - 4 ICUs in New Zealand (3 general medical and surgical, 1 cardiothoracic)

- **Subjects:**
  - n=2262
    - 1152 patients in the buffered solution group
    - 1110 patients in the saline group

- **Intervention:**
  - Participating ICUs were assigned masked study fluids of either saline or buffered crystalloid (Plasma-Lyte) for alternating 7 week treatment blocks
    - Each ICU used each fluid twice over a 28 week study period

- **Primary Outcome:**
  - Proportion of patients with AKI according to the serum creatinine criteria of the risk, injury, failure, loss, end-stage (RIFLE) classification

SPLIT Trial (JAMA 2015): Outcomes

- **Baseline characteristics were similar between the two groups**
  - Mean age: ~60 years
  - 2/3 of the patients were men
  - Most patients were admitted to the ICU following elective surgery
    - Cardiovascular surgery was the most common
  - Mean(±SD) APACHE II scores were 14.1 (±6.9) for the buffered solution group vs. 14.1 (±6.7) for the saline group
### SPLIT Trial (JAMA 2015): Outcomes

<table>
<thead>
<tr>
<th>Table 2: Outcomes for Patients in the Intensive Care Unit Receiving Buffered Crystalloid vs. Saline Fluid Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Variable</td>
</tr>
<tr>
<td>Mortality</td>
</tr>
<tr>
<td>Acute kidney injury at hospital</td>
</tr>
<tr>
<td>Need for RRT</td>
</tr>
</tbody>
</table>

### What Can We Conclude?

- **Balanced vs. Unbalanced vs. Albumin**
  - Are these fair comparisons?
  - Fluid administration should be patient specific
    - Timing
    - Amount
    - Proper monitoring
- **Future studies:**
  - SaLT-ED: saline vs. LR or plasmalyte in the emergency department
  - RCTs in Europe and Australia looking at type and amount

### Interactive Question #2

- **When do you start stress-dose steroids in your septic shock patients?**
  a. Immediately upon diagnosis of septic shock
  b. After an initial vasopressor and fluid therapy have failed (ie. An additional vasopressor is needed)
  c. Never because I do not believe they work
Objective:

- Investigate the impact of early initiation of hydrocortisone on the clinical course of septic shock and cytokine release.

Design:

- Nonrandomized, prospective, longitudinal study in seven ICUs and four general wards.

Subjects:

- 170 patients with septic shock treated with norepinephrine and hydrocortisone 50 mg every 6 hours for 7 days.

Intervention:

- None but patients were divided into 2 groups:
  - Early initiation of hydrocortisone (4 hours): n=66
  - Late initiation of hydrocortisone (1-8 hours): n=104

Primary Outcome:

- Effect of time delay of initiation of hydrocortisone after start of vasopressors on final outcome (survival).

Surviving Sepsis Guidelines

- “We suggest not using intravenous hydrocortisone as a treatment of adult septic shock patients if adequate fluid resuscitation and vasopressor therapy are able to restore hemodynamic stability. If this is not achievable, we suggest intravenous hydrocortisone alone at a dose of 200 mg per day (grade 2C).”

Critical Illness-Related Adrenal/Corticosteroid Insufficiency

- Hypothalamic-pituitary-adrenal (HPA) axis dysfunction and adrenal failure:
  - Incidence as high as 60% in severe sepsis and septic shock.
  - Mechanisms of inadequate cortisol production during critical illness are poorly understood.
  - Likely include decreased production of CRH, ACTH, and cortisol.

- Corticosteroid tissue resistance:
  - Glucocorticoid receptors (GR) transcriptional incompetence.
  - Decreased nuclear translocation of the glucocorticoid-GR α complex.
  - Well known manifestation of chronic inflammatory diseases such as COPD, severe asthma, systemic lupus erythematosus, ulcerative colitis, and rheumatoid arthritis.

- Hypotension refractory to fluids and requirement of vasopressors is a common manifestation.

Corticosteroids for Septic Shock

- First use might date back to 1963 (Cooperative Study Group).
- 2 large trials with conflicting results:

- Early Administration of Hydrocortisone Replacement After the Advent of Septic Shock: Impact of Survival and Immune Response.

- Proportion of survivors was higher in early initiation group:
  - 52.2% vs. 30.6%, p=0.012
Katsenos, et al. (Crit Care Med 2014): Results

**Table 1: Regression Forest and Logistic Regression Analysis of Factors Influencing Final Outcome**

<table>
<thead>
<tr>
<th>Model 1</th>
<th>Regression Model (APACH)</th>
<th>Logistic Regression Model (APACH)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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</tr>
<tr>
<td>APACHE I</td>
<td>B (95% CI)</td>
<td>B (95% CI)</td>
</tr>
<tr>
<td>&lt; 19</td>
<td>0.001 (0.000-0.001)</td>
<td>0.001 (0.000-0.001)</td>
</tr>
<tr>
<td>≥ 19</td>
<td>0.001 (0.000-0.001)</td>
<td>0.001 (0.000-0.001)</td>
</tr>
</tbody>
</table>

Patients with high APACHE score (≥ 19)
- Early initiation increased survival rate from 19.8% to 41.2%; p = 0.021

Patients with low APACHE score (< 19)
- Early initiation increased survival rate from 55.0% to 83.3%

---

**Table 2: 30-Day Mortality in Septic Shock Cohorts**

<table>
<thead>
<tr>
<th>cohort</th>
<th>Variable</th>
<th>Male/Female (%)</th>
<th>hypo/Severe (%)</th>
<th>sepsis severity</th>
<th>Mortality Rate (%)</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adjusted</td>
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</tbody>
</table>

**Objective:**
- Evaluate therapeutic benefit of early low-dose corticosteroid in patients with septic shock

**Design:**
- Retrospective propensity-matched cohort study in the ICUs of 28 academic and community hospitals in 3 countries

**Subjects:**
- 6663 patients
  - Matched cohort of 1838 who received therapy to 1838 who did not

**Intervention:**
- IV low-dose corticosteroids (150 to 300 mg) within 48 hours of diagnosis of septic shock

**Primary Outcome:**
- 30-day mortality

---

**Corticosteroids...Not Benign Drugs**

- Immunosuppression
  - Increased risk of infections (typical and opportunistic)
- Impaired wound healing
- Hyperglycemia
- Myopathy

- Hypokalemic metabolic acidosis
- Psychosis
- Gastric and duodenal ulcers
- HPA axis and GR suppression

---

**Low-Dose Corticosteroid Treatment in Septic Shock: A Propensity-Matching Study**


---

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  - Increased risk of infections (typical and opportunistic)
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- Hypokalemic metabolic acidosis
- Psychosis
- Gastric and duodenal ulcers
- HPA axis and GR suppression
### Should We Use a Continuous Infusion?

**Rationale:** Potentially less fluctuations in glucose control

Loisa, et al. – Prospective, randomized study of 48 septic shock patients
- Received hydrocortisone by bolus (n=23) or continuous infusion (n=22) (200 mg/day equivalent dose)
- Mean blood glucose (BG) was similar between the 2 groups, but number of hyperglycemic episodes was higher in the bolus group:
  - 15.7 ± 8.5 vs. 10.5 ± 8.6 episodes per patient, p=0.039
- More changes in insulin infusion rate needed to maintain strict normoglycemia (BG <125 mg/dL) in the bolus group:
  - 4.7 ± 2.2 vs. 3.4 ± 1.9 adjustments per patient per day, p=0.038
- No difference in shock reversal seen


Weber-Carstens, et al. – Observational, prospective, pilot study of 16 septic shock patients
- Received hydrocortisone continuous infusion of 200 mg/day and an insulin infusion to keep BG <150 mg/dL
- One 50 mg bolus dose of hydrocortisone given followed by a 6-hour observation period after which the infusions were continued
- Mean BG in steady state prior to the bolus was 128 mg/dL (range 114 to 141) vs. 6-hour post-bolus peak BG of 154 (range 132 to 178); p<0.01

Surviving Sepsis Guideline Recommendation: When hydrocortisone is given, use continuous flow (grade 2D)


### Should We Taper?

**Rationale:** Abruptly stopping corticosteroids may result in rebound of proinflammatory mediators with recurrence of shock features

Annane, et al. had an abrupt cessation of corticosteroids after 7 days
- No obviously reported rebound shock

Sprung, et al. had a 6 day taper
- 31% of patients in the hydrocortisone group had repeat shock

Surviving Sepsis Guideline Recommendation: We suggest that clinicians taper the treated patient from steroid therapy when vasoppressors are no longer required (grade 2D)

### What Can We Conclude?

Controversy still exists...
- Corticosteroid therapy should probably be used in patients refractory to fluid resuscitation and vasopressor therapy
  - May have a more pronounced benefit in sicker septic shock patients
  - May need to be given early in septic shock for benefit
- Randomized, controlled multicenter trials are required to confirm the findings of previous studies
    - Adjunctive corticosteroid treatment in critically ill patients with septic shock

### Controversies surrounding antimicrobial therapy?

**Should critically ill septic shock patients receive antimicrobial within 1-3 hours?**

### Is Time to Antimicrobials Important?

**Antimicrobial therapy:**
- Administration within the first hour of recognition of septic shock (grade 1B) and severe sepsis without shock (grade 1C)

<table>
<thead>
<tr>
<th>Authors</th>
<th>n</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kumar, et al</td>
<td>2,731</td>
<td>80% survival when antimicrobials received within first hour of hypotension</td>
</tr>
<tr>
<td></td>
<td></td>
<td>8% decrease in survival with each hour of delay</td>
</tr>
<tr>
<td>Gawinski, et al</td>
<td>261</td>
<td>25% mortality if antimicrobials given in ≤1 hr vs. 39% mortality if delayed &gt;1 hr (p&lt;0.05)</td>
</tr>
<tr>
<td>Parkarich, et al</td>
<td>291</td>
<td>12% mortality before shock recognition vs. 24% mortality after shock recognition</td>
</tr>
</tbody>
</table>
Early Administration of Antimicrobial Therapy

<table>
<thead>
<tr>
<th>Study</th>
<th>Protocol/Standard Therapy</th>
<th>Usual/Standard Care Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rivers et al.</td>
<td>EGDT Group</td>
<td>80.6% received abx within 6 hr</td>
</tr>
<tr>
<td>ARMS Trial</td>
<td>96.3% received abx within 6 hr</td>
<td>91.7% received abx within 6 hr</td>
</tr>
<tr>
<td>ProCESS</td>
<td>94.3% received abx within 6 hr</td>
<td>97.1% received abx within 6 hr</td>
</tr>
<tr>
<td>ARISE</td>
<td>100% received abx within 6 hr</td>
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</table>


Impact of Timing of Antibiotics on Outcomes in Severe Sepsis and Septic Shock: A Systematic Review and Meta-Analysis

- Meta-analysis of 11 publications to evaluate the timing of antibiotic administration and mortality
  - 16,178 total patients were evaluable
  - Primary outcome was mortality

<table>
<thead>
<tr>
<th>Pooled ORs for &lt; or &gt; 3 hr from triage</th>
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<tbody>
<tr>
<td>Pooled OR 1.16 (CI 0.92-1.46)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Pooled ORs &lt; or &gt; 1 hr from severe sepsis/shock recognition (n=11,017)</th>
</tr>
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<tbody>
<tr>
<td>Pooled OR 1.46 (CI 0.89-2.4)</td>
</tr>
</tbody>
</table>

- Limitations:
  - 7/18 eligible trials were excluded because authors could not get the data sets
  - No analysis on whether empiric therapy was appropriate

What Can We Conclude?...Follow the Guidelines!!!

Interactive Question #3

Does your institution have sepsis alerts or a sepsis team?

a. We have sepsis alerts
b. We have a sepsis team
c. We have both alerts and a team
Surviving Sepsis: Guidelines, Updated Bundles, and CMS Sepsis Core Measures

First 3 Hours

- Measure lactate
- Pre-antimicrobial blood cultures
- Broad spectrum antimicrobials
- Preferably within 1 hour
- 30 mL/kg crystalloid for hypotension or lactate concentration ≥ 4 mmol/L

First 6 Hours (updated)

- Apply vasopressors to maintain a mean arterial pressure (MAP) ≥ 65 if not response to initial fluids
- For persistent hypotension after initial fluid administration (MAP < 65 mm Hg) or initial lactate ≥4 mmol/L, reassess volume status and tissue perfusion
- Re-measure lactate if initial level elevated.

Role of A Pharmacist on Sepsis Teams

- Recently, Beardsley et al. described their experience implementing a Code Sepsis Team
  - Case study (part of the institution’s Code Sepsis initiative after a 2011 system-wide analysis)
  - Septic patient cases from May to July 2012 (baseline group) vs. cases from April 2013 to March 2014 (random sampling)

- Code Sepsis:
  - Nurse screening using standardized tool
  - Text page to inpatient pharmacy, respiratory therapy, lab, and ICU triage nurse
  - Activation of an electronic order set
  - Protocol allowing pharmacists to select antibiotics if providers are busy

Role of A Pharmacist on Sepsis Teams

- Mean time from rapid response nurse arrival on the unit to antibiotic administration decreased
  - 396 minutes to 51 minutes for patient in non-critical care units

Role of A Pharmacist on Sepsis Teams

- Controversies will always exist with respect to management of septic patients
- Must practice evidence-based medicine
  - Caveat...not all patients are the same and thus evidence must be applied appropriately
- Multidisciplinary approach to sepsis management is warranted given the morbidity and mortality associated with the syndrome

Summary

- Controversies will always exist with respect to management of septic patients
- Must practice evidence-based medicine
  - Caveat...not all patients are the same and thus evidence must be applied appropriately
- Multidisciplinary approach to sepsis management is warranted given the morbidity and mortality associated with the syndrome

Role of A Pharmacist on Sepsis Teams

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<th>Included Population</th>
<th>Intervention</th>
<th>Primary Outcome</th>
<th>Results</th>
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<tbody>
<tr>
<td>Flynn, et al. (2014)</td>
<td>Retrospective, case-control study</td>
<td>All septic patient cases from September 2010 to September 2011 vs. cases from September 2008 to August 2009 (historical control)</td>
<td>Coordinated Response to Sepsis (CaRTS): 1. electronic order set for patients suspected of developing sepsis 2. automated deployment of pharmacy and nursing after order activation 3. hospital-wide &quot;sepsis carts&quot;</td>
<td>Proportion of patients with appropriate antibiotic administration within 1 hr of sepsis recognition</td>
<td>48 patients and 50 historical controls were included for analysis. CaRTS intervention group had a higher odds of antibiotic administration within 1 hour compared with controls (OR 22.4, 95% CI 7.5–69), and were more likely to have a CVP ≥8 mm Hg at 6 hours (OR 2.4, 95% CI 1.0–5.6).</td>
</tr>
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Role of A Pharmacist on Sepsis Teams

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Phillip Mohorn, PharmD, BCPS, BCCCP
Clinical Assistant Professor
South Carolina College of Pharmacy, USC Campus
SCSHP 2016 Annual Meeting
March 14, 2016

SHADES OF GREY: PHARMACOLOGIC CONTROVERSIES SURROUNDING THE MANAGEMENT OF CRITICALLY ILL SEPTIC PATIENTS