Supplementary Online Content

Shankar-Hari M, Phillips GS, Levy ML, et al; Sepsis Definitions Task Force. 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.* doi:10.1001/jama.2016.0289.

This supplementary material was provided by the authors to give readers additional information about their work.

eMethods 1. Systematic Review, Meta-analysis, and Meta-Regression

Background and problem definition
Currently, there are no gold standard diagnostic criteria for septic shock.[4] We hypothesised that the variation in septic shock mortality could be due to the differences in septic shock definition and operationalization of these definitions, the case-mix, the setting, and cohort recruitment year. We tested this hypothesis by performing a systematic review of observational studies in adults reporting septic shock epidemiology, followed by random effect meta-analysis of mortality by criteria and by using meta-regression models.

Study population, Exposure and study designs
Clinical illness (exposure) reviewed was sepsis. We included only adult population, defined as age >19years, using the Medline filter for age. Only observational (non-interventional) studies were included in this systematic review.[4] To avoid variability in outcomes related to primary exposure, reports of specific pathogens, specific patient groups and critical illnesses such as burns, and interventional before-after studies were excluded. Studies that report sepsis case definition and sepsis mortality were included.

Study outcome(s)
The primary outcome was to explore the relationship between criteria and reported mortality. The secondary outcomes were the different criteria used in septic shock case definitions reported in the literature.

Search strategy
The search involved the Medline database, between 01/01/1992 and 12/25/2015. The first author of the paper (MSH) conducted the literature search, with input from co-authors and members of the Task Force. The search strategy including keywords, exploded fields and limits are presented in eTable-1. Eligible studies were identified with title and abstract screening. Eligibility criteria for full text review were reporting of sepsis epidemiology. All the reference lists of studies eligible for full text review were hand searched for additional files. In addition, the references lists of systematic review[5], editorials, and review article files identified by this search were also checked and included for full text assessment.

Data extraction and reporting
Data extracted from the studies include sample size, recruitment period, geographic region, number of centres, hospital settings, sepsis case definition, septic shock case definition and acute mortality for sepsis and septic shock when reported. A formal study quality assessment was not done for this systematic review. Sepsis definitions were coded either as Consensus[6,7] or other [Definitions are summarized in Table-1 in the main manuscript]. Septic shock criteria were coded using hypotension, vasopressors, and hypoperfusion variables as occurring either alone or in combinations as defined in studies. When studies used International Classification of Diseases codes to identify septic shock patients without description of the underlying variables, they were coded as such. Similarly, in studies where Consensus Definitions are cited without description of

the variables, they were grouped separately. The World Health Organization [WHO] regions were coded using the country of patient recruitment into six regions: WHO African Region; WHO Region of the Americas; WHO South-East Asia Region; WHO European Region; WHO Eastern Mediterranean Region and WHO Western Pacific Region.[8] In studies where patient recruitment occurred in more than one geographic region, these studies were grouped separately. The mid cohort year was defined as cohort recruitment year as per calendar year reported. If the study population recruitment spanned a number of years mid period was used. If studies spanned two calendar years, the cohort year was coded as the calendar year with more number of months from start of recruitment. Number of sites contributing to data was coded as single center and multi center. The intensive care unit [ICU] beds per 100,000 population[9,10-15] was recorded from previously published data. The ICU beds/100,000 population were Japan =4;Portugal =4.2; Thailand =6; Finland =6.1;Norway =8; Australia and New Zealand = 8.9; Scotland=6.1; Spain =9.7; France =11.6; Italy =12.5; Brazil =13; Canada =13.5; Croatia =14.7; Korea =17; Germany =29.2 and United States of America =20. Per capita ICU bed data was unavailable for Columbia and Saudi Arabia. International cohorts were coded as bed unavailable.

Statistics

For meta-analysis and meta-regression, only studies reporting septic shock mortality were included. A random effects mata-analysis of septic shock mortality, by definitional groups was completed. In addition, we included septic shock specific data from ANZICS [provided by Bellomo R et al]; GiViTI [provided by Bertolini G et al]**;** Cub-REA [provided by Aegerter P, Guidet B, Annane D for the Cub-REA network] databases.[4] In the meta-analysis, data from the current paper is also included - SSC refers to n=18,840 patients included in the study and SSC-group 1 refers to the group of patients meeting the new septic shock criteria. In one study, the sepsis definition could not be ascertained[16]. In studies where septic shock patients were reported using multiple criteria, this data is presented with the criteria in parenthesis if separate outcomes could be ascertained. When two authors had the same surname or when multiple papers from same authors are presented, the publication year in parenthesis is reported. Details are provided in eTable2 study summaries.

From the total population of sepsis patients reported, the number of septic shock patients and the corresponding number of deaths were calculated from the studies. This data was then used to generate the proportion and standard error of proportions. Random effects meta-analysis was done by grouping definitions into either 'Consensus' definitions[6,7] or 'other' definitions [ICD based derivations[1-3,17,18]; APACHE codes[19], based on previous clinical trials[20,21]] and by septic shock criteria as described above. Two meta-regression models were generated to address statistical heterogeneity in the septic shock mortality, which involved recoding of variables as described. Statistical heterogeneity was assessed using I^2 and Tau^2 statistics. Meta analysis and meta regression were done using 'Stata 13.1 (StataCorp, College Station, Texas).

Results

Ninety-two studies met the criteria for qualitative review as they reported sepsis outcomes. Forty-four studies met criteria for quantitative review and meta-analysis as they reported septic shock specific mortality. The disparity within clinical definition and criteria identified using qualitative review of studies are presented in Table1 (main manuscript) and in eTable2.

In the original 1992 version, septic shock was explicitly considered as a subset of severe sepsis and defined as "*sepsis-induced hypotension, persisting despite adequate fluid resuscitation, along with the presence of hypoperfusion abnormalities or organ dysfunction*" [6]. Sepsis-induced hypotension was defined "*by the presence of a systolic BP <90 mm Hg or its reduction by ≥40 mmHg from the baseline, in the absence of other causes of hypotension (e.g. cardiogenic shock*)."Septic shock was re-defined by the 2001 International Sepsis Definitions Conference as "*a state of acute circulatory failure characterized by persistent arterial hypotension unexplained by other causes.*" For adults, hypotension was defined as "*a systolic arterial pressure (SAP) <90 mm Hg, a mean arterial pressure (MAP) <60, or a reduction in SAP of >40 mm Hg from baseline, despite adequate volume resuscitation, in the absence of other causes for hypotension*". No definition was provided to characterize 'adequate' fluid resuscitation. The 2012 Surviving Sepsis Campaign (SSC) [22] guidelines modified this definition so that septic shock became "*sepsis-induced hypotension persisting despite adequate fluid resuscitation.*" The SSC defined sepsis-induced hypotension as either a SAP <90 mmHg, or MAP <70 mmHg, or a SBP decrease >40 mmHg or <2 standard deviations below normal for age in the absence of other causes of hypotension. The SSC also separately defined "*sepsis-induced tissue hypoperfusion as infection-induced hypotension, elevated lactate, or oliguria"*.

Observational studies have used different criteria to identify sepsis and septic shock (highlighted in Table 1 main manuscript) that, in sum, can be classified as the presence of infection (presumed or confirmed) in conjunction with varying combinations of:

(i) hypotension (SAP <90 mmHg OR MAP <60 or <70 mmHg OR fall in SAP pressure >40 mmHg from baseline) …

AND/OR

(ii) … that persists despite 'adequate fluid resuscitation' (either unspecified OR after challenges of 20 ml/kg OR 1000 ml)

AND/OR

(iii) abnormal biochemical variables (e.g. lactate >2 or >4 mmol/L or base deficit >5 mmol/l)

AND/OR

(iv) use of inotropes and/or vasopressors [not necessarily above a pre-specified dose]

AND/OR

(v) new onset organ dysfunction (defined variably using various scoring systems such as APACHE II, APACHE III, or the cardiovascular component of the SOFA score).

Further complexity, often overlooked in these operationalization, include:

(i) Variable end-points of adequacy of fluid resuscitation (rarely defined or reported);
(ii) Variable durations of hypotension and/or vasopressor therapy, and
(iii) The underlying blood pressure of the patient
(iv) Formal assessment of the potential hypotensive effect of other co-morbidities, co-interventions such as vasodilator use, prior antihypertensive, and myocardial depression due to sedative agents are seldom reported.

Please refer to main manuscript for results from random effects meta-analyses. eTables 3a and 3b for meta-regression results and eFigures1 and eFigures2 for additional results.

eMethods 2. Delphi Survey Questionnaires

Survey of Task Force to inform Septic shock re-definition

Introduction:

The 2001 International Sepsis Definitions Conference defined septic shock as "*a state of acute circulatory failure characterized by persistent arterial hypotension unexplained by other causes*." Within this definition [in adults], hypotension was defined as "*a systolic arterial pressure (SAP) <90 mm Hg, a mean arterial pressure (MAP) <60, or a reduction in SAP of >40 mm Hg from baseline, despite adequate volume resuscitation, in the absence of other causes for hypotension*". The MAP definitions in this document differ from those used by both the Surviving Sepsis Campaign (<70mmHg) and the SOFA score (also MAP <70mmHg).

Secondly, the utility and cut-off values for lactate may need to be clarified within a new septic shock definition. There is an obvious disconnect between the high ED department lactates yet relatively low mortalities recorded in ARISE and ProCESS, and the much lower lactates and much higher mortalities seen in recent ICU patient studies (e.g. the Scandinavian TRISS and Italian ALBIOS studies).

Thirdly, other parameters used to qualify the definition of hypotension are currently either not considered, stated, or are somewhat variable, namely (a) adequacy of fluid resuscitation and (b) duration of hypotension.

Fourth, the use of vasopressors, ± an accompanying (variably defined) low blood pressure definition, are also used by some to define shock.

Aim

To assess current consensus on the following domains:
Domain 1: Components of the septic shock definition
Domain 2: Hypotension, persisting hypotension, adequacy of resuscitation
Domain 3: Use of vasopressors
Domain 4: Use of lactate
Domain 5: Severity of septic shock
Your feedback will be used to inform the variables required for analyses and to support the new definition.

Domain 1: COMPONENTS OF SEPTIC SHOCK DEFINITION

Q1. In your opinion, which of the following variables in the current septic shock definition are should be included in the updated definitions?

- Hypotension ☐
- Persistent hypotension ☐
- Adequate fluid resuscitation ☐

Q2. In your opinion, which of the following variables could add value by improving the current septic shock definition (please tick all you would like to see included)?

- Raised lactate ☐
- Base deficit ☐
- Use of vasopressor therapy ☐
- Presence of other organ dysfunction ☐
- Others [please specify]

Domain 2: HYPOTENSION; PERSISTING HYPOTENSION; RESUSCITATION

A. HYPOTENSION

Q3. Currently, systolic blood pressure OR mean arterial pressure OR a reduction in systolic pressure >40mmHg from baseline are used in defining hypotension. In your opinion, should these three different blood pressure variables be retained within the new hypotension for septic shock?

ANSWER: Likert scale agreement 5 point: Nether agree nor disagree

Q4 If disagree/strongly disagree to Q3 above, please state which you would KEEP in the definition

- systolic arterial pressure ☐
- mean arterial pressure ☐
- fall in systolic arterial pressure >40 mmHg ☐
- Other [please specify]

Q5: Currently two different MAP values are used in defining septic shock (Sepsis Definition = <60, SOFA and SSC <70).
If you selected MAP in Q4 above, should there be one single definition of MAP?

ANSWER: Likert scale agreement 5 point: Nether agree nor disagree

Q6: If agree/strongly agree to Q5, please state which MAP cut-off value you prefer

- <60 mmHg ☐
- <70 mmHg ☐
- Other [please specify]

Q7: If the patient is known to be chronically hypertensive, should a different cut-off target be used?

ANSWER: Likert scale agreement 5 point: Nether agree nor disagree

Q8: If agree/strongly agree to Q7, please state target

B. PERSISTING HYPOTENSION

Q9: In the current definitions, persisting hypotension is not explicitly defined.
In your opinion, is there a need to define persisting hypotension?

ANSWER: Likert scale agreement 5 point: Agree

Q10: If you agree/strongly agree to Q9, do you feel 'persisting hypotension' should be defined using (tick all that apply)

- Duration of hypotension ☐
- Valid surrogate, such as need for vasopressors ☐
- Other [please specify]

Q11: If you ticked 'yes' to 'duration of hypotension' in Q10 above, please state how long this duration should be in the free text box below

If you would to us to consider other variables in defining persisting hypotension, please highlight in the free text box below.

C. ADEQUACY OF RESUSCITATION

Q12: In your opinion, is there a need to define 'adequacy of resuscitation'?
ANSWER: Likert scale agreement 5 point: Agree
Q13. If you agree/strongly agree to Q12, should 'adequate resuscitation' be defined using (please tick all that apply):
- Fluid boluses to a physiological endpoint ☐
- Biochemical end-points, e.g. lactate ☐
- Ongoing need for vasopressors after predefined fluid bolus e.g. 1L ☐
- Other [Please specify]

Q14: If you ticked 'yes' to 'fluid boluses to a physiological endpoint' in Q13 above, please state in the text box below which endpoints you would use

Q15: If you ticked 'yes' to 'Ongoing need for vasopressors after predefined fluid bolus' in Q13 above, please state what amount of fluid you would give (ml, ml/kg)

If you would to us to consider other variables in defining adequacy of resuscitation, please highlight in the free text section.

Domain 3: USE OF VASOPRESSORS

Currently, the need for vasopressors is used as a surrogate for persisting hypotension, although it is not explicitly stated in the definitions. Furthermore, organ dysfunction scores used to define septic shock provide a construct including dose of the drug – e.g. SOFA score.
(n.b. use of vasopressors to describe severity will be discussed in Domain 5)

Q16. In your opinion, should the need for vasopressor therapy be used as a variable to define septic shock?
ANSWER: Likert scale agreement 5 point: Agree
Q17. If you agree/strongly agree to Q16, should a minimum dose of vasopressor be stated?
ANSWER: Likert scale agreement 5 point: Disagree
Q18: If you ticked 'agree/strongly agree' to 'minimum dose' in Q17 above, please state what dose level you would use

If you would to us to consider other aspects of vasopressor use, please highlight in the free text section.

Domain 4: USE OF LACTATE

Q19. Should lactate be used as a biochemical definition of septic shock, even in the absence of hypotension?
ANSWER: Likert scale agreement 5 point: Agree
Q20. If lactate is included as part of the definition, what cut-off would you like to use to identify septic shock?
- >4 mmol/L ☐
- >3 mmol/L ☐
- >2 mmol/L ☐
- Generate a new cut-off using database of ED/general ward septic shock patients with acute hospital mortality as outcome ☐

- Other cut offs or outcomes [please specify]

If you would to us to consider other aspects of lactate use, please highlight in the free text section (n.b. use of lactate to describe severity will be discussed in Domain 5)

Domain 5: SEVERITY OF SEPTIC SHOCK ASSESSMENT

Q21. In your opinion, is there a need for a severity grading of septic shock?

ANSWER: Likert scale agreement 5 point: Nether agree nor disagree

Q22. If you agree/strongly agree to Q21, what variables would you like to see within the definition of shock severity (please tick all you feel should be included)?

Vasopressor dose ☐

Lactate level ☐

Other [Please specify]

Q23. If you agree/strongly agree to Q21, how many points should be there on the severity scale (assuming 0 = no septic shock)

1 ☐

2 ☐

3 ☐

4 ☐

Q24: If you answered 'yes' to vasopressor dose in Q22, how should dose of vasopressor be defined?

- Spot dose of vasopressor ☐
- Average dose of vasopressor over a defined period ☐
    - o if 'yes' please specify how long (hours)
- Peak dose of vasopressor over a defined period ☐
- Other [Please specify]

Q25: If you answered 'yes' to lactate in Q22, how should the lactate level be used as a variable in defining the severity of septic shock?

- Spot level of lactate (when BP ± vasopressor dose recorded) ☐
- Average level of lactate over a defined period ☐
    - o if 'yes' please specify how long (hours)
- Peak level of lactate over a defined period ☐
- Other way of looking at lactate [Please specify]

Q26. Should a composite score be used, taking into account both the BP target and the vasopressor dose being given? (thus, if aiming for a MAP of 75 mmHg in a particular patient, much more vasopressor would be needed compared to a target MAP of 60 mmHg)

ANSWER: Likert scale agreement 5 point: Nether agree nor disagree

If you would to us to consider other variables in defining septic shock, please highlight in the free text section below.

SURVEY 2

Conclusions from the first Septic Shock definition survey:

- 88% of taskforce (TF) members wanted **persistent hypotension**, **requirement for vasopressors** and **raised lactate** to be included in the updated definition.

- Most (71%) wanted a definition for 'persistent' hypotension; all but one of these voters suggested **need for vasopressor therapy** as a surrogate to define persistent hypotension.

Q1. The TF voted that the new septic shock definition should use high lactate and/or persistent hypotension. However, these could either stand-alone or be used in combination. Which of the following choices do you prefer?
(Please tick one box only)
Persistent hypotension (as defined) AND raised lactate ☐
Persistent hypotension (as defined) OR raised lactate ☐
Other ☐
Please make any comments in the free text box below

Q2. ***"The TF members could not agree on endpoint[s] that define adequate resuscitation in patients with septic shock. As resuscitation is an iterative process this should be separated from the concept of persistent hypotension."***
Would you agree with this statement regarding adequacy of resuscitation?
ANSWER: Likert scale agreement 5 point: Agree
Please make any comments in the free text box below

Q3. No consensus was achieved regarding an endpoint to mark adequacy of fluid resuscitation. Would you agree with the following definition for 'persistent hypotension' that offers a compromise solution?
"Persistent hypotension is defined as hypotension persisting despite fluid resuscitation of at least 20 ml/kg that requires vasopressor therapy for at least 60 minutes to keep MAP >60 mmHg."
ANSWER: Likert scale agreement 3 point: Agree
Please comment in the free text box below.
If you would prefer an alterative, please state whether you would like:
- ***a different duration of hypotension***
- ***and/or a different amount of fluid (including zero)***
- ***and/or a different wording***
- ***and/or another definition***

Q4. Approximately half the TF voted for including lactate in the definition, wanted a cut-off value to be determined by mining 'big data' to determine sensitivity/specificity of acute hospital mortality? Are you happy with this proposal?
ANSWER: Likert scale agreement 3 point: Agree
Please comment in the free text box below.

eMethods 3. The Surviving Sepsis Campaign Database

Sites and patient selection

The SSC registry is an international multi-center database drawn from 218 hospitals. The analysis set was constructed from subjects entered into the SSC database between January 2005 and March 2010. The process of participation in the SSC is described elsewhere[23]. Eligible subjects were those having a suspected site of infection, two or more systemic inflammatory response syndrome (SIRS) criteria, and one or more organ dysfunction criteria[7]. Clinical characteristics and time of presentation with severe sepsis were collected for longitudinal analysis. Time of presentation was determined through chart review for the diagnosis of severe sepsis and defined in instructions to data collectors on the SSC website and in educational materials. For patients from the Emergency Department (ED), the time of presentation was defined as the time of triage.

Data collection

Data were entered into the SSC database locally at individual hospitals into pre-established, non-modifiable fields. Data stripped of private health information were submitted every 30 days to the secure master server at the Society of Critical Care Medicine (Mount Prospect, Ill.).

Institutional Review Board (IRB) approval

The global SSC improvement initiative was approved by the Cooper University Hospital Institutional Review Board (Camden, NJ) as meeting criteria for exempt status. The US Department of Health and Human Services' Office for Human Research Protections reiterated that quality improvement activities such as SSC often qualify for IRB exemption and do not require individual informed consent.

Analysis set construction

Inclusion in the SSC database was limited to sites with at least 20 subjects and at least 3 months of subject enrollment. The updated working definition of septic shock variables in this analysis included all patients whose lactate > 2 mmol/L or MAP < 65 mm Hg after fluids, or received vasopressors. The severe sepsis group included those whose lactate ≤ 2 mmol/L and whose MAP ≥ 65 mm Hg either before or after fluids, and did not receive vasopressors.

Organ dysfunction assessment

Organ dysfunction is a Boolean term in the SSC database. Cardiovascular dysfunction is defined as systolic blood pressure <90 mmHg OR mean arterial pressure <65 mmHg OR systolic blood pressure decrease >40 mmHg from baseline values. Respiratory dysfunction is defined as bilateral pulmonary infiltrates with new [increased] inspired oxygen requirement to maintain arterial saturations >90% OR Bilateral pulmonary infiltrates with a PaO_2/FiO_2 ratio <300mmHg. Renal dysfunction is defined as creatinine >2 mg/dL [178.8 μmol/L] OR urine output <0.5 ml/kg/hr for >2 hours. Hepatic dysfunction is defined as bilirubin >2 mg/dL [34.2 μmol/L]. Hematological dysfunction is defined as platelet count <100,000 OR Coagulopathy [INR>1.5 or APTTR>60

seconds]. Acutely altered metial status is defined as neurological dysfunction. Serum lactate and glucose are recorded as continuous variable in the database.

Covariates in the GEE model

A GEE population-averaged logistic regression model included the following covariates: 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 (>101 °F), hypothermia (<96.8 °F), chills with rigor, tachypnea (>20 breaths/min), leukopenia (<4000 cells/μL), hyperglycemia (plasma glucose >120 mg/dL), platelet count <100,000, and coagulopathy]

eTable 1. Search Strategy for Systematic Review

"Search (((((sepsis[Title/Abstract]) OR sepsis[MeSH Major Topic])) OR ((septic shock[MeSH Major Topic]) OR septic shock[Title/Abstract]))) AND ((epidemiology[Title/Abstract]) OR epidemiology[MeSH Major Topic]) Filters: Publication date from 1992/01/01 to 2015/12/25; Humans; English; Adult: 19+ years"
"Search (((sepsis[Title/Abstract]) OR sepsis[MeSH Major Topic])) OR ((septic shock[MeSH Major Topic]) OR septic shock[Title/Abstract])"
"Search (septic shock[MeSH Major Topic]) OR septic shock[Title/Abstract]"
"Search (sepsis[Title/Abstract]) OR sepsis[MeSH Major Topic]"
"Search (epidemiology[Title/Abstract]) OR epidemiology[MeSH Major Topic]"
"Search septic shock[Title/Abstract]"
"Search septic shock[MeSH Major Topic]"
"Search sepsis[MeSH Major Topic]"
"Search sepsis[Title/Abstract]"
"Search epidemiology[MeSH Major Topic]"
"Search epidemiology[Title/Abstract]"

eTable 2. Studies Included in the Systematic Review Arranged by Publication Date

First author Reference number (publication year)	No.	Recruitment period	Geographic Region	Single center (S) /multi-center (M) [N]	Hospital setting	Sepsis case definition cited	Septic shock definition and criteria	Acute Mortality % (95% CI)
Whittaker SA[24] (2015)	1853	2005 and 2009	USA	Single center	ICU and non-ICU	Bone[6] and Levy[7]	SSC based	5.2% in non-ICU and 22.5% in ICU patients with severe sepsis
Cross G[25] (2015)	159 with sepsis	1st April to 30th June 2011	Australia	Single center	Hospital cases	Bone[6]	Not described	25.0% sepsis
Vincent JL[26] (2014)	10,069	2012	International [84 countries]	Multicenter [730]	ICU	Study specific	CVS SOFA score >2	35·3% (33·5–37·1) for sepsis
Stevenson EK[27] (2014)	Variable sample sizes	1993 to 2009	USA	Multicenter [NIS data]	Hospital including ICU patients	ICD-9 Severe sepsis case identification	ICD-9 septic shock code 785.52 Angus algorithm and Martin algorithm	Trends in change reported.
Ortiz G[28] (2014)	826	2007 – 2008	Colombia	Multi center (n=10)	ICU	CDC definitions for infection and Bone[6]	CVS SOFA score >2	45.1%
Ogura H[29] (2014)	14,417	06/2010 to 05/2011	Japan	Multicenter [15]	ICU	Bone[6] and Levy[7]	CVS SOFA score >2	41.5%

First author Reference number (publication year)	No.	Recruitment period	Geographic Region	Single center (S) /multi-center (M) [N]	Hospital setting	Sepsis case definition cited	Septic shock definition and criteria	Acute Mortality % (95% CI)
Liu V[30] (2014)	55,008 to 80,678 [KPNC] & 280,663 to 717,718 [NIS]	2012	USA [Northern California]	Multicenter [NIS data]	Hospital including ICU patients	ICD-9 vs. Angus Algorithm	ICD-9 septic shock code 785.52 + Hypotension and/or Lactate>4mmol/L	23.3%
Leligdowicz A[31] (2014)	7,974	1989 to 2008	Canada, the United States, and Saudi Arabia	Multicenter [N=29]	ICU	Bone[6]	No description	52.0%
Koupetori M[32] (2014)	754	2006-2013	Greece	Multicenter (n=46)	ICU and non-ICU	Levy[7]	No description	30.5% severe sepsis
Goncalves-Pereira J[33] (2014)	1652 with sepsis	May 2009 to December 2010	Portugal	Multi center (n=14)	ICU	Levy[7]	No description (Bone Definitions cited)	48.8%
Kaukonen KM[19] (2014)	101,064	2000 to 2012	Australia and New Zealand	Multicenter [N=171]	ICU	Bone[6]	CVS failure: lowest MAP <65 mmHg or lowest systolic pressure <90 mmHg APACHE III codes for septic shock	40.3% in 2000 22.0% in 2012

First author Reference number (publication year)	No.	Recruitment period	Geographic Region	Single center (S) /multi-center (M) [N]	Hospital setting	Sepsis case definition cited	Septic shock definition and criteria	Acute Mortality % (95% CI)
Bouza C[34] (2014)	240,939	2006 to 2011	Spain	Multicenter	Hospital using National Minimum Basic Data Set	ICD-9 codes	CVS: 785.5 with all sub codes Shock without trauma: 785.1, 785.52, 785.9 Hypotension: 458 with sub codes (458.0, 458.8 458.9) Nonspecific low blood pressure reading: 796.3	43.0% for severe sepsis
Storgaard M[35] (2013)	212 with severe sepsis/shock	Since 1994	Denmark	National registries	Hospital admissions	CDC definitions for infection and Bone[6]	CVS: Systolic blood pressure <90mmHg or fall >40mmHg	33.0% (25.%-41%) for severe sepsis
Whittaker SA[36] (2013)	1,735	2005 to 2009	University of Pennsylvania	Single center	ICU admissions from Emergency Department	ICD-9 vs. Angus Algorithm	ICD-9 septic shock (785.52) Shock was defined as systolic blood pressure less than 90 mm Hg after fluid resuscitation (1500 mL) or use of vasoactive agents.	36.4%

First author Reference number (publication year)	No.	Recruitment period	Geographic Region	Single center (S) /multi-center (M) [N]	Hospital setting	Sepsis case definition cited	Septic shock definition and criteria	Acute Mortality % (95% CI)
Stiermaier T[37] (2013)	139 with sepsis	2007	General Hospital of Vienna	Single center	Hospital admissions	ICD-10 and Bone[6] in ICU admissions	No description	48.8 [severe sepsis]
Sakr Y[38] (2013)	446 with sepsis	2006	Piedmont region, Italy	Multi-center [N=24]	ICU	Bone[6]	No description	58.6 (50.5-66.3)
Rohde JM[39] (2013)	3,146 with severe sepsis	2009 to 2010	University of Michigan	Single center	Hospital admissions	ICD-9	Levy et al cited for organ dysfunction definitions	Not extractable

First author Reference number (publication year)	No.	Recruitment period	Geographic Region	Single center (S) /multi-center (M) [N]	Hospital setting	Sepsis case definition cited	Septic shock definition and criteria	Acute Mortality % (95% CI)
Quenot JP[20] (2013)	1,495 with septic shock	2009 to 2011	North-East France	Multi center [n=14]	ICU	Only Septic shock population included as described	Infection requiring initiation of vasopressors despite adequate vascular filling, with at least one of the following hypoperfusion criteria: (1) metabolic acidosis (base excess ≥5 mEq/L, alkaline reserve <18 mEq/L or lactate ≥2.5 mmol/L); (2) oliguria/ renal insufficiency (<0.5 mL/kg/h for 3 h or elevation >50% of baseline creatinine); or (3) hepatic dysfunction (AST or ALT >500 IU/L or bilirubin >34 μmol/L).	48.7%

First author Reference number (publication year)	No.	Recruitment period	Geographic Region	Single center (S) /multi-center (M) [N]	Hospital setting	Sepsis case definition cited	Septic shock definition and criteria	Acute Mortality % (95% CI)
Nesseler N[40] (2013)	96	2008 to 2010	France	Single center	ICU	Bone[6]	Bone et al cited for septic shock	32.0%
Gray A[41] (2013)	626	2009	Scotland	Multi center [N=20]	Emergency Department	SSC	No description	28.3% [severe sepsis + septic shock]
Gaieski DF[17] (2013)	Variable	2004 to 2009	USA	Multicenter (NIS data)	Hospital admissions	ICD-9 vs. Angus vs. Martin vs. Wang vs. Dombrovskiy Algorithms	ICD-9 septic shock (785.52)	14.7% to 29.9% for severe sepsis
Czupryna P[42] (2013)	107	1997 to 2010	Poland	Single center	Hospital admissions	Levy[7]	SBP<90; MAP<60 or Fall in SBP>40	30.9% for severe sepsis
Seymour CW[43] (2012)	13,249 severe sepsis	2000 to 2009	USA (Pre-hospital Kings County)	Multi center	Emergency Medical Services encounters	ICD-9 [Angus Algorithm]	No description	19.6% for severe sepsis
Sancho S[44] (2012)	371	10/1998 to 02/2010	Valencia, Spain	Single center	Hospital admissions	Bone[6] + Nosocomial bacteremia	No description	59.3% ICU mortality severe sepsis/shock

First author Reference number (publication year)	No.	Recruitment period	Geographic Region	Single center (S) /multi-center (M) [N]	Hospital setting	Sepsis case definition cited	Septic shock definition and criteria	Acute Mortality % (95% CI)
Klein Klouwenberg PMC[45] (2012)	1,072	01/2009 to 10/2010	Netherlands	Single center	ICU	Multiple algorithms tested	Refractory hypotension Refractory hypotension with other organ system failure	45% 62%
Park DW[46] (2012)	1,192	2005 to 2009	Korea	Multi center [n=12]	ICU	Bone[6]	Either SBP ≤ 90 mmHg or MAP ≤ 70 mmHg for at least 1 hour after adequate fluid resuscitation or use of vasopressors to maintain systolic blood pressure > 90 mmHg or mean arterial pressure > 70 mmHg.	30.8%
Levy MM[47] (2012)	25375	2005-2010	International	Multi center	ICU; non-ICU; Emergency department	Levy[7]	Surviving sepsis campaign	As previously reported

First author Reference number (publication year)	No.	Recruitment period	Geographic Region	Single center (S) /multi-center (M) [N]	Hospital setting	Sepsis case definition cited	Septic shock definition and criteria	Acute Mortality % (95% CI)
Lagu T[48] (2012)	4,799,565 sepsis cases	2003 to 2007	USA	Multi center (NIS database)	Hospital	ICD-9-CM	CVS: 785.5 with all sub codes Shock without trauma: 785.1, 785.52, 785.9 Hypotension: 458 with sub codes (458.0, 458.8 458.9) Nonspecific low blood pressure reading: 796.3	Not extractable
Bastani A[49] (2012)	267	2007 to 2010	USA	Single center	ICU	SSC	No description but Early Goal Directed therapy referenced	33.3% for severe sepsis/shock

First author Reference number (publication year)	No.	Recruitment period	Geographic Region	Single center (S) /multi-center (M) [N]	Hospital setting	Sepsis case definition cited	Septic shock definition and criteria	Acute Mortality % (95% CI)
Zahar JR[50] (2011)	3,588	1996 to 2009	France	Multi center [N=12]	ICU	Bone[6]	Sepsis-induced hypotension persisting despite adequate fluid resuscitation together with organ dysfunction OR Patients receiving inotropic or vasoactive agents who had organ dysfunction but who were no longer hypotensive	46.0%

First author Reference number (publication year)	No.	Recruitment period	Geographic Region	Single center (S) /multi-center (M) [N]	Hospital setting	Sepsis case definition cited	Septic shock definition and criteria	Acute Mortality % (95% CI)
Vesteinsdottir E[51] (2011)	115 severe sepsis/ shock	2008 to 2009	Iceland	Multi center [N=20]	ICU	Bone[6]	Sepsis-induced hypotension persisting despite adequate fluid resuscitation together with organ dysfunction; Patients receiving inotropic or vasoactive agents to maintain MAP>65 or SBP>90mmHg	29.6% severe sepsis/septic shock
Rosado V[52] (2011)	30	2007 to 2009	Peurto Rico	Single center	ICU	ICD-9	Not described	66.0% severe sepsis/shock
Rodriguez F[53] (2011)	2,681	2007 to 2008	Columbia	Multi center [N=10]	Hospital cohort	CDC definitions	Sepsis-induced hypotension persisting despite adequate fluid resuscitation + need for vasoactive agents to maintain MAP>65 or SBP>90mmHg	45.6%

First author Reference number (publication year)	No.	Recruitment period	Geographic Region	Single center (S) /multi-center (M) [N]	Hospital setting	Sepsis case definition cited	Septic shock definition and criteria	Acute Mortality % (95% CI)
Phua J[54] (2011)	1285	2009	Asian countries	Multi center [N=150]	ICU	Levy[7] SSC	Hypotension or on vasopressors [H/V] Hyperlactatemia >4mmol/L [LCT]	H+V=77.1% LCT=38.3%
Moore LJ[55] (2011)	231	2007-2009	Houston, Texas, USA	Single center	ICU [Surgical]	Bone[6]	SIRS + infection + acute cardiac dysfunction that is defined by the following (must meet both criteria): (1) intravenous fluid challenge >20 mL/kg/ideal body weight of isotonic crystalloid infusion or central venous pressure >8 mm Hg or PCWP >12 mm Hg and (2) requirement of vasopressors to increase MAP >65 mm Hg.	36.0%

First author Reference number (publication year)	No.	Recruitment period	Geographic Region	Single center (S) /multi-center (M) [N]	Hospital setting	Sepsis case definition cited	Septic shock definition and criteria	Acute Mortality % (95% CI)
Davis JS[56] (2011)	1191	2007 to 2008	Northern territory of Australia	Single center	Hospital admissions	PROWESS Definition	Not described	17.1% severe sepsis/septic shock
Wilhems SB[18] (2010)	37,990	01/1987 to 12/2005	Sweden	Multi center Swedish Hospital Discharge Register	Hospital admissions includes ICU	ICD-9 and ICD-10 codes mirroring Bone Definition	Angus algorithm, Martin algorithm and Flatten H description of ICD based data extraction Septic shock is not described	22.1 to 29.2% for sepsis depending on algorithm
Shen HN[57] (2010)	5,258	1997 to 2006	Taiwan	Multi center National Health Insurance Program	Hospital admissions	ICD-9 + Angus Algorithm	No description	30.8% severe sepsis/shock
Levy MM[23] (2010)	15,022	2005 to 2008	International	Multi center [N=165]	ICU; Emergency Department; Ward	Bone[6] SSC	Lactate>4 [LCT] Vasopressors [V] Lactate>4 + vasopressors [LCT/V]	LCT=29.9% V=36.7% LCT/V=46.1% Overall 38.4%

First author Reference number (publication year)	No.	Recruitment period	Geographic Region	Single center (S) /multi-center (M) [N]	Hospital setting	Sepsis case definition cited	Septic shock definition and criteria	Acute Mortality % (95% CI)
Kauss IA[58] (2010)	1,179	2004 to 2005	Brazil	Single center	ICU	Bone[6]	Sepsis + arterial hypotension needing vasopressors, despite initial volume resuscitation.	72.7% [68.1 – 76.9%]
Husak L[59] (2010)	30,587	04/2004 to 03/2009	Canada [excluding Quebec]	Multi center (discharge abstract database)	Hospital and Emergency Department	ICD-10	No description	45.2% severe sepsis
Bateman BT[60] (2010)	2,039,776	1997 to 2006	USA	Multicenter (NIS data) Post operative sepsis	Post operative sepsis	ICD-9	ICD-9 septic shock (785.52)	44.4% in1997 to 34.0% in 2006 for severe sepsis
Vogel TR[61] (2009)	N=1,276,451	1990 to 2006	New Jersey, USA	Multi center (HCUP data)	Post operative sepsis	ICD-9 and surgical diagnosis related group	CVS failure (785.50, 785.51, 785.59, 458.0, 458.8, 458.9, 796.3, 427.5) Septic shock NOT explicitly stated	45.7% severe sepsis

First author Reference number (publication year)	No.	Recruitment period	Geographic Region	Single center (S) /multi-center (M) [N]	Hospital setting	Sepsis case definition cited	Septic shock definition and criteria	Acute Mortality % (95% CI)
Povoa PR[62] (2009)	897	2004 to 2005	Portugal	Multi center [n=17]	ICU	Bone[6]	State of acute circulatory failure characterized by persistent arterial hypotension (SBP <90mmHg, MAP<60mmHg,or a reduction in SBP of >40 mm Hg from baseline) despite adequate fluid resuscitation	44.0% [ICU mortality]

First author Reference number (publication year)	No.	Recruitment period	Geographic Region	Single center (S) /multi-center (M) [N]	Hospital setting	Sepsis case definition cited	Septic shock definition and criteria	Acute Mortality % (95% CI)
Peake SL[63] (2009)	324	2006 to 2007	Australia and New Zealand	Multi center [n=32]	Emergency Department	Levy[7]	EITHER: Blood pressure (BP) criteria (one or more of the following): (i) SBP <90 mmHg OR >40 mmHg fall below premorbid SBP OR MAP<65 mmHg, after ≥500 ml intravenous fluid challenge over 30–60min; (ii) requirement for vasoactive infusion for ≥30 min to maintain BP OR: Metabolic acidosis criteria (one or more of the following): arterial or venous: (i) blood lactate >4.0 mmol/L [LCT]; (ii) anion gap >20 mEq/L; (iii) serum bicarbonate <16.0 mmol/L.	BP=23.0% LCT=26.9% Overall: 23.1%

First author Reference number (publication year)	No.	Recruitment period	Geographic Region	Single center (S) /multi-center (M) [N]	Hospital setting	Sepsis case definition cited	Septic shock definition and criteria	Acute Mortality % (95% CI)
Khwannimit B[64] (2009)	390	2004 to 2006	Thailand	Single center	ICU	Bone[6]	SBP<90 mmHg or MAP<65 mmHg] for at least 1 h despite adequate fluid resuscitation (CVP>8 mmHg or PAOP >12 mmHg) or use of a vasopressor (dopamine >5 mg/kg per min or norepinephrine, epinephrine any dose) for >1 h in an attempt to maintain SBP >90 mmHg or MAP>65mmHg	54.1%
Beale R[65] (2009)	12,570 adults	2002 to 2005	International (13 countries)	Multi center [n=276)	ICU	Bone[6]	CVS dysfunction is defined as hypotension in the absence of causes other than sepsis.	49.6% severe sepsis
Baharoon S[66] (2009)	165	2004	Makkah, Saudi Arabia	Multi center (n=2)	ICU	Levy[7]	No description	54.7% severe sepsis/septic shock

First author Reference number (publication year)	No.	Recruitment period	Geographic Region	Single center (S) /multi-center (M) [N]	Hospital setting	Sepsis case definition cited	Septic shock definition and criteria	Acute Mortality % (95% CI)
Angkasekwinai N[16] (2009)	3541	2007	Thailand	Single center	Hospital admissions	Bone[6]	No data available	52.6%
Rezende E[67] (2008)	5,332	2004	Brazil	Single center	Emergency Department	Bone[6]	No description CVS dysfunction defined as hypotension or need for vasoactive drugs	64.0% severe sepsis

First author Reference number (publication year)	No.	Recruitment period	Geographic Region	Single center (S) /multi-center (M) [N]	Hospital setting	Sepsis case definition cited	Septic shock definition and criteria	Acute Mortality % (95% CI)
Blanco J[68] (2008)	4,317	2002	Spain	Multi center (N=14)	ICU	PROWESS Criteria	Shock: SBP ≤90 mmHg or MAP ≤70 mmHg, during at least 1 hour despite adequate resuscitation with fluids or adequate intravascular volume; or use of vasopressors (dopamine ≥5 µg/Kg/minute; noradrenalin or adrenalin at any dose; dobutamine was not taken into account). Unexplained metabolic acidosis (pH <7.30 or base excess ≤-5 mmol/l) associated with an arterial lactate concentration ≥ 2 mmol/l with no other apparent cause.	54.3% severe sepsis + shock
Beovic B[69] (2008)	701	2004	Slovenia	Multi center [n=28]	ICU	Bone[6]	No description	45.1% severe sepsis

First author Reference number (publication year)	No.	Recruitment period	Geographic Region	Single center (S) /multi-center (M) [N]	Hospital setting	Sepsis case definition cited	Septic shock definition and criteria	Acute Mortality % (95% CI)
Andreu BallesterJC[70] (2008)	33,767	1995 to 2004	Valencia, Spain	Multi center [n=26]	Hospital admissions	ICD-9	CVS (785.5 with all sub codes, 427.5, 458.0, 458.8, 458.9, and 796.3) Septic shock is not described	42.5% severe sepsis and shock
Wang HE[3] (2007)	331.5 million ED visits	2001 to 2004	USA	Multi center	National Hospital Ambulatory Medical Care Survey	ICD-9 and Levy	CVS (785.5 with sub codes, 458.0, 458.8, 458.9)	Not extractable
Sakr Y[71] (2007)	3,147	2002	Europe (24 countries)	Multi center (N=198)	ICU	Bone[6]	Referred to Bone Criteria	54.1%
Karlsson S[72] (2007)	4,500	11/2004 to 02/2005	Finland	Multi center (N=24)	ICU	Bone[6]	Not described	24.7% [refractive shock]

First author Reference number (publication year)	No.	Recruitment period	Geographic Region	Single center (S) /multi-center (M) [N]	Hospital setting	Sepsis case definition cited	Septic shock definition and criteria	Acute Mortality % (95% CI)
Esteban A[73] (2007)	15,852	03/2003 to 06/2003	Madrid, Spain	Multi center [N=3]	Ward and ICU	Bone[6]	Sepsis and at least one of the following criteria: SBP <90 mm Hg despite adequate fluid administration, need for inotropes or vasopressors (excluding dopamine >5 μg/kg/min), or SBP decrease of >40 mm Hg from usual baseline level.	45.7%
Engel C[74] (2007)	3,877	1 day in 2003	Germany	Multi center [n=454]	ICU	Bone[6]	Sepsis or severe sepsis with persistent hypotension despite adequate fluid resuscitation or the necessity of vasopressor administration to maintain a MAP>= 70 mmHg	62.4% [55.2 – 69.2]

First author Reference number (publication year)	No.	Recruitment period	Geographic Region	Single center (S) /multi-center (M) [N]	Hospital setting	Sepsis case definition cited	Septic shock definition and criteria	Acute Mortality % (95% CI)
Cheng B[75] (2007)	3,6665	12/2004 to 11/2005	China	Multi center [n=10]	Surgical ICUs	Bone[6] and Levy[7]	No description	48.7% severe sepsis
Vincent JL[76] (2006)	3,147	2 weeks in 05/2002	Europe (24 countries)	Multi center (N=198)	ICU	Bone[6]	No description	54.1% ICU mortality
Tanriover MD[77] (2006)	69	01/2002 to 06/2003	Turkey	Single center	Hospital charts	Diagnostic code of sepsis/septicaemia/bacteremia	No description	Not extractable
Strehlow MC [78] (2006)	2.8 million sepsis	1992 to 2001	USA	Multi center	National Hospital Ambulatory Medical Care Survey	ICD-9 codes Martin Algorithm & Bone[6] Definitions	ICD-9 codes for organ dysfunction	Not extractable
Shapiro N[79] (2006)	3,102	02/2000 to 02/2001	Boston, USA	Single center	Emergency Department	Bone	Suspected infection and hypotension (SBP<90) which persisted after a crystalloid fluid challenge of 20-30 cc/kg.	27.8%
Harrison DA[80] (2006)	92,672	12/1995 to 01/2005	United Kingdom	Multi center ICNARC database	ICU	PROWESS criteria	No description. CVS dysfunction is coded as severe sepsis	48.3 to 44.7 severe sepsis/shock

First author Reference number (publication year)	No.	Recruitment period	Geographic Region	Single center (S) /multi-center (M) [N]	Hospital setting	Sepsis case definition cited	Septic shock definition and criteria	Acute Mortality % (95% CI)
Gasparovic V[81] (2006)	456 sepsis	11/2004 to 10/2005	Croatia	Multi center [n=24]	ICU	Bone[6]	Hypotension of <100 mm Hg despite volume replacement	34.1%
Degoricija V[82] (2006)	314	01/2000 to 12/2005	Croatia	Single center	ICU	Bone[6] and Levy[7]	Not described	72.1% and 74.4% if MODS
Zahorec R[83] (2005)	124 sepsis	07/2002 to 12/2002	Slovakia	Multi center [n=12]	ICU	Bone[6]	Organ dysfunction defined as per PROWESS	51.2% severe sepsis/shock
Sundararajan V[84] (2005)	33,741	07/1999 to 06/2003	Victoria, Australia	Multi center Population database	Hospital admissions	ICD-10 Bone[6]	ICD-10 codes based on Martin Algorithm 785.59	29.5% severe sepsis
Laupland KB[85] (2005)	251	07/1999 to 03/2002	Calgary, Canada	Multi center Population databse	ICU	SIRS + bacteremia	BSI-associated sepsis patients that required a vasopressor infusion at any dose	51.0% [28 day mortality]

First author Reference number (publication year)	No.	Recruitment period	Geographic Region	Single center (S) /multi-center (M) [N]	Hospital setting	Sepsis case definition cited	Septic shock definition and criteria	Acute Mortality % (95% CI)
Adrie C[86] (2005)	1698	04/1997 to 12/2000	France	Multi center [n=6]	ICU	Bone[6]	CVS failure = need for vasopressors and/or inotropic drugs, and/or SBP of <90 mm Hg, and/ or drop in SBP >40 mm Hg from baseline	39% severe sepsis/shock

First author Reference number (publication year)	No.	Recruitment period	Geographic Region	Single center (S) /multi-center (M) [N]	Hospital setting	Sepsis case definition cited	Septic shock definition and criteria	Acute Mortality % (95% CI)
Van Gestel A[87] (2004)	151	One day [11/12/2001]	Netherlands	Multi center [N=47]	ICU	Bone[6]	Septic shock = Sepsis + CVS organ failure + metabolic dysfunction during the first 24 hours of ICU admission. CVS failure: SBP ≤ 90 mmHg or MAP≤ 70 mmHg for 1 hour, despite adequate fluid resuscitation, or the need to administer vasopressors in order to maintain SBP≥ 90 mmHg or MAP≥ 70 mmHg. Metabolic dysfunction: metabolic acidosis (pH ≤ 7.30 or base deficit ≥ 5.0 mmol/l) in association with a plasma lactate level > 3.0 mmol/l	Not extractable

First author Reference number (publication year)	No.	Recruitment period	Geographic Region	Single center (S) /multi-center (M) [N]	Hospital setting	Sepsis case definition cited	Septic shock definition and criteria	Acute Mortality % (95% CI)
Silva E[88] (2004)	1383	05/2001 to 01/2002	Brazil	Multi center [n=5]	ICU	Bone[6]	Septic shock was defined as severe sepsis and vasoactive drug requirement (SOFA 3–4).	52.2%
Laupland KB[89] (2004)	1,981	05/1999 to 04/2000	Calgary, Canada	Multi center Population database	ICU	SIRS + bacteremia	BSI-associated septic shock was the subset of BSI-associated sepsis patients that presented with hypotension [MAP<60mmHg].	49.0%
Flaatten H[90] (2004)	6665	1999	Norway	Multi center Norwegian patient registry	Hospital data	ICD-10	A41.9 – septic shock I50.9 – Unspecified heart failure	29.3%

First author Reference number (publication year)	No.	Recruitment period	Geographic Region	Single center (S) /multi-center (M) [N]	Hospital setting	Sepsis case definition cited	Septic shock definition and criteria	Acute Mortality % (95% CI)
Finfer S[91] (2004)	5878	05/1999 to 07/1999	Australia/ New Zealand	Multi center [N=21]	ICU	Bone[6] PROWESS	SBP<90 mmHg or a MAP<70 mmHg for at least 1 h despite adequate fluid resuscitation, adequate intravascular volume status, and/or need for vasopressors to maintain systolic blood pressure >90 mmHg or MAP >70 mmHg for >1 h	32.4% severe sepsis/ shock
Brun-Buisson [92] (2004)	3738	2 weeks in 11/2001	France	Multi center [n=206]	ICU	Bone[6]	No description	35.0% severe sepsis/shock
Padkin A[93] (2003)	56,673	1995 to 2000	England/Wales and Northern Ireland	Multi center [n=91]	ICU	PROWESS trial	No description	47.3% severe sepsis/shock

First author Reference number (publication year)	No.	Recruitment period	Geographic Region	Single center (S) /multi-center (M) [N]	Hospital setting	Sepsis case definition cited	Septic shock definition and criteria	Acute Mortality % (95% CI)
Martin GS[2] (2003)	10,319,418 sepsis	1979 to 2000	USA	Multi center Hospital discharge data	Hospital admissions	ICD-9	ICD-9 CVS codes 458.0 - Hypotension, postural; 785.5 Shock; 785.51 cardiogenic shock and 785.59 septic; 796.3 Transient hypotension	70.0% severe sepsis/shock
Annane D[94] (2003)	100,554	1993 to 2000	France	Multi center [n=22]	ICU	Bone[6]	Not described	60.1%

First author Reference number (publication year)	No.	Recruitment period	Geographic Region	Single center (S) /multi-center (M) [N]	Hospital setting	Sepsis case definition cited	Septic shock definition and criteria	Acute Mortality % (95% CI)
Alberti C[95] (2002)	14,364	05/1997 to 05/1998	International – Europe, Canada and Israel	Multi center (n=28)	ICU	Bone[6]	Sepsis-induced hypotension persisting despite adequate fluid resuscitation along with the presence of hypoperfusion abnormalities or organ dysfunction (patients receiving inotropic or vasopressor agents may no longer be hypotensive by the time they manifest hypoperfusion abnormalities or organ dysfunction but would be considered to have septic shock).	47.2% to 63.8%
Angus DC[1] (2001)	192,980	1995	USA	Multi center [n=847]	Hospital discharge records	ICD-9 Angus derivation	CVS organ dysfunction Shock without trauma ICD codes (785.5 and 458)	Sepsis 28.6%

First author Reference number (publication year)	No.	Recruitment period	Geographic Region	Single center (S) /multi-center (M) [N]	Hospital setting	Sepsis case definition cited	Septic shock definition and criteria	Acute Mortality % (95% CI)
Wichmann MW[96] (2000)	48,136	02/1991 to 06/1998	Germany	Single center	Surgical ICU	Bone[6]	Need for catecholamine therapy despite adequate fluid support	65.7% severe sepsis/shock
Schoenberg MH[97] (1998)	664	1997	Germany	Single center	Surgical ICU	Bone[6]	Severe sepsis concomitant with arterial hypotension with a SBP<90 mmHg and/or the need for vasopressor treatment with noradrenaline and/or adrenaline (infusion rate >0.1 μg/kg/min) and/or dopamine (infusion rate >5 μg/kg/min) despite adequate volume resuscitation	40.0%

First author Reference number (publication year)	No.	Recruitment period	Geographic Region	Single center (S) /multi-center (M) [N]	Hospital setting	Sepsis case definition cited	Septic shock definition and criteria	Acute Mortality % (95% CI)
Lundberg JS[98] (1998)	41	08/1992 to 04/1993	USA	Single center	ICU	Bacteremia + Bone[6]	Septic shock = a) at least two criteria SIRS; b) positive blood culture(s); c) systematic manifestation of peripheral hypoperfusion, defined as lactic acidosis, oliguria, or acute alteration of mental status; and d) hypotension, defined as systolic blood pressure (BP) <90 mm Hg unresponsive to a 500-mL fluid bolus or requiring use of vasopressors to keep the systolic BP of >90 mm Hg. If the patient had been hypertensive, a decrease of 40 mm Hg systolic BP was considered the criterion for hypotension.	46.0%

First author Reference number (publication year)	No.	Recruitment period	Geographic Region	Single center (S) /multi-center (M) [N]	Hospital setting	Sepsis case definition cited	Septic shock definition and criteria	Acute Mortality % (95% CI)
Sands KE[99] (1997)	1342	01/1993 to 04/1994	USA	Multi center [n=8]	Hospital admissions	Bone[6]	Presence of sepsis syndrome plus a >40mmHg drop in SBP unresponsive to a fluid challenge, occurring within 24 hours before or 6hours after the onset of sepsis syndrome.	34.0% 28 day mortality sepsis syndrome
Sasse KC[100] (1995)	153	01/1987 to 03/1991	USA	Single center	ICU	Bone[6]	Not described	51.0% severe sepsis

First author Reference number (publication year)	No.	Recruitment period	Geographic Region	Single center (S) /multi-center (M) [N]	Hospital setting	Sepsis case definition cited	Septic shock definition and criteria	Acute Mortality % (95% CI)
Salvo I[101] (1995)	1101	04/1993 to 03/1994	Italy	Multi center [n=99]	ICU	Bone[6]	Sepsis with hypotension, despite adequate fluid resuscitation, along with the presence of perfusion abnormalities that may include, but are not limited to lactic acidosis, oliguria, or an acute alteration in mental status. Patients who are on inotropic or vasopressor agents may not be hypotensive at the time that per- fusion abnormalities are measured Hypotension: A systolic BP of <90 mmHg or a reduction of >40mmHg from baseline in the absence of other causes for Hypotension.	81.8%

First author Reference number (publication year)	No.	Recruitment period	Geographic Region	Single center (S) /multi-center (M) [N]	Hospital setting	Sepsis case definition cited	Septic shock definition and criteria	Acute Mortality % (95% CI)
Rangel-Frausto MS[102] (1995)	3708	08/1992 to 04/1993	USA	Multi center [n=3]	ICU	Bone[6]	Septic shock was defined as a patient with hypotension not responsive to a 500-mL intravenous fluid challenge plus manifestations of peripheral hypoperfusion. Patients without hypotension but receiving more than 5mcg/kg/minute of dopamine or any other vasopressor	46.0%
Pittet D[103] (1995)	170	04/1992	USA	Single center	Surgical ICU	Bone[6]	Shock was defined as SBP<90 mmHg OR a fall in SBP equal to or greater than 50 percent for hypertensive patients; or blood pressure requiring a continuous infusion of vasopressors.	58%

First author Reference number (publication year)	No.	Recruitment period	Geographic Region	Single center (S) /multi-center (M) [N]	Hospital setting	Sepsis case definition cited	Septic shock definition and criteria	Acute Mortality % (95% CI)
McLauchlan GJ[21] (1995)	125	01/1990 to 06/1993	Edinburgh, Scotland	Single center	ICU	Study specific	Not described	72.0%
Brun-Buisson[104] (1995)	11,828	01/1993 to 02/1993	France	Multi center [n=170]	ICU	Bone[6]	Shock was defined as hypotension persisting at least 1 hour despite administration of fluids, associated with signs of organ dysfunction or hypoperfusion. Hypotension = SBP<90 or drop >40mmHg from baseline	59.0% severe sepsis/shock
Dahmash NS [105] (1993)	45	02/1989 to 05/1991	Saudi Arabia	Single center	ICU	Study specific	Not described	40.0%

The study specific checklist included: cohort recruitment period, cohort size, cohort location [geographic; Emergency department [ED]; Ward; Intensive Care unit [ICU]], sepsis and septic shock definitions and acute mortality as reported in the document. Angus algorithm[1] = ICD-9-CM code for infection + Organ Dysfunction code; Martin algorithm[2] = ICD-9-CM codes for septicaemia, bacteraemia, or fungaemia + Organ Dysfunction code. Wang[3] and Dombrovskiy algorithms use ICD-9 infection along with ICD-9 severe sepsis codes; PROWESS criteria are the trial based criteria, which uses 3 systemic inflammatory response syndrome and one or more organ dysfunction to define severe sepsis. USA – United

States of America; ICU – Intensive Care unit; Bone – refers to Bone R et al Consensus definitions; Levy – refers to Levy MM et al Consensus Definitions; CDC – Centre for Disease Control and Prevention; ICD – International Classification of Diseases; SOFA score – refers to Sepsis (Sequential) Organ Failure Score; NIS data = The National (Nationwide) Inpatient Sample data; CVS – Cardiovascular system; APACHE score – Acute Physiology and Chronic Health Evaluation Scores; SSC – Surviving Sepsis Campaign; SIRS – systemic inflammatory response syndrome; BSI – blood stream infection; SBP = systolic blood pressure; MAP – Mean arterial pressure; CVP – central venous pressure; PAWP – Pulmonary artery wedge pressure.

eTable 3. Meta-regression Analysis

eTable 3A. Model Without ICU Beds/100,000 Population

Variable	Coefficient	Standard error	t	p>|t|	95%CI of coefficient
Sepsis Case Definition	-0.018	0.048	-0.38	0.709	-0.114 – 0.079
Septic Shock Criteria	-0.008	0.009	-0.86	0.396	-0.027 – 0.011
Mid cohort year	-0.007	0.004	-1.75	0.087	-0.016 – 0.011
Single vs Multicenter	-0.0311	0.050	-0.62	0.540	-0.013 – 0.071
WHO regions	-0.002	0.009	-0.24	0.808	-0.021 – 0.017
Constant	15.47	8.500	1.82	0.076	-1.664 – 32.605

The table shows the summary of the random effects meta-regression model described in eMethods1. The number of observations in this model was 49. The estimate of between study variance (tau^2) was 0.019 and the proportion of residual variation due to heterogeneity (I^2_res) was 99.54%. The proportion of between-study variance explained by covariates included in this model was 0.69%. The joint test for all covariates in the model was not significant (p=0.44).

eTable 3B. Model With ICU Beds/100,000 Population

Variable	Coefficient	Standard error	t	p>|t|	95%CI of coefficient
Sepsis Case Definition	-0.058	0.062	-0.93	0.360	-0.186 – 0.070
Septic Shock Criteria	-0.004	0.011	-0.33	0.743	-0.025 – 0.018
Mid cohort year	-0.009	0.005	-1.80	0.082	-0.019 – 0.001
Single vs Multicenter	-0.053	0.055	-0.95	0.348	-0.166 – 0.060
WHO regions	-0.019	0.027	-0.69	0.498	-0.075 – 0.037
Per capital ICU beds	-0.004	0.005	-0.87	0.392	-0.014 – 0.006
Constant	18.81	10.03	1.88	0.071	-1.698 – 39.313

The table shows the summary of the random effects meta-regression model described in eMethods1, where per-capita ICU beds data was available to be included as a covariate. The number of observations in this model was 36, due to either lack of per capita bed data or international cohorts. The estimate of between study variance (tau^2) was 0.02 and the proportion of residual variation due to heterogeneity (I^2_res) was 98.54%. The proportion of between-study variance explained by covariates included in this model was 2.11%. The joint test for all covariates in the model was not significant (p=0.39)

eTable 4. Responses to Key Delphi Survey Questions

Phase 1 (N=17 responses)	Response N (%)		
	A	N	D
1. Currently, systolic blood pressure OR mean arterial pressure OR a reduction in systolic pressure >40mmHg from baseline are used in defining hypotension. In your opinion, should these three different blood pressure variables be retained within the new hypotension for septic shock?	7 (41.2%)	1 (5.9%)	9 (52.9%)
2. Currently two different MAP values are used in defining septic shock (Sepsis Definition = <60, SOFA and SSC <70). Should there be one single definition of MAP?	14 (82.4%)	1 (5.9%)	2 (11.8%)
3. If the patient is known to be chronically hypertensive, should a different cut-off target be used?	6 (35.3%)	2 (11.8%)	9 (52.9%)
4. In the current definitions, persisting hypotension is not explicitly defined. In your opinion, is there a need to define persisting hypotension?	12 (70.6%)	1 (5.9%)	4 (23.5%)
5. In your opinion, is there a need to define 'adequacy of resuscitation'?	13 (76.5%	1 (5.9%)	3 (17.6%)
6. In your opinion, should the need for vasopressor therapy be used as a variable to define septic shock?	15 (88.2%)	1 (5.9%)	1 (5.9%)
7. Should lactate be used as a biochemical definition of septic shock, even in the absence of hypotension?	11 (64.7%)	4 (23.5%)	2 (11.8%)
8. In your opinion, is there a need for a severity grading of septic shock?	8 (47.1%)	4 (23.5%)	5 (29.4%)
Phase 2 (N=17 responses)			
1. "The TF members could not agree on endpoint[s] that define adequate resuscitation in patients with septic shock. As resuscitation is an iterative process this should be separated from the concept of persistent hypotension." Would you agree with this statement regarding adequacy of resuscitation?	9 (52.9)%	0	8 (47.1%)
2. No consensus was achieved regarding an endpoint to mark adequacy of fluid resuscitation. Would you agree with the following definition for 'persistent hypotension' that offers a compromise solution? "Persistent hypotension is defined as hypotension persisting despite fluid resuscitation of at least 20 ml/kg that requires vasopressor therapy for at least 60 minutes to keep MAP >60 mmHg."	11 (64.7%)	0	7 (41.2)%
3. Approximately half the TF voted for including lactate in the definition, wanted a cut-off value to be determined by mining 'big data' to determine sensitivity/specificity of acute hospital mortality? Are you happy with this proposal?	13 (76.9%)	0	4 (23.1%)

Phase 3 (N=18 responses)			
1. The TF members were given four choices for the septic shock updated criteria and were asked to provide their first and second choice independently. The reported proportions represent cumulative first or second choices. a. Lactate alone b. Hypotension alone c. Vasopressor dependent hypotension OR lactate d. Vasopressor dependent hypotension AND lactate	2 (11.1%) 5 (27.8%) 10 (55.6%) 13 (72.2%)		

Response[A,N,D] A= Agree or strongly agree; N= Neither agree nor disagree; D= Disagree or strongly disagree

eTable 5. Potential Septic Shock Cohorts

Variable	Hypotension after fluids	Vasopressor	Raised Lactate >2 mmol/L
Group 1	Yes	Yes	Yes
Group 2	Yes	Yes	No
Group 3	Yes	No	Yes
Group 4	No	No	Yes
Group 5	No hypotension before fluids	No	Yes
Group 6	Yes	No	No

The three variables proposed from the Delphi process could be present as single variables, simultaneously, or in pairs i.e. hypotension AND/OR need for vasopressor therapy AND/OR abnormal lactate. Abnormal lactate refers to concentrations greater than 2mmol/L. Hypotension refers to mean arterial pressure less than 65mmHg in SSC database and systolic blood pressure less than 100mmHg in HER datasets. The field 'crystalloids' coded as a binary variable within the SSC database defined the 'after fluids' term, which refers to resuscitation. We defined cryptic shock as persistently elevated lactate 'after fluids'. Hypotension and Vasopressor therapy are related variables. Hypotension was assumed when vasopressor therapy was administered. Therefore, the groups were collapsed down to six.

- Group 1: Hypotensive after fluids requiring vasopressor therapy with lactate >2 mmol/L
- Group 2: Hypotensive after fluids requiring vasopressor therapy with lactate <2 mmol/L
- Group 3: Hypotensive after fluids with lactate >2 mmol/L
- Group 4: Raised lactate after fluids = 'cryptic' shock
- Group 5: Isolated lactate >2 mmol/L without hypotension or need for vasopressor, thus doesn't mandate resuscitation coding within the SSC database and therefore does not meet 'cryptic shock' definition
- Group 6: Hypotension after fluids and lactate<2mmol/L and no use of vasopressor

eTable 6. Cohort Characteristics of Patients in SSC Database

Patient characteristics	Total = 18,840 N [%]	ED = 10,843 N[%]	Ward = 5934 N [%]	ICU = 2063 N [%]
Site of infection				
Pneumonia	8,286 [44.0]	5,026 [46.4]	2,256 [38.0]	1,004 [48.7]
Urinary Infection	4,258 [22.6]	3,172 [29.3]	875 [14.8]	211 [10.2]
Abdominal	4,384 [23.3]	1,801 [16.6]	2,019 [34.0]	564 [27.3]
Meningitis	248 [1.3]	171 [1.6]	51 [0.9]	26 [1.3]
Skin/bone	1,302 [6.9]	822 [7.6]	372 [6.3]	108 [5.2]
Wound	803 [4.3]	468 [4.3]	262 [4.4]	73 [3.5]
Catheter	695 [3.7]	309 [2.9]	279 [4.7]	107 [5.2]
Endocarditis	185 [1.0]	113 [1.0]	61 [1.0]	11 [0.5]
Device	203 [1.1]	120 [1.1]	68 [1.2]	15 [0.7]
Other infection	2,345 [12.5]	1,466 [13.5]	637 [10.7]	242 [11.7]
Hypotension mmHg				
• MAP<65	13,678 [72.6]	7,639 [70.5]	4,448 [75.0]	1,591 [77.1]
• SBP<90	14,609 [77.5]	8,294 [76.5]	4,663 [78.6]	1,652 [80.1]
• Fall in SBP>40	8,333 [44.2]	4,660 [43.0]	2,711 [45.7]	962 [46.6]
• MAP<65 & SBP<90	12,626 [67.0]	7,189 [66.3]	4,003 [67.5]	1,434 [69.5]
Lactate mmol/L				
• ≤2	4,135 [22.0]	1,924 [17.7]	1,538 [25.9]	673 [32.6]
• >2 to ≤ 3	5,006 [26.6]	2,807 [25.9]	1,618 [27.3]	581 [28.2]
• >3 to ≤ 4	3,395 [18.0]	2,113 [19.5]	973 [16.4]	309 [15.0]
• >4	6,304 [33.5]	3,999 [36.9]	1,805 [30.4]	500 [24.2]
$ScvO_2$				
• No (>70%>24 hrs)	537 [3.0]	264 [2.5]	202 [3.5]	71 [3.5]
• Yes (>70% <24 hrs)	6,940 [38.1]	3,464 [33.1]	2,500 [43.5]	976 [48.3]
• Not obtained	6,179 [33.9]	3,877 [37.0]	1,741 [30.3]	561 [27.8]
• N/A	4,576 [25.1]	2,864 [27.4]	1,301 [22.7]	411 [20.4]

Patient characteristics	Total = 18,840 N [%]	ED = 10,843 N[%]	Ward = 5934 N [%]	ICU = 2063 N [%]
Vasopressors				
• No	374 [2.0]	257 [2.4]	92 [1.6]	25 [1.2]
• Yes	12,505 [66.4]	6,619 [61.0]	4,314 [72.7]	1,572 [76.2]
• N/A	5,961 [31.6]	3,967 [36.6]	1,528 [25.8]	466 [22.6]
Baseline non-CVS OD				
• Pulmonary	4,588 [24.4]	2,246 [20.7]	1,679 [28.3]	663 [32.1]
• Renal	3,879 [36.5]	3,946 [36.4]	2,189 [36.9]	744 [36.1]
• Hepatic	1,879 [10.0]	995 [9.2]	659 [11.1]	225 [10.9]
• Hematologic	4,588 [24.4]	2,484 [22.9]	1,606 [27.1]	498 [24.1]
• Acute altered mental status	5,806 [30.8]	3,577 [33.0]	1,698 [28.6]	531 [25.7]
Septic shock				
+ 0 non-CVS OD	5,418 [28.8]	3,190 [29.4]	1,599 [26.9]	629 [30.5]
+ 1 non-CVS OD	6,365 [33.8]	3,789 [34.9]	1,953 [32.9]	623 [30.2]
+ 2 non-CVS OD	4,487 [23.8]	2,473 [22.8]	1,520 [25.6]	494 [23.9]
+ 3 non-CVS OD	1,951 [10.4]	1,086 [10.0]	637 [10.7]	228 [11.1]
+ 4 non-CVS OD	547 [2.9]	270 [2.5]	198 [3.3]	79 [3.8]
+ 5 non-CVS OD	72 [0.4]	35 [0.3]	27 [0.5]	10 [0.5]
Mortality				
Septic shock overall	6,533 [34.7]	3,014 [27.8]	2,559 [43.1]	960 [46.5]
+ 0 non-CVS OD	1,444 [26.7]	636 [19.9]	562 [35.2]	298 [37.7]
+ 1 non-CVS OD	2,037 [32.0]	953 [25.2]	798 [40.9]	421 [43.9]
+ 2 non-CVS OD	1,756 [39.1]	793 [32.1]	721 [47.4]	348 [50.0]
+ 3 non-CVS OD	931 [47.7]	462 [42.5]	341 [53.5]	172 [57.0]
+ 4 non-CVS OD	323 [59.1]	152 [56.3]	120 [60.6]	71 [68.3]
+ 5 non-CVS OD	42 [58.3]	18 [51.4]	17 [63.0]	9 [64.3]

ED: Emergency department; ICU: Intensive Care Unit; MAP: Mean arterial pressure in mmHg; SBP: systolic blood pressure in mmHg; $ScvO_2$: Central venous saturations; N/A: Not applicable; Non-CVS OD: non-cardiovascular organ dysfunction.

eTable 7. Generalized Estimating Equation (GEE) Population-Averaged Logistic Regression Model for Hospital Mortality Prediction and Risk Adjustment

Variables	N	Hospital mortality, N (%)	Coefficient	Standard error	Z-value	p-value	OR[1]	95% CI of OR	
Group									
1 (referent)	8,520	3,602 (42.3)	0.000				1.00		
2	3,985	1,198 (30.1)	-0.567	0.044	-12.84	< 0.001	0.57	0.52	0.62
3	223	64 (28.7)	-0.431	0.165	-2.62	0.009	0.65	0.47	0.90
4	3,266	839 (25.7)	-0.336	0.069	-4.85	< 0.001	0.71	0.62	0.82
5	2,696	802 (29.7)	-0.265	0.079	-3.37	0.001	0.77	0.66	0.90
6	150	28 (18.7)	-1.133	0.235	-4.81	< 0.001	0.32	0.20	0.51
Admit									
ED (referent)	10,843	3,014 (27.8)	0.000				1.00		
Ward	5,934	2,559 (43.1)	0.476	0.044	10.72	< 0.001	1.61	1.48	1.76
ICU	2,063	960 (46.5)	0.621	0.060	10.32	< 0.001	1.86	1.65	2.09
Region									
Europe (referent)	4,415	1,947 (44.1)	0.000				1.00		
USA	12,724	3,706 (29.1)	-0.192	0.072	-2.68	0.007	0.83	0.72	0.95
South America	1,701	880 (51.7)	0.642	0.102	6.31	< 0.001	1.90	1.56	2.32
Antibiotics									
No (referent)	237	120 (50.6)	0.000				1.00		
Yes	13,979	4,553 (32.6)	-0.366	0.146	-2.51	0.012	0.69	0.52	0.92
Started previously	4,624	1,860 (40.2)	-0.286	0.149	-1.92	0.055	0.75	0.56	1.01
Steroids									
No (referent)	6,619	2,272 (34.3)	0.000				1.00		
Yes	6,927	2,747 (39.7)	0.148	0.040	3.69	< 0.001	1.16	1.07	1.25
Not obtained	753	364 (48.3)	0.410	0.083	4.94	< 0.001	1.51	1.28	1.77
Ln(glucose)			-0.079	0.038	-2.10	0.036	0.92	0.86	1.00
Pulmonary OD	4,588	1,945 (42.4)	0.185	0.043	4.31	< 0.001	1.20	1.11	1.31
Renal OD	6,879	2,782 (40.4)	0.262	0.036	7.34	< 0.001	1.30	1.21	1.39
Hepatic OD	1,879	849 (45.2)	0.198	0.055	3.59	< 0.001	1.22	1.09	1.36

Variables	N	Hospital mortality, N (%)	Coefficient	Standard error	Z-value	p-value	OR[1]	95% CI of OR	
Mental OD	5,806	2,176 (37.5)	0.258	0.037	6.89	< 0.001	1.30	1.20	1.39
Pneumonia	8,286	3,109 (37.5)	0.327	0.041	8.04	< 0.001	1.39	1.28	1.50
Urinary infection	4,258	1,074 (25.2)	-0.213	0.046	-4.61	< 0.001	0.81	0.74	0.89
Abdominal	4,384	1,795 (40.9)	0.223	0.045	4.94	< 0.001	1.25	1.14	1.37
Meningitis	248	64 (25.8)	-0.272	0.156	-1.75	0.080	0.76	0.56	1.03
Hyperthermia	7,817	2,179 (27.9)	-0.333	0.037	-8.88	< 0.001	0.72	0.67	0.77
Hypothermia	2,842	1,349 (47.5)	0.398	0.048	8.24	< 0.001	1.49	1.36	1.64
Chills	1,297	343 (26.5)	-0.387	0.073	-5.29	< 0.001	0.68	0.59	0.78
Tachypnea	11,185	3,979 (35.6)	0.102	0.035	2.88	0.004	1.11	1.03	1.19
Leukopenia	1,670	728 (43.6)	0.256	0.057	4.46	< 0.001	1.29	1.15	1.45
Hyperglycemia	4,113	1,351 (32.8)	-0.172	0.043	-4.00	< 0.001	0.84	0.77	0.92
Platelet	2,293	1,080 (47.1)	0.292	0.051	5.72	< 0.001	1.34	1.21	1.48
Coagulopathy	3,076	1,468 (47.7)	0.442	0.045	9.79	< 0.001	1.56	1.42	1.70
Constant			-0.921	0.248	-3.72				

The risk adjusted odds ratios for the 6 groups are shown in this table. Variables used to define septic shock groups 1-6 [lactate, vasopressor, hypotension after fluids] were not used as adjustment variables in this regression model as they were used to define the six groups. OR: odds ratio; ED: Emergency department; ICU: Intensive Care Unit; USA: United States of America. Glucose increments are in 1mmol/L in the model.; OD – organ dysfunction.

eTable 8. Generalized Estimating Equation (GEE) Population-Averaged Logistic Regression Model for Estimation of Lactate Effect on Hospital Mortality (N = 18,840)

Variables	N	Hospital mortality, N (%)	Coefficient	Standard error	Z-value	*p*-value	OR	95% CI of OR	
Ln(lactate)			0.483	0.028	17.42	< 0.001	1.62	1.54	1.71
Vasopressors									
No (referent)	374	92 (24.6)	0.000				1.00		
Yes	12,505	4,800 (38.4)	0.261	0.138	1.89	0.059	1.30	0.99	1.70
Crystalloids									
No (referent)	2696	802 (29.7)	0.000				1.00		
Yes	16,144	5,731 (35.5)	-0.634	0.097	-6.52	< 0.001	0.53	0.44	0.64
Admit									
ED (referent)	10,843	3,014 (27.8)	0.000				1.00		
Ward	5,934	2,559 (43.1)	0.406	0.046	8.90	< 0.001	1.50	1.37	1.64
ICU	2,063	960 (46.5)	0.467	0.062	7.55	< 0.001	1.59	1.41	1.80
Region									
Europe (referent)	4,415	1,947 (44.1)	0.000				1.00		
USA	12,724	3,706 (29.1)	-0.153	0.070	-2.17	0.030	0.86	0.75	0.99
South America	1,701	880 (51.7)	0.599	0.100	6.01	< 0.001	1.82	1.50	2.21
Antibiotics									
No (referent)	237	120 (50.6)	0.000				1.00		
Yes	13,979	4,553 (32.6)	-0.375	0.149	-2.52	0.012	0.69	0.51	0.92
Started previously	4,624	1,860 (40.2)	-0.280	0.153	-1.83	0.067	0.76	0.56	1.02
Steroids									
No (referent)	6,619	2,272 (34.3)	0.000				1.00		
Yes	6,927	2,747 (39.7)	0.086	0.041	2.10	0.036	1.09	1.01	1.18
Not obtained	753	364 (48.3)	0.395	0.085	4.66	< 0.001	1.48	1.26	1.75
Ln(glucose)			-0.106	0.039	-2.74	0.006	0.90	0.83	0.97
Pulmonary OD	4,588	1,945 (42.4)	0.177	0.055	3.24	0.001	1.19	1.07	1.33
Renal OD	6,879	2,782 (40.4)	0.239	0.037	6.53	< 0.001	1.27	1.18	1.36
Hepatic OD	1,879	849 (45.2)	0.162	0.057	2.86	0.004	1.18	1.05	1.31

Variables	N	Hospital mortality, N (%)	Coefficient	Standard error	Z-value	*p*-value	OR	95% CI of OR	
Mental OD	5,806	2,176 (37.5)	0.190	0.038	4.95	< 0.001	1.21	1.12	1.30
Ventilation	9,947	4,674 (47.0)	0.806	0.039	20.66	< 0.001	2.24	2.07	2.42
Pneumonia	8,286	3,109 (37.5)	0.253	0.042	6.02	< 0.001	1.29	1.19	1.40
Urinary Infection	4,258	1,074 (25.2)	-0.129	0.048	-2.71	0.007	0.88	0.80	0.96
Abdominal	4,384	1,795 (40.9)	0.120	0.047	2.58	0.010	1.13	1.03	1.24
Meningitis	248	64 (25.8)	-0.403	0.158	-2.55	0.011	0.67	0.49	0.91
Hyperthermia	7,817	2,179 (27.9)	-0.322	0.038	-8.38	< 0.001	0.72	0.67	0.78
Hypothermia	2,842	1,349 (47.5)	0.343	0.050	6.92	< 0.001	1.41	1.28	1.55
Chills	1,297	343 (26.5)	-0.299	0.075	-3.98	< 0.001	0.74	0.64	0.86
Tachypnea	11,185	3,979 (35.6)	0.118	0.036	3.25	0.001	1.13	1.05	1.21
Leukopenia	1,670	728 (43.6)	0.224	0.059	3.81	< 0.001	1.25	1.11	1.40
Hyperglycemia	4,113	1,351 (32.8)	-0.202	0.044	-4.60	< 0.001	0.82	0.75	0.89
Platelet	2,293	1,080 (47.1)	0.287	0.052	5.49	< 0.001	1.33	1.20	1.48
Coagulopathy	3,076	1,468 (47.7)	0.395	0.046	8.52	< 0.001	1.49	1.36	1.63
Screen lactate	12,566	4,398 (35.0)	-0.102	0.043	-2.34	0.019	0.90	0.83	0.98
Pulmonary	2,222	987 (44.2)	-0.211	0.069	-3.05	0.002	0.81	0.71	0.93
Constant			-0.841	0.297	-2.83	0.005			

The risk adjusted odds ratios for the individual criterion variables from second stage of Delphi (lactate, vasopressor, and fluids) are provided in this table. For the reported adjusted odds ratios the outcome is ‘acute hospital mortality’ in septic shock group. The odds ratios in this regression model were generated by back-transforming the adjusted natural log of the serum lactate coefficient to the original units for serum lactate in mmol/L. OR: odds ratio; ED: Emergency department; ICU: Intensive Care Unit; USA: United States of America; Glucose and Lactate increments are in 1mmol/L. OD – organ dysfunction.

eTable 9. Characteristics of Lactate Cut-off Values for Complete Case Analysis by Combining Patients in Groups 1 and 2

Characteristic	Lactate ≥ 2 mmol/L	Lactate ≥ 3 mmol/L	Lactate ≥ 4 mmol/L
Complete case analysis [N = 12,475]*			
Hospital mortality, %	4165/12475=33.3 (32.4-34.3)	4454/12475=35.7 (34.8-36.6)	4752/12475=38.1 (37.2-39.0)
Sensitivity, %	3584/4782=74.9 (73.7-76.2)	2766/4782=57.8 (56.4-59.2)	2191/4782=45.8 (44.4-47.2)
Specificity, %	2787/7693=36.2 (35.2-37.3)	4422/7693=57.5 (56.4-58.6)	5434/7693=70.6 (69.6-71.7)
PPV, %	3584/8490=42.2 (41.2-43.3)	2766/6037=45.8 (44.6-47.1)	2191/4450=49.2 (47.8-50.7)
NPV, %	2787/3985=69.9 (68.5-71.4)	4422/6438=68.7 (67.5-69.8)	5434/8025=67.7 (66.7-68.7)

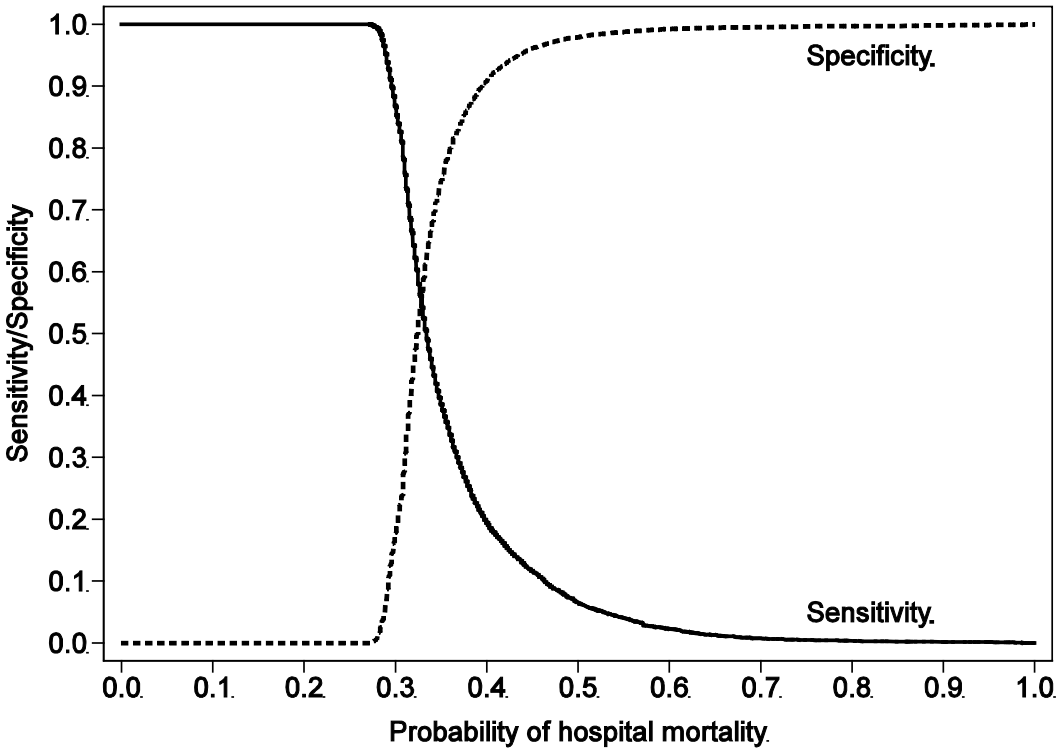
*Analysis ignored observations where serum lactate values > 100 mmol/L

eTable 10. Descriptive Data on UPMC and KPNC Cohorts

	UPMC		KPNC	
Variables	**Infection + >=1 SOFA point**	**Septic Shock[a]**	**Infection + >=1 SOFA point**	**Septic Shock[a]**
Number of patients	13,133	5984 (46)	139,888	54,135 (39)
Age, yrs [IQR]*	63 [52, 75]	64 [52, 76]	72 [59 - 83]	73 [60 - 83]
Male sex, no. (%)	6,827 (52)	3,161 (53)	68,213 (49)	27,539 (51)
SOFA[1] score*	5 [3 – 9]	7 [4 – 11]	2 [1 - 4]	3 [2 - 6]
SIRS[1]	3 [2 – 4]	3 [2 – 4]	NA	NA
ICU-LOS* days	6 [3 – 12]	6 [3 – 12]	2 [1 - 4]	2 [1 - 5]
Hosp-LOS* days	11 [6 – 18]	11 [6 – 19]	4 [2 - 7]	4 [3 - 7]
Mortality[2] N (%)	2,634 (20)	1,821 (30)	11,334 (8)	7,598 (14)

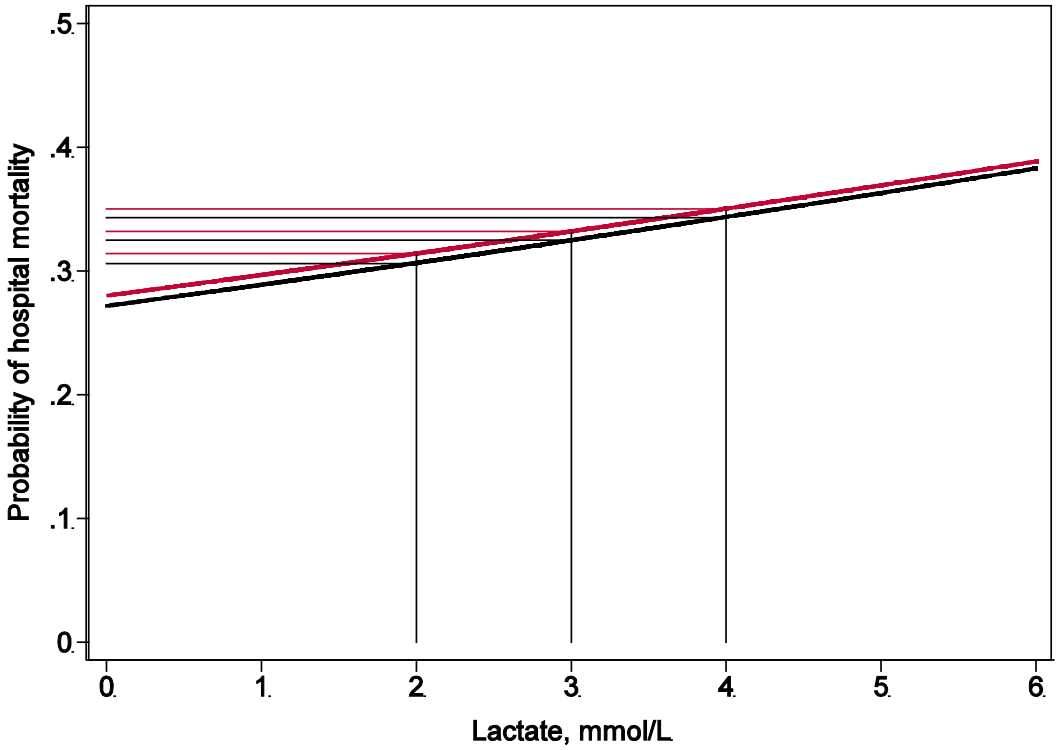
*Data presented as median [IQR]; [1]SIRS and SOFA data represent worst values in 24 hours after infection identified. [a]Represents any of the NEW Septic Shock groups 1 to 4. [2] Refers to acute hospital mortality; LOS – length of stay; SIRS – Systemic inflammatory response syndrome; ICU – Intensive Care Unit; SOFA- Sepsis Organ failure score

eFigure 1. Probability of Hospital Mortality Derived Using Regression Model for Full Case and Imputed Analyses



Black lines are based on the complete case analysis septic shock population (N = 18,840) while red lines are based on the imputed missing serum lactate population (N = 22,182). Probability of hospital mortality expressed as a proportion (range 0 – 1) and is based on a logistic regression model where the dependent variable is hospital mortality and the independent variable is continuous serum lactate (mmol/L) (eTable8). The lines produced by the logistic regression model show the relationship between predicted hospital mortality and serum lactate (mmol/L). The serumn lactate level is truncated at 6mmol/L since approximately 85% of the observations are ≤ 6 mmol/L

eFigure 2. Sensitivity and Specificity by the Probability of Hospital Mortality



Probability of hospital mortality expressed as a proportion (range 0 – 1) and is based on a logistic regression model where the dependent variable is hospital mortality and the independent variable is continuous serum lactate (mmol/L) (eTable8). The specific values of serum lactate the corresponding probability of hospital mortality are reported to show the performance characteristics of serum lactate levels (Table-4 and eTable9 for Group-1 and Group-2).

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