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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)

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Abstract

IMPORTANCE—Septic shock currently refers to a state of acute circulatory failure associated with infection. Emerging biological insights and reported variation in epidemiology challenge the validity of this definition.

OBJECTIVE—To develop a new definition and clinical criteria for identifying septic shock in adults.

DESIGN, SETTING, AND PARTICIPANTS—The Society of Critical Care Medicine and the European Society of Intensive Care Medicine convened a task force (19 participants) to revise current sepsis/septic shock definitions. Three sets of studies were conducted: (1) a systematic review and meta-analysis of observational studies in adults published between January 1, 1992, and December 25, 2015, to determine clinical criteria currently reported to identify septic shock and inform the Delphi process; (2) a Delphi study among the task force comprising 3 surveys and discussions of results from the systematic review, surveys, and cohort studies to achieve consensus on a new septic shock definition and clinical criteria; and (3) cohort studies to test variables identified by the Delphi process using Surviving Sepsis Campaign (SSC) (2005–2010; n = 28 150), University of Pittsburgh Medical Center (UPMC) (2010–2012; n = 1 309 025), and Kaiser Permanente Northern California (KPNC) (2009–2013; n = 1 847 165) electronic health record (EHR) data sets.

MAIN OUTCOMES AND MEASURES—Evidence for and agreement on septic shock definitions and criteria.

RESULTS—The systematic review identified 44 studies reporting septic shock outcomes (total of 166 479 patients) from a total of 92 sepsis epidemiology studies reporting different cutoffs and combinations for blood pressure (BP), fluid resuscitation, vasopressors, serum lactate level, and base deficit to identify septic shock. The septic shock–associated crude mortality was 46.5% (95%CI, 42.7%–50.3%), with significant between-study statistical heterogeneity (I^2 = 99.5%; τ^2 = 182.5; P < .001). The Delphi process identified hypotension, serum lactate level, and vasopressor therapy as variables to test using cohort studies. Based on these 3 variables alone or in combination, 6 patient groups were generated. Examination of the SSC database demonstrated that the patient group requiring vasopressors to maintain mean BP 65 mmHg or greater and having a serum lactate level greater than 2 mmol/L (18 mg/dL) after fluid resuscitation had a significantly higher mortality (42.3%[95%CI, 41.2%–43.3%]) in risk-adjusted comparisons with the other 5 groups derived using either serum lactate level greater than 2 mmol/L alone or combinations of hypotension, vasopressors, and serum lactate level 2 mmol/L or lower. These findings were validated in the UPMC and KPNC data sets.

CONCLUSIONS AND RELEVANCE—Based on a consensus process using results from a systematic review, surveys, and cohort studies, septic shock is defined as a subset of sepsis in which underlying circulatory, cellular, and metabolic abnormalities are associated with a greater risk of mortality than sepsis alone. Adult patients with septic shock can be identified using the clinical criteria of hypotension requiring vasopressor therapy to maintain mean BP 65 mmHg or greater and having a serum lactate level greater than 2 mmol/L after adequate fluid resuscitation.

Consensus definitions, generated in 1991[1] and revisited in 2001,[2] describe septic shock as a state of cardiovascular dysfunction associated with infection and unexplained by other causes. The increasing availability of large electronic health record (EHR) data sets, registries, national case mix programs, trial data sets, and claims databases using *International Classification of Diseases* code shave since generated multiple observational studies reporting septic shock epidemiology. However, variable interpretation and application of the consensus definitions[1,2] have contributed to variable estimates of both incidence and outcomes.[3–8] It is unclear to what extent these variations represent true differences or an artifact attributable to inconsistent use of definitions.[8,9] Furthermore, emerging insights into sepsis pathophysiology[10–13] warrant a review of the current septic shock definition and the criteria used to identify it clinically.

Against this background, the Society of Critical Care Medicine (SCCM) and the European Society of Intensive Care Med (ESICM) convened an international task force to review definitions of sepsis and septic shock in January 2014.To support the task force deliberations on redefining septic shock, a series of activities was performed: a systematic review and meta-analysis of criteria used in observational studies reporting sepsis epidemiology in adults; a Delphi study to achieve consensus; cohort studies using the Surviving Sepsis Campaign (SSC) registry; and subsequent testing of the applicability of the new criteria in patients with suspected infection from 2 large EHR-derived data sets. The aims of this study were to develop an updated septic shock definition and to derive clinical criteria for identifying patients with septic shock meeting this updated definition. Specifically, this updated definition and these criteria are intended to provide a standard classification to facilitate clinical care, future clinical research, and reporting.

Methods

In this article, “definition” refers to a description of septic shock and “clinical criteria” to variables used to identify adult patients with septic shock.

Task Force

The SCCM and ESICM each nominated cochairs of the task force and provided unrestricted funding support toward the work conducted. The 2 cochairs then selected 17 other task force participants based on their scientific expertise in sepsis epidemiology, clinical trials, and basic or translational research. Task force participants are listed at the end of the article. The task force retained complete autonomy for all decisions. ESICM and SCCM had no role in study design, conduct, or analysis but were consulted for peer review and endorsement of the manuscript.[14]

Systematic Review and Meta-analysis

The aims of the systematic review were to assess the different criteria used to identify adult patients with septic shock and whether these criteria were associated with differences in reported outcomes. MEDLINE was searched using search terms, MeSH headings, and combinations of *sepsis*, *septic shock*, and *epidemiology* and limits of human studies; adults 19 years or older; English-language publications; and publication dates between January 1, 1992 (1991 definitions[1]), and December 25, 2015. For full-text review, only noninterventional studies reporting sepsis epidemiology and all-cause mortality were included. Randomized clinical trials were excluded, because the additional inclusion and exclusion criteria might confound the effect of criteria on mortality (the study objective).[8] To avoid variability in outcomes related to specific pathogens, specific patient groups, and interventional before-and-after studies, studies reporting these populations were also excluded. Data were extracted on cohort recruitment period, cohort characteristics, setting, criteria used to identify septic shock, and acute mortality. Detailed methods, including search strategy, are presented in eMethods 1 and eTable 1 in the Supplement.

Delphi Study

To generate consensus on the septic shock definition and criteria, 3 face-to-face meetings, 3-round sequential pretested questionnaires, and email discussions among the task force participants were conducted. One task force member did not participate in these surveys because of lack of content expertise, and 1 did not respond to the first 2 surveys. Questionnaires were developed, refined, and administered consisting of single- and multiple-answer questions, free-text comments, and a 5-point Likert agreement scale. For consensus discussions and noting agreement, the 5-point Likert agreement scales were grouped at the tails of the scale choices (ie, “strongly disagree” grouped with “disagree”; “strongly agree” grouped with “agree”). All outputs from the systematic review, surveys, and the results of cohort studies were made available to participants throughout the Delphi study.

In the first round (August 2014), using 26 questions in 4 domains, agreement and opinions were explored on (1) components of the new septic shock definition; (2) variables and their cutoffs identified by the systematic review; (3) definitions of, and criteria for, hypotension, persistent hypotension, adequacy of resuscitation, and resuscitation end points; and (4) septic shock severity scoring. In the second round (November 2014), 4 questions were used to generate statements for key terms (persistent hypotension, adequacy of resuscitation, and septic shock) and to reach agreement on test variables and outcomes for subsequent analysis of predictive validity. The objectives of the third round (January 2015) were to establish a consensus definition of septic shock and related clinical criteria. In the third survey, the task force members were given 4 choices for the septic shock updated criteria ([1] serum lactate level alone; [2] hypotension alone; [3] vasopressor-dependent hypotension or serum lactate level; [4] vasopressor-dependent hypotension and serum lactate level) and were asked to provide their first and second choices. The cumulative first or second choices were used to agree on the reported septic shock criteria.

Questionnaire items were accepted if agreement exceeded 65%. Choices for which agreement was less than 65% were rediscussed to achieve consensus or were eliminated, as

appropriate to achieve the project aims. The survey questionnaires are presented in eMethods 2 in the Supplement.

Cohort Studies

The institutional review boards of Cooper University Hospital (Camden, New Jersey),[15] University of Piitsburgh Medical Center (UPMC; a network of hospitals in western Pennsylvania), and Kaiser Permanente Northern California (KPNC)[16] provided ethics approvals for research using the SSC and EHR data sets, respectively.

The SSC registry includes data collected from 218 hospitals in 18 countries on 28 150 patients with suspected infection who, despite adequate fluid resuscitation as judged by the collecting sites, still had 2 or more systemic inflammatory response syndrome criteria and 1 or more organ dysfunction criteria (eMethods 3 in the Supplement). The SSC database setup, inclusion, and reporting items are described in detail elsewhere.[6,17] To select clinical criteria for the new septic shock definition, an analysis data set was created that included all patients with a serum lactate level measurement or a mean arterial pressure less than 65 mmHg after fluids, or who received vasopressors.

For external validation, mortality was determined using the same clinical criteria in patients with suspected infection (cultures taken, antibiotics commenced) within 2 large EHR databases from UPMC (12 hospitals, 2010–2012,n = 1 309 025) and KPNC (20 hospitals, 2009–2013, n = 1 847 165). Three variables (hypotension, highest serum lactate level, and vasopressor therapy as a binary variable [yes/no]) were extracted from these 2 data sets during the 24-hour period after infection was suspected. Descriptive analyses, similar to those performed on the SSC data set, were then undertaken. Because of constraints on data availability, hypotension was considered present if systolic blood pressure was 100 mmHg or less for any single measurement taken during the 24-hour period after infection was suspected. Serum lactate levels were measured in 9% of infected patients at UPMC and in 57%of those at KPNC after implementation of a sepsis quality improvement program.

Statistics

Meta-analysis—A random effects meta-analysis of septic shock mortality by study-specific septic shock criteria and sepsis definitions was performed. Two meta-regression models of septic shock mortality were tested with the covariates: sepsis definition, criteria for shock, mid–cohort-year of study population, single center or multicenter, and World Health Organization member state regions.[18] These 2 models (with and without per capita intensive care unit beds) were generated to account for international cohorts and countries for which per capita intensive care unit bed data were unavailable (See eMethods 1 in the Supplement for details).

Cohort Studies—Hospital mortality was used as the primary outcome for derivation and descriptive validation analysis. Using the 3 dichotomous variables identified in round 2 of the Delphi process, the SSC cohort was divided into 6 groups and the variables tested either alone or in combination: (1) hypotension (mean arterial pressure <65 mm Hg) after fluid administration; (2) vasopressor therapy; and (3) serum lactate level greater than 2 mmol/L or

2 mmol/L or less (to convert serum lactate values to mg/dL, divide by 0.111). Hypotension was assumed when vasopressor therapy was being administered, generating 6 distinct potential septic shock patient groups using the 3 selected variables (eTable 5 in the Supplement). Analyses were performed using either the 6 groups or the 3 dichotomous variables as the risk factor. Subsequent analyses using the serum lactate level as a categorical variable were performed using a χ^2 test of trend for mortality.

Currently, there are no gold standard septic shock criteria for predictive validity comparisons.[8] Thus, these analyses aimed to identify a patient population that has the attributes of the newly proposed definition, which includes higher mortality compared with other patient populations commonly reported as having septic shock in the literature identified by the systematic review. Therefore, the independent relationship between the 3 potential criterion variables (hypotension, serum lactate level, and vasopressor therapy) agreed on the second round of the Delphi process and a future outcome (hospital mortality) was tested using 2 generalized estimating equation population-averaged logistic regression models with exchangeable correlation structure, where hospital site was the panel variable.

The first model used the potential septic shock groups 1 to 6 derived from these variables (eTable 5 in the Supplement), with group 1 as the referent group and adjusted for other covariates to assess true mortality difference between these groups. The second model assessed the independent association of these 3 potential criterion variables on hospital mortality adjusted for other covariates. These models also included an a priori adjustment variable for covariates including region (United States and Europe), location where sepsis was suspected (emergency department, ward, or critical care unit), antibiotic administration, steroid use, organ dysfunction (pulmonary, renal, hepatic, and acutely altered mental state), infection source (pneumonia, urinary tract infection, abdominal, meningitis and other), hyperthermia (>38.3°C), hypothermia (<36°C), chills with rigor, tachypnea (>20/min), leukopenia (<4000 cells/μL), hyperglycemia (plasma glucose level >120 mg/dL [6.7 mmol/L), platelet count <100 $\times 10^3$/μL, and coagulopathy.

These models were used to estimate acute hospital mortality odds ratios (ORs) and adjusted ORs for mortality per-unit increase in the serum lactate level using continuous natural log–transformed serum lactate level. The operating characteristics (sensitivity/specificity over hospital mortality curves; positive and negative predictive values) of different serum lactate cutpoints (2, 3, and 4 mmol/L) were also tested using the logistic regression model. Multiple imputations (n = 20) were used to assess the statistical effect of missing serum lactate values.

$P < .05$ (2-sided) was considered statistically significant. All analyses were performed using Stata version 13.1 (StataCorp).

Results

Systematic Review and Meta-analysis

The systematic review identified 44 studies (166 479 patients) reporting septic shock mortality[5–7,19–59] from a total of 92 studies reporting sepsis cohorts between 1987 and

2015[5–7,19–107] (Figure 1; eTable 2 in the Supplement). Different shock criteria were used for systolic blood pressure (<90 mmHg; <100 mmHg; decrease >40 mmHg; or decrease >50% of baseline value if hypertensive), mean arterial pressure (<70; <65; <60 mm Hg), serum lactate level (>4, >2.5, >2, >1 mmol/L) and base deficit (−5 mmol/L) (Table 1; eTable 2 in the Supplement). Temporal relationships between resuscitation status and end points to shock diagnosis were seldom reported. The studies differed in the description of resuscitation, persistent hypotension, and in their vasopressor definitions when using the cardiovascular Sequential [Sepsis-related] Organ Failure Assessment (SOFA) score categories.[113] Diverse infection and organ dysfunction codes were also used in the *International Classification of Diseases*–based derivations.[63,70,79,90] Variables highlighted in Table 1 and in eTable 2 in the Supplement informed the Delphi survey questions.

The random-effects meta-analysis showed significant heterogeneity in septic shock mortality (mean mortality, 46.5% [95% CI, 42.7%–50.3%], with a near 4-fold variation from 23.0% to 81.8%; I^2 = 99.5%; τ^2 = 182.5; and P < .001) (Figure 2). Statistically significant heterogeneity was also observed in random-effects meta-analysis by clinical criteria reported for septic shock case definition in studies (Table 2). The meta-regression models described could not explain this heterogeneity (eTable 3A and eTable 3B in the Supplement).

Delphi Study

In the first round, informed by the systematic review, 15 task force members (88%) voted to include persistent hypotension, vasopressor therapy, and hyperlactatemia in the updated criteria. There was no agreement on the lower cutoff for serum lactate level in this round. Eleven members (65%) voted that including fluid resuscitation would improve the criteria. The task force determined that neither a severity grading for septic shock nor criteria for either adequacy of fluid resuscitation or persistent hypotension should be proposed because of the nonstandardized use of hemodynamic monitoring, resuscitation protocols, and vasopressor dosing in clinical practice. (Other results are reported in eTable 4 in the Supplement.)

In Delphi round 2, the task force was provided with a preliminary descriptive analysis from the SSC database. With agreement on the description of the septic shock illness concept, 3 test variables (hypotension after fluid resuscitation, vasopressor therapy, and serum lactate level) were agreed on for predictive validity analyses. The “after fluids” field in the SSC database was used as a proxy for resuscitation. The need for vasopressors was agreed as a proxy for persistent hypotension by 95%of the task force. Twelve members (71%) voted that a minimum vasopressor dose should not be proposed in view of the variability in blood pressure targets and resuscitation protocols identified by the systematic review, and because of variable sedation use. Vasopressor therapy was therefore treated as a binary variable within the analysis. To derive an optimal cutoff for serum lactate level, 13 task force members (77%) agreed on acute hospital mortality as the outcome variable. The test variables could be present either alone or in combinations, thus identifying 6 potential groups of patients with septic shock (Table 3; eTable 5 in the Supplement).

Prior to the final round of the Delphi process, all analyses from the SSC data set and the EHR data sets were provided. These findings generated the new definition—“septic shock is

defined as a subset of sepsis in which underlying circulatory, cellular, and metabolic abnormalities are associated with a greater risk of mortality than sepsis alone"—and the clinical criteria described below.

Cohort Studies

SSC Database—Patients with serum lactate levels greater than 4 mmol/L who did not receive fluids as recommended by the SSCguidelines[111] (n = 790 [2.8%]) were excluded. Patients without any serum lactate values measured were excluded initially for full case analysis (n = 4419 [15.7%]) but were reassessed in the missing data analysis. Of the 22 941 remaining patients, 4101 coded as having severe sepsis were excluded from this analysis, generating the analysis set of 18 840 patients who were either hypotensive after fluids or required vasopressors or had a serum lactate level measurement (Figure 3 and Table 3). Hypotension was reported in 83.1%, serum lactate level greater than 2 mmol/L in 78.1%, and receipt of vasopressors in 66.4%. Overall, crude hospital mortality was 34.7%. Cohort characteristics by setting are shown in eTable 6 in the Supplement.

Predictive Validity of Potential Septic Shock Groups—Of the 6 groups of potential patients with septic shock (Table 3), the most prevalent was group 1 (hypotension + vasopressor therapy + serum lactate level >2 mmol/L) (n = 8520); followed by groups 2 (n = 3985) and 4 (n = 3266). Crude hospital mortality rates in these 3 groups were 42.3%, 30.1%, and 25.7%, respectively. Statistically significant increasing trends in crude mortality were observed over increasing serum lactate level categories within groups (χ^2 test of trend: $P < .001$ for groups 1 and 4, $P = .04$ for group 3). The adjusted OR for hospital mortality using group 1 for reference was significantly lower in all other groups ($P < .01$ for groups 2 to 6), suggesting that group 1 represents a distinct subpopulation with a significantly greater risk of death (eTable 7 in the Supplement). By a majority (cumulative first choice, 72.2%; second choice, 55.6%) (eTable 4 in the Supplement), the task force agreed that group 1 was most consistent with the proposed septic shock definition, thus generating the new septic shock criteria.

Derivation of Serum Lactate Cutoff Value and Missing Data Analysis—In the generalized estimating equation model (shown in eTable 8 in the Supplement), serum lactate level was associated with mortality, and the adjusted OR for hospital mortality increased linearly with increasing serum lactate level. An increase in serum lactate level from 2 to 10 mmol/L increased the adjusted OR for hospital mortality from 1.4 (95%CI, 1.35–1.45) to 3.03 (95%CI, 2.68–3.45) (referent lactate = 1; Figure 4). A serum lactate level greater than 2 mmol/L was chosen as the preferred cutoff value for the new septic shock criteria, the rationale being the trade-off between highest sensitivity (82.5% when using the n = 18 840 subset, and 74.9%when using patients in groups 1 and 2 combined [n = 12 475]), and the decision from the Delphi process to identify the lowest serum lactate level independently associated with a greater risk of death (OR of 1.4 at a lactate value of 2 mmol/L) (Table 4; eTable 9, eFigure 1, and eFigure 2 in the Supplement).

Predicated on this understanding of the SSC database structure and the regression analyses completed (eTable 6, eTable 7, and eTable 8 in the Supplement), we assumed that data were

missing at random; ie, any difference between observed values and missing values did not depend on unobserved data. Complete case analysis was therefore performed, followed by multiple imputation analysis to support the missing-at-random assumption.[114] The ORs for mortality per unit increase in serum lactate level using complete case analysis (n = 18 840) and imputed analyses (n = 22 182) were similar (1.09 [95%CI, 1.08–1.10]; $P < .001$ vs 1.09 [95%CI, 1.08–1.09]; $P < .001$, respectively). The imputed and complete case analysis probabilities of hospital mortality were also similar (36.4% and 35.5%, respectively).

EHR Data Sets

The UPMC and KPNC EHRs included 148 907 and 321 380 adult patients with suspected infection, respectively (eTable 10 in the Supplement). Forty-six percent (n = 5984) of UPMC patients and 39% (n = 54 135) of KPNC patients with 1 or more SOFA score points and suspected infection fulfilled criteria for 1 of the 6 potential septic shock groups described. Patients meeting group 1 criteria (hypotension + vasopressor therapy + serum lactate level >2 mmol/L) comprised 5.3% (UPMC) and 14.9% (KPNC) of the EHR population of patients with suspected infection and had a mortality of 54%and 35%, respectively. Similar to the SSC database, crude mortality rates within each group were higher among those with higher serum lactate levels (Table 5).

Discussion

The systematic review illustrated the variability in criteria currently used to identify septic shock, whereas the meta-analysis demonstrated the heterogeneity in mortality. Informed by this systematic review, a Delphi process was used to reach a consensus definition of septic shock and related clinical criteria. Three large data sets were then used to determine the predictive validity of these criteria. Septic shock was defined as a subset of sepsis in which circulatory, cellular, and metabolic abnormalities are associated with a greater risk of mortality than sepsis alone. The clinical criteria representing this definition were the need for vasopressor therapy to maintain a MAP of 65 mm Hg or greater and having a serum lactate level greater than 2 mmol/L persisting after fluid resuscitation.

The proposed definition and criteria of septic shock differ from prior definitions[1,2,111] in 2 respects: (1) the need for both a serum lactate level and vasopressor-dependent hypotension (ie, cardiovascular SOFA score ≥2) instead of either alone and (2) a lower serum lactate level cutoff of 2 mmol/L vs 4 mmol/L as currently used in the SSC definitions. In the new septic shock definition, an increase in serum lactate level is positioned as a proxy for a cellular metabolic abnormality, and as a variable independently associated with acute mortality (predictive validity), which is consistent with the published literature.[115–118] An elevated serum lactate level is not specific for cellular dysfunction in sepsis[118,119] but has face validity given the lack of a superior yet readily available alternative. This present study identifies a lower serum lactate level cutoff as an independent prognostic variable when compared with a recent analysis of the entire SSC database. This disparity is explained by using a data set of 18 840 patients in the analysis in this study rather than the total 28 150-patient SSC data set used by Casserly et al.[17] From this subpopulation 6 groups were identified and analyzed as risk strata within the generalized estimating equation model and

performance-tested for various serum lactate level cutoffs. The group with a significantly greater risk of death was then selected. In contrast, Casserly et al[17] reported the independent relationship of hypotension and serum lactate levels with mortality in severe sepsis.

The 6 potential septic shock patient groups analyzed in this study also provide an explanation for the heterogeneity in septic shock mortality highlighted by the meta-analysis. Depending on the group selected, septic shock mortality ranged from 12.8%to 51.2%within the SSC data set and from 7.0% to 64.0% in the EHR data sets. The KPNC EHR data set corroborated the consistent trends of higher mortality associated with a higher serum lactate level, even in a population with a wider range of illness severity captured by more prevalent measurement of serum lactate levels.

The key strengths of the present study are in the methodology used to arrive at the new definition and clinical criteria for septic shock, a clinical syndrome with a range of signs, symptoms, and biochemical abnormalities that are not pathognomonic. Furthermore, the supporting studies (systematic review, Delphi process, and analyses of the SSC and EHR cohorts) were iterative and concurrent with the consensus process, a significant step forward from previous definitions.

This study also has several limitations. First, the systematic review did not formally assess study quality and was restricted to MEDLINE publications, adult populations, and observational studies reporting epidemiology. Second, only the Delphi-derived variables were tested in multiple data sets to generate the proposed septic shock criteria. Other variables, including tissue perfusion markers (eg, base deficit, oliguria, acute alteration in mentation), blood pressure characteristics (eg, diastolic pressure), resuscitation end points (eg, central venous saturation, lactate clearance), and numerous biomarkers reported in the literature,[17] could potentially improve on the proposed septic shock criteria but were not included. However, operationalizing the definition of septic shock with 3 commonly measured variables should increase both generalizability and clinical utility. Third, the lack of a gold standard diagnostic criteria for septic shock[8] precludes comparative assessment of these proposed criteria. Fourth, all data sets had missing data that could potentially introduce a form of selection bias.[120] In the primary data set (SSC database) this issue was addressed by demonstrating that full case analysis is an appropriate method (see “Derivation of Serum Lactate Cutoff Value and Missing Data Analysis”). Fifth, serum lactate measurements are not universally available, especially outside of a critical care setting or in resource-limited environments. Although feasibility is a quality indicator for a definition,[8] identification of a critically ill patient would generally trigger obtaining a serum lactate measurement, both to stratify risk and to monitor the response totreatment.[17] Sixth, although the proposed new definition and clinical criteria for sepsis are arbitrary, these do have predictive validity for mortality, alongsidefaceandcontentvalidity.[8]

This study represents one step in an ongoing iterative process and provides a resourceful structure and a predictive validity standard for future investigations in this area. Prospective validation of the clinical criteria may improve on the variables and cutoffs proposed herein, and identification and validation of novel markers of organ dysfunction and shock may replace lactate level.[8]

Conclusions

Based on a consensus process using results from a systematic review, surveys, and cohort studies, septic shock is defined as a subset of sepsis in which underlying circulatory, cellular, and metabolic abnormalities are associated with a greater risk of mortality than sepsis alone. Adult patients with septic shock can be identified using the clinical criteria of hypotension requiring use of vasopressors to maintain mean blood pressure of 65 mm Hg or greater and having a serum lactate level greater than 2 mmol/L persisting after adequate fluid resuscitation.

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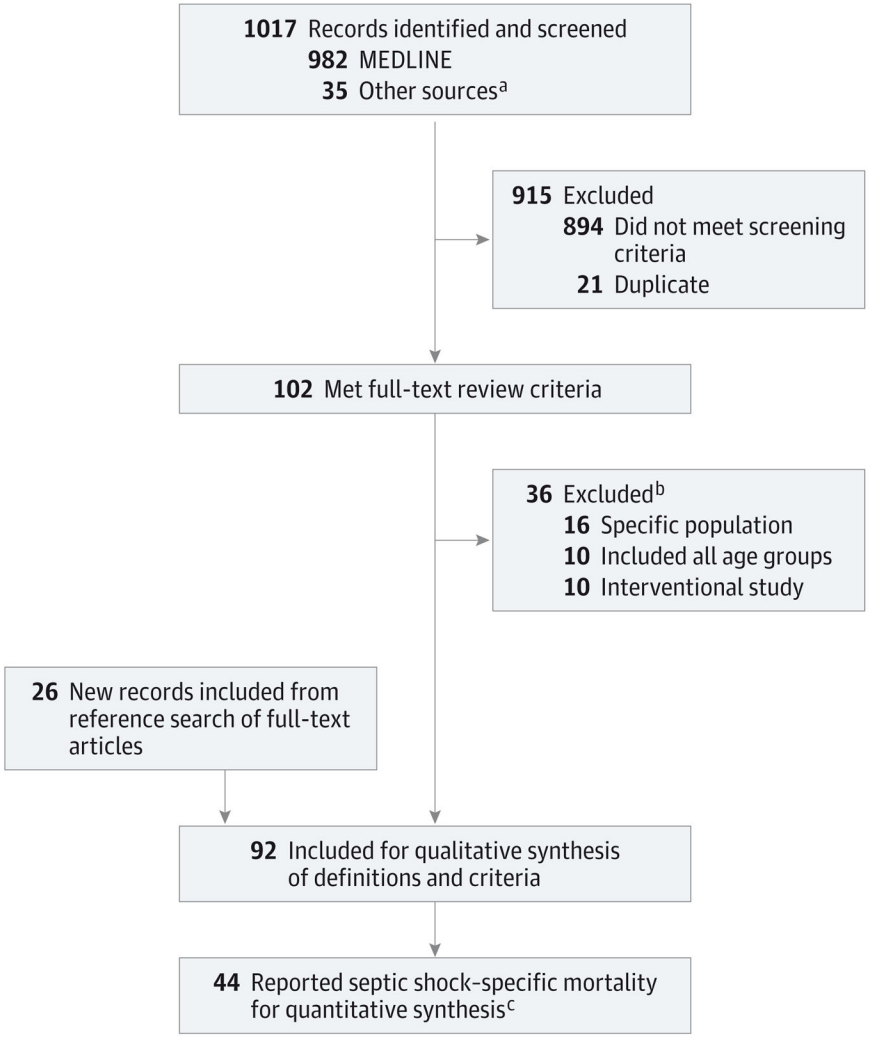

Figure 1.

Study Identification and Selection Process Used in the Systematic Review

[a]Nonduplicate references from other sources included review articles.[3,108–110] See eMethods 1 in the Supplement for further details of search strategy.

[b]Refers to records that were excluded after reference screening of full text articles. The screening criteria for full text inclusion were reporting of all case sepsis epidemiology in adult populations without specific assessment of interventions. The qualitative review assessed sepsis and septic shock definitions and criteria. The records included in the qualitative review (92 studies[5–7,19–107]) are presented in eTable 2 in the Supplement. The quantitative review assessed septic shock criteria and mortality.

[c]Refers to the records included for quantitative assessment of septic shock mortality and the heterogeneity by criteria using random-effects meta-analysis (44 studies[5–7,19–59]) (eTable 2 in the Supplement).

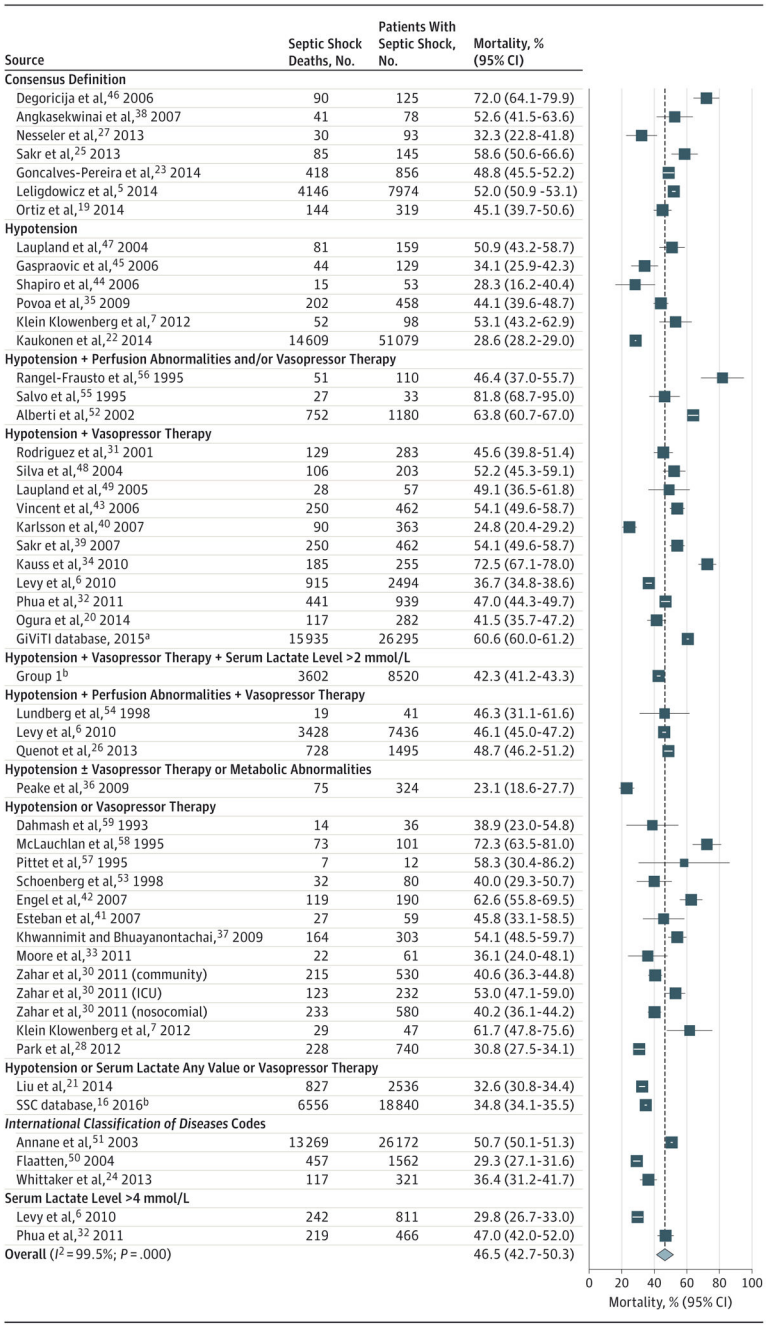

Figure 2.

Random-Effects Meta-analysis of Studies Identified in the Systematic Review, Reporting Septic Shock Mortality

Forty-four studies report septic shock–associated mortality[5–7,19–59] and were included in the quantitative synthesis using random-effects meta-analysis. The Surviving Sepsis Campaign (SSC) database analyses with similar data are reported in 2 studies[6,29]; therefore, only one of these was used in the meta-analysis reported.[6] Levy et al report 3 septic shock subsets,[6] Klein Klowenberg et al report 2 (restrictive and liberal),[7] Zahar et al report 3 (community-

acquired, ICU-acquired, and nosocomial infection–associated septic shock),[30] and Phua et al report 2 groups,[32] which were treated as separate data points in the meta-analysis. Studies under "consensus definition" cite the Sepsis Consensus Definitions.[1,2] The categorization used to assess heterogeneity does not fully account for septic shock details in individual studies.

SI conversion factor: To convert serum lactate values to mg/dL, divide by 0.111.

[a]Data obtained from GiViTI database provided by Bertolini et al (published 2015[8]).

[b]The mortality data of Group 1 patients (new septic shock population) and the overall potential septic shock patient populations (n = 18 840) described in the manuscript from the current study using the Surviving SSC database are also included in the meta-analysis. Septic shock–specific data were obtained from Australian & New Zealand Intensive Care Society Adult Patient Database (ANZICS), from a previously published report.[22] This results in 52 data points for random-effects meta-analysis.

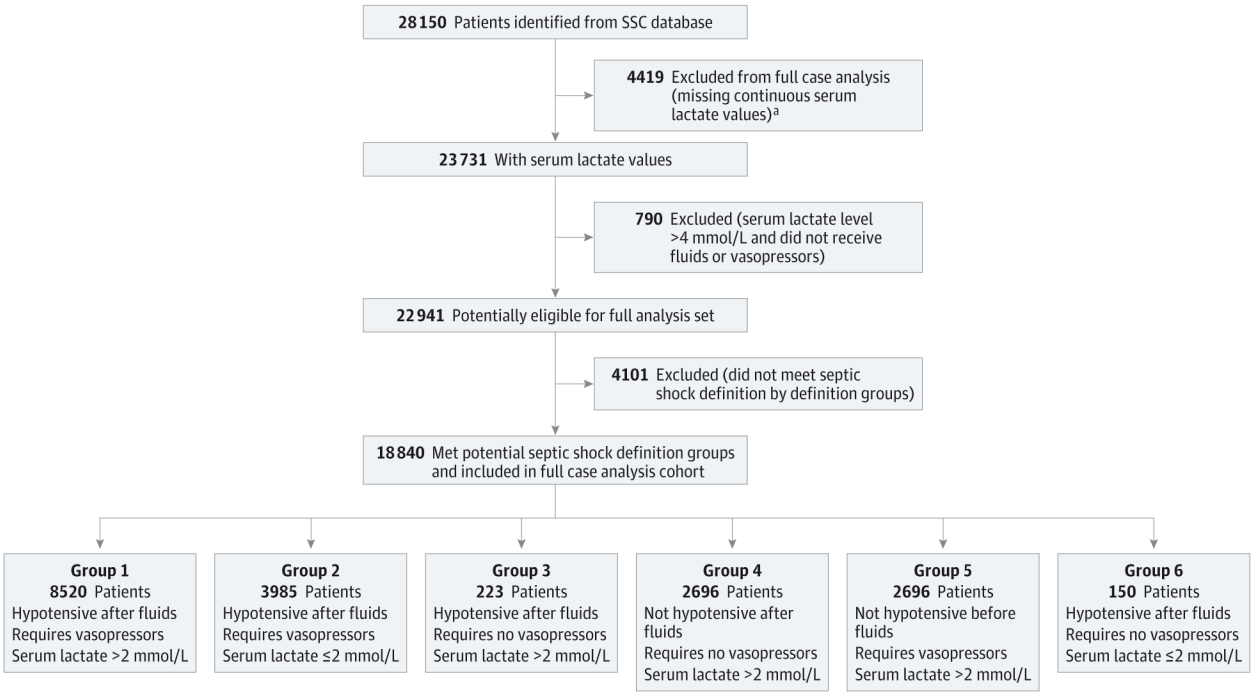

Figure 3.

Selection of Surviving Sepsis Campaign Database Cohort

Hypotension was defined as mean arterial pressure less than 65 mm Hg. Vasopressor therapy to maintain mean arterial pressure of 65 mm Hg or higher is treated as a binary variable. Serum lactate level greater than 2 mmol/L (18 mg/dL) is considered abnormal. The “after fluids” field in the Surviving Sepsis Campaign (SSC) database was considered equivalent to adequate fluid resuscitation. “Before fluids” refers to patients who did not receive fluid resuscitation. Serum lactate level greater than 2 mmol/L after fluid resuscitation but without hypotension or need for vasopressor therapy (group 4) is defined as “cryptic shock.” Missing serum lactate level measurements (n = 4419 [15.7%]) and patients with serum lactate levels greater than 4 mmol/L (36 mg/dL) who did not receive fluids as per SSC guidelines (n = 790 [2.8%]) were excluded from full case analysis. Of the 22 941 patients, 4101 who were coded as having severe sepsis were excluded. Thus, the remaining 18 840 patients were categorized within septic shock groups 1 to 6.

[a]Patients with screening serum lactate levels coded as greater than 2 mmol/L (n=3342) were included in the missing-data analysis.

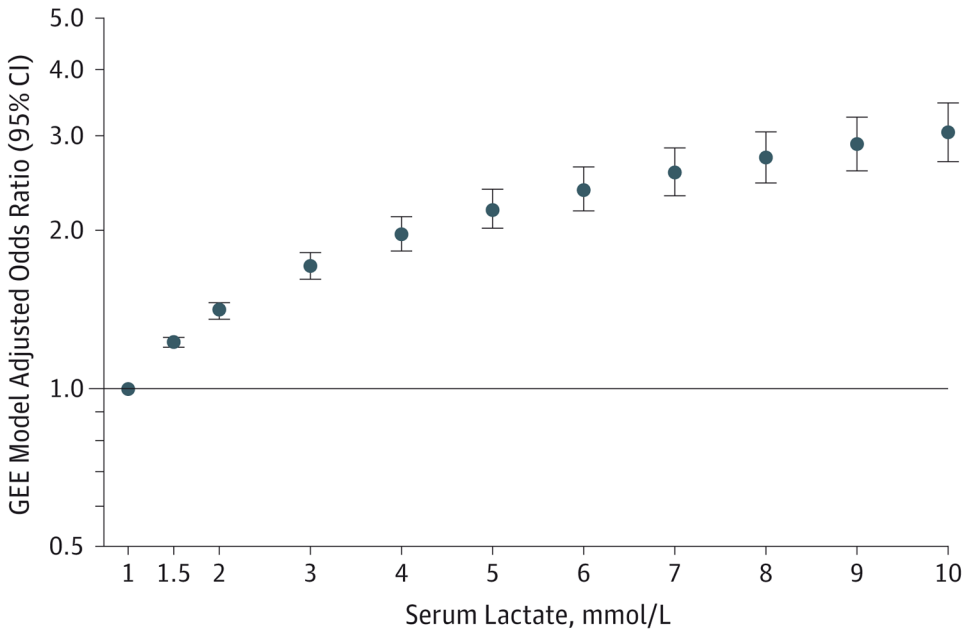

Figure 4.

Serum Lactate Level Analysis

Adjusted odds ratio for actual serum lactate levels for the entire septic shock cohort (N = 18 840). The covariates used in the regression model include region (United States and Europe), location where sepsis was suspected (emergency department, ward, or critical care unit), antibiotic administration, steroid use, organ failures (pulmonary, renal, hepatic, and acutely altered mental state), infection source (pneumonia, urinary tract infection, abdominal, meningitis, and other), hyperthermia (>38.3°C), hypothermia (<36°C), chills with rigor, tachypnea (>20/min), leukopenia (<4000 cells/μL), hyperglycemia (plasma glucose >120 mg/dL [6.7 mmol/L]), platelet count <100 $\times 10^3$/μL, and coagulopathy (eMethods 3 in the Supplement). The adjusted odds ratio (OR) for the 6 groups presented in eTable 7 in the Supplement and the adjusted OR for the individual variables (lactate, vasopressor therapy, and fluids) are reported in eTable 8 in the Supplement. To convert serum lactate values to mg/dL, divide by 0.111.

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Table 1

Summary of Septic Shock Definitions and Criteria Reported in the Studies Identified by the Systematic Review[a]

	Septic Shock Case Definitions and Corresponding Variables Reported in Literature				
	Consensus Definitions		Other Definitions		
Criteria	**Bone et al[1]**	**Levy et al[2]**	**SSC[111]**	**Trial-based[112]**	**Other Description of Criteria Variables**
Infection	Suspected or proven	Suspected or proven	Suspected or proven	Suspected or proven	Bacteremia, culture positive; CDC definitions for infection
SIRS criteria, No.	2	One or more of 24 variables[b]	2	3	NA
Septic shock description	Sepsis-induced hypotension despite adequate resuscitation OR receiving vasopressors/Inotropes plus presence of perfusion abnormalities	State of acute circulatory failure characterized by persistent arterial hypotension after adequate resuscitation unexplained by other causes	Sepsis-induced hypotension persisting despite adequate fluid resuscitation	Cardiovascular dysfunction defined as hypotension despite adequate resuscitation or need for vasopressors	Precoded data using *ICD-9* and *ICD-10* codes[c]
Hypotension, mm Hg					
Systolic BP	<90	<90	<90	<90	<100
Decrease in systolic BP	Decrease >40	Decrease >40	Decrease >40	NA<70	>50% decrease in hypertension
MAP	No	<60	<70	Hypotension lasting >1 h after resuscitation	<65
Adequate resuscitation definition	Not defined	Not defined	Goals set as CVP 8–12 mm Hg; urine output ≥0.5 mL/kg/h; $ScvO_2$ >70%	Not defined	After resuscitation fluids (0.5 L; 1 L; 1.5 L; 20 mL/kg ideal body weight
Vasopressor use	Yes (not absolute requirement)	Yes (CVS SOFA score)	Yes (not absolute requirement)	Yes (not absolute requirement)	Vasoactive drugs required for >30 min
Hypoperfusion abnormalities	Hypoperfusion abnormality defined as lactic acidosis; oliguria; low Glasgow Coma Score	Tissue hypoperfusion defined as serum lactate >1 mmol/L or delayed capillary refill	Tissue hypoperfusion defined as infection-induced hypotension, elevated serum lactate (>4 mmol/L), or oliguria	No description	Serum lactate >2.5 mmol/L; base deficit >5 mEq/L, alkaline reserve <18 mEq/L; CVP <8; PCWP <12
Data points from included studies, No. (%)[d]	39 (75)		13 (25)		

Criteria	Septic Shock Case Definitions and Corresponding Variables Reported in Literature				Other Description of Criteria Variables
	Consensus Definitions		Other Definitions		
	Bone et al[1]	Levy et al[2]	SSC[111]	Trial-based[112]	
Sample size, No.	158 354		8125		
Mortality by septic shock definition using random-effects meta analysis, % (95% CI)	47.2 (42.7–51.7)		44.2 (38.5–49.9)		
I^2, %[e]	99.6		95.9		
τ^2 [f]	191.21		94.9		
P value heterogeneity	<.001		<.001		

Abbreviations: BP, blood pressure; CDC, Centers for Disease Control and Prevention; CVP, central venous pressure; CVS, cardiovascular system; *ICD, International Classification of Diseases*; MAP, mean arterial pressure; NA, not applicable; PCWP, pulmonary capillary wedge pressure; SBP, systolic blood pressure; $ScvO_2$, central venous oxygen saturation; SIRS, systemic inflammatory response syndrome; SOFA, Sequential [Sepsis-related] Organ Failure Assessment; SSC, Surviving Sepsis Campaign.

SI conversion factor: To convert serum lactate values to mg/dL, divide by 0.111.

[a] The summary table was generated from eTable 2 data from 92 studies.[5–7,19–107]

[b] Levy et al highlight an extended variable list as a replacement for SIRS criteria consisting of general (n = 7); inflammatory (n = 5); hemodynamic (n = 3); organ dysfunction (n = 7) and tissue perfusion (n = 2) variables.[2]

[c] Different *ICD-9* codes are reported to identify septic shock in the literature. These include shock without trauma code 785.50 with all subcodes (785.51, 785.52, 785.59), hypotension code 458 with subcodes (458.0, 458.8 458.9), cardiovascular failure code 427.5 and the nonspecific low blood pressure code 796.3.

[d] Studies reporting 2 or more subsets,[6,7,30,32] current study (whole population and Group 1), and GiViTI database account for 52 data points from 44 studies. See Figure 2 notes for further details.

[e] I^2 is the percentage of between-study heterogeneity that is attributable to a true variability in septic shock mortality, rather than sampling variation, implying heterogeneity.

[f] τ^2 refers to the between-study variance within groups in random-effects meta-analysis.

Table 2

Random Effects Meta-Analysis by Septic Shock Criteria Groups

Septic Shock Case Definition Criteria[a]	No.[b]	Mortality, No. of Events/No. of Patients (%) [95% CI][c]	Heterogeneity Statistic[d]	df	*P* Value	I^2, %[e]	τ^2[f]
Consensus definitions cited (no description)	7	4954/9590 (51.6) [46.3–56.9]	53.2	6	<.001	88.7	39.9
Hypotension	6	15 003/51 976 (39.8) [30.1–49.5]	100.5	5	<.001	95.0	129.5
Hypotension + perfusion abnormalities and/or vasopressor therapy	3	830/1323 (63.3) [48.3–78.4]	20.4	2	<.001	90.2	155.8
Hypotension + vasopressor therapy	11	18 446/32 095 (48.9) [40.5–57.4]	919.8	10	<.001	98.9	195.8
Hypotension + vasopressor therapy + serum lactate level >2 mmol/L	1	3602/8520 (42.3) [41.2–43.3]		0			
Hypotension + perfusion abnormalities + vasopressor therapy	3	4175/8972 (47.0) [45.0–49.0]	3.4	2	.19	40.5	1.33
Hypotension ± vasopressor therapy or metabolic abnormalities	1	75/324 (23.1) [18.6–27.7]		0			
Hypotension or vasopressor therapy	13	1286/2971 (48.4) [41.3–55.5]	165.3	12	<.001	92.7	142.3
Hypotension or serum lactate any value or vasopressor therapy	2	7383/21 376 (33.9) [31.8–36.0]	4.9	1	.03	79.4	1.9
International Classification of Diseases codes	3	13 843/28 055 (38.9) [22.5–55.2]	343.8	2	<.001	99.4	205.6
Serum lactate level >4 mmol/L	2	461/1277 (38.3) [21.5–55.1]	32.6	1	.005	96.9	142.6
Overall	52	70 058/166 479 (46.5) [42.7–50.3]	11026.7	51	<.001	99.5	182.5

Abbreviation: df, degree of freedom.

SI conversion factor: To convert serum lactate values to mg/dL, divide by 0.111.

[a] Interpretation of the operationalization described for criteria to detect a septic shock case in individual studies reporting septic shock mortality.

[b] Number of data points from studies included in the systematic review shown in Figure 2 (see Figure 2 legend).

[c] Septic shock mortality was reported by 44 studies. Four studies report septic shock subsets[6,7,30,32]; data obtained from GiViTi database provided by Bertolini et al[8] and the current septic shock study resulting in 52 data points (further information provided in Figure 2 legend).

[d] The categorization used to assess heterogeneity does not fully account for septic shock details in individual studies.

[e] Percentage of between-study heterogeneity attributable to true variability in septic shock mortality, rather than sampling variation, implying heterogeneity.

[f] τ^2 refers to the between-study variance within groups in random-effects meta-analysis.

Table 3

Distribution of Septic Shock Cohorts and Crude Mortality From Surviving Sepsis Campaign Database (n = 18 840 patients)

Cohorts[a]	Lactate Category, mmol/L[b]	No. (% of total) [n = 18 840]	Acute Hospital Mortality, No. (%) [95% CI]	χ^2 Test for Trend	Mortality, Adjusted OR (95% CI)[c]	*P* Value[c]
Group 1 (hypotensive after fluids and vasopressor therapy and serum lactate levels >2 mmol/L)	>2 to ≤3	2453 (13.0)	818 (33.3) [31.5–35.3]	<.001	1 [Reference]	
	>3 to ≤4	1716 (9.1)	621 (36.2) [33.9–38.5]			
	>4	4351 (23.1)	2163 (49.7) [48.2–51.2]			
	All	8520 (45.2)	3602 (42.3) [41.2–43.3]			
Group 2 (hypotensive after fluids and vasopressor therapy and serum lactate levels ≤2 mmol/L)	≤2	3985 (21.2)	1198 (30.1) [28.6–31.5]	NA[d]	0.57 (0.52–0.62)	<.001
Group 3 (hypotensive after fluids and no vasopressors and serum lactate levels >2 mmol/L)	>2 to ≤3	69 (0.4)	15 (21.7) [12.7–33.3]	.04	0.65 (0.47–0.90)	.009
	>3 to ≤4	57 (0.3)	14 (24.6) [14.1–37.8]			
	>4	97 (0.5)	35 (36.1) [26.6–46.5]			
	All	223 (1.2)	64 (28.7) [22.9–35.1]			
Group 4 (serum lactate levels >2 mmol/L and no hypotension after fluids and no vasopressors)	>2 to ≤3	860 (4.6)	179 (20.8) [18.1–23.7]	<.001	0.71 (0.62–0.82)	<.001
	>3 to ≤4	550 (2.9)	105 (19.1) [15.9–22.6]			
	>4	1856 (9.9)	555 (29.9) [27.8–32.0]			
	All	3266 (17.3)	839 (25.7) [24.2–27.2]			
Group 5 (serum lactate levels between 2–4 mmol/L and no hypotension before fluids and no vasopressors)	>2 to ≤3	1624 (8.6)	489 (30.1) [27.9–32.4]	NA[d]	0.77 (0.66–0.90)	.001
	>3 to ≤4	1072 (5.7)	313 (29.2) [26.5–32.0]			
	>4	790[e]				
	All	2696 (14.3)	802 (29.7) [28.0–31.5]			
Group 6 (hypotensive after fluids and no vasopressors and serum lactate ≤2 mmol/L)	≤2	150 (0.8)	28 (18.7) [12.8–25.8]	NA[d]	0.32 (0.20–0.51)	<.001

Abbreviations: NA, not available; OR, odds ratio.

SI conversion factor: To convert serum lactate values tomg/dL, divide by 0.111.

[a] Mean arterial pressure less than 65 mm Hg was used to define hypotension. “After fluids” was defined using the field “crystalloids” coded as a binary term within the Surviving Sepsis Campaign database.

[b] Using χ^2 tests, trends in mortality across serum lactate categories within groups (>2 to ≤3 mmol/L; >3 to ≤4 mmol/L and >4 mmol/L) were assessed.

[c] Refers to the adjusted OR generated using generalized estimating equation regression model (eTable 7 in the Supplement).

[d] χ^2 test for trend could only be performed if there were 3 or more serum lactate categories.

[e] Excluded from full case analysis.

Table 4

Characteristics of Serum Lactate Level Cutoff Values for Complete Case Analysis and Imputation Analysis Using Surviving Sepsis Campaign Database

	Serum Lactate Level, mmol/L					
	>2		>3		>4	
Characteristic	Died/Total	% (95% CI)	Died/Total	% (95% CI)	Died/Total	% (95% CI)
Complete Case Analysis (n = 18 795)						
Hospital mortality, %	5757/18 795	30.6 (29.9–31.4)	6101/18 795	32.5 (31.8–33.2)	6456/18 975	34.3 (33.7–35.0)
Sensitivity, %	5372/6509	82.5 (81.6–83.4)	3779/6509	58.1 (56.8–59.3)	2811/6509	43.2 (42.0–44.4)
Specificity, %	2748/12 286	22.4 (21.6–23.1)	6418/12 286	52.2 (51.4–53.1)	8564/12 286	69.7 (68.9–70.5)
PPV, %	5372/14 910	36.0 (35.3–36.8)	3779/9647	39.2 (38.2–40.2)	2811/6533	43.0 (41.8–44.2)
NPV, %	2748/3885	70.7 (69.3–72.2)	6418/9148	70.1 (69.2–71.1)	8564/12 286	69.8 (69.0–70.7)
Imputed Missing Serum Lactate Level (n = 22 182)						
Hospital mortality, %	6965/22 182	31.4 (30.8–32.0)	7363/22 182	33.2 (32.6–33.8)	7772/22 182	35.0 (34.4–35.7)
Sensitivity, %	6457/7748	83.3 (82.5–84.2)	4461/7748	57.6 (56.5–58.7)	2931/7748	37.8 (36.7–38.9)
Specificity, %	3341/14 434	23.1 (22.5–23.8)	7833/14 434	54.3 (53.5–55.1)	10 801/14 434	74.8 (74.1–75.5)
PPV, %	6457/17 550	36.8 (36.1–37.5)	4461/11 062	40.3 (39.4–41.2)	2931/6564	44.6 (43.4–45.8)
NPV, %	3341/4634	72.1 (70.8–73.4)	7833/11 120	70.4 (69.6–71.3)	10 801/15 618	69.2 (68.4–69.9)

Abbreviations: NPV, negative predictive value; PPV, positive predictive value.

SI conversion factor: To convert serum lactate values tomg/dL, divide by 0.111.

Table 5

Crude Mortality in Septic Shock Groups From UPMC and KPNC Data sets

		UPMC			KPNC		
			Acute Hospital Mortality			Acute Hospital Mortality	
Variable[a]	Highest Serum Lactate Levels 24 h After Infection Identified, mmol/L	No. (%) (n = 5984)	No.	% (95% CI)	No. (%) (n = 54 135)	No.	% (95% CI)
Group 1	>2 (all)	315 (5.3)	171	54.3 (48.6–59.9)	8051 (14.9)	2835	35.2 (34.2–36.3)
	>3	246 (4.1)	147	59.8 (53.3–65.9)	6006 (11.1)	2355	39.2 (38.0–40.5
	>4	189 (3.2)	120	63.5 (56.2–70.4)	4438 (8.2)	1939	43.7 (42.2–45.2)
Group 2	≤2	147 (2.5)	37	25.2 (18.4–33.0)	3094 (5.7)	582	18.8 (17.4–20.2)
Group 3	>2 (all)	3544 (59.2)	1278	36.1 (34.5–37.7)	12 781 (23.6)	2120	16.6 (15.9–17.2)
	>3	2492 (41.6)	1058	42.5 (40.5–44.4)	6417 (11.9)	1381	21.5 (20.5–22.5)
	>4	1765 (29.5)	858	48.6 (46.3–51.0)	3316 (6.1)	914	27.6 (26.0–29.1)
Groups 4 and 5	>2 (all)	1978 (33.1)	355	17.9 (16.3–19.7)	30 209 (55.8)	2061	6.8 (6.5–7.1)
	>3	1033 (17.3)	224	21.7 (19.2–24.3)	12 450 (23.0)	1138	9.1 (8.6–9.7)
	>4	566 (9.4)	146	25.8 (22.2–29.6)	5394 (9.9)	637	11.8 (11.0–12.7)

Abbreviations: KPNC, Kaiser Permanente Northern California; SSC, Surviving Sepsis Campaign; UPMC, University of Pittsburgh Medical Center.

SI conversion factor: To convert serum lactate values tomg/dL, divide by 0.111.

[a]Group 1 refers to patients with hypotension + vasopressors + serum lactate levels greater than 2 mmol/L. Group 2 refers to patients with hypotension + vasopressors + serum lactate levels less than 2 mmol/L. Group 3 refers to patients with hypotension and serum lactate levels greater than 2 mmol/L. Groups 4 and 5 refer to isolated serum lactate level greater than 2 mmol/L. Counts within a group are not mutually exclusive, as those with serum lactate levels greater than 2 mmol/L will include those in the higher serum lactate cutoffs.