Severe Sepsis and Septic Shock
The Evolution and Evidence:
From Protocols to Public Policy

CMS Sepsis Measure (SEP-10)

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Vice Chairman and Research Director
Departments of Emergency Medicine and Surgery
Henry Ford Hospital
Clinical Professor, Wayne State University
Topics

• Sepsis Diagnosis
  – SIRS vs. qSOFA

• New Sepsis Definitions
  – Change practice?

• CMS sepsis measure
  – History

• The 3 hour components:
  – Antibiotics therapy
  – Source control
  – Risk Stratification
  – Lactate levels
  – Repeat lactate

• The shock components

• Fluid therapy
  – The fluid bolus
  – LR vs. NS
  – Outcome evidence

• Vasopressor use
  – Best endpoint
  – Fluid or pressors

• Perfusion Assessment
  – Tools

• Steroid Use

• SEP-1 Outcomes
The Burden of Sepsis?
$33.164 Billion/year.

8.7% of aggregate hospital costs.

Most expensive hospital admission for all party payer's.

#1 cause of ICU admission for the elderly.

Leading cause of in-hospital mortality.

Most common cause of hospital readmission.
The Morbidity Impact
Morbidity or Disabilities

Psychiatric Disease

Disabilities (Amputations)

Chronic Lung Disease (ARDS)

Neuromuscular Disorders

Chronic Heart Failure

Kidney Failure and Dialysis
Sepsis-Associated 30-Day Risk-Standardized Readmissions: Analysis of a Nationwide Medicare Sample*

Brett C. Norman, MD¹,²; Colin R. Cooke, MD, MSc, MS³⁻⁵; E. Wes Ely, MD, MPH¹,⁶⁻⁸; John A. Graves, PhD²

**TABLE 4. Readmission Rates by Quartile of Composite All-Cause Mortality Measurement**

<table>
<thead>
<tr>
<th>Composite Mortality Score—Higher Mortality by Increasing Quartile</th>
<th>Mean Risk-Standardized Readmission Rates (%)</th>
<th>p &lt; 0.001</th>
</tr>
</thead>
<tbody>
<tr>
<td>First quartile</td>
<td>30.7</td>
<td></td>
</tr>
<tr>
<td>Second quartile</td>
<td>29.9</td>
<td></td>
</tr>
<tr>
<td>Third quartile</td>
<td>29.0</td>
<td></td>
</tr>
<tr>
<td>Fourth quartile</td>
<td>28.7</td>
<td></td>
</tr>
</tbody>
</table>
What is Sepsis?:
The Early Pathogenesis
Sepsis: A Complex and Dynamic Landscape

Systemic Inflammatory Response Syndrome (SIRS)
A clinical response arising from a nonspecific insult, including ≥ 2 of the following:

- Temperature ≥38°C or ≤36°C
- HR ≥90 beats/min
- Respirations ≥20/min
- WBC count ≥12,000/mm³ or ≤4,000/mm³ or >10% bands
- PaCO₂ < 32mmHg

Resolution of local inflammation

OR and Recovery
The Landscape of Sepsis Care
In 1997
115 million visits/year.

2.9% of hospital admits are severe sepsis and septic shock.

- 1,600,000 admissions per year through the ED.

ED waiting times (5-6 hours) approaching 24 hours.

Impact of delayed transfer of critically ill patients from the emergency department to the intensive care unit

Donald B. Chaffin, MD, MS, FCCM; Stephen Trzeciak, MD, MPH; Antonios Likourezos, MA, MPH; Brigitte M. Baumann, MD, MSCE; R. Phillip Dellinger, MD, FCCM; for the DELAY-ED study group

(Crit Care Med 2007; 35:1477–1483)

- 67 minute delay to ICU arrival.#
- 3 fold increase in mortality.

67 minute delay to ICU arrival.

3 fold increase in mortality.

After ICU Admission:

- > 6 hour total delay for hemodynamic optimization.
- ICU is poor

Shock mortality rate:

- ICU - 24% to 70%.

A Need to Change the Paradigm of Current Sepsis Management
Emergency department overcrowding in the United States: an emerging threat to patient safety and public health

S Trzeciak, E P Rivers

<table>
<thead>
<tr>
<th>Condition</th>
<th>Cases/year</th>
<th>Mortality (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke</td>
<td>591,996</td>
<td>6-7</td>
</tr>
<tr>
<td>AMI</td>
<td>540,891</td>
<td>10</td>
</tr>
<tr>
<td>Trauma</td>
<td>697,025</td>
<td>5-16</td>
</tr>
<tr>
<td>Sepsis</td>
<td>859,858</td>
<td>15-20</td>
</tr>
<tr>
<td>Severe Sepsis</td>
<td>791,000</td>
<td>27-40</td>
</tr>
<tr>
<td>Septic Shock</td>
<td>200,000</td>
<td>36-47</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>1,187,180</td>
<td>5-9</td>
</tr>
</tbody>
</table>
What About Guidelines for Sepsis?
Suspected infection and document source within 2 h

The high-risk patient: blood pressure < 90 mm Hg after 20-40 mL/kg volume challenge or lactic acid > 4 mmol/L

Antibiotics within 1 h and source control

CVP

< 8 mm Hg

Crystalloid

> 8-12 mm Hg

> 12 mm Hg

Decrease O₂ consumption

MAP

< 65 or

> 90 mm Hg

Vasoactive agent(s)

ScvO₂

< 70%

Packed red blood cells to Hct > 30%

< 70%

Inotrope(s)

> 70%

No

Goals achieved
Changing the Landscape
Systems Approach To Poor Sepsis Care

Recognition of poor sepsis care in the US ED’s
Early Recognition (SIRS) + Risk Stratification (Lactate)
Cultures, Antibiotics and Source Control
Recognition of Global Tissue Hypoxia and Cryptic Shock
Hemodynamic Optimization and Immuno modulation
Continuous Quality Improvement
1. Measure lactate
2. Blood cultures/appropriate cultures
3. Give broad spectrum antibiotics
4. Fluid Challenge of 30 cc/kg if (hypotension/lactate > 4mM/L)

5. If persistent hypotension
   - vasopressor to maintain MAP > 65 mmHg

6. Document perfusion:

   "Sepsis focused exam completed."
   or
   "I performed a reassessment of perfusion (or volume) status."

   You don't even need to provide vitals.
   This QNet webpage offers further guidance if need.
   https://cms-ip.custhelp.com/app/answers/detail/a_id/165223

7. Re-measure lactate within 6 hours
The Fundamental Evidence for the SEP-1 Bundle Components
The Origin of SIRS

SIRS is diagnosed when two or more of the following are present:
1. Fever >38°C or temperature <36°C
2. Heart rate >90 beats per minute (not appropriate in children)
3. Respiratory rate >20 breaths per minute or a PaCO₂ <4.3 kPa (32 mm Hg)
4. White blood cell count <4 x 10⁹ cells/L or >12 x 10⁹ cells/L or >10% bands

1991
### SIRS in the Emergency Department

**Table 2.** Linear Trends of ED LOS and Cost, Hospital Admissions, Hospital LOS and Total Inpatient Costs by Number of SIRS Criteria and Pairwise Comparisons within ED LOS and Cost, Hospital LOS and Total Inpatient Cost by Number of SIRS Criteria

<table>
<thead>
<tr>
<th>Number of SIRS Criteria (SC)</th>
<th>N</th>
<th>ED LOS Hours (SD)</th>
<th>ED Cost Dollars (SD)</th>
<th>Hospital Admissions N</th>
<th>Hospital LOS Days (SD)</th>
<th>Inpatient Cost Dollars (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 Criteria</td>
<td>395 (39.9)</td>
<td>5.8 (4.7)</td>
<td>351 (289)</td>
<td>44 (11.1)</td>
<td>3.8 (2.7)</td>
<td>10,996 (11,992)</td>
</tr>
<tr>
<td>1 Criteria</td>
<td>349 (35.2)</td>
<td>6.3 (4.6)</td>
<td>396 (276)</td>
<td>57 (16.3)</td>
<td>5.1 (5.6)</td>
<td>11,882 (15,727)</td>
</tr>
<tr>
<td>2 Criteria</td>
<td>175 (17.6)</td>
<td>8.0 (6.1)</td>
<td>448 (34)</td>
<td>59 (33.7)</td>
<td>7.5 (12.6)</td>
<td>16,214 (19,518)</td>
</tr>
<tr>
<td>3 Criteria</td>
<td>62 (6.3)</td>
<td>8.0 (5.4)</td>
<td>454 (59)</td>
<td>35 (56.5)</td>
<td>10.0 (10.6)</td>
<td>25,681 (39,343)</td>
</tr>
<tr>
<td>4 Criteria</td>
<td>10 (1.0)</td>
<td>8.6 (6.0)</td>
<td>606 (192)</td>
<td>8 (80.0)</td>
<td>11.4 (14.1)</td>
<td>43,973 (78,221)</td>
</tr>
</tbody>
</table>

*P*-value for Linear Trend: ≤0.0001 ≤0.001 ≤0.001 ≤0.01 ≤0.01

ED, emergency department; LOS, length of stay; SC, SIRS Criteria; SD, standard deviation.

Importance of Documentation
Pneumonia and Creatinine of 4.2 mg/dl is Severe Sepsis
### SIRS due to pneumonia (without documentation of sepsis)

<table>
<thead>
<tr>
<th>Example 1</th>
<th>Example 2</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PDX</strong></td>
<td><strong>PDX</strong></td>
</tr>
<tr>
<td>J18.9</td>
<td>A41.9</td>
</tr>
<tr>
<td><strong>SDX</strong></td>
<td><strong>SDX</strong></td>
</tr>
<tr>
<td></td>
<td>J18.9</td>
</tr>
<tr>
<td><strong>DRG</strong></td>
<td><strong>DRG</strong></td>
</tr>
<tr>
<td>195</td>
<td>871</td>
</tr>
<tr>
<td><strong>Pneumonia W/O CC/MCC</strong></td>
<td><strong>Sepsis W MCC</strong></td>
</tr>
<tr>
<td>RW: 0.71</td>
<td>RW: 1.79</td>
</tr>
<tr>
<td>GLOS 2.8</td>
<td>GLOS 5</td>
</tr>
<tr>
<td>$4,970*</td>
<td>$12,548*</td>
</tr>
</tbody>
</table>

*Base rate of $7000 used for illustrative purposes

PDX: Principal diagnosis
SDX: Secondary diagnosis
DRG: Diagnostic related group

### Sepsis due to pneumonia

MCC: Major complication or comorbidity
CC: Complication or comorbidity
GLOS: Geometric mean length of stay
RW: Relative weight
Assessment of Clinical Criteria for Sepsis For the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3)

Christopher W. Seymour, MD, MSc; Vincent X. Liu, MD, MSc; Theodore J. Iwashyna, MD, PhD; Frank M. Brunkhorst, MD; Thomas D. Rea, MD, MPH; André Scherag, PhD; Gordon Rubenfeld, MD, MSc; Jeremy M. Kahn, MD, MSc; Manu Shankar-Hari, MD, MSc; Mervyn Singer, MD, FRCP; Clifford S. Deutschman, MD, MS; Gabriel J. Escobar, MD; Derek C. Angus, MD, MPH

JAMA  February 23, 2016  Volume 315, Number 8
qSOFA

Hypotension
Systolic BP <100 mmHg

Altered
Mental Status

Tachypnea
RR >22/Min

Score of 22 Criteria Suggests a Greater Risk of a Poor Outcome
A Comparison of the Quick-SOFA and Systemic Inflammatory Response Syndrome Criteria for the Diagnosis of Sepsis and Prediction of Mortality
A Systematic Review and Meta-Analysis

Rodrigo Serafim, MD; José Andrade Gomes, MD; Jorge Salluh, MD, PhD; and Pedro Póvoa, MD, PhD

CHEST 2018; 153(3):646-655
### Mortality

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>qSOFA Mean</th>
<th>qSOFA SD</th>
<th>Total</th>
<th>Mean</th>
<th>SIRS Mean</th>
<th>SIRS SD</th>
<th>Total</th>
<th>Weight</th>
<th>Std. Mean Difference IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>April, 2017</td>
<td>0.66</td>
<td>2.61</td>
<td>214</td>
<td>0.65</td>
<td>2.61</td>
<td>214</td>
<td>0.7%</td>
<td></td>
<td>0.00 (-0.19 to 0.19)</td>
</tr>
<tr>
<td>Churpek, 2017</td>
<td>0.69</td>
<td>1.34</td>
<td>30,677</td>
<td>0.65</td>
<td>1.34</td>
<td>30,677</td>
<td>31.9%</td>
<td></td>
<td>0.03 (0.01 to 0.05)</td>
</tr>
<tr>
<td>Finkelszttein, 2017</td>
<td>0.74</td>
<td>0.47</td>
<td>152</td>
<td>0.59</td>
<td>0.5</td>
<td>152</td>
<td>0.5%</td>
<td></td>
<td>0.31 (0.08 to 0.53)</td>
</tr>
<tr>
<td>Freund, 2017</td>
<td>0.8</td>
<td>1.59</td>
<td>879</td>
<td>0.65</td>
<td>0.83</td>
<td>879</td>
<td>2.8%</td>
<td></td>
<td>0.12 (0.02 to 0.21)</td>
</tr>
<tr>
<td>Park, 2017</td>
<td>0.733</td>
<td>1.54</td>
<td>1,009</td>
<td>0.59</td>
<td>1.46</td>
<td>1,009</td>
<td>3.2%</td>
<td></td>
<td>0.09 (0.00 to 0.18)</td>
</tr>
<tr>
<td>Raith, 2017</td>
<td>0.607</td>
<td>0.88</td>
<td>184,875</td>
<td>0.58</td>
<td>0.88</td>
<td>184,875</td>
<td>42.6%</td>
<td></td>
<td>0.03 (0.02 to 0.04)</td>
</tr>
<tr>
<td>Williams, 2017</td>
<td>0.73</td>
<td>0.48</td>
<td>8,871</td>
<td>0.72</td>
<td>0.48</td>
<td>8,871</td>
<td>18.3%</td>
<td></td>
<td>0.02 (-0.01 to 0.05)</td>
</tr>
</tbody>
</table>

**Total (95% CI)**

- qSOFA: 226,677
- SIRS: 226,677
- Mean: 100.0%
- Std. Mean Difference: 0.03 (0.02 to 0.05)

**Heterogeneity**
- Tau^2 = 0.00
- Chi^2 = 11.39, df = 6 (P = .08)
- I^2 = 47%

**Test for overall effect**
- Z = 4.12 (P < .0001)

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**Figure 4** - *Forest plot of mortality.* Effects measure = risk ratio; analysis model = random effects; statistical method = I^2 heterogeneity. The “diamond” at the bottom represents the 95% CI. IV = initialization vector; qSOFA = quick Sepsis-related Organ Failure Assessment; SIRS = systemic inflammatory response syndrome; Std = standard.
<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Mean</th>
<th>SD</th>
<th>Total</th>
<th>Mean</th>
<th>SD</th>
<th>Total</th>
<th>Weight</th>
<th>Std. Mean Difference IV, Random, 95% CI</th>
<th>Std. Mean Difference IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Churpek, 2017</td>
<td>0.88</td>
<td>0.45</td>
<td>30,677</td>
<td>0.38</td>
<td>0.45</td>
<td>30,677</td>
<td>14.4%</td>
<td>1.11 (1.09 to 1.13)</td>
<td></td>
</tr>
<tr>
<td>Donnelly, 2017</td>
<td>0.54</td>
<td>0.02</td>
<td>2,593</td>
<td>0.12</td>
<td>0.26</td>
<td>2,593</td>
<td>14.3%</td>
<td>2.28 (2.21 to 2.35)</td>
<td></td>
</tr>
<tr>
<td>Dorsett, 2017</td>
<td>0.39</td>
<td>0.5</td>
<td>152</td>
<td>0.16</td>
<td>0.38</td>
<td>152</td>
<td>14.2%</td>
<td>0.52 (0.29 to 0.75)</td>
<td></td>
</tr>
<tr>
<td>Freund, 2017</td>
<td>0.74</td>
<td>0.45</td>
<td>879</td>
<td>0.25</td>
<td>0.45</td>
<td>879</td>
<td>14.3%</td>
<td>1.09 (0.99 to 1.19)</td>
<td></td>
</tr>
<tr>
<td>Raiith, 2017</td>
<td>0.86</td>
<td>0.11</td>
<td>184,875</td>
<td>0.54</td>
<td>0.11</td>
<td>184,875</td>
<td>14.4%</td>
<td>2.91 (2.90 to 2.92)</td>
<td></td>
</tr>
<tr>
<td>Siddiqui, 2017</td>
<td>0.62</td>
<td>0.47</td>
<td>58</td>
<td>0.42</td>
<td>0.51</td>
<td>58</td>
<td>14.0%</td>
<td>0.41 (0.04 to 0.77)</td>
<td></td>
</tr>
<tr>
<td>Williams, 2017</td>
<td>0.47</td>
<td>0.48</td>
<td>8,871</td>
<td>0.1</td>
<td>0.34</td>
<td>8,871</td>
<td>14.4%</td>
<td>0.89 (0.86 to 0.92)</td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>228,105</strong></td>
<td></td>
<td><strong>228,105</strong></td>
<td></td>
<td><strong>100.0%</strong></td>
<td></td>
<td><strong>1.32 (0.40 to 2.24)</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: $\tau^2 = 1.53$; $\text{Chi}^2 = 43948.08$, df = 6 ($P < .00001$); $I^2 = 100\%$
Test for overall effect: $Z = 2.81$ ($P = .005$)

Figure 5 – Forest plot of sensitivity for **diagnosis of sepsis**. Effects measure = risk ratio; analysis model = random effects; statistical method = $I^2$ heterogeneity. The “diamond” at the bottom represents the 95% CI. See Figure 4 legend for expansion of abbreviations.
Conclusions

The SIRS was more sensitive and significantly superior to the qSOFA for sepsis diagnosis, and the qSOFA was better than the SIRS for prediction of inhospital mortality. Considering the present results, future studies should focus on the prospective evaluation of more homogeneous methodologies comparing both criteria as a part of the decision-making process for clinicians caring for septic patients.
qSOFA does not replace SIRS in the definition of sepsis

Jean-Louis Vincent¹*, Greg S. Martin² and Mitchell M. Levy³
As opposed to early identification, the proposed task force definitions may delay the diagnosis of sepsis until patients are much sicker. Although the task force’s definition structure may identify patients with the highest likelihood of poor outcomes, it does not clearly identify patients in the early stages of sepsis when rapid resuscitation provides the greatest patient benefit and improves survival. A change to the existing definition could disrupt the 15-year trend toward further reduction in sepsis mortality. Prior to changing the widespread and understood definitions used in SEP-1, rigorous clinical investigation will be required of the task force’s proposed definitions. In the coming years, CMS will track the research and field testing that the proposed definitions will inspire.

Sean R. Townsend, MD  
Emanuel Rivers, MD, MPH  
Lemeneh Tefera, MD, MSc

Author Affiliations: California Pacific Medical Center, San Francisco (Townsend); Department of Emergency Medicine, Henry Ford Hospital, Detroit, Michigan (Rivers); Quality Measurement and Value-Based Incentives Group, Centers for Medicare & Medicaid Services, Baltimore, Maryland (Tefera).
Physical Examination in Sepsis
<table>
<thead>
<tr>
<th>Signs</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Postural hypotension</td>
<td>29</td>
<td>81</td>
</tr>
<tr>
<td>2. Skin, mucous membranes</td>
<td>85</td>
<td>58</td>
</tr>
<tr>
<td>3. Mental status</td>
<td>57</td>
<td>73</td>
</tr>
<tr>
<td>4. Capillary refill</td>
<td>34</td>
<td>95</td>
</tr>
</tbody>
</table>

(JAMA 1999; 281:1027)
Fig. 3. (A) Normal capillary refill time of less than 3.5 seconds. (B) Abnormal capillary refill time of greater than 5 seconds.
RESEARCH ARTICLE

Capillary refill time during fluid resuscitation in patients with sepsis-related hyperlactatemia at the emergency department is related to mortality

Barbara Lara¹, Luis Enberg¹, Marcos Ortega², Paula Leon², Cristobal Krippper¹, Pablo Aguilera¹, Eduardo Kattan², Ricardo Castro², Jan Bakker²,⁴,⁵, Glenn Hernandez²*

¹ Programa de Medicina de Urgencia, Facultad de Medicina, Pontificia Universidad Católica de Chile, Santiago, Chile, ² Departamento de Medicina Intensiva, Facultad de Medicina, Pontificia Universidad Católica de Chile, Santiago, Chile, ³ Erasmus MC University Medical Center, Dept. Intensive Care Adults, Rotterdam, CA, The Netherlands, ⁴ Division of Pulmonary, Allergy, and Critical Care Medicine, Department of Medicine, Columbia University Medical Center, New York, NY, United States of America, ⁵ Division of Pulmonary, and Critical Care Medicine, New York University—Langone, New York, NY, United States of America

PLOS ONE | https://doi.org/10.1371/journal.pone.0188548  November 27, 2017
Table 3. Physiologic parameters and outcomes of patients with abnormal CRT at admission according to CRT status after initial fluid resuscitation.

<table>
<thead>
<tr>
<th>Physiologic parameters after FR and outcomes</th>
<th>Normal CRT After FR N:23</th>
<th>Abnormal CRT after FR N:6</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (bpm)</td>
<td>97 ± 14</td>
<td>99 ± 23</td>
<td>0.91</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>122 ± 30</td>
<td>101 ± 26</td>
<td>0.22</td>
</tr>
<tr>
<td>Mean arterial pressure (mmHg)</td>
<td>83 ± 20</td>
<td>76 ± 23</td>
<td>0.45</td>
</tr>
<tr>
<td>Respiratory rate (bpm)</td>
<td>24 ± 5</td>
<td>23 ± 7</td>
<td>0.48</td>
</tr>
<tr>
<td>Temperature (°C)</td>
<td>37 ± 1</td>
<td>36 ± 0.7</td>
<td>0.05</td>
</tr>
<tr>
<td>Capillary refill time (seconds)</td>
<td>2.3 ± 0.6</td>
<td>6.1 ± 3.2</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Lactate (mmol/L)</td>
<td>3.4 ± 2.4</td>
<td>11 ± 7</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>SOFA day 1</td>
<td>4[2–6]</td>
<td>9[9–10]</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>MV</td>
<td>2 (9%)</td>
<td>4 (67%)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>MV [days]</td>
<td>2.5 [1–4]</td>
<td>2.5 [1–15.5]</td>
<td>0.80</td>
</tr>
<tr>
<td>ICU admission</td>
<td>4 (17%)</td>
<td>5 (83%)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>ICU length of stay (days)</td>
<td>2[1.5–5.5]</td>
<td>6[1–20]</td>
<td>0.64</td>
</tr>
<tr>
<td>Need of RRT</td>
<td>0 (0%)</td>
<td>2 (33%)</td>
<td>0.04</td>
</tr>
<tr>
<td>Hospital length of stay (days)</td>
<td>9[5–11]</td>
<td>12.5[1–35]</td>
<td>0.53</td>
</tr>
<tr>
<td>Hospital mortality</td>
<td>2 (9%)</td>
<td>4 (67%)</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>
SvO₂ 60% was significantly correlated with knee mottling and high CVP indicating myocardial dysfunction.
Mottling score predicts survival in septic shock

Mottling score

5

4

3

2

1

SCORE 2

SCORE 4
Antibiotic Therapy
Empiric Antibiotic Treatment Reduces Mortality in Severe Sepsis and Septic Shock From the First Hour: Results From a Guideline-Based Performance Improvement Program

Ricard Ferrer, MD, PhD; Ignacio Martin-Loeches, MD, PhD; Gary Phillips, MAS; Tiffany M. Osborn, MD, MPH; Sean Townsend, MD; R. Phillip Dellinger, MD, FCCP, FCCM; Antonio Artigas, MD, PhD; Christa Schorr, RN, MSN; Mitchell M. Levy, MD, FCCP, FCCM

Crit Care Med, 2014
Empiric Antibiotic Treatment Reduces Mortality in Severe Sepsis and Septic Shock From the First Hour: Results From a Guideline-Based Performance Improvement Program

Ricard Ferrer, MD, PhD; Ignacio Martin-Loeches, MD, PhD; Gary Phillips, MAS; Tiffany M. Osborn, MD, MPH; Sean Townsend, MD; R. Phillip Dellinger, MD, FCCP, FCCM; Antonio Artigas, MD, PhD; Christa Schorr, RN, MSN; Mitchell M. Levy, MD, FCCP, FCCM

<table>
<thead>
<tr>
<th>Time to Antibiotics (Hr)</th>
<th>OR*</th>
<th>95% CI</th>
<th>p</th>
<th>Probability of Mortality (%)b</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–1^c</td>
<td>1.00</td>
<td>0.97–1.18</td>
<td>0.165</td>
<td>24.6</td>
<td>23.2–26.0</td>
</tr>
<tr>
<td>1–2</td>
<td>1.07</td>
<td>0.97–1.18</td>
<td>0.165</td>
<td>25.9</td>
<td>24.5–27.2</td>
</tr>
<tr>
<td>2–3</td>
<td>1.14</td>
<td>1.02–1.26</td>
<td>0.021</td>
<td>27.0</td>
<td>25.3–28.7</td>
</tr>
<tr>
<td>3–4</td>
<td>1.19</td>
<td>1.04–1.35</td>
<td>0.009</td>
<td>27.9</td>
<td>25.6–30.1</td>
</tr>
<tr>
<td>4–5</td>
<td>1.24</td>
<td>1.06–1.45</td>
<td>0.006</td>
<td>28.8</td>
<td>25.9–31.7</td>
</tr>
<tr>
<td>5–6</td>
<td>1.47</td>
<td>1.22–1.76</td>
<td>&lt;0.001</td>
<td>32.3</td>
<td>28.5–36.2</td>
</tr>
<tr>
<td>&gt;6</td>
<td>1.52</td>
<td>1.36–1.70</td>
<td>&lt;0.001</td>
<td>33.1</td>
<td>30.9–35.3</td>
</tr>
</tbody>
</table>

8.5% Increase in Mortality
Increased Time to Initial Antimicrobial Administration Is Associated With Progression to Septic Shock in Severe Sepsis Patients

Bristol B. Whiles, BS¹; Amanda S. Deis, MS¹; Steven Q. Simpson, MD²

(Crit Care Med 2017; 45:623–629)
Figure 1. Temperature and crude mortality all patients, 35°C = 95°F, 36°C = 96.8°F, 37°C = 98.6°F, 38°C = 100.4°F, 39°C = 102.2°F, 40°C = 104°F, 41°C = 105.8°F.
The Absence of Fever Is Associated With Higher Mortality and Decreased Antibiotic and IV Fluid Administration in Emergency Department Patients With Suspected Septic Shock

Daniel J. Henning, MD, MPH; Jeremy R. Carey, MD; Kimie Oedorf, BSc; Danielle E. Day, BSc; Colby S. Redfield, MD; Colin J. Huguenel, MD; Jonathan C. Roberts, MD; Leon D. Sanchez, MD, MPH; Richard E. Wolfe, MD; Nathan I. Shapiro, MD, MPH

Critical Care Medicine, 2017

**TABLE 4. Results From the Multivariable Logistic Regression Model Predicting Mortality**

<table>
<thead>
<tr>
<th>Covariate</th>
<th>OR</th>
<th>95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Afebrile</td>
<td>4.29</td>
<td>2.24–8.23</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Tachypnea &gt; 24 breaths/min</td>
<td>2.14</td>
<td>1.12–4.07</td>
<td>0.02</td>
</tr>
<tr>
<td>Bicarbonate &lt; 20 mEq/L</td>
<td>2.31</td>
<td>1.21–4.41</td>
<td>0.01</td>
</tr>
<tr>
<td>Lactate (mmol/L)</td>
<td>1.42</td>
<td>1.23–1.64</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>No emergency department antibiotics</td>
<td>0.26</td>
<td>0.09–0.80</td>
<td>0.02</td>
</tr>
<tr>
<td>Total IV fluids (L)</td>
<td>0.69</td>
<td>0.57–0.85</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

Area under the curve = 0.83 (95% CI, 0.78–0.88)  
Hosmer-Lemeshow $\chi^2 = 6.24$ ($p = 0.62$)

OR = odds ratio.
### TABLE 1. (Continued). Distribution of Risk Factors by Temperature Strata

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>&lt; 37°C (98.6°F)</th>
<th>37–38.29°C (98.6–100.92°F)</th>
<th>38.3–39.49°C (100.9–103.1°F)</th>
<th>≥ 39.5°C (103.1°F)</th>
<th>( p^* )</th>
<th>Missing Temperature</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quality of care % achieved</td>
<td>35 (13)</td>
<td>42 (10)</td>
<td>50 (9)</td>
<td>59 (9)</td>
<td>&lt; 0.001</td>
<td>41 (29)</td>
</tr>
<tr>
<td>Time to antibiotics (median, IQR)</td>
<td>1 hr 44 min, 43 min to 3 hr 20 min (13)</td>
<td>1 hr 14 min, 35 min to 2 hr 35 min (10)</td>
<td>1 hr 0 min, 26 min to 2 hr 0 min (10)</td>
<td>49 min, 22 min to 1 hr 47 min (9)</td>
<td>0.0001</td>
<td>1 hr 27 min, 40 min to 3 hr 35 min (29)</td>
</tr>
<tr>
<td>AB within 1 hr</td>
<td>70 (13)</td>
<td>80 (10)</td>
<td>87 (9)</td>
<td>87 (9)</td>
<td>&lt; 0.001</td>
<td>73 (29)</td>
</tr>
<tr>
<td>AB within 3 hr</td>
<td>90 (11)</td>
<td>95 (9)</td>
<td>96 (9)</td>
<td>96 (8)</td>
<td>&lt; 0.001</td>
<td>93 (27)</td>
</tr>
<tr>
<td>BC before AB(^c)</td>
<td>81 (6)</td>
<td>77 (7)</td>
<td>84 (6)</td>
<td>87 (8)</td>
<td>0.008</td>
<td>78 (22)</td>
</tr>
<tr>
<td>IV fluids within 1 hr(^c)</td>
<td>72</td>
<td>78</td>
<td>77</td>
<td>81</td>
<td>0.02</td>
<td>66</td>
</tr>
<tr>
<td>Lactate or base excess in 1h measured</td>
<td>65</td>
<td>67</td>
<td>71</td>
<td>76</td>
<td>0.003</td>
<td>61</td>
</tr>
<tr>
<td>Lactate within 1 hr</td>
<td>25 (24)</td>
<td>32 (20)</td>
<td>39 (19)</td>
<td>43 (19)</td>
<td>&lt; 0.001</td>
<td>33 (45)</td>
</tr>
<tr>
<td>Bundle 1 hr–optimal score(^c)</td>
<td>7 (14)</td>
<td>8 (11)</td>
<td>8 (10)</td>
<td>7 (9)</td>
<td>0.84</td>
<td>10 (14)</td>
</tr>
</tbody>
</table>

Treatment limitations % of patients (missing values, %)

| At 48 hr | 18 (5) | 14 (5) | 12 (5) | 10 (5) | 0.004 | 20 (10) |
# Delayed Second Dose Antibiotics for Patients Admitted From the Emergency Department With Sepsis: Prevalence, Risk Factors, and Outcomes

Daniel Leisman, BS\textsuperscript{a,2}; Victor Huang, MD\textsuperscript{1}; Qiuping Zhou, DO\textsuperscript{1}; Jeanie Gribben, BS\textsuperscript{1}; Andrea Bianculli, BS\textsuperscript{1}; Michelle Bernshteyn, BS\textsuperscript{3}; Mary Frances Ward, RN, MS, ANP\textsuperscript{4,5}; Sandra M. Schneider, MD\textsuperscript{1,6}

Critical Care Medicine, 2017

## TABLE 3. Summary of Adjusted Regression (Exploratory) Analyses Evaluating Major Delay in Second Antibiotic Administration as a Predictor of Patient Outcomes

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Regression Type</th>
<th>Model Fit</th>
<th>Model Output</th>
<th>Effect Size</th>
<th>95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary outcome</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mortality\textsuperscript{a}</td>
<td>Logistic</td>
<td>$\chi^2 = 5.9; p = 0.65$</td>
<td>OR</td>
<td>1.61</td>
<td>1.01–2.57</td>
<td>0.046</td>
</tr>
<tr>
<td><strong>Secondary outcomes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospital length of stay\textsuperscript{b}</td>
<td>Cox</td>
<td>–</td>
<td>Inverse hazard ratio</td>
<td>1.16</td>
<td>0.97–1.39</td>
<td>0.11</td>
</tr>
<tr>
<td>ICU admission\textsuperscript{c}</td>
<td>Logistic</td>
<td>$\chi^2 = 5.9; p = 0.66$</td>
<td>OR</td>
<td>1.49</td>
<td>0.92–2.40</td>
<td>0.103</td>
</tr>
<tr>
<td>Mechanical ventilation after second antibiotic dose\textsuperscript{d}</td>
<td>Logistic</td>
<td>$\chi^2 = 4.2; p = 0.84$</td>
<td>OR</td>
<td>2.44</td>
<td>1.27–4.69</td>
<td>0.007</td>
</tr>
</tbody>
</table>
Importance of Blood Cultures and Adequacy of Antibiotics
Initiation of Inappropriate Antimicrobial Therapy Results in a 5-Fold 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 and Dan Chateau

Chest: Prepublished online August 20, 2009; DOI 10.1378/chest.09-0087
The Importance of Source Control
Source control in the management of severe sepsis and septic shock: An evidence-based review

John C. Marshall, MD; Ronald V. Maler, MD, FACS; Maria Jimenez, MD; E. Patchen Dellinger, MD

Crit Care Med, 2004

Table 1
Core elements of source control

<table>
<thead>
<tr>
<th>Core element</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drainage</td>
<td>The evacuation of infected fluid through the opening of an abscess, by incision or by the insertion of a drain. Drainage converts a closed abscess into a controlled sinus or fistula.</td>
</tr>
<tr>
<td></td>
<td>Incision and drainage of an ischiorectal abscess</td>
</tr>
<tr>
<td></td>
<td>Percutaneous drainage of a diverticular abscess</td>
</tr>
<tr>
<td></td>
<td>Open surgical drainage of a subphrenic abscess</td>
</tr>
<tr>
<td>Debridement</td>
<td>The removal of devitalized or infected solid tissue</td>
</tr>
<tr>
<td></td>
<td>Wet-to-dry dressings of an infected surgical wound</td>
</tr>
<tr>
<td></td>
<td>Surgical excision of infected pancreatic necrosis</td>
</tr>
<tr>
<td></td>
<td>Excision of gangrenous soft tissue or intestine</td>
</tr>
<tr>
<td>Device removal</td>
<td>The removal of a prosthetic device that has become colonized by microorganisms living in a biofilms</td>
</tr>
<tr>
<td></td>
<td>Removal of an infected central venous or urinary catheter</td>
</tr>
<tr>
<td></td>
<td>Excision of an infected vascular graft</td>
</tr>
<tr>
<td></td>
<td>Replacement of an endotracheal tube by a tracheostomy tube</td>
</tr>
<tr>
<td>Definitive measures</td>
<td>Other interventions performed to remove a focus of infection and to restore optimal function and quality of life</td>
</tr>
<tr>
<td></td>
<td>Excision of diverticular disease and restoration of intestinal continuity</td>
</tr>
<tr>
<td></td>
<td>Decortication following drainage of an empyema</td>
</tr>
<tr>
<td></td>
<td>Repair of an abdominal wall hernia following treatment of peritonitis</td>
</tr>
</tbody>
</table>
Surgical delay is a critical determinant of survival in perforated peptic ulcer

Original article

D. L. Buck¹, M. Vester-Andersen² and M. H. Møller³ on behalf of the Danish Clinical Register of Emergency Surgery

Every hour of delay from admission to surgery was associated with an adjusted 2.4% decreased probability of survival compared with the previous hour.
Risk Stratification for Early Detection of High Risk Patients:

Changing the way we detect illness severity
Emergency Department Hypotension Predicts Sudden Unexpected In-hospital Mortality*
A Prospective Cohort Study

Alan E. Jones, MD; Vasileios Yianoulis, BS; Charles Johnson, BS; and Jeffrey A. Kline, MD

In-Hospital Mortality in Septic Patients
By Hypotension Nadir

- < 80: 15.8%
- 80-89: 9.7%
- 90-99: 9.0%
- ≥ 100: 3.6%

Note: Based on data from 700 adults. Source: Dr. Marchick
A Subtle and Deadly Disease Transition
Using a 279 year old definition

ER or Ward

ICU

Mortality (%)

3 7 10 16
No SIRS SIRS2 SIRS3 SIRS4 Sepsis Severe sepsis Septic shock

Blood volume lost

10% 20% 30%

MAP ~ SVR \times CO

SVR

MAP

CO

46
Global Tissue Hypoxia: A More Sensitive Measure of Shock

Glucose → Small amount of energy

Anaerobic metabolism (without oxygen)

Pyruvic acid → Lactic acid

Lactic acid > 4 mM/L

Oxygen Demand

Global Tissue Hypoxia
Where did a Lactate cut point of 4 come from?

56 patients with clinical signs of shock:
- Hypovolemia (17), Sepsis (9), cardiac failure (7), neural dys. & endocrine def. (4), vascular obs. (2), mixed (9), unclassified (8)

Broder G, Weil MH. *Science* 1964;143:1457-1459

Fig. 3. Excess lactate related to the probability of survival of patients in shock.
### Screening for Severe Illness

Infection and Lactate (LA $> 4$ mM/L)

<table>
<thead>
<tr>
<th>#SIRS</th>
<th>SIRS Ward (%)</th>
<th>SIRS + LA Ward (%)</th>
<th>SIRS + LA ICU</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>11.6</td>
<td>33.3</td>
<td>0</td>
</tr>
<tr>
<td>1</td>
<td>14.7</td>
<td>15.4</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>34.6</td>
<td>40.0</td>
<td>62.5</td>
</tr>
<tr>
<td>3</td>
<td>55.4</td>
<td>84.6</td>
<td>94.5</td>
</tr>
<tr>
<td>4</td>
<td>70.0</td>
<td>100</td>
<td>100</td>
</tr>
</tbody>
</table>

≥ 2 of the following is SIRS:
- Temperature $\geq 38^\circ$C or $\leq 36^\circ$C
- HR $\geq 90$ beats/min
- Respirations $\geq 20$/min
- WBC count $\geq 12,000$/mm$^3$ or $\leq 4,000$/mm$^3$
  - or $>10\%$ bands
- PaCO2 $< 32$mmHg

Cryptic Shock
Sudden Cardiopulmonary Complications
ED
Floors
20%
Early Cardiac Arrest in Patients Hospitalized With Pneumonia

A Report From the American Heart Association’s Get With the Guidelines-Resuscitation Program

Gordon E. Carr, MD; Trevor C. Yuen, BA; John F. McConville, MD; John P. Kress, MD, FCCP; Terry L. VandenHoek, MD; Jesse B. Hall, MD, FCCP; and Dana P. Edelson, MD; for the American Heart Association’s Get With the Guidelines-Resuscitation (National Registry of CPR) Investigators*
12.1% of All Cardiac Arrests Are pneumonia
The Hemodynamics of Septic Shock
Increased Metabolic Demands:
Fever, Tachypnea

Hypovolemia, Vasodilation &
Myocardial Depression

Microvascular Alterations:
Impaired Tissue Oxygen Utilization

Cytopathic Tissue Hypoxia

Fink, Crit Care Clin, 2002
Importance of the Fluid Challenge
Patterns and Outcomes Associated With Timeliness of Initial Crystalloid Resuscitation in a Prospective Sepsis and Septic Shock Cohort

Daniel E. Leisman, BS; Chananaya Goldman, MD; Martin E. Doerfler, MD; Kevin D. Masick, PhD; Susan Dries, RN, PhD; Eric Hamilton, BA; Mangala Narasimhan, DO; Gadzhieh Zaidi, MD; Jason A. D’Amore, MD; John K. D’Angelo, MD

Critical Care Medicine, 2017

Increased Fluid Administration in the First Three Hours of Sepsis Resuscitation Is Associated With Reduced Mortality
A Retrospective Cohort Study

Sarah J. Lee, MD, MPH; Kparom Ramay, MBBS, MD; John G. Park, MD, FACP; Omeje Giw; Guangli Li, MD, and Rahul Kashyap, MBBS

CHEST 2014; 146(4):908-915

INFECTION DISEASE/ORIGINAL RESEARCH

Association of Fluid Resuscitation Initiation Within 30 Minutes of Severe Sepsis and Septic Shock Recognition With Reduced Mortality and Length of Stay

Daniel Leisman, BS; Benjamin Wia, BA; Martin Doerfler, MD; Andrea Bianculli, BA; Mary Frances Ward, RN, MS; Meredith Akerman, MS; John K. D’Angelo, MD; Jason A. Zemmel D’Amore, MD

*Corresponding Author. E-mail: deleisman@gmail.com

ORIGINAL ARTICLE

Multicenter Implementation of a Treatment Bundle for Patients with Sepsis and Intermediate Lactate Values

Vincent X. Liu, MD; John W. Morehouse, Jr; Gregory P. Malech, MD; Jay Soule, MD; Thomas Russel, MD; Melinda Skeath, MD; Carmen Adams, MD; Gabriel J. Escobar, MD; and Alan Whippy, MD

1Kaiser Permanente Division of Research, Oakland, California; 2The Permanente Medical Group, Oakland, California; and 3Kaiser Foundation Hospitals and Health Plan, Oakland, California

American Journal of Respiratory and Critical Care Medicine Volume 193 Number 11 | June 1, 2016
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients (hospital)</td>
<td>18,122</td>
<td>8.8</td>
<td>9.3</td>
<td>7.9</td>
<td>0.02</td>
</tr>
<tr>
<td>All patients (30-day)</td>
<td></td>
<td>13.7</td>
<td>14.1</td>
<td>12.6</td>
<td>0.03</td>
</tr>
<tr>
<td>History of heart failure (hospital)</td>
<td>4,144</td>
<td>13.0</td>
<td>14.8</td>
<td>11.6</td>
<td>0.03</td>
</tr>
<tr>
<td>History of heart failure (30-day)</td>
<td></td>
<td>18.8</td>
<td>20.7</td>
<td>17.8</td>
<td>0.13</td>
</tr>
<tr>
<td>History of kidney disease (hospital)</td>
<td>6,285</td>
<td>9.7</td>
<td>11.5</td>
<td>7.5</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>History of kidney disease (30-day)</td>
<td></td>
<td>15.9</td>
<td>17.7</td>
<td>13.3</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Heart failure or kidney disease (hospital)</td>
<td>8,322</td>
<td>10.7</td>
<td>12.5</td>
<td>8.7</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Heart failure or kidney disease (30-day)</td>
<td></td>
<td>16.8</td>
<td>18.3</td>
<td>14.5</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>No heart failure or kidney disease (hospital)</td>
<td>9,800</td>
<td>7.4</td>
<td>6.5</td>
<td>7.2</td>
<td>0.40</td>
</tr>
<tr>
<td>No heart failure or kidney disease (30-day)</td>
<td></td>
<td>11.3</td>
<td>10.5</td>
<td>10.8</td>
<td>0.60</td>
</tr>
</tbody>
</table>
Does the type of fluid matter?
Balanced Crystalloids versus Saline in Critically Ill Adults

Matthew W. Semler, M.D., Wesley H. Self, M.D., M.P.H.,
Jonathan P. Wanderer, M.D., Jesse M. Ehrenfeld, M.D., M.P.H.,
Li Wang, M.S., Daniel W. Byrne, M.S., Joanna L. Stollings, Pharm.D.,
Avinash B. Kumar, M.D., Christopher G. Hughes, M.D.,
Antonio Hernandez, M.D., Oscar D. Guillaume, M.D., M.P.H.,
Addison K. May, M.D., Liza Weavind, M.B., B.Ch., Jonathan D. Casey, M.D.,
Edward D. Siew, M.D., Andrew D. Shaw, M.B., Gordon R. Bernard, M.D.,
and Todd W. Rice, M.D., for the SMART Investigators
and the Pragmatic Critical Care Research Group*
Balanced Crystalloids versus Saline in Critically Ill Adults

Among patients with sepsis, 30-day in-hospital mortality was 25.2% with balanced crystalloids and 29.4% with saline (adjusted odds ratio, 0.80; 95% CI, 0.67 to 0.97; P=0.02).
• All 30 subjects tolerated the entire 30 mL/kg treatment, which took, on average, 47 min.

• In comparing the increase in lactate in the LR group (0.93 mmol/L) to that in the NS group (0.37 mmol/L),

• The difference between groups is 0.56 (95% CI .0.33 to 1.45).
Perfusion Assessment: Adjuncts to Titrating Fluid and Vasoactive Therapy
Volume Responsive Algorithm

Volume Responsive SVV > 13%

YES

NO

Semi-recumbent position

Passive leg raising

Expiration

Controlled Ventilation

Inspiration

Controlled Ventilation
High versus Low Blood-Pressure Target in Patients with Septic Shock

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<table>
<thead>
<tr>
<th>Variable</th>
<th>Low-Target Group (N = 388)</th>
<th>High-Target Group (N = 388)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cumulative fluid intake from day 1 to day 5 — liters</td>
<td>10.0 (5.8–14.0)</td>
<td>10.5 (5.5–14.0)</td>
<td>0.89</td>
</tr>
<tr>
<td>Cumulative urine output from day 1 to day 5 — liters</td>
<td>6.7 (2.9–10.7)</td>
<td>6.9 (2.4–10.7)</td>
<td>0.87</td>
</tr>
<tr>
<td>Cumulative fluid balance from day 1 to day 5 — liters</td>
<td>2.8 (0.0–6.2)</td>
<td>2.4 (0.0–6.0)</td>
<td>0.74</td>
</tr>
<tr>
<td>Median dose of norepinephrine (IQR) — µg/kg/min</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 1</td>
<td>0.45 (0.17–1.21)</td>
<td>0.58 (0.26–1.80)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Day 2</td>
<td>0.16 (0.03–0.48)</td>
<td>0.38 (0.14–0.90)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Day 3</td>
<td>0.02 (0.00–0.16)</td>
<td>0.14 (0.01–0.50)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Day 4</td>
<td>0.00 (0.00–0.05)</td>
<td>0.03 (0.00–0.22)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Day 5</td>
<td>0.00 (0.00–0.03)</td>
<td>0.01 (0.00–0.15)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Duration of catecholamine infusion — days</td>
<td>3.7±3.2</td>
<td>4.7±3.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Primary outcome: death at day 28 — no. (%)</td>
<td>132 (34.0)</td>
<td>142 (36.6)</td>
<td>0.57</td>
</tr>
<tr>
<td>Secondary outcomes — no./total no.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death at day 90‡</td>
<td>164 (42.3)</td>
<td>170 (43.8)</td>
<td>0.74</td>
</tr>
<tr>
<td>Survival at day 28 without organ support‡</td>
<td>241 (62.1)</td>
<td>235 (60.6)</td>
<td>0.66</td>
</tr>
<tr>
<td>Doubling of plasma creatinine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low-Target Group</td>
<td>161 (41.5)</td>
<td>150 (38.7)</td>
<td>0.42</td>
</tr>
<tr>
<td>High-Target Group</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No chronic hypertension</td>
<td>71/215 (33.0)</td>
<td>85/221 (38.5)</td>
<td>0.32</td>
</tr>
<tr>
<td>Chronic hypertension</td>
<td>90/173 (52.0)</td>
<td>65/167 (38.9)</td>
<td>0.02</td>
</tr>
<tr>
<td>Renal-replacement therapy from day 1 to day 7</td>
<td>139 (35.8)</td>
<td>130 (33.5)</td>
<td>0.50</td>
</tr>
<tr>
<td>Low-Target Group</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No chronic hypertension</td>
<td>66/215 (30.7)</td>
<td>77/221 (34.8)</td>
<td>0.36</td>
</tr>
<tr>
<td>Chronic hypertension</td>
<td>73/173 (42.2)</td>
<td>53/167 (31.7)</td>
<td>0.046</td>
</tr>
<tr>
<td>Serious adverse events — no. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any</td>
<td>69 (17.8)</td>
<td>74 (19.1)</td>
<td>0.64</td>
</tr>
<tr>
<td>Acute myocardial infarction</td>
<td>2 (0.5)</td>
<td>7 (1.8)</td>
<td>0.18</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>11 (2.8)</td>
<td>26 (6.7)</td>
<td>0.02</td>
</tr>
<tr>
<td>Ventricular fibrillation or tachycardia</td>
<td>15 (3.9)</td>
<td>22 (5.7)</td>
<td>0.24</td>
</tr>
<tr>
<td>Digital ischemia</td>
<td>9 (2.3)</td>
<td>10 (2.6)</td>
<td>0.82</td>
</tr>
<tr>
<td>Mesenteric ischemia</td>
<td>9 (2.3)</td>
<td>9 (2.3)</td>
<td>1.00</td>
</tr>
<tr>
<td>Bleeding</td>
<td>42 (10.8)</td>
<td>31 (8.0)</td>
<td>0.22</td>
</tr>
</tbody>
</table>
Fluid vs Complications

Complications

Optimal volume

Hypovolemia\textsuperscript{3}  Fluid  Overload\textsuperscript{4,5,6}
CRYSTALLOID LIBERAL OR VASOPRESSORS EARLY RESUSCITATION IN SEPSIS (CLOVERS)

- Optional additional 10 cc/kg fluid bolus and then vasopressors for MAP < 90mmHG
- Additional fluids may be administered for:
  - persistent lactate > 4 mmol/l
  - refractory hypotension after maximizing levophed dosing
  - severe hypotension (MAP < 50 mm hg).
Early Use of Corticosteroids?
Hydrocortisone plus Fludrocortisone for Adults with Septic Shock

Figure 1. 90-Day Survival Distributions.

Shown are survival curves from randomization up to 90 days. The survival rate was significantly higher in the hydrocortisone-plus-fludrocortisone group than in the placebo group.
Early Administration of Hydrocortisone Replacement After the Advent of Septic Shock: Impact on Survival and Immune Response*

Chrysostomos S. Katsanos, MD; Anastasia N. Antonopoulou, MD, PhD; Efterpi N. Apostolidou, MD, PhD; Aikaterini Ioakimidou, MD; Georgia Th. Kalpakou, MD; Metaxia N. Papanikolaou, MD, PhD; Aikaterini C. Pistikli, MD; Margarita C. Mpalla, MD; Michael D. Paraschos, MD; Maria A. Patrani, MD; Maria E. Pratikaki, MD, PhD; Theodoros A. Retsas, MD; Athina A. Savva, MD; Spyridoula D. Vassiliagkou, MD, MSc; Alexandra A. Lekkou, MD, PhD; Ioanna Dimopoulou, MD; Christina Routsi, MD, PhD; Konstantinos E. Mandragos, MD, PhD; on behalf of the Hellenic Sepsis Study Group

(Crit Care Med 2014; 42:1651-1657)

- 14.5% Reduction in Vasopressor Use if Optimized with EGDT
- Hold steroid use until the patient has been resuscitated and endpoints met (6-8 hours)
- CST is optional and consider a baseline cortisol
ScvO2

Oxygen Delivery

Cardiac Output
- Heart Rate
- Stroke Volume

Haemoglobin
- Bleeding
- Haemodilution
- Anaemia

Oxygenation
- SaO2
- FiO2
- Ventilation

Oxygen Consumption

Metabolic Demand
- Fever
- Anxiety
- Pain
- Shivering
- Muscle Activity

Optimal HR

Preload

Afterload

Contractility

Bleeding

Fluid Shifts

Vascular Resistance

Heart Disease
Persistence of Central Venous Oxygen Desaturation During Early Sepsis Is Associated With Higher Mortality
A Retrospective Analysis of the ALBIOS Trial

Alessandro Protti, MD; Serge Masson, PhD; Roberto Latini, MD; Roberto Fumagalli, MD; Marilena Romero, PhD; Carla Pessina, MD; Giovanni Pasetti, MD; Gianni Tognoni, MD; Antonio Pesenti, MD; Luciano Gattinoni, MD; and Pietro Caironi, MD

Chest, 2018
• Trials published more recently that were consistently negative enrolled many subjects with an ScvO$_2$ >70%,

• They could have hardly benefited from early goal-directed therapy because they lacked the condition that was meant to be treated.

• Our own results were positive when referring to subjects with initial ScvO$_2$ < 70%, just as in the first positive trial.

• At the same time, they were negative (no better outcome) when referring to subjects with initial ScvO$_2$ >70%, just as in the subsequent three negative trials.
The Outcomes of Sepsis Guidelines to Health Care Policy
Mortality %

Pre-EGDT  Control  EGDT  2018

30%

The New England Journal of Medicine

EARLY GOAL-DIRECTED THERAPY IN THE TREATMENT OF SEVERE SEPSIS AND SEPTIC SHOCK

EMANUEL RIVERS, M.D., M.P.H., BRYANT NGUYEN, M.D., SUZANNE HAVSTAD, M.A., JULIE RESSLER, B.S., ALEXANDRIA MUZZIN, B.S., BERNHARD KNOLBLICH, M.D., EDWARD PETERSON, PH.D., AND MICHAEL TOMLANOVICH, M.D., FOR THE EARLY GOAL-DIRECTED THERAPY COLLABORATIVE GROUP

November 8, 2001

EGDT after a 20 Years
NEJM, 2001
Nearly 50,000 patients with sepsis treated at 149 New York hospitals.

Compliance with early intravenous, fluids, antibiotics, and other elements of the early-resuscitation bundle increased from 41.5% to 55.2%.

Mortality fell from 30.2% to 25.4%.
An Infection, Unnoticed, Turns Unstoppable
Association Between the New York Sepsis Care Mandate and In-Hospital Mortality for Pediatric Sepsis

Idris V. R. Evans, MD, MSc; Gary S. Phillips, MAS; Elizabeth R. Alpern, MD, MSCE; Derek C. Angus, MD, MPH; Marcus E. Friedrich, MD; Niranjan Kissoon, MD; Stanley Lemeshow, PhD; Mitchell M. Levy, MD; Margaret M. Parker, MD; Kathleen M. Terry, PhD; R. Scott Watson, MD, MPH; Scott L. Weiss, MD, MSCE; Jerry Zimmerman, MD, PhD; Christopher W. Seymour, MD, MSc
1669 Pediatric cases of sepsis reported (59 hospitals)

193 Excluded
   128 Prior admissions for sepsis during the study period
   55 Bundled elements clinically contraindicated
   10 Excluded from protocol, reason not recorded

1476 Eligible cases (59 hospitals)

297 Excluded (protocol not initiated, including all cases from 5 hospitals)

1179 Included in the primary analysis (54 hospitals)
   294 Completed the 1-h bundle within 1 h
   885 Did not complete the 1-h bundle within 1 h

24.9% Compliance
## Association Between the New York Sepsis Care Mandate and In-Hospital Mortality for Pediatric Sepsis

<table>
<thead>
<tr>
<th>Model</th>
<th>Total Deaths/Total No. (%)</th>
<th>Risk-Adjusted In-Hospital Mortality, % (95% CI)</th>
<th>Risk Difference From Adjusted Model, % (95% CI)</th>
<th>Adjusted Odds Ratio for In-Hospital Mortality (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Completed Within 1 h</td>
<td>Not Completed Within 1 h</td>
<td>Completed Within 1 h</td>
<td>Not Completed Within 1 h</td>
</tr>
<tr>
<td>Completion of the entire 1 h bundle within 1 h</td>
<td>22/294 (7.5)</td>
<td>17/885 (13.2)</td>
<td>8.7 (5.4-12.0)</td>
<td>12.7 (10.5-14.7)</td>
</tr>
<tr>
<td>Antibiotics administered within 1 h</td>
<td>89/798 (11.2)</td>
<td>50/381 (13.1)</td>
<td>11.1 (9.1-13.1)</td>
<td>13.2 (9.7-16.6)</td>
</tr>
<tr>
<td>Blood cultures prior to antibiotics completed within 1 h</td>
<td>71/740 (9.6)</td>
<td>68/439 (15.5)</td>
<td>10.7 (8.3-13.0)</td>
<td>13.3 (10.5-16.0)</td>
</tr>
<tr>
<td>Intravenous fluid bolus completed within 1 h</td>
<td>59/548 (10.8)</td>
<td>80/631 (12.7)</td>
<td>11.2 (8.3-14.1)</td>
<td>12.3 (9.6-15.0)</td>
</tr>
</tbody>
</table>
• Measure lactate level. Remeasure if initial lactate is >2 mmol/L.
• Obtain blood cultures prior to administration of antibiotics.
• Administer broad-spectrum antibiotics.
• Begin rapid administration of 30ml/kg crystalloid for hypotension or lactate ≥4 mmol/L.
• Apply vasopressors if patient is hypotensive during or after fluid resuscitation to maintain MAP ≥65 mm Hg.

*“Time zero” or “time of presentation” is defined as the time of triage in the Emergency Department or, if presenting from another care venue, from the earliest chart annotation consistent with all elements of sepsis (formerly severe sepsis) or septic shock ascertained through chart review.

Fig. 1 Hour-1 Surviving Sepsis Campaign Bundle of Care
The Surviving Sepsis Campaign: A Rush to Judgment
Sepsis Guidelines Spark EM Petition

BY RUTH SORELLE, MPH

It took all of one day for emergency physicians to organize opposition after an update to the Surviving Sepsis Campaign Bundle was released online.

The day after the new version was released, Scott D. Weingart, MD, the editor-in-chief of EMCrit (https://emcrit.org), and Josh Farkas, MD, the editor-in-chief of PulmCrit (http://bit.ly/PulmCrit), posted a petition calling for its retraction. Their petition was signed by more than 4,000 people as of press time. (emcrit.org/sscpetition.)

The new bundle, written by Mitchell M. Levy, MD; Laura E. Evans, MD, MSc; and Andrew Rhodes, MBBS, all members of either the Surviving Sepsis Campaign executive or... Continued on page 33
### 2015 Q4 | 2016 Q1 | 2016 Q2

<table>
<thead>
<tr>
<th><strong>Number of patients</strong></th>
<th>159,289 eligible cases</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Measure Pass Rate</strong></td>
<td>35.2% 40.5% 44.9%</td>
</tr>
<tr>
<td><strong>Severe Sepsis Mortality</strong></td>
<td>28-32%</td>
</tr>
<tr>
<td><strong>Septic Shock Mortality</strong></td>
<td>38-42%</td>
</tr>
<tr>
<td><strong>Mortality Reduction Rate</strong></td>
<td>8.3% 8.8% 8.3%</td>
</tr>
<tr>
<td><strong>Potential Savable Deaths</strong></td>
<td>2,783 2,864 2,411</td>
</tr>
</tbody>
</table>
1. Measure lactate
2. Blood cultures/appropriate cultures
3. Give broad spectrum antibiotics
4. Fluid Challenge of 30 cc/ kg if (hypotension/lactate > 4mM/L)
5. If persistent hypotension
   – vasopressor to maintain MAP > 65 mmHg
6. Document perfusion:
   "Sepsis focused exam completed."
   or
   "I performed a reassessment of perfusion (or volume) status."
   You don't even need to provide vitals.
   This QNet webpage offers further guidance if need.
   https://cms-ip.custhelp.com/app/answers/detail/a_id/165223
7. Re-measure lactate within 6 hours