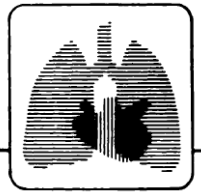
Choc septique

Cas particulier du choc septique

Etat hémodynamique
hyperdynamique



accp/sccm consensus conference

Definitions for Sepsis and Organ Failure and Guidelines for the Use of Innovative Therapies in Sepsis

THE ACCP/SCCM CONSENSUS CONFERENCE COMMITTEE:

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(Chest 1992; 101:1644-55)

Sepsis et sepsis sévère définition de 1992

- **SIRS** (syndrome de réponse inflammatoire systémique) : si deux ou plus des conditions suivantes sont remplies (1992)
  - température < 36°C ou > 38°C
  - fréquence cardiaque > 90/min
  - fréquence respiratoire > 20/min ou PaCO2 < 32 mm Hg
  - leucocytose > 12.000/mm3, < 4.000/mm3 ou présence de formes immatures circulantes (> 10 % des cellules)
- **Sepsis** : si le SIRS est dû à une infection: voir tableau 2003
- **Sepsis sévère** : si le sepsis est associé à une dysfonction organique, de l'hypoperfusion (acidose lactique, oligurie, troubles de conscience,...) ou de l'hypotension artérielle (TAs < 90 mmHg ou chute de > 40 mmHg de la valeur de base sans autre raison connue)
- **Choc septique** : sepsis avec hypotension, malgré un remplissage adéquat, avec des signes d'hypoperfusion
  - l'hypotension peut manquer si des agents vasopresseurs sont administrés

Intensive Care Med (2003) 29:530–538
DOI 10.1007/s00134-003-1662-x

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2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference

Table 1 Diagnostic criteria for sepsis

Infection[a]
Documented or suspected *and* some of the following[b]:
General parameters
Fever (core temperature >38.3°C)
Hypothermia (core temperature <36°C
Heart rate >90 bpm or >2 SD above the normal value for age
Tachypnea: >30 bpm
Altered mental status
Significant edema or positive fluid balance (>20 ml/kg over 24 h)
Hyperglycemia (plasma glucose >110 mg/dl or 7.7 mM/l) in the absence of diabetes
Inflammatory parameters
Leukocytosis (white blood cell count >12,000/µl)
Leukopenia (white blood cell count <4,000/µl)
Normal white blood cell count with >10% immature forms
Plasma C reactive protein >2 SD above the normal value
Plasma procalcitonin >2 SD above the normal value
Hemodynamic parameters
Arterial hypotension[b] (systolic blood pressure <90 mmHg, mean arterial pressure <70, or a systolic blood pressure decrease >40 mmHg in adults or <2 SD below normal for age)
Mixed venous oxygen saturation >70%[b]
Cardiac index >3.5 l min^{-1} m^{-2}[c,d]
Organ dysfunction parameters
Arterial hypoxemia (PaO_2/FIO2 <300)
Acute oliguria (urine output <0.5 ml kg^{-1} h^{-1} or 45 mM/l for at least 2 h)
Creatinine increase ≥0.5 mg/dl
Coagulation abnormalities (international normalized ratio >1.5 or activated partial thromboplastin time >60 s)
Ileus (absent bowel sounds)
Thrombocytopenia (platelet count <100,000/µl)
Hyperbilirubinemia (plasma total bilirubin >4 mg/dl or 70 mmol/l)
Tissue perfusion parameters
Hyperlactatemia (>3 mmol/l)
Decreased capillary refill or mottling

[a] Defined as a pathological process induced by a micro-organism

[b] Values above 70% are normal in children (normally 75–80%) and should therefore not be used as a sign of sepsis in newborns or children

[c] Values of 3.5–5.5 are normal in children and should therefore not be used as a sign of sepsis in newborns or children

[d] Diagnostic criteria for sepsis in the pediatric population is signs and symptoms of inflammation plus infection with hyper- or hypothermia (rectal temperature >38.5°C or <35°C), tachycardia (may be absent in hypothermic patients) and at least one of the following indications of altered organ function: altered mental status, hypoxemia, elevated serum lactate level, and bounding pulses

Table 2 Severe sepsis

Severe sepsis definition = sepsis-induced tissue hypoperfusion or organ dysfunction (any of the following thought to be due to the infection)
Sepsis-induced hypotension
Lactate above upper limits laboratory normal
Urine output <0.5 mL kg^{-1} h^{-1} for more than 2 h despite adequate fluid resuscitation
Acute lung injury with Pao_2/Fio_2 <250 in the absence of pneumonia as infection source
Acute lung injury with Pao_2/Fio_2 <200 in the presence of pneumonia as infection source
Creatinine >2.0 mg/dL (176.8 μmol/L)
Bilirubin >2 mg/dL (34.2 μmol/L)
Platelet count <100,000 μL
Coagulopathy (international normalized ratio >1.5)

Intensive Care Med (2013) 39:165–228
DOI 10.1007/s00134-012-2769-8

GUIDELINES

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Surviving Sepsis Campaign: International Guidelines for Management of Severe Sepsis and Septic Shock, 2012

Définition

Le sepsis sévère correspond à une insuffisance circulatoire reflétée par :

- une hypotension artérielle (PAS < 90 mm Hg – ou chute > 40 mm Hg ou PAM < 65 mm Hg)
- des signes d'altération de la perfusion tissulaire: oligurie, troubles de coagulation, troubles de l'état mental, troubles de la vascularisation cutanée
- une augmentation de la lactatémie (> 2 mEq/L)

... dans le contexte d'une source infectieuse et d'un agent infectieux identifiés

Evolution des concepts

- Le sepsis n'est plus considéré comme seulement une réaction inflammatoire systémique. Il y a également une réponse anti-inflammatoire et une réponse immunitaire à l'agression.
- Il est plutôt la conséquence d'une réaction « inadaptée » avec dysfonction d'un ou de plusieurs organes

Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

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)

Manu Shankar-Hari, MD, MSc; Gary S. Phillips, MAS; Mitchell L. Levy, MD; Christopher W. Seymour, MD, MSc; Vincent X. Liu, MD, MSc; Clifford S. Deutschman, MD; Derek C. Angus, MD, MPh; Gordon D. Rubenfeld, MD, MSc; Mervyn Singer, MD, FRCP; for the Sepsis Definitions Task Force

JAMA. 2016;315(8):775-787. doi:10.1001/jama.2016.0289

Définitions

Box 3. New Terms and Definitions

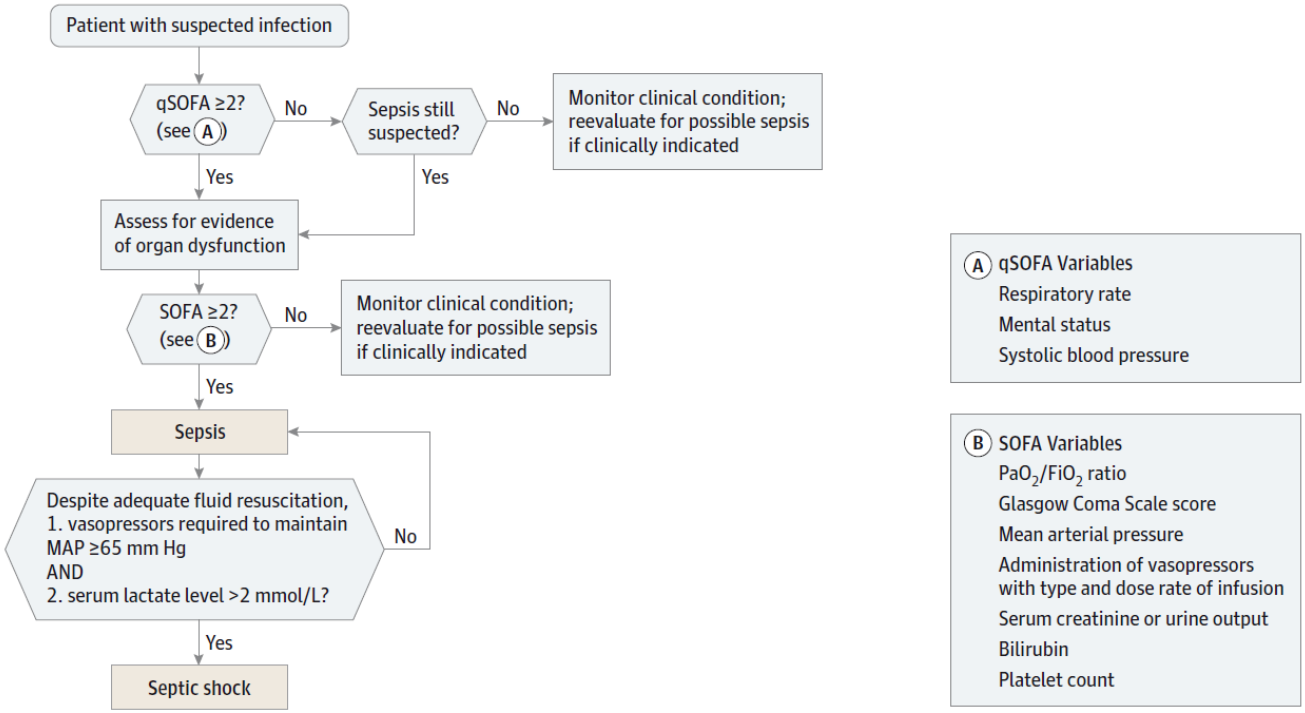
- Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection.
- Organ dysfunction can be identified as an acute change in total SOFA score ≥2 points consequent to the infection.
  - The baseline SOFA score can be assumed to be zero in patients not known to have preexisting organ dysfunction.
  - A SOFA score ≥2 reflects an overall mortality risk of approximately 10% in a general hospital population with suspected infection. Even patients presenting with modest dysfunction can deteriorate further, emphasizing the seriousness of this condition and the need for prompt and appropriate intervention, if not already being instituted.
- In lay terms, sepsis is a life-threatening condition that arises when the body's response to an infection injures its own tissues and organs.
- Patients with suspected infection who are likely to have a prolonged ICU stay or to die in the hospital can be promptly identified at the bedside with qSOFA, ie, alteration in mental status, systolic blood pressure ≤100 mm Hg, or respiratory rate ≥22/min.
- Septic shock is a subset of sepsis in which underlying circulatory and cellular/metabolic abnormalities are profound enough to substantially increase mortality.
- Patients with septic shock can be identified with a clinical construct of sepsis with persisting hypotension requiring vasopressors to maintain MAP ≥65 mm Hg and having a serum lactate level >2 mmol/L (18 mg/dL) despite adequate volume resuscitation. With these criteria, hospital mortality is in excess of 40%.

Abbreviations: MAP, mean arterial pressure; qSOFA, quick SOFA; SOFA: Sequential [Sepsis-related] Organ Failure Assessment.

Table 2. Terminology and *International Classification of Diseases* Coding

Current Guidelines and Terminology	Sepsis	Septic Shock
1991 and 2001 consensus terminology[9,10]	Severe sepsis Sepsis-induced hypoperfusion	Septic shock[13]
2015 Definition	Sepsis is life-threatening organ dysfunction caused by a dysregulated host response to infection	Septic shock is a subset of sepsis in which underlying circulatory and cellular/metabolic abnormalities are profound enough to substantially increase mortality
2015 Clinical criteria	Suspected or documented infection and an acute increase of ≥2 SOFA points (a proxy for organ dysfunction)	Sepsis[a] and vasopressor therapy needed to elevate MAP ≥65 mm Hg and lactate >2 mmol/L (18 mg/dL) despite adequate fluid resuscitation[13]
Recommended primary *ICD* codes[a]		
ICD-9	995.92	785.52
ICD-10[a]	R65.20	R65.21
Framework for implementation for coding and research	Identify suspected infection by using concomitant orders for blood cultures and antibiotics (oral or parenteral) in a specified period[b] Within specified period around suspected infection[c]: 1. Identify sepsis by using a clinical criterion for life-threatening organ dysfunction 2. Assess for shock criteria, using administration of vasopressors, MAP <65 mm Hg, and lactate >2 mmol/L (18 mg/dL)[d]	

Figure. Operationalization of Clinical Criteria Identifying Patients With Sepsis and Septic Shock



The baseline Sequential [Sepsis-related] Organ Failure Assessment (SOFA) score should be assumed to be zero unless the patient is known to have preexisting (acute or chronic) organ dysfunction before the onset of infection. qSOFA indicates quick SOFA; MAP, mean arterial pressure.

Table 1. Sequential [Sepsis-Related] Organ Failure Assessment Score[a]

	Score				
System	0	1	2	3	4
Respiration					
Pao_2/Fio_2, mm Hg (kPa)	≥400 (53.3)	<400 (53.3)	<300 (40)	<200 (26.7) with respiratory support	<100 (13.3) with respiratory support
Coagulation					
Platelets, $\times 10^3/\mu L$	≥150	<150	<100	<50	<20
Liver					
Bilirubin, mg/dL (μmol/L)	<1.2 (20)	1.2-1.9 (20-32)	2.0-5.9 (33-101)	6.0-11.9 (102-204)	>12.0 (204)
Cardiovascular	MAP ≥70 mm Hg	MAP <70 mm Hg	Dopamine <5 or dobutamine (any dose)[b]	Dopamine 5.1-15 or epinephrine ≤0.1 or norepinephrine ≤0.1[b]	Dopamine >15 or epinephrine >0.1 or norepinephrine >0.1[b]
Central nervous system					
Glasgow Coma Scale score[c]	15	13-14	10-12	6-9	<6
Renal					
Creatinine, mg/dL (μmol/L)	<1.2 (110)	1.2-1.9 (110-170)	2.0-3.4 (171-299)	3.5-4.9 (300-440)	>5.0 (440)
Urine output, mL/d				<500	<200

Abbreviations: Fio_2, fraction of inspired oxygen; MAP, mean arterial pressure; Pao_2, partial pressure of oxygen.

[a] Adapted from Vincent et al.[27]

[b] Catecholamine doses are given as μg/kg/min for at least 1 hour.

[c] Glasgow Coma Scale scores range from 3-15; higher score indicates better neurological function.

Échelle de coma de Glasgow

N 15; coma si < 9; coma grave si <5

TABLEAU 2

Échelle de Glasgow et de Liège

Ouverture des yeux (E)

- spontanée 4
- stimulation verbale 3
- stimulation douloureuse 2
- absente 1

Réponse motrice (M)

- sur commande 6
- réactivité aux stimuli douloureux
  - → localisateur 5
  - → retrait 4
  - → stéréotypé en flexion 3
  - → stéréotypé en extension 2
  - → absente 1

Réponse verbale (V)

- orientée 5
- confuse 4
- incohérente 3
- incompréhensible 2
- absente 1

Réflexes du tronc (Liège)

- fronto-orbiculaire 5
- oculo-céphalique vertical 4
- photomoteur 3
- oculo-céphalique horizontal 2
- oculo-cardiaque 1
- aucun 0

LA REVUE DU PRATICIEN VOL. 62
Janvier 2012

Les principaux foyers sources

- Cutanés
- Digestifs : angiocholite, diverticulite, entérite
- Respiratoires : pneumonie, pleurésie, abcès
- Urinaires : pyélonéphrite, prostatite, sonde
- Gynécologiques : salpingite, post-partum
- Veineux : cathéter
- Cardiaque : endocardite
- Cervico-facial : pharyngite, angine, otite, sinusite
- Neuro-méningé
- Ostéo-articulaire

Chez l'opéré récent

- Infection site opératoire
- Pneumopathie
- Infection urinaire
- Phlébite
- Infection sur cathéter

Signes cliniques du choc

- hypotension artérielle
- tachycardie (pouls filant)
- « choc chaud »: extrémités vasodilatées, rouges, chaudes, sèches
- hyperventilation (acidose métabolique)
- lipothymie, apathie, agitation
- oligurie, anurie

Prélèvements à réaliser

A. Microbiologiques:

- hémocultures : périphériques et par toutes les voies des cathéters en place (à mettre également en culture en cas de retrait)
- urines (avec EMU)
- si indiqué : expectorations, LCR, frottis de gorge ...

B. Biologiques:

- fonction rénale : ionogramme, urée, créatinine
- examen hématologique complet avec formule
- tests inflammatoires : CRP, fibrinogène
- tests hépatiques
- coagulation
- gazométrie artérielle et acide lactique

Traitement spécifique

- identifier le foyer infectieux :
  - pulmonaire (radiographie, expectorations)
  - urinaire (EMU, culture)
  - cutané (purpura, macropapules, pustules)
  - neuroméningé (PL)
  - abdominal (RX abdomen à blanc, échographie)
  - endocardite (échographie cardiaque)
  - ....
- toujours faire des hémocultures
- débuter l'antibiothérapie sur un pari bactériologique

Choix des antibiotiques

- sepsis sans foyer : une β-lactamine à large spectre (céphalosporine ou Tienam^{R} ou Méronem^{R} ou Tazocin^{R}) + aminoside (Amikacine-Amukin^{R}) : 15 mg/kg 1 x/j (DT 1,5 g/j)
- infections abdominales pelviennes (anaérobies) : Tienam^{R}/Méronem^{R} ou Tazocin^{R} + aminoside
- suspicion d'infection à staphylocoque : β-lactamine à large spectre + vancomycine (Vancocin^{R} 2 x 1 g i.v.)
- neutropénie fébrile : céphalosporine ou Tienam^{R}/Méronem^{R} ou Tazocin^{R} + amikacine

Le pronostic est lié à la durée de l'hypotension avant l'antibiothérapie

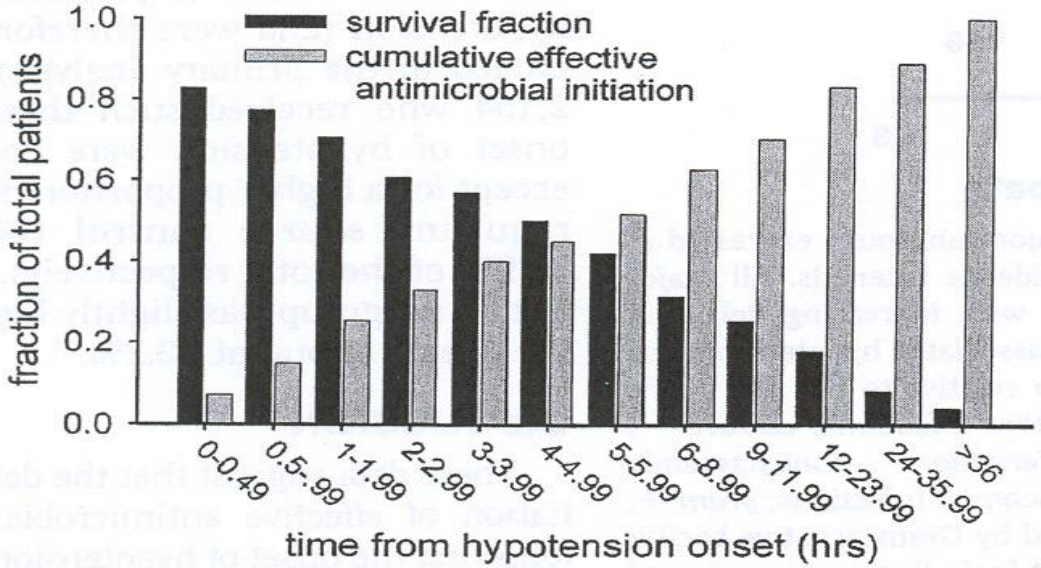


Figure 1. Cumulative effective antimicrobial initiation following onset of septic shock-associated hypotension and associated survival. The x-axis represents time (hrs) following first documentation of septic shock-associated hypotension. *Black bars* represent the fraction of patients surviving to hospital discharge for effective therapy initiated within the given time interval. The *gray bars* represent the cumulative fraction of patients having received effective antimicrobials at any given time point.

Kumar; 2006; 34 : 1589-96

Traitement du choc

- monitorer la lactatémie : dosages réguliers (toutes les 2 h, selon la clinique)
- oxygénothérapie, éventuellement ventilation artificielle (pas de sédation avant instauration vasopresseurs)
- 4 phases successives :

1ère phase

remplissage adéquat

- par exemple 500 à 1000 ml d'un expanseur en 15-30 min
- maintenir l'hématocrite à au moins 25 à 30%

2ème phase

en cas de réponse non satisfaisante au remplissage adéquat : noradrénaline i.v. : 0,02 à 0,1 µg/kg/min (alternative: dopamine i.v. : 5 à 20 γ/kg/min, non disponible en Belgique)

<u>objectifs</u> :

PAS > 90 mm Hg et/ou PAM > 60 mm Hg

lactatémie < 2 mEq/L

diurèse > 20 ml/h

3ème phase

en cas d'échec: échographie cardiaque et/ou un cathéterisme cardiaque droit:

- une hypovolémie (↓ PVC, ↓ PAPO, ↓ IC) : poursuivre le remplissage sous cathécolamines, en recherchant une cause à l'hypovolémie (ex. hémorragie)
- une dysfonction ventriculaire gauche (dilatation ventriculaire, hypokinésie globale ou segmentaire, ↓ IC avec ↑ PAPO) : associer dobutamine (5 à 20 γ/kg/min) et noradrénaline
- **un profil hémodynamique classique de choc septique après remplissage vasculaire** (hyperdynamique : IC > 4,5 L/min et RVS < 800 dynes. sec/cm^5.m^2) : augmenter la noradrénaline jusqu'à 10 µg/kg/min… ou **corticoïdes** (pour renverser l'insensibilité aux catécholamines) : Solucortef^R 300 mg en 24h en perfusion continue ou en 3-4 bolus (durée minimale : 5 jours)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Hydrocortisone plus Fludrocortisone for Adults with Septic Shock

D. Annane, A. Renault, C. Brun-Buisson, B. Megarbane, J.-P. Quenot, S. Siami, A. Cariou, X. Forceville, C. Schwebel, C. Martin, J.-F. Timsit, B. Misset, M. Ali Benali, G. Colin, B. Souweine, K. Asehnoune, E. Mercier, L. Chimot, C. Charpentier, B. François, T. Boulain, F. Petitpas, J.-M. Constantin, G. Dhonneur, F. Baudin, A. Combes, J. Bohé, J.-F. Loriferne, R. Amathieu, F. Cook, M. Slama, O. Leroy, G. Capellier, A. Dargent, T. Hissem, V. Maxime, and E. Bellissant, for the CRICS-TRIGGERSEP Network*

N Engl J Med 2018;378:809-18.
DOI: 10.1056/NEJMoa1705716

METHODS

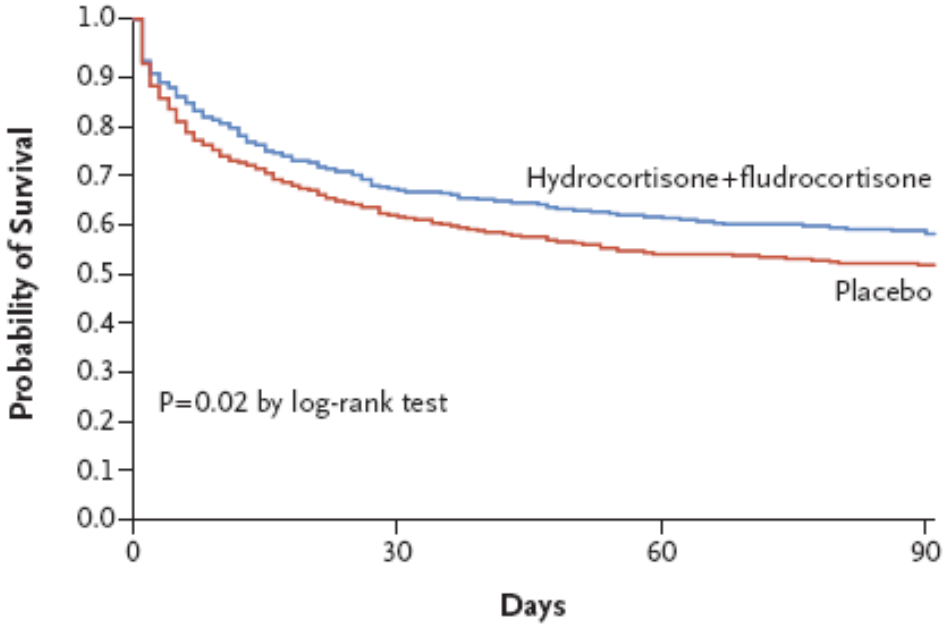
In this multicenter, double-blind, randomized trial with a 2-by-2 factorial design, we evaluated the effect of hydrocortisone-plus-fludrocortisone therapy, drotrecogin alfa (activated), the combination of the three drugs, or their respective placebos. The primary outcome was 90-day all-cause mortality. Secondary outcomes included mortality at intensive care unit (ICU) discharge and hospital discharge and at day 28 and day 180 and the number of days alive and free of vasopressors, mechanical ventilation, or organ failure. After drotrecogin alfa (activated) was withdrawn from the market, the trial continued with a two-group parallel design. The analysis compared patients who received hydrocortisone plus fludrocortisone with those who did not (placebo group).

Table 1. Baseline Characteristics of the Patients.*

Characteristic	Placebo (N = 627)	Hydrocortisone plus Fludrocortisone (N = 614)	All Patients (N = 1241)
Male sex — no./total no. (%)	424/626 (67.7)	402/614 (65.5)	826/1240 (66.6)
Age — yr†	66±15	66±14	66±14
Admission from a medical ward — no./total no. (%)	499/616 (81.0)	495/601 (82.4)	994/1217 (81.7)
SAPS II‡	56±19	56±19	56±19
SOFA score§	11±3	12±3	12±3
Community-acquired infection — no./total no. (%)	459/608 (75.5)	468/602 (77.7)	927/1210 (76.6)
Site of infection — no./total no. (%)¶			
Unknown	18/626 (2.9)	11/614 (1.8)	29/1240 (2.3)
Lung	363/626 (58.0)	373/614 (60.7)	736/1240 (59.4)
Abdomen	68/626 (10.9)	74/614 (12.1)	142/1240 (11.5)
Urinary tract	118/626 (18.8)	102/614 (16.6)	220/1240 (17.7)
Positive blood culture — no./total no. (%)	229/626 (36.6)	225/614 (36.6)	454/1240 (36.6)
Documented pathogen — no./total no. (%)	441/626 (70.4)	450/614 (73.3)	891/1240 (71.9)
Gram-positive bacteria — no./total no. (%)	228/626 (36.4)	235/614 (38.3)	463/1240 (37.3)
Gram-negative bacteria — no./total no. (%)	264/626 (42.2)	261/614 (42.5)	525/1240 (42.3)
Adequate antimicrobial therapy — no./total no. (%)	602/626 (96.2)	595/614 (96.9)	1197/1240 (96.5)
Vasopressor administration			
Epinephrine			
No. of patients	58	53	111
Dose — μg/kg/min	1.74±2.41	2.31±6.62	2.01±4.88
Norepinephrine			
No. of patients	552	534	1086
Dose — μg/kg/min	1.14±1.66	1.02±1.61	1.08±1.63
Mechanical ventilation — no./total no. (%)	569/623 (91.3)	567/614 (92.3)	1136/1237 (91.8)
Renal-replacement therapy — no./total no. (%)	168/598 (28.1)	161/596 (27.0)	329/1194 (27.6)

Table 2. Trial Outcomes.*

Outcome	Placebo (N=627)	Hydrocortisone plus Fludrocortisone (N=614)	All Patients (N=1241)	Relative Risk (95% CI)†	P Value
Primary outcome: death from any cause at day 90 — no. (%)	308 (49.1)	264 (43.0)	572 (46.1)	0.88 (0.78–0.99)	0.03
Secondary outcomes					
Death from any cause					
At day 28 — no. (%)	244 (38.9)	207 (33.7)	451 (36.3)	0.87 (0.75–1.01)	0.06
At ICU discharge — no./total no. (%)	257/627 (41.0)	217/613 (35.4)	474/1240 (38.2)	0.86 (0.75–0.99)	0.04
At hospital discharge — no./total no. (%)	284/627 (45.3)	239/613 (39.0)	523/1240 (42.2)	0.86 (0.76–0.98)	0.02
At day 180 — no./total no. (%)	328/625 (52.5)	285/611 (46.6)	613/1236 (49.6)	0.89 (0.79–0.99)	0.04
Decision to withhold or withdraw active treatment by day 90 — no./total no. (%)	61/626 (9.7)	64/614 (10.4)	125/1240 (10.1)	1.07 (0.77–1.49)	0.69
Vasopressor-free days to day 28‡					
Mean	15±11	17±11	16±11	—	<0.001
Median (IQR)	19 (1–26)	23 (5–26)	21 (2–26)		
Ventilator-free days to day 28‡					
Mean	10±11	11±11	11±11	—	0.07
Median (IQR)	4 (0–21)	10 (0–22)	8 (0–21)		
Organ-failure–free days to day 28‡					
Mean	12±11	14±11	13±11	—	0.003
Median (IQR)	12 (0–24)	19 (0–25)	15 (0–24)		



No. at Risk				
Hydrocortisone+ fludrocortisone	614	405	372	353
Placebo	627	381	333	319

Figure 1. 90-Day Survival Distributions.

Shown are survival curves from randomization up to 90 days. The survival rate was significantly higher in the hydrocortisone-plus-fludrocortisone group than in the placebo group.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Adjunctive Glucocorticoid Therapy in Patients with Septic Shock

B. Venkatesh, S. Finfer, J. Cohen, D. Rajbhandari, Y. Arabi, R. Bellomo, L. Billot, M. Correa, P. Glass, M. Harward, C. Joyce, Q. Li, C. McArthur, A. Perner, A. Rhodes, K. Thompson, S. Webb, and J. Myburgh, for the ADRENAL Trial Investigators and the Australian–New Zealand Intensive Care Society Clinical Trials Group*

ABSTRACT

BACKGROUND

Whether hydrocortisone reduces mortality among patients with septic shock is unclear.

METHODS

We randomly assigned patients with septic shock who were undergoing mechanical ventilation to receive hydrocortisone (at a dose of 200 mg per day) or placebo for 7 days or until death or discharge from the intensive care unit (ICU), whichever came first. The primary outcome was death from any cause at 90 days.

RESULTS

From March 2013 through April 2017, a total of 3800 patients underwent randomization. Status with respect to the primary outcome was ascertained in 3658 patients (1832 of whom had been assigned to the hydrocortisone group and 1826 to the placebo group). At 90 days, 511 patients (27.9%) in the hydrocortisone group and 526 (28.8%) in the placebo group had died (odds ratio, 0.95; 95% confidence interval [CI],

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Venkatesh at the Department of Intensive Care, Wesley Hospital, 451 Coronation Dr., Auchenflower, Brisbane, QLD 4066, Australia, or at bvenkatesh@georgeinstitute.org.au.

*A full list of investigators in the ADRENAL Trial is provided in the Supplementary Appendix, available at NEJM.org.

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DOI: 10.1056/NEJMoa1705835

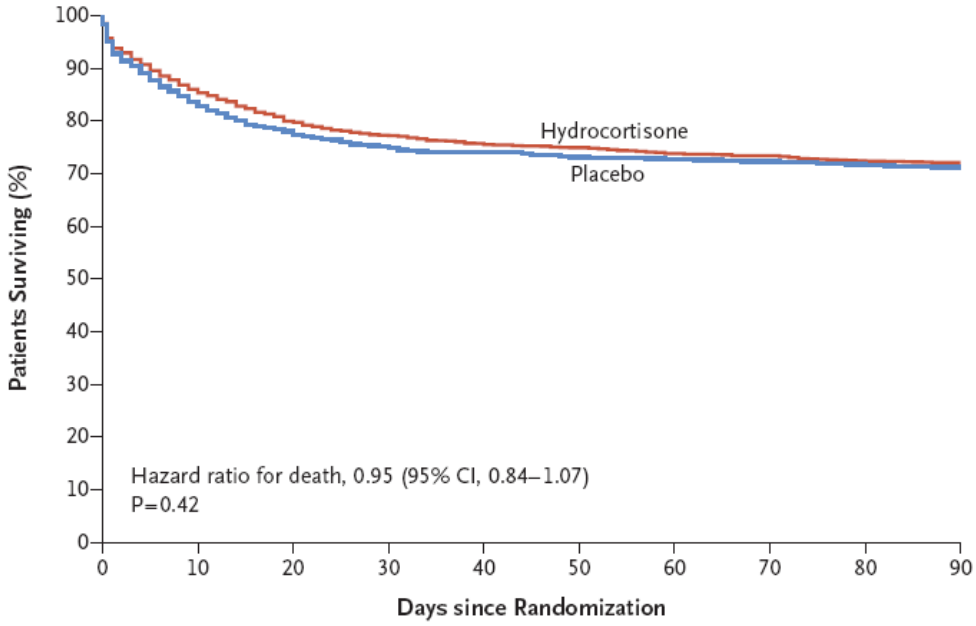
Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Hydrocortisone (N=1853)	Placebo (N=1860)
Age — yr	62.3±14.9	62.7±15.2
Male sex — no./total no. (%)	1119/1853 (60.4)	1140/1860 (61.3)
Weight — kg	85.8±26.6	85.6±26.3
Admission type — no./total no. (%)†		
Medical	1273/1849 (68.8)	1266/1857 (68.2)
Surgical	576/1849 (31.2)	591/1857 (31.8)
APACHE II score‡		
Median	24.0	23.0
Interquartile range	19.0–29.0	18.0–29.0
Therapy at baseline — no./total no. (%)§		
Mechanical ventilation	1845/1849 (99.8)	1855/1857 (99.9)
Inotropes or vasopressors	1843/1853 (99.5)	1854/1860 (99.7)
Norepinephrine	1823/1853 (98.4)	1821/1860 (97.9)
Vasopressin	280/1853 (15.1)	321/1860 (17.3)
Epinephrine	134/1853 (7.2)	113/1860 (6.1)
Other	157/1853 (8.5)	173/1860 (9.3)
Antimicrobial agent	1817/1848 (98.3)	1821/1857 (98.1)
Renal-replacement therapy	228/1849 (12.3)	242/1857 (13.0)

Table 2. Outcomes.*

Outcome	Hydrocortisone (N=1853)	Placebo (N=1860)	Odds Ratio, Hazard Ratio, or Absolute Difference (95% CI)	P Value
Primary outcome				
90-day mortality — no./total no. (%)	511/1832 (27.9)	526/1826 (28.8)	0.95 (0.82 to 1.10)†	0.50
Secondary outcomes				
28-day mortality — no./total no. (%)	410/1841 (22.3)	448/1840 (24.3)	0.89 (0.76 to 1.03)†	0.13
Median time to resolution of shock (IQR) — days	3 (2 to 5)	4 (2 to 9)	1.32 (1.23 to 1.41)‡	<0.001
Recurrence of shock — no. (%)	365 (19.7)	343 (18.4)	1.07 (0.94 to 1.22)†	0.32
Median time to discharge from the ICU (IQR) — days	10 (5 to 30)	12 (6 to 42)	1.14 (1.06 to 1.23)‡	<0.001
No. of days alive and out of the ICU	58.2±34.8	56.0±35.4	2.26 (0.04 to 4.49)§	0.047¶
Median time to discharge from the hospital (IQR) — days	39 (19 to NA)	43 (19 to NA)	1.06 (0.98 to 1.15)‡	0.13
No. of days alive and out of the hospital	40.0±32.0	38.6±32.4	1.45 (–0.59 to 3.49)§	0.16
Median time to cessation of initial mechanical ventilation (IQR) — days	6 (3 to 18)	7 (3 to 24)	1.13 (1.05 to 1.22)‡	<0.001
No. of days alive and free from mechanical ventilation	61.2±35.6	59.1±36.1	2.18 (–0.11 to 4.46)§	0.06
Recurrence of mechanical ventilation — no./total no. (%)	180/1842 (9.8)	154/1850 (8.3)	1.18 (0.96 to 1.45)†	0.11
No. of days alive and free from renal-replacement therapy	42.6±39.1	40.4±38.5	2.37 (–2.00 to 6.75)§	0.29
Use of renal-replacement therapy — no. (%)	567 (30.6)	609 (32.7)	0.94 (0.86 to 1.03)†	0.18
New-onset bacteremia or fungemia — no. (%)	262 (14.1)	262 (14.1)	1.00 (0.86 to 1.16)†	0.96
Blood transfusion — no./total no. (%)	683/1848 (37.0)	773/1855 (41.7)	0.82 (0.72 to 0.94)†	0.004

A Survival

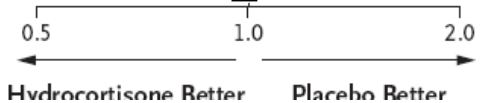


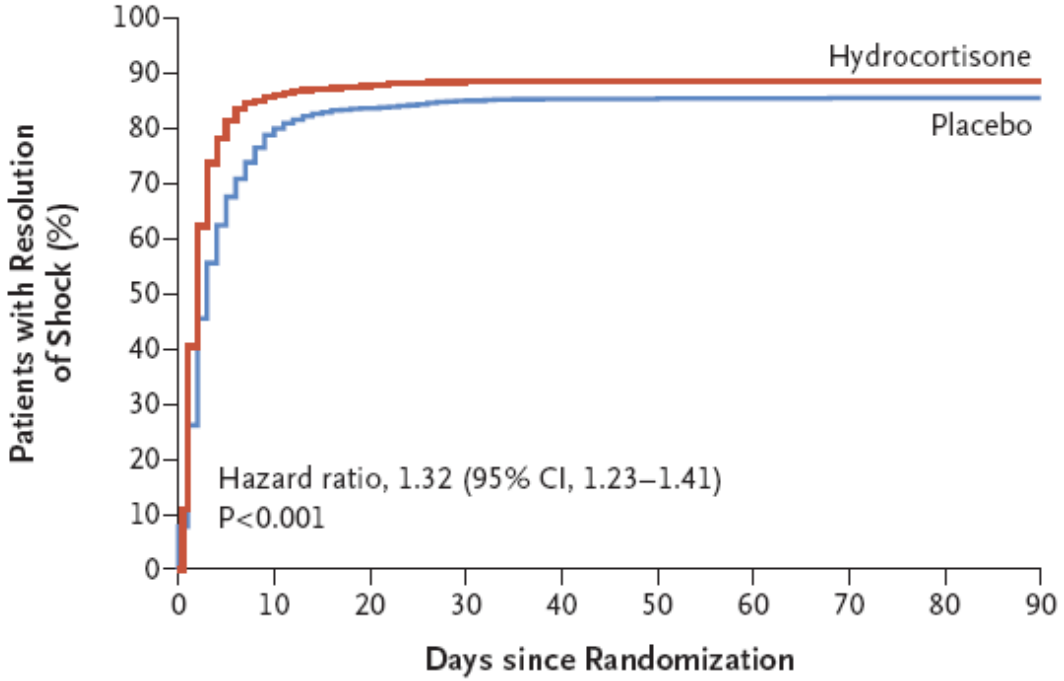
No. at Risk

Hydrocortisone	1832	1591	1481	1418	1388	1374	1356	1348	1328	1321
Placebo	1826	1546	1433	1376	1354	1337	1330	1322	1312	1300

B Subgroup Analysis of Death at 90 Days

Subgroup	Hydrocortisone	Placebo	Odds Ratio (95% CI)	P Value for Interaction
	no. of patients with event/total no. of patients (%)			
Sex				0.53
Male	312/1106 (28.2)	336/1122 (29.9)	0.92 (0.76–1.10)	
Female	199/726 (27.4)	190/704 (27.0)	1.01 (0.80–1.28)	
Admission type				0.73
Surgical	125/568 (22.0)	138/580 (23.8)	0.91 (0.69–1.21)	
Medical	386/1264 (30.5)	388/1245 (31.2)	0.97 (0.81–1.15)	
Catecholamine dose				0.25
≤15 μg/min	224/968 (23.1)	228/995 (22.9)	1.02 (0.82–1.26)	
>15 μg/min	281/849 (33.1)	291/805 (36.1)	0.86 (0.70–1.05)	
Site of sepsis				0.63
Pulmonary	243/799 (30.4)	250/828 (30.2)	0.99 (0.80–1.23)	
Other	268/1033 (25.9)	276/998 (27.7)	0.92 (0.76–1.12)	
APACHE II score				0.17
≥25	326/840 (38.8)	297/785 (37.8)	1.01 (0.83–1.24)	
<25	184/990 (18.6)	229/1039 (22.0)	0.82 (0.66–1.02)	
Time from shock onset to randomization				0.08
<6 hr	110/352 (31.2)	96/344 (27.9)	1.16 (0.83–1.61)	
6 to <12 hr	127/511 (24.9)	153/486 (31.5)	0.71 (0.54–0.94)	
12 to <18 hr	119/437 (27.2)	106/423 (25.1)	1.13 (0.83–1.54)	
≥18 hr	154/525 (29.3)	167/566 (29.5)	0.99 (0.76–1.29)	





No. at Risk

Hydrocortisone	1843	104	34	9	6	3	3	2	1	0
Placebo	1854	213	53	19	8	6	4	0	0	0

Figure 2. Cumulative Incidence Function of Time from Randomization to Resolution of Shock.

The cumulative incidence function plot was created by treating death as a competing risk.

dysfonction ventriculaire gauche

- la dysfonction cardiaque apparaît secondairement, nécessitant un support inotrope d'environ 48 h
- mécanisme : hypersécrétion NOS-2 dans les cavités cardiaques et autres muscles (diaphragme, grand droit) : NO se transforme en un dérivé peroxynitrite $ONOO^-$ réagissant avec les tyrosines des protéines musculaires avec formation de nitrotyrosine … et le muscle est bloqué
- BNP : taux très élevé non lié à la dépression myocardique mais à une diminution de son catabolisme par baisse de l'activité d'une endopeptidase vasculaire responsable de la destruction du BNP : donc rôle pronostic mais pas prédicteur de la dysfonction cardiaque
- détection : troponine circulante
- confirmation : échocardiographie (dilatation ventriculaire, hypokinésie globale ou segmentaire) ou hémodynamique invasive (baisse IC avec aaugmentation PAPO)

Penser à une étiologie infectieuse non couverte

- Abcès profond ou collection non drainée
- Fungémie ou autre infection non bactérienne
- Infection à staphylocoque
- Bactérie résistante aux antibiotiques prescrits

4ème phase

en cas d'insuffisance circulatoire persistante malgré la correction de l'hypovolémie et de la fonction ventriculaire gauche :

- passer à l'adrénaline
- sinon envisager :
  - augmentation les doses de catécholamines à niveaux très importants
  - associations de plusieurs catécholamines (ex. adrénaline, dopamine ...)
  - bleu de méthylène

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Early, Goal-Directed Therapy for Septic Shock — A Patient-Level Meta-Analysis

The PRISM Investigators*

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DOI: 10.1056/NEJMoa1701380

EARLY GOAL-DIRECTED THERAPY IN THE TREATMENT OF SEVERE SEPSIS AND SEPTIC SHOCK

EMANUEL RIVERS, M.D., M.P.H., BRYANT NGUYEN, M.D., SUZANNE HAVSTAD, M.A., JULIE RESSLER, B.S., ALEXANDRIA MUZZIN, B.S., BERNHARD KNOBLICH, M.D., EDWARD PETERSON, PH.D., AND MICHAEL TOMLANOVICH, M.D., FOR THE EARLY GOAL-DIRECTED THERAPY COLLABORATIVE GROUP*

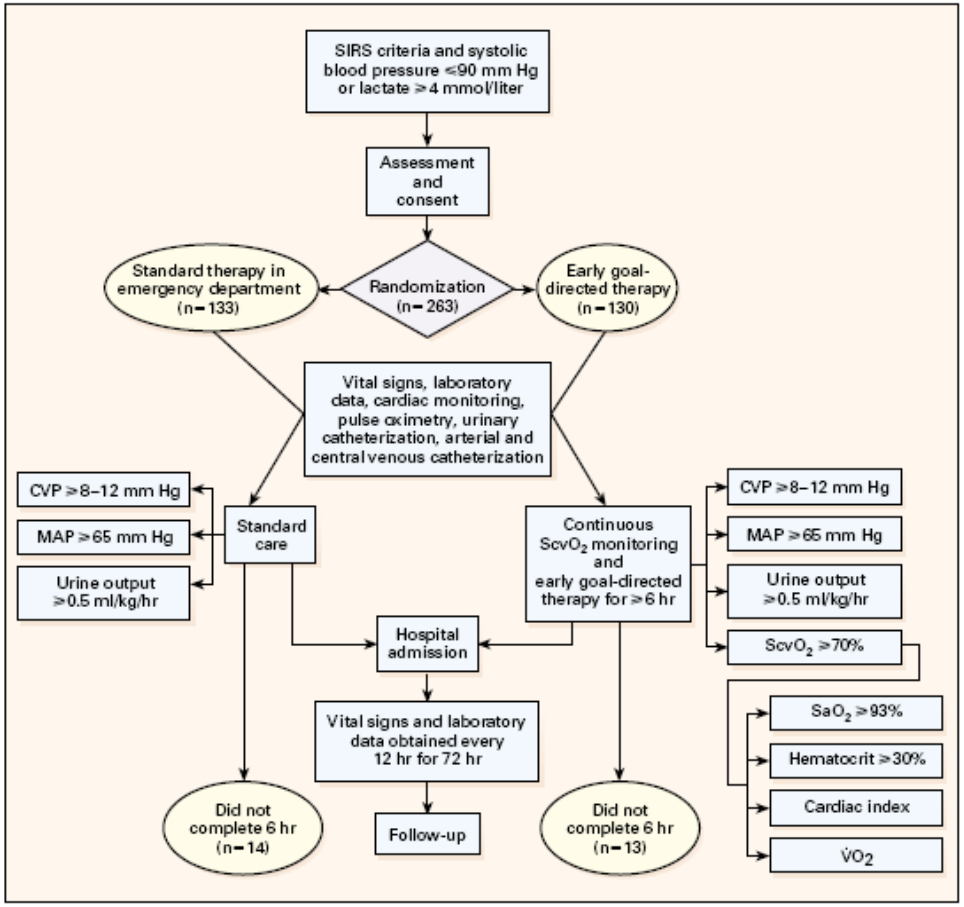
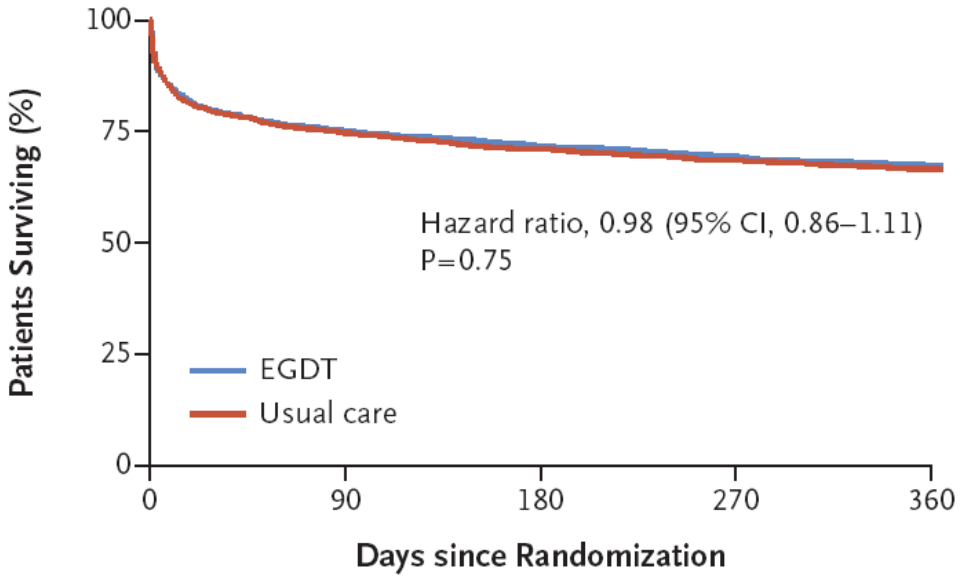


Figure 1. Overview of Patient Enrollment and Hemodynamic Support.

Table 2. Outcomes.*

Outcome	EGDT (N=1857)	Usual Care (N=1880)	Incremental Effect (95% CI)	P Value	
				Overall Comparison	Comparison among Trials
Primary outcome: death at 90 days — no./total no. (%)	462/1852 (24.9)	475/1871 (25.4)	0.97 (0.82 to 1.14)†‡	0.68	0.73
Secondary outcomes: mortality					
Death at hospital discharge — no./total no. (%)§	370/1857 (19.9)	365/1878 (19.4)	1.02 (0.85 to 1.21)†	0.86	0.42
Death at 28 days — no./total no. (%)	375/1854 (20.2)	385/1873 (20.6)	0.96 (0.81 to 1.15)†	0.68	0.57



No. at Risk					
EGDT	1857	1391	1287	1209	1119
Usual care	1880	1395	1295	1206	1110

Figure 1. Patient Survival over a Period of 1 Year.

There was no significant difference in the duration of survival to 1 year between the group that received early, goal-directed therapy (EGDT) and the group that received usual care. Data with respect to survival were censored at the actual date that the patient was last known to be alive or at 365 days. CI denotes confidence interval.

Intensive Care Med (2008) 34:1955–1960
DOI 10.1007/s00134-008-1274-6

EDITORIAL

Daniel A. Sweeney
Robert L. Danner
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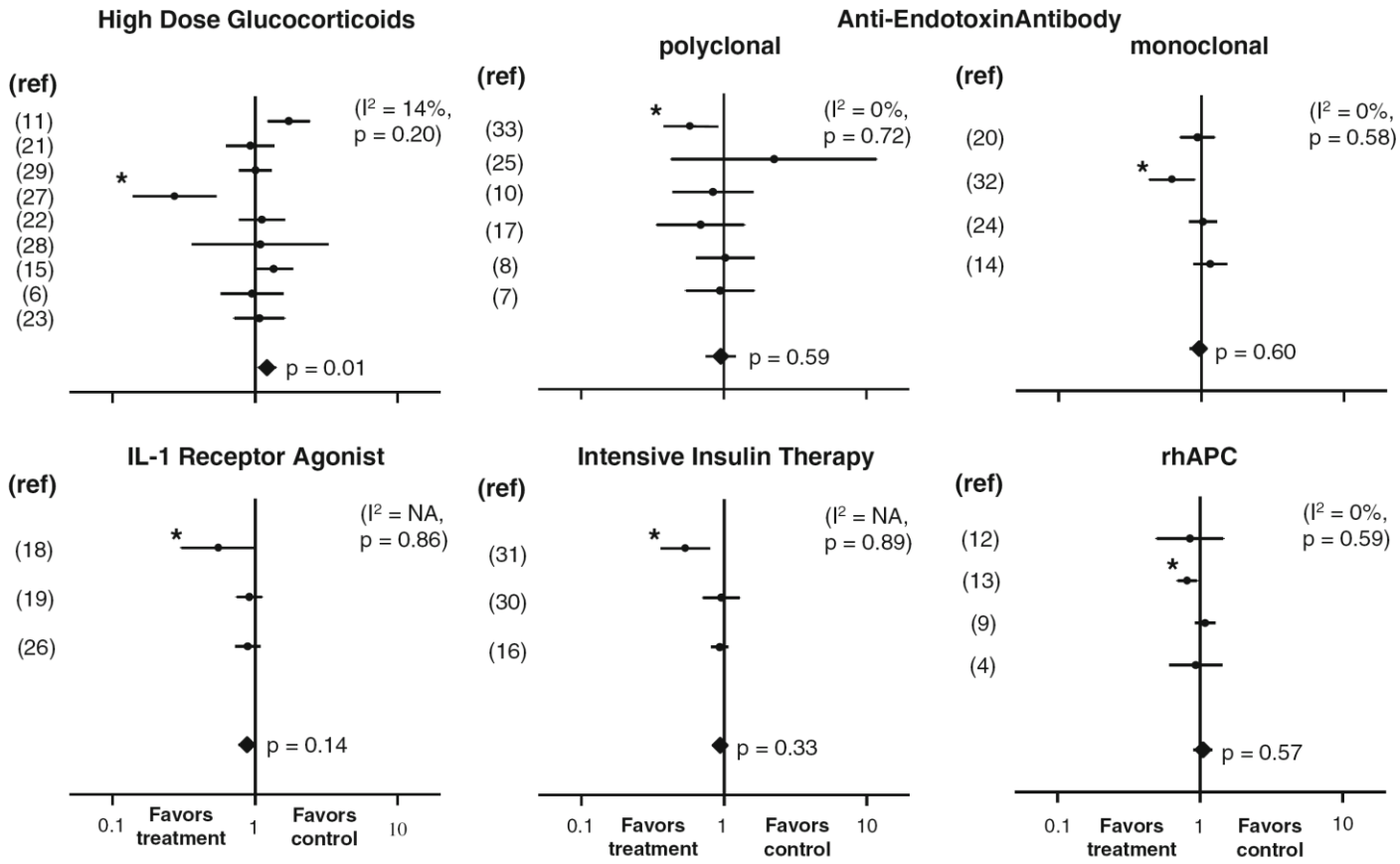
Charles Natanson

Once is not enough: clinical trials in sepsis


High Dose Glucocorticoids
(ref)
(11)
(21)
(29)
(27)
(22)
(28)
(15)
(6)
(23)
*
(I² = 14%, p = 0.20)
p = 0.01
Anti-EndotoxinAntibody
polyclonal
(ref)
(33)
(25)
(10)
(17)
(8)
(7)
*
(I² = 0%, p = 0.72)
p = 0.59
monoclonal
(ref)
(20)
(32)
(24)
(14)
*
(I² = 0%, p = 0.58)
p = 0.60
IL-1 Receptor Agonist
(ref)
(18)
(19)
(26)
*
(I² = NA, p = 0.86)
p = 0.14
0.1
Favors treatment
1
Favors control
10
Intensive Insulin Therapy
(ref)
(31)
(30)
(16)
*
(I² = NA, p = 0.89)
p = 0.33
0.1
Favors treatment
1
Favors control
10
rhAPC
(ref)
(12)
(13)
(9)
(4)
*
(I² = 0%, p = 0.59)
p = 0.57
0.1
Favors treatment
1
Favors control
10
Relative Risk of Death (95% Confidence Interval)

Complication : syndrome de défaillance multiviscérale

- **= SDMV ou MOF (multiple organ failure)**
- Syndrome caractérisé par la défaillance d'au moins 2 organes, avec un pronostic d'autant plus sombre que le nombre d'organes atteints est élevé. Il n'y a pas à ce sujet consensus sur un système de score unique en réanimation.

défaillance	KNAUS	TRAN	FAGON
cardiovasculaire	(au moins 1 critère)		(au moins 1 critère)
	FC < 55/min PAM < 50 mmHg TV et/ou FV pH <7,25 avec PaCO2 > 50 mmHg	FC £ 50/min PAM £ 50 mmHg TV ou FV ou arrêt cardiaque ou infarctus nécessité expanseurs ou drogues vasoactives pour maintenir PAs > 100	PAs < 90 avec signes d'hypoperfusion périphérique drogues inotropes ou vasopressives pour maintenir PAs > 90
respiratoire	(au moins 1 critère) FR < 6 ou > 50/min PaCO2 > 50 mmHg AaDO2 > 350 mmHg VA au 4e jour	FR £ 5 ou ³ 50/min VA pdt ³ 3 j ou avec FiO2 >0,4 ou PEEP > 5 cm H2O	(au moins 1 critère) PaO2 < 60 avec FiO2 = 0,21 VA
rénale	(au moins 1 critère sans IRC) diurèse < 480 ml/24 h (ou < 160ml/8h) urée>100 mg/dl créatinine > 3,5 mg/dl	créatinine ³ 3,5 mg/dl épuration extrarénale	(au moins 1 critère) créatinine > 3,6 diurèse < 500 ml/24h (180 ml/8h) épuration extrarénale
hématologique	(au moins 1 critère) GB < 1000 plaquettes < 20.000 hématocrite < 20 %	GB £ 300 plaquettes £ 50.000 Ht £ 20 % CIVD	(au moins 1 critère) Ht £ 20 % GB < 2000 plaquettes < 40.000
neurologique	Glasgow < 6 (en l'absence de sédation)	idem	idem ou confusion brutale
hépatique		ictère clinique bilirubine ≥ 3 mg/dl sGPT > x 2 encéphalopathie hépatique	(au moins 1 critère) bilirubine > 6 mg/dl Ph Alc > x 3
gastrointestinale		ulcère aigu hémorragique pancréatite aiguë Hh cholécystite aiguë alithiasique entérocolite nécrosante perforation digestive	

Table 3 The SOFA score

SOFA score	1	2	3	4
Respiration				
PaO_2/FiO_2, mmHg	<400	<300	<200	<100
			—— with respiratory support ——	
Coagulation				
Platelets $\times 10^3/mm^3$	<150	<100	<50	<20
Liver				
Bilirubin, mg/dl	1.2–1.9	2.0–5.9	6.0–11.9	>12.0
(μmol/l)	(20–32)	(33–101)	(102–204)	(<204)
Cardiovascular				
Hypotension	MAP < 70 mmHg	Dopamine ≤5 or dobutamine (any dose)[a]	Dopamine >5 or epinephrine ≤0.1 or norepinephrine ≤0.1	Dopamine >15 or epinephrine >0.1 or norepinephrine >0.1
Central nervous system				
Glasgow Coma Score	13–14	10–12	6–9	<6
Renal				
Creatinine, mg/dl	1.2–1.9	2.0–3.4	3.5–4.9	>5.0
(μmol/l) or urine output	(110–170)	(171–299)	(300–440) or <500 ml/day	(>440) or <200 ml/day

[a] Adrenergic agents administered for at least 1 h (doses given are in μg/kg·min)

Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

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)

Manu Shankar-Hari, MD, MSc; Gary S. Phillips, MAS; Mitchell L. Levy, MD; Christopher W. Seymour, MD, MSc; Vincent X. Liu, MD, MSc; Clifford S. Deutschman, MD; Derek C. Angus, MD, MPh; Gordon D. Rubenfeld, MD, MSc; Mervyn Singer, MD, FRCP; for the Sepsis Definitions Task Force

JAMA. 2016;315(8):775-787. doi:10.1001/jama.2016.0289

DESIGN, SETTING, AND PARTICIPANTS The Society of Critical Care Medicine and the European Society of Intensive Care Medicine convened a task force (19 participants) to revise current sepsis/septic shock definitions. Three sets of studies were conducted: (1) a systematic review and meta-analysis of observational studies in adults published between January 1, 1992, and December 25, 2015, to determine clinical criteria currently reported to identify septic shock and inform the Delphi process; (2) a Delphi study among the task force comprising 3 surveys and discussions of results from the systematic review, surveys, and cohort studies to achieve consensus on a new septic shock definition and clinical criteria; and (3) cohort studies to test variables identified by the Delphi process using Surviving Sepsis Campaign (SSC) (2005-2010; n = 28 150), University of Pittsburgh Medical Center (UPMC) (2010-2012; n = 1309 025), and Kaiser Permanente Northern California (KPNC) (2009-2013; n = 1847 165) electronic health record (EHR) data sets.

Figure 1. Study Identification and Selection Process Used in the Systematic Review

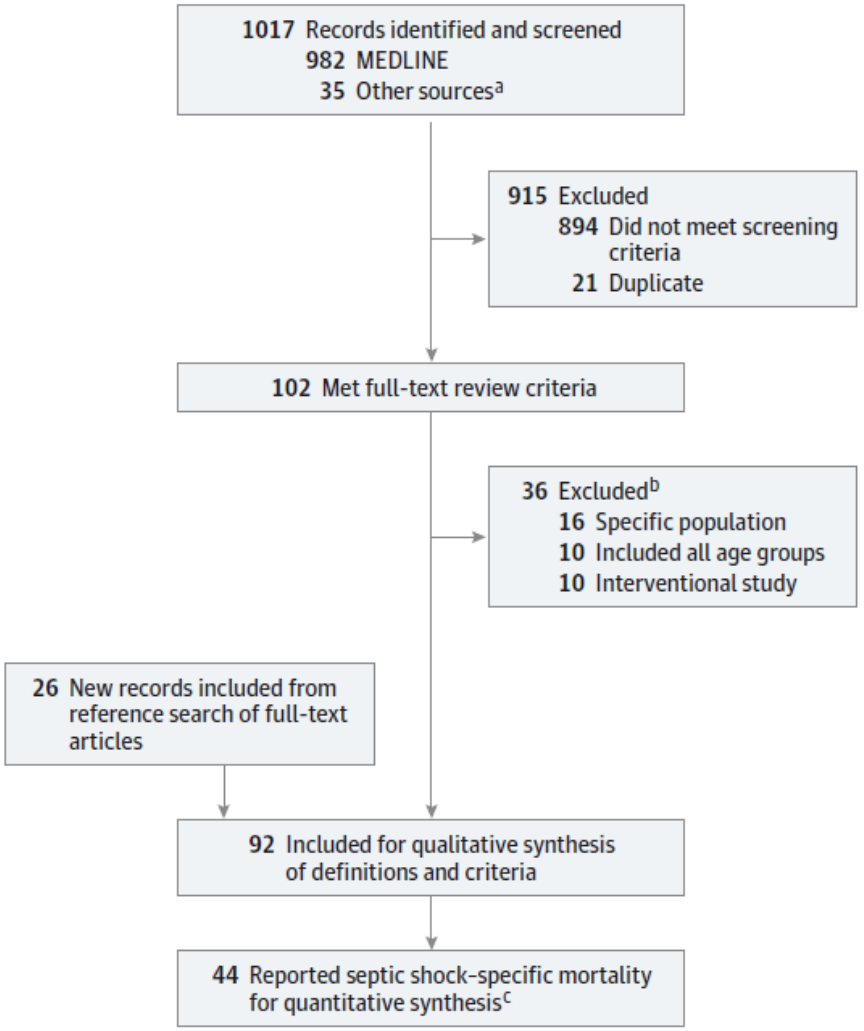


Table 1. Summary of Septic Shock Definitions and Criteria Reported in the Studies Identified by the Systematic Review[a]

Criteria	Septic Shock Case Definitions and Corresponding Variables Reported in Literature				Other Description of Criteria Variables
	Consensus Definitions		Other Definitions		
	Bone et al[1]	Levy et al[2]	SSC[111]	Trial-based[112]	
Infection	Suspected or proven	Suspected or proven	Suspected or proven	Suspected or proven	Bacteremia, culture positive; CDC definitions for infection
SIRS criteria, No.	2	One or more of 24 variables[b]	2	3	NA
Septic shock description	Sepsis-induced hypotension despite adequate resuscitation OR receiving vasopressors/Inotropes plus presence of perfusion abnormalities	State of acute circulatory failure characterized by persistent arterial hypotension after adequate resuscitation unexplained by other causes	Sepsis-induced hypotension persisting despite adequate fluid resuscitation	Cardiovascular dysfunction defined as hypotension despite adequate resuscitation or need for vasopressors	Precoded data using *ICD-9* and *ICD-10* codes[c]
Hypotension, mm Hg					
Systolic BP	<90	<90	<90	<90	<100
Decrease in systolic BP	Decrease >40	Decrease >40	Decrease >40	NA<70	>50% decrease in hypertension
MAP	No	<60	<70	Hypotension lasting >1 h after resuscitation	<65
Adequate resuscitation definition	Not defined	Not defined	Goals set as CVP 8-12 mm Hg; urine output ≥0.5 mL/kg/h; $ScvO_2$ >70%	Not defined	After resuscitation fluids (0.5 L; 1 L; 1.5 L; 20 mL/kg ideal body weight
Vasopressor use	Yes (not absolute requirement)	Yes (CVS SOFA score)	Yes (not absolute requirement)	Yes (not absolute requirement)	Vasoactive drugs required for >30 min
Hypoperfusion abnormalities	Hypoperfusion abnormality defined as lactic acidosis; oliguria; low Glasgow Coma Score	Tissue hypoperfusion defined as serum lactate >1 mmol/L or delayed capillary refill	Tissue hypoperfusion defined as infection-induced hypotension, elevated serum lactate (>4 mmol/L), or oliguria	No description	Serum lactate >2.5 mmol/L; base deficit >5 mEq/L, alkaline reserve <18 mEq/L; CVP <8; PCWP <12
Data points from included studies, No. (%)[d]	39 (75)		13 (25)		
Sample size, No.	158 354		8125		
Mortality by septic shock definition using random-effects meta analysis, % (95% CI)	47.2 (42.7-51.7)		44.2 (38.5-49.9)		
I^2, %[e]	99.6		95.9		
τ^2[f]	191.21		94.9		
P value heterogeneity	<.001		<.001		

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

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

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

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

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

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

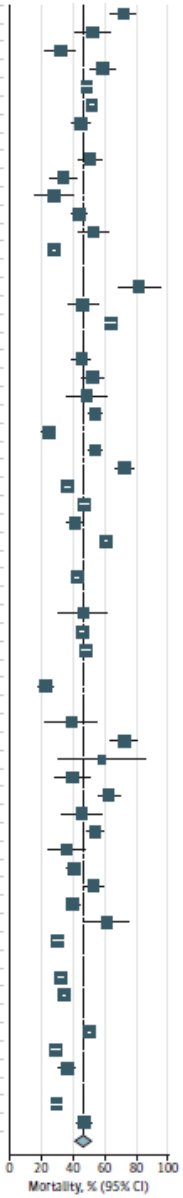
[e] I^2 is the percentage of between-study heterogeneity that is attributable to a true variability in septic shock mortality, rather than sampling variation, implying heterogeneity.

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

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

Figure 2. Random-Effects Meta-analysis of Studies Identified in the Systematic Review, Reporting Septic Shock Mortality

Source	Septic Shock Deaths, No.	Patients With Septic Shock, No.	Mortality, % (95% CI)
Consensus Definition			
Degoricija et al,[46] 2006	90	125	72.0 (64.1-79.9)
Angkasekwinai et al,[38] 2007	41	78	52.6 (41.5-63.6)
Nesseler et al,[27] 2013	30	93	32.3 (22.8-41.8)
Sakr et al,[25] 2013	85	145	58.6 (50.6-66.6)
Goncalves-Pereira et al,[23] 2014	418	856	48.8 (45.5-52.2)
Leligdowicz et al,[5] 2014	4146	7974	52.0 (50.9 -53.1)
Ortiz et al,[19] 2014	144	319	45.1 (39.7-50.6)
Hypotension			
Laupland et al,[47] 2004	81	159	50.9 (43.2-58.7)
Gaspraovic et al,[45] 2006	44	129	34.1 (25.9-42.3)
Shapiro et al,[44] 2006	15	53	28.3 (16.2-40.4)
Povoa et al,[35] 2009	202	458	44.1 (39.6-48.7)
Klein Klowenberg et al,[7] 2012	52	98	53.1 (43.2-62.9)
Kaukonen et al,[22] 2014	14609	51079	28.6 (28.2-29.0)
Hypotension + Perfusion Abnormalities and/or Vasopressor Therapy			
Rangel-Frausto et al,[56] 1995	51	110	46.4 (37.0-55.7)
Salvo et al,[55] 1995	27	33	81.8 (68.7-95.0)
Alberti et al,[52] 2002	752	1180	63.8 (60.7-67.0)
Hypotension + Vasopressor Therapy			
Rodriguez et al,[31] 2001	129	283	45.6 (39.8-51.4)
Silva et al,[48] 2004	106	203	52.2 (45.3-59.1)
Laupland et al,[49] 2005	28	57	49.1 (36.5-61.8)
Vincent et al,[43] 2006	250	462	54.1 (49.6-58.7)
Karlsson et al,[40] 2007	90	363	24.8 (20.4-29.2)
Sakr et al,[39] 2007	250	462	54.1 (49.6-58.7)
Kauss et al,[34] 2010	185	255	72.5 (67.1-78.0)
Levy et al,[6] 2010	915	2494	36.7 (34.8-38.6)
Phua et al,[32] 2011	441	939	47.0 (44.3-49.7)
Ogura et al,[20] 2014	117	282	41.5 (35.7-47.2)
GiViTI database, 2015[a]	15935	26295	60.6 (60.0-61.2)
Hypotension + Vasopressor Therapy + Serum Lactate Level >2 mmol/L			
Group 1[b]	3602	8520	42.3 (41.2-43.3)
Hypotension + Perfusion Abnormalities + Vasopressor Therapy			
Lundberg et al,[54] 1998	19	41	46.3 (31.1-61.6)
Levy et al,[6] 2010	3428	7436	46.1 (45.0-47.2)
Quenot et al,[26] 2013	728	1495	48.7 (46.2-51.2)
Hypotension ± Vasopressor Therapy or Metabolic Abnormalities			
Peake et al,[36] 2009	75	324	23.1 (18.6-27.7)
Hypotension or Vasopressor Therapy			
Dahmash et al,[59] 1993	14	36	38.9 (23.0-54.8)
McLauchlan et al,[58] 1995	73	101	72.3 (63.5-81.0)
Pittet et al,[57] 1995	7	12	58.3 (30.4-86.2)
Schoenberg et al,[53] 1998	32	80	40.0 (29.3-50.7)
Engel et al,[42] 2007	119	190	62.6 (55.8-69.5)
Esteban et al,[41] 2007	27	59	45.8 (33.1-58.5)
Khwannimit and Bhuyaromtachal,[37] 2009	164	303	54.1 (48.5-59.7)
Moore et al,[33] 2011	22	61	36.1 (24.0-48.1)
Zahar et al,[30] 2011 (community)	215	530	40.6 (36.3-44.8)
Zahar et al,[30] 2011 (ICU)	123	232	53.0 (47.1-59.0)
Zahar et al,[30] 2011 (nosocomial)	233	580	40.2 (36.1-44.2)
Klein Klowenberg et al,[7] 2012	29	47	61.7 (47.8-75.6)
Park et al,[28] 2012	228	740	30.8 (27.5-34.1)
Hypotension or Serum Lactate Any Value or Vasopressor Therapy			
Liu et al,[21] 2014	827	2536	32.6 (30.8-34.4)
SSC database,[16] 2016[b]	6556	18840	34.8 (34.1-35.5)
***International Classification of Diseases* Codes**			
Annane et al,[51] 2003	13269	26172	50.7 (50.1-51.3)
Flaatten,[50] 2004	457	1562	29.3 (27.1-31.6)
Whittaker et al,[24] 2013	117	321	36.4 (31.2-41.7)
Serum Lactate Level >4 mmol/L			
Levy et al,[6] 2010	242	811	29.8 (26.7-33.0)
Phua et al,[32] 2011	219	466	47.0 (42.0-52.0)
Overall (I^2 = 99.5%; P = .000)			46.5 (42.7-50.3)



Forty-four studies report septic shock–associated mortality[5-7,19-59] and were included in the quantitative synthesis using random-effects meta-analysis. The Surviving Sepsis Campaign (SSC) database analyses with similar data are reported in 2 studies[6,29]; therefore, only one of these was used in the meta-analysis reported.[6] Levy et al report 3 septic shock subsets,[6] Klein Klowenberg et al report 2 (restrictive and liberal),[7] Zahar et al report 3 (community-acquired, ICU-acquired, and nosocomial infection–associated septic shock),[30] and Phua et al report 2 groups,[32] which were treated as separate data points in the meta-analysis. Studies under "consensus definition" cite the Sepsis Consensus Definitions.[1,2] The categorization used to assess heterogeneity does not fully account for septic shock details in individual studies.

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

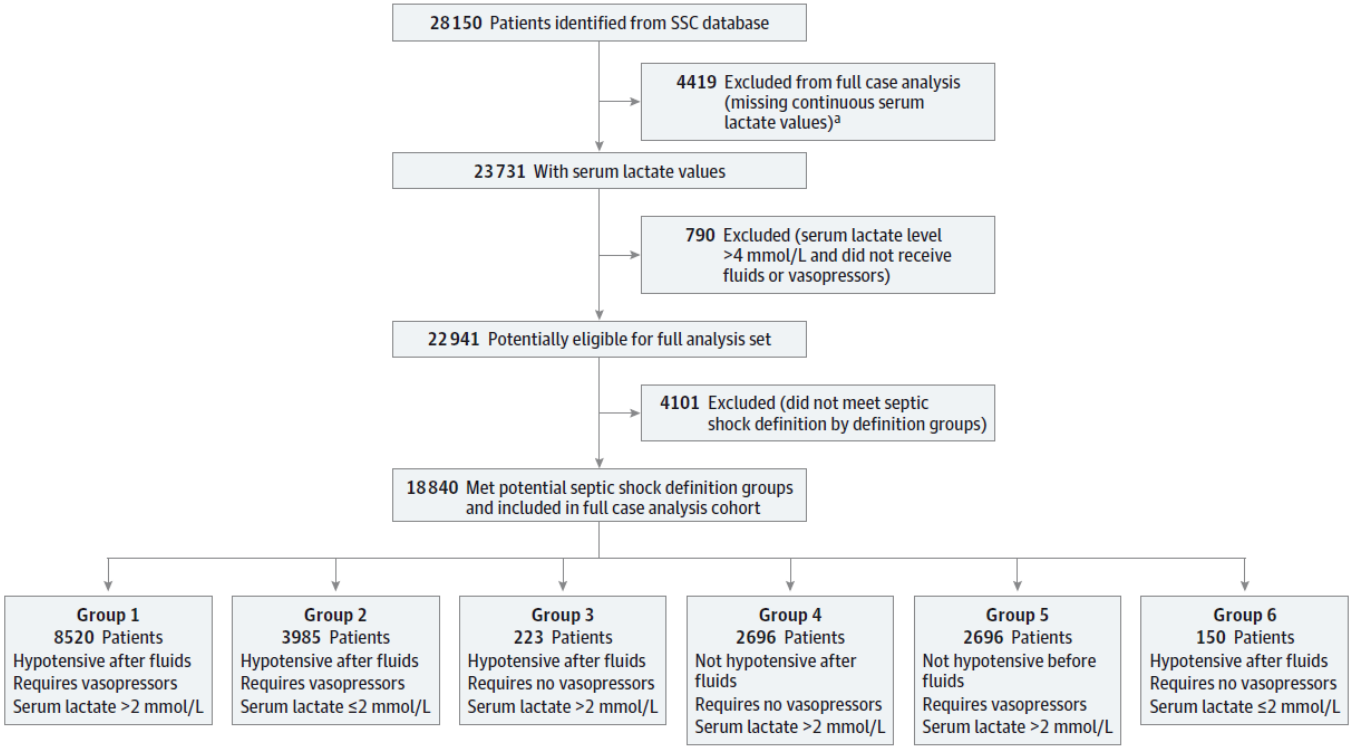
[a] Data obtained from GiViTI database provided by Bertolini et al (published 2015[18]).

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

Table 2. Random Effects Meta-Analysis by Septic Shock Criteria Groups

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

Figure 3. Selection of Surviving Sepsis Campaign Database Cohort



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

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

Nouvelles études de validation

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Prognostic Accuracy of the SOFA Score, SIRS Criteria, and qSOFA Score for In-Hospital Mortality Among Adults With Suspected Infection Admitted to the Intensive Care Unit

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Table 2. Crude and Adjusted AUROCs for Discrimination Characteristics of SOFA, SIRS Criteria, and qSOFA on ICU Admission Among Patients With Infection in the ANZICS Adult Patient Database Cohort (N = 184 875)

				Between-Group Difference		
	SIRS	qSOFA	SOFA	SIRS Criteria vs qSOFA	qSOFA vs SOFA	SIRS Criteria vs SOFA
In-Hospital Mortality						
Crude AUROC (99% CI)	0.589 (0.585 to 0.593)	0.607 (0.603 to 0.611)	0.753 (0.750 to 0.757)	0.018 (0.013 to 0.023)	0.146 (0.142 to 0.151)	0.164 (0.159 to 0.169)
Adjusted AUROC (99% CI)[a]	0.755 (0.752 to 0.759)	0.762 (0.758 to 0.765)	0.815 (0.811 to 0.818)	0.006 (0.005 to 0.008)	0.053 (0.050 to 0.056)	0.059 (0.056 to 0.062)
P value	<.001	<.001	<.001	<.001	<.001	<.001
Mechanically Ventilated, In-Hospital Mortality						
Crude AUROC (99% CI)	0.58 (0.574 to 0.586)	0.585 (0.579 to 0.591)	0.734 (0.729 to 0.74)	0.005 (−0.001 to 0.012)	0.149 (0.143 to 0.155)	0.154 (0.147 to 0.162)
Adjusted AUROC (99% CI)	0.726 (0.72 to 0.731)	0.731 (0.725 to 0.736)	0.793 (0.788 to 0.797)	0.005 (0.002 to 0.008)	0.062 (0.058 to 0.066)	0.067 (0.062 to 0.071)
P value	<.001	<.001	<.001	<.001	<.001	<.001
Nonventilated, In-Hospital Mortality						
Crude AUROC (99% CI)	0.591 (0.585 to 0.597)	0.625 (0.62 to 0.631)	0.723 (0.718 to 0.729)	0.035 (0.028 to 0.042)	0.098 (0.092 to 0.104)	0.133 (0.125 to 0.14)
Adjusted AUROC (99% CI)	0.774 (0.769 to 0.779)	0.783 (0.778 to 0.788)	0.805 (0.8 to 0.809)	0.009 (0.007 to 0.011)	0.021 (0.018 to 0.025)	0.031 (0.027 to 0.034)
P value	<.001	<.001	<.001	<.001	<.001	<.001
Composite Outcome (In-Hospital Mortality or Length of ICU Stay ≥3 days)						
Crude AUROC (99% CI)	0.609 (0.606 to 0.612)	0.606 (0.602 to 0.609)	0.736 (0.733 to 0.739)	−0.003 (−0.007 to 0)	0.131 (0.127 to 0.134)	0.127 (0.123 to 0.131)
Adjusted AUROC (99% CI)[b]	0.691 (0.688 to 0.694)	0.69 (0.687 to 0.0.693)	0.761 (0.758 to 0.764)	−0.001 (−0.003 to 0.001)	0.071 (0.069 to 0.074)	0.07 (0.067-0.073)
P value	<.001	<.001	<.001	<.001	<.001	<.001

	SIRS	qSOFA	SOFA	Between-Group Difference		*P* Value
				SOFA vs SIRS	SOFA vs qSOFA	
In-Hospital Mortality (Primary Outcome)						
Crude AUROC (99% CI)	0.589 (0.585-0.593)	0.607 (0.603-0.611)	0.753 (0.750-0.757)	0.164 (0.159-0.169)	0.146 (0.142-0.151)	<.001
In-Hospital Mortality or ICU Stay ≥3 Days (Secondary Outcome)						
Crude AUROC (99% CI)	0.609 (0.606-0.612)	0.606 (0.602-0.609)	0.736 (0.733-0.739)	0.127 (0.123-0.131)	0.131 (0.127-0.134)	<.001

CONCLUSIONS AND RELEVANCE Among adults with suspected infection admitted to an ICU, an increase in SOFA score of 2 or more had greater prognostic accuracy for in-hospital mortality than SIRS criteria or the qSOFA score. These findings suggest that SIRS criteria and qSOFA may have limited utility for predicting mortality in an ICU setting.

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Prognostic Accuracy of Sepsis-3 Criteria for In-Hospital Mortality Among Patients With Suspected Infection Presenting to the Emergency Department

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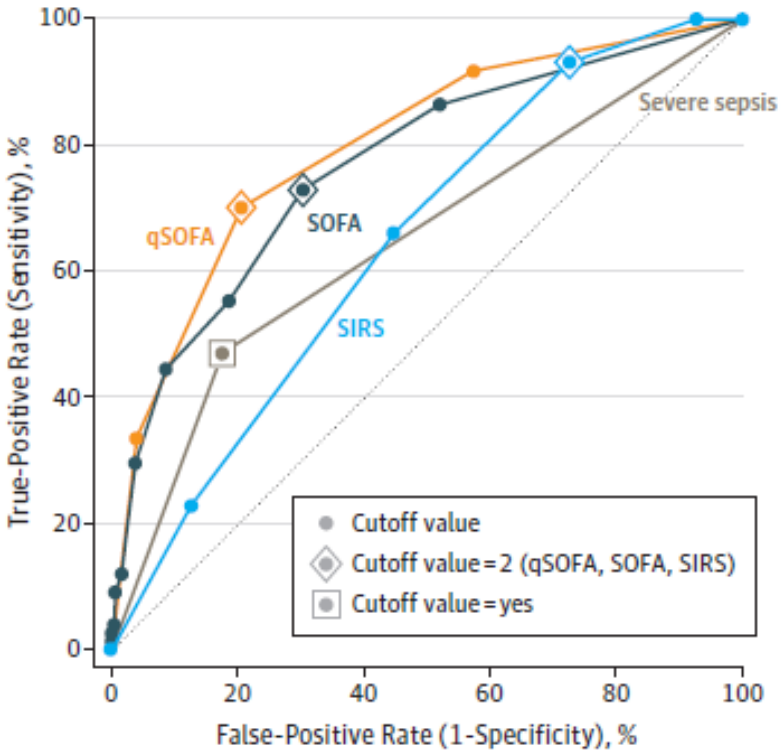
RESULTS Of 1088 patients screened, 879 were included in the analysis. Median age was 67 years (interquartile range, 47-81 years), 414 (47%) were women, and 379 (43%) had respiratory tract infection. Overall in-hospital mortality was 8%: 3% for patients with a qSOFA score lower than 2 vs 24% for those with qSOFA score of 2 or higher (absolute difference, 21%; 95% CI, 15%-26%). The qSOFA performed better than both SIRS and severe sepsis in predicting in-hospital mortality, with an area under the receiver operating curve (AUROC) of 0.80 (95% CI, 0.74-0.85) vs 0.65 (95% CI, 0.59-0.70) for both SIRS and severe sepsis ($P < .001$; incremental AUROC, 0.15; 95% CI, 0.09-0.22). The hazard ratio of qSOFA score for death was 6.2 (95% CI, 3.8-10.3) vs 3.5 (95% CI, 2.2-5.5) for severe sepsis.

CONCLUSIONS AND RELEVANCE Among patients presenting to the emergency department with suspected infection, the use of qSOFA resulted in greater prognostic accuracy for in-hospital mortality than did either SIRS or severe sepsis. These findings provide support for the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) criteria in the emergency department setting.

Figure 2. Receiver Operating Characteristic Curves for In-Hospital Mortality



qSOFA indicates quick Sequential Organ Failure Assessment; SIRS, systemic inflammatory response syndrome; and SOFA, Sequential [Sepsis-related] Organ Failure Assessment. The area under the receiver operating characteristic curves for qSOFA is 0.80 (95% CI, 0.74-0.85); SOFA, 0.77 (95% CI, 0.71-0.82); SIRS, 0.65 (95% CI, 0.59-0.70); and severe sepsis, 0.65 (95% CI, 0.59-0.70).

REVIEW

Annals of Internal Medicine

Prognostic Accuracy of the Quick Sequential Organ Failure Assessment for Mortality in Patients With Suspected Infection

A Systematic Review and Meta-analysis

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Background: The quick Sequential Organ Failure Assessment (qSOFA) has been proposed for prediction of mortality in patients with suspected infection.

Purpose: To summarize and compare the prognostic accuracy of qSOFA and the systemic inflammatory response syndrome (SIRS) criteria for prediction of mortality in adult patients with suspected infection.

Data Sources: Four databases from inception through November 2017.

Study Selection: English-language studies using qSOFA for prediction of mortality (in-hospital, 28-day, or 30-day) in adult patients with suspected infection in the intensive care unit (ICU), emergency department (ED), or hospital wards.

Data Extraction: Two investigators independently extracted data and assessed study quality using standard criteria.

Data Synthesis: Thirty-eight studies were included (n = 385 333). qSOFA was associated with a pooled sensitivity of 60.8% (95% CI, 51.4% to 69.4%) and a pooled specificity of 72.0% (CI, 63.4% to 79.2%) for mortality. The SIRS criteria were associated with a pooled sensitivity of 88.1% (CI, 82.3% to 92.1%) and a pooled specificity of 25.8% (CI, 17.1% to 36.9%). The pooled sensitivity of qSOFA was higher in the ICU population (87.2% [CI, 75.8% to 93.7%]) than the non-ICU population (51.2% [CI, 43.6% to 58.7%]). The pooled specificity of qSOFA was higher in the non-ICU population (79.6% [CI, 73.3% to 84.7%]) than the ICU population (33.3% [CI, 23.8% to 44.4%]).

Limitation: Potential risk of bias in included studies due to qSOFA interpretation and patient selection.

Conclusion: qSOFA had poor sensitivity and moderate specificity for short-term mortality. The SIRS criteria had sensitivity superior to that of qSOFA, supporting their use for screening of patients and as a prompt for treatment initiation.

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For author affiliations, see end of text.

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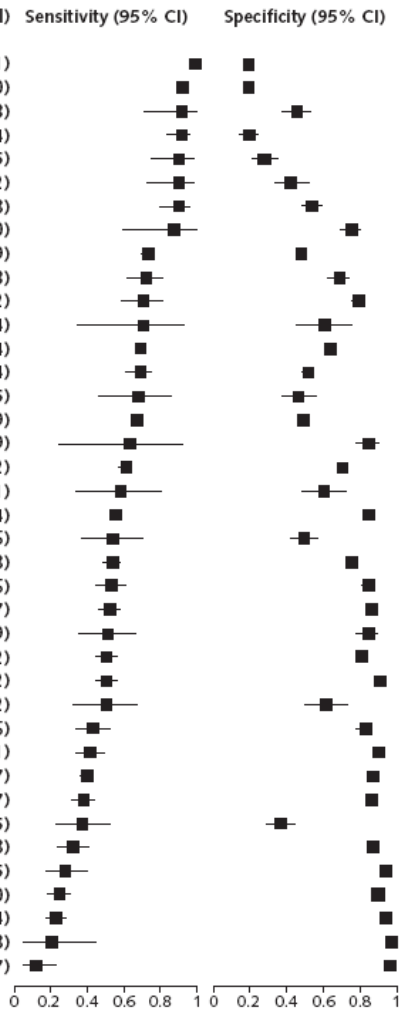
Table 1. Characteristics of the 38 Included Studies*

Description	Frequency, *n* (%)†
Continent	
North America	14 (36.8)
Europe	9 (23.7)
Asia	9 (23.7)
Australia/Oceania	4 (10.5)
Africa	2 (5.3)
Year of publication	
2016	8 (21.1)
2017	30 (78.9)
Publication type	
Full-text article	36 (94.7)
Conference abstract	2 (5.3)
Study design	
Prospective cohort	14 (36.8)
Retrospective cohort	24 (63.2)
Population	
ICU	8 (20.5)
ED only	18 (46.2)
ED and hospital ward	9 (23.1)
Hospital ward only	4 (10.3)
Median sample size (IQR), *n*	1071 (240–6024)
Definition of "suspected infection"	
Attending physician diagnosis of infection	13 (34.2)
Initiation of body fluid cultures and/or antibiotic treatment	10 (26.3)
Symptom criteria	7 (18.4)
Chart review by investigator	3 (7.9)
ICD-9 coding	3 (7.9)
Unknown	2 (5.3)
Outcome	
In-hospital mortality	28 (73.7)
28-d mortality	5 (13.2)
30-d mortality	5 (13.2)

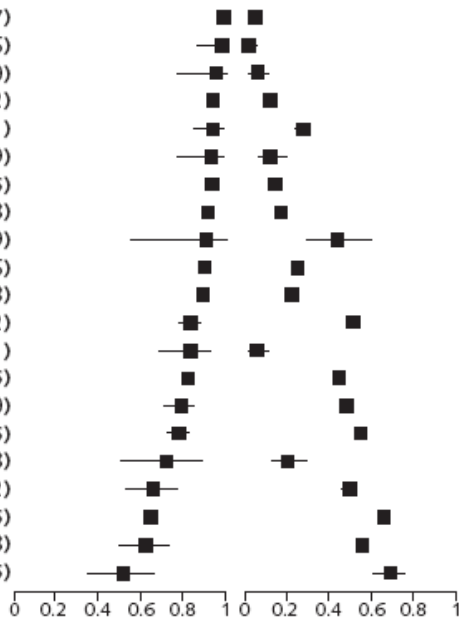
ED = emergency department; ICD-9 = International Classification of Diseases, Ninth Revision; ICU = intensive care unit; IQR = interquartile range.
* Percentages may not sum to 100 due to rounding.
† Unless otherwise indicated.

Figure 1. Forest plots of sensitivity and specificity for qSOFA (*top*) and the SIRS criteria (*bottom*) in the 38 included studies (39 cohorts).

Study, Year (Reference)	TPs, *n*	FPs, *n*	FNs, *n*	TNs, *n*	Sensitivity (95% CI)	Specificity (95% CI)
qSOFA						
Khwannimit et al, 2017 (45)	1027	1054	18	251	0.98 (0.97–0.99)	0.19 (0.17–0.21)
Seymour et al, 2016 (11) (ICU)	1186	5381	103	1262	0.92 (0.90–0.93)	0.19 (0.18–0.20)
Haydar et al, 2017 (39)	20	96	2	80	0.91 (0.71–0.99)	0.45 (0.38–0.53)
Umemura et al, 2017 (56)	99	225	10	53	0.91 (0.84–0.96)	0.19 (0.15–0.24)
April et al, 2017 (25)	35	127	4	48	0.90 (0.76–0.97)	0.27 (0.21–0.35)
Finkelsztein et al, 2017 (32)	26	71	3	52	0.90 (0.73–0.98)	0.42 (0.33–0.52)
Burnham and Kollef, 2017 (27)	60	205	7	238	0.90 (0.80–0.96)	0.54 (0.49–0.58)
Huson et al, 2017 (41)	13	78	2	236	0.87 (0.60–0.98)	0.75 (0.70–0.80)
Johnson et al, 2016 (44)	788	4137	299	3834	0.72 (0.70–0.75)	0.48 (0.47–0.49)
Huson et al, 2017 (42)	76	112	30	240	0.72 (0.62–0.80)	0.68 (0.63–0.73)
Freund et al, 2017 (33)	52	166	22	639	0.70 (0.59–0.80)	0.79 (0.76–0.82)
Siddiqui et al, 2017 (54)	7	19	3	29	0.70 (0.35–0.93)	0.60 (0.45–0.74)
Churpek et al, 2017 (29)	1133	10595	516	18433	0.69 (0.66–0.71)	0.64 (0.63–0.64)
Hwang et al, 2017 (43)	144	573	67	611	0.68 (0.62–0.74)	0.52 (0.49–0.54)
Forward et al, 2017 (34)	17	73	8	63	0.68 (0.46–0.85)	0.46 (0.38–0.55)
Raith et al, 2017 (52)	22758	76853	11311	72156	0.67 (0.66–0.67)	0.48 (0.48–0.49)
Quinten et al, 2017 (51)	5	29	3	156	0.63 (0.24–0.91)	0.84 (0.78–0.89)
Giamarellos-Bourboulis et al, 2017 (35)	528	755	340	1813	0.61 (0.57–0.64)	0.71 (0.69–0.72)
LeGuen et al, 2018 (37)	11	31	8	47	0.58 (0.33–0.80)	0.60 (0.49–0.71)
Seymour et al, 2016 (11) (outside ICU)	1037	10342	849	54294	0.55 (0.53–0.57)	0.84 (0.84–0.84)
Sterling et al, 2017 (55)	21	116	18	115	0.54 (0.37–0.70)	0.50 (0.43–0.56)
Chen et al, 2016 (28)	291	271	256	823	0.53 (0.49–0.57)	0.75 (0.73–0.78)
Park et al, 2017 (49)	84	136	75	714	0.53 (0.45–0.61)	0.84 (0.81–0.86)
Henning et al, 2017 (40)	172	1042	161	6259	0.52 (0.46–0.57)	0.86 (0.85–0.87)
Piano et al, 2017 (50)	23	31	22	164	0.51 (0.36–0.66)	0.84 (0.78–0.89)
Ranzani et al, 2017 (53)	189	1071	187	4577	0.50 (0.45–0.55)	0.81 (0.80–0.82)
Williams et al, 2017 (60)	164	741	163	7803	0.50 (0.45–0.56)	0.91 (0.91–0.92)
Wang et al, 2017 (58)	18	31	18	50	0.50 (0.33–0.67)	0.62 (0.50–0.72)
Wang et al, 2016 (57)	56	60	75	286	0.43 (0.34–0.52)	0.83 (0.78–0.86)
Donnelly et al, 2017 (31)	67	228	96	2070	0.41 (0.33–0.49)	0.90 (0.89–0.91)
Moskowitz et al, 2017 (48)	465	2986	728	19985	0.39 (0.36–0.42)	0.87 (0.87–0.87)
Guirgis et al, 2017 (38)	125	412	207	2553	0.38 (0.32–0.43)	0.86 (0.85–0.87)
Weigle et al, 2016 (59)	17	112	29	66	0.37 (0.23–0.52)	0.37 (0.30–0.45)
de Groot et al, 2017 (30)	46	278	97	1859	0.32 (0.25–0.40)	0.87 (0.85–0.88)
González Del Castillo et al, 2017 (36)	20	63	52	936	0.28 (0.18–0.40)	0.94 (0.92–0.95)
Amland and Sutariya, 2017 (24)	55	594	170	5173	0.24 (0.19–0.31)	0.90 (0.89–0.90)
Kolditz et al, 2016 (47)	81	562	280	8404	0.22 (0.18–0.27)	0.94 (0.93–0.94)
Kim et al, 2017 (46)	4	18	16	577	0.20 (0.06–0.44)	0.97 (0.95–0.98)
Askim et al, 2017 (26)	8	59	60	1408	0.12 (0.05–0.22)	0.96 (0.95–0.97)



SIRS criteria						
Khwannimit et al, 2017 (45)	1030	1236	15	69	0.99 (0.98–0.99)	0.05 (0.04–0.07)
April et al, 2017 (25)	38	171	1	4	0.97 (0.87–1.00)	0.02 (0.01–0.06)
Haydar et al, 2017 (39)	21	167	1	10	0.95 (0.77–1.00)	0.06 (0.03–0.10)
Churpek et al, 2017 (29)	1547	25 550	102	3478	0.94 (0.93–0.95)	0.12 (0.12–0.12)
Freund et al, 2017 (33)	69	584	5	221	0.93 (0.85–0.98)	0.27 (0.24–0.31)
Finkelsztein et al, 2017 (32)	27	108	2	15	0.93 (0.77–0.99)	0.12 (0.07–0.19)
Raith et al, 2017 (52)	31 648	127 062	2382	21 882	0.93 (0.93–0.93)	0.15 (0.15–0.15)
Seymour et al, 2016 (11) (ICU)	1173	5514	116	1129	0.91 (0.89–0.93)	0.17 (0.16–0.18)
Siddiqui et al, 2017 (54)	9	27	1	21	0.90 (0.55–1.00)	0.44 (0.29–0.59)
Johnson et al, 2016 (44)	974	5978	113	1993	0.90 (0.88–0.91)	0.25 (0.24–0.26)
Ranzani et al, 2017 (53)	334	4432	42	1216	0.89 (0.85–0.92)	0.22 (0.20–0.23)
Henning et al, 2017 (40)	229	3159	47	3315	0.83 (0.78–0.87)	0.51 (0.50–0.52)
Weigle et al, 2016 (59)	38	167	8	11	0.83 (0.69–0.92)	0.06 (0.03–0.11)
Moskowitz et al, 2017 (48)	978	12 864	215	10 107	0.82 (0.80–0.84)	0.44 (0.43–0.45)
Donnelly et al, 2017 (31)	128	1264	35	1166	0.79 (0.71–0.85)	0.48 (0.46–0.50)
Williams et al, 2017 (60)	253	3923	74	4621	0.77 (0.72–0.82)	0.54 (0.53–0.55)
Forward et al, 2017 (34)	18	108	7	28	0.72 (0.51–0.88)	0.21 (0.14–0.28)
González Del Castillo et al, 2017 (36)	47	508	25	491	0.65 (0.53–0.76)	0.49 (0.46–0.52)
Seymour et al, 2016 (11) (outside ICU)	1207	22 623	679	42 013	0.64 (0.62–0.66)	0.65 (0.65–0.65)
Askim et al, 2017 (26)	42	620	26	770	0.62 (0.49–0.73)	0.55 (0.53–0.58)
Piano et al, 2017 (50)	23	62	22	133	0.51 (0.36–0.66)	0.68 (0.61–0.75)



FN = false-negative; FP = false-positive; ICU = intensive care unit; qSOFA = quick Sequential Organ Failure Assessment; SIRS = systemic inflammatory response syndrome; TN = true-negative; TP = true-positive.

Table 2. Overall, Subgroup, and Sensitivity Analyses of Summary Estimates for qSOFA and the SIRS Criteria

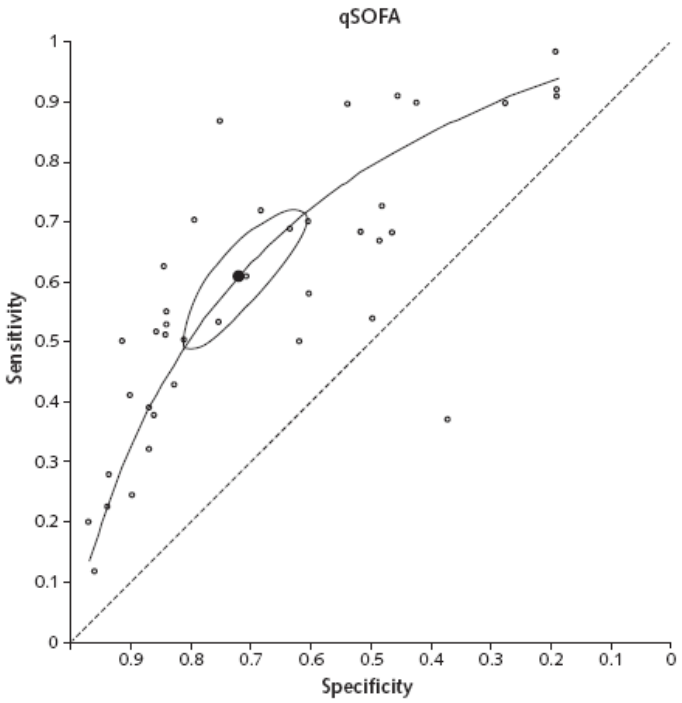
Variable	qSOFA	SIRS Criteria
Cohorts (patients), *n* (*n*)		
Overall	39 (385 333)	21 (352 571)
ICU patients only	8 (203 229)	7 (202 738)
Patients outside ICU only	31 (182 104)	14 (149 833)
ED patients only	19 (61 894)	9 (49 640)
In-hospital mortality	29 (356 455)	18 (341 171)
28- or 30-d mortality	10 (28 878)	3 (11 400)
Abstracts excluded	37 (376 051)	19 (343 289)
Studies applying qSOFA to specific populations excluded	25 (369 881)	16 (342 419)
Studies with high risk of bias excluded	17 (339 042)	10 (324 101)

Variable	qSOFA	SIRS Criteria
Sensitivity (95% CI), %		
Overall	60.8 (51.4–69.4)	88.1 (82.3–92.1)
ICU patients only	87.2 (75.8–93.7)	93.9 (88.5–96.8)
Patients outside ICU only	51.2 (43.6–58.7)	82.2 (74.5–87.9)
ED patients only	46.7 (38.3–55.2)	83.6 (75.9–89.1)
In-hospital mortality	66.4 (56.6–75.1)	90.0 (84.9–93.5)
28- or 30-d mortality	43.2 (27.7–60.1)	70.0 (60.7–77.8)
Abstracts excluded	61.0 (51.2–70.0)	87.8 (81.3–92.3)
Studies applying qSOFA to specific populations excluded	64.2 (51.4–75.2)	90.1 (84.5–93.8)
Studies with high risk of bias excluded	69.6 (54.8–81.2)	91.7 (85.3–95.4)
Specificity (95% CI), %		
Overall	72.0 (63.4–79.2)	25.8 (17.1–36.9)
ICU patients only	33.3 (23.8–44.4)	13.0 (6.6–23.8)
Patients outside ICU only	79.6 (73.3–84.7)	34.2 (22.6–48.0)
ED patients only	81.3 (72.8–87.5)	30.6 (17.7–47.5)
In-hospital mortality	65.5 (55.7–74.2)	22.2 (14.0–33.3)
28- or 30-d mortality	86.0 (74.8–92.7)	53.1 (50.4–55.7)
Abstracts excluded	73.3 (64.7–80.4)	27.2 (17.7–39.5)
Studies applying qSOFA to specific populations excluded	70.3 (58.4–80.0)	23.1 (14.2–35.2)
Studies with high risk of bias excluded	61.5 (46.6–74.5)	18.4 (9.6–32.5)

Variable	qSOFA	SIRS Criteria
Positive likelihood ratio (95% CI)		
Overall	2.168 (1.820–2.582)	1.187 (1.090–1.293)
ICU patients only	1.307 (1.193–1.432)	1.079 (1.022–1.139)
Patients outside ICU only	2.501 (2.063–3.033)	1.248 (1.087–1.434)
ED patients only	2.491 (1.858–3.339)	1.205 (1.013–1.434)
In-hospital mortality	1.926 (1.607–2.308)	1.157 (1.067–1.254)
28- or 30-d mortality	3.080 (2.242–4.231)	1.490 (1.287–1.726)
Abstracts excluded	2.285 (1.927–2.709)	1.206 (1.098–1.326)
Studies applying qSOFA to specific populations excluded	2.164 (1.757–2.665)	1.171 (1.071–1.281)
Studies with high risk of bias excluded	1.809 (1.473–2.222)	1.124 (1.030–1.226)
Negative likelihood ratio (95% CI)		
Overall	0.545 (0.470–0.633)	0.463 (0.398–0.537)
ICU patients only	0.385 (0.245–0.606)	0.473 (0.449–0.499)
Patients outside ICU only	0.614 (0.549–0.687)	0.521 (0.417–0.652)
ED patients only	0.656 (0.585–0.737)	0.536 (0.376–0.765)
In-hospital mortality	0.512 (0.425–0.618)	0.450 (0.396–0.513)
28- or 30-d mortality	0.661 (0.538–0.813)	0.566 (0.419–0.766)
Abstracts excluded	0.532 (0.456–0.620)	0.448 (0.392–0.511)
Studies applying qSOFA to specific populations excluded	0.509 (0.415–0.625)	0.430 (0.379–0.487)
Studies with high risk of bias excluded	0.494 (0.387–0.630)	0.453 (0.410–0.500)

ED = emergency department; ICU = intensive care unit; qSOFA = quick Sequential Organ Failure Assessment; SIRS = systemic inflammatory response syndrome.

Our findings support continued use of the SIRS criteria for screening of patients with infection who are at risk for future deterioration. qSOFA was more sensitive among ICU patients than non-ICU patients, possibly due to differences in test application among ICU patients.



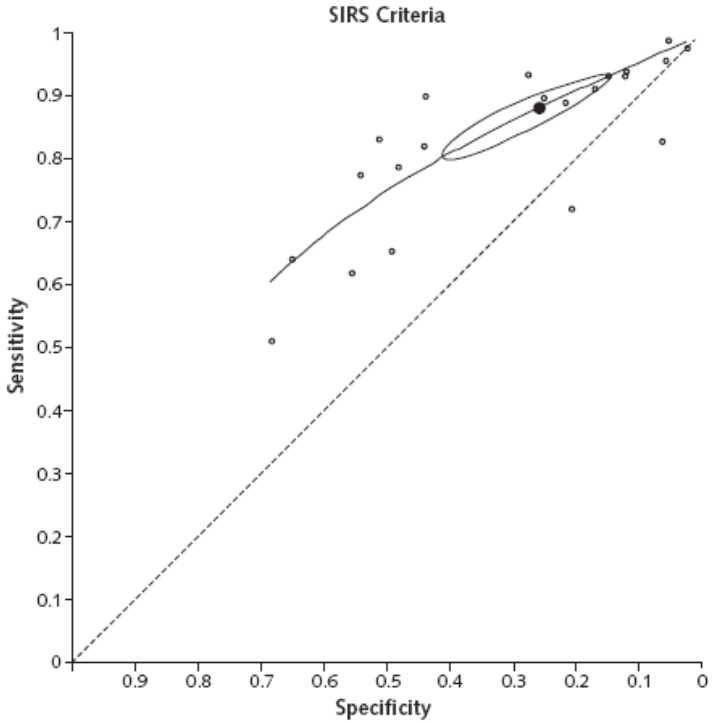


Table 3. Distribution of Septic Shock Cohorts and Crude Mortality From Surviving Sepsis Campaign Database (n = 18 840 patients)

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

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

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

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

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

[c] Refers to the adjusted OR generated using generalized estimating equation regression model (eTable7 in the Supplement).

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

[e] Excluded from full case analysis.

Table 4. Characteristics of Serum Lactate Level Cutoff Values for Complete Case Analysis and Imputation Analysis Using Surviving Sepsis Campaign Database

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

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

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

Table 5. Crude Mortality in Septic Shock Groups From UPMC and KPNC Data sets

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

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

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

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

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

Clinical Review & Education

Special Communication | CARING FOR THE CRITICALLY ILL PATIENT

The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3)

Mervyn Singer, MD, FRCP; Clifford S. Deutschman, MD, MS; Christopher Warren Seymour, MD, MSc; Manu Shankar-Hari, MSc, MD, FFICM; Djillali Annane, MD, PhD; Michael Bauer, MD; Rinaldo Bellomo, MD; Gordon R. Bernard, MD; Jean-Daniel Chiche, MD, PhD; Craig M. Coopersmith, MD; Richard S. Hotchkiss, MD; Mitchell M. Levy, MD; John C. Marshall, MD; Greg S. Martin, MD, MSc; Steven M. Opal, MD; Gordon D. Rubenfeld, MD, MS; Tom van der Poll, MD, PhD; Jean-Louis Vincent, MD, PhD; Derek C. Angus, MD, MPH

JAMA. 2016;315(8):801-810. doi:10.1001/jama.2016.0287

PROCESS A task force (n = 19) with expertise in sepsis pathobiology, clinical trials, and epidemiology was convened by the Society of Critical Care Medicine and the European Society of Intensive Care Medicine. Definitions and clinical criteria were generated through meetings, Delphi processes, analysis of electronic health record databases, and voting, followed by circulation to international professional societies, requesting peer review and endorsement (by 31 societies listed in the Acknowledgment).

Définitions

Box 3. New Terms and Definitions

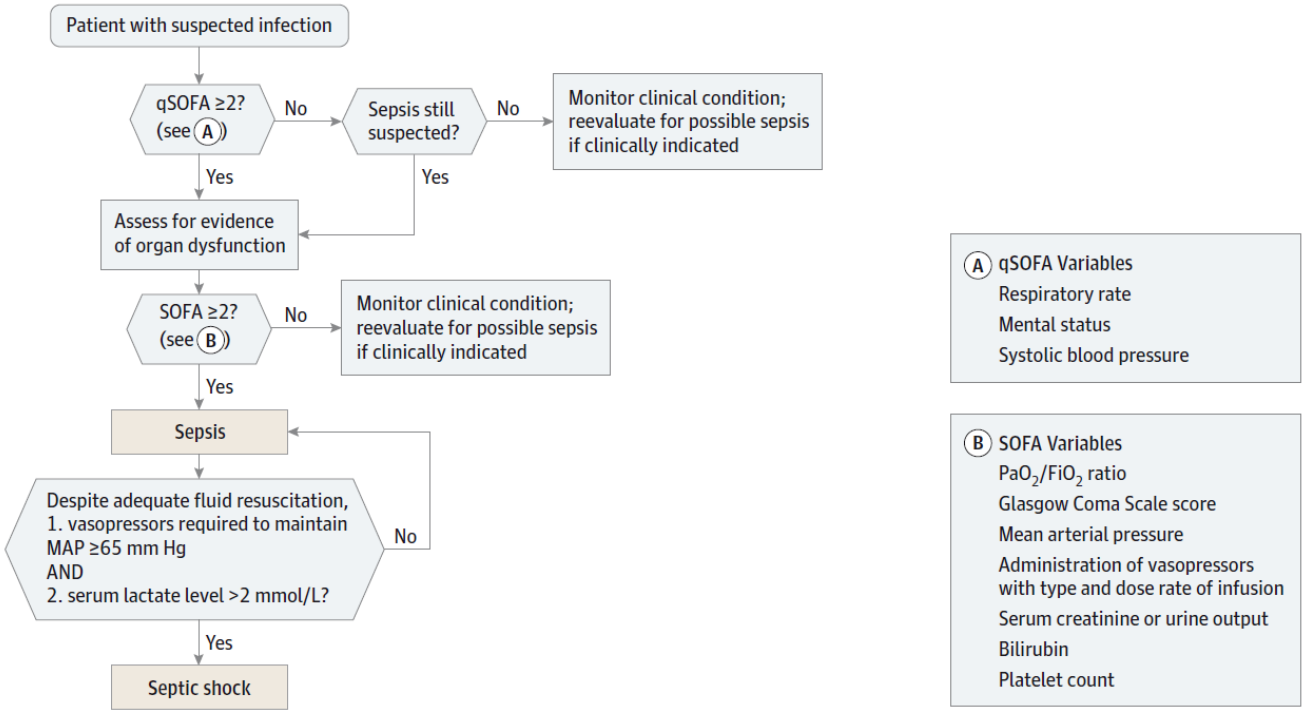
- Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection.
- Organ dysfunction can be identified as an acute change in total SOFA score ≥2 points consequent to the infection.
  - The baseline SOFA score can be assumed to be zero in patients not known to have preexisting organ dysfunction.
  - A SOFA score ≥2 reflects an overall mortality risk of approximately 10% in a general hospital population with suspected infection. Even patients presenting with modest dysfunction can deteriorate further, emphasizing the seriousness of this condition and the need for prompt and appropriate intervention, if not already being instituted.
- In lay terms, sepsis is a life-threatening condition that arises when the body's response to an infection injures its own tissues and organs.
- Patients with suspected infection who are likely to have a prolonged ICU stay or to die in the hospital can be promptly identified at the bedside with qSOFA, ie, alteration in mental status, systolic blood pressure ≤100 mm Hg, or respiratory rate ≥22/min.
- Septic shock is a subset of sepsis in which underlying circulatory and cellular/metabolic abnormalities are profound enough to substantially increase mortality.
- Patients with septic shock can be identified with a clinical construct of sepsis with persisting hypotension requiring vasopressors to maintain MAP ≥65 mm Hg and having a serum lactate level >2 mmol/L (18 mg/dL) despite adequate volume resuscitation. With these criteria, hospital mortality is in excess of 40%.

Abbreviations: MAP, mean arterial pressure; qSOFA, quick SOFA; SOFA: Sequential [Sepsis-related] Organ Failure Assessment.

Table 2. Terminology and *International Classification of Diseases* Coding

Current Guidelines and Terminology	Sepsis	Septic Shock
1991 and 2001 consensus terminology[9,10]	Severe sepsis Sepsis-induced hypoperfusion	Septic shock[13]
2015 Definition	Sepsis is life-threatening organ dysfunction caused by a dysregulated host response to infection	Septic shock is a subset of sepsis in which underlying circulatory and cellular/metabolic abnormalities are profound enough to substantially increase mortality
2015 Clinical criteria	Suspected or documented infection and an acute increase of ≥2 SOFA points (a proxy for organ dysfunction)	Sepsis[a] and vasopressor therapy needed to elevate MAP ≥65 mm Hg and lactate >2 mmol/L (18 mg/dL) despite adequate fluid resuscitation[13]
Recommended primary *ICD* codes[a]		
ICD-9	995.92	785.52
ICD-10[a]	R65.20	R65.21
Framework for implementation for coding and research	Identify suspected infection by using concomitant orders for blood cultures and antibiotics (oral or parenteral) in a specified period[b] Within specified period around suspected infection[c]: 1. Identify sepsis by using a clinical criterion for life-threatening organ dysfunction 2. Assess for shock criteria, using administration of vasopressors, MAP <65 mm Hg, and lactate >2 mmol/L (18 mg/dL)[d]	

Figure. Operationalization of Clinical Criteria Identifying Patients With Sepsis and Septic Shock



The baseline Sequential [Sepsis-related] Organ Failure Assessment (SOFA) score should be assumed to be zero unless the patient is known to have preexisting (acute or chronic) organ dysfunction before the onset of infection. qSOFA indicates quick SOFA; MAP, mean arterial pressure.

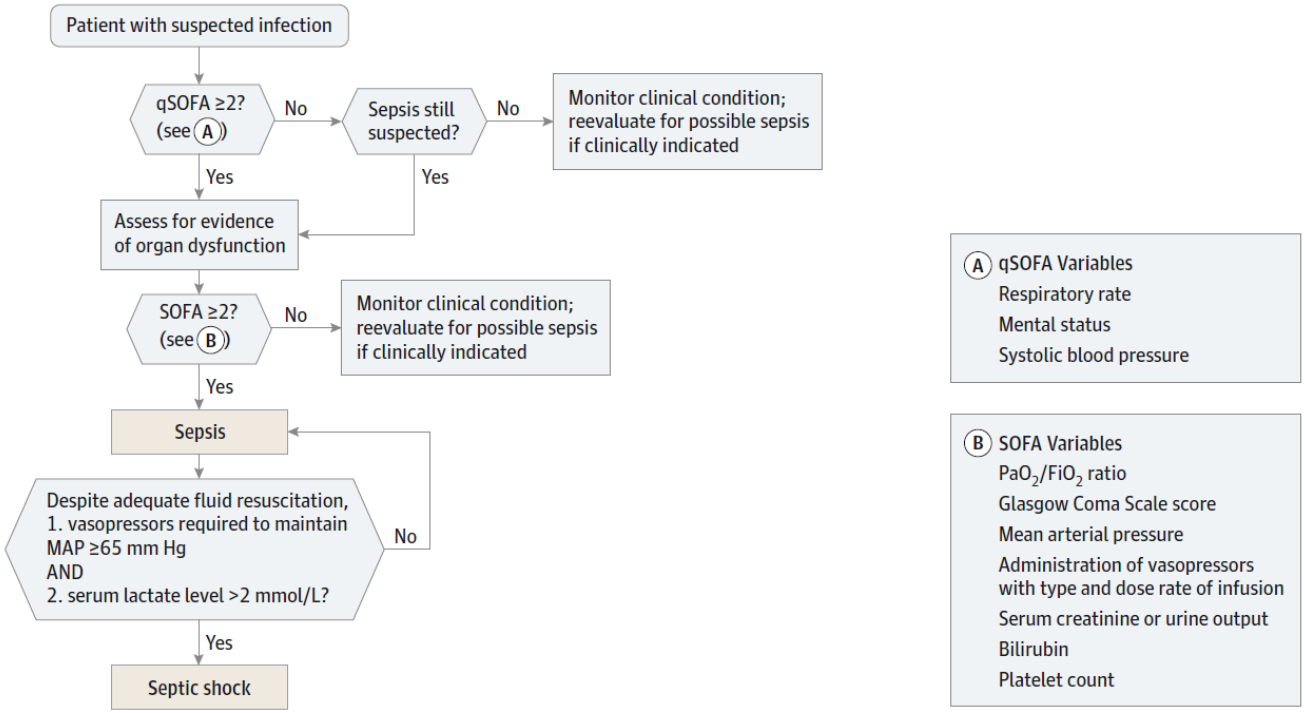
Box 4. qSOFA (Quick SOFA) Criteria

Respiratory rate ≥22/min

Altered mentation

Systolic blood pressure ≤100 mm Hg

Figure. Operationalization of Clinical Criteria Identifying Patients With Sepsis and Septic Shock



The baseline Sequential [Sepsis-related] Organ Failure Assessment (SOFA) score should be assumed to be zero unless the patient is known to have preexisting (acute or chronic) organ dysfunction before the onset of infection. qSOFA indicates quick SOFA; MAP, mean arterial pressure.

Table 1. Sequential [Sepsis-Related] Organ Failure Assessment Score[a]

	Score				
System	0	1	2	3	4
Respiration					
Pao_2/Fio_2, mm Hg (kPa)	≥400 (53.3)	<400 (53.3)	<300 (40)	<200 (26.7) with respiratory support	<100 (13.3) with respiratory support
Coagulation					
Platelets, $\times 10^3/\mu L$	≥150	<150	<100	<50	<20
Liver					
Bilirubin, mg/dL (μmol/L)	<1.2 (20)	1.2-1.9 (20-32)	2.0-5.9 (33-101)	6.0-11.9 (102-204)	>12.0 (204)
Cardiovascular	MAP ≥70 mm Hg	MAP <70 mm Hg	Dopamine <5 or dobutamine (any dose)[b]	Dopamine 5.1-15 or epinephrine ≤0.1 or norepinephrine ≤0.1[b]	Dopamine >15 or epinephrine >0.1 or norepinephrine >0.1[b]
Central nervous system					
Glasgow Coma Scale score[c]	15	13-14	10-12	6-9	<6
Renal					
Creatinine, mg/dL (μmol/L)	<1.2 (110)	1.2-1.9 (110-170)	2.0-3.4 (171-299)	3.5-4.9 (300-440)	>5.0 (440)
Urine output, mL/d				<500	<200

Abbreviations: Fio_2, fraction of inspired oxygen; MAP, mean arterial pressure; Pao_2, partial pressure of oxygen.

[a] Adapted from Vincent et al.[27]

[b] Catecholamine doses are given as μg/kg/min for at least 1 hour.

[c] Glasgow Coma Scale scores range from 3-15; higher score indicates better neurological function.

Échelle de coma de Glasgow

N 15; coma si < 9; coma grave si <5

TABLEAU 2

Échelle de Glasgow et de Liège

Ouverture des yeux (E)

- spontanée 4
- stimulation verbale 3
- stimulation douloureuse 2
- absente 1

Réponse motrice (M)

- sur commande 6
- réactivité aux stimuli douloureux
  - → localisateur 5
  - → retrait 4
  - → stéréotypé en flexion 3
  - → stéréotypé en extension 2
  - → absente 1

Réponse verbale (V)

- orientée 5
- confuse 4
- incohérente 3
- incompréhensible 2
- absente 1

Réflexes du tronc (Liège)

- fronto-orbiculaire 5
- oculo-céphalique vertical 4
- photomoteur 3
- oculo-céphalique horizontal 2
- oculo-cardiaque 1
- aucun 0

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MEETING REPORT

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The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure

On behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine (see contributors to the project in the appendix)

Use of the SOFA score to assess the incidence of organ dysfunction/failure in intensive care units: Results of a multicenter, prospective study

Jean-Louis Vincent, MD, PhD, FCCM; Arnaldo de Mendonça, MD; Frâncis Cantraine, MD; Rui Moreno, MD; Jukka Takala, MD, PhD; Peter M. Suter, MD, FCCM; Charles L. Sprung, MD, JD, FCCM; Francis Colardyn, MD; Serge Blecher, MD; on behalf of the working group on "sepsis-related problems" of the European Society of Intensive Care Medicine

Objective: To evaluate the use of the Sequential Organ Failure Assessment (SOFA) score in assessing the incidence and severity of organ dysfunction in critically ill patients.

Design: Prospective, multicenter study.

Setting: Forty intensive care units (ICUs) in 16 countries.

Patients: Patients admitted to the ICU in May 1995 (n = 1,449), excluding patients who underwent uncomplicated elective surgery with an ICU length of stay <48 hrs.

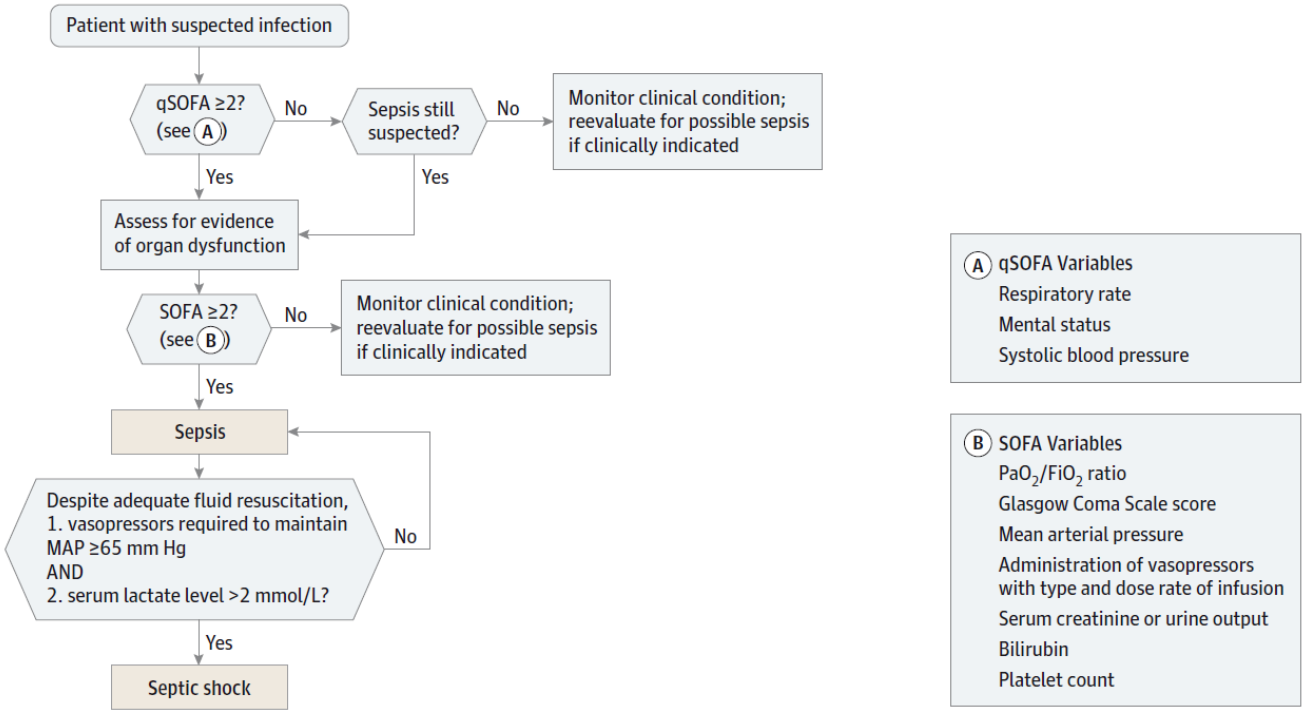
Interventions: None.

Measurements and Main Results: The main outcome measures included incidence of dysfunction/failure of different organs and the relationship of this dysfunction with outcome. In this cohort of patients, the median length of ICU stay was 5 days, and the ICU mortality rate was 22%. Multiple organ dysfunction and high SOFA scores for any individual organ were associated with increased mortality. The presence of infection on admission (28.7% of patients) was associated with higher SOFA scores for each organ. The evaluation of a subgroup of 544 patients who stayed in the ICU for at least 1 wk showed that survivors and nonsurvivors followed a different course. This subgroup had greater respiratory, cardiovascular, and neurologic scores than the other patients. In this subgroup, the total SOFA score increased in 44% of the nonsurvivors but in only 20% of the survivors ($p < .001$). Conversely, the total SOFA score decreased in 33% of the survivors compared with 21% of the nonsurvivors ($p < .001$).

Conclusions: The SOFA score is a simple, but effective method to describe organ dysfunction/failure in critically ill patients. Regular, repeated scoring enables patient condition and disease development to be monitored and better understood. The SOFA score may enable comparison between patients that would benefit clinical trials. (Crit Care Med 1998; 26:1793–1800)

KEY WORDS: outcome; morbidity; organ failure; critically ill; intensive care; respiratory failure; renal failure; hepatic failure; coagulation abnormalities; neurologic dysfunction; circulatory shock; circulatory failure

Figure. Operationalization of Clinical Criteria Identifying Patients With Sepsis and Septic Shock



The baseline Sequential [Sepsis-related] Organ Failure Assessment (SOFA) score should be assumed to be zero unless the patient is known to have preexisting (acute or chronic) organ dysfunction before the onset of infection. qSOFA indicates quick SOFA; MAP, mean arterial pressure.

Research

Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

Assessment of Clinical Criteria for Sepsis
For the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3)

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IMPORTANCE The Third International Consensus Definitions Task Force defined sepsis as "life-threatening organ dysfunction due to a dysregulated host response to infection." The performance of clinical criteria for this sepsis definition is unknown.

OBJECTIVE To evaluate the validity of clinical criteria to identify patients with suspected infection who are at risk of sepsis.

DESIGN, SETTINGS, AND POPULATION Among 1.3 million electronic health record encounters from January 1, 2010, to December 31, 2012, at 12 hospitals in southwestern Pennsylvania, we identified those with suspected infection in whom to compare criteria. Confirmatory analyses were performed in 4 data sets of 706 399 out-of-hospital and hospital encounters at 165 US and non-US hospitals ranging from January 1, 2008, until December 31, 2013.

Table 1. Variables for Candidate Sepsis Criteria Among Encounters With Suspected Infection

Systemic Inflammatory Response Syndrome (SIRS) Criteria (Range, 0-4 Criteria)	Sequential [Sepsis-related] Organ Failure Assessment (SOFA) (Range, 0-24 Points)	Logistic Organ Dysfunction System (LODS) (Range, 0-22 Points)[a]	Quick Sequential [Sepsis-related] Organ Failure Assessment (qSOFA) (Range, 0-3 Points)
Respiratory rate, breaths per minute	Pao_2/Fio_2 ratio	Pao_2/Fio_2 ratio	Respiratory rate, breaths per minute
White blood cell count, 10^9/L	Glasgow Coma Scale score	Glasgow Coma Scale score	Glasgow Coma Scale score
Bands, %	Mean arterial pressure, mm Hg	Systolic blood pressure, mm Hg	Systolic blood pressure, mm Hg
Heart rate, beats per minute	Administration of vasopressors with type/dose/rate of infusion	Heart rate, beats per minute	
Temperature, °C	Serum creatinine, mg/dL, or urine output, mL/d	Serum creatinine, mg/dL	
Arterial carbon dioxide tension, mm Hg	Bilirubin, mg/dL	Bilirubin, mg/dL	
	Platelet count, 10^9/L	Platelet count, 10^9/L	
		White blood cell count, 10^9/L	
		Urine output, L/d	
		Serum urea, mmol/L	
		Prothrombin time, % of standard	

The Logistic Organ Dysfunction System

A New Way to Assess Organ Dysfunction in the Intensive Care Unit

Jean-Roger Le Gall, MD; Janelle Klar, MS; Stanley Lemeshow, PhD; Fabienne Saulnier, MD; Corinne Alberti, MD; Antonio Artigas, MD; Daniel Teres, MD; for the ICU Scoring Group

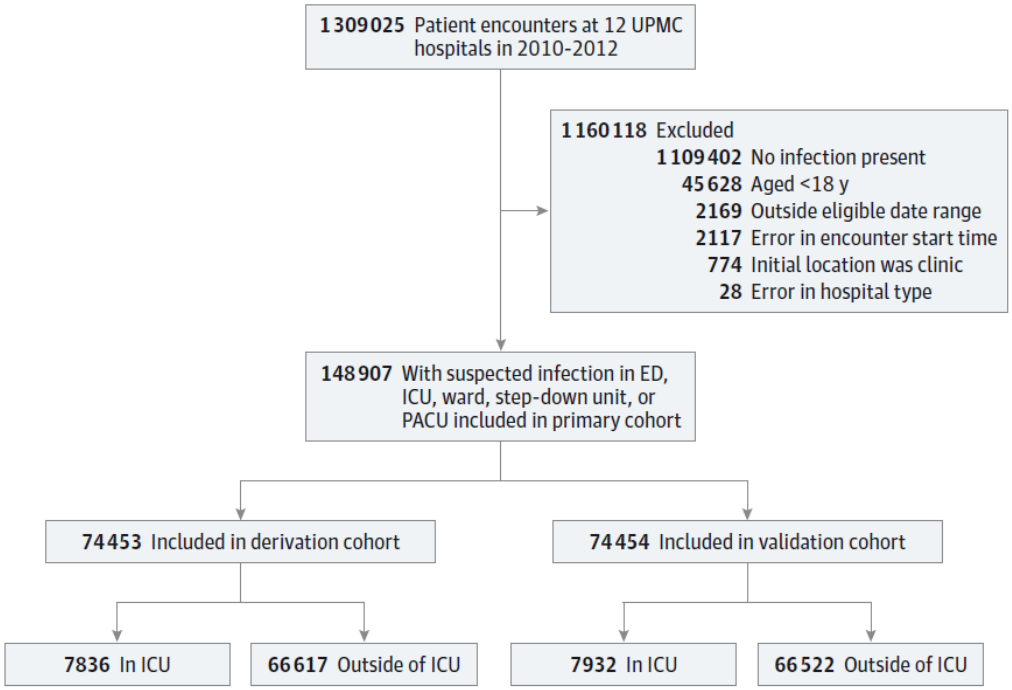
JAMA. 1996;276:802-810

Table 5.—Scoring for the Logistic Organ Dysfunction (LOD) System*

	LOD Points						
	Increasing Severity/ Decreasing Values			Organ Dysfunction Free	Increasing Severity/ Increasing Values		
Organ System Measures	5	3	1	0	1	3	5
Neurologic							
Glasgow Coma Score	3-5	6-8	9-13	14-15	...	...	...
Cardiovascular							
Heart rate, beats/min	<30	...	...	30-139	≥140	...	...
or	or			and	or		
Systolic blood pressure, mm Hg	<40	40-69	70-89	90-239	240-269	≥270	...
Renal							
Serum urea, mmol/L (g/L)	...	...	...	<6 (<0.36)	6-9.9 (0.36-0.59)	10-19.9 (0.60-1.19)	≥20 (≥1.20)
or							
Serum urea nitrogen, mmol/L (mg/dL)	...	...	...	<6 (<17)	6-9.9 (17-<28)	10-19.9 (28-<56)	≥20 (≥56)
				and	or	or	
Creatinine, μmol/L (mg/dL)	...	...	...	<106 (<1.20)	106-140 (1.20-1.59)	≥141 (≥1.60)	...
				and		or	
Urine output, L/d	<0.5	0.5-0.74	...	0.75-9.99	...	≥10	...
Pulmonary							
Pao_2 (mm Hg)/FIO_2 on MV or CPAP		<150	≥150	No ventilation; no CPAP	...	...	...
(Pao_2 [kPa]/FIO_2)		(<19.9)	(≥19.9)	no IPAP	...	...	...
Hematologic							
White blood cell count, $\times 10^9$/L	...	<1.0	1.0-2.4	2.5-49.9	≥50.0	...	...
			or	and			
Platelets, $\times 10^9$/L	...	...	<50	≥50	...	...	...
Hepatic							
Bilirubin, μmol/L (mg/dL)	...	...	...	<34.2 (<2.0)	≥34.2 (≥2.0)	...	...
				and	or		
Prothrombin time, s above standard (% of standard)	...	...	(<25%)	≤3 (≥25%)	>3	...	...

*To calculate the LOD score, each organ system receives points for the single variable associated with the most points. For example, if the worst heart rate of the day was 25 beats/min (5 LOD points), but the systolic blood pressure remained at 50 mm Hg (3 LOD points), then 5 LOD points are assigned. The points are not added to obtain 8 LOD points for the organ dysfunction: the maximum number of points for an organ is 5, and the maximum LOD score is 22. Ellipses indicate data not applicable; FIO_2, fraction of inspired oxygen; MV, mechanical ventilation; CPAP, continuous positive airway pressure; and IPAP, intermittent positive airway pressure.

Figure 1. Accrual of Encounters for Primary Cohort



ED indicates emergency department; ICU, intensive care unit; PACU, postanesthesia care unit.

Table 2. Summary of Data Sets

Characteristics	UPMC[a]	KPNC	VA	ALERTS	KCEMS
Years of cohort	2010-2012	2009-2013	2008-2010	2011-2012	2009-2010
No. of hospitals	12	20	130	1	14
Total No. of encounters	1 309 025	1 847 165	1 640 543	38 098	50 727
Data source and study design	Retrospective study of EHRs	Retrospective study of EHRs	Retrospective study of EHRs	Prospective cohort study	Retrospective study of administrative records
Setting	Integrated health system in southwestern Pennsylvania	Integrated health system in northern California	All hospitals in the US VA system	Single university hospital, Jena, Germany	Out-of-hospital records from integrated emergency medical services system in King County, Washington
Definition of suspected infection	Combination of body fluid culture and nonprophylactic antibiotic administration in the EHR[b]	Combination of body fluid culture and nonprophylactic antibiotic administration in the EHR[b]	Combination of body fluid culture and nonprophylactic antibiotic administration in the EHR[b]	CDC criteria for hospital-acquired infections[c]	*ICD-9-CM* codes for infection, with present-on-admission indicators[d]
No. with suspected infection (% of total)	148 907 (11)	321 380 (17)	377 325 (23)	1186 (3)	6508 (13)
Location at onset of infection, No. (%) infected					
Intensive care unit	15 768 (11)	7031 (2)	73 264 (19)	300 (25)	0
Outside of intensive care unit	133 139 (89)	314 349 (98)	304 061 (81)	886 (75)	6508 (100)
In-hospital mortality, No. (%) infected[e]	6347 (4)	16 092 (5)	22 593 (6)	210 (18)	700 (11)

Abbreviations: KCEMS, King County Emergency Medical Services; KPNC, Kaiser Permanente Northern California; EHR, electronic health record; *ICD-9-CM*, *International Classification of Diseases, Ninth Revision, Clinical Modification*; VA, Veterans Administration.

[c] Patients were enrolled in ALERTS if the in-hospital stay was longer than 48 hours and in-person prospective screening revealed hospital-acquired infection criteria according to Centers for Disease Control and Prevention (CDC) guidelines.[7]

Table 3. Characteristics of Encounters With Suspected Infection in the Primary Cohort at 12 UPMC Hospitals From 2010 to 2012 (N = 148 907)[a]

Variables	All Encounters	Derivation Cohort		Validation Cohort	
		ICU Encounters	Encounters Outside of ICU	ICU Encounters	Encounters Outside of ICU
Total encounters with suspected infection, No.	148 907	7836	66 617	7932	66 522
Infection type, No. (%)[b]					
Presumed	112 850 (76)	7282 (93)	49 287 (74)	7351 (93)	48 930 (74)
Confirmed bacteremia	6875 (5)	646 (8)	2780 (4)	652 (8)	2797 (4)
Age, mean (SD), y	61 (19)	62 (17)	61 (20)	62 (17)	60 (20)
Male, No. (%)	63 311 (43)	4192 (54)	27 418 (41)	4255 (54)	27 446 (41)
Race/ethnicity, No. (%)					
White	113 029 (76)	5774 (74)	50 843 (76)	5881 (74)	50 531 (76)
Black	20 892 (14)	808 (10)	9552 (14)	777 (10)	9755 (15)
Other	14 986 (10)	1254 (16)	6222 (9)	1274 (16)	6236 (9)
Weighted Charlson comorbidity index, median (IQR)	1 (0-2)	1 (0-2)	1 (0-2)	1 (0-2)	1 (0-2)
Surgery prior to infection suspected, No. (%)	17 327 (12)	2153 (27)	6517 (10)	2171 (27)	6486 (10)
Onset of infection within 48 h of admission, No. (%)	128 358 (86)	6022 (77)	58 187 (87)	5993 (76)	58 156 (87)
Unit location at time infection suspected, No. (%)					
Emergency department	65 934 (44)		32 902 (50)		33 032 (50)
Ward	49 354 (33)		24 787 (37)		24 567 (37)
ICU	15 768 (11)	7836 (100)		7932 (100)	
Postacute care unit or procedure unit	1965 (1)		960 (1)		1005 (2)
Step-down unit	15 662 (11)		7855 (12)		7807 (12)
Other or missing data	224 (<1)		113 (<1)		111 (<1)
SIRS near onset of suspected infection[c]					
Mean (SD)	1.3 (1.1)	2.5 (1.0)	1.2 (1.1)	2.5 (1.0)	1.2 (1.0)
Median (IQR)	1 (0-2)	3 (2-3)	1 (0-2)	3 (2-3)	1 (0-2)
SOFA near onset of suspected infection[d]					
Mean (SD)	2.0 (2.7)	6.3 (4.0)	1.4 (1.9)	6.2 (3.9)	1.4 (2.0)
Median (IQR)	1 (0-3)	6 (3-9)	1 (0-2)	6 (3-9)	1 (0-2)
LODS near onset of suspected infection[e]					
Mean (SD)	2.0 (2.8)	6.3 (3.9)	1.5 (2.1)	6.3 (3.8)	1.5 (2.1)
Median (IQR)	1 (0-3)	6 (4-9)	1 (0-3)	6 (3-9)	1 (0-3)
Serum lactate measured on day of infection, No. (%)	13 492 (9)	3187 (41)	3611 (5)	3067 (39)	3627 (5)
Serum lactate ≥2.0 mmol/L, No. (%)	6177 (4)	1643 (21)	1444 (2)	1555 (20)	1535 (2)
ICU admission, No. (%)	37 528 (25)	7836 (100)	10 935 (16)	7932 (100)	10 825 (16)
Hospital length of stay, median (IQR), d	6 (3-10)	12 (7-20)	6 (3-9)	12 (7-19)	6 (3-9)
Hospital mortality, No. (%)	6347 (4)	1298 (17)	1874 (3)	1289 (16)	1886 (3)

RESULTS In the primary cohort, 148 907 encounters had suspected infection (n = 74 453 derivation; n = 74 454 validation), of whom 6347 (4%) died. Among ICU encounters in the validation cohort (n = 7932 with suspected infection, of whom 1289 [16%] died), the predictive validity for in-hospital mortality was lower for SIRS (AUROC = 0.64; 95% CI, 0.62-0.66) and qSOFA (AUROC = 0.66; 95% CI, 0.64-0.68) vs SOFA (AUROC = 0.74; 95% CI, 0.73-0.76; *P* < .001 for both) or LODS (AUROC = 0.75; 95% CI, 0.73-0.76; *P* < .001 for both). Among non-ICU encounters in the validation cohort (n = 66 522 with suspected infection, of whom 1886 [3%] died), qSOFA had predictive validity (AUROC = 0.81; 95% CI, 0.80-0.82) that was greater than SOFA (AUROC = 0.79; 95% CI, 0.78-0.80; *P* < .001) and SIRS (AUROC = 0.76; 95% CI, 0.75-0.77; *P* < .001). Relative to qSOFA scores lower than 2, encounters with qSOFA scores of 2 or higher had a 3- to 14-fold increase in hospital mortality across baseline risk deciles. Findings were similar in external data sets and for the secondary outcome.

Figure 3. Area Under the Receiver Operating Characteristic Curve and 95% Confidence Intervals for In-Hospital Mortality of Candidate Criteria (SIRS, SOFA, LODS, and qSOFA) Among Suspected Infection Encounters in the UPMC Validation Cohort (N = 74 454)

A ICU encounters (n = 7932)

	SIRS	SOFA	LODS	qSOFA
SIRS	**0.64 (0.62-0.66)**	0.43 (0.41-0.46)	0.41 (0.38-0.43)	0.46 (0.43-0.48)
SOFA	<.001	**0.74 (0.73-0.76)**	0.87 (0.87-0.88)	0.65 (0.63-0.66)
LODS	<.001	0.20	**0.75 (0.73-0.76)**	0.76 (0.75-0.77)
qSOFA	.01	<.001	<.001	**0.66 (0.64-0.68)**

B Non-ICU encounters (n = 66 522)

	SIRS	SOFA	LODS	qSOFA
SIRS	**0.76 (0.75-0.77)**	0.52 (0.51-0.53)	0.43 (0.42-0.44)	0.61 (0.61-0.62)
SOFA	<.001	**0.79 (0.78-0.80)**	0.80 (0.80-0.81)	0.59 (0.58-0.60)
LODS	<.001	<.001	**0.81 (0.80-0.82)**	0.68 (0.68-0.69)
qSOFA	<.001	<.001	.72	**0.81 (0.80-0.82)**

ICU indicates intensive care unit; LODS, Logistic Organ Dysfunction System; qSOFA, quick Sequential [Sepsis-related] Organ Function Assessment; SIRS, systemic inflammatory response syndrome; SOFA, Sequential [Sepsis-related] Organ Function Assessment. The area under the receiver operating characteristic curve (AUROC) data in the blue-shaded diagonal cells derive from models that include baseline variables plus candidate criteria. For comparison, the AUROC of the baseline model alone is 0.58 (95% CI, 0.57-0.60) in the ICU and 0.69 (95% CI, 0.68-0.70) outside of the ICU. Below the AUROC data cells are *P* values for comparisons between criteria, while above the AUROC data cells are Cronbach α data (with bootstrap 95% confidence intervals), a measure of agreement.

Table 4. Odds Ratios for Baseline Model and qSOFA Variables for In-Hospital Mortality in the UPMC Derivation Cohort (N = 74 453)

	Total No. With Categorical Variable	Deaths, No. (% of Total)	In-Hospital Mortality, Adjusted Odds Ratio (95% CI)
Baseline risk model[a]			
Age, y[b]			1.03 (1.03-1.03)
Charlson comorbidity index[b]			1.13 (1.11-1.15)
Race/ethnicity			
White	56 617	2470 (4)	1 [Reference]
Black	10 360	319 (3)	0.89 (0.79-1.01)
Other	7476	383 (5)	1.37 (1.22-1.53)
Male			
No	42 843	1467 (3)	1 [Reference]
Yes	31 610	1705 (5)	1.56 (1.45-1.68)
qSOFA model[c]			
Respiratory rate, /min			
<22	45 398	676 (1)	1 [Reference]
≥22	29 055	2496 (9)	3.18 (2.89-3.50)
Systolic blood pressure, mm Hg			
>100	44 669	789 (2)	1 [Reference]
≤100	29 784	2383 (8)	2.61 (2.40-2.85)
Altered mental status, Glasgow Coma Scale score			
14-15	66 879	1677 (3)	1 [Reference]
≤13	7574	1495 (20)	4.31 (3.96-4.69)

Table 5. AUROCs for In-Hospital Mortality for qSOFA in External Data Sets

Data Set and Infection Type	No. of Patients With Suspected Infection	AUROC (95% CI)	
		Baseline Model	Baseline Model + qSOFA
KPNC (all suspected infections)	321 380	0.67 (0.67-0.67)	0.78 (0.78-0.78)
ICU patients	7031	0.64 (0.62-0.66)	0.72 (0.70-0.73)
Non-ICU patients	314 349	0.68 (0.67-0.68)	0.78 (0.78-0.79)
VA (all suspected infections)[a]	377 325	0.73 (0.73-0.74)	0.78 (0.78-0.79)
ALERTS (hospital-acquired infections)	1186	0.55 (0.51-0.60)	0.73 (0.69-0.77)
KCEMS (community-acquired infections)	6508	0.59 (0.57-0.62)	0.71 (0.69-0.73)

Abbreviations: AUROC, area under the receiver operating characteristic curve; ICU, intensive care unit; KCEMS, King County Emergency Medical Services; KPNC, Kaiser Permanente Northern California; qSOFA, quick Sequential [Sepsis-related] Organ Function Assessment; VA, Veterans Administration.

[a] The VA data did not include Glasgow Coma Scale scores; the qSOFA is a modified 2-variable model (systolic blood pressure and respiratory rate only), with a range from 0 to 2 points.

CONCLUSIONS AND RELEVANCE Among ICU encounters with suspected infection, the predictive validity for in-hospital mortality of SOFA was not significantly different than the more complex LODS but was statistically greater than SIRS and qSOFA, supporting its use in clinical criteria for sepsis. Among encounters with suspected infection outside of the ICU, the predictive validity for in-hospital mortality of qSOFA was statistically greater than SOFA and SIRS, supporting its use as a prompt to consider possible sepsis.

EDITORIAL

Editorials represent the opinions of the authors and *JAMA* and not those of the American Medical Association

New Definitions for Sepsis and Septic Shock
Continuing Evolution but With Much Still to Be Done

Edward Abraham, MD

JAMA February 23, 2016 Volume 315, Number 8 **757**

The epidemiologic strengths of the new consensus conference definitions of sepsis and septic shock are accompanied by weaknesses in their ability to be used in the treatment of individual patients or in clinical trials. Although the new definitions provide a broad view of the universe of sepsis and may help in facilitating early identification of patients with this condition, they will be of only limited help in directing specific therapies to individual patients or in designing clinical trials focused on specific mechanisms of sepsis-induced organ dysfunction.