

# Sepsis 2018: Definitions and Guideline Changes

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## Abstract

**Background:** Sepsis is a global healthcare issue and continues to be the leading cause of death from infection. Early recognition and diagnosis of sepsis is required to prevent the transition into septic shock, which is associated with a mortality rate of 40% or more.

**Discussion:** New definitions for sepsis and septic shock (Third International Consensus Definitions for Sepsis and Septic Shock [Sepsis-3]) have been developed. A new screening tool for sepsis (quick Sequential Organ Failure Assessment [qSOFA]) has been proposed to predict the likelihood of poor outcome in out-of-intensive care unit (ICU) patients with clinical suspicion of sepsis. The Surviving Sepsis Campaign Guidelines were recently updated and include greater evidence-based recommendations for treatment of sepsis in attempts to reduce sepsis-associated mortality. This review discusses the new Sepsis-3 definitions and guidelines.

**Keywords:** sepsis; sepsis guidelines; Sepsis-3 definition; septic shock; Surviving Sepsis Campaign

**S**EPSIS CONTINUES TO BE a major health problem worldwide and is associated with high mortality rates. The Intensive Care Over Nations (ICON) study provided global epidemiologic data on 10,069 intensive care unit (ICU) patients and confirmed that 2,973 (29.5%) of patients had sepsis on admission or during their ICU stay. In patients with sepsis, ICU mortality was 25.8%, and hospital mortality was 35.3%, which was a significantly higher mortality rate than in the general ICU population (ICU mortality, 16.2%; hospital mortality, 24.2%) [1]. Optimal evidence-based treatment of sepsis is therefore needed in attempts to reduce mortality, led over the last decade by the Surviving Sepsis Campaign (SSC). The first step in implementation of optimal sepsis treatment is identification of patients with sepsis. This article discusses the new Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) definitions for sepsis and septic shock and the new 2016 SSC guidelines.

## Sepsis-3: New Definitions

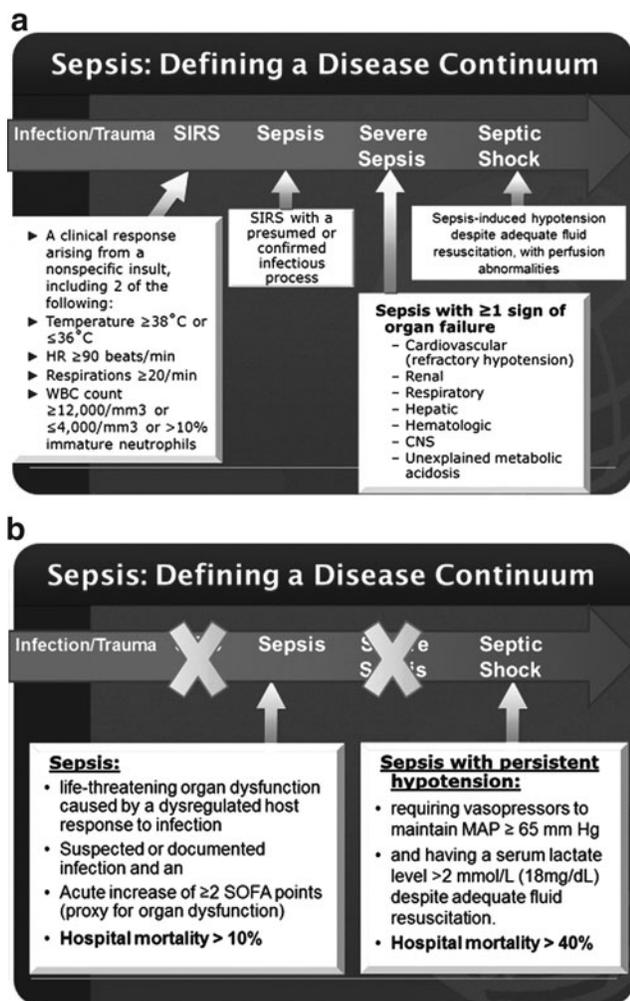
Initial sepsis definitions were developed at a 1991 consensus conference [2] with a subsequent update in the sepsis definitions in 2001 that simply expanded the list of signs and symptoms of sepsis to reflect clinical bedside experience [3]. The initial sepsis definitions included sepsis (systemic inflammatory response syndrome [SIRS] and suspected infec-

tion), severe sepsis (sepsis and organ dysfunction) and septic shock (sepsis and hypotension despite adequate fluid resuscitation; Fig. 1).

An international task force with 19 participants was convened by the Society of Critical Care Medicine (SCCM) and the European Society of Intensive Care Medicine (ESICM) to revise the current sepsis and septic shock definitions. Using an expert Delphi consensus process, this group developed the new Sepsis-3 definitions [4,5]. They moved away from the association between infection and inflammation and completely abandoned SIRS criteria.

Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection. The clinical criteria for sepsis include suspected or documented infection and an acute increase of two or more Sequential Organ Failure Assessment (SOFA) points as a proxy for organ dysfunction. Septic shock is defined as a subset of sepsis in which underlying circulatory and cellular/metabolic abnormalities are profound enough to increase mortality substantially. Septic shock is defined by the clinical criteria of sepsis and vasopressor therapy needed to elevate mean arterial pressure  $\geq 65$  mm Hg and lactate  $>2$  mmol/L (18 mg/dL) despite adequate fluid resuscitation (Fig. 1).

The mortality rate associated with the new septic shock definition is high (40%) compared with a mortality rate of 10% with the new sepsis definition. A systematic review



**FIG. 1.** Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3): (a) Original Sepsis-2 definitions; (b) New Sepsis-3 definitions.

identified 44 studies reporting septic shock outcomes, and the Delphi process identified hypotension, lactate concentration, and vasopressor therapy as clinical criteria to identify patients with septic shock. Based on these parameters, specific patient groups with or without these clinical criteria were developed, and their prevalence and associated mor-

tality rates were examined in the SSC database (Table 1). The group requiring vasopressors to maintain mean arterial pressure 65 mm Hg or greater and a lactate concentration  $> 2$  mmol/L (18 mg/dL) after fluid resuscitation (group 1) had a higher mortality (42.3%) in risk-adjusted comparisons with the other five groups. This analysis led to the new Sepsis-3 septic shock definition [6]. It should also be noted, however, that patients who met the Sepsis-2 criteria for septic shock (group 2) with hypotension, requiring vasopressors, but without lactate elevation, also had a high mortality rate of 30.1%. The higher mortality rate associated with this new definition of septic shock has important implications for trial design in septic shock and may allow decreased sample size for future septic shock trials [7].

Controversy remains regarding the inclusion of lactate in the Sepsis-3 septic shock definition and the exact lactate measurement ( $> 2$  mmol/L) used in the definition. One study analyzed a prospective cohort of ICU patients with sepsis ( $n = 632$ ) and documented that patients meeting the Sepsis-3 definition of septic shock had a higher mortality than patients meeting the Sepsis-2 definition (38.9% vs. 34.0%), but only lactate values  $\geq 6$  mmol/L were associated with increased ICU mortality [8]. Others report concern that lactate is a sensitive but not specific indicator of cellular or metabolic stress rather than “shock.”

#### SIRS versus SOFA and qSOFA in Sepsis

A retrospective analysis of the Australian and New Zealand Intensive Care Society (ANZICS) database (2000–2013) included 109,663 patients with infection and organ failure to validate the severe sepsis definition [9]. It was reported that 87.9% of patients had two or more SIRS criteria but 12.1% did not. Using SIRS alone missed one in eight patients with severe sepsis. The study confirmed that each additional SIRS criteria increased mortality by 13% in a linear manner without a transitional increase when two SIRS criteria were met. They concluded that the use of two or more SIRS criteria alone lacked both sensitivity and specificity for diagnosing severe sepsis in ICU patients.

The subsequent analysis of clinical criteria for the new Sepsis-3 definitions compared SIRS criteria, the SOFA score, the Logistic Organ Dysfunction System (LODS) score, and the quick SOFA (qSOFA) score (range, 0–3 points, with one point each for systolic hypotension  $\leq 100$  mm Hg], tachypnea  $\geq 22/\text{min}$ ], or altered mentation). The SOFA score (Table 2)

**TABLE 1.** DISTRIBUTION AND MORTALITY IN SEPTIC SHOCK COHORTS FROM SURVIVING SEPSIS CAMPAIGN DATABASE

	Hypotension after fluids	Vasopressors	Lactate $> 2$ mmol/L	Prevalence, Surviving Sepsis Campaign Database ( $n = 18,840$ patients)	Hospital mortality
Group 1 <sup>a</sup>	Yes	Yes	Yes	8,520 (45.2%)	42.3%
Group 2 <sup>b</sup>	Yes	Yes	No	3,985 (21.2%)	30.1%
Group 3	Yes	No	Yes	223 (1.2%)	28.7%
Group 4	No	No	Yes	3,266 (17.3%)	25.7%
Group 5	Never (pre)	No	Yes	2,696 (14.3%)	29.7%
Group 6	Yes	No	No	150 (0.8%)	18.7%

<sup>a</sup>Meets criteria for new Sepsis-3 septic shock definition.

<sup>b</sup>Meets criteria for old Sepsis-2 septic shock definition.

Data compiled from: Shankar-Hari M, Phillips GS, Levy ML, et al. Developing a new definition and assessing new clinical criteria for septic shock. For the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA 2016;315:775–787.

Sepsis-3 = Third International Consensus Definitions for Sepsis and Septic Shock.

TABLE 2. SEQUENTIAL (SEPSIS-RELATED) ORGAN FAILURE ASSESSMENT (SOFA) SCORE<sup>a</sup>

System	Score				
	0	1	2	3	4
Respiration Pao <sub>2</sub> /Fio <sub>2</sub> , mm Hg (kPa)	≥400 (53.3)	<400 (53.3)	<300 (40)	<200 (26.7) with respiratory support	<100 (13.3) with respiratory support
Coagulation Platelets, × 10 <sup>3</sup> /μL	≥150	<150	<100	<50	<20
Liver Bilirubin, mg/dL (μ mol/L)	<1.2 (20)	1.2–1.9 (20–32)	2.0–5.9 (33–101)	6.0–11.9 (102–204)	>12.0 (204)
Cardiovascular	MAP ≥70 mm Hg	MAP <70 mm Hg	Dopamine <5 or dobutamine (any dose) <sup>b</sup>	Dopamine 5.1–15 or epinephrine ≤0.1 or norepinephrine ≤0.1 <sup>b</sup>	Dopamine >15 or epinephrine >0.1 or norepinephrine >0.1 <sup>b</sup>
Central nervous system Glasgow coma scale score <sup>c</sup>	15	13–14	10–12	6–9	<6
Renal Creatinine, mg/dL (μ mol/L)	<1.2 (110)	1.2–1.9 (110–170)	2.0–3.4 (171–299)	3.5–4.9 (300–440)	>5.0 (440)
Urine output, mL/d				<500	<200

Fio<sub>2</sub>=fraction of inspired oxygen; MAP=mean arterial pressure; Pao<sub>2</sub>=partial pressure of oxygen.

<sup>a</sup>Adapted from Vincent et al. [10].

<sup>b</sup>Catecholamine doses are given as μg/kg/min for at least 1 hour.

<sup>c</sup>Glasgow coma scale scores range from 3–15; higher score indicates better neurological function.

is widely used in critical care research, but is not a common clinical tool used at the bedside in the ICU [10].

The qSOFA score (Fig. 2) was developed as a simple screening tool to identify patients with possible sepsis. A qSOFA score of two or more identifies a patient at greater risk of poor outcome. Among non-ICU encounters in patients with suspected infection, qSOFA had a predictive validity for in-hospital mortality (area under the receiver operating characteristic curve [AUROC] 0.81) that was greater than the full SOFA score (AUROC 0.79) and SIRS (AUROC 0.76; Table 3). In contrast, however, in the ICU, the predictive

validity for in-hospital mortality was lower for qSOFA (AUROC 0.66) and SIRS (AUROC 0.64) compared with the full SOFA score (AUROC 0.74) [5].

The use of the SOFA score in the Sepsis-3 definition is challenging, because SOFA is a complicated score that is not calculated routinely in ICUs at the bedside. Systemic inflammatory response syndrome and qSOFA are scores that are easily calculated at the bedside for use in the screening of patients with possible sepsis. A retrospective cohort analysis of the ANZICS database that was used to assess SIRS in the severe sepsis definition was also used to compare the

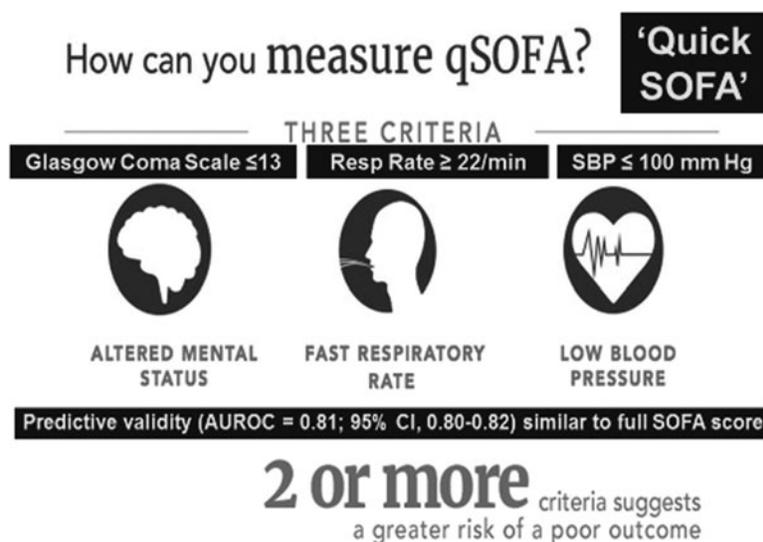


FIG. 2. Quick Sequential Organ Failure Assessment (qSOFA) score for sepsis.

TABLE 3. IN-HOSPITAL MORTALITY PREDICTION AMONG PATIENTS WITH POSSIBLE INFECTION OUTSIDE OF THE INTENSIVE CARE UNIT

Test	AUROC curve	Sensitivity for mortality	Specificity for mortality
SIRS $\geq 2$	0.76	64%	65%
SOFA $\geq 2$	0.79	68%	67%
qSOFA $\geq 2$	0.81	55%	84%

AUROC=area under the receiver operating curve; SIRS=systemic inflammatory response syndrome; SOFA=Sequential Organ Failure Assessment score; qSOFA=quick Sequential Organ Failure Assessment score.

prognostic accuracy of the SOFA score, SIRS criteria, and qSOFA score for in-hospital mortality among adults with suspected infection admitted to the ICU. The SOFA score increased by two or more points in 90.1%; 86.7% had SIRS score of two or more, and 54.4% had a qSOFA score of two or more. An increase in SOFA score of two or more had greater prognostic accuracy for in-hospital mortality (AUROC 0.753) than SIRS (AUROC 0.589) or the qSOFA score (AUROC 0.607) [11].

Interestingly, qSOFA failed validation in a study of 30,677 patients with suspected infection from the emergency department and ward at the University of Chicago. Systemic inflammatory response syndrome, qSOFA, Modified Early Warning Score (MEWS), and National Early Warning Score (NEWS; Table 4) were compared. Using the highest non-ICU score of patients, two or more SIRS had a sensitivity of 91% and specificity of 13% for the composite outcome (death or ICU transfer) compared with 54% and 67% for qSOFA of two or more, 59% and 70% for MEWS of five or more, and 67% and 66% for NEWS of eight or more, respectively. The authors concluded that the qSOFA score should not replace general early warning scores when risk-stratifying patients with suspected infection [12].

In contrast, an international prospective cohort study from Europe included 879 patients in the emergency department

with suspected infection and examined qSOFA as a mortality predictor. The overall in-hospital mortality was low (8%). The qSOFA performed better than SIRS and SOFA in prediction of in-hospital mortality (AUROC 0.8 qSOFA vs. 0.77 SOFA and 0.65 SIRS). Both qSOFA and SOFA had lower sensitivity (qSOFA 70%, SOFA 73% vs. SIRS 93%), and SIRS had lower specificity (qSOFA 79%, SOFA 70%, SIRS 27%) [13]. The use of qSOFA versus SIRS score for a sepsis screen actually depends on whether you desire increased sensitivity or specificity.

There is still controversy regarding the new Sepsis-3 definitions [14–16]. Some organizations have not endorsed the new Sepsis-3 definitions, including the American College of Chest Physicians [17], the Infectious Disease Society of America, the Latin American Sepsis Institute [18], American College of Emergency Physicians, none of the emergency medicine societies, and none of the hospital medicine societies. Additional prospective validation of the new Sepsis-3 definitions is clearly warranted.

### SSC Guidelines

The SSC guidelines for the management of severe sepsis and septic shock were first published in 2004 [19] with an update in 2008 [20] and 2012 [21]. The overall goal of the SSC was to reduce mortality from severe sepsis and septic shock. Active participation in the SSC was associated with increased guideline adherence and reductions in sepsis-related mortality [22]. Adherence to the SSC guidelines was promoted via the use of SSC bundles, which included elements to be completed in a specific timeframe after the diagnosis of sepsis.

### SSC bundles

The SSC bundles have changed during the SSC guideline updates (Table 5). The differences between the 2008 and 2012 bundles included an increase in fluid resuscitation recommended for sepsis-induced tissue hypoperfusion

TABLE 4. THE MODIFIED EARLY WARNING SCORE (MEWS), AND NATIONAL EARLY WARNING (NEWS) SCORES

<i>Modified Early Warning Score (MEWS)</i>							
Score	3	2	1	0	1	2	3
Respiratory rate ( $\text{min}^{-1}$ )		$\leq 8$		9–14	15–20	21–29	$> 29$
Heart rate ( $\text{min}^{-1}$ )		$\leq 40$	41–50	51–100	101–110	111–129	$> 129$
Systolic BP (mmHg)	$\leq 70$	71–80	81–100	101–199		$\geq 200$	
Urine output (ml/kg/h)	Nil	$< 0.5$					
Temperature ( $^{\circ}\text{C}$ )		$\leq 35$	35.1–36	36.1–38	38.1–38.5	$\geq 38.6$	
Neurological				Alert	Reacting to voice	Reacting to pain	Unresponsive
<i>National Early Warning Score (NEWS)</i>							
Physiological parameters	3	2	1	0	1	2	3
Respiration rate	$\leq 8$		9–11	12–20		21–24	$\geq 25$
Oxygen saturations	$\leq 91$	92–93	94–95	$\geq 96$			
Any supplemental oxygen		Yes		No			
Temperature	$\leq 35.0$		35.1–36.0	36.1–38.0	38.1–39.0	$\geq 39.1$	
Systolic BP	$\leq 90$	91–100	101–110	111–219			$\geq 220$
Heart rate	$\leq 40$		41–50	51–90	91–110	111–130	$\geq 131$
Level of consciousness				A			V.P. or U

\*The NEWS initiative flowed from the Royal College of Physicians' NEWSDIG, and was jointly developed and funded in collaboration with the Royal College of Physicians, Royal College of Nursing, National Outreach Forum and NHS Training for Innovation.

TABLE 5. DIFFERENCE IN THE SURVIVING SEPSIS CAMPAIGN BUNDLES, 2008 (LEFT) VS. 2012 (RIGHT)

<i>Sepsis resuscitation bundle</i>	<i>Surviving sepsis campaign bundles</i>
<p>To be accomplished as soon as possible and scored over the first 6 hours:</p> <ol style="list-style-type: none"> <li>1. Measure serum lactate.</li> <li>2. Obtain blood cultures prior to antibiotic administration.</li> <li>3. From the time of presentation, administer broad-spectrum antibiotics within 3 hours for ED admissions and 1 hour for non-EDICU admissions.</li> <li>4. In the event of hypotension and/or lactate &gt;36 mg/dL:               <ol style="list-style-type: none"> <li>a) Deliver an initial minimum of 20 mL/kg of crystalloid (or colloid equivalent).</li> <li>b) Apply vasopressors for hypotension that does not respond to initial fluid resuscitation to maintain mean arterial pressure (MAP) &gt;65 mm Hg.</li> </ol> </li> <li>5. In the event of persistent hypotension despite fluid resuscitation (septic shock) and/or lactate &gt;4 mmol/L (36 mg/dL):               <ol style="list-style-type: none"> <li>a) Achieve central venous pressure (CVP) of &gt;8–12 mmHg.</li> <li>b) Achieve central venous oxygen saturation (ScvO<sub>2</sub>) of &gt;70%.</li> </ol> </li> </ol>	<p>To be completed within 3 hours:</p> <ol style="list-style-type: none"> <li>1. Measure lactate level</li> <li>2. Obtain blood cultures prior to administration of antibiotics</li> <li>3. Administer broad spectrum antibiotics</li> <li>4. Administer 30 mL/kg crystalloid for hypotension or lactate ≥4 mmol/L</li> </ol> <p>To be completed within 6 hours:</p> <ol style="list-style-type: none"> <li>5. Apply vasopressors (for hypotension that does not respond to initial fluid resuscitation) to maintain a mean arterial pressure (MAP) ≥65 mm Hg</li> <li>6. In the event of persistent arterial hypotension despite volume resuscitation (septic shock) or initial lactate ≥4 mmol/L (36 mg/dL)               <ul style="list-style-type: none"> <li>-Measure central venous pressure (CVP)*</li> <li>-Measure central venous oxygen saturation (ScvO<sub>2</sub>)*</li> </ul> </li> <li>7. Remeasure lactate if initial lactate was elevated*</li> </ol>
<p><i>Sepsis management bundle</i></p> <p>To be accomplished as soon as possible and scored over the first 24 hours:</p> <ol style="list-style-type: none"> <li>1. Administer low-dose steroids for septic shock in accordance with a standardized ICU policy.</li> <li>2. Administer drotrecogin alfa (activated) in accordance with a standardized ICU policy.</li> <li>3. Glucose control maintained above lower limit of normal, but &lt;150 mg/dl.</li> <li>4. Maintain inspiratory plateau pressures at &lt;30 cm H<sub>2</sub>O for mechanically ventilated patients.</li> </ol>	

\*Targets for quantitative resuscitation included in the guidelines are CVP of ≥8 mm Hg, ScvO<sub>2</sub> of ≥70%, and normalization of lactate. From: [www.survivingsepsis.org](http://www.survivingsepsis.org)

(20 mL/kg crystalloid in 2008; 30 mL/kg in 2012 for treatment of hypotension or elevated lactate) and discontinuation of the 2008 sepsis management bundle (steroids, activated protein C, glycemic control, and low plateau pressures in mechanically ventilated patients).

A global, prospective, observational quality improvement study of compliance with the 2012 SSC bundles in patients with severe sepsis or septic shock included 1,794 patients from 62 countries, and documented that overall compliance was low, at only 19% for the three-hour bundle, and 36% for the six-hour bundle. However, SSC bundle compliance was associated with a 40% reduction in the odds of dying in hospital with the three-hour bundle and 36% for the six-hour bundle [23].

The most recent guideline update was published in 2016 [24] and includes new three-hour and six-hour SSC bundles (Table 6). The most recent SSC bundles focus on early antibiotic treatment and fluid resuscitation to be initiated within three hours. Early identification of patients with sepsis, early intravenous fluid resuscitation, and early intravenous antibiotic administration are the mainstay of sepsis management.

Consistent in all of the SSC bundles is the recommendation for antibiotic administration within one hour of diagnosis of sepsis. In a study of 28,150 patients with severe sepsis and septic

shock, in-hospital mortality was 19.7%, and delay in the first antibiotic administration was associated with increased risk of death [25].

The major change from the 2012 SSC bundle is the removal of early goal-directed therapy recommendations (resuscitation targets central venous pressure [CVP] ≥8, central venous oxygen saturation [ScvO<sub>2</sub>] ≥ 70%, and normalization of lactate) in the six-hour SSC bundle. The 2016 SSC bundle recommends serial re-assessment of volume status and tissue perfusion with dynamic assessments of fluid responsiveness including physical examination to evaluate for hypoperfusion, bedside cardiovascular ultrasound, passive leg elevation, or fluid challenge.

The new SSC guidelines 2016 also recognize that we are in an era of “personalized” medicine and “one size does not fit all.” Therefore, the SSC bundle recommendations are not meant to be implemented without interval re-evaluation. For example, in a patient with sepsis with severe hypoxemia and acute respiratory distress syndrome or heart failure, fluid resuscitation of 30 mL/kg may not be appropriate and vasopressor or cardiotoxic medications may be indicated to optimize tissue perfusion [26]. We are beginning to determine risk factors for patients who are not fluid responsive in septic shock (heart failure, hypothermia, immunocompromised,

TABLE 6. SURVIVING SEPSIS CAMPAIGN BUNDLE 2016

*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  $\geq 4$  mmol/L.  
 “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 severe sepsis or septic shock ascertained through chart review.

*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)  $\geq 65$  mm Hg.
6. In the event of persistent hypotension after initial fluid administration (MAP  $< 65$  mm Hg) or if initial lactate was  $\geq 4$  mmol/L, re-assess volume status and tissue perfusion and document findings according to Table 1.
7. Re-measure lactate if initial lactate elevated.

*Document reassessment of volume status and tissue perfusion with***Either:**

- Repeat focused exam (after initial fluid resuscitation) including vital signs, cardiopulmonary, capillary refill, pulse, and skin findings.

**Or two of the following:**

- Measure CVP.
- Measure ScvO<sub>2</sub>.
- Perform bedside cardiovascular ultrasound.
- Perform dynamic assessment of fluid responsiveness with passive leg raise or fluid challenge.

From: [www.survivingsepsis.org](http://www.survivingsepsis.org)

TABLE 7. SURVIVING SEPSIS CAMPAIGN GUIDELINE CHANGES COMPARING 2012 AND 2016 RECOMMENDATIONS

	2012	2016
Sepsis definition	Systemic manifestation of infection plus suspected infection Severe sepsis: sepsis plus organ dysfunction	Life-threatening organ dysfunction caused by dysregulated response to infection. No severe sepsis definition
Initial resuscitation	At least 30 mL/kg in the first 3 h; crystalloid fluid (no albumin if patients require substantial fluids) Early goal-directed therapy protocolized care including CVP, ScVO <sub>2</sub> . Normalize lactate	Use dynamic resuscitation markers (passive leg elevation, TTE). Target MAP 65 mm Hg. Re-assess hemodynamic status to guide resuscitation. Normalize lactate
Vasopressors	Target MAP 65 mm Hg Norepinephrine vasopressor of choice; epinephrine if not at target MAP or vasopressin to reduce norepinephrine requirement. Avoid dopamine in most patients.	
Steroids	Only indicated in septic shock refractory to adequate fluids and vasopressors	
Antibiotic administration	Administration of effective IV antimicrobial agents within the first hour of recognition of septic shock and severe sepsis without septic shock. Initial empiric anti-infective therapy of one or more drugs that have activity against all likely pathogens. Combination empirical therapy for neutropenic patients with severe sepsis and for patients with difficult-to-treat, multi-drug-resistant bacterial pathogens such as <i>Acinetobacter</i> and <i>Pseudomonas</i> spp. Antimicrobial regimen should be reassessed daily for potential deescalation. Use of low procalcitonin levels or similar biomarkers to assist the clinician in the discontinuation of empiric antibiotics in patients who initially appeared septic, but have no subsequent evidence of infection	We recommend that administration of IV antimicrobials be initiated as soon as possible after recognition and within 1 h for both sepsis and septic shock. Initial IV broad-spectrum antibiotic agents to cover all potential pathogens. The addition of a second gram-negative agent to the empiric regimen is recommended for critically ill patients with sepsis at high risk of infection with multi-drug-resistant pathogens (e.g., <i>Pseudomonas</i> , <i>Acinetobacter</i> , etc.) to increase the probability of at least one active agent being administered May use procalcitonin to guide de-escalation of antibiotic therapy.
Source control	Achieve within 12 h, if feasible	Achieve as soon as medically and logically feasible

CVP=central venous pressure; ScVO<sub>2</sub>=central venous oxygen saturation; MAP=mean arterial pressure; TTE=transthoracic echocardiography; IV=intravenous.

TABLE 8. STRONG RECOMMENDATIONS FROM THE SURVIVING SEPSIS CAMPAIGN 2016 GUIDELINES

- 
- 30 mL/kg crystalloid fluid resuscitation within the first 3 h
  - Crystalloids as fluid of choice for initial resuscitation
  - Against the use of hydroxyethyl starches for intra-vascular volume replacement
  - Initial target mean arterial pressure of 65 mm Hg in septic shock requiring vasopressors
  - Norepinephrine as first-line vasopressor
  - Administer antibiotics within 1 h of recognition
  - Empiric broad-spectrum antimicrobial therapy to cover all likely pathogens
  - Red blood cell transfusion only when hemoglobin <7 unless extenuating circumstances (myocardial infarction, severe hypoxemia, acute hemorrhage)
  - Target tidal volume 6 mL/kg for ARDS, plateau pressure upper limit 30 cm H<sub>2</sub>O
  - Conservative fluid strategy in ARDS in patients without hypoperfusion
  - Against the use of pulmonary artery catheter for patients with sepsis-induced ARDS
  - Prone position for sepsis-induced ARDS with PaO<sub>2</sub>/FiO<sub>2</sub> ratio <150
  - Against use of beta-2 agonists for patients with sepsis-induced ARDS without bronchospasm
  - Against use of HFOV in adult patients with sepsis-induced ARDS
  - Elevate head of bed 30–45 degrees in mechanically ventilated patients, spontaneous breathing trials, and a weaning protocol
  - Blood glucose control via protocol targeting blood glucose <180 g/dL
  - Pharmacologic VTE prophylaxis, unfractionated or low molecular weight heparin
  - Stress ulcer prophylaxis for patients with risk factors for GI bleeding
  - Early enteral nutrition, against parenteral nutrition in the first 7 d
  - Against use of omega-3 fatty acids as an immune supplement
  - Incorporate goals of care into treatment planning using palliative care principles where appropriate
- 

ARDS=acute respiratory distress syndrome; HFOV=high-frequency oscillatory ventilation; VTE=venous thromboembolism; GI=gastrointestinal.

hyperlactemia, and coagulopathy) and may need to investigate alternate therapies in this population with sepsis with a phenotype for refractory hypotension [27].

### SSC Guidelines 2016 Changes

A number of evidence-based changes in recommendations are evident in the 2016 SSC Guidelines (Table 7). The most substantial change in the new guidelines is that for initial resuscitation, protocolized care with early goal-directed therapy is no longer recommended. There are no changes in recommendations regarding vasopressors (norepinephrine first-choice vasopressor, add vasopressin or epinephrine if not at target mean arterial pressure) and steroids (consider for patients with septic shock refractory to adequate fluids and vasopressors). The new guidelines include a number of strong recommendations with moderate or high-quality evidence (Table 8). A few of these changes are highlighted below.

#### *Mean arterial pressure target*

The new guidelines continue to recommend a target mean arterial pressure of 65 mm Hg over higher targets. A multi-center open-label trial of 776 patients with septic shock confirmed that resuscitation with a higher mean arterial pressure target of 80–85 mm Hg had no impact on 28-day or 90-day mortality [28]. But the new guidelines now also recommend: “When a better understanding of any patient’s condition is obtained, this target should be individualized to the pertaining circumstances.” This again reflects a move toward personalized care of the patient with sepsis in the ICU.

#### *Early goal-directed therapy*

A single-center randomized trial of early goal-directed therapy (six-hour resuscitation protocol to achieve specific blood pressure, CVP, ScVO<sub>2</sub>, and hemoglobin, compared

with usual care in patients with septic shock reported a reduction in hospital mortality from 46.5% to 30.5% [29]. Early goal-directed therapy was recommended in all previous SSC guidelines, but has been removed from the 2016 guidelines.

Three multi-center randomized controlled clinical trials (Protocolized Care for Early Septic Shock, Australasian Resuscitation in Sepsis Evaluation, and Protocolised Management in Sepsis) showed no benefit to early goal-directed therapy in the treatment of septic shock. Protocolized Care for Early Septic Shock (ProCESS) [30] was conducted in the United States, Australasian Resuscitation in Sepsis Evaluation (ARISE) [31] was conducted in Australia and New Zealand, and Protocolised Management in Sepsis (ProMISE) [32] was conducted in the United Kingdom. A trial-level meta-analysis confirmed no overall benefit from early goal-directed therapy in septic shock [33]. A patient-level meta-analysis of the three trials included 3,723 patients, and 90-day mortality was similar for early goal-directed therapy (24.9%) and usual care (25.4%). A sub-group analysis of patients with worse shock (higher lactate, combined hypotension and high lactate, or higher predicted risk of death) also confirmed that early goal-directed therapy was not associated with improved survival. Early goal-directed therapy was associated with increased ICU days, cardiovascular support, and higher costs [34].

#### *Blood product transfusion*

The 2016 SSC guidelines includes a significant change in the recommendation for red blood cell (RBC) transfusion: “We recommend that RBC transfusion occur only when hemoglobin concentration decreases to <7 g/dL in adults in the absence of extenuating circumstances, such as myocardial ischemia, severe hypoxemia, or acute hemorrhage (strong recommendation, high quality of evidence).” This is different than the 2012 guidelines that recommended early goal-directed therapy with a target hemoglobin of 10 g/dL in

the early resuscitation of patients with sepsis. This significant change is based on the results of the Transfusion Requirements in Septic Shock (TRISS) trial that compared a transfusion threshold of 7 versus 9 g/dL in patients with septic shock after ICU admission. No differences in 90-day mortality, ischemic events, or use of life support was identified and significantly fewer RBC transfusions were administered in the 7 g/dL threshold group [35]. A sub-group analysis of the TRISS trial also observed no survival benefit in any sub-groups of transfusion with a higher hemoglobin threshold [36]. The three early goal-directed therapy trials reviewed above also provide additional indirect evidence that targeting a hemoglobin concentration of 10 g/dL in the early goal-directed therapy protocol group was not associated with improved outcomes.

#### Source control

Two new best practice statements are included in the 2016 guidelines recommending prompt source control of infection as quickly as possible:

1. We recommend that a specific anatomic diagnosis of infection requiring emergent source control be identified or excluded as rapidly as possible in patients with sepsis or septic shock, and that any required source control intervention be implemented as soon as medically and logistically practical after the diagnosis is made (BPS).
2. We recommend prompt removal of intravascular access devices that are a possible source of sepsis or septic shock after other vascular access has been established (BPS).

#### Summary

Early recognition and diagnosis of sepsis is required to prevent the transition into septic shock, which is associated with a mortality rate of 40% or more. New definitions for sepsis and septic shock (Sepsis-3) have been developed. The new Sepsis-3 definition is “life-threatening organ dysfunction caused by a dysregulated host response to infection.” The clinical criteria for sepsis include suspected or documented infection and an acute increase of two or more SOFA points as a proxy for organ dysfunction. Septic shock is defined by the clinical criteria of sepsis and vasopressor therapy needed to elevate mean arterial pressure  $\geq 65$  mm Hg and lactate  $> 2$  mmol/L (18 mg/dL) despite adequate fluid resuscitation. A new screening tool for sepsis (qSOFA) has been proposed that includes Glasgow Coma Score of 13 or less, respiratory rate of 22 or more per minute, and systolic blood pressure  $\leq 100$  mm Hg. A qSOFA score of two or more identifies a patient at greater risk of poor outcome. The SSC guidelines were updated recently and include greater evidence-based recommendations for treatment of sepsis in attempts to reduce sepsis-associated mortality.

#### Author Disclosure Statement

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