Published in final edited form as:

Ann Emerg Med. 2017 October ; 70(4): 544–552.e5. doi:10.1016/j.annemergmed.2017.01.008.

An Emergency Department validation of the SEP-3 Sepsis and Septic Shock definitions and comparison with 1992 Consensus definitions

Daniel J Henning, MD¹, Michael A Puskarich, MD², Wesley H Self, MD³, Michael D Howell, MD⁴, Michael W Donnino, MD^{5,6}, Donald M Yealy, MD⁷, Alan E Jones, MD², and Nathan I Shapiro, MD⁵

¹Division of Emergency Medicine, University of Washington, Seattle, WA

²Department of Emergency Medicine, University of Mississippi, Jackson, MI

³Department of Emergency Medicine, Vanderbilt, Nashville, TN

⁴Center for Healthcare Delivery Science and Innovation, University of Chicago Medicine, Chicago, Illinois

⁵Department of Emergency Medicine, Beth Israel Deaconess Medical Center, Boston, MA

⁶Department of Medicine, Division of Pulmonary and Critical Care, Beth Israel Deaconess Medical Center, Boston, MA

⁷Department of Emergency Medicine, University of Pittsburgh and UPMC, Pittsburgh, PA

Abstract

Background—The Third International Consensus Definitions Task Force (SEP-3) proposed revised criteria defining sepsis and septic shock. We sought to: 1) evaluate the performance of the SEP-3 definitions for prediction of in-hospital mortality in an Emergency Department (ED) population, and 2) compare the performance of the SEP-3 definitions to the previous definitions.

Methods—Secondary analysis of three prospectively collected, observational cohorts of infected ED subjects 18 years old. The primary outcome was all-cause in-hospital mortality. Based on the SEP-3 definitions, we calculated test characteristics of sepsis (qSOFA score ≥ 2) and septic shock (vasopressor dependence plus lactate >2.0 mmol/L) for mortality and compared them to the original 1992 consensus definitions.

Corresponding Author: Nathan I. Shapiro, MD, MPH, Beth Israel Deaconess Medical Center, Department of Emergency Medicine, 1 Deaconess Road, CC2-W, Boston, MA 02215, nshapiro@bidmc.harvard.edu.

Conflicts of Interest: DH, MH, DY, have no conflicts of interest to declare.

Author Contributions: DH, AJ, and NS were responsible for the study concept and design. Data analysis was performed by DH and NS, and all authors contributed to the interpretation of results. MH, DH, and NS created the included figures. DH and NS drafted the original manuscript, and all authors contributed to the review and editing of the final manuscript. All authors contributed to the decision to submit the manuscript for publication.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Results—We identified 7,754 ED patients with suspected infection overall; 117 had no documented mental status evaluation, leaving 7,637 patients included in the analysis. The mortality rate for the overall population was 4.4% (95% CI: 3.9 – 4.9%). The mortality rate for patients with qSOFA ≥ 2 was 14.2% (12.2 – 16.2%), with a sensitivity of 52% (46 – 57%) and specificity of 86% (85 – 87%) to predict mortality. The original SIRS-based 1992 consensus sepsis definition had a 6.8% (6.0 – 7.7%) mortality rate, sensitivity of 83% (79 – 87%) and specificity of 50% (49 – 51%). The SEP-3 septic shock mortality was 23% (16 – 30%), with a sensitivity of 12% (11 – 13%) and specificity of 98.4% (98.1 – 98.7%). The original 1992 septic shock definition had a 22% (17 – 27%) mortality rate, sensitivity of 23% (18 – 28%), and specificity of 96.6% (96.2 – 97.0%).

Conclusion—Both the new SEP-3 and original sepsis definitions stratify ED patients at risk for mortality, albeit with differing performances. In terms of mortality prediction, the SEP-3 definitions had improved specificity, but at the cost of sensitivity. Use of either approach requires a clearly intended target – more sensitivity versus specificity.

Introduction

In 1992, Bone et al published consensus definitions for sepsis revolving around the Systemic Inflammatory Response Syndrome (SIRS) criteria.¹ The SIRS construct helped to identify an inflammatory response, which in the presence of an infection defined “sepsis”.^{1,2} This unified communication in both the clinical and research settings. However, criticism arose around the definitions being overly sensitive and non-specific. For example, a young adult with routine streptococcal pharyngitis may exhibit fever and tachycardia, meeting the definition of sepsis; this patient often has no increased risk of severe short-term adverse effects from the infection. Over the last two decades, many noted the limitations of SIRS criteria,³⁻⁵ prompting calls to revisit the definition of sepsis.^{6,7}

The Third International Consensus Definitions Task Force (SEP-3) revisited the sepsis definitions and published a set of revised definitions.^{8,9} To aid the effort, research using two large datasets guided derivation of criteria to risk-stratify patients with infection based on the likelihood of in-hospital mortality. The quick SOFA (qSOFA) score emerged as a tool to identify those septic patients at higher risk of short-term death, drawing observations from initial features in the Emergency Department (ED) and other settings.¹⁰ The qSOFA score targets easy bedside application and uses three clinical criteria with each receiving one point if present: respiratory rate ≥ 22 breaths per minute, altered mental status, and hypotension defined by a systolic blood pressure (SBP) < 100 mmHg. A qSOFA score of two or greater was associated with an increased risk of mortality. The definitions group proposed using a suspected infection plus a qSOFA ≥ 2 to help identify patients with potential sepsis in the non-ICU setting. The SEP-3 authors state that qSOFA ≥ 2 should prompt clinicians to investigate for organ dysfunction, as these patients may be septic.

The SEP-3 group redefined “septic shock” as patients with hypotension requiring vasopressor support to maintain a mean arterial pressure of 65 mmHg *and* a lactate > 2.0 mmol/L after adequate resuscitation.^{8,11} This definition sought to select patients with a higher acuity by including vasopressors as a criteria along with a biochemical response. This

enhances specificity for the most ill septic patients, though the overall impact on care across the sepsis spectrum is unknown.

The SEP-3 authors acknowledge that these new definitions require validation in specific clinical settings, including the ED. We sought to: 1) to evaluate the performance of the SEP-3 qSOFA criteria and revised septic shock definition in predicting mortality in ED patients with a suspected infection, and 2) to compare the performance of the SEP-3 definitions to the previous 1992 Consensus criteria of sepsis, severe sepsis, and septic shock.

Methods

This is a secondary analysis of three prospectively collected, observational cohorts of patients with clinically suspected infection. The setting for the first two cohorts was a 600-bed, urban tertiary care center with approximately 50,000 ED visits per year, and the third cohort was enrolled in an 800-bed, urban academic tertiary care hospital with ~100,000 patient visits per year. The first cohort was enrolled between December 2003 - September 2004, the second cohort between September 2005 – September 2006, and the third cohort between July 2004 - June 2005 (Supplemental Table 1). The institutional review boards of both participating medical centers approved our study. We used the STROBE guidelines for reporting this observational study.¹²

Each study included subjects 18 years or older. To identify patients with suspected infection in the first two cohorts, we reviewed all patients with an ED admission diagnosis consistent with infection (i.e. pneumonia) or possibly infection related (i.e., shortness of breath); the inter-rater reliability for this approach was excellent (Cohen's $\kappa = 0.9$). All records with suspected infection underwent a confirmatory review based on ED presentation as documented in the medical decision making portion of the chart. We declared subjects as having a clinically suspected infection if they met any of the following criteria: 1) a documented source of infection; 2) documentation of a clinical diagnosis of infection by the ED clinician; or 3) administration of antibiotics in the ED. We assembled the third cohort of subjects using a standard random sampling methodology, using randomly selected 24-hour periods, equally dispersed over four 3-month blocks, resulting in 182 enrollment days.¹⁴ Inclusion criteria were ED patients age 18 years or older, hospital admission, and suspected infection defined by antibiotic administration in the ED. We abstracted ED charts without any subsequent knowledge of the hospital course. For the first two cohorts, subject data and outcomes were abstracted manually by trained research assistants, and in the third cohort, subject data was abstracted using a computer program with manual review, augmented by manual abstraction of any missing data and outcomes (Supplemental Table 1).

Definitions (Table 1)

SEP-3 definitions—We calculated the qSOFA score by assigning patients one point for each of the following: SBP ≥ 100 mm Hg, respiratory rate ≥ 22 breaths per minute, and/or altered mental status documented by the physician, using the most abnormal value during the care interval.^{8,9} We defined septic shock based on the SEP-3 criteria as a vasopressor infusion and a serum lactate concentration ≥ 2.0 mmol/L.¹¹

1992 Consensus criteria definitions—We defined sepsis as two or more SIRS criteria (heart rate ≥ 90 beats/minute, respiratory rate ≥ 20 breaths/minute, white blood cell count $\geq 12,000$ or $\leq 4,000$ cells/mm³ or bands $>10\%$, temperature ≥ 100.5 or $\leq 96^\circ$ F) plus a suspected infection, using vital signs and laboratory studies obtained at any point during the ED stay. We defined severe sepsis as suspected infection plus organ dysfunction. We used previously reported modified definitions for *organ dysfunction*: neurologic (altered mental status by history or exam), cardiovascular (systolic blood pressure <90 mm Hg), hematologic (platelets $<100,000$ cells/mm³, renal (creatinine >2.0 mg/dl not known to be chronic), metabolic (lactic acid >4.0 mmol/L), and pulmonary (respiratory rate >20 breaths per minute or hypoxemia, defined as pulse oximetry $<90\%$ on room air or 95% while breathing supplemental oxygen).¹⁵ We defined septic shock based on the 1992 Consensus guidelines as hypotension (SBP <90 mmHg) after fluid resuscitation or the initiation of vasopressor infusion.¹

We used the most abnormal vital signs during the ED stay, so definition criteria could be met at any point during the ED stay. We excluded subjects without documented mental status exams when assessing qSOFA. Similarly, we excluded those without a blood lactate measured when assessing the septic shock definition. The full data needed to assess the 1992 sepsis definitions were not available for the third cohort, so we calculated this portion only using the first two cohorts.

Outcomes

The primary outcome was all-cause in-hospital mortality, defined as death prior to hospital discharge.

Analysis

We calculated each individual patient qSOFA score, and we then calculated the sensitivity and specificity of qSOFA ≥ 2 for in-hospital mortality for each cohort and overall dataset. Likewise, we calculated the test characteristics for the prior definitions of sepsis (SIRS ≥ 2 plus a suspected infection) and severe sepsis for mortality in the first two datasets. We calculated an AUC for the qSOFA score to predict mortality in each cohort. As a sensitivity analysis, we recalculated the qSOFA test characteristics when the excluded patients from Cohort 3 were included with a presumed normal mental status. For septic shock, we report the test characteristic for sepsis syndromes defined by the 1992 Consensus guidelines and SEP-3 definitions of septic shock for in-hospital mortality in the first two datasets. When calculating test characteristics for the SEP-3 septic shock definition, we removed subjects without a lactate measured. As a sensitivity analysis, we re-calculated test characteristics after adding these patients back into the population and compared results. Lastly, to evaluate whether lactate concentrations would improve the predictive value of the qSOFA score, we performed a sensitivity analysis by adding patients with lactate >2.0 mmol/L and 4.0 mmol/L to the SEP-3 sepsis definition. We also calculated the net reclassification improvement (NRI) to quantify the improvement in risk stratification when including a lactate concentration.

Role of the funding source

There is no funding source to report.

Results

There were a total of 7,754 patients with suspected infection among the three eligible ED cohorts. There were 117 patients without a mental status exam excluded from the third cohort, leaving 7,637 patients for analysis (Figure 1). Among this group, 333/7637 (4.4%, 95% CI: 3.9 – 4.9%) died in-hospital. The demographics, comorbid distribution, and the rates of adverse outcomes were similar among the three cohorts (Table 2).

Among the combined datasets, 15.9% (95% CI: 15.1 – 16.7%) of patients met the proposed SEP-3 sepsis criteria of qSOFA ≥ 2 in the ED (Table 3). The in-hospital mortality was 14.2% (12.2 – 16.2%) for those with a qSOFA ≥ 2 compared to 2.5% (2.1 – 2.9%) for qSOFA < 2 . Overall, the sensitivity of qSOFA ≥ 2 to predict in-patient mortality was 52% (46 – 57%) and specificity was 86% (85 – 87%) (Table 3). The operating test characteristics were similar across the three cohorts supporting the validity of the findings. The sensitivity analysis that included the originally excluded patients from Cohort 3 resulted in similar test characteristics (Supplemental Table 2). The overall AUC for qSOFA was 0.77 (Cohort 1: 0.79, Cohort 2: 0.76, Cohort 3: 0.76).

When utilizing the 1992 sepsis criteria based on having two or more SIRS criteria, 50.2% (49.0 – 51.4%) of subjects met the sepsis definition (Table 3). Compared to the qSOFA definition, the 1992 sepsis criteria subjects had a lower overall mortality rate of 6.8% (6.0 – 7.7%), with a higher sensitivity of 83% (79 – 87%) and lower specificity of 50% (49 – 51%) for predicting mortality. We also assessed the 1992 definition for severe sepsis, which was not included in the revised definitions. For severe sepsis, 37.5% (36.4 – 38.7%) of subjects met the 1992 Consensus definition, with a mortality rate of 9.7% (8.5 – 10.9%), a 78% (73 – 83%) sensitivity and 64% (63 – 65%) specificity. The severe sepsis definition had a higher sensitivity than the qSOFA score, but lower specificity. Compared to the 1992 sepsis definition, sensitivity was similar, but specificity was higher.

Of the 6750 subjects in the first two cohorts, using qSOFA ≥ 2 to screen for septic patients instead of ≥ 2 SIRS criteria resulted in 2385 (35%, 34 – 36%) less patients meeting criteria for sepsis. Among the 2385 patients who were qSOFA negative were 93 (28%) of the 333 deaths in the group.

In the 4526 patients with a lactate level available, we assessed the SEP-3 septic shock definition. There were 2.9% (2.4 – 3.4%) of subjects who met the SEP-3 criteria for septic shock, and 22.9% (15.7 – 30.1%) of these died (Table 4). Overall, the SEP-3 septic shock definition had a sensitivity of 12% (11 – 13%) and specificity of 98.4% (98.1 – 98.7%) for mortality when considering all patients meeting study inclusion criteria. We performed a sensitivity analysis by adding patients with missing lactate measurements and assuming values were normal; the results were similar (Supplemental Table 3). There were 4.2% (3.7 – 4.7%) of patients who met the 1992 Consensus definition of septic shock. In comparison to the SEP-3 septic shock definition, the 1992 Consensus definition had a comparable in-hospital mortality rate of 22.2% (17.4 – 27.0%), with a higher sensitivity of 23% (22 – 24%) and similar specificity of 96.6% (96.2 – 97.0%).

Testing the addition of lactate

To evaluate whether including lactate concentrations would improve the predictive value of the qSOFA score, we performed a sensitivity analysis by adding patients with lactate >2.0 mmol/L and 4.0 mmol/L to those meeting the SEP-3 sepsis definition (Table 5). Adding a lactate >2.0 mmol/L to the SEP-3 qSOFA score improved the sensitivity of the definition, while decreasing the specificity, compared to qSOFA 2 alone. The NRI when including lactate >2.0 mmol/L was 11%: 22/83 (29%) events correctly moved to an increased risk category and 380/2049 (18%) non-events incorrectly moved to increased risk category. The NRI when including lactate >4.0 mmol/L was 9%: 29/276 (11%) events correctly increased risk category and 127/6474 (2%) non-events with incorrectly increased risk category.

Limitations

One limitation to utilizing the SEP-3 approach is the construct of using mortality as a gold standard for the definition of a disease state. Using mortality to define sepsis or septic shock carries a risk that septic patients are misclassified as not having the disease. Some patients who may be critically ill with sepsis and manifest all of the pathophysiologic derangements of the disease survive, while some who die may not actually have sepsis.

As with any secondary analysis, we collected these data used for another purpose, with the possibility of misclassification bias through incomplete data recording or assessment of covariates. However, those studies targeted the same topic and outcomes, mitigating the risk. Like any clinical trial, threats from missing data exist, especially with mental status exams (in Cohort 3) and lactate measurements. We did analyze the SEP-3 septic shock definition with and without the patients missing measured lactate levels with essentially equivalent results, again mitigating the concern. We did not prospectively ask that each data element be assessed for the specific purpose of the current study. The omission of qSOFA and organ dysfunction criteria could change the test characteristics for qSOFA and severe sepsis in each cohort.

Our datasets did not include patients who were discharged from the ED, potentially overestimating the specificity of each definition since discharged patients have an inherently lower risk of mortality. The timing of the observation (2003 – 2006) may also create observations that could vary if applied to a more contemporaneous population. However, the similarity between the mortality rates seen in this study and the SEP-3 derivation study make the likelihood that mortality is overestimated in our study less likely. Lastly, patients with infection may have been missed in the ED, potentially causing a selection bias if patient with missed infection had different predictors of mortality than those with infection diagnosed in the ED.

Discussion

The consensus sepsis definition efforts initiated more than 25 years ago created a foundation for both the clinical identification and research of sepsis. Since sepsis continues to be defined in the context of mortality risk instead of a defining underlying pathophysiologic mechanism, the challenge of balancing sensitivity and specificity for the prediction of

mortality continues with the SEP-3 iteration of the sepsis definitions. Having an approach that fits the needs of both the clinical and research environments is challenging, recognizing that trade-off between sensitivity, specificity, and bedside usability varies based on the setting and application.

The SEP-3 definitions of septic shock identified far fewer patients compared to the 1992 consensus definition of septic shock, yet definitions shared a similar mortality rate (23% vs 22%) in our cohorts. While the SEP-3 criteria for septic shock more narrowly defines the target population, this occurs at the trade-off of identifying fewer patients. It is possible that the lower number of patients meeting SEP-3 septic shock criteria will limit both the clinical and research utility of these criteria. Similarly, qSOFA is not inherently better or worse than SIRS criteria for identifying those at risk for sepsis and harm - these tools each embrace different predictive outcomes, one targeting a sensitive approach (SIRS of 2 or more) suited for early care and allowing fewer missed cases of progression, and another focusing on a specific identification of the higher strata of illness (qSOFA) that can aid later care decisions and pool cohorts with narrow but high risk of death. Depending on the clinical setting, one approach may be superior – though in the ED, early care often seeks avoiding delayed recognition and care to improve overall later outcomes. In contrast to the SEP-3 conclusions, serum lactate levels improved the sensitivity of qSOFA and modestly improved the classification of patients at both the 2 mmol/L and 4 mmol/L thresholds.

Our data also highlight the utility of the original 1992 “severe sepsis” definition – a term dropped in SEP-3 – as a meaningful criteria and risk stratification approach, especially early in care. Patients meeting severe sepsis criteria had a mortality rate of 9.7%, while maintaining a similar sensitivity (78%) to the 1992 Consensus definition of “sepsis,” but with a higher specificity. The severe sepsis definition identified more patients with infection that will suffer in-hospital mortality than qSOFA 2, with a specificity of 64%, indicating reasonable utility in identifying sick patients for clinical purposes and research. Compared with a SOFA score 2 in the SEP-3 validation cohort, which had 68% sensitivity and 67% specificity in the non-ICU setting, the severe sepsis test characteristics likewise compare favorably. Severe sepsis appears to preserve the screening strength of SIRS and the research utility of qSOFA 2, and as a prognostic test, we submit that it may be a better definition of sepsis than either the 1992 sepsis definition or proposed SEP-3 qSOFA definition. Additionally, the notion of organ-compromising infection has face validity and overall warrants future consideration.

Conclusions

We found that both the new SEP-3 and original sepsis definitions stratify ED patients at risk for mortality, albeit with differing performances. Compared to the SIRS-based 1992 Consensus sepsis definition, the revised SEP-3 definitions and qSOFA risk assessment tool are generally less sensitive but more specific for mortality. The lower sensitivity and more narrow population meeting criteria should be recognized when integrating either definition into ED clinical care. Future efforts may consider revisiting the prior severe sepsis definition as an alternative based on its better balance of sensitivity and specificity.

Acknowledgments

MP and AJ report grant funding from the NIH. MD reports grant funding from Bristol Myers Squibb. WS reports grant funding from BioMerieux, Affinium Pharmaceuticals, Astute Medical, BRAHMS GmbH/Thermo-Fischer, Pfizer, Rapid Pathogen Screening, BioAegis Inc., and Sphingotec GmbH; consulting fees from Abbott Point of Care and Cemptra Pharmaceuticals; and stipends for participating in the Scientific Advisory Committees for Vanaxis Inc and BioFire Diagnostics. NS reports his involvement in the DSMB of Cumberland Pharmaceuticals and grant support from Cheetah Medical, Thermo-Fischer, and Rapid Pathogen Screening

References

1. Bone RC, Balk RA, Cerra FB, et al. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. The ACCP/SCCM Consensus Conference Committee. American College of Chest Physicians/Society of Critical Care Medicine. *Chest*. 1992; 101(6): 1644–1655. [PubMed: 1303622]
2. Levy MM, Fink MP, Marshall JC, et al. 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. *Critical Care Medicine*. 2003; 31(4):1250–1256. [PubMed: 12682500]
3. Jones AE, Shapiro NI, Trzeciak S, et al. Lactate clearance vs central venous oxygen saturation as goals of early sepsis therapy: a randomized clinical trial. *JAMA : the journal of the American Medical Association*. 2010; 303(8):739–746. [PubMed: 20179283]
4. Kaukonen KM, Bailey M, Pilcher D, Cooper DJ, Bellomo R. Systemic inflammatory response syndrome criteria in defining severe sepsis. *New England Journal of Medicine*. 2015; 372(17): 1629–1638. [PubMed: 25776936]
5. Gille-Johnson P, Hansson KE, Gårdlund B. Severe sepsis and systemic inflammatory response syndrome in emergency department patients with suspected severe infection. *Scand J Infect Dis*. 2013; 45(3):186–193. [PubMed: 23113708]
6. Vincent JL, Opal SM, Marshall JC, Tracey KJ. Sepsis definitions: time for change. *Lancet*. 2013; 381(9868):774–775. [PubMed: 23472921]
7. Balk RA. Systemic inflammatory response syndrome (SIRS) Where did it come from and is it still relevant today? *Virulence*. 2014; 5(1):20–26. [PubMed: 24280933]
8. Singer M, Deutschman CS, Seymour CW, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *JAMA*. 2016; 315(8):801–810. [PubMed: 26903338]
9. Seymour CW, Liu VX, Iwashyna TJ, et al. Assessment of Clinical Criteria for Sepsis: For the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *JAMA*. 2016; 315(8): 762–774. [PubMed: 26903335]
10. Moskowitz A, Andersen LW, Cocchi M, Donnino MW. The Misapplication of Severity-of-Illness Scores Toward Clinical Decision Making. *Am J Respir Crit Care Med*. 2016 epub ahead of publication.
11. 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(8):775–787. [PubMed: 26903336]
12. von Elm E, Altman DG, Egger M, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *Lancet*. 2007; 370(9596):1453–1457. [PubMed: 18064739]
13. Shapiro NI, Howell MD, Talmor D, et al. Serum lactate as a predictor of mortality in emergency department patients with infection. *Annals of Emergency Medicine*. 2005; 45(5):524–528. [PubMed: 15855951]
14. Howell MD, Donnino M, Clardy P, Talmor D, Shapiro NI. Occult hypoperfusion and mortality in patients with suspected infection. *Intensive Care Med*. 2007; 33(11):1892–1899. [PubMed: 17618418]
15. Jones AE, Yiannibas V, Johnson C, Kline JA. Emergency department hypotension predicts sudden unexpected in-hospital mortality: a prospective cohort study. *Chest*. 2006; 130(4):941–946. [PubMed: 17035422]

16. Shapiro NI, Howell MD, Bates DW, Angus DW, Ngo L, Talmor D. The Association of Sepsis Syndrome and Organ Dysfunction With Mortality in Emergency Department Patients With Suspected Infection. *Annals of Emergency Medicine*. 2006; 48(5):1–9. [PubMed: 16781914]
17. Shapiro NI, Wolfe RE, Moore RB, Smith E, Burdick E, Bates DW. Mortality in Emergency Department Sepsis (MEDS) score: A prospectively derived and validated clinical prediction rule. *Critical Care Medicine*. 2003; 31(3):670–675. [PubMed: 12626967]
18. Howell MD, Talmor D, Schuetz P, Hunziker S, Jones AE, Shapiro NI. Proof of principle: The predisposition, infection, response, organ failure staging system. *Critical Care Medicine*. 2001; 39(2):322–327.

Figure 1.

STROBE guidelines flowchart demonstrating the cohorts used and the number of patients in each that met criteria for each definition.

Figure 2.

Proportional demonstration of the incidence of SIRS-based and qSOFA-based sepsis definitions, as well as the overlap with mortality among all ED patient with infection. Percentages in white demonstrate the proportion of each definition and mortality among the 6750 patients between Cohorts 1 and 2. Percentages in black boxes denote the proportion of total patients with each sepsis definition combination, with and without mortality. Of patients who died, 8/276 (2.9%) were identified by qSOFA alone, 101/276 (36.5%) by SIRS alone, 128/276 (46.4%) by both criteria, and 39/276 (14.2%) did not meet either criteria.

Figure 3. Visual demonstration of sensitivity (top) and specificity (bottom) for both SIRS-based, qSOFA-based, and severe sepsis definitions. qSOFA detected 21% fewer patients with infection who died during hospitalization compared to SIRS.

Table 1

Criteria used to define sepsis, severe sepsis, and septic shock.

1992 Consensus Definitions		SEP-3 Definitions	
Sepsis	<i>2 of more Systemic Inflammatory Response Syndrome (SIRS) Criteria:</i> <ul style="list-style-type: none"> • Temperature > 38 C or < 36 C • Heart Rate > 90 beats/minute • Respiratory Rate > 20 breaths/minute • White Blood Cell count > 12,000 cells/mL³ 	Sepsis	<i>2 or more qSOFA criteria:</i> <ul style="list-style-type: none"> • Respiratory Rate > 20 breaths/minute • Systolic Blood Pressure < 100 mmHg • Altered Mental Status
Severe Sepsis	<i>Sepsis + Evidence of organ dysfunction:</i> <ul style="list-style-type: none"> • Neurologic: Altered Mental Status by history or exam • Cardiovascular: SBP < 90 mmHg after fluid challenge • Metabolic: Lactate > 4.0 mmol/L • Hematologic: Platelets < 100,000 cells/mL³ • Renal: Creatinine > 2.0 mg/dL, not known to be chronic • Pulmonary: Respiratory rate > 20 breaths/minute or Pulse oximetry < 90% on room air or < 95% while breathing supplemental oxygen > 4 L/min 		
Septic Shock	<i>Sepsis + Evidence of hypoperfusion:</i> <ul style="list-style-type: none"> • Vasopressor Requirement • Hypotension after at least 2 L intravenous fluids 	Septic shock	<i>Vasopressor requirement to maintain MAP > 65 and serum lactate > 2.0 mmol/L</i>

Table 2

Demographics, comorbidities, and mortality.

Covariate	Cohort 1	Cohort 2	Cohort 3
n	2132	4618	887
Demographics			
Male %	1112 (52.2)	2236 (51.6)	451 (50.9)
Age, mean (SD)	56.9 (20.8)	59.9 (19.9)	54.4 (18.9)
Vital Signs (SD)			
Max Heart Rate (beats/minute)	96 (20.3)	97 (20.7)	105 (21.5)
Max Respiratory Rate (Breaths/Minute)	21 (5.7)	21 (5.9)	24 (6.8)
Min Systolic Blood Pressure (mmHg)	119 (25.8)	116 (24.0)	116 (25.0)
Comorbidities (%)			
Diabetes	565 (26.5)	1040 (22.5)	211 (23.8)
COPD	268 (12.6)	357 (7.7)	147 (16.6)
Malignancy	43 (2.0)	124 (2.7)	50 (5.6)
Liver Disease	138 (6.5)	286 (6.2)	48 (5.4)
Overall Mortality (%)	83 (3.9)	193 (4.2)	57 (6.4)

Table 3

Prevalence, mortality, and test characteristics for the SEP-3 sepsis definition and the 1992 Consensus definition of sepsis and severe sepsis. Sens = sensitivity, spec = specificity, PPV = positive predictive value, and NPV = negative predictive value.

Population	Total n	Criteria Fulfilled n (%)	Mortality n (%)	Sens % (95% CI)	Spec % (95% CI)	PPV % (95% CI)	NPV % (95% CI)
qSOFA 2							
Overall	7637	1214 (15.9)	172 (14.2)	52 (46 - 57%)	86 (85 - 87%)	14 (13 - 15%)	98 (98-98%)
Cohort 1	2132	314 (14.7)	45 (14.3)	54 (44 - 65%)	87 (85 - 88%)	14 (10 - 18%)	98 (97 - 99%)
Cohort 2	4618	689 (14.9)	91 (13.5)	47 (40 - 54%)	87 (86 - 88%)	14 (13- 15%)	97 (97 - 97%)
Cohort 3	887	211 (23.8)	36 (17.1)	63 (51 - 76%)	79 (76 - 82%)	14 (12 - 16%)	97 (96 - 98%)
Sepsis*							
Overall	6750	3388 (50.2)	229 (6.8)	83 (79 - 87%)	50 (49 - 51%)	7 (6 - 8%)	96 (96 - 96%)
Cohort 1	2132	1064 (49.9)	70 (6.6)	84 (77 - 92%)	52 (41- 62%)	7 (6 - 8%)	99 (99 - 99%)
Cohort 2	4618	2324 (50.3)	159 (6.8)	82 (77 - 88%)	51 (50 - 53%)	7 (6 - 8%)	99 (99 - 99%)
Severe Sepsis*							
Overall	6750	2241 (33.2)	216 (9.7)	78 (73 - 83%)	64 (63 - 65%)	10 (9 - 11)	99 (99 - 99%)
Cohort 1	2132	774 (36.2)	70 (9.0)	84 (77 - 92%)	66 (64 - 68%)	9 (7 - 11%)	99 (99 - 99%)
Cohort 2	4618	1467 (31.8)	146 (10.0)	76 (70 - 82%)	70 (69 - 72%)	10 (9 - 12%)	99 (99 - 99%)

* Modified version of the 1992 Consensus Guidelines for sepsis definitions. 16

Prevalence, mortality, and test characteristics for the SEP-3 septic shock definition and the 1992 Consensus definition of septic shock. Sens = sensitivity, spec = specificity, PPV = positive predictive value, and NPV = negative predictive value.

Table 4

Population	Total n	Criteria Fulfilled (%)	Mortality (%)	Sens (%) (95% CI)	Spec (%) (95% CI)	PPV (%) (95% CI)	NPV (%) (95% CI)
SEP-3 Septic Shock							
Overall	4526	131 (2.9)	30 (22.9)	12 (11 - 13%)	98 (98 - 98%)	23 (22 - 24%)	95 (94 - 96%)
Cohort 1	1287	17 (1.3)	7 (41.8)	10 (8 - 12%)	99 (98 - 100%)	41 (38 - 44%)	95 (94 - 96%)
Cohort 2	3239	114 (3.5)	23 (20.1)	13 (12 - 14%)	97 (96 - 98%)	20 (19 - 21%)	95 (94 - 96%)
1992 Consensus Guidelines Septic Shock							
Overall	6750	283 (4.2%)	63 (22.2%)	23 (22 - 24%)	97 (97 - 97%)	22 (21 - 23%)	97 (97 - 97%)
Cohort 1	2132	121 (5.7%)	35 (28.9%)	13 (6 - 21%)	98 (97 - 98%)	29 (27 - 31%)	98 (97 - 99%)
Cohort 2	4618	162 (3.5%)	28 (17.3%)	15 (10 - 20%)	97 (97 - 98%)	17 (12 - 23%)	96 (95 - 97%)

Table 5

Incidence, mortality, and test characteristics for the SEP-3 sepsis definition when patients with lactate > 2.0mmol/L or >4.0mmol/L are included in the definition. Sens = sensitivity, spec = specificity, PPV = positive predictive value, and NPV = negative predictive value.

Population	Total n	Criteria Fulfilled (%)	Mortality n (%)	Sens (%) (95% CI)	Spec (%) (95% CI)	PPV (%) (95% CI)	NPV (%) (95% CI)
qSOFA 2	7637	1214 (15.9%)	172 (14.2%)	52% (46 - 57%)	86 (85 - 87%)	14 (13 - 15%)	98 (98-98%)
qSOFA 2 or Lactate > 2 mmol/L							
Overall	6750	2258 (33.5%)	216 (9.6%)	78% (77 - 79%)	68 (67 - 69%)	10 (9 - 11%)	99 (99 - 99%)
Cohort 1	2132	716 (33.6%)	67 (9.4%)	81 (79 - 83%)	68 (66 - 70%)	9 (8 - 10%)	99 (99 - 99%)
Cohort 2	4618	1542 (33.4%)	149 (9.7%)	77 (76 - 78%)	69 (68 - 70%)	10 (9 - 11%)	99 (99 - 99%)
qSOFA 2 or Lactate > 4 mmol/L							
Overall	6750	1159 (17.2%)	165 (14.2%)	60% (59 - 61%)	85 (84 - 86%)	14 (13 - 15%)	98 (98 - 98%)
Cohort 1	2132	362 (17.0%)	53 (14.6%)	64 (62 - 66%)	85 (83 - 87%)	15 (13 - 17%)	98 (97 - 99%)
Cohort 2	4618	797 (17.3%)	112 (14.1%)	58 (57 - 59%)	85 (84 - 86%)	14 (13 - 15%)	98 (98 - 98%)