Supplementary Material*

Pepper DJ, Jaswal D, Sun J, Welsh J, Natanson C, Eichacker PQ. Evidence underpinning the U.S. government–mandated hemodynamic interventions for sepsis. A systematic review. Ann Intern Med. 2018. doi:10.7326/M17-2947

* This supplementary material was provided by the authors to give readers further details on their article. The material was reviewed but not copyedited.

Database search

Total: 56,563 records
Search 1: 51,935 total records [46,498 records (2/7/17) and 5,437 records (updated 11/28/17)]
Search 2: 4,628 total records [3,780 records (2/7/17) and 848 records (updated 11/28/17)]
Initial search (2/7/17): 50,278 records
Updated search (11/28/17): 6,285 records

Search 1: 51,935 records

PUBMED: 11,393 records (2/7/17) and 2,099 records (11/28/17)

(sepsis[majr] OR sepsis[tiab] OR septic[tiab] OR septicemia[tiab]) AND (physical examination[mesh] OR "physical examination"[tiab] OR "vital signs"[tiab] OR "heart rate"[tiab] OR "blood pressure"[tiab] OR "arterial pressure"[tiab] OR respiration[mesh] OR "respiratory rate"[tiab] OR "cardiopulmonary examination"[tiab] OR "cardiovascular examination"[tiab] OR "cardiac examination"[tiab] OR pulmonary edema[mesh] OR "pulmonary edema"[tiab] OR jugular veins[mesh] OR "jugular vein"[tiab] OR "jugular veins"[tiab] OR "pulmonary congestion"[tiab] OR "shock index"[tiab] OR "capillary refill"[tiab] OR skin temperature[mesh] OR "skin temperature"[tiab] OR "skin color"[tiab] OR "peripheral circulation"[tiab] OR pulse[tiab] OR skin/blood supply[mesh] OR mottling[tiab] OR mottled[tiab]) NOT "Animals"[Mesh:NoExp] NOT pig NOT pigs NOT swine NOT rat NOT rats NOT mouse NOT mice NOT dog NOT dogs NOT prenatal NOT infant NOT infants NOT neonatal NOT newborn NOT baby NOT babies NOT child NOT children NOT pediatric NOT pediatrics (5185 citations)

(sepsis[majr] OR sepsis[tiab] OR septic[tiab] OR septicemia[tiab]) AND ("goal directed"[tiab] OR ultrasound[tiab] OR ultrasonography[mesh] OR ultrasonography[tiab] OR echocardiography[mesh] OR echocardiography[tiab] OR heart ventricles[mesh] OR "heart ventricles"[tiab] OR ventricular function[mesh] OR "ventricular function"[tiab] OR ventricular dysfunction[mesh] OR "ventricular dysfunction"[tiab] OR venae cavae[mesh] OR "vena cava"[tiab] OR "caval index"[tiab] OR stroke volume[mesh] OR "stroke volume"[tiab] OR cardiac output[mesh] OR "cardiac output"[tiab] OR cardiac volume[mesh] OR "cardiac volume"[tiab] OR blood flow velocity[mesh] OR "blood flow velocity"[tiab] OR "speckle tracking"[tiab] OR "leg raise"[tiab] OR fluid therapy[mesh] OR "fluid therapy"[tiab] OR "fluid challenge"[tiab] OR "fluid titration"[tiab] OR "volume expansion"[tiab] OR "volume administration"[tiab] OR doppler[tiab] OR plethysmography[mesh] OR plethysmography[tiab] OR bioimpedance[tiab] OR bioreactance[tiab]) NOT "Animals"[Mesh:NoExp] NOT pig NOT pigs NOT swine NOT rat NOT rats NOT mouse NOT mice NOT dog NOT dogs NOT prenatal NOT infant NOT infants NOT neonatal NOT newborn NOT baby NOT babies NOT child NOT children NOT pediatric NOT pediatrics (5434 citations)

(sepsis[majr] OR sepsis[tiab] OR septic[tiab] OR septicemia[tiab]) AND (lactates/blood[mesh] OR lactate[tiab] OR lactates[tiab] OR lactic acid/blood[mesh] OR "lactic acid"[tiab] OR vasoconstrictor agents/therapeutic use[mesh] OR vasoconstrictor[tiab] OR vasoconstrictors[tiab] OR vasopressor[tiab] OR vasopressors[tiab] OR vascular resistance/drug effects[mesh] OR "vascular resistance"[tiab] OR "fluid bolus"[tiab] OR fluid therapy[mesh] OR "fluid therapy"[tiab] OR "30cc/kg"[tiab] OR "30ml/kg"[tiab] OR crystalloid solutions[nm] OR "crystalloid solution"[tiab] OR "crystalloid solutions"[tiab] OR "ringer's lactate"[tiab] OR "sodium chloride"[tiab] OR adrenaline[tiab] OR amrinone/therapeutic use[mesh] OR amrinone[tiab] OR dobutamine/therapeutic use[mesh] OR dobutamine[tiab] OR dopamine/therapeutic use[mesh] OR dopamine[tiab] OR epinephrine/therapeutic use[mesh] OR epinephrine[tiab] OR

inotrope[tiab] OR inotropes[tiab] OR milrinone/therapeutic use[mesh] OR milrinone[tiab] OR nitroprusside/therapeutic use[mesh] OR nitroprusside[tiab] OR norepinephrine/therapeutic use[mesh] OR norepinephrine[tiab] OR noradrenaline[tiab] OR "nor-adrenaline"[tiab] OR phenylephrine/therapeutic use[mesh] OR phenylephrine[tiab]) NOT "Animals"[Mesh:NoExp] NOT pig NOT pigs NOT swine NOT rat NOT rats NOT mouse NOT mice NOT dog NOT dogs NOT prenatal NOT infant NOT infants NOT neonatal NOT newborn NOT baby NOT babies NOT child NOT children NOT pediatric NOT pediatrics (4323 citations)

EMBASE: 21,326 records (2/7/17) and 1,609 records (11/28/17)

'sepsis'/exp/mj OR sepsis:ab,ti OR septic:ab,ti OR septicemia:ab,ti AND ('physical examination'/exp/mj OR 'physical examination':ab,ti OR 'vital sign'/exp/mj OR 'vital signs':ab,ti OR 'heart rate'/exp/mj OR 'heart rate':ab,ti OR 'blood pressure'/exp/mj OR 'blood pressure':ab,ti OR 'arterial pressure'/exp/mj OR 'arterial pressure':ab,ti OR 'breathing'/exp/mj OR 'breathing rate'/exp/mj OR 'respiratory rate':ab,ti OR 'body temperature'/exp/mj OR 'body temperature measurement'/exp/mj OR 'body temperature monitoring'/exp/mj OR 'body temperature':ti,ab OR 'cardiovascular system examination'/exp/mj OR 'cardiovascular examination':ab,ti OR 'cardiopulmonary examination':ab,ti OR 'cardiac examination':ab,ti OR 'lung edema'/exp/mj OR 'pulmonary edema':ab,ti OR 'jugular vein'/exp/mj OR 'jugular vein':ab,ti OR 'jugular veins':ab,ti OR 'lung congestion'/exp/mj OR 'pulmonary congestion':ab,ti OR 'shock index':ab,ti OR 'capillary refill':ab,ti OR 'skin temperature'/exp/mj OR 'skin temperature':ab,ti OR 'skin color'/exp/mj OR 'skin color':ab,ti OR 'peripheral circulation'/exp/mj OR 'peripheral circulation':ab,ti OR 'skin blood flow'/exp/mj OR 'pulse rate'/exp/mj OR pulse:ab,ti OR mottling:ab,ti OR mottled:ab,ti) NOT prenatal NOT infant NOT infants NOT neonatal NOT newborn NOT baby NOT babies NOT child NOT children NOT pediatric NOT pediatrics AND [humans]/lim (6967 citations)

'sepsis'/exp/mj OR sepsis:ti,ab OR septic:ti,ab OR septicemia:ti,ab AND ('goal directed':ti,ab OR 'ultrasound'/exp/mj OR ultrasound:ti,ab OR 'echography'/exp/mj OR ultrasonography:ti,ab OR 'echocardiography'/exp/mj OR echocardiography:ti,ab OR 'heart ventricle'/exp/mj OR 'heart ventricles':ti,ab OR 'heart ventricle function'/exp/mj OR 'ventricular function':ti,ab OR 'ventricular dysfunction':ti,ab OR 'cava vein'/exp/mj OR 'vena cava':ti,ab OR 'caval index':ti,ab OR 'heart stroke volume'/exp/mj OR 'stroke volume':ti,ab OR 'heart output'/exp/mj OR 'cardiac output':ti,ab OR 'heart volume'/exp/mj OR 'cardiac volume':ti,ab OR 'blood flow velocity'/exp/mj OR 'blood flow velocity':ti,ab OR 'speckle tracking echocardiography'/exp/mj OR 'speckle tracking':ti,ab OR 'leg raise':ti,ab OR 'fluid therapy'/exp/mj OR 'fluid therapy':ti,abOR 'fluid challenge':ti,ab OR 'fluid titration':ti,ab OR 'volume expansion':ti,ab OR 'volume administration':ti,ab OR doppler:ti,ab OR 'plethysmography'/exp/mj OR plethysmography:ti,ab OR bioimpedance:ti,ab OR bioreactance:ti,ab) NOT prenatal NOT infant NOT infants NOT neonatal NOT newborn NOT baby NOT babies NOT child NOT children NOT pediatric NOT pediatrics AND [humans]/lim (7145 citations)

'sepsis'/exp/mj OR sepsis:ab,ti OR septic:ab,ti OR septicemia:ab,ti AND ('lactic acid derivative'/exp/mj OR lactate:ti,ab OR lactates:ti,ab OR 'lactic acid'/exp/mj OR 'lactic acid':ti,ab OR 'vasoconstrictor agent'/exp/mj OR vasoconstrictor:ti,ab OR vasoconstrictors:ti,ab OR vasopressor:ti,ab OR vasopressors:ti,ab OR 'vascular resistance'/exp/mj OR 'vascular resistance':ti,ab OR 'fluid bolus':ti,ab OR 'fluid therapy'/exp/mj OR 'fluid therapy':ti,ab OR '30cc/kg':ti,ab OR '30ml/kg':ti,ab OR 'crystalloid'/exp/mj OR 'crystalloid solution':ti,ab OR 'crystalloid solutions':ti,ab OR 'ringer lactate':ti,ab OR 'sodium chloride':ti,ab OR 'adrenalin'/exp/mj OR adrenaline:ti,ab OR 'amrinone'/exp/mj OR

amrinone:ti,ab OR 'dobutamine'/exp/mj OR dobutamine:ti,ab OR 'dopamine'/exp/mj OR dopamine:ti,ab OR epinephrine:ti,ab OR inotrope:ti,ab OR inotropes:ti,ab OR 'milrinone'/exp/mj OR milrinone:ti,ab OR 'nitroprusside sodium'/exp/mj OR nitroprusside:ti,ab OR 'noradrenalin'/exp/mj OR norepinephrine:ti,ab OR noradrenaline:ti,ab OR 'nor-adrenaline':ti,ab OR 'phenylephrine'/exp/mj OR phenylephrine:ti,ab) NOT prenatal NOT infant NOT infants NOT neonatal NOT newborn NOT baby NOT babies NOT child NOT children NOT pediatric NOT pediatrics AND [humans]/lim (7214 citations)

SCOPUS: 9,813 records (2/7/17) and 1,443 records (11/28/17)

TITLE-ABS (sepsis OR septic OR septicemia) AND TITLE-ABS ("physical examination" OR "vital signs" OR "heart rate" OR "blood pressure" OR "arterial pressure" OR "respiratory rate" OR "cardiopulmonary examination" OR "cardiovascular examination" OR "cardiac examination" OR "pulmonary edema" OR "jugular vein" OR "jugular veins" OR "pulmonary congestion" OR "shock index" OR "capillary refill" OR "skin temperature" OR "skin color" OR "peripheral circulation" OR pulse OR mottling OR mottled OR "goal directed" OR ultrasound OR ultrasonography OR echocardiography OR "heart ventricles" OR "ventricular function" OR "ventricular dysfunction" OR "vena cava" OR "caval index" OR "stroke volume" OR "cardiac output" OR "cardiac volume" OR "blood flow velocity" OR "speckle tracking" OR "leg raise" OR "fluid challenge" OR "fluid titration" OR "volume expansion" OR "volume administration" OR doppler OR plethysmography OR bioimpedance OR bioreactance)

TITLE-ABS (sepsis OR septic OR septicemia) AND TITLE-ABS (lactate OR lactates OR "lactic acid" OR vasoconstrictor OR vasoconstrictors OR vasopressor OR vasopressors OR "vascular resistance" OR "fluid bolus" OR "fluid therapy" OR "30cc/kg" OR "30ml/kg" OR "crystalloid solution" OR "crystalloid solutions" OR "ringer's lactate" OR "sodium chloride" OR adrenaline OR amrinone OR dobutamine OR dopamine OR epinephrine OR inotrope OR inotropes OR milrinone OR nitroprusside OR norepinephrine OR noradrenaline OR "nor-adrenaline" OR phenylephrine)

(TITLE-ABS (sepsis OR septic OR septicemia) AND TITLE-ABS ("physical examination" OR "vital signs" OR "heart rate" OR "blood pressure" OR "arterial pressure" OR "respiratory rate" OR "cardiopulmonary examination" OR "cardiovascular examination" OR "cardiac examination" OR "pulmonary edema" OR "jugular vein" OR "jugular veins" OR "pulmonary congestion" OR "shock index" OR "capillary refill" OR "skin temperature" OR "skin color" OR "peripheral circulation" OR pulse OR mottling OR mottled OR "goal directed" OR ultrasound OR ultrasonography OR echocardiography OR "heart ventricles" OR "ventricular function" OR "ventricular dysfunction" OR "vena cava" OR "caval index" OR "stroke volume" OR "cardiac output" OR "cardiac volume" OR "blood flow velocity" OR "speckle tracking" OR "leg raise" OR "fluid challenge" OR "fluid titration" OR "volume expansion" OR "volume administration" OR doppler OR plethysmography OR bioimpedance OR bioreactance)) OR (TITLE-ABS (sepsis OR septic OR septicemia) AND TITLE-ABS (lactate OR lactates OR "lactic acid" OR vasoconstrictor OR vasoconstrictors OR vasopressor OR vasopressors OR "vascular resistance" OR "fluid bolus" OR "fluid therapy" OR "30cc/kg" OR "30ml/kg" OR "crystalloid solution" OR "crystalloid solutions" OR "ringer's lactate" OR "sodium chloride" OR adrenaline OR amrinone OR dobutamine OR dopamine OR epinephrine OR inotrope OR inotropes OR milrinone OR nitroprusside OR norepinephrine OR noradrenaline OR "nor-

adrenaline" OR phenylephrine)) AND (EXCLUDE (EXACTKEYWORD , "Nonhuman") OR EXCLUDE (EXACTKEYWORD , "Animals") OR EXCLUDE (EXACTKEYWORD , "Animal Experiment") OR EXCLUDE (EXACTKEYWORD , "Animal Model") OR EXCLUDE (EXACTKEYWORD , "Animal") OR EXCLUDE (EXACTKEYWORD , "Rat") OR EXCLUDE (EXACTKEYWORD , "Rats") OR EXCLUDE (EXACTKEYWORD , "Infant") OR EXCLUDE (EXACTKEYWORD , "Infant, Newborn") OR EXCLUDE (EXACTKEYWORD , "Newborn") OR EXCLUDE (EXACTKEYWORD , "Disease Models, Animal") OR EXCLUDE (EXACTKEYWORD , "Child, Preschool") OR EXCLUDE (EXACTKEYWORD , "Rats, Sprague-Dawley") OR EXCLUDE (EXACTKEYWORD , "Swine") OR EXCLUDE (EXACTKEYWORD , "Preschool Child") OR EXCLUDE (EXACTKEYWORD , "Pregnancy"))

WEB OF SCIENCE CORE COLLECTION: 1,952 records (2/7/17) and 206 records (11/28/17)

TITLE: (sepsis OR septic OR septicemia) AND TITLE: ("physical examination" OR "vital signs" OR "heart rate" OR "blood pressure" OR "arterial pressure" OR "respiratory rate" OR "cardiopulmonary examination" OR "cardiovascular examination" OR "cardiac examination" OR "pulmonary edema" OR "jugular vein" OR "jugular veins" OR "pulmonary congestion" OR "shock index" OR "capillary refill" OR "skin temperature" OR "skin color" OR "peripheral circulation" OR pulse OR mottling OR mottled OR "goal directed" OR ultrasound OR ultrasonography OR echocardiography OR "heart ventricles" OR "ventricular function" OR "ventricular dysfunction" OR "vena cava" OR "caval index" OR "stroke volume" OR "cardiac output" OR "cardiac volume" OR "blood flow" OR "speckle tracking" OR "leg raise" OR fluid OR fluids OR "volume expansion" OR "volume administration" OR doppler OR plethysmography OR bioimpedance OR bioreactance) NOT TOPIC: (pig OR pigs OR swine OR rat OR rats OR mouse OR mice OR dog OR dogs OR prenatal OR infant OR infants OR neonatal OR newborn OR baby OR babies OR child OR children OR pediatric OR pediatrics) (1220 citations)

TITLE: (sepsis OR septic OR septicemia) AND TITLE: (lactate OR lactates OR "lactic acid" OR vasoconstrictor OR vasoconstrictors OR vasopressor OR vasopressors OR "vascular resistance" OR "fluid bolus" OR "fluid therapy" OR "30cc/kg" OR "30ml/kg" OR "crystalloid solution" OR "crystalloid solutions" OR "ringer's lactate" OR "sodium chloride" OR adrenaline OR amrinone OR dobutamine OR dopamine OR epinephrine OR inotrope OR inotropes OR milrinone OR nitroprusside OR norepinephrine OR noradrenaline OR "nor-adrenaline" OR phenylephrine) NOT TOPIC: (pig OR pigs OR swine OR rat OR rats OR mouse OR mice OR dog OR dogs OR prenatal OR infant OR infants OR neonatal OR newborn OR baby OR babies OR child OR children OR pediatric OR pediatrics)

Clinical trials.gov: 2,014 records (2/7/17) and 80 records (11/28/17)
Sepsis OR Septic shock

Search 2: 4,628 records

PubMed: 1,497 records (2/7/17) and 335 records (11/28/17)
(sepsis[majr] OR sepsis[tiab] OR septic[tiab] OR septicemia[tiab]) AND ("sepsis bundle"[tiab] OR bundle[ti] OR "sepsis bundles"[tiab] OR bundles[ti] OR "sepsis protocol"[tiab] OR protocol[ti] OR "sepsis protocols"[tiab] OR protocols[ti] OR "surviving sepsis"[tiab] OR "Guideline Adherence"[Majr] OR guideline[ti] OR guidelines[ti]) NOT "Animals"[Mesh:NoExp]

EMBASE: 1,155 records (2/7/17) and 232 records (11/28/17)
'sepsis'/exp/mj OR sepsis:ti,ab OR septic:ti,ab OR septicemia:ti,ab AND ('sepsis bundle':ti,ab OR bundle:ti OR 'sepsis bundles':ti,ab OR bundles:ti OR 'sepsis protocol':ti,ab OR protocol:ti OR 'sepsis protocols':ti,ab OR protocols:ti OR 'surviving sepsis':ti,ab OR 'protocol compliance'/exp/mj OR guideline:ti OR guidelines:ti) AND ([article]/lim OR [article in press]/lim OR [erratum]/lim OR [review]/lim) AND [humans]/lim

Scopus: 841 records (2/7/17) and 190 records (11/28/17)
TITLE-ABS (sepsis OR septic OR septicemia) AND TITLE-ABS ("sepsis bundle" OR "sepsis bundles" OR "sepsis protocol" OR "sepsis protocols" OR "surviving sepsis campaign" OR "surviving sepsis guidelines") AND (EXCLUDE(EXACTKEYWORD,"Nonhuman")) AND (LIMIT-TO(DOCTYPE,"ar") OR LIMIT-TO(DOCTYPE,"re") OR LIMIT-TO(DOCTYPE,"ip") OR LIMIT-TO(DOCTYPE,"er"))

TITLE (sepsis OR septic OR septicemia) AND TITLE (bundle OR bundles OR protocol OR protocols OR "surviving sepsis") AND (EXCLUDE(EXACTKEYWORD,"Nonhuman")) AND (LIMIT-TO(DOCTYPE,"ar") OR LIMIT-TO(DOCTYPE,"re") OR LIMIT-TO(DOCTYPE,"ip") OR LIMIT-TO(DOCTYPE,"er"))

Web of Science: 287 records (2/7/17) and 91 records (11/28/17)
TITLE: (sepsis OR septic OR septicemia) AND TITLE: (bundle OR bundles OR protocol OR protocols OR "surviving sepsis" OR guideline OR guidelines)
Refined by: DOCUMENT TYPES: (ARTICLE OR CORRECTION OR REVIEW)
Timespan: All years. Indexes: SCI-EXPANDED.

Data extraction tool

Section 1. Study Design

1. Last name of first author/ year of publication
2. Prospective vs. Retrospective
3. Observational vs. Interventional
4. Study Period
5. Region/ Country study was conducted
6. Number of study sites
7. Study location (ED, ICU or both)
8. Number of patients enrolled
9. Use a consensus definition of sepsis, severe sepsis, septic shock (Yes [Y], No [N])

   If yes, specify definition:

   If no, specify sepsis definition used:
10. Inclusion criteria
11. Exclusion criteria
12. Primary endpoint
13. Secondary endpoints
14. Mortality definition

Section 2. Study Characteristics

1. Age: Mean (SD) or Median (IQR) reported (Yes [Y], No [N])

2. Sex: frequency (%) reported (Yes [Y], No [N])

3. Co-morbidities at admission
    a. Frequency reported across groups reported (Yes [Y], No [N])
        i. COPD
        ii. CHF
        iii. HTN
        iv. Renal disease
        v. DM
        vi. Liver disease
        vii. Immunocompromised (HIV, Steroids, Chemotherapy, Malignancy)

4. Illness severity at baseline across groups (Yes [Y], No [N])

    If yes, specify which severity scores were used: _____

5. Site of infection reported (Yes [Y], No [N])

6. Reports percentage of patients with positive blood cultures (Yes [Y], No [N])

7. Reports prcentage of patients requiring source control (Yes [Y], No [N])

8. Reports percentage of patient who had baseline serum lactate measured (Yes [Y], No [N])

9. Reports baseline BP (Yes [Y], No [N])

10. Reports mechanical ventilation at baseline (Yes [Y], No [N])

11. Baseline imbalances exist (Yes [Y], No [N])

12. List baseline imbalances if present

    -
    -
    -
    -
    -
    -
    -
    -

Section 3. Study Outcomes

1. Reports survival (Yes [Y], No [N])

2. Reports organ failure (Yes [Y], No [N])

   If yes, specify organ failures:

3. Follow-up
   a. Reports number of patients made DNR (Yes [Y], No [N])
   b. Report follow-up duration (Yes [Y], No [N])

Section 4. Hemodynamic and Infection Components

1. Reports Location of Intervention (Emergency Room [ER], Intensive Care Unit[ICU], Ward[W])

2. If randomized, Report time from onset of sepsis/shock to randomization (Yes [Y], No [N])

3. If randomized, Report therapy (Fluids, pressors etc) administered before randomization (Yes [Y], No [N])

4. Reports number of patients in each arm (Yes [Y], No [N])

5. List all the hemodynamic therapies/ interventions in the intervention arm

6. List all the hemodynamic therapies/ interventions in the comparison arm

7. List all the infection therapies/ interventions in the intervention arm

8. List all the infection therapies/ interventions in the comparison arm

Section 5. CMS SEP-1 Components

	Comparison arm	Intervention arm
N=		
1. Initial Lactate		
Reported	(Yes [Y], No [N])	(Yes [Y], No [N])
Measured within 3 hours	(Yes [Y], No [N])	(Yes [Y], No [N])
Time to initial lactate (SD/IQR)		
Lactate value: Mean (SD) or Median (IQR)		
Percentage with initial lactate		
2. Broad spectrum antibiotics		
Reported	(Yes [Y], No [N])	(Yes [Y], No [N])
Measured within 3 hours	(Yes [Y], No [N])	(Yes [Y], No [N])
Time to antibiotics, mean/median (SD/IQR)		
Percentage with broad spectrum Abx		
3. Blood cultures		
Reported	(Yes [Y], No [N])	(Yes [Y], No [N])
Performed within 3 hours	(Yes [Y], No [N])	(Yes [Y], No [N])
Time to cultures, mean/median (SD/IQR)		
Percentage with blood cultures		
4. Repeat lactate		
Reported	(Yes [Y], No [N])	(Yes [Y], No [N])
Measured within 6 hours	(Yes [Y], No [N])	(Yes [Y], No [N])
Time to repeat lactate (SD/IQR)		
Lactate value at __ hrs: Mean (SD) or Median (IQR)		
Percentage with repeat lactate		
4. 30mL/kg fluid bolus		
Weight reported in study	(Yes [Y], No [N])	(Yes [Y], No [N])
Volume is based on weight in study	(Yes [Y], No [N])	(Yes [Y], No [N])
Fluid bolus infused within 3 hours	(Yes [Y], No [N])	(Yes [Y], No [N])
Time to bolus, mean/median (SD/IQR)		
Volume infused in __ hrs, mean/ median (SD/IQR)		
Percentage with 30mL/kg fluid bolus		
5. Vasopressors		
Given	(Yes [Y], No [N])	(Yes [Y], No [N])
Started within 6 hours	(Yes [Y], No [N])	(Yes [Y], No [N])
Time to vasopressors, mean/median (SD/IQR)		
Dose of vasopressors, mean/median (SD/IQR)		
Percentage with vasopressors		
6. Section F		
Specify component of Section F		
Performed	(Yes [Y], No [N])	(Yes [Y], No [N])
Performed within 6 hours	(Yes [Y], No [N])	(Yes [Y], No [N])

Section 6: Statistical Issues

1. Mortality outcome reported using: [Univariate or Multivariate analysis]

2. Other outcomes reported using: [Univariate or Multivariate analysis]

3. Specify other outcomes reported: _____

4. Comparison groups in statistical analysis (select relevant options)

    a. Bundle vs. other (Yes [Y], No [N])

        If yes then specify other: _____

    b. Component vs. component (Yes [Y], No [N])

        If yes, then specify

        i. Component in Intervention arm: _____

        ii. Component in Comparison arm: _____

5. Did study assess compliance across groups (Yes [Y], No [N])

    If yes, Compliance in intervention arm: ____%

    Compliance in comparison arm: ____%

6. Were any other interventions performed in this study (Yes [Y], No [N])

    If yes, specify: [ ] Educational program/ slide sets

    [ ] Quality improvement project

    [ ] Sepsis team

    [ ] Triage or early sepsis alert

    [ ] Electronic reminder

    [ ] Other: _____

Section 7. Bias Assessment: Cochrane Criteria for Randomized Clinical Trials

1. **Random sequence generation**
    a) Describes method used to allocate control and treatment group (Yes [Y], No [N])
    b) Method of randomization (Simple [S], Restricted [R], Adaptive [A], Not reported [NR])

2. **Allocation concealment**
    a) Allocation method was adequately concealed (Yes [Y], No [N])
    b) Allocation Concealment: (sequentially numbered, opaque, sealed envelopes [SNOSE], central randomization [CR], Not reported [NR])

3. **Blinding of participants**
    a) Study participants were sufficiently blinded to intervention (Yes [Y], No [N])
    b) Blinding (Unblinded [U], Single [S], Double [D], Triple [T], Not reported [NR])

4. **Blinding of outcome assessment**
    a) Investigators were blinded to outcome (Yes [Y], No [N])

5. **Incomplete outcome data**
    a) Incomplete outcome data was adequately addressed
    b) All enrolled patients accounted for (Yes [Y], No [N])
    c) Report number of patients screened (flow sheet) (Yes [Y], No [N])
    d) Report number patients excluded (flow sheet) (Yes [Y], No [N])

6. **Selective reporting**
    a) Reporting of results free from suggestion of selective outcome reporting i.e. protocol was published prior to the study (Yes [Y], No [N])
    b) Report pre-specified primary outcome (Yes [Y], No [N])
    c) Report all pre-specified secondary outcomes (Yes [Y], No [N])
    d) Report adverse outcomes (Yes [Y], No [N])

7. **Other**
    a. Study was free from other sources of bias (Yes [Y], No [N])
    b. Industry Funding [I], Government Funding (G), Not reported [NR])
    c. Was the trial stopped early (Yes [Y], No [N])
    d. Study plan published (yes [Y], No [N])
    e. Conflicts reported (Yes [Y], No [N])

Section 8. Bias Assessment: Newcastle-Ottawa Quality Assessment Scale for Cohort Studies

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability

A. Selection

1) Representativeness of the exposed cohort

a) Truly representative of the average cohort of patients with sepsis *
b) Somewhat representative of the average cohort of patients with sepsis *
c) Selected group of users e.g. nurses, volunteers
d) No description of the derivation of the cohort

2) Selection of the non-exposed cohort

a) Drawn from the same community as the exposed cohort *
b) Drawn from a different source
c) No description of the derivation of the non-exposed cohort

3) Ascertainment of exposure

a) Secure record (e.g. medical records) *
b) Structured interview *
c) Written self report
d) No description

4) Demonstration that outcome of interest was not present at start of study

a) Yes *
b) No

B. Comparability

1) Comparability of cohorts on the basis of the design or analysis

a) Study performs multivariate analysis that controls for severity of illness *
b) Study performs multivariate analysis that controls for ALL of the following: age, co-morbidity, and site of infection *

C. Outcome

1) Assessment of outcome

a) Independent blind assessment *
b) Record linkage *
c) Self report
d) No description

2) Was follow-up long enough for outcomes to occur

a) Yes (ICU stay, hospital stay, 28d, 30d and 60d considered adequate follow up period for outcome of interest) *
b) No

3) Adequacy of follow up of cohorts

a) Complete follow up - all subjects accounted for *
b) Subjects lost to follow up unlikely to introduce bias; small number lost to follow-up (> 90 % follow up), or description provided of those lost) *
c) Follow up rate < 90% and no description of those lost
d) No statement

Supplement Table 1:
Evaluation of Quantity, Quality, and Consistency of Body of Evidence for Structure, Process, and Intermediate Outcome Measures

DEFINITION/ RATING	**QUANTITY** OF BODY OF EVIDENCE	**QUALITY** OF BODY OF EVIDENCE	**CONSISTENCY** OF RESULTS OF BODY OF EVIDENCE
Definition	*Total number of studies (not articles or papers)*	*Certainty or confidence in the estimates of benefits and harms to patients across studies in the body of evidence related to study factorsa including: study design or flaws; directness/indirectness to the specific measure (regarding the population, intervention, comparators, outcomes); imprecision (wide confidence intervals due to few patients or events)*	*Stability in both the direction and magnitude of clinically/practically meaningful benefits and harms to patients (benefit over harms) across studies in the body of evidence*
High	5+ studies[b]	Randomized controlled trials (RCTs) providing direct evidence for the specific measure focus, with adequate size to obtain precise estimates of effect, and without serious flaws that introduce bias	Estimates of clinically/practically meaningful benefits and harms to patients are consistent in direction and similar in magnitude across the preponderance of studies in the body of evidence
Moderate	2-4 studies[b]	• Non-RCTs with control for confounders that could account for other plausible explanations, with large, precise estimate of effect OR • RCTs without serious flaws that introduce bias, but with either indirect evidence or imprecise estimate of effect	Estimates of clinically/practically meaningful benefits and harms to patients are consistent in direction across the preponderance of studies in the body of evidence, but may differ in magnitude If only one study, then the estimate of benefits greatly outweighs the estimate of potential harms to patients (one study cannot achieve high consistency rating)
Low	1 study[b]	• RCTs with flaws that introduce bias OR • Non-RCTs with small or imprecise estimate of effect, or without control for confounders that could account for other plausible explanations	• Estimates of clinically/practically meaningful benefits and harms to patients differ in both direction and magnitude across the preponderance of studies in the body of evidence OR • Wide confidence intervals prevent estimating net benefit. If only one study, then estimate of benefits do not greatly outweigh harms to patients
Insufficient to Evaluate *(See Table 3 for exceptions.)*	• No empirical evidence OR • Only selected studies from a larger body of evidence	• No empirical evidence OR • Only selected studies from a larger body of evidence	No assessment of magnitude and direction of benefits and harms to patients

[a]*Study designs* that affect certainty of confidence in estimates of effect include: randomized controlled trials (RCTs), which control for both observed and unobserved confounders, and non-RCTs (observational studies) with various levels of control for confounders.
Study flaws that may bias estimates of effect include: lack of allocation concealment; lack of blinding; large losses to follow-up; failure to adhere to intention to treat analysis; stopping early for benefit; and failure to report important outcomes.
Imprecision with wide confidence intervals around estimates of effects can occur in studies involving few patients and few events.
Indirectness of evidence includes: indirect comparisons (e.g., two drugs compared to placebos rather than head-to head); and differences between the population, intervention, comparator interventions, and outcome of interest and those included in the relevant studies.
[b]The suggested number of studies for rating levels of quantity is considered a general guideline.

Obtained from page 10 of the NQF's 2013 Review and Update of Guidance for Evaluating Evidence and Measure Testing [8]

Supplement Table 2. Study Characteristics

Author (y)	Study Design	Number of Patients		Sepsis Type	Study Country	Number of Study Sites	Location of Patients
		Control Group	Intervention Group				
Studies with serial lactate measurements							
Jansen ('10)[23]	RCT	67	68	SS	Holland	4	ICU
Xiaochun ('15)[24]	RCT	50	50	SSh	China	16	ICU
Nguyen ('07)[25]	OS-CCC	253	77	S	USA	1	ED+ICU
Dettmer ('15)[26]	OS-CCC	111	132	SS/SSh	USA	1	ED
McColl ('16)[27]	OS-BACC	167	185	S/SS	Canada	2	ED
Studies with a 30ml/kg fluid infusion							
La Rosa ('12)[28]	OS-CCC	24	34	SS/SSh	USA	1	ICU
Hayden ('16)[29]	OS-BACC	108	130	S/SSh	USA	1	ED
Leisman 2012* ('16)[30]	OS-CCC	4769	1050	SS/SSh	USA	11	ED+ICU
Leisman 2014*('16)[30]	OS-CCC	958	739	SS/SSh	USA	1	ED+ICU
Leisman 2015* ('16)[30]	OS-CCC	5124	2115	SS/SSh	USA	9	ED+ICU
Ferreras ('17)[31]	OS-BACC	222	222	S/SSh	Spain	6	ED
Teles ('17)[32]	OS-CCC	46	121	S/SS/Sh	Brazil	1	ICU + Wards
Studies with serial lactate measurements and a 30ml/kg fluid infusion							
Liu ('15)[33]	OS-BACC	5942	6544	S	USA	21	ED+ICU
Rhodes ('15)[34]	OS-CCC	734	90	S/SSh	62†	618	ED+ICU
Siontis ('15)[35]	OS-BACC	51	41	S	USA	1	ICU
Grek ('16)[36]	OS-BACC	25	424	S	USA	1	ED
Studies assessing fluid responsiveness							
Hou ('16)[37]	RCT	32	32	S	USA	10	ED
Kuan ('16)[38]	RCT	61	61	S	Singapore	1	ED
Cronhjort ('17)[39]	RCT	18	16	SSh	Sweden	1	ICU
Studies assessing SEP-1 Bundle							
Ramsdell ('17)[40]	OS-BACC	48	110	SS/SSh	USA	1	ICU + Wards

RCT = randomized controlled trial; OS = observational Study; BACC = before and after cohort control; CCC = concurrent cohort control; S = sepsis; SS = severe sepsis; SSh = septic shock; ED = emergency Department; ICU = intensive care unit

* one publication included comparisons of control and intervention patients from each of three distinct patient populations admitted to study hospitals over periods ending in either 2012, 2014 or 2016 and each group and comparison was analyzed as a single study here

† study conducted in patients from hospitals in 62 different countries from Africa, Asia, Europe, North America, South America and Oceania

Supplement Table 3. Summary of whether gender, co-morbidities and illness severity were reported in both the intervention and control arms

Author (y)	Age	Co-morbidities	Illness Severity Score	Type of Illness Severity Score
Studies with serial lactate measurements				
Jansen ('10)[23]	No	No	Yes	APACHE II
Xiaochun ('15)[24]	Yes	Yes	No	-
Nguyen ('07)[25]	Yes	No	Yes	APACHE II, MEDS, SAPS
Dettmer ('15)[26]	Yes	Yes	Yes	SOFA
McColl ('16)[27]	Yes	Yes	Yes	CTAS
Studies with 30ml/kg fluid infusion				
La Rosa ('12)[28]	Yes	No	Yes	MEDS
Hayden ('16)[29]	Yes	No	No	-
Leisman 2012* ('16)[30]	Yes	No	No	-
Leisman 2014 *('16)[30]	Yes	Yes	No	-
Leisman 2015* ('16)[30]	Yes	Yes	No	-
Ferreras ('17)[31]	Yes	Yes	Yes	SOFA
Teles ('17)[32]	Yes	Yes	Yes	APACHE II
Studies with serial lactate measurements and 30ml/kg fluid infusion				
Liu ('15)[33]	Yes	Yes	Yes	LAPS 2
Rhodes ('15)[34]	No	No	No	-
Siontis ('15)[35]	Yes	No	Yes	APACHE, SOFA
Grek ('16)[36]	Yes	No	Yes	APACHE
Studies with assessment of fluid responsiveness				
Hou ('16)[37]	Yes	Yes	Yes	APACHE II, SOFA
Kuan ('16)[38]	Yes	Yes	Yes	MEDS, MPM, SOFA
Cronhjort ('17)[39]	Yes	Yes	Yes	SAPS3, SOFA
Studies assessing SEP-1 Bundle				
Ramsdell ('17)[40]	Yes	No	Yes	SOFA

APACHE II = Acute Physiology and Chronic Health Evaluation; CTAS = Canadian Triage Acuity Scale**;** LAPS 2 = Laboratory-Based Acute Physiology Score**;** MEDS = Mortality in Emergency Department Sepsis (MEDS) score**;** MPM = Mortality Probabilities Models**;** NR = not reported; SAPS =Simplified Acute Physiology Score**;** SOFA = Sequential Organ Failure Assessment (SOFA) Score

* See Table 1 and text for description of these three cohorts

Supplement Table 4. Summary of treatments employed in studies

Author (y)	Treatments and/or Measures		Type of Sepsis Bundle[†]
	Intervention	Control	
Studies with serial lactate (SL) measurements			
Jansen ('10)[23]	EGDT with SL	EGDT without SL	NA
Xiaochun ('15)[24]	EGDT with SL	EGDT without SL	NA
Nguyen ('07)[25]	Bundle with SL completed	Bundle with SL not completed	6h
Dettmer ('15)[26]	2nd Lactate obtained	2nd Lactate not obtained	NA
McColl ('16)[27]	Bundle with SL	No Bundle	3h
Studies with a 30ml/kg fluid infusion			
La Rosa ('12)[28]	Bundle with 30mL/kg	No Bundle	6h
Hayden ('16)[29]	Bundle with 30mL/kg	No Bundle	3h
Leisman 2012* ('16)[30]	Bundle with 30mL/kg completed	Bundle with 30mL/kg not completed	3h
Leisman 2014* ('16)[30]	Bundle with 30mL/kg completed	Bundle with 30mL/kg not completed	3h
Leisman 2015* ('16)[30]	Bundle with 30mL/kg completed	Bundle with 30mL/kg not completed	3h
Ferreras ('17)[31]	Bundle with 30mL/kg completed	No Bundle	3h
Teles ('17)[32]	Bundle with 30mL/kg completed	Bundle with 30mL/kg not completed	3h
Studies with serial lactate measurements and a 30ml/kg fluid infusion			
Liu ('15)[33]	Bundle with SL and 30mL/kg	No Bundle	3h
Rhodes ('15)[34]	Bundle with SL and 30ml/kg Completed	Bundle with SL and 30mL/kg not completed	6h
Siontis ('15)[35]	CPOE Bundle with SL and 30mL/kg	No CPOE Bundle	6h
Grek ('16)[36]	Bundle with SL and 30mL/kg	No Bundle	6h
Studies assessing fluid responsiveness			
Hou ('16)[37]	FR determined with PLR and NiCOM	Usual care	NA
Kuan ('16)[38]	FR determined with FC and NiCOM	Usual care	NA
Cronhjort ('17)[39]	FR determined with PLR and PiCCO®	Usual care	NA
Studies assessing SEP-1 Bundle			
Ramsdell ('17)[40]	SEP-1 Bundle	No SEP-1 Bundle	3h + 6h

EGDT = early goal directed therapy; SL = serial lactate measuremebnt; CPOE – computerized physician order entry; NA = not applicable; PLR = passive leg raise; FC = fluid challenges; NiCOM = noninvasive cardiac output monitoring

* See Table 1 and text for description of these three cohorts

[†] Bundle refers to a group of treatments and/or measurements that septic patients were supposed to receive as quickly as possible within 3 or 6h of presentation

Supplement Table 5. Treatments and/or measurements compared in intervention and control groups

Author (y)	Intervention Group	Control Group
	Studies with serial lactate measurements	
Jansen ('10)[23]	Hemodynamic support targeted to achieve the following: HR<100 BPM, MAP≤60 mmHg, CVP 8–12 mmHg (12–15 with MV) during fluid challenges, UO>0.5 ml/kg/h, SaO_2≥92%, Hb≥7.0 g/dl (>10.0g/dl if cardiac ischemia), and $ScvO_2$, CR or SE at MDs discretion **plus decrease the lactate levels by ≥ 20% every 2h over 8h.**	Hemodynamic support targeted the same goals as in the intervention group but **did not include lactate levels**.
Xiaochun ('15)[24]	Hemodynamic support targeted to achieve the following within 6h: MAP≥65 mmHg, CVP 8-12 mmHg, UO>0.5 ml/kg-h, $ScvO_2$ ≥70% plus achieve **a lactate clearance of ≥10% or an initial/repeat lactate<2.0 mmol within 6h.**	Hemodynamic support targeted the same goals as in the control group but **did not include lactate clearance or reductions in lactate levels**.
Nguyen ('07)[25]	Bundle completed that included the first three components and either of the last two components: - CVP/$ScvO_2$ monitoring begun within 2h - Give antibiotics within 4h - Attain CVP 8mmHg; SBP 90mmHg or MAP 65mmHg; and $ScvO_2$ 70% within 6h - Give steroid if patient is on vasopressor or if adrenal insufficiency is suspected - **Measure lactate**	Bundle not completed
Dettmer ('15)[26]	Initial lactate ≥4mmol/L and **second lactate drawn** while in the ED	Initial lactate ≥4mmol/L but **no second lactate drawn** while in the ED
McColl ('16)[27]	Treated with bundle that included: - BC, early antibiotics, infection source control - Vital signs q10 min - **Measure lactate q2h x 3** - MV for respiratory failure - If no central line: NS 500ml q15min for goal of HR<100, MAP>65, UO> 0.5ml/kg/hr; NE for MAP<65 after 2L crystalloids - If central line: achieve CVP 8-12mmHg; NE if MAP<65 after 2L crystalloids - Hydrocortisone for persistent hypotension	Not treated with bundle
	Studies with a 30ml/kg fluid infusion	
La Rosa ('12)[28]	Bundle completed that included: - Empiric antibiotics by 3h for ED and by 1h for non-ED admissions - Achieve CVP 8–12 mmHg - **Administer 30mL/kg over 1h** for hypotension and/or lactate >4 mmol/L - Additional fluid if CVP<8 or persistent hypotension - Vasopressors for persistent hypotension despite fluid and/or lactate >4 mmol/L	Bundle not completed

Hayden ('16)[29]	Treated with bundle that included: - Broad-spectrum antibiotics - Obtain BC, lactate, and other labs - **Administer 30ml/kg NS bolus via pressure bag**	Not treated with bundle
Leisman 2012* ('16)[30]	Bundle completed that included: - BC drawn before antibiotics - Broad-spectrum antibiotics within180min - Lactate result available within 90min of order - **30mL/kg crystalloid bolus** initiated within 30min of time 0	Bundle not completed
Leisman 2014* ('16)[30]	Bundle completed that included: - BC drawn before antibiotics - Broad-spectrum antibiotics within 180 min - Lactate result available within 90 min - **30mL/kg crystalloid bolus** initiated within 30min of time 0	Bundle not completed
Leisman 2015* ('16)[30]	Bundle completed that included: - BC drawn before antibiotics - Broad-spectrum antibiotics within 180min - Lactate result available within 90min - **30mL/kg crystalloid bolus** initiated within 30min of time 0	Bundle not completed
Ferreras ('17)[31]	Treated with bundle that included: - Antibiotics within 1 hour - Obtain BC before antibiotics, lactate, and other labs - **Administer 30ml/kg fluid volume**	Not treated with bundle
Teles ('17)[32]	Bundle completed that included: - Lactate and cultures collection - Broad-spectrum antibiotics within 1hour - Rapid **30mL/kg crystalloid bolus**	Bundle not completed
	Studies with serial lactate measurements and a 30ml/kg fluid infusion	
Liu ('15)[33]	Treated with bundle that included: - Administer antibiotics within 3h - **Re-measure lactate within 1-4h** of initial lactate level - **Order 30ml/kg fluids within 3h** (or at least 2L)	Not treated with bundle

Rhodes ('15)[34]	Bundle completed that included: Within 3h - Lactate level measured - BC obtained before antibiotics - Broad-spectrum antibiotics administered - **Administer 30mL/kg crystalloids** for hypotension or lactate ≥4 mmol/L Within 6h - **Re-measure lactate** if initial lactate increased - Administer vasopressors for MAP<65mmHg despite initial fluid resuscitation - Measure CVP and $ScvO_2$ for MAP<65mmHg despite initial fluid resuscitation or the initial lactate≥ 4 mmol/L.	Bundle not completed
Siontis ('15)[35]	Treated with bundle that included: - Obtain lactate level - Administer appropriate antibiotics within 1h - **Administer 30mL/kg fluid** - Insert central line - Obtain $ScvO_2$ every 1-2 h - **Re-measure lactate every 1-2h** - Vasopressor if MAP<65mmHg despite fluids or MAP<50 for >15min - Target $ScvO_2$>70% and decreasing lactate	Not treated with bundle
Grek ('16)[36]	Treated with bundle that included: - **Re-measure lactate** for initial >4mmol/L - BC prior to antibiotics - Antibiotic administration within 3h - **Administer 30mL/kg fluid** - Place central venous line if lactate >4 - Measure CVP and $ScvO_2$	Not treated with bundle
	Studies assessing fluid responsiveness	
Hou ('16)[37]	Patients had fluid responsiveness tested with **sequential fluid challenges and NiCOM measures** as follows: - Every 1h for up to 4h patients challenged with 5mL/kg fluid and SV measured before and after fluid with NiCOM - Patients were considered fluid responsive if SV increased by 10% by the end of or within 5 min of fluid challenge - Fluid responsive patients received a 1L crystalloid infusion over a 30 to 60min period - Protocol stopped after four cycles or a stopping point met (e.g. worsening respiratory status or new hypotension/vasopressor use) - Patients remained eligible for fluid administration if initial testing was negative but subsequent testing was positive - Serum lactate was measured initially and at 4h	Treatment at discretion of the treating physician but required an initial and repeat lactate at 4h but **could not include cardiac output measures**.

Kuan ('16)[38]	Patients had fluid responsive tested with **sequential passive leg raise maneuvers and NiCOM measures** as follows: - Before resuscitation and then 30min after each fluid treatment patients underwent a passive leg raise maneuver and SVI was measured immediately before and at the end of the leg raise with NiCOM - Patients were considered fluid responsive if SVI increased by > 10% - Patients with an increase in SVI >20% received 1000mL crystalloid - Patients with an increase in SVI >10% and <20% received 500mL crystalloid - Change in SVI≤10% and MAP≥65 mm Hg were the hemodynamic goals - Vasopressors were started for change in SVI<10% and MAP<65mmHg	Treatment at discretion of the treating physician in accordance with current best practice including the administration of intravenous fluids, vasopressors, and inotropes to attain an MAP≥65 mmHg. **No passive leg-raising maneuvers**.
Cronhjort ('17)[39]	Patients had fluid responsiveness tested with **sequential fluid challenges and PICCO®** as follows: - Protocol applied when physician considered it necessary to administer a fluid bolus - Before resuscitation, patients underwent a passive leg raise maneuver and MAP, CI, SVI was measured immediately before and at the end of the leg raise with PICCO® - Patients were considered fluid responsive if SVI increased by ≥ 10% - Patients with an increase in SVI ≥20% received fluid volume and rate at clinician discretion - Patients with an increase in SVI <10% did not receive fluid administration	Treatment at discretion of the treating physician but not allowed to perform passive leg raise tests.
	Studies Asssesing SEP-1 Bundle	
Ramsdell ('17)[40]	Patients received SEP-1 Bundle including: **3-hour** - Initial lactate level measurement - Broad spectrum or other antibiotics administered - Blood cultures drawn prior to antibiotics - Resuscitation with 30 ml/kg crystalloid fluids if septic shock **6-hour** - Repeat lactate level measurement only if initial lactate level is elevated (≥2mmol/L) - Vasopressors for persistent hypotension - Volume status and tissue perfusion assessment if persistent hypotension or initial lactate ≥4mmol/L	Patients did not receive SEP-1 Bundle but managed according to treating physician

HR = heart rate; BPM = beat per minute; MAP = mean arterial blood pressure; CVP = central venous pressure; UO = urine output; SaO2 = arterial blood oxygen saturation; Hb = hemoglobin; ScvO2 = central venous oxygen saturation; CR = capillary refill; SE = skin exam; ED = emergency department; BC = blood culture; MV = mechanical ventilation; NS = normal saline; NE = norepinephrine; NiCOM = noninvasive cardiac output monitor; CI: cardiac index; SV = stroke volume; SVI = stroke volume index
* See Table 1 and text for description of these three cohorts

Supplement Table 6. Summary of the outcomes reported in analyzed studies

Author	Primary Endpoint	Secondary Endpoint(s)	Mortality Definition	Adjusted Mortality Reported	Variables Adjusted for in Multivariate Analysis	Assessed Adverse Events[†]
Studies with serial lactate measurements						
Jansen ('10)[23]	M	ILOS, HLOS	HM	NA	NA	No
Xiaochun ('15)[24]	M	MV duration, ILOS	28d M	NA	NA	No
Nguyen ('07)[25]	Comp.	M, HLOS	HM	Yes	Acute illness, bundle components	No
Dettmer ('15)[26]	28d M	SOFA; ILOS; VFd; VPFd	28d M	No	Not reported	No
McColl ('16)[27]	30d M	Time to MD assessment, therapy and LC, ICU admit, VP	30d M	Yes	Age, Acute Illness, Co-morbidities	No
Studies with 30ml/kg fluid infusion						
La Rosa ('12)[28]	Comp.	M	HM	Yes	Age, Acute Illness	No
Hayden ('16)[29]	Time to interventions	M	HM	No	NR	No
Leisman 2012* ('16)[30]	HM	ICU admit, VP	HM	Yes	Age, Acute Illness	No
Leisman 2014 *('16)[30]	HM	ICU admit, VP, HLOS, HC	HM	Yes	Age, Acute Illness, Co-morbidities	No
Leisman 2015* ('16)[30]	HM	ICU admit, ILOS, VP, MV, HLOS, HC	HM	Yes	Age, Acute Illness, Co-morbidities	No
Ferreras ('17)[31]	30d M	HM, Comp	30d M	No	NR	No
Teles ('17)[32]	M	ILOS	HM	Yes	Age, Acute Illness, Co-morbidities	No
Studies with serial lactate measurements and 30ml/kg fluid infusion						
Liu ('15)[33]	HM	-	HM	Yes	Age, Sex, Acute Illness, Co-morbidities	No
Rhodes ('15)[34]	M and Comp.	-	HM	Yes	ICU admission, Acute Illness	No
Siontis ('15)[35]	Comp.	M, LOS	30d M	No	NR	No
Grek ('16)[36]	Comp.	HM, CLABSI	HM	No	NR	No
Studies with assessment of fluid responsiveness						
Hou ('16)[37]	SOFA	M; fluids; LC	NR	NA	NA	No
Kuan ('16)[38]	LC	M, LOS, HC, VP	28d HM	NA	NA	Yes (Intubation rate)
Cronhjort ('17)[39]	Weight gain	M, ILOS; fluids	30d M	NA	NA	No
Studies Assessing SEP-1 Bundle						
Ramsdell ('17)[40]	Comp.	HLOS, ILOS, HM	HM	No	NR	No

mortality: M = mortality; HM = hospital mortality; 28d M = 28-day mortality; 30d M = 30-day mortality; NR = not reported; NA = not applicable; length of stay: LOS = length of stay; ILOS = ICU length of stay; HLOS = hospital length of stay; CLABSI = central line associated bloodstream infection; Comp. = compliance; fluids = volume of fluids infused; HC = hospital cost; ICU admit = ICU admission; LC = lactate clearance; MV = mechanical ventilation duration; RS = resuscitation success;
SOFA = Sequential Organ Failure Assessment; VFd = ventilator free days; VP = vasopressor; VPFd = vasopressor free days
* See Table 1 and text for description of these three cohorts; † Assessed adverse events = fluid overload or cardiac events reported for both the control and intervention arms

Supplement Table 7. Adjunctive Aids

	Adjunctive Aid[†]	Prioritized Care Aid			Educational Aid
		Sepsis Alert	Expedited consult	Screening checklist	Lectures/ Meetings
Studies with Serial Lactate Measurements					
Jansen ('10)[23]	No	-	-	-	-
Xiaochun ('15)[24]	No	-	-	-	-
Nguyen ('07)[25]	Yes	-	-	+	+
Dettmer ('15)[26]	No	-	-	-	-
McColl ('16)[27]	Yes	+	+	+	-
Studies with 30 mL/kg Fluid Infusion					
La Rosa ('12)[28]	Yes	+	-	-	-
Hayden ('16)[29]	Yes	+	-	-	-
Leisman 2012* ('16)[30]	Yes	+	-	-	-
Leisman 2014* ('16)[30]	Yes	+	-	-	-
Leisman 2015* ('16)[30]	Yes	+	-	-	-
Ferreras ('17)[31]	Yes	+	-	+	+
Teles ('17)[32]	No	-	-	-	-
Studies with Serial Lactate Measurements and a 30 mL/kg Fluid Infusion					
Liu ('15)[33]	Yes	-	-	-	+
Rhodes ('15)[34]	No	-	-	-	-
Siontis ('15)[35]	Yes	-	-	+	+
Grek ('16)[36]	Yes	+	+	-	-
Studies Assessing Fluid Responsiveness					
Hou ('16)[37]	No	-	-	-	-
Kuan ('16)[38]	No	-	-	-	-
Cronhjort ('17)[39]	No	-	-	-	-
Studies Assessing SEP-1 Bundle					
Ramsdell ('17)[40]	Yes	+	-	+	+

* See Table 1 and text for description of these three cohorts

[†] Adjunctive aids included prioritized care aids (e.g. sepsis pager/alert systems, expedited sepsis consults and sepsis checklists/ triage sysems) or educational aids introduced to improve recognition or management of septic patients by providers (e.g. lectures or meetings)

Supplement Table 8. Risk of bias assessment for analyzed studies

A. Randomized Clinical Trials (Cochrane Risk of Bias Tool)

Author (y)	Selection Bias		Performance Bias	Detection Bias	Attrition Bias	Reporting Bias
	Random Sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data addressed	Free of Selective reporting
Studies of serial lactate measurements						
Jansen ('10)[23]	Yes	Yes	No	No	UK	UK ‖
Xiaochun ('15)[24]	Yes	No	No	No	No ¶	UK
Studies of fluid responsiveness with passive leg raising or fluid challenges						
Hou ('16)[37]	Yes	UK	No	No	No ¶	Yes
Kuan ('16)[38]	Yes	UK	No	No	Yes	UK
Cronhjort ('17)[39]	Yes	UK	No	No	Yes	UK

B. Observational Studies (Newcastle-Ottawa Tool)

Author (y)	Selection Bias			Comparability Bias†		Outcome Bias‡		
	Intervention Group Represents at Risk Patients§	Control Group From Same Population as Intervention Group	Data Obtained from Secure Source	Controlled for Severity of Illness	Controlled for co-morbidity, age, and site of infection	Mortality Assessed Blindly or from Record Linkage	≥ 28d Mortality Reported	Adequacy of follow-up
Studies of serial lactate measurements								
Nguyen ('07)[25]	UK	Yes	Yes	No	No	Yes	No **	UK
Dettmer ('15)[26]	Yes	Yes	Yes	No	No	UK	Yes	UK
McColl ('16)[27]	Yes	Yes	Yes	No	No	Yes	Yes	Yes
Studies of 30mL/kg fluid infusion								
La Rosa ('12)[28]	Yes	Yes	Yes	Yes	No	Yes	No **	UK
Hayden ('16)[29]	Yes	Yes	Yes	No	No	Yes	No **	UK
Leisman 2012* ('16)[30]	Yes	Yes	Yes	Yes	No	Yes	No **	Yes
Leisman 2014 *('16)[30]	Yes	Yes	Yes	Yes	No	Yes	No **	Yes
Leisman 2015* ('16)[30]	Yes	Yes	Yes	Yes	No	Yes	No **	Yes
Ferreras ('17)[31]	Yes	Yes	Yes	No	No	Yes	Yes	UK
Teles ('17)[32]	Yes	Yes	Yes	Yes	No	Yes	No **	UK
Studies of serial lactate measurements and 30mL/kg fluid infusion								
Liu ('15)[33]	Yes	Yes	Yes	Yes	No	Yes	Yes	UK
Rhodes ('15)[34]	UK	Yes	UK	Yes	No	UK	No **	UK
Siontis ('15)[35]	UK	UK	Yes	No	No	UK	Yes	UK
Grek ('16)[36]	Yes	No	Yes	No	No	Yes	No **	UK
Studies of SEP-1 Bundle								
Ramsdell ('17)[40]	Yes	Yes	Yes	No	No	Yes	No **	UK

UK = unknown; * See Table 1 and text for description of these three cohorts; † mortality adjusted for severity of acute illness or co-morbid conditions including all of the following: age, chronic illness and site of infection; ‡ mortality at ≥28d was considered long enough follow-up and reports had to state that follow-up was adequate; § randomly selected patients or all consecutively encountered patients; ‖ Did not report adverse events; ¶ Study did not provide flowsheet showing patients screened or reasons for exclusion after screening; ** Reported mortality less than 28-d mortality

Supplement Table 9. Reported Organ Dysfunction at Baseline and Administered Interventions in SEP-1 Bundle study [40]

	Control arm (n=48)	Intervention arm (n=110)
Reported Organ dysfunction, n (%)		
Hypotension (SBP < 90mmHg or MAP < 65mmHg)	37 (77)	58 (53) ‖
Serum creatinine (> 2mg/dL)	23 (48)	31 (28) ‖
Acute respiratory failure (mechanical ventilation)	15 (31)	25 (23)
Reported Interventions, n (%)		
1. Initial Lactate		
Measured within 3 hours	30 (63)	97 (88) ‖
2. Broad spectrum antibiotics		
Administered within 3 hours	39 (81)	99 (90)
Time to antibiotics, mean/median (SD/IQR)	NR	NR
3. Blood cultures		
Performed within 3 hours	44 (92)	97 (88)
4. 30mL/kg fluid bolus		
*Administered within 3 hours if septic shock **	7 (37)	27 (71) ‖
Actual volume of administered fluid	NR	NR
5. Repeat lactate		
Re-measured within 6 hours if initial lactate > 2mmol/L †	10 (32)	55 (81) ‖
Change in therapy due to result of repeat lactate level	NR	NR
6. Vasopressors		
Started within 6 hours if persistent hypotension ‡	3 (60)	5 (63)
7. Volume status and tissue perfusion assessment		
Performed within 6 hours if persistent hypotension and/or lactate > 4mmol/L §	0 (0)	8 (35) ‖
Focused examination performed within 6 hours	NR	NR
Bedside ultrasound performed within 6 hours	NR	NR
Fluid responsiveness performed within 6 hours	NR	NR
8. Adjunctive Aids		
Priority Care Aids	-	+
Educational Aids	-	+
Reported Outcome, n (%)		
In-hospital mortality	13 (27)	16 (15)

NR = not reported
* Control group (n=19), Intervention group (n=38)
† Control group (n=31), Intervention group (n=69)
‡ Control group (n=5), Intervention group (n=8)
§ Control group (n=19), Intervention group (n=38)
‖ P <0.050

Supplement Table 10. Summary of studies registered in clinicaltrials.gov that address SEP-1's individual interventions *

NCT Number	Study name	Study Description	Location	Recruitment	Mortality is Primary Outcome	Study Start Date	Status	Comments
NCT00270673	-	Early lactate-directed therapy *vs.* hemodynamic support without lactate levels	Netherlands	135	Yes	February 2006	Completed and published Jansen *et al.*[23]	-
NCT01484106	COMMIT	Fluid responsiveness using passive leg raise and NICOM *vs.* Usual care	USA	65	No	November 2011	Completed and published Hou *et al.*[37]	-
NCT01453270	AGONIST	Fluid responsiveness using passive leg raise and NICOM *vs.* Usual care	Singapore	122	No	November 2011	Completed and published Kuan *et al.*[38]	-
NCT02301585	OFTaPLR	Fluid responsiveness using passive leg raise *vs.* Usual care	Sweden	34	No	February 2014	Completed and published Cronhjort *et al.*[39]	Terminated due to futility
NCT02346331	-	Fluid boluses guided by physical examination *vs.* Usual care	Kenya	198	No	January 2015	Active, completed enrolment August 2016	Awaiting publication
NCT02846948	ECHOCARD	Echo guided fluid resuscitation *vs.* Usual care	Lithuania	160	No	January 2016	Active, anticipated completion: February 2018	-
NCT02354742	ECHO RCT	Echo guided fluid resuscitation *vs.* early goal directed therapy	USA	80	No	December 2014	Active, anticipated completion: June 2018	-
NCT03020407	-	Titrated (10±5mL/kg) fluid therapy strategy using IVC ultrasound *vs.* Fixed (30mL/kg) fluid strategy	Thailand	254	Yes	January 2017	Active, anticipated completion: April 2019	-
NCT03214913	-	Titrated (10±5mL/kg) fluid therapy strategy using clinician judgment *vs.* Fixed (30mL/kg) fluid strategy	China	550	Yes	January 2018	Active, anticipated completion: June 2021	-

* As of December 11 2017, no trials were registered in clinicaltrials.gov that assess the SEP-1 Bundle in its entirety

PROSPERO International prospective register of systematic reviews

Evidence for the hemodynamic interventions in the SEP-1 performance measure

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Review question(s)

In patients with sepsis, does the published literature show an improved survival with the use of the hemodynamic interventions included in the Center for Medicare and Medicaid Service's (CMS) Severe Sepsis and Septic Shock Early Management Bundle performance measure (SEP-1)?

Searches

We will perform a systematic search of MEDLINE, EMBASE, Scopus and the Web of Science for relevant citations of published studies through November 30, 2016 using individualized search strategies prepared for each database.

Also, to identify ongoing or planned trials of adults with sepsis, severe sepsis or septic shock, we will search ClinicalTrials.gov.

Types of study to be included

We will include randomized and observational studies of adults presenting with sepsis, severe sepsis or septic shock, and that compare the survival effects of the interventions noted above either individually or when combined in a bundle, to a control group. We anticipate that most studies will be observational studies and that a minority will be randomized controlled trials (RCTs). RCTs and observational studies will be analyzed separately. For observational studies, we will perform subgroup analysis using only studies that provide multivariate analyses accounting for co-morbidities and severity of illness if such studies are available.

Condition or domain being studied

The National Quality Forum (NQF) endorsed and CMS has instituted a performance measure to be applied to patients presenting with sepsis termed the Severe Sepsis and Septic Shock Early Management Bundle (SEP-1). The primary purpose of this performance measure is to decrease hospital mortality and costs of care related to sepsis, severe sepsis and septic shock. The performance measure includes five interventions (both treatments and measures) related to the hemodynamic management of patients with sepsis: In adults with severe sepsis, initial lactate level measurement must be performed within 3 hours of presentation, and repeat lactate level measurement must be performed within 6 hours of presentation, if initial lactate level is elevated. In adults with septic shock, resuscitation with 30ml/kg crystalloid fluids must be performed within 3 hours of presentation. Within 6 hours of presentation of septic shock, adults must receive vasopressors if hypotension persists after fluid administration. Also, if hypotension persists after fluid administration or if the initial lactate level is > 4 mmol/L, then a volume status and tissue perfusion assessment must be performed. According to the CMS performance measure, assessment of volume status and tissue perfusion requires either a focused physical exam (vital signs, cardiopulmonary exam, capillary refill evaluation, peripheral pulse assessment and skin examination – all must be performed), or any two of the following: measure CVP, measure ScvO2, bedside cardiovascular ultrasound, or passive leg raise or fluid challenge. At present CMS requires that providers report on their institution's use of the interventions in this performance measure. Subsequently, however, CMS will require that providers complete all interventions. This performance measure is complex and requires substantial hospital resources to achieve compliance. Our systematic review and meta-analysis will focus on the evidence supporting the use of each of these hemodynamic interventions in decreasing mortality from sepsis, as well as the length of hospital stay, organ failure and cost of care.

Our primary question is:

Do published studies show that these interventions either individually or when combined in a bundle decrease mortality when compared to a control group?

Participants/ population

We will include adults (at least 18 years old) requiring early management (within 6 hours of presentation) of sepsis, severe sepsis or septic shock. The definitions of sepsis, severe sepsis and septic shock for each study will be recorded. Each study must include at least one intervention and one control group, and outcome of interest (see below). The control group will be those that do not receive the intervention or those that receive usual care.

Intervention(s), exposure(s)

The Severe Sepsis and Septic Shock Early Management Bundle includes five hemodynamic interventions either as measures or treatments:

1. Initial lactate level measurement within 3 hours of severe sepsis presentation;

2. Repeat lactate level measurement within 6 hours of severe sepsis presentation, only if initial lactate level is elevated;

3. Resuscitation with 30 ml/kg crystalloid fluids within 3 hours of septic shock presentation;

4. Administration of vasopressors within 6 hours of septic shock presentation, only if hypotension persists after fluid administration;

5. A volume status and tissue perfusion assessment within 6 hours of septic shock presentation, only if hypotension persists after fluid administration or initial lactate > 4 mmol/L.

Volume status and tissue perfusion assessment consists of either:

A. A focused exam including:

• Vital signs; AND

• Cardiopulmonary exam; AND

• Capillary refill evaluation; AND

• Peripheral pulse evaluation; AND

• Skin examination.

OR

B. Any two of the following four:

• Central venous pressure measurement;

• Central venous oxygen measurement;

• Bedside cardiovascular ultrasound;

• Passive leg raise or fluid challenge.

We will assess the evidence supporting the survival benefit of each of these hemodynamic interventions. Each component in the volume status and tissue perfusion assessment will also be examined individually.

Comparator(s)/ control

The control group will be those that do not receive the intervention or those that receive usual care.

Outcome(s)

Primary outcomes

Hospital survival (or 30-day or 60-day or 90-day or ICU survival, prioritized in that order).

Secondary outcomes

1. Length of hospitalization;

2. Costs of care;

3. Organ failure.

Data extraction, (selection and coding)

A standardized form will be made for data abstraction. The following data will be extracted from original articles: the name of the first author; publication year; country; study design; sample size; study period; mean age of study population; male percentage; sepsis definition; sepsis site (pulmonary, urinary tract, or soft tissue); severity of illness (e.g. APACHE, SAP scores); comorbid illnesses (e.g. diabetes, COPD, cancer, immunodeficiency) and lifestyle factors (e.g. smoking, ethanol use); study setting (i.e. emergency department, intensive care unit or hospital ward); inclusion of the performance measure interventions either individually or in a bundle; type of control group not receiving the intervention; time from presentation of sepsis to when the interventions were performed; survival; length of hospitalization; development of organ injury and costs of care. Data used for meta-analysis will include the numbers of survivors and non-survivors. When the report has only one outcome, we will contact the authors for other outcome data.

Risk of bias (quality) assessment

Two independent reviewers will assess papers selected for potential risk of bias. Any disagreements that arise between the reviewers will be resolved through discussion, or with a third reviewer. We will use the Newcastle-Ottawa Scale for evaluation of observational studies (before-after, cohort or case-controlled studies. This scale comprises eight items that evaluate the quality of observational studies regarding selection, comparability and outcome/exposure. For randomized controlled trials, we will use the Cochrane Collaboration's risk of bias assessment tool. This tool assesses selection bias (random sequence generation and allocation concealment), performance bias (blinding of personnel and participants), detection bias (blinding of outcome assessment), attrition bias (incomplete outcome data) and reporting bias (selective reporting). We will assess its effect by doing subgroup analysis based on the risk of bias.

Strategy for data synthesis

Studies will be grouped according to priority, as follows: i) study design (randomized controlled trial vs. observational study), ii) whether the intervention or its component parts (listed above) were investigated as part of a bundle or as an individual intervention, and iii) the particular hemodynamic intervention. For each group, the study characteristics (including their specific study design, study details and a description of the number and characteristics of the study participants included) will be presented in summary tables. For the analysis, we will perform separate subgroup analyses for each study design, bundle/intervention if sufficient numbers of studies are available. Otherwise, an attempt will be made to model the effect of each intervention if we can reasonably assume their effects are additive.

Risk ratios [RR] of mortality will be analyzed using random-effects models, with 0.5 added to zero cells. Heterogeneity among studies will be assessed statistically using the standard Q statistic and I-squared values. Subgroup analyses based on different study designs and/or patient characteristics (e.g. age, severity of illness, co-morbidities, etc.) will be performed if appropriate. Publication bias will be assessed by funnel plot and Egger's regression.

Analysis of subgroups or subsets

Subgroup analyses based on different study designs and/or patient characteristics (e.g. age, severity of illness, co-morbidities, etc.) will be performed if appropriate.

Contact details for further information

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Conflicts of interest
None known

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Hemodynamics; Humans; Outcome Assessment (Health Care); Quality of Health Care; Sepsis; Shock, Septic; Treatment Outcome

Stage of review
Ongoing

Date of registration in PROSPERO
08 December 2016

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08 December 2016

Stage of review at time of this submission	Started	Completed
Preliminary searches	Yes	Yes
Piloting of the study selection process	No	No
Formal screening of search results against eligibility criteria	No	No
Data extraction	No	No
Risk of bias (quality) assessment	No	No
Data analysis	No	No