Advances in the Management of Shock: Cardiogenic Shock and Septic Shock

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Disclosures

• No financial disclosures but Stanford will be a site for the levosimendan cardiac surgery study
• At the conclusion of the activity participants should be able to:
  – Discuss the current approach to management of the patient with cardiogenic shock
  – Discuss the current approach to management of the patient with septic shock
  – Recognize common complications associated with inappropriate management of cardiogenic and septic shock
Shock

“a condition of profound hemodynamic and metabolic disturbance characterized by failure of the circulatory system to maintain adequate perfusion of vital organs. It may result from inadequate blood volume (hypovolemic shock), inadequate cardiac function (cardiogenic shock), or inadequate vasomotor tone (neurogenic shock and septic shock)”

--Dorland’s Medical Dictionary
Shock

“a rude unhinging of the machinery of life”

--Gross, 1872
### Types of Shock

<table>
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<tr>
<th>Physiologic abnormality</th>
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</table>
Advances in Cardiogenic Shock

• Reperfusion after acute MI
• Mechanical circulatory assist devices
• Cardiac resynchronization therapy
• Inotropic and vasodilator agents
Intra-Aortic Balloon Counterpulsation

Graph showing IABP (Intra-Aortic Balloon Pump) with labeled phases of unassisted systole, diastolic augmentation, and assisted systole.
IABP for Cardiogenic Shock Due to Myocardial Infarction

- Unverzagt, Cochrane Database Syst Rev 2011; CD007398
  - No mortality benefit in 5 trials

![Graph showing mortality over days since randomization for IABP and control groups with N = 598. P = 0.92 by log-rank test.]
Advances in VAD Therapy

• Concept of bridge to transplant, bridge to device, bridge to recovery, and destination therapy
REMATCH Study

• Rose, NEJM 2001; 345: 1435
• 129 patients with end-stage heart failure randomized to HeartMate XVE or to medical therapy (not transplant candidates)
Advances in VAD Therapy

• Concept of bridge to transplant, bridge to device, bridge to recovery, and destination therapy

• Percutaneous cannulation
Percutaneous LVAD

- Kar B, J Am Coll Cardiol 2011; 57:688
  - Severe refractory cardiogenic shock
  - 117 patients with TandemHeart percutaneous VAD
Percutaneous LVAD

- Kar B, J Am Coll Cardiol 2011; 57:688
  - Severe refractory cardiogenic shock
  - 117 patients with TandemHeart percutaneous VAD
  - CI increased from 0.52 to 3.0 L/min/m²
  - Systolic BP increased from 75 to 100 mm Hg
  - PAOP decreased from 32 to 17 mm Hg
  - 55% survival at 6 months
Advances in VAD Therapy

• Concept of bridge to transplant, bridge to device, bridge to recovery, and destination therapy
• Percutaneous cannulation
• 1st generation devices: Pulsatile (Thoratec), no LV ejection
• 2nd generation devices: Continuous axial flow (impeller), LV ejection
Impeller Technology
Advances in VAD Therapy

• Concept of bridge to transplant, bridge to device, bridge to recovery, and destination therapy
• Percutaneous cannulation
• 1st generation devices: Pulsatile (Thoratec), no LV ejection
• 2nd generation devices: Continuous axial flow (impeller), LV ejection
• 3rd generation: Centrifugal pump with magnetically levitated rotor, LV ejection
  – CentriMag: Peripheral VAD
  – Heartware: place in LV apex
Interagency Registry for Mechanically Assisted Circulatory Support

J Heart Lung Transplant 2012; 31:117
INTERMACS - Kaplan-Meier Survival by Flow Type and Device
Primary Prospective Implants: June 23, 2006 to June 30, 2014

Flow Type and Device
- Continuous - LVAD (n = 10280, Deaths = 2542)
- Continuous - BiVAD (n = 302, Deaths = 142)
- Pulsatile - LVAD (n = 612, Deaths = 232)
- Pulsatile - BiVAD (n = 328, Deaths = 125)
- Pulsatile - TAH (n = 272, Deaths = 73)

Shaded areas indicate 70% confidence limits
p (log-rank) = <.0001
Event: Death (censored at transplant or recovery)
Primary Implant Enrollment: n=4366

- Continuous Flow Intracorporeal LVAD Pump
- Pulsatile Flow Intracorporeal TAH
- Pulsatile Flow Intracorporeal LVAD Pump
- Pulsatile Flow Paracorporeal LVAD Pump

INTERMACS
Interagency Registry for Mechanically Assisted Circulatory Support
J Heart Lung Transplant 2012; 31:117
Advances in Cardiogenic Shock

- Reperfusion after acute MI
- Mechanical circulatory assist devices
- Cardiac resynchronization therapy
- Inotropic and vasodilator agents
Cardiac Resynchronization Therapy
Cardiac Resynchronization Therapy

- Young, JAMA 2003; 28:2685
  - MIRACLE ICD trial
  - Improved quality of life, functional class, treadmill test

- Huang, Int J Cardiol 2010;145:413
  - Meta-analysis of 7 randomized trials
  - Mortality OR 0.55 (0.40 – 0.76)
Advances in Cardiogenic Shock

- Reperfusion after acute MI
- Mechanical circulatory assist devices
- Cardiac resynchronization therapy
- Inotropic and vasodilator agents
## Inotropic and Vasodilator Agents

<table>
<thead>
<tr>
<th>Agent</th>
<th>Mechanism</th>
<th>Dose</th>
<th>BP</th>
<th>HR</th>
<th>CO</th>
<th>SVR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dobutamine</td>
<td>B1 &gt; β2 &gt; α</td>
<td>2-15 mcg/kg/min</td>
<td>↓</td>
<td>↑</td>
<td>↑↑</td>
<td>↓</td>
</tr>
<tr>
<td>Milrinone</td>
<td>PDE-3 inhibitor</td>
<td>0.2 – 0.75 mcg/kg/min</td>
<td>↓↓</td>
<td>↑</td>
<td>↑↑</td>
<td>↓↓</td>
</tr>
<tr>
<td>Levosimendan</td>
<td>Calcium sensitizer</td>
<td>0.05 - 0.2 mcg/kg/min</td>
<td>→</td>
<td>→</td>
<td>↑↑</td>
<td>↓↓</td>
</tr>
<tr>
<td>Epinephrine</td>
<td>B1 = β2 &gt; α</td>
<td>0.01 - 0.3 mcg/kg/min</td>
<td>↑</td>
<td>↑</td>
<td>↑↑</td>
<td>↓</td>
</tr>
<tr>
<td>Norepinephrine</td>
<td>B1 &gt; α &gt; β2</td>
<td>0.01 - 0.1 mcg/kg/min</td>
<td>↑↑</td>
<td>→</td>
<td>→</td>
<td>↑↑</td>
</tr>
<tr>
<td>Dopamine</td>
<td>B</td>
<td>2 – 5 mcg/kg/min</td>
<td>↑↑</td>
<td>↑</td>
<td>↑↑</td>
<td>↓</td>
</tr>
<tr>
<td>Dopamine</td>
<td>α</td>
<td>5 – 20 mcg/kg/min</td>
<td>↑↑</td>
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Dobutamine, milrinone, and dopamine may worsen outcome in heart failure patients

Adapted from Nativi-Nicalu, Curr Opin Cardiol 2014; 29:250
Nesiritide

- Synthetic brain natriuretic peptide (BNP)
- Balanced arterial and venous vasodilation
- Decreases RAP and PAP
- Increases cardiac output
- Increases salt and water excretion
Nesiritide in Decompensated Heart Failure

- **PRECEDEMENT study** *(Am Heart J 2002; 144:1102)*
  - Similar hemodynamic effects to dobutamine but without the tachycardia and ventricular ectopy

- **VMAC study** *(JAMA 2002; 287: 1531)*
  - Greater decrease in PAOP and greater symptomatic improvement compared to nitroglycerin
Nesiritide

• Mentzer, J Am Coll Cardiol 2007; 49:716
  – Patients with EF < 40% undergoing CABG randomized to nesiritide or placebo
  – Nesiritide decreased renal dysfunction, increased urine output, decreased LOS, and decreased mortality
Nesiritide

- Lingegowda, Clin Cardiol 2010;33:217
- RCT of prophylactic nesiritide for the prevention of acute kidney injury in patients undergoing high-risk CV surgery
- Nesiritide decreased acute kidney injury but did not affect need for acute dialysis, short-term, or long-term survival
ASCEND-HF Trial

• O’Connor, NEJM 2011; 365:32
• 7141 patients with acute heart failure randomized to nesiritide or placebo
• Nesiritide group had slightly better improvement in dyspnea (44% vs. 42%), but no difference in mortality, readmissions, or renal dysfunction
• Not recommended for treatment of acute heart failure
ROSE Acute Heart Failure Trial

- Chen, JAMA 2013; 310:2533
  - RCT of dopamine (2 mcg/kg/min), low dose nesiritide (0.005 mcg/kg/min) or placebo in 360 patients with acute heart failure and renal dysfunction
  - No effect on urine output, renal function, or clinical outcome
RELAX-AHF Trial

• Teerlink, Lancet 2013; 381:29
• Serelaxin (recombinant human relaxin-2) produces systemic and renal vasodilation
• RCT of 48 hours of serelaxin vs. placebo for treatment of acute heart failure in 1,161 patients without hypotension
• Serelaxin improved dyspnea and decreased ICU and hospital LOS without affecting renal function or in-hospital mortality
RELAX-AHF Trial

Placebo: 65 deaths (11.3%)
Serelaxin: 42 deaths (7.3%)

HR 0.63 (95% CI 0.43-0.93)
p = 0.02
Levosimendan

- Inotropic and vasodilator effects
  - Sensitizes contractile apparatus of the heart to calcium
  - Opens potassium channels in vascular smooth muscle
  - Increases cardiac output without increasing myocardial oxygen consumption; may decrease blood pressure
  - Pulmonary vasodilation
  - Decreases heart failure symptoms

- Landoni, Crit Care Med 2012; 40:634
  - Meta-analysis of 45 studies with 5,480 patients
  - Decreased mortality
    - Overall: OR 0.80 (0.72 – 0.89)
    - Cardiology: OR 0.67 (0.35 – 0.76)
    - Cardiac surgery : OR 0.52 (0.35 – 0.76)

- Registry study for cardiac surgery indication in progress
Septic Shock: Case

- 55 year old man with colon cancer underwent transverse colectomy 6 days ago
- Subsequently developed abdominal pain, tachycardia, and fever
- Evaluation demonstrated anastomotic breakdown with peritonitis
- During surgery for repair, now has HR 135, BP 70/50 despite 3 liters of saline, plus boluses of phenylephrine and ephedrine
# Types of Shock

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Sepsis and Septic Shock

- 751,000 cases per year in the United States
  - Incidence increasing by 1.5% per year
- Half will require intensive care
- 215,000 will die
  - Similar to acute myocardial infarction
  - Order of magnitude greater than AIDS
  - Will double by 2050
- Cost of $16.7 billion
Pope John Paul II died of septic shock in 2005
A mother who died six days after giving birth could have been saved if she had been treated earlier, a coroner has concluded.
DEFINITIONS IN SEPTIC SHOCK

• 1991 ACCP/SCCM Consensus Conference
• Systemic inflammatory response syndrome (SIRS)
  – A clinical response arising from a nonspecific insult manifest by two or more of the following:
    • Temperature $\geq 38^\circ$ C or $\leq 36^\circ$ C
    • HR $\geq 90$ beats/min
    • Respirations $\geq 20$/min
    • WBC $\geq 12,000$ or $< 4,000$ or $> 10\%$ bands
DEFINITIONS IN SEPTIC SHOCK

• Infection
  – Inflammatory response to microorganisms

• SIRS
  – Systemic inflammatory response due to a variety of insults (e.g., pancreatitis)

• Sepsis
  – SIRS plus infection

• Severe sepsis
  – Sepsis with one or more organ dysfunctions or hypotension

• Septic shock
  – Severe sepsis with hypotension despite fluid resuscitation
Mortality In Sepsis

Rangel-Frausto, JAMA 1995; 273:117
Therapy of Septic Shock

• Therapy of sepsis (antibiotics and source control)
• Hemodynamic therapy
• Adjunctive therapy
• Surviving Sepsis Campaign: International Guidelines for Management of Severe Sepsis and Septic Shock

• Dellinger, Crit Care Med 2013; 41: 580
Antibiotic Therapy

• Mortality decreases with appropriate antibiotic therapy
• Choice based on multiple factors
  – Suspected organism and site of infection
  – Hospital vs. community-acquired
  – Host factors
  – Severity of infection
  – Local antibiotic sensitivity patterns
• Initial therapy should be broad spectrum and then narrowed when susceptibilities known
SSC Infection Control Recommendations

- Cultures before antimicrobial therapy
- Intravenous antimicrobials within the first hour
- One or more drugs that have activity against all likely pathogens
- Antimicrobial regimen should be reassessed daily for potential de-escalation  
  – Use of procalcitonin levels or similar biomarkers
- Source control; percutaneous drainage for severely septic patients
- Oral chlorhexidine gluconate to reduce the risk of ventilator-associated pneumonia
Resuscitation from Septic Shock
Early Goal-Directed Therapy

  - 263 patients with severe sepsis and septic shock
  - Randomized to standard therapy or early goal-directed therapy (EGDT)
  - Standard therapy
    - Crystalloid boluses for CVP 8-12
    - Vasopressors/vasodilators for MAP 65-90
    - Urine output $\geq 0.5$ ml/kg/h
EGDT Protocol

- **EGDT**
  - Catheter for measurement of central venous oxygen saturation (ScvO2)
  - If ScvO2 < 70%
    - RBC transfusion to hematocrit > 30%
    - Dobutamine up to 20 μg/kg/min
    - Sedation and mechanical ventilation
EGDT Decreased Mortality

Alternative Resuscitation Strategies

- Jones, JAMA 2010;303:739
  - Lactate clearance equivalent to ScvO₂
  - RCT of 3 strategies (n = 1,341)
    - EGDT (mortality 21%)
    - Non-invasive clinical protocol (mortality 18%)
      - Shock index (HR/SBP)
      - Evidence of fluid overload
    - Best clinical judgment (mortality 19%)
Alternative Resuscitation Strategies

  - RCT of EGDT vs. standard care; n = 1,600

<table>
<thead>
<tr>
<th></th>
<th>EGDT</th>
<th>Standard Care</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluids (6 hours)</td>
<td>1,964 ml</td>
<td>1,713</td>
</tr>
<tr>
<td>RBC transfusion</td>
<td>14%</td>
<td>7%</td>
</tr>
<tr>
<td>Vasopressors</td>
<td>67%</td>
<td>58%</td>
</tr>
<tr>
<td>Dobutamine</td>
<td>15%</td>
<td>3%</td>
</tr>
<tr>
<td>90 day mortality</td>
<td>18.6%</td>
<td>18.8%</td>
</tr>
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</table>

![Graph showing survival probability over time]
SSC Resuscitation Recommendations

• Protocolized, quantitative resuscitation (EGDT)

• Target resuscitation to normalize lactate in patients with elevated lactate levels
Hemodynamic Therapy

- Preload
- Afterload
- Contractility
Preload and Compliance
Preload in Septic Shock

- Preload defined by pressure (PAOP) or volume (LVEDV)
- Compliance in septic shock is often increased
  - Volume administration should be guided by response to intravenous boluses
  - Dynamic assessments such as pulse pressure variation with respiration or IVC diameter
Choice of Fluid in Septic Shock

- Rochwerg, Ann Intern Med 2014; 161:347

<table>
<thead>
<tr>
<th>Study, Year (Reference)</th>
<th>Events/Total, n/N</th>
<th>Weight, %</th>
<th>Odds Ratio: M-H, Fixed (95% CI)</th>
</tr>
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<td></td>
<td>Colloids</td>
<td>Crystalloids</td>
<td>Odds Ratio: M-H, Fixed (95% CI)</td>
</tr>
<tr>
<td>Haupt and Rackow, 1982 (38)</td>
<td>8/13</td>
<td>3/4</td>
<td>0.2</td>
</tr>
<tr>
<td>Finfer et al, 2004 (2)</td>
<td>185/603</td>
<td>217/615</td>
<td>20.4</td>
</tr>
<tr>
<td>Brunhorst et al, 2008 (1)</td>
<td>107/261</td>
<td>93/274</td>
<td>7.3</td>
</tr>
<tr>
<td>Li et al, 2008 (39)</td>
<td>14/30</td>
<td>20/30</td>
<td>1.5</td>
</tr>
<tr>
<td>McIntyre et al, 2008 (41)</td>
<td>9/21</td>
<td>7/19</td>
<td>0.6</td>
</tr>
<tr>
<td>Dubin et al, 2010 (37)</td>
<td>3/12</td>
<td>7/13</td>
<td>0.7</td>
</tr>
<tr>
<td>Myburgh et al, 2012 (3)</td>
<td>248/976</td>
<td>224/945</td>
<td>23.3</td>
</tr>
<tr>
<td>Lv et al, 2012 (40)</td>
<td>7/22</td>
<td>12/20</td>
<td>1.2</td>
</tr>
<tr>
<td>Guidet et al, 2012 (6)</td>
<td>40/99</td>
<td>32/95</td>
<td>2.7</td>
</tr>
<tr>
<td>Perner et al, 2012 (4)</td>
<td>202/398</td>
<td>173/400</td>
<td>11.6</td>
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<tr>
<td>Haase et al, 2013 (5)</td>
<td>44/117</td>
<td>50/124</td>
<td>4.2</td>
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<tr>
<td>Annane et al, 2013 (16)</td>
<td>252/774</td>
<td>286/779</td>
<td>26.4</td>
</tr>
<tr>
<td>Total</td>
<td>3326</td>
<td>3318</td>
<td>100.00</td>
</tr>
<tr>
<td>Total events</td>
<td>1119</td>
<td>1124</td>
<td></td>
</tr>
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</table>

Heterogeneity: chi-square = 23.20; I^2 = 53%
Test for overall effect: Z = 0.18 (P = 0.85)
### Benefits of Balanced Crystalloids

**Table 4. NMA Results of 6-Node Analysis, Including Confidence Assessments**

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Trials With Direct Comparisons, ( n )</th>
<th>Direct Estimate (95% CI); Quality of Evidence</th>
<th>Indirect Estimate (95% CrI); Quality of Evidence</th>
<th>NMA Estimate (95% CrI)*; Quality of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>L-HES vs. saline</td>
<td>4</td>
<td>1.07 (0.89–1.29); Moderate†</td>
<td>0.59 (0.25–1.35); Very low††§</td>
<td>1.04 (0.87–1.25); Moderate</td>
</tr>
<tr>
<td>H-HES vs. saline</td>
<td>3</td>
<td>0.64 (0.30–1.37); Moderate†</td>
<td>1.13 (0.71–1.80); Very low††</td>
<td>0.95 (0.64–1.41); Moderate</td>
</tr>
<tr>
<td>Albumin vs. saline</td>
<td>2</td>
<td>0.81 (0.64–1.03); Moderate†</td>
<td>0.96 (0.14–6.31); Very low††</td>
<td>0.82 (0.65–1.04); Moderate</td>
</tr>
<tr>
<td><strong>Balanced crystalloid vs. saline</strong></td>
<td><strong>0</strong></td>
<td><strong>–</strong></td>
<td><strong>0.78 (0.58–1.05); Low††</strong></td>
<td><strong>0.78 (0.53–1.05); Low</strong></td>
</tr>
<tr>
<td>Gelatin vs. saline</td>
<td>0</td>
<td>–</td>
<td>1.04 (0.46–2.32); Very low††</td>
<td>1.04 (0.46–2.32); Very low</td>
</tr>
<tr>
<td>H-HES vs. L-HES</td>
<td>0</td>
<td>–</td>
<td>0.91 (0.63–1.33); Low††</td>
<td>0.91 (0.63–1.33); Low</td>
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<tr>
<td><strong>Balanced crystalloid vs. L-HES</strong></td>
<td><strong>2</strong></td>
<td><strong>0.80 (0.61–1.04); Moderate§</strong></td>
<td><strong>0.44 (0.19–0.97); Moderate†</strong></td>
<td><strong>0.75 (0.56–0.97); Moderate†</strong></td>
</tr>
<tr>
<td>Albumin vs. L-HES</td>
<td>0</td>
<td>–</td>
<td>0.79 (0.59–1.06); Low††</td>
<td>0.79 (0.59–1.06); Low</td>
</tr>
<tr>
<td><strong>Balanced crystalloid vs. H-HES</strong></td>
<td><strong>1</strong></td>
<td><strong>0.74 (0.52–1.05); Moderate†</strong></td>
<td>**1.35 (0.63–2.92); Very low††</td>
<td></td>
</tr>
<tr>
<td>Gelatin vs. H-HES</td>
<td>2</td>
<td>1.40 (0.35–5.56); Low†</td>
<td>0.83 (0.52–1.33); Low††</td>
<td>0.87 (0.55–1.36); Low</td>
</tr>
<tr>
<td>Albumin vs. H-HES</td>
<td>0</td>
<td>–</td>
<td>1.00 (0.44–2.21); Very low††</td>
<td>1.00 (0.44–2.21); Very low</td>
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<td><strong>Balanced crystalloid vs. H-HES</strong></td>
<td><strong>1</strong></td>
<td><strong>1.09 (0.55–2.19); Low†</strong></td>
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<tr>
<td>Gelatin vs. balanced crystalloid</td>
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<td>1.34 (0.61–2.89); Very low††</td>
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CrI = credibility interval; H-HES = high-molecular-weight hydroxyethyl starch; L-HES = low-molecular-weight hydroxyethyl starch; NMA = network meta-analysis.

* Higher of direct or indirect confidence.
† Rated down for imprecision.
‡ Rated down for indirectness.
§ Rated down for inconsistency (\( I^2 = 80\% \); \( P = 0.03 \) for heterogeneity).
|| Rated down 2 levels for imprecision.
### Benefits of Albumin

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<td>0.64 (0.30-1.37); Moderate†</td>
<td>1.13 (0.71-1.80); Very low††</td>
<td>0.95 (0.64-1.41); Moderate</td>
</tr>
<tr>
<td>Albumin vs. saline</td>
<td>2</td>
<td>0.81 (0.64-1.03); Moderate†</td>
<td>0.96 (0.14-6.31); Very low††</td>
<td>0.82 (0.63-1.04); Moderate</td>
</tr>
<tr>
<td>Balanced crystalloid vs. saline</td>
<td>0</td>
<td>–</td>
<td>0.78 (0.58-1.05); Low‡‡</td>
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<td>Gelatin vs. saline</td>
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<td>2</td>
<td>0.80 (0.61-1.04); Moderate§</td>
<td>0.44 (0.19-0.97); Moderate‡</td>
<td>0.73 (0.58-0.97); Moderate‡</td>
</tr>
<tr>
<td>Gelatin vs. L-HES</td>
<td>0</td>
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<td>Albumin vs. H-HES</td>
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<td></td>
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<tr>
<td>Balanced crystalloid vs. H-HES</td>
<td>1</td>
<td>0.74 (0.52-1.05); Moderate†</td>
<td>1.35 (0.63-2.92); Very low†‖</td>
<td>0.82 (0.60-1.13); Moderate</td>
</tr>
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<td>†</td>
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<tr>
<td>Balanced crystalloid vs. albumin</td>
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<td>Gelatin vs. albumin</td>
<td>0</td>
<td>–</td>
<td>1.26 (0.55-2.90); Very low††</td>
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<tr>
<td>Gelatin vs. balanced crystalloid</td>
<td>0</td>
<td>–</td>
<td>1.34 (0.61-2.89); Very low†‖</td>
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</tr>
</tbody>
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Crl = credibility interval; H-HES = high-molecular-weight hydroxyethyl starch; L-HES = low-molecular-weight hydroxyethyl starch; NMA = network meta-analysis.

* Higher of direct or indirect confidence.
† Rated down for imprecision.
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§ Rated down for inconsistency ($I^2 = 80\%$; $P = 0.03$ for heterogeneity).
‖ Rated down 2 levels for imprecision.
<table>
<thead>
<tr>
<th>Comparison</th>
<th>Trials With Direct Comparisons, n</th>
<th>Direct Estimate (95% CI); Quality of Evidence</th>
<th>Indirect Estimate (95% CrI); Quality of Evidence</th>
<th>NMA Estimate (95% CrI)*; Quality of Evidence</th>
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<td>L-HES vs. saline</td>
<td>4</td>
<td>1.07 (0.89–1.29); Moderate†</td>
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CrI = credibility interval; H-HES = high-molecular-weight hydroxyethyl starch; L-HES = low-molecular-weight hydroxyethyl starch; NMA = network meta-analysis.
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* Rated down 2 levels for imprecision.
Contractility in Septic Shock

• Patients have increased cardiac output after optimization of preload
• Increased cardiac output is predominantly due to tachycardia
  – \( CO = SV \times HR \)
• End-diastolic volume is increased
• Ejection fraction is decreased despite decreased afterload
  – \( SV = EF \times EDV \)
  – Marked decrease in contractility
Pressure-Volume Curve

- Normal
- Sepsis

SV
ESPVR

PRESSURE
VENTRICULAR VOLUME
Inotropic Therapy

- Dobutamine
- Milrinone
- Dopamine
- Epinephrine
- Norepinephrine
Dobutamine

- Doses of 5 – 20 µg/kg/min
- Beta-adrenergic effects
- Marked increase in cardiac output due to both increased heart rate and stroke volume
- Decreased SVR
- Variable effect on blood pressure
Dopamine

- Doses of 2 – 20 µg/kg/min
- Dopaminergic, beta-adrenergic, and alpha-adrenergic effects
- In septic shock, increases cardiac output primarily by increasing stroke volume and heart rate
- No change in SVR
- Frequent tachycardia and arrhythmias
- No benefit on renal blood flow
Epinephrine

- Doses 20-300 ng/kg/min
- Beta and alpha-adrenergic effects
- Dose-related increase in blood pressure
  - Increased cardiac output (heart rate and stroke volume) at lower doses
  - Increased SVR at higher doses
Afterload

• BP = CO X SVR
• Hypotension in septic shock is due to decreased SVR
• In hyperdynamic septic shock, titrated vasopressor therapy can increase blood pressure without decreasing organ perfusion (gut, kidneys) and cardiac output
Norepinephrine

- Doses of 20-500 ng/kg/min
- Alpha-adrenergic > beta-adrenergic effects
- Increases blood pressure due to increased SVR
- No change in heart rate or cardiac output
- Increases GFR and maintains renal blood flow
Vasopressin

- Vasopressin normally maintains SVR by V1 receptors on smooth muscle
- Vasopressin does not constrict renal vasculature and dilates (via nitric oxide) cerebral, coronary, and pulmonary vasculature
Choice of Vasopressors

• Annane, Lancet 2007; 370:676
  – RCT (n = 330) of epinephrine vs. (NE + dobutamine)
  – Epinephrine had increased lactic acidosis but equivalent outcome

• Myburgh, Intensive Care Med 2008; 34:2226
  – RCT (n = 280) of epinephrine vs. NE
  – Epinephrine had increased lactic acidosis but equivalent outcome
Choice of Vasopressors

• DeBacker, NEJM 2010; 362:779
  – RCT (n = 1,679) of dopamine vs. NE
  – More arrhythmias with dopamine
  – Trend towards higher mortality with dopamine

• Russell, NEJM 2008; 358:877
  – RCT (n = 778) of vasopressin vs. NE
  – Overall outcomes similar in the two groups
  – Trend towards improved outcome with vasopressin in less severe septic shock (NE < 15 mcg/min)
SSC Hemodynamic Guidelines (I)

- Initial fluid challenge of ≥ 30 mL/kg of crystalloids
- Albumin when patients require substantial amounts of crystalloids
- Do not use hydroxyethyl starches (increased renal failure)
- Continue fluid administration as long as there is hemodynamic improvement either based on dynamic (e.g., change in pulse pressure, stroke volume variation) or static (e.g., arterial pressure, heart rate) variables
- Vasopressor therapy to target a mean arterial pressure (MAP) of 65 mm Hg
- Arterial catheter for all patients requiring vasopressors
- Norepinephrine as the first choice vasopressor
- Epinephrine when an additional agent is needed to maintain MAP
SSC Hemodynamic Guidelines (II)

- Vasopressin not recommended as single agent vasopressor
- Vasopressin 0.03 units/minute can be added to norepinephrine (NE) to raise MAP or decrease NE dose
- Dopamine only in highly selected patients (e.g., patients with low risk of tachyarrhythmias and bradycardia)
- Low-dose dopamine should not be used for renal protection
- Phenylephrine not recommended except when (a) NE is associated with serious arrhythmias, (b) cardiac output is known to be high or (c) as salvage therapy for refractory hypotension
- Do not use a strategy to increase cardiac index to predetermined supranormal levels
- A trial of dobutamine infusion up to 20 micrograms/kg/min in the presence of (a) myocardial dysfunction with low cardiac output, or (b) ongoing signs of hypoperfusion, despite adequate intravascular volume and blood pressure
Steroid Therapy

• High dose steroids
  – Beneficial effects (Schumer, 1976)
  – No benefit in subsequent studies
• Cronin, Crit Care Med 1995; 23:1430
  – Meta-analysis of 9 randomized trials
  – No benefit and possibly harmful
Steroid Therapy In Septic Shock

- Annane, JAMA 2002; 288:862
  - 310 patients with septic shock requiring vasopressors on mechanical ventilation
  - All patients received corticotropin stimulation test (normal is an increase by > 9 μg/dL)
  - Randomized to placebo or to hydrocortisone (50 mg q 6h) plus fludrocortisone (50 mcg q day)
  - Steroid therapy resulted in increased reversal of shock and decreased 28 day mortality only in patients who did not have a normal response to the corticotropin stimulation test
CORTICUS Trial

• Sprung, NEJM 2008; 358:111
  – RCT (n = 499) of hydrocortisone 50 mg q 6h
  – Faster reversal of shock: 3.3 vs. 5.8 days
  – Increased superinfections including new sepsis
  – No difference in mortality in either corticotropin responders or non-responders
  – But patients were less severely ill than in the Annane trial
Intubation and Adrenal Insufficiency

- Chan, Crit Care Med 2012; 40:2945
  - Meta-analysis of studies using etomidate for intubation in patients with severe sepsis or septic shock
  - Etomidate increased incidence of adrenal insufficiency (RR 1.33)
  - Etomidate increased mortality (RR 1.20) in patients with sepsis
Intubation and Adrenal Insufficiency

• Payen, Crit Care Med 2012; 40:21
  – RCT of hydrocortisone after intubation with etomidate for septic shock
  – Etomidate group had more patients with adrenal insufficiency (91% vs. 84%)
  – ICU outcome equal in the two groups
Adjunctive Therapies in Septic Shock

- Septic shock viewed as a condition of excessive inflammatory response
- Long history of failed clinical trials
  - Opal, JAMA 2013; 309:1154
  - Eritoran blocks LPS from binding to the TLR4 receptor
    - No benefit on mortality (28% vs. 27%)
- Focus is moving towards individualized therapy since inflammation and immunosuppression are both parts of sepsis
PROWESS Trial

  – 840 patients with severe sepsis
  – Randomized to placebo or to
    • rhAPC; Xigris; drotrecogin alfa (activated) at 24 μg/kg/h for 96 hours
    • Mortality decreased from 30.8% to 24.7%
PROWESS-SHOCK Trial

• Ranieri, N Engl J Med 2012; 366:2055
  – 1,696 patients with septic shock randomized to rhAPC vs. placebo
  – Trend towards increased mortality with rhAPC (26% vs. 24%)
  – No benefit in any subgroup
  – Xigris withdrawn from the market in October, 2011
SSC Adjunctive Therapy Guidelines

• Corticosteroids only for refractory shock
  – Hydrocortisone at 200 mg/day, continuous infusion
• Not use ACTH stimulation test
• Not use intravenous immunoglobulins
• rhAPC is no longer available
SSC Supportive Therapy Guidelines

- Use lung protective mechanical ventilation
- Use of a weaning protocol with spontaneous breathing trials
- A conservative fluid strategy without a pulmonary artery catheter for patients with sepsis-induced ARDS
- Glucose control ≤180 mg/dL
- Not use sodium bicarbonate therapy
- Pharmacological prophylaxis against venous thromboembolism
- Oral or enteral feedings, as tolerated; avoid mandatory full caloric feeding in the first
- Address goals of care as early as feasible
Mortality of Septic Shock

Friedman, Crit Care Med 1998; 26: 2078
Mortality of Septic Shock

• Mortality of septic shock has decreased to approximately 25% in four recent trials
  – PROWESS-SHOCK (25%)
  – ACCESS (eritoran) (27%)
  – ProCESS (20%)
  – ARISE (19%)

• We must be doing something right!
Summary: Approach to Septic Shock

- Early identification of sepsis
- Rapid broad-spectrum antibiotics
- Arterial catheter
- Adequate fluid administration
- Vasopressor support with norepinephrine; addition of vasopressin if needed
- Dobutamine for inotropic support
- Hydrocortisone for intubated patients who remain hypotensive despite fluids
- Outstanding intensive care
Thank You!