SURVIVING SEPSIS IN THE ERA OF NEW DEFINITIONS

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POTENTIAL CONFLICTS OF INTEREST

• No potential financial COI
• Potential intellectual COI
  • Surviving Sepsis Campaign Guidelines Committee
  • Guidelines lead for 2004, 2008 and 2012 SSC guidelines
  • Executive Committee SSC 2002-2014
Evolution of Sepsis Performance Improvement

New Sepsis Definitions

New Definitions and Sepsis Performance Improvement
Evolution of Sepsis Performance Improvement
Surviving Sepsis Campaign

• Phase 1
  • Barcelona Declaration 2002

• Phase 2
  • Guidelines

• Phase 3
  • Mortality 25%
2004 GUIDELINES

Surviving Sepsis Campaign guidelines for management of severe sepsis and septic shock

R. Phillip Dellinger, MD; Jean M. Carlet, MD; Henry Masur, MD; Henwig Gerlach, MD, PhD; Thierry Calandra, MD; Jonathan Cohen, MD; Juan Gea-Banacloche, MD, PhD; Didier Keh, MD; John C. Marshall, MD; Margaret M. Parker, MD; Graham Ramsay, MD; Janice L. Zimmerman, MD; Jean-Louis Vincent, MD, PhD; Mitchell M. Levy, MD; for the Surviving Sepsis Campaign Management Guidelines Committee

GUIDELINES TO BUNDLES - 2004

Surviving Sepsis Campaign guidelines for management of severe sepsis and septic shock

F. Phillip Dellinger, MD; Jean M. Carlet, MD; Henry Masur, MD; Harvey G. Gerlach, MD, PhD; Thierry Calandra, MD; Jonathan Cohen, MD; Juan Gas-Bastida, MD, PhD; Diederik K. Kehl, MD; John C. Marshall, MD; Margaret M. Parker, MD; Graham Ramsay, MD; Joanna L. Zimmerman, MD; Jean-Louis Vincent, MD, PhD; Mitchell M. Levy, MD; for the Surviving Sepsis Campaign Guidelines Management Committee


Objectives In 2003, critical care and infection disease experts representing 11 international organizations developed management guidelines for severe sepsis and septic shock that would be relatively easy to use for the bedside clinician. For patient welfare and to improve outcome, the guidelines were developed to be a practical framework and not impossible to meet. The Surviving Sepsis Campaign, an international effort to increase awareness and improve outcomes in patients with severe sepsis, was launched. Although the recent guidelines for sepsis management are updated, they largely follow the 2001 guidelines developed by the Surviving Sepsis Campaign. Some recommendations in the guidelines have been revised to incorporate recent evidence, but the overall scope and rigor of the guidelines remain the same.

Methods We used a modified Delphi methodology for grading recommendations, built on a 2001 publication sponsored by the International Sepsis Forum. We undertook a systematic review of the literature guiding the panel to create recommendations grades and revisions to recommendations, which led to the highest level of evidence. Recommendations were reviewed to ensure clear and unambiguous language, favoring shorter statements. Statements in the guidelines are supported by references cited in text. In some cases, evidence was not available or was not readily available, so the guidelines provide additional expert opinion derived from clinical experience. The guidelines are intended for use in all critical care settings, including inpatient and outpatient settings.

Severe Sepsis Bundles:

Sepsis Resuscitation Bundle (To be accomplished as soon as possible and scored over first 6 hours):
1. Serum lactate measured.
2. Blood cultures obtained prior to antibiotic administration.
3. From the time of presentation, broad-spectrum antibiotics administered within 3 hours for CDI admissions and 1 hour for non-CDI ICU admissions.
4. In the event of hypotension and/or lactate >4 mmol/L (36 mg/dL)
   a. Give an initial resuscitation dose of 20 mg/kg of vasopressin (or equivalent)*
   b. Apply vasopressors for hypotension not responding to initial fluid resuscitation to maintain mean arterial pressure (MAP) ≥65 mm Hg
5. In the event of persistent hypotension despite fluid resuscitation (septic shock) and/or lactate >4 mmol/L (36 mg/dL)
   a. Achieve central venous pressure (CVP) of 8-12 mm Hg
   b. Achieve central venous oxygen saturation (ScvO2) of ≥70%**

Sepsis Management Bundle (To be accomplished as soon as possible and scored over first 24 hours):
1. Low-dose steroids* administered for septic shock in accordance with standardized ICU policy.
2. Drotrecogin alfa (activated) administered in accordance with a standardized ICU policy.
3. Glucose control maintained ≤150 mg/dL (8.3 mmol/L)
4. Inotropic or vasoactive pressors maintained >30 cm H2O for mechanically ventilated patients

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*Use the individual shock measurement tool for vasopressor challenge
**Achieving a mixed venous oxygen saturation (ScvO2) of 65% is an acceptable alternative.
Special Article

Surviving Sepsis Campaign: International guidelines for management of severe sepsis and septic shock: 2008

R. Phillip Dellinger, MD; Mitchell M. Levy, MD; Jean M. Carlet, MD; Julian Bion, MD; Margaret M. Parker, MD; Roman Jaeschke, MD; Konrad Reinhart, MD; Derek C. Angus, MD, MPH; Christian Brun-Buisson, MD; Richard Beale, MD; Thierry Calandra, MD, PhD; Jean-Francois Dhainaut, MD; Herwig Gerlach, MD; Maureen Harvey, RN; John J. Marini, MD; John Marshall, MD; Marco Ranieri, MD; Graham Ramsay, MD; Jonathan Sevransky, MD; B. Taylor Thompson, MD; Sean Townsend, MD; Jeffrey S. Vender, MD; Janice L. Zimmerman, MD; Jean-Louis Vincent, MD, PhD; for the International Surviving Sepsis Campaign Guidelines Committee
SSC International Performance Improvement Program 2005-2011
Surviving Sepsis Campaign: Association Between Performance Metrics and Outcomes in a 7.5-Year Study

Mitchell M. Levy, MD, FCCM¹; Andrew Rhodes, MB BS, MD (Res)²; Gary S. Phillips, MAS³;
Sean R. Townsend, MD⁴; Christa A. Schorr, RN, MSN⁵; Richard Beale, MB BS⁶;
Tiffany Osborn, MD, MPH⁷; Stanley Lemeshow, PhD⁸; Jean-Daniel Chiche, MD⁹;
Antonio Artigas MD, PhD¹⁰; R. Phillip Dellinger, MD, FCCM¹¹

¹Alpert Medical School at Brown University, Rhode Island Hospital, Providence, Rhode Island.
²Adult Critical Care Directorate, St. George’s Healthcare NHS Trust and St George’s University of London, London, United Kingdom.
³The Ohio State University Center for Biostatistics, Columbus, Ohio.
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Institute of Healthcare Improvement (sepsis consultant) and received support for participation in review activities from Rhode Island Hospital, LifeSpan Partner. His institution received grant support from a NIH grant and the Murdoch Children’s Research Institution. Dr. Chiche served as board member for GF Healthcare and Nestlé and consulted for Astra
SSC Mortality


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 Jacsik, MD; Tiffany M. Osborn, MD, MPH; Mark E. Nannally, MD; Sean R. Townsend, MD; Konrad Reinhard, 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

Objective: To provide an update to the “Surviving Sepsis Campaign Guidelines for Management of Severe Sepsis and Septic Shock,” last published in 2008.

Design: A consensus committee of 68 international experts representing 38 international organizations was convened. Nominal groups were assembled at key international meetings for those committee members attending the conferences. A formal conflict of interest policy was developed at the start of the process and enforced throughout. The entire guidelines process was conducted independently of any industry funding. A stand-alone meeting was held for all subgroup heads, co-chairs, and selected individuals. Teleconferences and email-based discussion among subgroups and among the entire committee served as an integral part of the development.

Methods: The authors were advised to follow the principles of the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system to guide assessment of quality of evidence from high (A) to low (D) and to determine the strength of recommendations as strong (1) or weak (2). The potential drawbacks of making strong recommendations in the presence of low-quality evidence were emphasized. Some recommendations were ungraded (UNC). Recommendations were classified into three groups: those directly targeting severe sepsis; those targeting general care of the critically ill patient and considered high priority in severe sepsis; and those targeting specific population needs.

Results: Key recommendations and suggestions, filtered by category, include: early quantitative resuscitation of the septic patient during the first 6 hours after recognition (1C); blood cultures
2012 NQF: SEPSIS 0500

TO BE COMPLETED WITHIN 3 HOURS OF TIME OF PRESENTATION:

1. Measure lactate level
2. Obtain blood cultures prior to administration of antibiotics
3. Administer broad spectrum antibiotics
4. Administer 30ml/kg crystalloid for hypotension or lactate ≥4mmol/L
TO BE COMPLETED WITHIN 6 HOURS OF TIME OF PRESENTATION:

5. Apply vasopressors (for hypotension that does not respond to initial fluid resuscitation to maintain a mean arterial pressure (MAP) ≥65mmHg)

6. In the event of persistent arterial hypotension despite volume resuscitation (septic shock) or initial lactate ≥4 mmol/L (36mg/dl):
   - Measure central venous pressure (CVP)
   - Measure central venous oxygen saturation (ScvO2)

7. Remeasure lactate if elevated.
A Randomized Trial of Protocol-Based Care for Early Septic Shock

The ProCESS Investigators*


Over 1500 Patients

Goal-Directed Resuscitation for Patients with Early Septic Shock

The ARISE Investigators and the ANZICS Clinical Trials Group*


1600 Patients
SEPSIS BUNDLE PROJECT (SEP) NATIONAL HOSPITAL INPATIENT QUALITY MEASURES

SEP-1 EARLY MANAGEMENT BUNDLE, SEVERE SEPSIS/SEPTIC SHOCK

Discharges 10-01-2015 (4Q15) through 06-30-16 (2Q16)
SEP-1  Two Clocks

**Severe Sepsis**

- 3 hour

**Septic Shock**

- 6 hour
SEPTIC SHOCK REASSESSMENT FOR INTRAVASCULAR VOLUME STATUS AND TISSUE PERFUSION

Remaining hypotensive after fluid bolus or initial lactate ≥4
After fluid bolus

Physical Exam (ALL)
• Vital Signs (T, HR, RR, BP)
• Cardiopulmonary exam
• Capillary refill evaluation
• Peripheral Pulse evaluation
• Skin evaluation

Hemodynamics (2 of 4)
• CVP
• SVO2
• Bedside cardiovascular ultrasound
• Passive leg raise / fluid challenge
Sepsis Definitions
In the beginning...

“Sepsis Syndrome”
Objective: To define the terms "sepsis" and "organ failure" in a precise manner.

Data Sources: Review of the medical literature and the use of expert testimony at a consensus conference.

Setting: American College of Chest Physicians (ACCP) headquarters in Northbrook, IL.

Participants: Leadership members of ACCP/Society of Critical Care Medicine (SCCM).

Results: An ACCP/SCCM Consensus Conference was held in August of 1991 with the goal of agreeing on a set of definitions that could be applied to patients with sepsis and its sequelae.

Recommended when dealing with septic patients as an adjunctive tool to assess mortality. Appropriate methods and applications for the use and testing of new therapies were recommended.

Conclusion: The use of these terms and techniques should assist clinicians and researchers who deal with sepsis and its sequelae. (Crit Care Med 1992; 20:864–874)

Key Words: consensus development conferences; shock, septic; organ failure; hypotension; severity of illness index; critical care; intensive care unit; bacterial infection; sepsis
Members of the ACCP/SCCM Consensus Conference Committee include: Roger C. Bone, MD, FCCM, Conference Chairperson; Robert A. Balk, MD; Frank B. Cerra, MD, FCCM; R. Phillip Dellinger, MD, FCCM; Alan M. Fein, MD, FCCM; William A. Knaus, MD; Roland M.H. Schein, MD, FCCM; and William J. Sibbald, MD, FCCM, Session Chairpersons; Jerome H. Abrams, MD; Gordon R. Bernard, MD; James W. Biondi, MD; James E. Calvin, Jr, MD; Robert Demling, MD; Patrick J. Fahey, MD; Charles J. Fisher, Jr, MD; FCCM; Cory Franklin, MD; Kenneth J. Gorelick, MD; Mark A. Kelley, MD; Dennis G. Maki, MD; John C. Marshall, MD; William W. Merrill, MD; John P. Pribble, PharmD; Eric C. Rackow, MD; Timothy C. Rodell, MD; John N. Sheagren, MD; Michael Silver, MD; Charles L. Sprung, MD, FCCM; Richard C. Straube, MD; Martin J. Tobin, MD; Gordon M. Trenholme, MD; Douglas P. Wagner, PhD; C. Douglas Webb, MD; Janice C. Wherry, MD, PhD; Herbert P. Wiedemann, MD; Cornelius H. Wortel, MD, Faculty.

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SEPSIS DEFINITIONS 1992

Systemic Inflammatory Response Syndrome (SIRS)

Sepsis
- SIRS + infection

Severe Sepsis
- Sepsis + organ failure

Septic Shock
- Severe sepsis + hypotension despite adequate fluid resuscitation

CHEST 1992
SIRS Criteria (≥ 2)
- Temperature > 38 C < 36 C
- Heart rate > 90 bpm
- Respiratory rate > 20 /min or a PaCO2 < 32 mmHg
- White blood cell count > 12,000 / cu mm or < 4,000 / cu mm, or > 10 bands
2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference

Mitchell M. Levy, MD, FCCP; Mitchell P. Fink, MD, FCCP; John C. Marshall, MD; Edward Abraham, MD; Derek Angus, MD, MPH, FCCP; Deborah Cook, MD, FCCP; Jonathan Cohen, MD; Steven M. Opal, MD; Jean-Louis Vincent, MD, FCCP, PhD; Graham Ramsay, MD; For the International Sepsis Definitions Conference

Objective: In 1991, the American College of Chest Physicians (ACCP) and the Society of Critical Care Medicine (SCCM) convened a “Consensus Conference,” the goals of which were “to provide a conceptual and a practical framework to define the systemic inflammatory response to infection, which is a progressive injurious process that falls under the generalized term ‘sepsis’ and includes sepsis-associated organ dysfunction as well.” The general definitions introduced as a result of that conference have been widely used in practice and have served as the foundation for inclusion criteria for numerous clinical trials of therapeutic interventions. Nevertheless, there has been an impetus from experts in the field to modify these definitions to reflect our current understanding of the pathophysiology of these syndromes.

Design: Several North American and European intensive care societies agreed to revisit the definitions for sepsis and related conditions. This conference was sponsored by the SCCM, The European Society of Intensive Care Medicine (ESICM), The American College of Chest Physicians (ACCP), the American Thoracic Society (ATS), and the Surgical Infection Society (SIS).

Methods: The conference was attended by 29 participants from Europe and North America. In advance of the conference, five subgroups were formed to evaluate the following areas: signs and symptoms of sepsis, cell markers, cytokines, microbiologic data, and coagulation parameters. The subgroups corresponded electronically before the conference and met in person during the conference. A spokesperson for each group presented the deliberation of each group to all conference participants during a plenary session. A writing committee was formed at the conference and developed the current article based on executive summary documents generated by each group and the plenary group presentations. The present article serves as the final report of the 2001 International Sepsis Definitions Conference.

Conclusion: This document reflects a process whereby a group of experts and opinion leaders revisited the 1992 sepsis guidelines and found that apart from expanding the list of signs and symptoms of sepsis to reflect clinical bedside experience, no evidence exists to support a change to the definitions. This lack of evidence serves to underscore the challenge still present in diagnosing sepsis in 2003 for clinicians and researchers and also provides the basis for introducing PIRO as a hypothesis-generating model for future research. (Crit Care Med 2003; 31:1250–1256)

Key Words: sepsis; severe sepsis; septic shock; systemic inflammatory response syndrome; PIRO
### 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference

#### Diagnostic criteria for sepsis

- Infection, documented or suspected plus some of the following findings:
  - Temperature $>38.3^\circ\text{C}$ or $>36^\circ\text{C}$
  - Heart rate $>90$ min or $>2$ SD above normal value for age
  - Arterial hypotension (SBP $<90$ mm Hg, MAP $<70$ or an SBP decrease $>40$ in adults or $<$ SD below normal for age)
  - Mixed venous oxygen saturation ($\text{SVO}_2$) $>70$
  - Cardiac index $>3.5$ L/min/M$^2$
  - Tachypnea
  - Decreased capillary refill or mottling
  - Altered mental status
  - Significant edema or positive fluid balance
  - Hyperglycemia in the absence of diabetes
  - WBC count $>12,000$ µL or $<4000$ µL
  - Normal WBC with $>10\%$ immature forms
  - Plasma C-reactive protein $>2$ SD above the normal value
  - Plasma procalcitonin $>SD$ above the normal value
  - Hyperlactatemia ($>1$ mmol/L)
  - Evidence of organ dysfunction:
    - Arterial hypoxemia ($\text{PaO}_2/\text{FiO}_2 < 300$)
    - Acute oliguria
    - Creatinine increase $>0.5$ mg/dL
    - Coagulation abnormalities (INR $>1.5$ or a PTT $>60$s)
    - Ileus
    - Thrombocytopenia
    - Hyperbilirubinemia

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INR—International Normalized Ratio; MAP—mean arterial pressure; PTT—partial thromboplastin time; SBP—systolic blood pressure; SD—standard deviation; WBC—white blood cell.
The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3)
INFECTION → INFECTION

SEPSIS × → INFECTION

SEVERE SEPSIS × → INFECTION

SEPTIC SHOCK → SEPTIC SHOCK

* Elevated lactate
Recommended de-emphasis of SIRS
You're too SENSITIVE

SIRS
Systemic Inflammatory Response Syndrome Criteria in Defining Severe Sepsis

Kirs-Maija Kaukonen, M.D., Ph.D., Michael Bailey, Ph.D., David Pilcher, F.C.I.C.M., D. Jamie Cooper, M.D., Ph.D., and Rinaldo Bellomo, M.D., Ph.D.
1/8<sup>th</sup> Empty

Or

7/8 Full
**SEQUENTIAL [SEPSIS-RELATED] ORGAN FAILURE ASSESSMENT SCORE (SOFA)**

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<th>System</th>
<th>Score</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
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</thead>
<tbody>
<tr>
<td><strong>Respiration</strong></td>
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<td>$P_aO_2/F_iO_2$, mm Hg (kPa)</td>
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<td>$\geq 400$ (53.3)</td>
<td>$&lt;400$ (53.3)</td>
<td>$&lt;300$ (40)</td>
<td>$&lt;200$ (26.7) with respiratory support</td>
<td>$&lt;100$ (13.3) with respiratory support</td>
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<td><strong>Coagulation</strong></td>
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<td>Platelets, $\times 10^3/\mu L$</td>
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<td>$\geq 150$</td>
<td>$&lt;150$</td>
<td>$&lt;100$</td>
<td>$&lt;50$</td>
<td>$&lt;20$</td>
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<td><strong>Liver</strong></td>
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<td>Bilirubin, mg/dL ($\mu mol/L$)</td>
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<td>$&lt;1.2$ (20)</td>
<td>$1.2-1.9$ (20-32)</td>
<td>$2.0-5.9$ (33-101)</td>
<td>$6.0-11.9$ (102-204)</td>
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<td>MAP $\geq 70$ mm Hg</td>
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<td>MAP $&lt;70$ mm Hg</td>
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<td>Dopamine $5.1-15$ or epinephrine $\leq 0.1$ or norepinephrine $\leq 0.1^b$</td>
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<td>Dopamine $&gt;15$ or epinephrine $&gt;0.1$ or norepinephrine $&gt;0.1^b$</td>
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<td><strong>Central nervous system</strong></td>
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<td>Glasgow Coma Scale score$^c$</td>
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<td>15</td>
<td>13-14</td>
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<td><strong>Renal</strong></td>
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<td>Creatinine, mg/dL ($\mu mol/L$)</td>
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<td>$&lt;1.2$ (110)</td>
<td>$1.2-1.9$ (110-170)</td>
<td>$2.0-3.4$ (171-299)</td>
<td>$3.5-4.9$ (300-440)</td>
<td>$&gt;5.0$ (440)</td>
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<td>Urine output, mL/d</td>
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Acute change in total SOFA score $\geq 2$ identifies mortality risk of approximately 10%
Quick SOFA or qSOFA

In patients with infection a qSOFA score $\geq 2$ is associated with higher mortality and prolonged ICU stay.
New Definitions and Sepsis Performance Improvement
2016 Definitions

• One common language for infected patients at risk for morbidity/mortality

Data Driven
SHOULD WE BE USING THE PROPOSED NEW DEFINITIONS?
Can we really forget about SIRS and “simple” sepsis?
ICD-10 is a new code set for reporting medical diagnoses & inpatient procedures.
SEPSIS BUNDLE PROJECT (SEP)
NATIONAL HOSPITAL INPATIENT QUALITY MEASURES

SEP-1 EARLY MANAGEMENT BUNDLE,
SEVERE SEPSIS/SEPTIC SHOCK

Discharges 10-01-2015 (4Q15) through 06-30-16 (2Q16)
Infection induced organ dysfunction and/or tissue hypoperfusion (IIODTH)
Thank You