Surviving Sepsis Campaign Guidelines 2012 & Update for 2015

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R. Phillip Dellinger, MD; Mitchell M. Levy, MD; Andrew Rhodes, MB BS; Djillali Annane, MD; Herwig Gerlach, MD, PhD; Steven M. Opal, MD; Jonathan E. Sevransky, MD; Charles L. Sprung, MD; Ivor S. Douglas, MD; Roman Jaeschke, MD; Tiffany M. Osborn, MD, MPH; Mark E. Nunnally, MD; Sean R. Townsend, MD; Konrad Reinhart, MD; Ruth M. Kleinpell, PhD, RN-CS; Derek C. Angus, MD, MPH; Clifford S. Deutschman, MD, MS; Flavia R. Machado, MD, PhD; Gordon D. Rubenfeld, MD; Steven A. Webb, MB BS, PhD; Richard J. Beale, MB BS; Jean-Louis Vincent, MD, PhD; Rui Moreno, MD, PhD; and the Surviving Sepsis Campaign Guidelines Committee including the Pediatric Subgroup*

Crit Care Med 2013; 41:580–637
Be appropriately aggressive

- “...the longer one delays aggressive metabolic targeted resuscitation, the less the observed benefit.”

  Michael Pinskey, MD, FCCP. CHEST 2007
Surviving Sepsis Campaign
www.survivingsepsis.org

- Dellinger et al 2004
  - Global Guidelines
  - 11 Organizations
  - 45 Recommendations
    - Graded quality of evidence
    - Strong/Weak
- Dellinger et al 2008
  - Updated info
  - 55 Experts
  - 15 Organizations
  - www.survivingsepsis.org

- Dellinger et al 2012
  - Updated information through fall 2012.
  - 30 international organizations
  - 68 international experts
  - Quality of evidence
    - GRADE A (high) through D (very low)
  - Strength of recommendations
    - 1 (strong) – we recommend
    - 2 (weak) – we suggest
Diagnostic Criteria for Sepsis

- **Sepsis**: infection + systemic manifestations of infection.

- **Severe Sepsis**: sepsis + sepsis-induced organ dysfunction or tissue hypoperfusion.

- **Septic Shock**: sepsis-induced hypotension persisting despite adequate fluid resuscitation.

- **Sepsis-induced tissue hypoperfusion**: infection-induced hypotension, elevated lactate, or oliguria.
### TABLE 1. Diagnostic Criteria for Sepsis

**Infection, documented or suspected, and some of the following:**

**General variables**
- Fever (>38.3°C)
- Hypothermia (core temperature <36°C)
- Heart rate >90/min or more than two SD above the normal value for age
- Tachypnea
- Altered mental status
- Significant edema or positive fluid balance (>20 mL/kg over 24 hr)
- Hyperglycemia (plasma glucose >140 mg/dL or 7.7 mmol/L) in the absence of diabetes

**Inflammatory variables**
- Leukocytosis (WBC count >12,000 μL⁻¹)
- Leukopenia (WBC count <4000 μL⁻¹)
- Normal WBC count with greater than 10% immature forms
- Plasma C-reactive protein more than two SD above the normal value
- Plasma procalcitonin more than two SD above the normal value

**Hemodynamic variables**
- Arterial hypotension (SBP <90 mm Hg, MAP <70 mm Hg, or an SBP decrease >40 mm Hg in adults or less than two SD below normal for age)

**Organ dysfunction variables**
- Arterial hypoxemia (\(P_{\text{ao}}/F_{\text{co}_2}\) < 300)
- Acute oliguria (urine output <0.5 mL/kg/hr for at least 2 hrs despite adequate fluid resuscitation)
- Creatinine increase >0.5 mg/dL or 44.2 μmol/L
- Coagulation abnormalities (INR >1.5 or aPTT >60 s)
- Illus (absent bowel sounds)
- Thrombocytopenia (platelet count <100,000 μL⁻¹)
- Hyperbilirubinemia (plasma total bilirubin >4 mg/dL or 70 μmol/L)

**Tissue perfusion variables**
- Hyperlactatemia (>1 mmol/L)
- Decreased capillary refill or mottling

WBC = white blood cell; SBP = systolic blood pressure; MAP = mean arterial pressure; INR = international normalized ratio; aPTT = activated partial thromboplastin time.

Diagnostic criteria for sepsis in the pediatric population are signs and symptoms of inflammation plus infection with hyper- or hypothermia (rectal temperature >38.5° or <35°C), tachycardia (may be absent in hypothermic patients), and at least one of the following indications of altered organ function: altered mental status, hypoxemia, increased serum lactate level, or bounding pulse.

<table>
<thead>
<tr>
<th>Table 2. Severe Sepsis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe sepsis definition = sepsis-induced tissue hypoperfusion or organ dysfunction (any of the following thought to be due to the infection)</td>
</tr>
</tbody>
</table>

- Sepsis-induced hypotension
- Lactate above upper limits laboratory normal
- Urine output < 0.5 mL/kg/hr for more than 2 hrs despite adequate fluid resuscitation
- Acute lung injury with PaO₂/FIO₂ < 250 in the absence of pneumonia as infection source
- Acute lung injury with PaO₂/FIO₂ < 200 in the presence of pneumonia as infection source
- Creatinine > 2.0 mg/dL (176.8 µmol/L)
- Bilirubin > 2 mg/dL (34.2 µmol/L)
- Platelet count < 100,000 µL
- Coagulopathy (international normalized ratio > 1.5)

Surviving Sepsis Campaign
Resuscitation & Infection Issues

- Initiate Early Goal Directed Therapy. (1C/2C)
- Begin immediately
- DO NOT WAIT FOR ICU
  - If hypotensive, or lactate >4mmol/L (1C), start protocol.
- Target normalization of lactate. (2C)
Early Goal Directed Therapy

Supplemental oxygen ± endotracheal intubation and mechanical ventilation

Central venous and arterial catheterization

Sedation, paralysis (if intubated), or both

CVP

8–12 mm Hg

MAP

>65 and ≤90 mm Hg

ScVo2

<70%

≥70%

Goals achieved

No

Yes

<8 mm Hg

Crystalloid

Colloid

<65 mm Hg

Vasoactive agents

>90 mm Hg

Transfusion of red cells until hematocrit ≥30%

<70%

Inotropic agents

Hospital admission
Early Goal Directed Therapy

Mortality (%)

Standard

EGDT
Surviving Sepsis Campaign
Resuscitation & Infection Issues

- Screening (1C), Performance Improvement (UG)

- Diagnosis
  - Cultures before abx, provided they don’t delay abx (1C)
    - Two or more blood cultures
      - Peripheral (percutaneous) AND central
  - Other cultures as indicated
  - Candidiasis assays (2B, 2C)
  - Imaging (UG)
Surviving Sepsis Campaign
Resuscitation & Infection Issues

- Antimicrobial Therapy
  - Administer IV antibiotics within 1 hour (1B, 1C)
  - One or more antimicrobials (1B)
  - Daily assessment for potential deescalation (1B)
    - Potential role for biomarkers (2C)
Surviving Sepsis Campaign
Resuscitation & Infection Issues

- Antimicrobial Therapy
  - Combination empiric therapy
    - Neutropenic patients (2B)
    - Difficult-to-treat, MDR pathogens (2B)
    - Severe infections.
      - \textit{P. aeruginosa} bacteremia, respiratory failure and shock.
        - Extended spectrum beta-lactam + AG or quinolone
      - \textit{Strep pneumoniae} bacteremia, shock.
        - Beta-lactam + macrolide.
Surviving Sepsis Campaign
Resuscitation & Infection Issues

- Antimicrobial Therapy
  - Duration 7-10 days +/- (2C)
  - Limit combo therapy to less than 3-5 days. (2B)

- Source control w/in 12hr, if possible. (1C)
  - Remove possibly infected lines. (UG)

- Infection Prevention
  - Selective oral & digestive decontamination to reduce VAP? (2B)
  - Chlorhexadine oropharyngeal decontamination to reduce VAP. (2B)
Antimicrobial therapy for patients with severe sepsis and septic shock: An evidence-based review

Pierre-Yves Bochud, MD; Marc Bonten, MD; Oscar Marchetti, MD; Thierry Calandra, MD, PhD

Association between timing of antibiotic administration and mortality from septic shock in patients treated with a quantitative resuscitation protocol*

Michael A. Puskarich, MD; Stephen Trzeciak, MD; Nathan I. Shapiro, MD; Ryan C. Arnold, MD; James M. Horton, MD; Jonathan R. Studnek, PhD; Jeffrey A. Kline, MD; Alan E. Jones, MD; on behalf of the Emergency Medicine Shock Research Network (EMSHOCKNET)

Early combination antibiotic therapy yields improved survival compared with monotherapy in septic shock: A propensity-matched analysis*

Anand Kumar, MD; Ryan Zarychanski, MD; Bruce Light, MD; Joseph Parrillo, MD; Dennis Maki, MD; Dave Simon, MD; Denny Laporta, MD; Steve Lapinsky, MD; Paul Ellis, MD; Yazdan Mirzanejad, MD; Greg Martinka, MD; Sean Keenan, MD; Gordon Wood, MD; Yaseen Arabi, MD; Daniel Feinstein, MD; Aseem Kumar, PhD; Peter Dodek, MD; Laura Kravetsky, BSc; Steve Doucette, MSc; the Cooperative Antimicrobial Therapy of Septic Shock (CATSS) Database Research Group

*Mercy4+
Impact of time to antibiotics on survival in patients with severe sepsis or septic shock in whom early goal-directed therapy was initiated in the emergency department

David F. Galeski, MD; Mark E. Mikkelsen, MD, MSCE; Roger A. Band, MD; Jesse M. Pines, MD, MBA, MSCE; Richard Massone, MD; Frances F. Furia, MD; Frances S. Shofer, PhD; Munish Goyal, MD

Initiation of Inappropriate Antimicrobial Therapy Results in a Fivefold Reduction of Survival in Human Septic Shock

Anand Kumar, Paul Ellis, Yaseen Arabi, Dan Roberts, Bruce Light, Joseph E. Parrillo, Peter Dodek, Gordon Wood, Aseem Kumar, David Simon, Cheryl Peters, Muhammad Ahsan, Dan Chateau and the Cooperative Antimicrobial Therapy of Septic Shock Database Research Group

Chest 2009;136;1237-1248; Prepublished online August 20, 2009; DOI 10.1378/chest.09-0087
Surviving Sepsis Campaign
Hemodynamic Support & Adjunctive Therapy

- Fluid Therapy
  - Resuscitate w/ crystalloid initially (1B)
    - consider albumin after substantial amounts of crystalloid (2C).
  - Avoid HES. (1B)
  - 30mL/kg for sepsis-induced tissue hypoperfusion. (1C)
  - Use a fluid challenge technique targeted toward assessing hemodynamic responsiveness. (UG)
EGDT - Volume

- More IVF/PRBC in 1st 6hr
  - IVF
    - EGDT 5L
    - Standard 3.5L
  - PRBC
    - EGDT 64.1%
    - Standard 18.5%

- Same I/O in 72hr
  - EGDT 13.36L
  - Standard 13.44L

Mortality (%)

![Mortality Graph]

[Graph showing mortality rates for Standard and EGDT with EGDT having lower mortality rates.]
EGDT - Volume

- IVF → pulmonary edema?
  - p/F same
  - Intubation rate same
  - >6hr, ETT
    - 2.6% vs 16%
  - Hospital stay ETT
    - 55.6% vs 70.6%

Figure 4. Comparing the PaO₂/fraction of inspired oxygen (FIO₂) ratios between the EGDT and standard-care groups. Despite more volume resuscitation in the EGDT group during initial 6 h, there was no net difference in PaO₂/FIO₂ ratio (p = 0.34).
Does Central Venous Pressure Predict Fluid Responsiveness? *: A Systematic Review of the Literature and the Tale of Seven Mares

Paul E. Marik, Michael Baram and Bobbak Vahid

*Chest 2008;134;172-178
DOI 10.1378/chest.07-2331
Does Central Venous Pressure Predict Fluid Responsiveness?*

A Systematic Review of the Literature and the Tale of Seven Mares

Paul E. Marik, MD, FCCP; Michael Baram, MD, FCCP; and Bobbak Vahid, MD
<table>
<thead>
<tr>
<th>Source</th>
<th>Setting</th>
<th>Type</th>
<th>Patients, No.</th>
<th>Methodology</th>
<th>AUC†</th>
<th>r, CVP/SI</th>
<th>r, ΔCVP/SI</th>
<th>CVP-R</th>
<th>CVP-NR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calvin et al, 1981</td>
<td>ICU</td>
<td>Mixed ICU</td>
<td>28</td>
<td>PAC/Scint</td>
<td>0.16</td>
<td>0.26</td>
<td>4.7</td>
<td>4.8</td>
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<td>Reuse et al, 1990</td>
<td>ICU</td>
<td>ICU</td>
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<td>Godje et al, 1998</td>
<td>ICU</td>
<td>CABG</td>
<td>30</td>
<td>PAC, COLD system†</td>
<td>0.09</td>
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<td>Wagner and Leatherman, 1998</td>
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<td>PAC</td>
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<td>Wiesenack et al, 2001</td>
<td>OR</td>
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<td>18</td>
<td>PAC, TPT</td>
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<td></td>
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<td>Berkenstad et al, 2001</td>
<td>OR</td>
<td>Neurosurgery</td>
<td>15</td>
<td>TPT</td>
<td>0.49</td>
<td>0.05</td>
<td>0.08</td>
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<td>Michard et al, 2000</td>
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<td>ICU</td>
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<td>TPT</td>
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<td>Reuter et al, 2002</td>
<td>ICU</td>
<td>CABG</td>
<td>20</td>
<td>TPT</td>
<td>0.42</td>
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<td>Reuter et al, 2003</td>
<td>ICU</td>
<td>CABG</td>
<td>26</td>
<td>PAC, TEE</td>
<td>0.71</td>
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<tr>
<td>Barbier et al, 2004</td>
<td>ICU</td>
<td>Sepsis</td>
<td>20</td>
<td>TEE</td>
<td>0.57</td>
<td>0.13</td>
<td>10</td>
<td>9</td>
<td></td>
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<td>Kramer et al, 2004</td>
<td>ICU</td>
<td>CABG</td>
<td>21</td>
<td>PAC</td>
<td>0.49</td>
<td>0.13</td>
<td>13.5</td>
<td>13.3</td>
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<tr>
<td>Marx et al, 2004</td>
<td>ICU</td>
<td>Sepsis</td>
<td>10</td>
<td>PAC, TPT</td>
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<td>0.28</td>
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<td>Preisman et al, 2005</td>
<td>OR</td>
<td>CABG</td>
<td>18</td>
<td>TPT, TEE</td>
<td>0.61</td>
<td></td>
<td>8.7</td>
<td>10</td>
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<tr>
<td>Perel et al, 2005</td>
<td>ICU</td>
<td>Vascular surgery</td>
<td>14</td>
<td>TEE</td>
<td>0.27</td>
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<td>9.6</td>
<td>12.2</td>
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</tr>
<tr>
<td>Hofer et al, 2005</td>
<td>OR</td>
<td>CABG</td>
<td>40</td>
<td>PAC, TEE</td>
<td>0.54</td>
<td>0.02</td>
<td>0.2</td>
<td></td>
<td></td>
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<tr>
<td>De Backer et al, 2005</td>
<td>ICU</td>
<td>ICU</td>
<td>60</td>
<td>PAC</td>
<td>0.54</td>
<td></td>
<td>10</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>Kumar et al, 2004</td>
<td>ICU</td>
<td>Healthy volunteers</td>
<td>12</td>
<td>PAC/Scint</td>
<td>0.58</td>
<td>0.32</td>
<td>0.22</td>
<td></td>
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<tr>
<td>Osman et al, 2007</td>
<td>ICU</td>
<td>Septic</td>
<td>96</td>
<td>PAC</td>
<td>0.36</td>
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<td>8</td>
<td>9</td>
<td></td>
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<tr>
<td>Magder and Bafaqeeh, 2007</td>
<td>ICU</td>
<td>CABG</td>
<td>66</td>
<td>PAC</td>
<td>0.56</td>
<td>0.18</td>
<td>0.11</td>
<td>8.7</td>
<td>9.7</td>
</tr>
<tr>
<td><strong>Pooled</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.56</td>
<td>0.18</td>
<td>0.11</td>
<td>8.7</td>
<td>9.7</td>
</tr>
</tbody>
</table>

*PAC = pulmonary artery catheter; TEE = transesophageal echocardiography; Scint = radionuclide scintography; TPT = transpulmonary thermodilution; CVP-R = baseline CVP of responders; CVP-NR = baseline CVP of nonresponders; SI = fluid responsiveness; see Table 1 for expansion of abbreviations.

†Area under ROC curve of CVP and fluid responsiveness.

‡COLD Z-021 system (Pulsion Medical Systems; Munich, Germany).
Does Central Venous Pressure Predict Fluid Responsiveness?*

A Systematic Review of the Literature and the Tale of Seven Mares

Paul E. Marik, MD, FCCP; Michael Baram, MD, FCCP; and Bobbak Vahid, MD

**Discussion**

The results of this systematic review are clear: (1) there is no association between CVP and circulating blood volume, and (2) CVP does not predict fluid responsiveness across a wide spectrum of clinical
Changes in BP Induced by Passive Leg Raising Predict Response to Fluid Loading in Critically Ill Patients

Thierry Boulain, Jean-Michel Achard, Jean-Louis Teboul, Christian Richard, Dominique Perrotin and Guy Ginies

*Chest 2002;121;1245-1252
DOI 10.1378/chest.121.4.1245
Changes in BP Induced by Passive Leg Raising Predict Response to Fluid Loading in Critically Ill Patients*

Thierry Boulain, MD; Jean-Michel Achard, MD; Jean-Louis Teboul, MD; Christian Richard, MD; Dominique Perrotin, MD; and Guy Ginies, MD

Sequence of passive leg raising (PLR)

- baseline 1
- PLR
- post-PLR
- 4 min.
- 4 min.
- 4 min.

Sequence of rapid fluid loading (RFL)

- baseline 2
- post-RFL
- 15 min.
- 20 min.

RFL-induced change in S (mL)

Four measurements of systolic and diastolic arterial pressures and heart rate at 1-min intervals, at each phase of the procedure

Measurements of cardiac output * (thermodilution) at each phase of the procedure
Predicting Fluid Responsiveness in ICU Patients*

A Critical Analysis of the Evidence

Frédéric Michard, MD, PhD; and Jean-Louis Teboul, MD, PhD

- **DYNAMIC >> STATIC**
  - Inspiratory decrease RAP > 1mmHg
    - 77-84% PPV, 81-93% NPV
  - Expiratory decrease SBP > 5mmHg
    - 95% PPV, 93% NPV
  - Respiratory PP variation > 13%
    - 94% PPV, 96% NPV
  - Respiratory change in Ao blood velocity > 12%
    - 91% PPV, 100% NPV
Fluid Therapy in Resuscitated Sepsis*: Less Is More

Lakshmi Durairaj and Gregory A. Schmidt

*Chest 2008;133;252-263
DOI 10.1378/chest.07-1496

Figure 5. Relationship of arterial pressure wave and passive respiration. Compared to end-expiration, the systolic pressure and pulse pressure rise during inspiration (INSP), then fall during expiration. PPmax = maximal pulse pressure; PPmin = minimal pulse pressure.
Table 3—How To Measure PPV*

<table>
<thead>
<tr>
<th>Step</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Check that cardiac rhythm is regular</td>
</tr>
<tr>
<td>2</td>
<td>Raise the tidal volume to 10 mL/kg of predicted body weight</td>
</tr>
<tr>
<td>3</td>
<td>Ensure that the patient is receiving ventilation passively or adjust further the rate, tidal volume, or degree of sedation to achieve this</td>
</tr>
<tr>
<td>4</td>
<td>Display or print the arterial pressure waveform for 30 s</td>
</tr>
<tr>
<td>5</td>
<td>Measure the minimum and maximum pulse pressure</td>
</tr>
<tr>
<td>6</td>
<td>Calculate PPV ( \frac{PP_{\text{max}} - PP_{\text{min}}}{\frac{PP_{\text{max}} + PP_{\text{min}}}{2}} \times 100% )</td>
</tr>
<tr>
<td>7</td>
<td>A value ≤ 13% predicts fluid responsiveness</td>
</tr>
</tbody>
</table>

*PPV: Positive Pressure Variation
Table 2—Recommendations for Fluid Management in Severe Sepsis

For the first 6 h of severe sepsis, infuse fluids liberally, targeting $SvO_2$ or $ScvO_2 > 70\%$
Subsequently, do not use “maintenance” fluids
Judge the intravascular volume daily (at least)
For new hypotension, tachycardia, or unexplained oliguria,
ascertain the cause and consider a fluid challenge:
When fluid challenge is of low risk, administer 500 to 1,000 mL of crystalloid;
When the risk of fluid challenge is not trivial (ALI/ARDS; oliguria; right ventricular dysfunction), use a dynamic predictor to guide fluid boluses
PLR for those with some measure of cardiac output;
PPV for those with regular rhythm and lack of spontaneous breathing;
Change in Pra for those with substantial inspiratory effort
Reassess the patient frequently because the hemodynamic state changes often
Fluid resuscitation in septic shock: A positive fluid balance and elevated central venous pressure are associated with increased mortality*

John H. Boyd, MD, FRCP(C); Jason Forbes, MD; Taka-aki Nakada, MD, PhD; Keith R. Walley, MD, FRCP(C); James A. Russell, MD, FRCP(C)

Crit Care Med 2011 Vol. 39, No. 2

- 778pt VASST
- Fluid balance @ 12hr & 4 days
- CVP correlated w/ net fluid balance up to 12hr, not after
- More fluid, higher CVP = higher mortality
- Blindly read 133 CXR
- 36 pts w/ ALI/ARDS
- Receiving albumin/furosemide vs placebo
  - Tx 3.3L neg, 10kg wt loss
Findings on the Portable Chest Radiograph Correlate With Fluid Balance in Critically Ill Patients

Greg S. Martin, E. Wesley Ely, Frank E. Carroll and Gordon R. Bernard

*Chest* 2002;122;2087-2095
DOI 10.1378/chest.122.6.2087
Careful w/ fluids…

Sepsis in European intensive care units: Results of the SOAP study*

Jean-Louis Vincent, MD, PhD, FCCM; Yasser Sakr, MB, BCh, MSc; Charles L. Sprung, MD; V. Marco Ranieri, MD; Konrad Reinhart, MD, PhD; Herwig Gerlach, MD, PhD; Rui Moreno, MD, PhD; Jean Carlet, MD, PhD; Jean-Roger Le Gall, MD; Didier Payen, MD; on behalf of the Sepsis Occurrence in Acutely Ill Patients Investigators

Crit Care Med 2006 Vol. 34, No. 2

The NEW ENGLAND JOURNAL of MEDICINE

Comparison of Two Fluid-Management Strategies in Acute Lung Injury

The National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network*
Consider diuresis...

**Negative Fluid Balance Predicts Survival in Patients With Septic Shock**: A Retrospective Pilot Study

Fadi Alsous, Mohammad Khamiees, Angela DeGirolamo, Yaw Amoateng-Adjepong and Constantine A. Manthous

*Chest* 2000;117;1749-1754
DOI 10.1378/chest.117.6.1749

**The Importance of Fluid Management in Acute Lung Injury Secondary to Septic Shock**

Claire V. Murphy, Garrett E. Schramm, Joshua A. Doherty, Richard M. Reichley, Ognjen Gajic, Bekele Afessa, Scott T. Micek and Marin H. Kollef

*Chest* 2009;136;102-109; Prepublished online March 24, 2009; DOI 10.1378/chest.08-2706
Fluid resuscitation in severe sepsis and septic shock: An evidence-based review

Jean-Louis Vincent, MD, PhD, FCCM; Herwig Gerlach, MD, PhD

Objective: In 2003, critical care and infectious disease experts representing 11 international organizations developed management guidelines for fluid resuscitation in severe sepsis and septic shock that would be of practical use for the bedside clinician, under the auspices of the Surviving Sepsis Campaign, an international effort to increase awareness and improve outcome in severe sepsis.

Design: The process included a modified Delphi method, a consensus conference, several subsequent smaller meetings of subgroups and key individuals, teleconferences, and electronic-based discussion among subgroups and among the entire committee.

Methods: The modified Delphi methodology used for grading recommendations built on a 2001 publication sponsored by the International Sepsis Forum. We undertook a systematic review of the literature graded along five levels to create recommendation grades from A to E, with A being the highest grade. Pediatric considerations to contrast adult and pediatric management are in the article by Parker et al. on p. S591.

Conclusion: Fluid resuscitation of severe sepsis may consist of natural or artificial colloids or crystalloids. Fluid challenge should be administered and repeated based on response (increase in blood pressure and urine output) and tolerance (evidence of intravascular volume overload). (Crit Care Med 2004; 32[Suppl.]:S451–S454)

Crystalloids or colloids

Boluses given & repeated based on response

Monitor tolerance (volume overload)
### Table 1—Hemodynamic Monitoring-Defined Primary Hemodynamic Variables*

<table>
<thead>
<tr>
<th>Noninvasive monitoring</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>ECG</td>
<td>HR, dysrhythmias, HR variability</td>
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<tr>
<td>Pulse oximetry</td>
<td>SpO₂, HR</td>
</tr>
<tr>
<td>Arterial pressure</td>
<td>Sphygmonanometry</td>
</tr>
<tr>
<td></td>
<td>Systolic and diastolic BP, HR, pulsus paradoxus</td>
</tr>
<tr>
<td>Central venous pressure</td>
<td>Jugular venous distention, hepatojugular reflux, cannon waves (A-V dissociation), tricuspid regurgitation</td>
</tr>
<tr>
<td>Invasive monitoring</td>
<td></td>
</tr>
<tr>
<td>Arterial catheterization</td>
<td>Systolic BP, diastolic BP, MAP, HR, and pulse pressure</td>
</tr>
<tr>
<td>Arterial blood gas analysis</td>
<td>pH, PaO₂, SaO₂, Pco₂, hemoglobin</td>
</tr>
<tr>
<td>Arterial pressure waveform analysis</td>
<td>Stroke volume, cardiac output, PPV and SVV</td>
</tr>
<tr>
<td>Central venous catheterization</td>
<td>Central venous pressure, venous pressure waveform (&quot;v&quot; waves), respiratory variations</td>
</tr>
<tr>
<td></td>
<td>Central venous blood gas analysis</td>
</tr>
<tr>
<td></td>
<td>pH, PCO₂, ScO₂, PevCO₂, hemoglobin</td>
</tr>
<tr>
<td>Thermodilution indices (when coupled to an arterial thermal sensor)</td>
<td>Stroke volume, cardiac output, intrathoracic blood volume, global end-diastolic volume, and DO₂</td>
</tr>
<tr>
<td>Pulmonary artery catheter</td>
<td>Systolic BP, diastolic BP, MAP, pressure waveform (&quot;v&quot; waves), and Ppao</td>
</tr>
<tr>
<td>Mixed venous blood gas analysis</td>
<td>pH, PVO₂, SVO₂, PvCO₂, hemoglobin</td>
</tr>
<tr>
<td>Thermodilution cardiac output (by thermodilution either intermittent or continuous)</td>
<td>Stroke volume, cardiac output, RV ejection fraction, and RV end-diastolic volume</td>
</tr>
<tr>
<td>Esophageal Doppler echocardiographic monitoring</td>
<td>Stroke volume, cardiac output, and SVV</td>
</tr>
</tbody>
</table>

### Table 2—Derived Hemodynamic Parameters From Hemodynamic Monitoring*

<table>
<thead>
<tr>
<th>Primary hemodynamic variables</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>HR, beats/min</td>
<td>MAP, mm Hg</td>
</tr>
<tr>
<td>Pra, mm Hg</td>
<td>MPAP, mm Hg</td>
</tr>
<tr>
<td>Ppa0, mm Hg</td>
<td>CO, L/min</td>
</tr>
<tr>
<td>SaO₂, %</td>
<td>SpO₂ as an estimate of SaO₂, %</td>
</tr>
<tr>
<td>SVO₂, %</td>
<td>Hb, g/dL</td>
</tr>
<tr>
<td>Height and weight needed to calculate BSA, m²</td>
<td></td>
</tr>
</tbody>
</table>

Calculated hemodynamic parameters

\[
CI = \frac{CO}{BSA}, \text{L/min/m}^2
\]

Stroke volume = \(\frac{CO}{HR} \times 1,000\), mL/min

Stroke index = stroke volume/BSA, mL/m²

LV stroke work = stroke volume × (MAP – Ppa0), mL • mm Hg

LV stroke work index = LV stroke work/BSA, mL • mm Hg/m²

Total peripheral resistance = \(\frac{(MAP – Pra)}{CO} \times 80\), dyne • s/cm²

Systemic vascular resistance = \(\frac{(MAP – Pra)}{CO} \times 80\), dyne • s/cm²

RV stroke work = stroke volume × (MPAP – Pra), mL • mm Hg

RV stroke work index = RV stroke work/BSA, mL • mm Hg/m²

Pulmonary vascular resistance = \(\frac{(MPAP – Ppa0)}{CO} \times 80\), dyne • s/cm²

Global DO₂ = CO × (SaO₂ – SVO₂) × Hb × 1.36 × 1,000, mL oxygen/min

Global DO₂ index = CI × (SaO₂ – SVO₂) × Hb × 1.36, mL oxygen/min

Global VO₂ = CO × SaO₂ × Hb × 1.36 × 1,000, mL oxygen/min

Global VO₂ index = CI × SaO₂ × Hb × 1.36 × 1,000, mL oxygen/min
**Figure 2.** Hemodynamic patterns of early severe sepsis and septic shock. Lactate levels and \( S\text{vO}_2/Sc\text{vO}_2 \) values can serve as surrogate markers for global tissue hypoxia during the delivery-dependent phase (A), delivery-independent phase (B), or pathologic delivery-dependent phase (C). Therapeutic patterns during each phase are shown in the table below the graph. r-APC = recombinant activated protein C; ↓ = decrease; ↑ = increase.
Resuscitate aggressively, then back off
Surviving Sepsis Campaign

Hemodynamic Support & Adjunctive Therapy

- **Vasopressors**
  - MAP ≥ 65 mmHg (1C)
  - 1st line is norepinephrine (1B)
  - Add, or use as 1st alternative: epinephrine (2B)
  - Vasopressin 0.03u/min added to norepi to raise MAP or decrease norepi need. (UG)
    - Not as single agent, not >0.04u/min. (UG).
Surviving Sepsis Campaign

Hemodynamic Support & Adjunctive Therapy

- **Vasopressors**
  - Dopamine only in highly selected patients. (2C)
  - Phenylephrine is not recommended, unless: (1C)
    - Norepi a/w serious arrhythmias
    - CO high, BP low
    - Salvage
  - No low-dose dopamine. (1A)
  - A-line as soon as practical (UG)
EGDT - Vasopressors

- **1st 6hr**
  - 30.3 vs 27.4%

- **Hr 7 – 72hr**
  - 42.9% vs 29.1%

- **Total**
  - 51.3% vs 36.8%
Avoid Dopamine

More arrhythmias & Higher mortality

Figure 3. Forest plot of risk ratio (RR) of death (28 days or nearest estimate) in interventional trials. The p value for aggregate RR of dopamine (dopa) compared to norepinephrine (norepi) in interventional studies was .035. Relative weights of the different trials in the analysis: Martin et al (27) 2%; Marik et al (30) 1%; Ruokonen et al (29) 1%; Mathur et al (25) 4%; De Backer et al (15) 81%; and Patel et al (16) 10%. No heterogeneity was observed (p = .77; I² = 0; confidence interval, 0%-25%).
EGDT - Vasopressors

  - Hemodynamic & O2 transport goals x 6hr
    - Dopamine 31% effective
    - Norepinephrine 93% effective
    - Survival 3:1 favoring NE (NS)

  - Metaanalysis.
    - 6 studies evaluating NE vs dopamine in (mostly) sepsis
    - 2043 pt
    - NE superior
Norepinephrine first.

Epinephrine 2\textsuperscript{nd} line

Phenylephrine last option.

Avoid dopamine, unless patient bradycardic, or maybe low CO
Surviving Sepsis Campaign

Hemodynamic Support & Adjunctive Therapy

- Inotropic Therapy
  - Dobutamine (1C)
    - Up to 20mcg/kg/min
    - For myocardial dysfunction
    - Ongoing signs of hypoperfusion despite adequate volume & MAP.
EGDT – Dobutamine

- Severe sepsis causes:
  - Ventricular dilatation
  - Low EF
  - Poor preload responsiveness
  - Low peak systolic pressure/end-systolic volume

- Drug of choice to increase CO
  - After IVF resuscitation

- If hypotensive, add pressor
EGDT – Dobutamine

- 13.7%
  - Mean 10mcg/kg/min, Max 20mcg/kg/min

- **OPTIMIZE PRELOAD FIRST**
  - 35.9% of pt w/ low ScvO2 only required IVF to achieve ScvO2>70%
    - (Did pt that got PRBC simply benefit from additional volume?)

- Monitor HR closely (goal < 110)
  - Reassess volume?
  - Switch vasopressor?
SURVIVING SEPSIS CAMPAIGN BUNDLES

TO BE COMPLETED WITHIN 3 HOURS:
1) Measure lactate level
2) Obtain blood cultures prior to administration of antibiotics
3) Administer broad spectrum antibiotics
4) Administer 30 mL/kg crystalloid for hypotension or lactate ≥4mmol/L

TO BE COMPLETED WITHIN 6 HOURS:
5) Apply vasopressors (for hypotension that does not respond to initial fluid resuscitation) to maintain a mean arterial pressure (MAP) ≥ 65 mm Hg
6) In the event of persistent arterial hypotension despite volume resuscitation (septic shock) or initial lactate ≥4 mmol/L (36 mg/dL):
   - Measure central venous pressure (CVP)*
   - Measure central venous oxygen saturation (Scvo₂)*
7) Remeasure lactate if initial lactate was elevated*

*Targets for quantitative resuscitation included in the guidelines are CVP of ≥8 mm Hg, Scvo₂ of ≥70%, and normalization of lactate.

Figure 1. Surviving Sepsis Campaign Care Bundles.
Point: Adherence to Early Goal-Directed Therapy: Does It Really Matter? Yes. After a Decade, the Scientific Proof Speaks for Itself

Emanuel P. Rivers

Chest 2010;138;476-480
DOI 10.1378/chest.10-1405

Figure 2. Peer-review publications that have examined early goal-directed therapy as an essential component of sepsis.
Surviving Sepsis Campaign

Hemodynamic Support & Adjunctive Therapy

- Steroids
  - Do not use IV hydrocortisone, unless refractory shock & hemodynamic instability despite volume & vasoactive meds. (2C)
    - If used, 200mg/day.
      - Continuous infusion. (2D)
  - ACTH stimulation test not recommended (2B)
  - Steroids may be weaned once off pressors (2D)
  - Use in shock only (1D)
984 episodes of severe sepsis, septic shock
Compliance w/ Resuscitation Bundle 12.7% → 37.7% → 53.7%
Mortality 30.3% → 28.3% → 22%
Sepsis Response Team associated with reduced risk of death
OR 0.657 (95%CI 0.456-0.945; p=.023)
Implementaiton of early goal-directed therapy for severe sepsis and septic shock: A decision analysis

David T. Huang, MD, MPH; Gilles Clermont, MD, CM, MSc, FCCM; Tony T. Dremsizov, MBA; Derek C. Angus, MD, MPH, FCCP, FCCM; on behalf of the ProCESS Investigators

Crit Care Med 2007 Vol. 35, No. 9

Reduce mortality, LOS...and...costs?

Cost-effectiveness of an emergency department-based early sepsis resuscitation protocol*

Alan E. Jones, MD; Jennifer L. Troyer, PhD; Jeffrey A. Kline, MD

Crit Care Med 2011 Vol. 39, No. 6
<table>
<thead>
<tr>
<th>Program</th>
<th>Total Patients, No.</th>
<th>Preimplementation</th>
<th>Postimplementation</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loma Linda University (6-h bundle)</td>
<td>390</td>
<td>233 (60.9) [0.33–0.43]</td>
<td>77 (20.8) [0.13–0.31]</td>
<td>Nguyen et al.(^{106}) implemented EGDIT and the 6-h sepsis bundle over a 2-yr trial period; there was no statistical difference in ED LOS or ICU LOS (for mortality: p = 0.01; RR, 0.53; OR, 0.4; RRR, 49.9%; ARR, 18.4%; NNT, 5)</td>
</tr>
<tr>
<td>Birmingham Heartlands(^{105})</td>
<td>107</td>
<td>52 (49) [0.36–0.62]</td>
<td>49 (23) [0.13–0.37]</td>
<td>Cao et al.(^{106}) reviewed daily/admission for severe sepsis and septic shock from ED to ICU settings; the rates of compliance with these sepsis bundles were 52% at 6 h and 30% at 24 h (for mortality: p = 0.048; RR, 0.7; OR, 0.49; RRR, 30%; ARR, 17.6%; NNT, 6)</td>
</tr>
<tr>
<td>Friedrich-Schiller (SOP)(^{110})</td>
<td>80</td>
<td>30 (53) [0.36–0.70]</td>
<td>30 (27) [0.14–0.48]</td>
<td>Konrad et al.(^{110}) examined outcomes of patients before and after implementing an SOP for patients with severe sepsis (for mortality: p &lt; 0.05; RR, 0.51; OR, 0.33; RRR, 49%; ARR, 26.0%; NNT, 4)</td>
</tr>
<tr>
<td>Redding Medical Center (shock team)(^{107})</td>
<td>85</td>
<td>30 (50) [0.35–0.60]</td>
<td>49 (33) [0.21–0.47]</td>
<td>Sebat et al.(^{107}) compared preimplementation and postimplementation results in a community hospital shock program; 1 yr after implementation, a significant reduction was seen in mortality, time until patients received central line placement, 2-l infusion of fluids, and antibiotic administration (for sepsis patients in particular: p = 0.05; RR, 0.05; OR, 0.48; RRR, 54.7%; ARR, 17.4%; NNT, 6)</td>
</tr>
<tr>
<td>Beth Israel Deaconess (sepsis team)(^{113})</td>
<td>167</td>
<td>51 (39.3) [0.19–0.43]</td>
<td>116 (20.3) [0.14–0.29]</td>
<td>Shapero et al.(^{113}) implemented a multidisciplinary sepsis team, utilizing an SOP procedure for sepsis; a statistically significant improvement in appropriate empiric antimicrobial coverage and higher glycemic control was found; there was a nonsignificant trend toward decreased mortality (p = 0.3; RR, 0.7; OR, 0.62; RRR, 31%; ARR, 9.0%; NNT, 11)</td>
</tr>
<tr>
<td>University of Medicine and Dentistry of New Jersey–Camden (EGDIT)(^{112})</td>
<td>38</td>
<td>16 (43.8) [0.17–0.6]</td>
<td>22 (18.2) [0.73–0.39]</td>
<td>Trzeciak et al.(^{112}) implemented a collaborative ED and ICU quality improvement initiative utilizing EGDIT; they found that 91% of patients with severe sepsis achieved the EGDIT hemodynamic and points of MAP ≥ 65 mm Hg and SvO₂ ≥ 70% in &lt; 6 h; nonsignificant decrease in mortality (p = 0.6; RR, 0.51; OR, 0.4; RRR, 48.9%; ARR, 17.4%; NNT, 6)</td>
</tr>
<tr>
<td>University of Pennsylvania (EGDIT)(^{111})</td>
<td>38</td>
<td>22 (58) [0.35–0.74]</td>
<td>13 (25) [0.10–0.50]</td>
<td>Credé et al.(^{111}) compared historical standard care for septic patients admitted to the ED who qualified and received EGDIT, and evaluated 28-d and 60-d mortality (p = 0.1; RR, 0.46; OR, 0.57; RRR, 54.9%; ARR, 30.9%; NNT, 3)</td>
</tr>
<tr>
<td>Holmenn University (SOP/ IHI)(^{112})</td>
<td>54</td>
<td>20 (47) [0.87–0.08]</td>
<td>34 (61) [0.18–0.48]</td>
<td>Vorderstrake et al.(^{112}) examined a hospital-wide program similar to that of Sebat et al.(^{107}); there were statistically significant decreases in time to antibiotic administration, CVP measurement, and attainment of MAP and SvO₂ goals (for mortality, p value, not reported; RR, 0.60; OR, 0.5; RRR, 54.3%; ARR, 16.1%; NNT, 6)</td>
</tr>
<tr>
<td>Good Samaritan (shock team)(^{113})</td>
<td>131</td>
<td>68 (43) [0.39–0.63]</td>
<td>63 (51) [0.18–0.39]</td>
<td>Armstrong et al.(^{113}) utilized a rapid-response team in a community hospital; significant reductions in time until administration of IV fluids, ICU admission, and intensive arrival; APACHE II scores were 21.9 and 23.0, respectively, for preimplementation and postimplementation (for mortality: p &lt; 0.03; RR, 0.53; OR, 0.35; RRR, 47.3%; ARR, 24%; NNT, 4)</td>
</tr>
<tr>
<td>Barnes Jewish Hospital (EGDIT)(^{114})</td>
<td>190</td>
<td>60 (48.3) [0.36–0.61]</td>
<td>60 (30) [0.20–0.43]</td>
<td>Mieck et al.(^{114}) found a significant mortality benefit when all components of this protocol including education, standing orders, and equipment were available; there was a decreased use of vasopressor and steroids (p = 0.04; RR, 0.65; OR, 0.46; RRR, 37.8%; ARR, 18.2%; NNT, 6)</td>
</tr>
<tr>
<td>Hoag Hospital(^{115})</td>
<td>78</td>
<td>12 (33.5) [0.13–0.60]</td>
<td>60 (21.7) [0.13–0.33]</td>
<td>Rogovin(^{115}) conducted a preimplementation and postimplementation study, and found decreased rate of critical care admission (12.3–10.5%; p = 0.033), a decreased median critical care LOS (5.4–3.7 d), and decreased critical care mortality reduction (18.5–12.0%; p = 0.132) (for overall mortality: p = 0.000; RR, 0.07; OR, 0.57; RRR, 33.3%; ARR, 10.8%; NNT, 9)</td>
</tr>
<tr>
<td>St. Paul’s Hospital, Vancouver(^{116})</td>
<td>96</td>
<td>51 (46.7) [0.34–0.60]</td>
<td>45 (32.3) [0.13–0.37]</td>
<td>Blom et al.(^{116}) studied 56 patients admitted to the ICU from the ED; mean APACHE II score was 24; there was no significant difference in time to ICU transfer (for mortality: p &lt; 0.018; RR, 0.49; OR, 0.34; RRR, 56.4%; ARR, 23.5%; NNT, 4)</td>
</tr>
<tr>
<td>Summary of all above centers(^{1})</td>
<td>1,298</td>
<td>671 (44.8) ± 7.8 [0.41–0.49]</td>
<td>627 (24.5) ± 5.5 [0.21–0.28]</td>
<td>For all centers reporting mortality data: RR, 0.54; OR, 0.39; RRR, 45%; ARR, 20.3%; NNT, 5</td>
</tr>
<tr>
<td>Summary of standard-care group(^{1})</td>
<td>1,298</td>
<td>133 (60.4) [0.36–0.53]</td>
<td>133 (60.0) [0.22–0.33]</td>
<td>Survivors in standard-care group had a significantly longer LOS (18.4 d) those in EGDIT group (14.0 d) to-hospital mortality: p &lt; 0.01; RR, 0.65; OR, 0.51; RRR, 34.1%; ARR, 15.1%; NNT, 7</td>
</tr>
</tbody>
</table>

*RR = relative risk; OR = odds ratio; RRR = relative risk reduction; ARR = absolute risk reduction; NNT = number needed to treat; CI = confidence interval; LOS = length of stay; SOP = standard operating procedure; IHI = Institute for Health Improvement.)
*Values are given as (total No. of patients) mean ± SD [95% CI].
SURVIVING SEPSIS CAMPAIGN BUNDLES

TO BE COMPLETED WITHIN 3 HOURS:
1) Measure lactate level
2) Obtain blood cultures prior to administration of antibiotics
3) Administer broad spectrum antibiotics
4) Administer 30 mL/kg crystalloid for hypotension or lactate ≥4 mmol/L

TO BE COMPLETED WITHIN 6 HOURS:
5) Apply vasopressors (for hypotension that does not respond to initial fluid resuscitation) to maintain a mean arterial pressure (MAP) ≥ 65 mm Hg
6) In the event of persistent arterial hypotension despite volume resuscitation (septic shock) or initial lactate ≥4 mmol/L (36 mg/dL):
   - Measure central venous pressure (CVP)*
   - Measure central venous oxygen saturation (Scvo₂)*
7) Remeasure lactate if initial lactate was elevated*

*Targets for quantitative resuscitation included in the guidelines are CVP of ≥8 mm Hg, Scvo₂ of ≥70%, and normalization of lactate.

Figure 1. Surviving Sepsis Campaign Care Bundles.
Lactic Acid
INFECTIONOUS DISEASE/BRIEF RESEARCH REPORT

Serum Lactate as a Predictor of Mortality in Emergency Department Patients With Infection

Nathan I. Shapiro, MD, MPH
Michael D. Howell, MD
Daniel Talmor, MD, MPH
Larry A. Nathanson, MD
Alan Lisbon, MD
Richard E. Wolfe, MD
J. Woodrow Weiss, MD

From the Department of Emergency Medicine (Shapiro, Wolfe, Nathanson), the Department of Medicine, Division of Pulmonary and Critical Care Medicine (Howell, Weiss), and the Department of Anesthesia and Critical Care (Talmor, Lisbon), Beth Israel Deaconess Medical Center, Boston, MA.

Ann Emerg Med. 2005;45:524-528

Serum lactate as a predictor of mortality in patients with infection

Higher LA = Higher Mortality risk
Lactic Acid

Serum lactate is associated with mortality in severe sepsis independent of organ failure and shock.

Mark E. Mikkelsen, MD, MS; Andrea N. Miltiades, BA; David F. Galeski, MD; Munish Goyal, MD; Barry D. Fuchs, MD; Chirag V. Shah, MD, MS; Scarlett L. Bellamy, ScD; Jason D. Christie, MD, MS

Crit Care Med 2009 Vol. 37, No. 5

Higher LA = Higher Mortality risk
Independent of presence of organ dysfunction or shock
Treating toward improving LA may improve outcomes in ICU patients...
Dynamic measurements are better
Dynamic measurements are better, especially if the dynamic is toward NORMAL…

But the ability to predict survival is limited.
LA vs ScvO2

Lactate Clearance vs Central Venous Oxygen Saturation as Goals of Early Sepsis Therapy
A Randomized Clinical Trial

Noninferior
But possibly underpowered, possible treatment bias, lack of protocol adherence, low use of dobutamine & blood, Hawthorne effect?
LA vs ScvO2

Blood lactate monitoring in critically ill patients: A systematic health technology assessment*

Tim C. Jansen, MD; Jasper van Bommel, MD, PhD; Jan Bakker, MD, PhD

Conclusions: The use of blood lactate monitoring has a place in risk-stratification in critically ill patients, but it is unknown whether the routine use of lactate as a resuscitation end point improves outcome. This warrants randomized controlled studies on the efficacy of lactate-directed therapy. (Crit Care Med 2009; 37:2827–2839)
No agreement between LA clearance & ScvO2 normalization

Normalized ScvO2 w/o LA clearance worse than LA clearance w/o normalized ScvO2
“Almost one-half of patients with vasopressor-dependant septic shock did not express lactate on presentation, although a high mortality rate remains in this population.”
Mercy STL Data

- LA < 2.5
- LA 2.5 – 4
- LA > 4

Same rate of vasopressor need…
Early Lactate-Guided Therapy in Intensive Care Unit Patients
A Multicenter, Open-Label, Randomized Controlled Trial
Where does EGDT come from?

\[
\text{DO2} = \text{CO} \times \text{CaO2} \neq \text{VO2}
\]

\[
\text{DO2} = \text{SV} \times \text{HR} \times 1.34 \times \text{Hb} \times \text{SaO2} \times 10 \neq \text{VO2}
\]

\[
\text{DO2} = (\text{preload + afterload + contractility}) \times \text{HR} \times 1.34 \times \text{Hb} \times \text{SaO2} \times 10 \neq \text{VO2}
\]
Adding LA clearance improves mortality

(Notice it says “adding”, not “substituting” 😊)
SURVIVING SEPSIS CAMPAIGN BUNDLES

TO BE COMPLETED WITHIN 3 HOURS:
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7) Remeasure lactate if initial lactate was elevated*

*Targets for quantitative resuscitation included in the guidelines are CVP of ≥8 mm Hg, Scvo₂ of ≥70%, and normalization of lactate.

Figure 1. Surviving Sepsis Campaign Care Bundles.
ProCESS - Cumulative Mortality.

ARISE - Probability of Survival and Subgroup Analyses of the Risk of Death at 90 Days.

ProMISe Kaplan–Meier Survival Estimates.

Adjusted hazard ratio, 0.94 (0.79–1.11); P=0.46
P=0.63 by log-rank test

### Study Comparisons

**EGDT / ProCESS / ARISE / ProMISe**

<table>
<thead>
<tr>
<th>Study</th>
<th>Location</th>
<th>Hospital</th>
<th>Study Size</th>
<th>Lactic Acid</th>
<th>APACHE II</th>
<th>ScVO2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rivers</td>
<td>US</td>
<td>1</td>
<td>263</td>
<td>7.3</td>
<td>20.9</td>
<td>49</td>
</tr>
<tr>
<td>ProCESS</td>
<td>US</td>
<td>31</td>
<td>1341</td>
<td>4.9</td>
<td>20.7</td>
<td>71</td>
</tr>
<tr>
<td>ARISE</td>
<td>Australia</td>
<td>51</td>
<td>1600</td>
<td>4.3</td>
<td>15.6</td>
<td>75</td>
</tr>
<tr>
<td>ProMISe</td>
<td>UK</td>
<td>56</td>
<td>1260</td>
<td>5.1</td>
<td>18.3</td>
<td>70</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study</th>
<th>Initial Fluids</th>
<th>Recruitment Criteria</th>
<th>Intervention</th>
<th>Control</th>
<th>Primary Outcome</th>
<th>EGDT Outcome</th>
<th>Control Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rivers</td>
<td>20-30 ml/kg</td>
<td>not specified</td>
<td>EGDT 6 hrs</td>
<td>usual therapy</td>
<td>in-hospital mortality</td>
<td>30.5</td>
<td>46.5</td>
</tr>
<tr>
<td>ProCESS</td>
<td>~20-30 ml/kg</td>
<td>&lt;12hr arrival, &lt;2 hr shock criteria</td>
<td>EGDT 6 hrs</td>
<td>PUT and UT</td>
<td>60 day mortality</td>
<td>21</td>
<td>18.2 (PUT) 18.9 (UT)</td>
</tr>
<tr>
<td>ARISE</td>
<td>1000 ml</td>
<td>&lt;6hr arrival, &lt;2hr shock criteria</td>
<td>EGDT 6 hrs</td>
<td>usual therapy</td>
<td>90 day mortality</td>
<td>18.6</td>
<td>18.8</td>
</tr>
<tr>
<td>ProMISe</td>
<td>1000 ml</td>
<td>&lt;6hr arrival, &lt;2 hr shock criteria</td>
<td>EGDT 6 hrs</td>
<td>usual therapy</td>
<td>90 day mortality</td>
<td>29.5</td>
<td>29.2</td>
</tr>
</tbody>
</table>
Surviving Sepsis Campaign 2015 Update

- In the event of persistent hypotension after initial fluid administration (MAP < 65 mm Hg) or if initial lactate was ≥4 mmol/L, re-assess volume status and tissue perfusion and document findings:
  - EITHER:
    - Repeat focused exam (after initial fluid resuscitation) by licensed independent practitioner including vital signs, cardiopulmonary, capillary refill, pulse, and skin findings.
  - OR TWO OF THE FOLLOWING:
    - Measure CVP
    - Measure ScvO2
    - Bedside cardiovascular ultrasound
    - Dynamic assessment of fluid responsiveness with passive leg raise or fluid challenge