Sepsis

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Objectives

- Understand the pathophysiology of sepsis
- Understand main therapeutic interventions in sepsis
- Apply concepts to the pregnant septic patient
Introduction

- Sepsis continues to be the most common cause of death in ICU’s
- Mortality is 30% for severe sepsis and up to 50% for septic shock

Crit Care Med 2001;29:1303-10
Massive Inflammation

Endothelial injury, third spacing and vasodilation

Activation of clotting cascade

DIC

Organ ischemia

Decreased CO (Echo !)

Commonly unmasked when vasopressors are used
Definitions

Systemic Inflammatory Response Syndrome

Two or more of:
- Temperature $> 38 \, ^\circ\text{C}$ or $< 36 \, ^\circ\text{C}$
- Heart rate $> 90$/min
- RR $> 20$/min or PaCO$_2 < 32$ mmHg
- WBC $> 12000$ or $< 4000$ or $> 10\%$ bands
**Definitions**

- **Sepsis** is defined as SIRS secondary to infection.
- **Severe sepsis** is present when associated organ dysfunction is present.
- **Septic shock** is sepsis with hypotension which persists despite adequate fluid resuscitation.

*Crit Care Med 1992;20: 864-74*
Definitions

Signs and symptoms of sepsis according to the 2001 Sepsis Definitions Conference

- Fever or hypothermia, tachycardia, tachypnea
- Positive fluid balance and peripheral edema
- Abnormal white blood cell count, elevated C reactive protein, procalcitonin, interleukin-6
- Hypotension-Increased cardiac output/low systemic vascular resistances
- Decreased urine output
- Hyperlactatemia, abnormal skin perfusion, hyperglycemia
- Elevated liver enzymes, thrombocytopenia, abnormal clotting times
- Hypoxemia, abnormal mental status
- Abnormal gastrointestinal motility
Initial actions

- Obtain cultures (at least 2 blood cx and include every vascular device in place for > 48 hrs)
- Empiric antibiotic (broad spectrum) therapy ASAP
- Achieve source control

Crit Care Med 2008;36(1):296-327
Fluid Therapy

Intravenous fluids are the mainstay of treatment for patients with hemodynamic instability secondary to severe sepsis

NEJM 2012;367(2):124-134
Crystalloids or colloids?

- Intravascular half life of **crystalloids** is 30-60 minutes
- Intravascular half life of **albumin (5%,25%)** is 16 hours
- No difference in outcomes !!!

**References**

NEJM 2004;350(22):2247-2256
Crit Care Med 2012;40(9):2543-2551
Crystalloids or colloids?

In sepsis, avoid the use of hydroxyethyl starch (even new generation products like 130/0.4) as increase mortality and kidney injury

NEJM 2012;367(2):124-134
Fluid Therapy

- Potential harms from unnecessary fluid:
  - Cerebral edema
  - Pulmonary edema
  - Heart edema (diastolic dysfunction)
  - Gut edema
  - Abdominal compartment syndrome
  - Poor wound/anastomosis healing
How to predict fluid responsiveness?

- CVP and PAOP are poor predictors

- Consider passive leg raising or Pulse Pressure variation

CHEST 2008;133:252-263
Cardiac Output

Pulse pressure variation

NO fluid response

Ascending part correlates with fluid response

Preload
Pulse Pressure Variation

- Requires:
  - Mechanical ventilation
  - Not triggering ventilator
  - Tidal volume 8-10 mL/Kg
  - Sinus rhythm

Pulse Pressure Variation

- During inspiration on a ventilator:
  - Less preload to the right heart
    (inter-ventricular septum not displaced)
  - More preload to the left heart
  - Decrease in afterload
Pulse Pressure Variation

- During **expiration** on a ventilator:
  
  More preload to the right heart  
  (inter-ventricular septum displaced to the left)

  Less preload to the left heart

  More afterload
If not on a ventilator

May consider passive leg raising with **non-invasive** measures of cardiac output
When to add pressors?

- When despite adequate fluid resuscitation, cannot maintain a mean arterial blood pressure $\geq 65$ mmHg

- May start with either norepinephrine or dopamine through a CVC
  (if fail, consider epinephrine)

Crit Care Med 2008; 36(1):296-327
Which pressor?

- **Surviving Sepsis Campaign 2008** recommends either norepinephrine or dopamine.
- Theoretical concerns of dopamine:
  - Decreased prolactin (↓ immunity)
  - Kidney medullar ischemia
  - Hypovolemia secondary to diuresis
  - Reduced blood flow to gut mucosa
  - Higher incidence of tachycardia

*Anesth Analg* 2004;98:461-468
*Crit Care Med* 2008; 36(1):296-327
Comparison of Dopamine and Norepinephrine in the Treatment of Shock

Daniel De Backer, M.D., Ph.D., Patrick Biston, M.D., Jacques Devriendt, M.D., Christian Madl, M.D., Didier Chocho, M.D., Cesar Aldecoa, M.D., Alexandre Brasseur, M.D., Pierre Defrance, M.D., Philippe Gottignies, M.D., and Jean-Louis Vincent, M.D., Ph.D., for the SOAP II Investigators*
Dopamine versus norepinephrine in the treatment of septic shock: A meta-analysis*

Daniel De Backer, MD, PhD; Cesar Aldecoa, MD; Hassane Njimi, MSc, PhD; Jean-Louis Vincent, MD, PhD, FCCM

Objectives: There has long-been controversy about the possible superiority of norepinephrine compared to dopamine in the treatment of shock. The objective was to evaluate the effects of norepinephrine and dopamine on outcome and adverse events in patients with septic shock.

Data Sources: A systematic search of the MEDLINE, Embase, Scopus, and CENTRAL databases, and of Google Scholar, up to June 30, 2011.

Study Selection and Data Extraction: All studies providing information on the outcome of patients with septic shock treated with dopamine compared to norepinephrine were included. Observational and randomized trials were analyzed separately. Because time of outcome assessment varied among trials, we evaluated 28-day mortality or closest estimate. Heterogeneity among trials was assessed using the Cochrane Q homogeneity test. A Forest plot was constructed and the aggregate relative risk of death was computed. Potential publication bias was evaluated using funnel plots.

Methods and Main Results: We retrieved five observational (1,360 patients) and six randomized (1,408 patients) trials, totaling 2,768 patients (1,474 who received norepinephrine and 1,294 who received dopamine). In observational studies, among which there was significant heterogeneity ($p < .001$), there was no difference in mortality (relative risk, 1.09; confidence interval, 0.84–1.41; $p = .72$). A sensitivity analysis identified one trial as being responsible for the heterogeneity; after exclusion of that trial, no heterogeneity was observed and dopamine administration was associated with an increased risk of death (relative risk, 1.23; confidence interval, 1.05–1.43; $p < .01$). In randomized trials, for which no heterogeneity or publication bias was detected ($p = .77$), dopamine was associated with an increased risk of death (relative risk, 1.12; confidence interval, 1.01–1.20; $p = .035$). In the two trials that reported arrhythmias, these were more frequent with dopamine than with norepinephrine (relative risk, 2.34; confidence interval, 1.46–3.77; $p = .001$).

Conclusions: In patients with septic shock, dopamine administration is associated with greater mortality and a higher incidence of arrhythmic events compared to norepinephrine administration. (Crit Care Med 2012; 40:725–730)

Key Words: adrenergic agents; adverse effects; mortality; outcome; vasopressor
Pressors, inotropes?

- 60% of patients with septic shock have global LV hypokinesia (EF<45%)
- May happen de novo in up to 34% of patients treated with norepinephrine alone
- Follow up LV kinetics daily in first days of pressor therapy
- May require addition of dobutamine

Crit Care Med 2008;36(6):1701-1706
Cardiac output-ScVO2 relation

O2 tissue extraction increases with decreased oxygen delivery
Vasopressin

- Septic shock associates with a relative vasopressin deficiency

- A recent multicenter randomized trial found no benefit of adding vasopressin to norepinephrine in septic shock

*N Engl J Med 2008;358(9):877-886*
Vasopressin

- The VASST trial did not address patients with catecholamine-resistant shock

- May consider adding to norepinephrine at doses of 0.03-0.04 U/min (no titration)

Crit Care Med 2008; 36(1):296-327
Adrenal gland in sepsis

- Cytokines suppress cortisol response to ACTH and also the vascular response to cortisol

- Critical illness related corticosteroid insufficiency may be present in up to 50-75% of patients with septic shock

*Crit Care Med 2004;32(11):S523-27*
Steroids in septic shock

- May improve hemodynamics by up-regulating cathecolamine receptors in vessel walls and resolve sepsis induced cardiac dysfunction

- Physiologic dose replacement down regulate excessive inflammation

*Ann Intern Med 2004;141:47-56*
Steroids in septic shock

JAMA 2002;288(7):862-71

Effect of Treatment With Low Doses of Hydrocortisone and Fludrocortisone on Mortality in Patients With Septic Shock
Annane trial (cont...)  

- Included patients only with pressor resistant shock  
- Used ACTH 250 µg test  
- Used hydrocortisone 50 mg IV q 6 hrs and fludrocortisone 50 µg qd DHT  
- Mortality improved with therapy  
  (28 day mortality 53% vs 63% in placebo)
Hydrocortisone Therapy for Patients with Septic Shock

Charles L. Sprung, M.D., Djillali Annane, M.D., Ph.D., Didier Keh, M.D., Rui Moreno, M.D., Ph.D., Mervyn Singer, M.D., F.R.C.P., Klaus Freivogel, Ph.D., Yoram G. Weiss, M.D., Julie Benbenishty, R.N., Armin Kalenka, M.D., Helmut Forst, M.D., Ph.D., Pierre-Francois Laterre, M.D., Konrad Reinhart, M.D., Brian H. Cuthbertson, M.D., Didier Payen, M.D., Ph.D., and Josef Briegel, M.D., Ph.D., for the CORTICUS Study Group*
CORTICUS trial

- Included septic patients who responded to pressor therapy
- Hydrocortisone 50 mg IV q 6 hrs
- Steroid therapy did not improve survival
- ACTH test did not discriminate between responders and non-responders to steroids
Current recommendation

- Do not perform ACTH test
- Hydrocortisone 200-300 mg/day (wean)
- Fludrocortisone is optional
- Only do steroids in septic shock NOT responsive to pressor therapy

Crit Care Med 2008;36(1):296-327
Resuscitation goals

- Normalization of hemodynamics may occur despite ongoing tissue hypoperfusion

Curr Opin Crit care 2012;18(3):267-72
Resuscitation goals

- Follow up lactate levels (may be normal in up to 45% of patients with septic shock)
- Combine with ScVO2

*Chest* 2011;140(6):1406-1412
Fluids and pressors

- The recent FACTT trial compared liberal vs conservative fluid management in patients NOT in shock with ALI/ARDS

- Patients on conservative fluid arm had less ventilator days, less ICU days, and a tendency to decreased 60-day mortality

### Table 2—Simplified Algorithm for Conservative Management of Fluids in Patients With ALI, Based on Protocol Used in the FACTT*

<table>
<thead>
<tr>
<th>CVP, mm Hg (Recommended)</th>
<th>PAOP, mm Hg (Optional)</th>
<th>MAP ≥ 60 mm Hg and Not Receiving Vasopressors for ≥ 12 h</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Average Urine Output &lt; 0.5 mL/kg/h</td>
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<tr>
<td>&gt; 8</td>
<td>&gt; 12</td>
<td>Furosemide†; reassess in 1 h</td>
</tr>
<tr>
<td>4–8</td>
<td>8–12</td>
<td>Fluid bolus as fast as possible‡; reassess in 1 h</td>
</tr>
<tr>
<td>&lt; 4</td>
<td>&lt; 8</td>
<td>Fluid bolus as fast as possible‡; reassess in 1 h</td>
</tr>
</tbody>
</table>

*CVP = central venous pressure; PAOP = pulmonary artery occlusion pressure; MAP = mean arterial pressure. Reprinted with the courtesy of the NHLBI Acute Respiratory Distress Syndrome Network. Patients must have had a MAP of > 60 mm Hg without requiring vasopressors for at least 12 h before this protocol is initiated.

†Furosemide dosing: begin with a 20-mg bolus, 3 mg/h infusion, or last known effective dose. Double each subsequent dose until the goal is achieved (oliguria reversal or intravascular pressure target), with a maximal dose of 160-mg bolus or 24 mg/h. Do not exceed 620 mg/d. If the patient has heart failure, treatment with dobutamine may be considered. Diuretic therapy should be withheld for patients with renal failure, which is defined as dialysis dependence, oliguria with a serum creatinine level of > 2 mg/dL, or oliguria with a serum creatinine level of < 2 mg/dL but with urinary indices indicative of acute renal failure.

‡Fluid bolus: 15 mL/kg crystalloid (round to nearest 250 mL) or 1 unit of packed RBCs or 25 g of albumin.
Glucose control in SICU

- Decreases mortality in ICU from 8% to 4.6%
  (60% were cardiac surgery patients)

- Benefits (80-110 mg/dL):
  - Less renal failure and RRT
  - Less days on ventilator
  - Less critical illness polyneuropathy
  - Less sepsis
  - Decreased median number of transfusions

  NEJM 2001; 345(19): 1359-67
### Figure 2. Association of Tight Glucose Control vs Usual Care With Hospital Mortality, Stratified by ICU Setting and Glucose Goal in Tight Control Group

<table>
<thead>
<tr>
<th>Source</th>
<th>Total No. of Patients</th>
<th>Tight Control</th>
<th>Usual Care</th>
<th>Relative Risk (95% CI)</th>
<th>Favors Tight Control</th>
<th>Favors Usual Care</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Surgical ICU</strong></td>
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<tr>
<td>Very tight control (glucose goal ≤110 mg/dL)</td>
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<tr>
<td>Van den Berghe et al., 2001</td>
<td>85/705</td>
<td>85/703</td>
<td>0.96 (0.98-0.99)</td>
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<tr>
<td>Stecher et al., 2006</td>
<td>9/57</td>
<td>9/60</td>
<td>1.05 (0.45-2.46)</td>
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<td><strong>Moderately tight control (glucose goal &lt;150 mg/dL)</strong></td>
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<tr>
<td>Kia et al., 2005</td>
<td>19/132</td>
<td>11/133</td>
<td>1.4 (0.96-3.3)</td>
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<tr>
<td>Grey and Perrieret, 2004</td>
<td>4/34</td>
<td>6/27</td>
<td>0.73 (0.17-1.69)</td>
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<tr>
<td>Bricotts et al., 2007</td>
<td>5/40</td>
<td>3/38</td>
<td>0.85 (0.5-2.02)</td>
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<tr>
<td>Bricotts et al., 2008</td>
<td>4/48</td>
<td>4/49</td>
<td>1.02 (0.37-3.05)</td>
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<tr>
<td>Chan et al., 2008</td>
<td>3/47</td>
<td>3/61</td>
<td>0.19 (2.53-5.11)</td>
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<td><strong>All surgical ICU patients</strong></td>
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<td>123/1141</td>
<td>0.89 (0.63-1.22)</td>
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<td><strong>Medical ICU</strong></td>
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<td>Very tight control (glucose goal ≤110 mg/dL)</td>
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<tr>
<td>Van den Berghe et al., 2006</td>
<td>222/509</td>
<td>224/605</td>
<td>0.99 (0.91-0.98)</td>
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<td>Fernandez et al., 2005</td>
<td>1/11</td>
<td>2/9</td>
<td>0.41 (0.04-3.82)</td>
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<td>Bland et al., 2005</td>
<td>1/5</td>
<td>2/5</td>
<td>0.50 (0.06-3.91)</td>
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<td>Cianfanelli et al., 2007</td>
<td>13/39</td>
<td>18/51</td>
<td>0.94 (0.43-2.08)</td>
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<td>Davies et al., 1991</td>
<td>6/35</td>
<td>6/34</td>
<td>0.97 (0.36-2.72)</td>
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<td>Walters et al., 2006</td>
<td>1/13</td>
<td>1/12</td>
<td>1.2 (0.12-12.48)</td>
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<td>Greys/GIST UK et al., 2007</td>
<td>76/464</td>
<td>86/469</td>
<td>0.89 (0.57-1.41)</td>
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<td>Bruno/THS et al., 2008</td>
<td>1/31</td>
<td>0/15</td>
<td>1.50 (0.08-34.79)</td>
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<td>366/1200</td>
<td>0.92 (0.82-1.04)</td>
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<td>Very tight control (glucose goal ≤110 mg/dL)</td>
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<td>Brunni/USP et al., 2008</td>
<td>61/247</td>
<td>75/289</td>
<td>0.95 (0.71-1.27)</td>
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<td>Davies/USCCTROL et al., 2007</td>
<td>107/500</td>
<td>89/551</td>
<td>1.03 (0.83-1.55)</td>
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<td>Moshenwa/Glycogenetic et al., 2005</td>
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<td>47/119</td>
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<td>Araki et al., 2006</td>
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<td>83/287</td>
<td>0.84 (0.64-1.09)</td>
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<td>Wang et al., 2006</td>
<td>7/58</td>
<td>2/58</td>
<td>0.87 (0.4-4.57)</td>
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<td>Yu et al., 2005</td>
<td>4/28</td>
<td>4/27</td>
<td>0.96 (0.27-3.47)</td>
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<td>Mitchell et al., 2006</td>
<td>9/35</td>
<td>3/35</td>
<td>3.00 (0.89-10.16)</td>
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<td>De La Rosa et al., 2006</td>
<td>102/254</td>
<td>86/230</td>
<td>1.05 (0.84-1.36)</td>
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<tr>
<td><strong>Moderately tight control (glucose goal &lt;150 mg/dL)</strong></td>
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<td>Farah et al., 2007</td>
<td>22/41</td>
<td>22/48</td>
<td>1.17 (0.77-1.78)</td>
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<td>McMullan LOGIC et al., 2007</td>
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<td>1.23 (0.39-3.94)</td>
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<td>Henderson/USCAR et al., 2005</td>
<td>5/32</td>
<td>7/35</td>
<td>0.78 (0.28-2.22)</td>
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<td>Azavedo et al., 2008</td>
<td>38/188</td>
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<td>0.91 (0.62-1.34)</td>
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<td><strong>All medical-surgical ICU patients</strong></td>
<td>472/1811</td>
<td>498/1847</td>
<td>0.95 (0.80-1.13)</td>
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<tr>
<td><strong>All critically ill patients</strong></td>
<td>892/4127</td>
<td>977/4188</td>
<td>0.93 (0.86-1.03)</td>
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</table>
Glucose control
Nice Sugar Trial

Tight glucose control lead to **higher mortality** (2.6%) as compared to insulin therapy only if >180 mg/dL

**NEJM 2009;360(13):1283-1297**
Current recommendations

Since the mortality benefit and safety of intensive insulin therapy have been recently questioned, currently it is recommended to maintain glucose levels at < 150 mg/dL.

Crit Care Med 2008;36(1):296-327
Nutrition in sepsis

- Early enteral nutrition
- Avoid over nutrition
- Deliver 20-25 Kcal/kg/day
- Deliver adequate amount of protein (1.2-2 gr/kg/day)

*J Parent Ent Nutr 2009;33(3):277-316*
Transfusion triggers

- Avoid PRBC unless hemoglobin is below 7 gr/dL (10 gr/dL if first 6 hours)
- Avoid platelets unless below 5000/mm³
- Avoid blood products to correct laboratory values

Others

- DVT prophylaxis
- EFM if viable
- Left lateral decubitus
- May administer steroids for lung maturity

Obstet Gynecol 2009;113(2):443-450
THANK YOU