The Surviving Sepsis Campaign: The New Guidelines and Bundles

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London, UK

On behalf of:
The European Society of Intensive Care Medicine
The Society of Critical Care Medicine
Surviving Sepsis Campaign: Timeline

- Barcelona Declaration
- Phase III starts: IHI partnership
- Guidelines Revision
- NEJM editorial
- Results published 15,000 pts 20% RRR
- Guidelines and Bundles Revision
- Relaunch Campaign
SSC Methodology: Multifaceted Intervention

- National/regional/network “launch meetings”
  - Identify local champions
  - Introduce sepsis bundles
  - Educational tools
    - SSC manual
    - SSC slides
      - Staff support for coordinating sites
      - Regular conference calls
- Website
  - SSC and IHI website
  - Sepsis list-serve
- Interactive database
  - Automated uploading to SSC server
  - Technical support
  - Local audit and feedback capabilities
Change in Compliance Over Time

Change in Mortality Over Time


* p<0.01 compared to site quarter 1
Cost Effectiveness of the Guidelines/bundles

<table>
<thead>
<tr>
<th></th>
<th>Control group (n = 854)</th>
<th>Treatment group (n = 1,465)</th>
<th>Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Length of stay (days)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICU</td>
<td>12.5 (15.9)</td>
<td>13.5 (17.7)</td>
<td>1.0 (– 0.4; 2.4)</td>
</tr>
<tr>
<td>Ward</td>
<td>10.8 (16.7)</td>
<td>12.6 (18.2)</td>
<td>1.8 (0.4; 3.3)</td>
</tr>
<tr>
<td>Total</td>
<td>23.3 (25.1)</td>
<td>26.1 (27.5)</td>
<td>2.8 (0.7; 5.0)</td>
</tr>
<tr>
<td><strong>Costs (2006 euros)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Costs</td>
<td>16,935 (18,525)</td>
<td>18,671 (20,792)</td>
<td>1,736 (114; 3,358)</td>
</tr>
<tr>
<td>LYG&lt;sup&gt;a&lt;/sup&gt;</td>
<td>5.44 (6.05)</td>
<td>5.98 (6.11)</td>
<td>0.54 (0.02; 1.05)</td>
</tr>
<tr>
<td>QALYs&lt;sup&gt;a&lt;/sup&gt;</td>
<td>3.75 (4.18)</td>
<td>4.12 (4.22)</td>
<td>0.37 (0.02; 0.73)</td>
</tr>
</tbody>
</table>

- **Adjusted ICER**
- **Adjusted ICUR**

4,435 euros per LYG
6,428 euros per QALY

Suarez et al. ICM 2010.
## SSC: Demographics

<table>
<thead>
<tr>
<th>Site Characteristic</th>
<th>Subjects, %</th>
<th>Sites, %</th>
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</thead>
<tbody>
<tr>
<td>N</td>
<td>27,836</td>
<td>1,553</td>
</tr>
<tr>
<td>Number of ICU beds</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 25</td>
<td>57.7</td>
<td>73.1</td>
</tr>
<tr>
<td>25 to 50</td>
<td>29.9</td>
<td>20.6</td>
</tr>
<tr>
<td>&gt; 50</td>
<td>12.4</td>
<td>6.3</td>
</tr>
<tr>
<td>Region</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Europe</td>
<td>23.7</td>
<td>31.3</td>
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<tr>
<td>North America</td>
<td>66.3</td>
<td>54.2</td>
</tr>
<tr>
<td>South America</td>
<td>10.0</td>
<td>14.6</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Patient Characteristics</th>
<th>Subjects, %</th>
<th>Hospital Mortality, %</th>
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</thead>
<tbody>
<tr>
<td>All</td>
<td>100.0</td>
<td>33.6</td>
</tr>
<tr>
<td>Source</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ED</td>
<td>54.3</td>
<td>27.0</td>
</tr>
<tr>
<td>ICU</td>
<td>33.2</td>
<td>40.5</td>
</tr>
<tr>
<td>Ward</td>
<td>12.5</td>
<td>44.3</td>
</tr>
</tbody>
</table>
## SSC: Demographics

<table>
<thead>
<tr>
<th>Patient Characteristics</th>
<th>Subjects, %</th>
<th>Hospital Mortality, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of acute organ dysfunction</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>43.5</td>
<td>26.5</td>
</tr>
<tr>
<td>2</td>
<td>34.0</td>
<td>34.0</td>
</tr>
<tr>
<td>3</td>
<td>16.2</td>
<td>43.5</td>
</tr>
<tr>
<td>4</td>
<td>5.1</td>
<td>53.1</td>
</tr>
<tr>
<td>5</td>
<td>1.2</td>
<td>66.7</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No cardiovascular dysfunction</td>
<td>10.6</td>
<td>28.0</td>
</tr>
<tr>
<td>Cardiovascular dysfunction no hypotension</td>
<td>19.7</td>
<td>23.7</td>
</tr>
<tr>
<td>Shock</td>
<td></td>
<td></td>
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<tr>
<td>Lactate &gt; 4</td>
<td>5.7</td>
<td>30.9</td>
</tr>
<tr>
<td>Vasopressors only</td>
<td>47.6</td>
<td>35.0</td>
</tr>
<tr>
<td>Lactate &gt; 4 and vasopressors</td>
<td>16.5</td>
<td>46.1</td>
</tr>
<tr>
<td>Total shock</td>
<td>69.8</td>
<td>37.3</td>
</tr>
</tbody>
</table>
The Surviving Sepsis Campaign: building upon success...?

- The Campaign has achieved its initial target
- Based upon bundles, not protocols or checklists
- There may be better approaches than bundles
- For now, unless we want to abandon the Campaign, the bundles need to change as the evidence changes
Revised SSC Bundles

• Based on 2012 SSC guideline Revision
  – Utilizing analysis of 28,000 pt SSC database
• New software being developed
• No industry funding utilized in revising guidelines or bundles
• Rigorous management of conflict of interest
New Policy to deal with Potential Conflicts of Interest

Surviving Sepsis Campaign – Guidelines Committee
Potential Non-Financial Conflict of Interest Statement

In addition to drafting a statement (ICMJE Uniform Disclosure Form; Sect 5.) describing relevant nonfinancial associations, relationships or accrued benefits, committee members are encouraged to comment specifically on the following areas:

i. What are the roles of guidelines in the care of patients with sepsis?

ii. What is the value of standardization and protocolization in the care of patients with sepsis?
Revised SSC Bundles

Management bundle dropped

- Inspiratory Plateau Pressure control
  - High compliance at outset of study
  - No significant change in compliance
- Glucose
  - Clouded by controversy
- Steroids
  - OR > 1.0 in SSC analysis
- rhAPC
  - Significant OR for survival
  - PROWESS-SHOCK ended use
Sepsis Resuscitation Bundle
(To be started immediately and completed within 3 hours)

• Serum lactate measured in 3 hours.
• Blood cultures obtained prior to antibiotic administration.
• Administer broad-spectrum antibiotics within 1 hour.
• In the event of hypotension and/or lactate > 4mmol/L, deliver a minimum bolus of 30 ml/kg of crystalloid within 1 hour.
1. We recommend obtaining appropriate cultures before antimicrobial therapy is initiated if such cultures do not cause significant delay (>45 minutes) in antimicrobial administration. To optimize identification of causative organisms, we recommend at least two blood cultures be obtained before antimicrobial therapy with at least one drawn percutaneously and one drawn through each vascular access device, unless the device was recently inserted (<48 hr) (Grade 1C).

2. Cultures of other sites (preferably quantitative where appropriate), such as urine, cerebrospinal fluid, wounds, respiratory secretions, or other body fluids that may be the source of infection should also be obtained before antimicrobial therapy if not associated with significant delay in antibiotic administration (grade 1C).
Diagnosis

3. We suggest the use of the 1,3 beta-D-glucan assay (2B), mannan and anti-mannan antibody assays for the early diagnosis of invasive candidiasis. (Grade 2C)

4. We recommend that imaging studies be performed promptly in attempts to confirm a potential source of infection. Sampling of potential sources of infection should occur as they are identified; however, some patients may be too unstable to warrant certain invasive procedures or transport outside of the ICU. Bedside studies, such as ultrasound, are useful in these circumstances (Grade 1C).
Antibiotic therapy

1. We recommend that intravenous antimicrobial therapy be started as early as possible and within the first hour of recognition of septic shock (1B) and severe sepsis without septic shock (grade 1C).

2. We recommend that initial empiric anti-infective therapy include one or more drugs that have activity against all likely pathogens (bacterial and/or fungal or viral) and that penetrate in adequate concentrations into the tissues presumed to be the source of sepsis (grade 1B).

3. The antimicrobial regimen should be reassessed daily to optimize activity, to prevent the development of resistance, to reduce toxicity, and to reduce costs. (grade 1C)
1. We recommend that a specific anatomical diagnosis of infection requiring consideration for emergent source control (e.g., necrotizing soft tissue infection, peritonitis complicated with intra-abdominal infection, cholangitis, intestinal infarction) be sought and diagnosed or excluded as rapidly as possible, and if needed, surgical drainage should be undertaken for source control within the first 12 hr after the diagnosis is made, if feasible (grade 1C).

2. We suggest that when infected peri-pancreatic necrosis is identified as a potential source of infection, definitive intervention is best delayed until adequate demarcation of viable and nonviable tissues has occurred (grade 2B).
Infection prevention

1. We suggest SOD and SDD to reduce the incidence of ventilator-associated pneumonia in health care settings in regions where this methodology has been found to be effective (2B).
Septic Shock Bundle
(To be started immediately and completed within 6 hours)

• Apply vasopressors for hypotension not responding to initial fluid resuscitation to maintain mean arterial pressure (MAP) $\geq 65$ mm Hg.

• In the event of persistent arterial hypotension despite volume resuscitation (septic shock) and/or initial lactate $> 4$ mmol/L (36 mg/dl):
  – Insert central line
  – Achieve central venous pressure (CVP) of $\geq 8$ mm Hg.
  – Achieve central venous oxygen saturation (ScvO2) of $\geq 70\%$.\textsuperscript{*}
Initial Resuscitation

1. We recommend the protocolized resuscitation of a patient with sepsis-induced shock, defined as tissue hypoperfusion (hypotension persisting after initial fluid challenge or blood lactate concentration 4 mmol/L). This protocol should be initiated as soon as hypoperfusion is recognized and should not be delayed pending ICU admission. During the first 6 hrs of resuscitation, the goals of initial resuscitation of sepsis-induced hypoperfusion should include all of the following as one part of a treatment protocol:

   • Central venous pressure (CVP): 8–12mm Hg
   • Mean arterial pressure (MAP) ≥ 65mm Hg
   • Urine output ≥ 0.5mL.kg–1.hr –1
   • Central venous (superior vena cava) or mixed venous oxygen saturation ≥ 70% or ≥ 65%, respectively

   (Grade 1C)
Initial Resuscitation

2. In patients with elevated lactate levels as a marker of tissue hypoperfusion we suggest targeting resuscitation to normalize lactate as rapidly as possible (grade 2C).

3. We suggest that during the first 6 hrs of resuscitation of severe sepsis or septic shock, if ScvO2 70% (or SvO2 equivalent of 65%), respectively persisted with fluid resuscitation to the central venous pressure target, then transfusion of packed red blood cells to achieve a hematocrit of 30% and/or administration of a dobutamine infusion (up to a maximum of 20 \( \mu g \cdot kg^{-1} \cdot min^{-1} \)) be used to achieve this goal (grade 1C).
Why continue with CVP and ScvO$_2$?

- Evidence base
  - Including (crucially) the success of the first phase of the Campaign itself
- Belief that patients with severe sepsis and septic shock should have a central line
- Limitations of all postulated alternative approaches
- Inability to generalise other technologies
  - Only a CVC/blood gas analyser combination is available (nearly) everywhere
Fluid therapy

1. We recommend crystalloids be used in the initial fluid resuscitation in patients (Grade 1A).

2. We suggest adding albumin in the initial fluid resuscitation regimen of severe sepsis and septic shock if the serum albumin is known or anticipated to be low (Grade 2B).

3. We recommend against the use of hydroxyethyl ethyl starches with molecular weight > 140 kDa and or a degree of substitution >0.4 (Grade 1B).
4. We recommend that initial fluid challenge in patients with sepsis-induced tissue hypoperfusion with suspicion of hypovolemic be started with $\geq 1000$ mL of crystalloids (to achieve a minimum of 30ml/kg of crystalloids in the first 4 to 6 hours). More rapid administration and greater amounts of fluid, may be needed in some patients (see Initial Resuscitation recommendations) (Grade 1B).

5. We recommend that a fluid challenge technique using incremental fluid boluses be applied wherein fluid administration is continued as long as the hemodynamic improvement either based on dynamic (e.g. delta pulse pressure, stroke volume variation…) or static (eg cardiac output, arterial pressure, heart rate) variables continues (Grade 1C).
Bicarbonate therapy

1. We recommend against the use of sodium bicarbonate therapy for the purpose of improving hemodynamics or reducing vasopressor requirements in patients with hypoperfusion-induced lactic acidemia with pH ≥ 7.15 (grade 1B).
Vasopressors

1. We recommend that vasopressor therapy initially target a mean arterial pressure (MAP) of 65 mm Hg (grade 1C).

2. We recommend norepinephrine as the first choice vasopressor (Grade 1B).

3. We recommend epinephrine (added or substituted) when an additional agent is needed to maintain adequate blood pressure (Grade 2B).

4. We suggest vasopressin 0.03 units/minute can be added to or substituted for norepinephrine (Grade 2).

5. We suggest dopamine as an alternative vasopressor agent to norepinephrine in highly selected patients at very low risk of arrhythmias and with low cardiac output and/or low heart rate. (Grade 2C).
Vasopressors

6. We recommend that low-dose dopamine not be used for renal protection (grade 1A).

7. We recommend that all patients requiring vasopressors have an arterial catheter placed as soon as practical if resources are available (grade 1B).
Inotropic Therapy

1. We recommend that a dobutamine infusion be administered or added to vasopressor (if in use) in the presence of (a) myocardial dysfunction as suggested by elevated cardiac filling pressures and low cardiac output, or (b) ongoing signs of hypoperfusion, despite achieving adequate intravascular volume and adequate mean arterial pressure. (grade 1C).

2. We recommend against the use of a strategy to increase cardiac index to predetermined supranormal levels (grade 1B).
Corticosteroids

1. We suggest that a minimum of five day course of continuous infusion of intravenous hydrocortisone (200-300 mg daily and no higher) be used only in adult septic shock patients who require persistent high dose of vasopressors to keep adequate blood pressure despite adequate fluid resuscitation (Grade 2C).

2. We suggest not using the ACTH stimulation test to identify the subset of adults with septic shock who should receive hydrocortisone (Grade 2B).

3. We suggest that patients with septic shock receive hydrocortisone rather than other steroids (Grade 2B). Further we recommend that hydrocortisone alone be used instead of hydrocortisone plus fludrocortisone (Grade 1B).
Recombinant Human Activated Protein C (rhAPC)

LILLY (ELI) & COMPANY - Withdrawal of Xigris

Tuesday, October 25, 2011 8:21 AM

Date: October 25, 2011
For Release: Immediately
Refer to: (317) 651-5557 - Tina Gaines, Lilly Bio-Medicines Communications
(317) 655-6874 - Phil Johnson, Investor Relations

Lilly Announces Withdrawal of Xigris® Following Recent Clinical Trial Results

INDIANAPOLIS, IN - Eli Lilly and Company (NYSE: LLY) announces withdrawal of its Xigris®[drotrecoginalfa (activated)] product in all markets following results of the PROWESS-SHOCK study, which showed the study did not meet the primary endpoint of a statistically significant reduction in 28-day all-cause mortality in patients with septic shock. The company is working with regulatory agencies on this withdrawal, and is in the process of notifying health care professionals and clinical trial investigators.

No recommendation will be made concerning drotrecogina alfa activated
Blood product administration

1. Once tissue hypoperfusion has resolved and in the absence of extenuating circumstances, such as myocardial ischemia (or other relevant cardiac diseases), severe hypoxemia acute hemorrhage, or lactic acidosis (see recommendations for initial resuscitation), we recommend that red blood cell transfusion is needed to maintain hemoglobin ≥7.0 g (Grade 1B).

2. We suggest that fresh frozen plasma not be used to correct laboratory clotting abnormalities in the absence of bleeding or planned invasive procedures (Grade 2D).

3. We recommend against anti-thrombin administration for the treatment of severe sepsis and septic shock (Grade 1B).
4. In patients with severe sepsis, we suggest that platelets be administered when counts are <5000/mm³ (5 x 10⁹/L) regardless of apparent bleeding (2C). We suggest platelet transfusion when counts are 5000–30,000/mm³ (5–30 x 10⁹/L) if the patient has a relevant risk of bleeding (2C). Higher platelet counts (≥50,000/mm³ [50 x 10⁹/L]) are recommended for surgery or invasive procedures (Grade 2C).
Glucose control

1. We recommend a protocolized approach to blood glucose management in ICU patients with severe sepsis, commencing insulin dosing when two consecutive blood glucose levels are equal to or greater than >180 mg/dL. This protocolized approach should target an upper blood glucose less than or equal to < 180 mg/dL [10mmol/l] rather than an upper target blood glucose greater than or equal to < 110 mg/dL [6.2 mmol/l] (Grade 1A).

2. We recommend that all patients receiving intravenous insulin receive a glucose calorie source and that blood glucose values be monitored every 1–2 hrs until glucose values and insulin infusion rates are stable and then every 4 hrs thereafter (Grade 1C).

3. We recommend that low glucose levels obtained with point-of-care testing of capillary blood be interpreted with caution, as such measurements may overestimate arterial blood or plasma glucose values.
Conclusions

• The Surviving Sepsis Campaign achieved the targeted goal of 25% mortality reduction
  – Clinical practice has been changed - irrevocably
• The Sponsoring Societies, and their Partners, are committed to the next phase
• The Guidelines, Bundles and implementation approach can and will be further improved
• Ethically, we need to make an intervention that we know works available to many more of our patients