ΠΑΝΕΠΙΣΤΗΜΙΟ ΠΑΤΡΩΝ
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# Σήψη-
# Πρωτόκολα Αντιμετώπισης

- ΗΠΑ: 2% ασθενών σε νοσοκομεία=σοβαρή σήψη
- Από τους προηγούμενους οι μισοί σε ΜΕΘ
- 10% όλων των εισαγωγών στις ΜΕΘ
- ΗΠΑ: 750000 ανά έτος
- Παγκοσμία: 19.000.000 και ο αριθμός μεγαλώνει

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GUIDELINES

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

Sepsis is defined as the presence (probable or documented) of infection together with systemic manifestations of infection. Severe sepsis is defined as sepsis plus sepsis-induced organ dysfunction or tissue hypoperfusion (Tables 1, 2) [6].

**Table 1** Diagnostic criteria for sepsis

| |
|---|
| Infection, documented or suspected, and some of the following: |
| General variables |
| Fever (>38.3 °C) |
| Hypothermia (core temperature <36 °C) |
| Heart rate >90 $min^{-1}$ or more than two SD above the normal value for age |
| Tachypnea |
| Altered mental status |
| Significant edema or positive fluid balance (> 20 mL/kg over 24 h) |
| Hyperglycemia (plasma glucose >140 mg/dL or 7.7 mmol/L) in the absence of diabetes |
| Inflammatory variables |
| Leukocytosis (WBC count >12,000 $\mu L^{-1}$) |
| Leukopenia (WBC count <4,000 $\mu L^{-1}$) |
| Normal WBC count with greater than 10 % immature forms |
| Plasma C-reactive protein more than two SD above the normal value |
| Plasma procalcitonin more than two SD above the normal value |
| Hemodynamic variables |
| Arterial hypotension (SBP <90 mmHg, MAP <70 mmHg, or an SBP decrease >40 mmHg in adults or less than two SD below normal for age) |
| Organ dysfunction variables |
| Arterial hypoxemia ($PaO_2/FiO_2$ <300) |
| Acute oliguria (urine output <0.5 mL $kg^{-1}$ $h^{-1}$ for at least 2 h despite adequate fluid resuscitation) |
| Creatinine increase >0.5 mg/dL or 44.2 μmol/L |
| Coagulation abnormalities (INR >1.5 or aPTT >60 s) |
| Ileus (absent bowel sounds) |
| Thrombocytopenia (platelet count <100,000 $\mu L^{-1}$) |
| Hyperbilirubinemia (plasma total bilirubin >4 mg/dL or 70 μmol/L) |
| Tissue perfusion variables |
| Hyperlactatemia (>1 mmol/L) |
| Decreased capillary refill or mottling |

*SD* standard deviation, *WBC* white blood cell, *SBP* systolic blood pressure, *MAP* mean arterial pressure, *INR* international normalized ratio, *aPTT* activated partial thromboplastin time

Diagnostic criteria for sepsis in the pediatric population are signs and symptoms of inflammation plus infection with hyper- or hypothermia (rectal temperature >38.5 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, increased serum lactate level, or bounding pulses

Adapted from [6]

**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) |

# Host – pathogen mismatch

The immune profile of this host-pathogen mismatch can be predominately proinflammatory (systemic inflammatory response syndrome, SIRS), mixed (mixed antagonistic response syndrome, MARS), or anti-inflammatory (compensatory anti-inflammatory response syndrome, CARS). The final result is various degrees of hyperinflammation, immunosuppression, abnormal coagulation, and microcirculatory dysfunction, all which may contribute to organ injury and cell death.[2,6]

Clinical diagnosis of *severe sepsis* or *septic shock* although valuable and of significant importance for the management of septic patients may lead to extremely heterogeneous cohorts in terms of patients' immunological status. This heterogeneity offers one explanation for the failure of prior trials of biologic therapies for sepsis, since treatments that focused on attenuating the initial inflammatory response of sepsis in a sense ignored and in fact might have exacerbated the progressive development of immunosuppression in some patients.[8-11]

CRITICAL CARE MEDICINE
Simon R. Finfer, M.D., and Jean-Louis Vincent, M.D., Ph.D., *Editors*

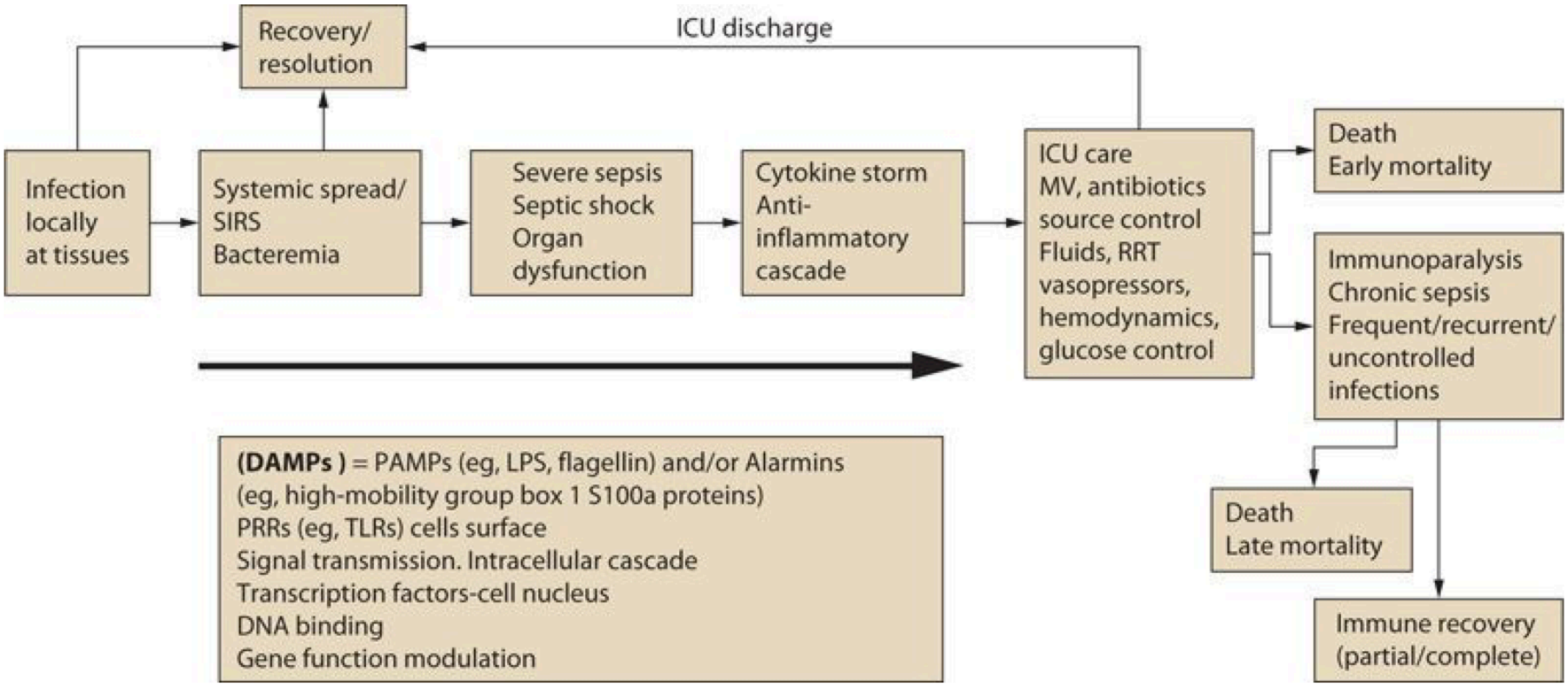
# Severe Sepsis and Septic Shock

Derek C. Angus, M.D., M.P.H., and Tom van der Poll, M.D., Ph.D.

Severe sepsis occurs as a result of both community-acquired and health care–associated infections. Pneumonia is the most common cause accounting for about half of all cases, followed by intraabdominal and urinary tract infections.[7,8,11,12] Blood cultures are typically positive in only one third of cases, and in up to a third of cases, cultures from all sites are negative.[7,11,13,14] *Staphylococcus aureus* and *Streptococcus pneumoniae* are the most common gram-positive isolates, whereas *Escherichia coli*, klebsiella species, and *Pseudomonas aeruginosa* predominate among gram-negative isolates.[11,14] An epidemiologic study of sepsis showed that during the period from 1979 to 2000, gram-positive infections overtook gram-negative infections.[15] However, in a more recent study involving 14,000 ICU patients in 75 countries, gram-negative bacteria were isolated in 62% of patients with severe sepsis who had positive cultures, gram-positive bacteria in 47%, and fungi in 19%.[12]

other.[30] The specific response in any patient depends on the causative pathogen (load and virulence) and the host (genetic characteristics and coexisting illnesses), with differential responses at local, regional, and systemic levels (Fig. 1). The composition and direction of the host response probably change over time in parallel with the clinical course. In general, proinflammatory reactions (directed at eliminating invading pathogens) are thought to be responsible for collateral tissue damage in severe sepsis, whereas antiinflammatory responses (important for limiting local and systemic tissue injury) are implicated in the enhanced susceptibility to secondary infections.

## EVOLUTION TO IMMUNOPARALYSIS (FIG. 62-1)[31]



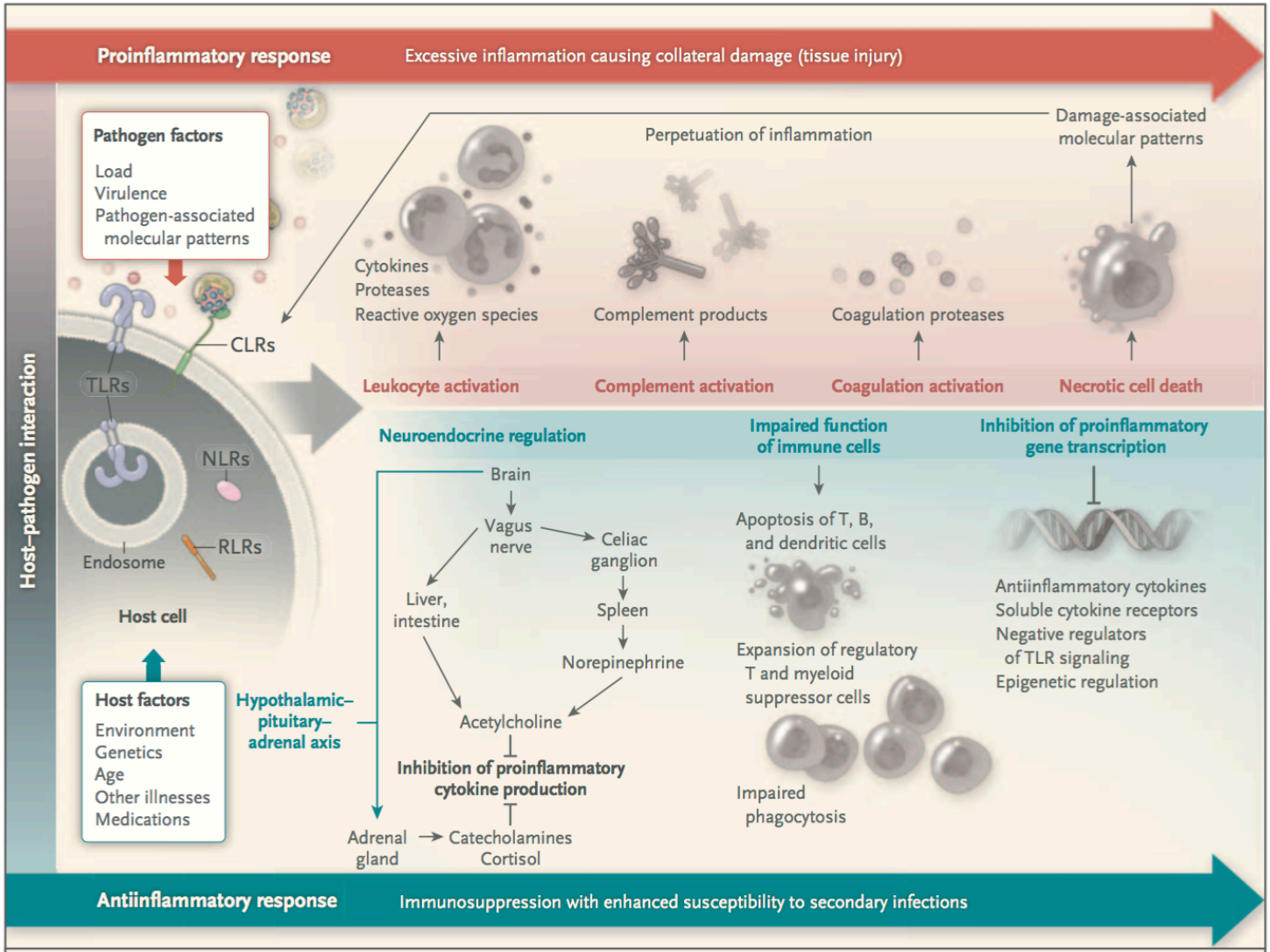



**Figure 1. The Host Response in Severe Sepsis.**

The host response to sepsis is characterized by both proinflammatory responses (top of panel, in red) and antiinflammatory immunosuppressive responses (bottom of panel, in blue). The direction, extent, and duration of these reactions are determined by both host factors (e.g., genetic characteristics, age, coexisting illnesses, and medications) and pathogen factors (e.g., microbial load and virulence). Inflammatory responses are initiated by interaction between pathogen-associated molecular patterns expressed by pathogens and pattern-recognition receptors expressed by host cells at the cell surface (toll-like receptors [TLRs] and C-type lectin receptors [CLRs]), in the endosome (TLRs), or in the cytoplasm (retinoic acid inducible gene 1–like receptors [RLRs] and nucleotide-binding oligomerization domain–like receptors [NLRs]). The consequence of exaggerated inflammation is collateral tissue damage and necrotic cell death, which results in the release of damage-associated molecular patterns, so-called danger molecules that perpetuate inflammation at least in part by acting on the same pattern-recognition receptors that are triggered by pathogens.

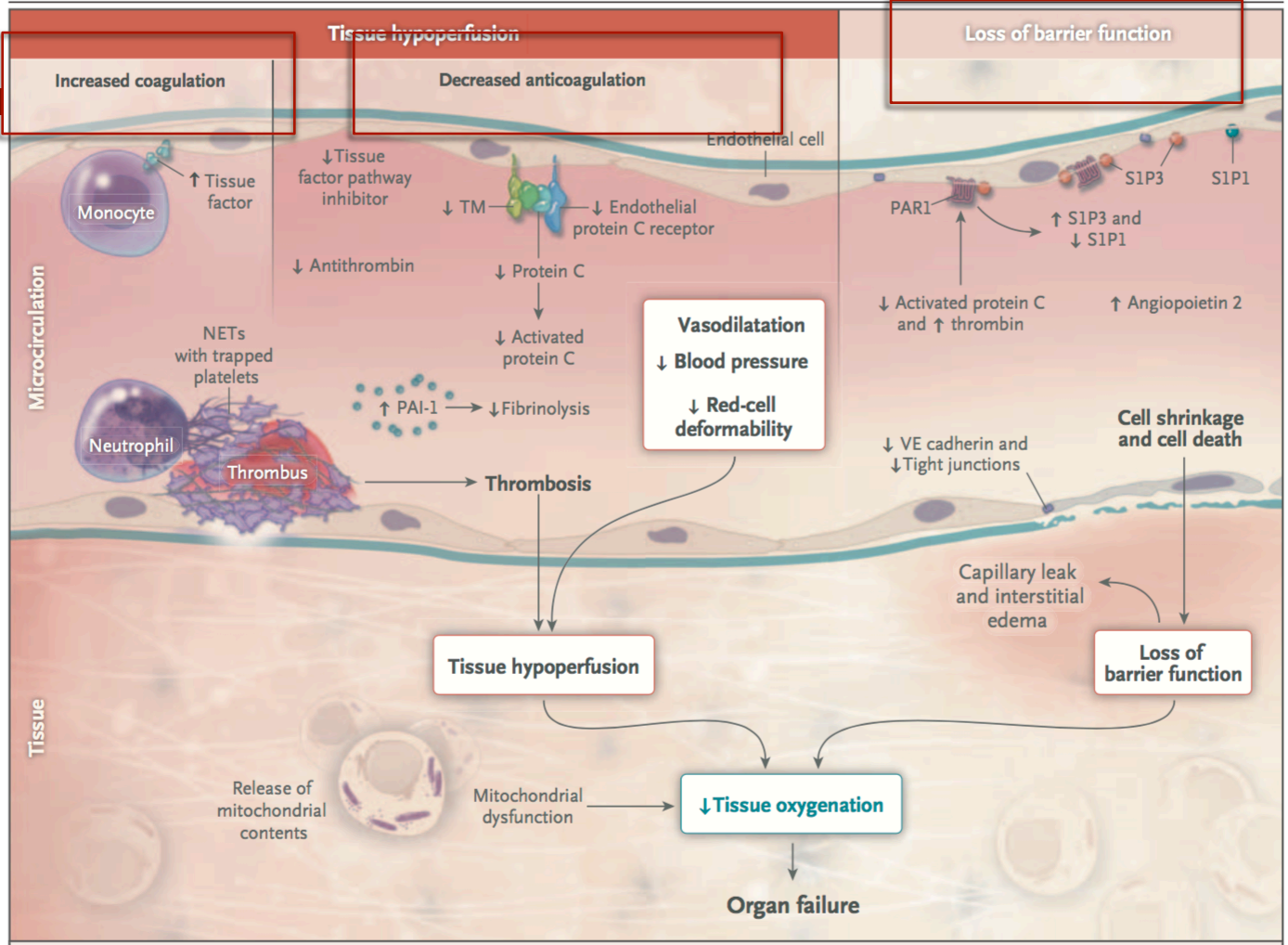



**Figure 2. Organ Failure in Severe Sepsis and Dysfunction of the Vascular Endothelium and Mitochondria.**

Sepsis is associated with microvascular thrombosis caused by concurrent activation of coagulation (mediated by tissue factor) and impairment of anticoagulant mechanisms as a consequence of reduced activity of endogenous anticoagulant pathways (mediated by activated protein C, antithrombin, and tissue factor pathway inhibitor), plus impaired fibrinolysis owing to enhanced release of plasminogen activator inhibitor type 1 (PAI-1). The capacity to generate activated protein C is impaired at least in part by reduced expression of two endothelial receptors: thrombomodulin (TM) and the endothelial protein C receptor. Thrombus formation is further facilitated by neutrophil extracellular traps (NETs) released from dying neutrophils. Thrombus formation results in tissue hypoperfusion, which is aggravated by vasodilatation, hypotension, and reduced red-cell deformability. Tissue oxygenation is further impaired by the loss of barrier function of the endothelium owing to a loss of function of vascular endothelial (VE) cadherin, alterations in endothelial cell-to-cell tight junctions, high levels of angiopoietin 2, and a disturbed balance between sphingosine-1 phosphate receptor 1 (S1P1) and S1P3 within the vascular wall, which is at least in part due to preferential induction of S1P3 through protease activated receptor 1 (PAR1) as a result of a reduced ratio of activated protein C to thrombin. Oxygen use is impaired at the subcellular level because of damage to mitochondria from oxidative stress.

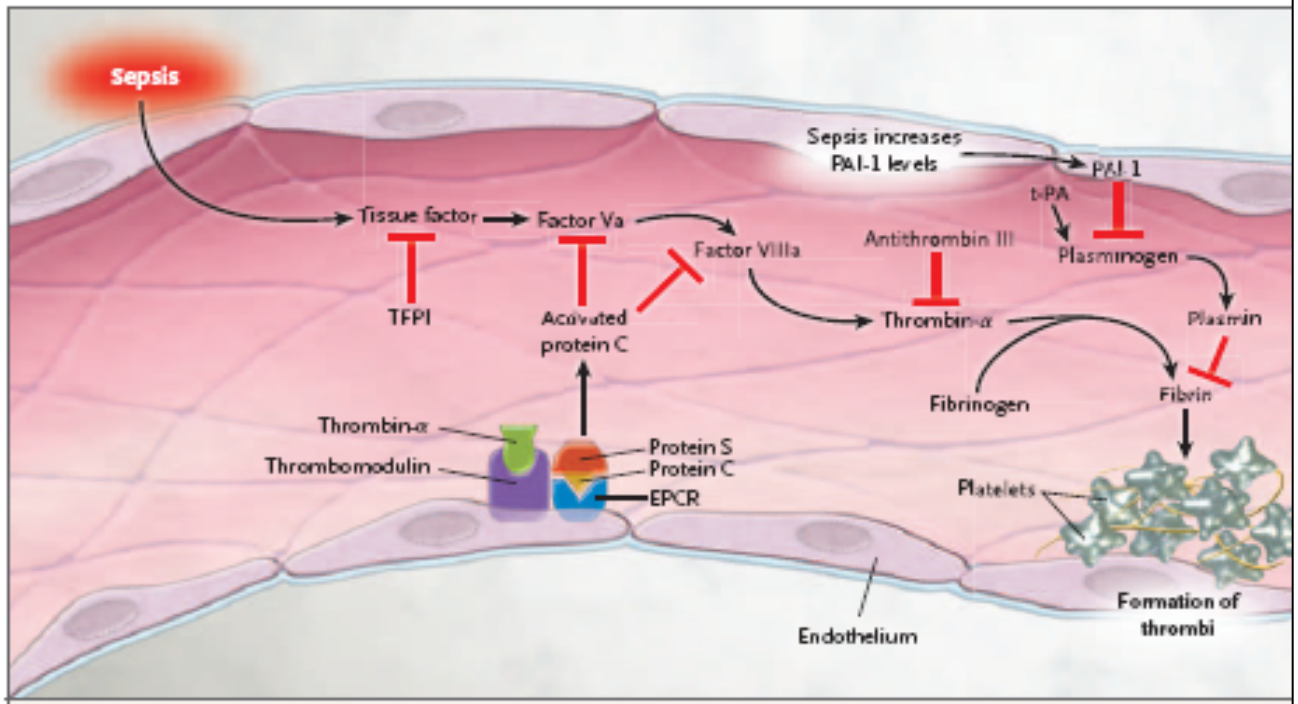



**Figure 2. Procoagulant Response in Sepsis.**

Sepsis initiates coagulation by activating endothelium to increase the expression of tissue factor. Activation of the coagulation cascade, and especially factors Va and VIIIa, leads to the formation of thrombin-α, which converts fibrinogen to fibrin. Fibrin binds to platelets, which in turn adhere to endothelial cells, forming microvascular thrombi. Microvascular thrombi amplify injury through the release of mediators and by microvascular obstruction, which causes distal ischemia and tissue hypoxia. Normally, natural anticoagulants (protein C and protein S), antithrombin III, and tissue factor–pathway inhibitor (TFPI) dampen coagulation, enhance fibrinolysis, and remove microthrombi. Thrombin-α binds to thrombomodulin on endothelial cells, which dramatically increases activation of protein C to activated protein C. Protein C forms a complex with its cofactor protein S. Activated protein C proteolytically inactivates factors Va and VIIIa and decreases the synthesis of plasminogen-activator inhibitor 1 (PAI-1). In contrast, sepsis increases the synthesis of PAI-1. Sepsis also decreases the levels of protein C, protein S, antithrombin III, and TFPI. Lipopolysaccharide and tumor necrosis factor α (TNF-α) decrease the synthesis of thrombomodulin and endothelial protein C receptor (EPCR), thus decreasing the activation of protein C. Sepsis further disrupts the protein C pathway because sepsis also decreases the expression of EPCR, which amplifies the deleterious effects of the sepsis-induced decrease in levels of protein C. Lipopolysaccharide and TNF-α also increase PAI-1 levels so that fibrinolysis is inhibited. The clinical consequences of the changes in coagulation caused by sepsis are increased levels of markers of disseminated intravascular coagulation and widespread organ dysfunction. t-PA denotes tissue plasminogen activator.

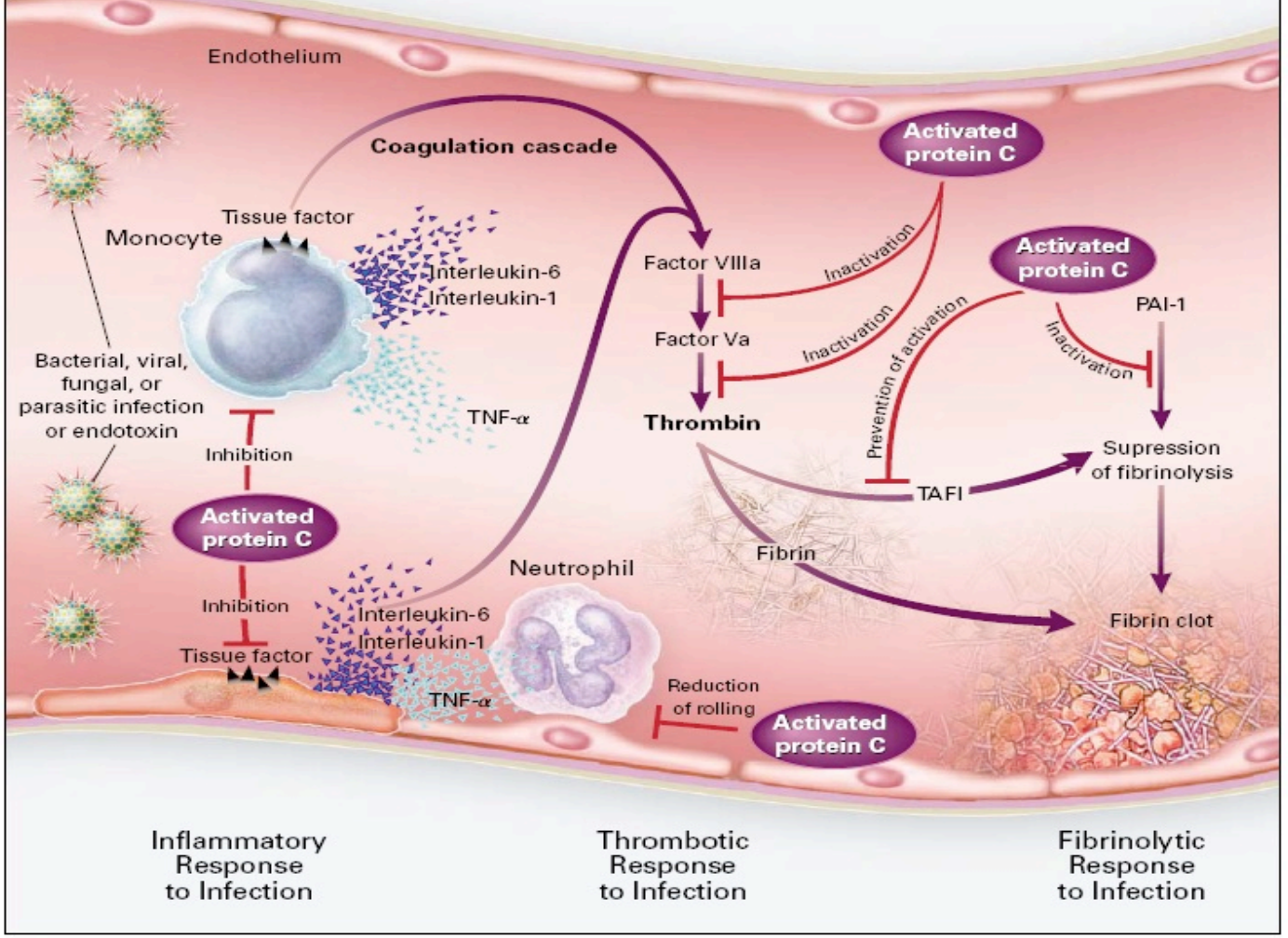
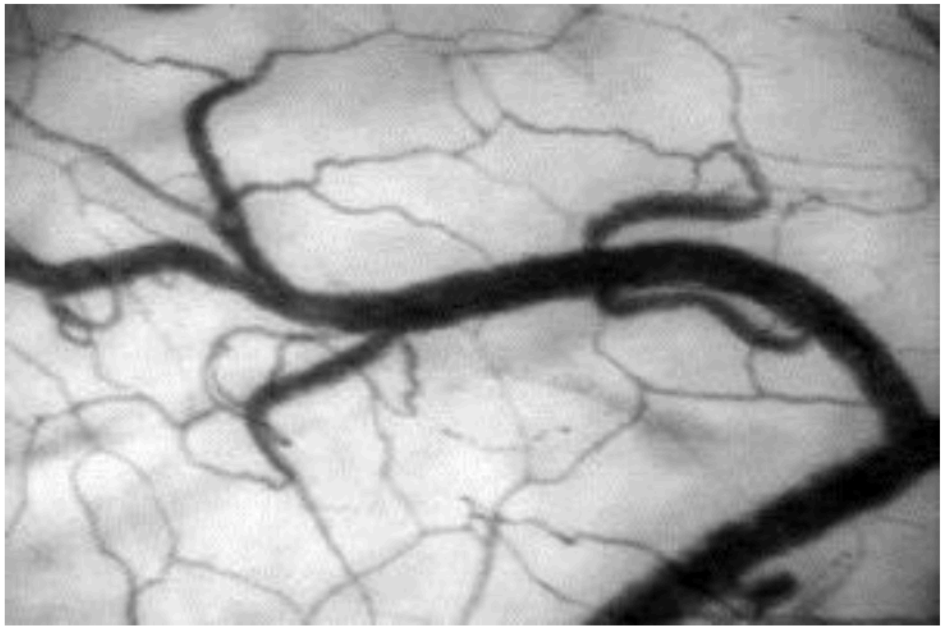
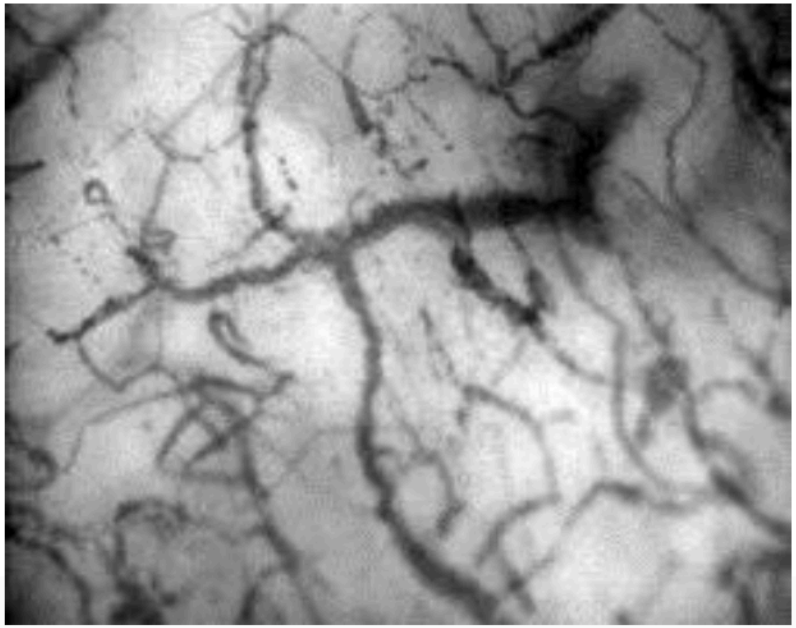



**Figure 1.** Proposed Actions of Activated Protein C in Modulating the Systemic Inflammatory, Procoagulant, and Fibrinolytic Host Responses to Infection.

The inflammatory and procoagulant host responses to infection are intricately linked. Infectious agents and inflammatory cytokines such as tumor necrosis factor α (TNF-α) and interleukin-1 activate coagulation by stimulating the release of tissue factor from monocytes and the endothelium. The presentation of tissue factor leads to the formation of thrombin and a fibrin clot. Inflammatory cytokines and thrombin can both impair the endogenous fibrinolytic potential by stimulating the release of plasminogen-activator inhibitor 1 (PAI-1) from platelets and the endothelium. PAI-1 is a potent inhibitor of tissue plasminogen activator, the endogenous pathway for lysing a fibrin clot. In addition, the procoagulant thrombin is capable of stimulating multiple inflammatory pathways and further suppressing the endogenous fibrinolytic system by activating thrombin-activatable fibrinolysis inhibitor (TAFI). The conversion of protein C, by thrombin bound to thrombomodulin, to the serine protease activated protein C is impaired by the inflammatory response. Endothelial injury results in decreased thrombomodulin levels. The end result of the host response to infection may be the development of diffuse endovascular injury, microvascular thrombosis, organ ischemia, multiorgan dysfunction, and death. Activated protein C can intervene at multiple points during the systemic response to infection. It exerts an antithrombotic effect by inactivating factors Va and VIIIa, limiting the generation of thrombin. As a result of decreased thrombin levels, the inflammatory, procoagulant, and antifibrinolytic response induced by thrombin is reduced. In vitro data indicate that activated protein C exerts an antiinflammatory effect by inhibiting the production of inflammatory cytokines (TNF-α, interleukin-1, and interleukin-6) by monocytes and limiting the rolling of monocytes and neutrophils on injured endothelium by binding selectins. Activated protein C indirectly increases the fibrinolytic response by inhibiting PAI-1.[12-17]





**Intravital sidestream dark field images of the sublingual microcirculation:**
capillaries with red cells flowing (normal, upper image) and obstructed with minimal flow (sepsis, lower image).

Images courtesy of C Ince, Amsterdam, the Netherlands

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

## Box 1. SIRS (Systemic Inflammatory Response Syndrome)

Two or more of:

- Temperature >38°C or <36°C
- Heart rate >90/min
- Respiratory rate >20/min or $Paco_2$ <32 mm Hg (4.3 kPa)
- White blood cell count >12 000/$mm^3$ or <4000/$mm^3$ or >10% immature bands

From Bone et al.[9]

## Improved Understanding of Sepsis Pathobiology

Sepsis is a multifaceted host response to an infecting pathogen that may be significantly amplified by endogenous factors.[14,15] The original conceptualization of sepsis as infection with at least 2 of the 4 SIRS criteria focused solely on inflammatory excess. However, the validity of SIRS as a descriptor of sepsis pathobiology has been challenged. Sepsis is now recognized to involve early activation of both pro- and anti-inflammatory responses,[16] along with major modifications in nonimmunologic pathways such as cardiovascular, neuronal, autonomic, hormonal, bioenergetic, metabolic, and coagulation,[14,17,18] all of which have prognostic significance. Organ dysfunction, even when severe, is not associated with substantial cell death.[19]

The JAMA Network

**Sepsis**

The current use of 2 or more SIRS criteria (Box 1) to identify sepsis was unanimously considered by the task force to be unhelpful. Changes in white blood cell count, temperature, and heart rate reflect inflammation, the host response to "danger" in the form of infection or other insults. The SIRS criteria do not necessarily indicate a dysregulated, life-threatening response. SIRS criteria are present in many hospitalized patients, including those who never develop infection and never incur adverse outcomes (poor discriminant validity).[25] In addition, 1 in 8 patients admitted to criti-

**Box 2. Key Concepts of Sepsis**

- Sepsis is the primary cause of death from infection, especially if not recognized and treated promptly. Its recognition mandates urgent attention.
- Sepsis is a syndrome shaped by pathogen factors and host factors (eg, sex, race and other genetic determinants, age, comorbidities, environment) with characteristics that evolve over time. What differentiates sepsis from infection is an aberrant or dysregulated host response and the presence of organ dysfunction.
- Sepsis-induced organ dysfunction may be occult; therefore, its presence should be considered in any patient presenting with infection. Conversely, unrecognized infection may be the cause of new-onset organ dysfunction. Any unexplained organ dysfunction should thus raise the possibility of underlying infection.
- The clinical and biological phenotype of sepsis can be modified by preexisting acute illness, long-standing comorbidities, medication, and interventions.
- Specific infections may result in local organ dysfunction without generating a dysregulated systemic host response.

# SOFA Score

**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.

### 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.

### Box 4. qSOFA (Quick SOFA) Criteria

Respiratory rate ≥22/min

Altered mentation

Systolic blood pressure ≤100 mm Hg

## Screening for Patients Likely to Have Sepsis

A parsimonious clinical model developed with multivariable logistic regression identified that any 2 of 3 clinical variables—Glasgow Coma Scale score of 13 or less, systolic blood pressure of 100 mm Hg or less, and respiratory rate 22/min or greater—offered predictive validity (AUROC = 0.81; 95% CI, 0.80-0.82) similar to that of the full SOFA score outside the ICU.[12] This model was robust

The Delphi process assessed agreements on descriptions of terms such as "hypotension," "need for vasopressor therapy," "raised lactate," and "adequate fluid resuscitation" for inclusion within the new clinical criteria. The majority (n = 14/17; 82.4%) of task force members voting on this agreed that hypotension should be denoted as a mean arterial pressure less than 65 mm Hg according to the pragmatic decision that this was most often recorded in data sets derived from patients with sepsis. Systolic blood pressure was used as a qSOFA criterion because it was most widely recorded in the electronic health record data sets.

A majority (11/17; 64.7%) of the task force agreed, whereas 2 (11.8%) disagreed, that an elevated lactate level is reflective of cellular dysfunction in sepsis, albeit recognizing that multiple factors, such as insufficient tissue oxygen delivery, impaired aerobic respiration, accelerated aerobic glycolysis, and reduced hepatic clearance, also contribute.[32] Hyperlactatemia is, however, a reasonable marker of illness severity, with higher levels predictive of higher mortality.[33] Criteria for "adequate fluid resuscitation" or "need for vasopressor therapy" could not be explicitly specified because these are highly user dependent, relying on variable monitoring modalities and hemodynamic targets for treatment.[34] Other aspects of management, such as sedation and volume status assessment, are also potential confounders in the hypotension-vasopressor relationship.

By Delphi consensus process, 3 variables were identified (hypotension, elevated lactate level, and a sustained need for vasopressor therapy) to test in cohort studies, exploring alternative

## Definition of Septic Shock

Septic shock is defined as a subset of sepsis in which underlying circulatory and cellular metabolism abnormalities are profound enough to substantially increase mortality (Box 3). The 2001 task force definitions described septic shock as "a state of acute circulatory failure."[10] The task force favored a broader view to differentiate septic shock from cardiovascular dysfunction alone and to recognize the importance of cellular abnormalities (Box 3). There was unanimous agreement that septic shock should reflect a more severe illness with a much higher likelihood of death than sepsis alone.

Clinical Review & Education

Special Communication | CARING FOR THE CRITICALLY ILL PATIENT

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The NEW ENGLAND JOURNAL of MEDICINE

REVIEW ARTICLE

CRITICAL CARE MEDICINE

Simon R. Finfer, M.D., and Jean-Louis Vincent, M.D., Ph.D., *Editors*

# Severe Sepsis and Septic Shock

Derek C. Angus, M.D., M.P.H., and Tom van der Poll, M.D., Ph.D.

**Table 2. Guidelines for the Treatment of Severe Sepsis and Septic Shock from the Surviving Sepsis Campaign.***

| Element of Care | Grade* |
|---|---|
| Resuscitation | |
| Begin goal-directed resuscitation during first 6 hr after recognition | |
| Begin initial fluid resuscitation with crystalloid and consider the addition of albumin | |
| Consider the addition of albumin when substantial amounts of crystalloid are required to maintain a | |
| Avoid hetastarch formulations | |
| Begin initial fluid challenge in patients with tissue hypoperfusion and suspected hypovolemia, to ach | |
| Continue fluid-challenge technique as long as there is hemodynamic improvement | |
| Use norepinephrine as the first-choice vasopressor to maintain a mean arterial pressure of ≥65 mm | |
| Use epinephrine when an additional agent is needed to maintain adequate blood pressure | 2B |
| Add vasopressin (at a dose of 0.03 units/min) with weaning of norepinephrine, if tolerated | UG |
| Avoid the use of dopamine except in carefully selected patients (e.g., patients with a low risk of arrhythmias and either known marked left ventricular systolic dysfunction or low heart rate) | 2C |
| Infuse dobutamine or add it to vasopressor therapy in the presence of myocardial dysfunction (e.g., elevated cardiac filling pressures or low cardiac output) or ongoing hypoperfusion despite adequate intravascular volume and mean arterial pressure | 1C |
| Avoid the use of intravenous hydrocortisone if adequate fluid resuscitation and vasopressor therapy restore hemodynamic stability; if hydrocortisone is used, administer at a dose of 200 mg/day | 2C |
| Target a hemoglobin level of 7 to 9 g/dl in patients without hypoperfusion, critical coronary artery disease or myocardial ischemia, or acute hemorrhage | 1B |
| Infection control | |
| Obtain blood cultures before antibiotic therapy is administered | 1C |
| Perform imaging studies promptly to confirm source of infection | UG |
| Administer broad-spectrum antibiotic therapy within 1 hr after diagnosis of either severe sepsis or septic shock | 1B/1C |
| Reassess antibiotic therapy daily for de-escalation when appropriate | 1B |
| Perform source control with attention to risks and benefits of the chosen method within 12 hr after diagnosis | 1C |
| Respiratory support | |
| Use a low tidal volume and limitation of inspiratory-plateau-pressure strategy for ARDS | 1A/1B |
| Apply a minimal amount of positive end-expiratory pressure in ARDS | 1B |
| Administer higher rather than lower positive end-expiratory pressure for patients with sepsis-induced ARDS | 2C |
| Use recruitment maneuvers in patients with severe refractory hypoxemia due to ARDS | 2C |
| Use prone positioning in patients with sepsis-induced ARDS and a ratio of the partial pressure of arterial oxygen (mm Hg) to the fraction of inspired oxygen of <100, in facilities that have experience with such practice | 2C |
| Elevate the head of the bed in patients undergoing mechanical ventilation, unless contraindicated | 1B |
| Use a conservative fluid strategy for established acute lung injury or ARDS with no evidence of tissue hypoperfusion | 1C |
| Use weaning protocols | 1A |

REVIEW ARTICLE

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# Severe Sepsis and Septic Shock

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| | |
|---|---|
| Central nervous system support | |
| Use sedation protocols, targeting specific dose-escalation end points | 1B |
| Avoid neuromuscular blockers if possible in patients without ARDS | 1C |
| Administer a short course of a neuromuscular blocker (<48 hr) for patients with early, severe ARDS | 2C |
| General supportive care | |
| Use a protocol-specified approach to blood glucose management, with the initiation of insulin after two consecutive blood glucose levels of >180 mg/dl (10 mmol/liter), targeting a blood glucose level of <180 mg/dl | 1A |
| Use the equivalent of continuous venovenous hemofiltration or intermittent hemodialysis as needed for renal failure or fluid overload | 2B |
| Administer prophylaxis for deep-vein thrombosis | 1B |
| Administer stress-ulcer prophylaxis to prevent upper gastrointestinal bleeding | 1B |
| Administer oral or enteral feedings, as tolerated, rather than either complete fasting or provision of only intravenous glucose within the first 48 hr after a diagnosis of severe sepsis or septic shock | 2C |
| Address goals of care, including treatment plans and end-of-life planning as appropriate | 1B |

* Data are adapted from Dellinger et al.[23] ARDS denotes acute respiratory distress syndrome, and ICU intensive care unit.

† For all grades, the number indicates the strength of the recommendation (1, recommended; 2, suggested), and the letter indicates the level of evidence, from high (A) to low (D), with UG indicating ungraded. Recommendations that are specific to pediatric severe sepsis include therapy with face-mask oxygen, high-flow nasal cannula oxygen, or nasopharyngeal continuous positive end-expiratory pressure in the presence of respiratory distress and hypoxemia (2C); use of physical examination therapeutic end points, such as capillary refill (2C); administration of a bolus of 20 ml of crystalloids (or albumin equivalent) per kilogram of body weight during a period of 5 to 10 minutes for hypovolemia (2C); increased use of inotropes and vasodilators in septic shock with low cardiac output associated with elevated systemic vascular resistance (2C); and use of hydrocortisone only in children with suspected or proven absolute adrenal insufficiency (2C).

‡ The guidelines recommend completing the initial fluid resuscitation within 3 hours (UG).

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# Developing a New Definition and Assessing New Clinical Criteria for Septic Shock

## For the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3)

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

### Systematic Review and Meta-analysis

The systematic review identified 44 studies (166 479 patients) reporting septic shock mortality[5-7,19-59] from a total of 92 studies reporting sepsis cohorts between 1987 and 2015[5-7,19-107] (**Figure 1**; eTable 2 in the Supplement). Different shock criteria were used for systolic blood pressure (<90 mm Hg; <100 mm Hg; decrease >40 mm Hg; or decrease >50% of baseline value if hypertensive), mean arterial pressure (<70; <65; <60 mm Hg), serum lactate level (>4, >2.5, >2, >1 mmol/L) and base deficit (−5 mmol/L) (**Table 1**;

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

| | Septic Shock Case Definitions and Corresponding Variables Reported in Literature | | | | |
|---|---|---|---|---|---|
| | Consensus Definitions | | Other Definitions | | |
| Criteria | Bone et al[1] | Levy et al[2] | SSC[111] | Trial-based[112] | |
| Infection | Suspected or proven | Suspected or proven | Suspected or proven | Suspected or proven | |
| SIRS criteria, No. | 2 | One or more of 24 variables[b] | 2 | 3 | |
| 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 | | |
| $\tau^{2f}$ | 191.21 | | 94.9 | | |
| *P* value heterogeneity | <.001 | | <.001 | | |

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πόσα διαφορετικά κριτήρια σε διαφορες παραμέτρους

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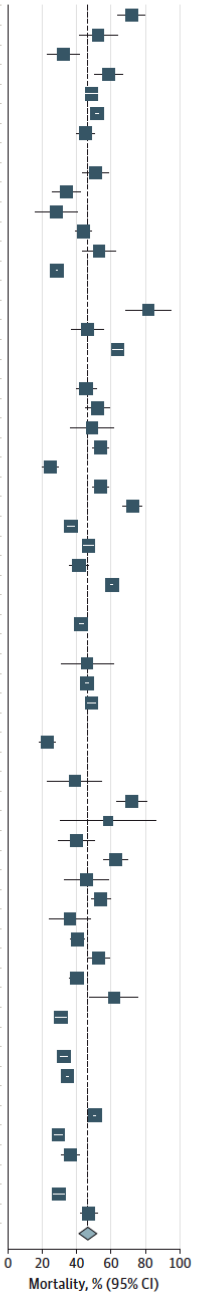
Reply

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

| | 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) |
| [illegible] | [illegible] | [illegible] | [illegible].8 (60.7-67.0) |
| [illegible] | [illegible] | [illegible] | .6 (39.8-51.4) |
| [illegible] | [illegible] | [illegible] | .2 (45.3-59.1) |
| [illegible] | [illegible] | [illegible] | .1 (36.5-61.8) |
| [illegible] | [illegible] | [illegible] | .1 (49.6-58.7) |
| [illegible] | [illegible] | [illegible] | .8 (20.4-29.2) |
| [illegible] | [illegible] | [illegible] | .1 (49.6-58.7) |
| [illegible] | [illegible] | [illegible] | .5 (67.1-78.0) |
| [illegible] | [illegible] | [illegible] | .7 (34.8-38.6) |
| [illegible] | [illegible] | [illegible] | .0 (44.3-49.7) |
| [illegible] | [illegible] | [illegible] | .5 (35.7-47.2) |
| [illegible] | [illegible] | [illegible] | .6 (60.0-61.2) |
| [illegible] | [illegible] | [illegible] | .3 (41.2-43.3) |
| [illegible] | [illegible] | [illegible] | .3 (31.1-61.6) |
| [illegible] | [illegible] | [illegible] | .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 Bhuayanontachai,[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) |




The random-effects meta-analysis showed significant heterogeneity in septic shock mortality (mean mortality, 46.5% [95% CI, 42.7%-50.3%], with a near 4-fold variation from 23.0% to 81.8%; $I^2$ = 99.5%; $\tau^2$ = 182.5; and $P$ < .001) (**Figure 2**). Statistically significant heterogeneity was also observed in random-effects meta-analysis by clinical criteria reported for septic shock case definition in studies (**Table 2**).

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between groups for mortality increased mortality compared to other groups

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

| Cohorts[a] | Lactate Category, mmol/L[b] | No. (% of total) [n = 18 840] | Acute Hospital Mortality, No. (%) [95% CI] | $\chi^2$ Test for Tre | | |
|---|---|---|---|---|---|---|
| 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.

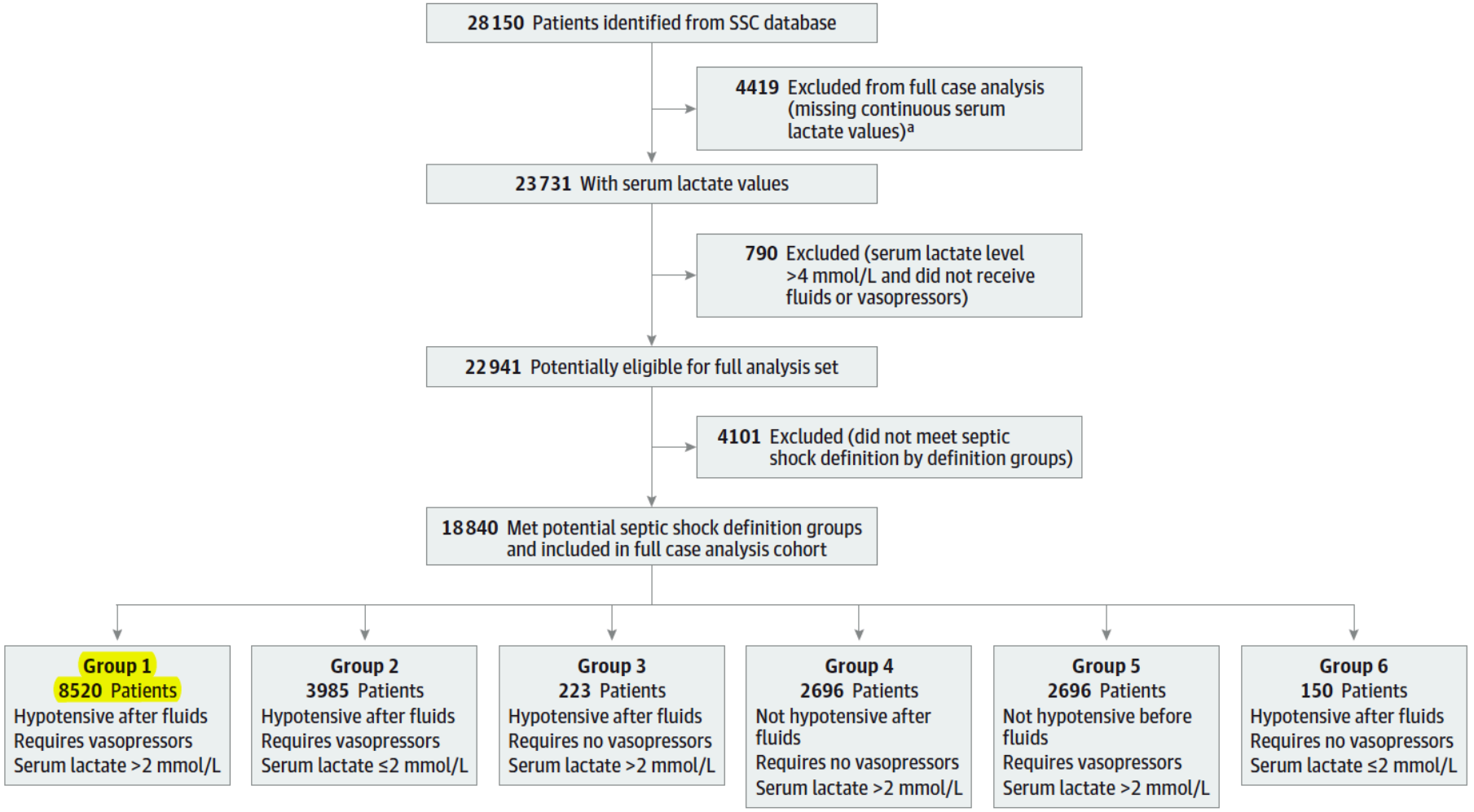
[b] Using $\chi^2$ tests, trends in mortality across serum lactate categories within groups (>2 to ≤3 mmol/L; >3 to ≤4 mmol/L and >4 mmol/L) were assessed.

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

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

[e] Excluded from full case analysis.

Figure 3. Selection of Surviving Sepsis Campaign Database Cohort



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## Predictive Validity of Potential Septic Shock Groups

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

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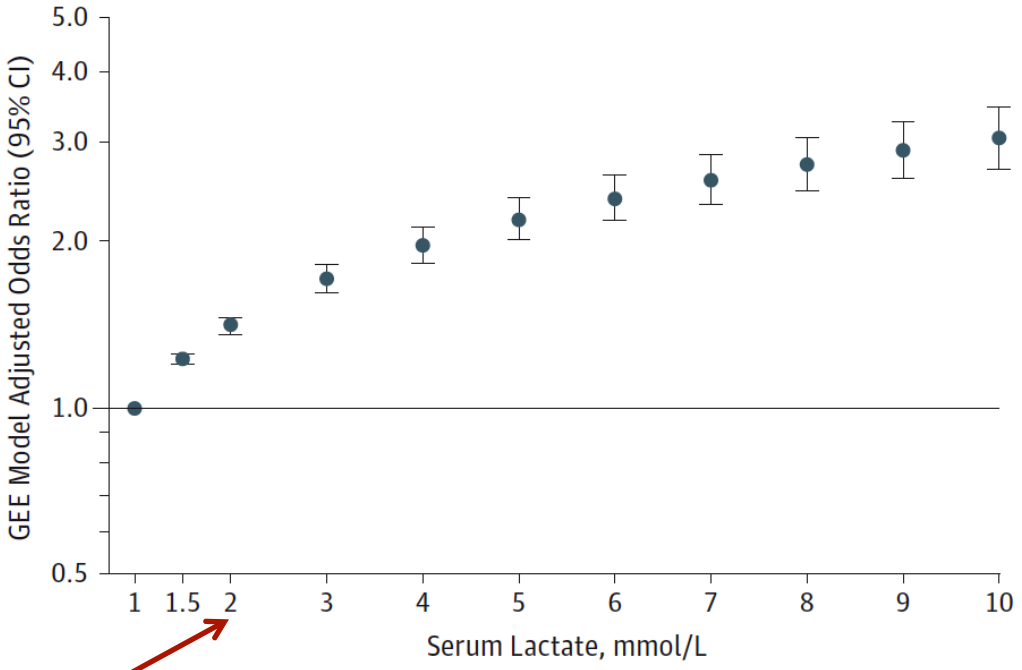
## Derivation of Serum Lactate Cutoff Value and Missing Data Analysis

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

## Figure 4. Serum Lactate Level Analysis




Cutoff value

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

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.

## Discussion

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

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**Table 3** Determination of the quality of evidence

| |
|---|
| Underlying methodology |
| A (high) RCTs |
| B (moderate) downgraded RCTs or upgraded observational studies |
| C (low) well-done observational studies with control RCTs |
| D (very low) downgraded controlled studies or expert opinion based on other evidence |
| Factors that may decrease the strength of evidence |
| 1. Poor quality of planning and implementation of available RCTs, suggesting high likelihood of bias |
| 2. Inconsistency of results, including problems with subgroup analyses |
| 3. Indirectness of evidence (differing population, intervention, control, outcomes, comparison) |
| 4. Imprecision of results |
| 5. High likelihood of reporting bias |
| Main factors that may increase the strength of evidence |
| 1. Large magnitude of effect (direct evidence, relative risk > 2 with no plausible confounders) |
| 2. Very large magnitude of effect with relative risk > 5 and no threats to validity (by two levels) |
| 3. Dose–response gradient |

*RCT* randomized controlled trial

**Table 4** Factors determining strong versus weak recommendation

| What should be considered | Recommended process |
|---|---|
| High or moderate evidence (is there high or moderate quality evidence?) | The higher the quality of evidence, the more likely a strong recommendation. |
| Certainty about the balance of benefits versus harms and burdens (is there certainty?) | The larger the difference between the desirable and undesirable consequences and the certainty around that difference, the more likely a strong recommendation. The smaller the net benefit and the lower the certainty for that benefit, the more likely a weak recommendation |
| Certainty in or similar values (is there certainty or similarity?) | The more certainty or similarity in values and preferences, the more likely a strong recommendation |
| Resource implications (are resources worth expected benefits?) | The lower the cost of an intervention compared to the alternative and other costs related to the decision–i.e., fewer resources consumed—the more likely a strong recommendation |

The GRADE system classifies recommendations as

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GUIDELINES

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

**Table 5** Recommendations: initial resuscitation and infection issues

A. Initial resuscitation
1. Protocolized, quantitative resuscitation of patients with sepsis-induced tissue hypoperfusion (defined in this document as hypotension persisting after initial fluid challenge or blood lactate concentration ≥4 mmol/L). Goals during the first 6 h of resuscitation:
   (a) Central venous pressure 8–12 mmHg
   (b) Mean arterial pressure (MAP) ≥ 65 mmHg
   (c) Urine output ≥ 0.5 mL $kg^{-1}$ h
   (d) Central venous (superior vena cava) or mixed venous oxygen saturation 70 or 65 %, respectively (grade 1C)
2. In patients with elevated lactate levels targeting resuscitation to normalize lactate as rapidly as possible (grade 2C)

B. Screening for sepsis and performance improvement
1. Routine screening of potentially infected seriously ill patients for severe sepsis to allow earlier implementation of therapy (grade 1C)
2. Hospital-based performance improvement efforts in severe sepsis (UG)

C. Diagnosis
1. Cultures as clinically appropriate before antimicrobial therapy if no significant delay (>45 min) in the start of antimicrobial(s) (grade 1C). At least 2 sets of blood cultures (both aerobic and anaerobic bottles) be obtained before antimicrobial therapy with at least 1 drawn percutaneously and 1 drawn through each vascular access device, unless the device was recently (<48 h) inserted (grade 1C)
2. Use of the 1,3 β-D-glucan assay (grade 2B), mannan and anti-mannan antibody assays (2C), if available and invasive candidiasis is in differential diagnosis of cause of infection.
3. Imaging studies performed promptly to confirm a potential source of infection (UG)

D. Antimicrobial therapy

D. Antimicrobial therapy

1. Administration of effective intravenous antimicrobials within the first hour of recognition of septic shock (grade 1B) and severe sepsis without septic shock (grade 1C) as the goal of therapy

2a. Initial empiric anti-infective therapy of one or more drugs that have activity against all likely pathogens (bacterial and/or fungal or viral) and that penetrate in adequate concentrations into tissues presumed to be the source of sepsis (grade 1B)

2b. Antimicrobial regimen should be reassessed daily for potential deescalation (grade 1B)

3. Use of low procalcitonin levels or similar biomarkers to assist the clinician in the discontinuation of empiric antibiotics in patients who initially appeared septic, but have no subsequent evidence of infection (grade 2C)

4a. Combination empirical therapy for neutropenic patients with severe sepsis (grade 2B) and for patients with difficult to treat, multidrug-resistant bacterial pathogens such as *Acinetobacter* and *Pseudomonas spp.* (grade 2B). For patients with severe infections associated with respiratory failure and septic shock, combination therapy with an extended spectrum beta-lactam and either an aminoglycoside or a fluoroquinolone is for *P. aeruginosa* bacteremia (grade 2B). A combination of beta-lactam and macrolide for patients with septic shock from bacteremic *Streptococcus pneumoniae* infections (grade 2B)

4b. Empiric combination therapy should not be administered for more than 3–5 days. De-escalation to the most appropriate single therapy should be performed as soon as the susceptibility profile is known (grade 2B)

5. Duration of therapy typically 7–10 days; longer courses may be appropriate in patients who have a slow clinical response, undrainable foci of infection, bacteremia with *S. aureus;* some fungal and viral infections or immunologic deficiencies, including neutropenia (grade 2C)

6. Antiviral therapy initiated as early as possible in patients with severe sepsis or septic shock of viral origin (grade 2C)

7. Antimicrobial agents should not be used in patients with severe inflammatory states determined to be of noninfectious cause (UG)

E. Source control

1. A specific anatomical diagnosis of infection requiring consideration for emergent source control be sought and diagnosed or excluded as rapidly as possible, and intervention be undertaken for source control within the first 12 h after the diagnosis is made, if feasible (grade 1C)

2. When infected peripancreatic necrosis is identified as a potential source of infection, definitive intervention is best delayed until adequate demarcation of viable and nonviable tissues has occurred (grade 2B)

3. When source control in a severely septic patient is required, the effective intervention associated with the least physiologic insult should be used (e.g., percutaneous rather than surgical drainage of an abscess) (UG)

4. If intravascular access devices are a possible source of severe sepsis or septic shock, they should be removed promptly after other vascular access has been established (UG)

F. Infection prevention

1a. Selective oral decontamination and selective digestive decontamination should be introduced and investigated as a method to reduce the incidence of ventilator-associated pneumonia; This infection control measure can then be instituted in health care settings and regions where this methodology is found to be effective (grade 2B)

1b. Oral chlorhexidine gluconate be used as a form of oropharyngeal decontamination to reduce the risk of ventilator-associated pneumonia in ICU patients with severe sepsis (grade 2B)

**Table 6** Recommendations: hemodynamic support and adjunctive therapy

G. Fluid therapy of severe sepsis

1. Crystalloids as the initial fluid of choice in the resuscitation of severe sepsis and septic shock (grade 1B).
2. Against the use of hydroxyethyl starches for fluid resuscitation of severe sepsis and septic shock (grade 1B).
3. Albumin in the fluid resuscitation of severe sepsis and septic shock when patients require substantial amounts of crystalloids (grade 2C).
4. Initial fluid challenge in patients with sepsis-induced tissue hypoperfusion with suspicion of hypovolemia to achieve a minimum of 30 mL/kg of crystalloids (a portion of this may be albumin equivalent). More rapid administration and greater amounts of fluid may be needed in some patients (grade 1C).
5. Fluid challenge technique be applied wherein fluid administration is continued as long as there is hemodynamic improvement either based on dynamic (e.g., change in pulse pressure, stroke volume variation) or static (eg, arterial pressure, heart rate) variables (UG).

H. Vasopressors

1. Vasopressor therapy initially to target a mean arterial pressure (MAP) of 65 mm Hg (grade 1C).
2. Norepinephrine as the first choice vasopressor (grade 1B).
3. Epinephrine (added to and potentially substituted for norepinephrine) when an additional agent is needed to maintain adequate blood pressure (grade 2B).
4. Vasopressin 0.03 units/minute can be added to norepinephrine (NE) with intent of either raising MAP or decreasing NE dosage (UG).
5. Low dose vasopressin is not recommended as the single initial vasopressor for treatment of sepsis-induced hypotension and vasopressin doses higher than 0.03-0.04 units/minute should be reserved for salvage therapy (failure to achieve adequate MAP with other vasopressor agents) (UG).
6. Dopamine as an alternative vasopressor agent to norepinephrine only in highly selected patients (eg, patients with low risk of tachyarrhythmias and absolute or relative bradycardia) (grade 2C).
7. Phenylephrine is not recommended in the treatment of septic shock except in circumstances where (a) norepinephrine is associated with serious arrhythmias, (b) cardiac output is known to be high and blood pressure persistently low or (c) as salvage therapy when combined inotrope/vasopressor drugs and low dose vasopressin have failed to achieve MAP target (grade 1C).
8. Low-dose dopamine should not be used for renal protection (grade 1A).
9. All patients requiring vasopressors have an arterial catheter placed as soon as practical if resources are available (UG).

I. Inotropic therapy

1. A trial of dobutamine infusion up to 20 micrograms/kg/min be administered or added to vasopressor (if in use) in the presence of (a) myocardial dysfunction as suggested by elevated cardiac filling pressures and low cardiac output, or (b) ongoing signs of hypoperfusion, despite achieving adequate intravascular volume and adequate MAP (grade 1C).
2. Not using a strategy to increase cardiac index to predetermined supranormal levels (grade 1B).

J. Corticosteroids

1. Not using intravenous hydrocortisone to treat adult septic shock patients if adequate fluid resuscitation and vasopressor therapy are able to restore hemodynamic stability (see goals for Initial Resuscitation). In case this is not achievable, we suggest intravenous hydrocortisone alone at a dose of 200 mg per day (grade 2C).
2. Not using the ACTH stimulation test to identify adults with septic shock who should receive hydrocortisone (grade 2B).
3. In treated patients hydrocortisone tapered when vasopressors are no longer required (grade 2D).
4. Corticosteroids not be administered for the treatment of sepsis in the absence of shock (grade 1D).
5. When hydrocortisone is given, use continuous flow (grade 2D).

Original Investigation | Caring for the Critically Ill Patient

November 1, 2016

# Effect of Hydrocortisone on Development of Shock Among Patients With Severe Sepsis

## The HYPRESS Randomized Clinical Trial

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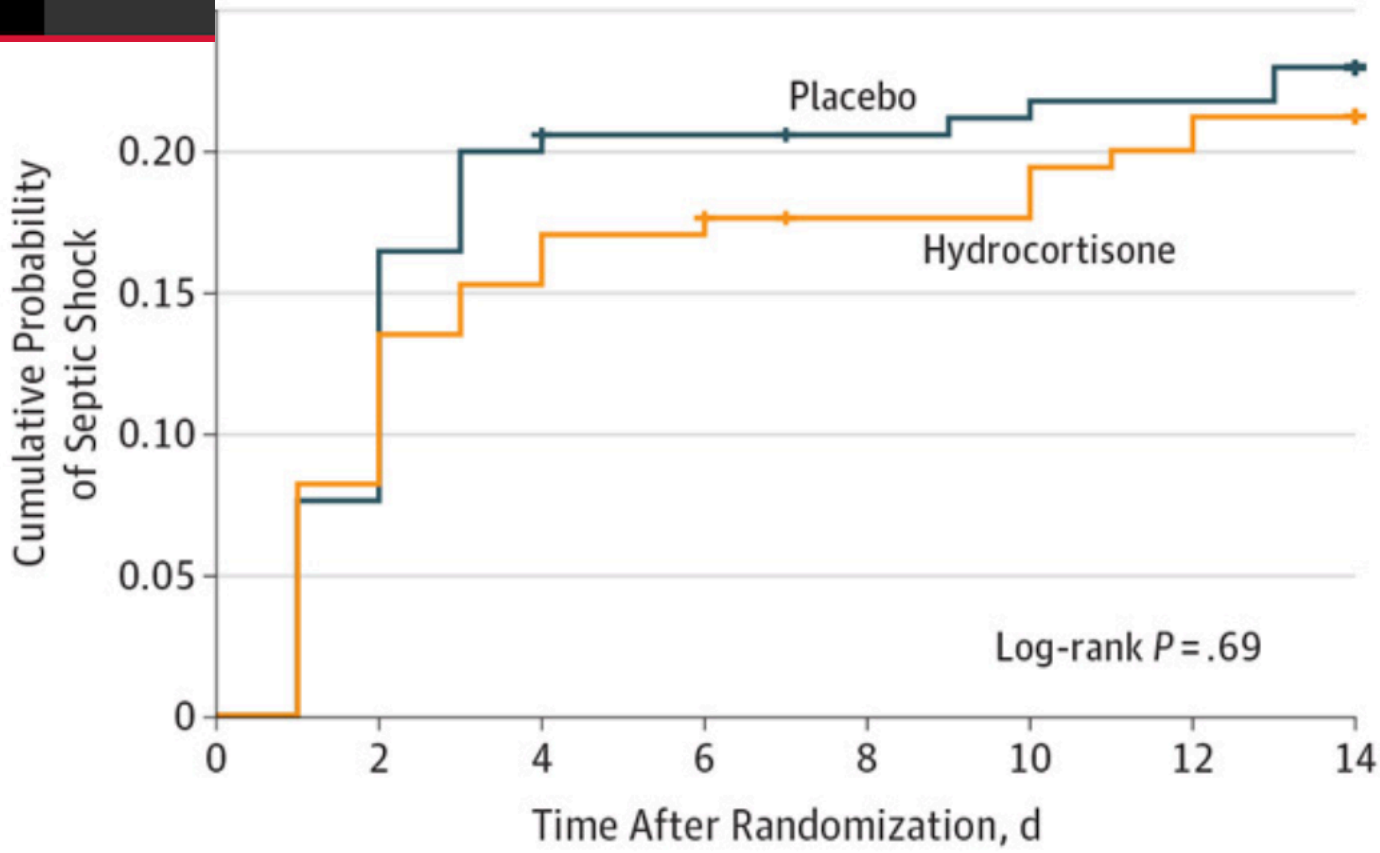
## Key Points

**Question** Does adjunctive early hydrocortisone therapy prevent the development of septic shock in patients with severe sepsis who are not in shock?

**Findings** In this randomized clinical trial that included 380 adults, occurrence of septic shock was not significantly different between patients who received hydrocortisone or placebo (21.2% vs 22.9%, respectively).

**Meaning** Administration of hydrocortisone did not prevent the development of shock in patients with severe sepsis.




| No. at risk | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Placebo | 176 | 161 | 139 | 136 | 134 | 131 | 130 | 128 |
| Hydrocortisone | 177 | 163 | 146 | 142 | 138 | 138 | 134 | 130 |

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SYSTEMATIC REVIEW

# Unexplained mortality differences between septic shock trials: a systematic analysis of population characteristics and control-group mortality rates

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## Abstract

**Purpose:** Although the definition of septic shock has been standardized, some variation in mortality rates among clinical trials is expected. Insights into the sources of heterogeneity may influence the design and interpretation of septic shock studies. We set out to identify inclusion criteria and baseline characteristics associated with between-trial differences in control group mortality rates.

**Methods:** We conducted a systematic review of RCTs published between 2006 and 2018 that included patients with septic shock. The percentage of variance in control-group mortality attributable to study heterogeneity rather than chance was measured by $I^2$. The association between control-group mortality and population characteristics was estimated using linear mixed models and a recursive partitioning algorithm.

**Results:** Sixty-five septic shock RCTs were included. Overall control-group mortality was 38.6%, with significant heterogeneity ($I^2 = 93\%$, $P < 0.0001$) and a 95% prediction interval of 13.5–71.7%. The mean mortality rate did not differ between trials with different definitions of hypotension, infection or vasopressor or mechanical ventilation inclusion criteria. Population characteristics univariately associated with mortality rates were mean Sequential Organ Failure Assessment score (standardized regression coefficient (β) = 0.57, P = 0.007), mean serum creatinine (β = 0.48, P = 0.007), the proportion of patients on mechanical ventilation (β = 0.61, P < 0.001), and the proportion with vasopressors (β = 0.57, P = 0.002). Combinations of population characteristics selected with a linear model and recursive partitioning explained 41 and 42%, respectively, of the heterogeneity in mortality rates.

**Conclusions:** Among 65 septic shock trials, there was a clinically relevant amount of heterogeneity in control group mortality rates which was explained only partly by differences in inclusion criteria and reported baseline characteristics.

**Keywords:** Septic shock, Heterogeneity, Clinical trials, Methodology, Meta-research, Machine learning

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## Introduction

The fundamental criteria from the consensus definitions of septic shock are used to select patients for inclusion in clinical studies [1–4]. While the mortality rate of septic shock was found to be 46% (95% confidence interval (CI) 43–50%) in a meta-analysis of observational cohorts [5], randomized controlled trials report more diverse numbers. For example, two high-profile septic shock trials published a year apart reported control group mortality rates as disparate as 16% [6] and 80% [7]. Despite the seemingly wide range of mortality rates there has not yet been a systematic inquiry into its patterns and possible causes.

Identifying the correct patient population to benefit from a specific therapy has been recognized as an essential condition for improving critical care research [8–10]. Yet large unexplained mortality differences among trials that all aim to include septic shock patients may hamper reproducibility and generalizability. Insights into the magnitude and sources of between-trial heterogeneity are therefore valuable in the design, reporting, and interpretation of septic shock trials. For example, incorrect prediction of baseline mortality rates has been identified as a major reason for negative critical care trials, as a discrepancy between expected and observed event rates often leads to underpowered studies [11].

We sought to quantify between-trial heterogeneity and identify inclusion criteria and population characteristics associated with differences in control group mortality rates.

## Methods

After a systematic search to identify all trials published in the past decade that aimed to include patients with septic shock, we used linear mixed models to estimate the total heterogeneity in control group mortality rates and its association with reported baseline characteristics. Using both a multivariate linear model and a machine learning algorithm, we estimated the proportion of heterogeneity that can be explained by population characteristics.

The review protocol was prospectively registered [12] and adheres to the PRISMA checklist [13], which is included in the electronic supplementary material (ESM). Study screening, application of the inclusion- and exclusion criteria and data-extraction were performed independently by two reviewers (HJdG and JP). Conflicting entries were resolved by consensus.

### Inclusion criteria and search strategy

PubMed, Embase, and the Cochrane Central Register of Controlled Trials were queried using the search term ["septic shock" AND (random* or rct)]. Embase was additionally queried using the search term "septic shock" with the randomized controlled trial filter activated. The queries were limited to publications from 1 January 2006 and the queries were last performed on 20 January 2018.

We limited the search to trials published between 2006 and 2018 as a compromise between the number of eligible studies and secular trends in clinical practice, research practice, and reporting standards. Publications from 2006 and later had sufficient lead time to incorporate the 2004 update of the Surviving Sepsis Campaign guidelines [4].

Eligible for inclusion were parallel-group randomized controlled trials with adult patients in septic shock according to the published consensus definitions or Surviving Sepsis Campaign guidelines [1, 2, 4]. Trials were excluded if the report was not written in English, if it was only available in abstract, if no baseline characteristics were reported, or if no mortality outcome was reported. Trials that aimed to include a specific subcategory of septic shock patients (e.g. "septic shock patients requiring renal replacement therapy") were also excluded, as these would be a major source of between-trial heterogeneity.

### Identification of the control group and variables of interest

Because the nature of the randomized intervention could contribute to heterogeneity, we focused on the control groups. For each trial, we identified the control group as defined by the authors as 'control group', 'usual care group', or a variation thereof. When no control group could be identified (in a comparison of two usual care therapies) we defined the control group as the means of the two groups in terms of sample size, mortality, and baseline characteristics. A sensitivity analysis was performed towards this construct by analyzing whether trials with and without specifically defined control groups differed in terms of mean mortality or the amount of between-trial heterogeneity.

For each trial, we recorded the type of intervention, single- or multicenter design, and the primary endpoint. Trials were graded according to the Jadad scale [14]. For the control group in each trial, we recorded the sample size, the reported baseline characteristics, and the mortality rates.

### Estimation of heterogeneity in mortality rates and associations with population characteristics

We used 28-day mortality throughout all analyses. For trials that did not report this outcome, we estimated 28-day mortality based on reported hospital, ICU, or 90-day mortality using linear regression with data from trials that reported both 28-day and another mortality measure.

To analyze mortality rates across trials we used a random-effects meta-regression model with the log odds of

mortality as dependent variable and a random intercept for each study. Each trial was weighted by the inverse of the sampling variance of the mortality rates. A maximum likelihood estimator was used to estimate the mean mortality (random effects pooled estimate), the between-study standard deviation due to heterogeneity ($\tau$), and the percentage of variation due to heterogeneity rather than change ($I^2$). To quantify between-trial heterogeneity, we report the 95% prediction interval (mean mortality $\pm$ 1.96 $\tau$), which represents the distribution of estimated future mortality rates based on observed mortalities weighted by sampling variance (trial size) and corrected for random chance [15]. In the absence of between-study heterogeneity, the 95% prediction interval is equal to the 95% confidence interval, but when significant heterogeneity is present the prediction interval estimates the bandwidth of expected mortality rates from similar studies [15, 16]. In other words, the 95% prediction interval can be thought of as the estimate of true between-study distribution of mortality rates. The prediction interval can therefore be used to guide power calculations for future studies [16].

The between-trial heterogeneity in mortality rates was calculated for subcategories of trials employing different inclusion criteria: confirmed or suspected infection; confirmed infection only; different definitions of hypotension; mandatory hyperlactatemia; mandatory vasopressor therapy; and mandatory mechanical ventilation. Differences in mortality rates between subcategories were calculated by addition of dummy variables to the mixed-effects model.

To estimate the association between study and population characteristics and mortality, these variables were added to the model as covariates. Residuals were checked for normality with Q–Q plots, and the goodness of fit of the log-linear model was compared with quadratic and power models by selecting the model with the lowest Akaike information criterion (AIC). To facilitate comparisons between variables, we report standardized regression coefficients ($\beta$) and the proportion of between-trial variability in mortality explained by the population variable (unadjusted $R^2$) for all univariate analyses.

#### Predicting mortality rates using a linear model and recursive partitioning

We then constructed a comprehensive model to predict between-study differences in mortality. Population variables that were reported by at least 25% of the included trials with a univariate regression $R^2 \geq 0.10$ were included as regressors in a multivariate model and removed in a stepwise manner for P values $\geq 0.05$. The threshold $R^2$ of 0.10 was a compromise between the number of variables and the limited number of observations. This model selection process was not prospectively protocolized as the number of eligible variables could not be estimated a priori. Multiple imputation (generating 20 datasets) with predictive mean matching was used for missing observations (i.e., missing population characteristics). The imputation methods are further described in section 7 of the ESM.

As a complementary approach to predict 28-day mortality rates from population characteristics, we constructed a regression tree model based on recursive partitioning (a machine learning algorithm) [17, 18] for its ability to handle partially missing observations (obviating the need for imputation) and its robustness to nonlinear relations. We set up the model to predict 28-day mortality based on all inclusion criteria and population characteristics. In short, the recursive partitioning algorithm selected the most informative variable, which was then 'split' at the value that best differentiates low from high mortality. The algorithm then selected the most informative variable for each of the two resulting subgroups, and split it again. When a splitting variable was missing for a specific trial, a surrogate variable (the variable most closely correlated to the splitting variable) was used. After multiple splits, this recursive partitioning resulted in a regression tree (similar to a decision tree) with subgroups of trials ranked from low to high expected mortality. $R^2$ represents the variance in mortality explained by the decision tree. Overfitting was examined using the cross-validated error.

For all analyses, $P < 0.05$ was considered significant. The analyses were performed in *R* version 3.4.2 using the *metafor*, *mice* and *rpart* packages [19–21].

## Results

#### Characteristics of the included trials

The search resulted in 65 trials that met all inclusion and exclusion criteria (eFigure 1 in the ESM), representing a total of 8634 control group patients [6, 7, 22–84]. A list of excluded trials is available in the ESM. The trial characteristics are presented in Table 1.

Twenty trials (31%) did not report 28-day mortality but only hospital mortality, ICU mortality, or 90-day mortality. Using trials that reported multiple mortality measures, 28-day mortality was estimated as a linear function of hospital mortality, ICU mortality, or 90-day mortality ($R^2$ values 0.99, 0.98, and 0.98, respectively). The estimates and validation plots are presented in eTable 1 and eFigure 2 of the ESM.

In 14 trials (21%) the control group could not be identified because two usual care therapies were compared. For these trials, the control group characteristics and mortality rates were defined as the means of the two treatment

**Table 1 Characteristics of included trials**

| | No. (%) or median (IQR) |
|---|---|
| Number of included trials | 65 |
| Control group sample size: median (IQR) | 34 (20–100) |
| Multicenter trials: n (%) | 28 (43) |
| Trial country: n (%) | |
| France | 12 (18) |
| China | 9 (14) |
| Italy | 8 (12) |
| USA | 6 (9) |
| India | 3 (5) |
| The Netherlands | 3 (5) |
| UK | 3 (5) |
| Other countries (1 each) | 13 (20) |
| Multinational trials | 9 (14) |
| Trial intervention: n (%) | |
| Drug | 44 (68) |
| Treatment bundle | 14 (21) |
| Device | 7 (11) |
| Primary endpoint: n (%) | |
| Mortality | 21 (32) |
| Other | 32 (49) |
| Not specified | 12 (18) |
| Jadad scale: median (IQR) | 3 (2–4) |
| Jadad scale components: n (%) | |
| Randomization | 65 (100) |
| Randomization appropriate | 45 (69) |
| Blinding | 23 (35) |
| Blinding appropriate | 19 (29) |
| Description of withdrawals and dropouts | 42 (65) |

*IQR* Interquartile range

groups. None of these 14 trials reported significant mortality differences between the treatment groups.

### The distribution of mortality rates

The control group mortality rates ranged between 13.8 and 84.6%, with a random-effects estimated mean mortality rate of 38.6%. There was significant heterogeneity among trials ($I^2 = 93\%$, $\tau = 0.710$, $p < 0.0001$), and the 95% prediction interval was 13.5–71.7%.

Figure 1 shows the mortality rates of trials categorized by inclusion criteria. The mean mortality rate did not differ between trials with different definitions of hypotension, infection (confirmed vs. suspected), or vasopressor or mechanical ventilation inclusion criteria. There were no significant differences in mean mortality rate or in heterogeneity between large vs. small trials, monocenter vs. multicenter trials, unblinded vs blinded trials, high-quality trials vs. low-quality trials, or trials with vs. without a specifically defined control group (eTable 2 in the ESM).

The exclusion criteria employed in the trials were too diverse for statistical analysis, but the total number of exclusion criteria (ranging from 0 to 30) was inversely associated with the mortality rate ($\beta = -0.375$, $R^2 = 0.14$, $P = 0.007$).

The heatmap in Fig. 2 provides an overview of the between-trial differences in mortality rates and population characteristics. The log-linear associations between the mortality rate and reported control group baseline characteristics are presented in Table 2 (goodness-of-fit statistics are reported in eTable 3 in the ESM). There was no significant decrease in mortality over the period 2006–2018, with only ($R^2$) 4% of heterogeneity explained by the year of publication (Table 2, eFigure 3). Baseline variables that were univariately associated with mortality were: mean Sequential Organ Failure Assessment (SOFA) score, the proportion of patients on mechanical ventilation, the proportion of patients on vasopressors, and mean serum creatinine. Regression plots of selected associations are shown in eFigure 3 of the ESM.

### Predicting mortality rates from population characteristics

Details of the variable selection process for the multivariate model are available in section 7 of the ESM. Significant independent variables in the final multivariate model were: baseline mean SOFA score ($\beta = 0.39$, standardized standard error (SSE) = 0.17, $P = 0.019$), the proportion of patients on mechanical ventilation ($\beta = 0.42$, SSE = 0.18, $P = 0.019$), and mean serum creatinine ($\beta = 0.31$, SSE = 0.10, $P = 0.0015$). The multivariate model $R^2$ was 0.41 with significant residual heterogeneity ($I^2 = 82\%$, $\tau = 0.544$, $P < 0.0001$). Figure 3 shows the predicted and actual mortality rates of the included trials.

The recursive partitioning algorithm resulted in a regression tree with the following variables as informative determinants of the mortality rate: mean age (split at 64.8 years); the proportion of patients with a respiratory infection (split at 54.5%); the proportion of patients on mechanical ventilation (split at 74.3%); and the proportion of male patients (splits at 63.8 and 53.8%). The $R^2$ value of the regression tree was 0.42. The cross-validated relative error decreases to below the root (split 0) value, which indicates that the tree was not overfitted. The results from the regression tree analysis are further described in eFigures 4 and 5 of the ESM (section 7).

## Discussion

In this analysis of 65 septic shock trials published in the past decade, we found a statistically significant and clinically relevant amount of heterogeneity in control group mortality rates. The mean mortality rate was 38.6% with

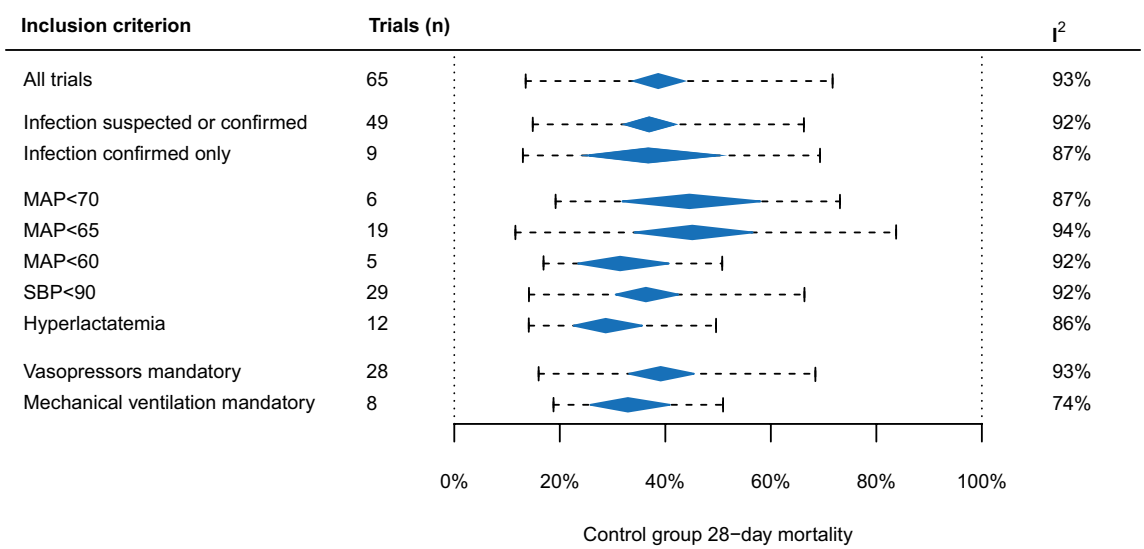


**Fig. 1** Control-group mortality rates categorized by trial inclusion criteria. The diamonds represent the mean mortality rates and 95% confidence intervals. The 95% prediction intervals (dashed lines) represents the estimated between-trial variability in mortality rates after adjusting for random chance and sample size. $I^2$ represents the proportion of between-trial variability that cannot be explained by chance. There were no significant differences in mean mortality rates between inclusion criteria. *MAP* mean arterial pressure, *SBP* systolic blood pressure

estimated 95% prediction limits of 13.5–71.7%, revealing a wide range in underlying mortality rates after discounting the effects of random change and small trials.

In contrast to findings from large observational studies that the mortality of sepsis has decreased in the past decade, we found only a small nonsignificant decline in the period 2006–2018 [85, 86]. Different inclusion definitions of septic shock did not affect mean mortality rates, but a higher total number of exclusion criteria was associated with lower mortality. We used three statistical methods to analyze the association between population characteristics and mortality.

The univariate associations reflect how the reader of a trial report could interpret the population characteristics in relation to the mortality rate, and shows that the proportion of ventilated patients, mean SOFA score, and the proportion of patients on vasopressor support were most informative (i.e. have highest standardized regression coefficients).

The multivariate linear model (with missing observations imputed) shows which combinations of characteristics were predictive of mortality if all trials hypothetically reported the same variables. A combination of three independently significant characteristics (mean SOFA score, proportion of ventilated patients, and mean creatinine) explained only 41% of the heterogeneity in mortality rates across trials.

The recursive partitioning algorithm, which is not limited by dependence on multiple imputation and the assumption of linearity, shows which characteristics were most informative, given that different trials report different characteristics. The resulting regression tree explained only 42% of the heterogeneity in mortality.

The linear model and the regression tree arrived at different predictor variables because the linear model is biased towards more informative linear associations, while the regression tree allows for nonlinear relations and is biased towards variables with less missing data.

In all, these results indicate that there are clinically significant between-trial differences in control group mortality rates, and that these differences are not associated with differences in inclusion criteria and only weakly associated with reported baseline characteristics. Visual inspection of the heatmap (Fig. 2) shows that there are no unambiguous patterns in the relation between population characteristics and mortality rates. This heterogeneity is reflected in our finding that different statistical methods result in different predictive variables.

### Possible sources of residual heterogeneity

Residual heterogeneity among trials may be caused by population differences in nutrition and socio-economic status, heterogenous exclusion criteria, incomplete reporting, between-trial differences in variable definitions, the timing of randomization, and differences in post-randomization co-interventions and standards of care.

We found that no single measure of chronic comorbidity was reported in more than 40% of the included trials and that characteristics of causative pathogens were

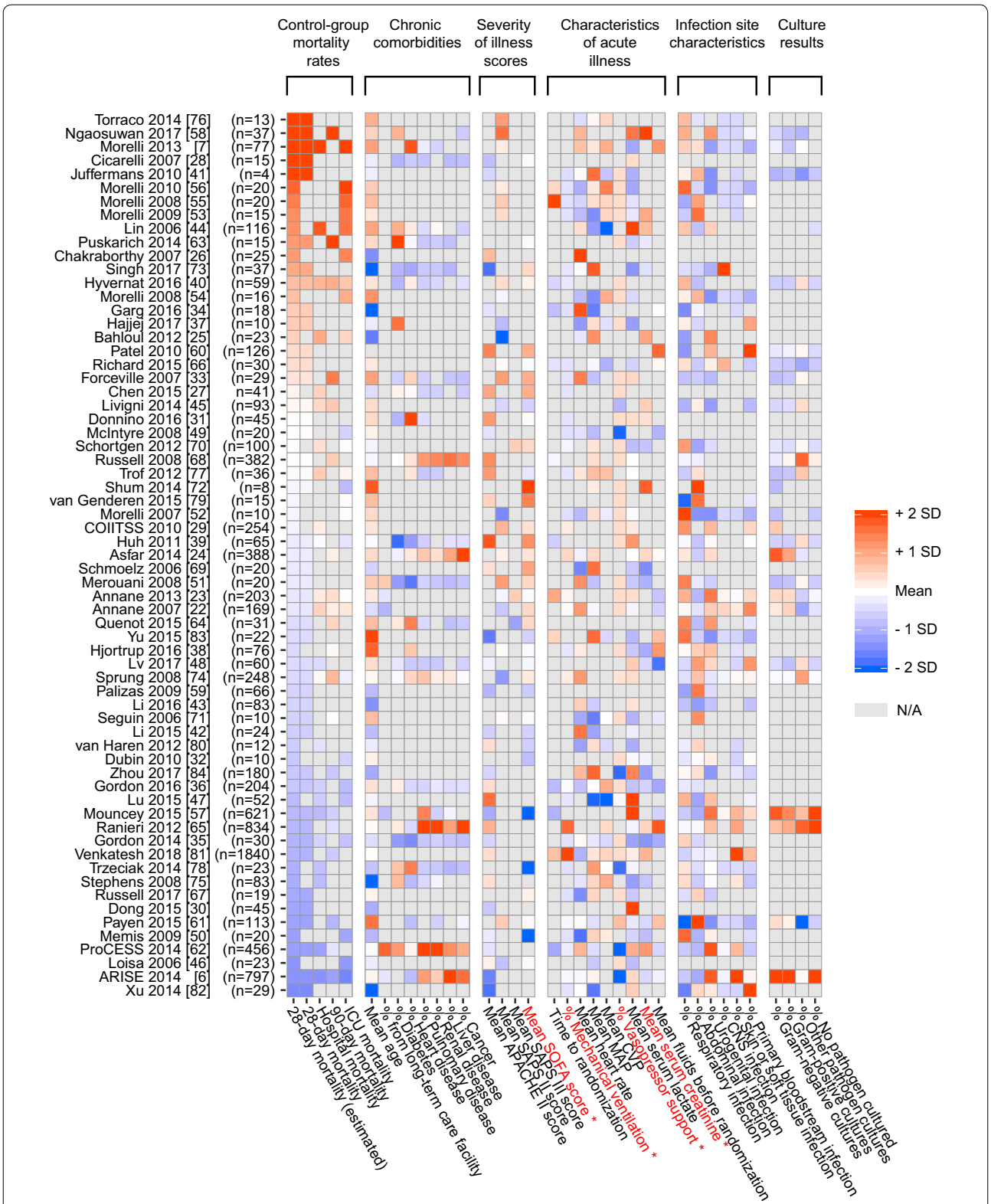


**Fig. 2** Heatmap of included trials (n = 65) and associated baseline characteristics, ranked by decreasing mortality rates. White tiles represent the mean value across trials, while red and blue tiles are indicative of higher and lower than average values, respectively. Gray tiles (N/A) are variables that were not reported. The 28-day mortality rate ranged between 13.8 and 84.6%, with a mean of 38.6%. *APACHE* Acute Physiology and Chronic Health Evaluation, *SAPS* Simplified Acute Physiology Score, *SOFA* Sequential Organ Failure Assessment score, *MAP* mean arterial pressure, *CVP* central venous pressure, *CNS* central nervous system. (Asterisk) Variables with a significant univariate association with 28-day mortality

**Table 2 Univariate associations between mortality rates and reported mean or median population characteristics**

| | Trials reporting variable (% of n = 56) | Mean (SD) | Standardized regression coefficient β ($R^2$) | P value |
|---|---|---|---|---|
| Publication year | 65 (100) | 2013.3 (3.58) | − 0.19 (0.04) | 0.197 |
| Age, years | 64 (98) | 62.9 (3.80) | 0.18 (0.03) | 0.160 |
| Male patients % | 63 (97) | 60.5 (5.80) | 0.02 (0.00) | 0.927 |
| Comorbidity characteristics | | | | |
| Charlson Comorbidity Index | 5 (8) | 1.90 (1.11) | 0.52 (0.27) | 0.183 |
| From long-term care facility % | 6 (9) | 5.8 (5.6) | 0.44 (0.20) | 0.312 |
| McCabe class I % | 6 (9) | 34.1 (15.2) | − 0.40 (0.16) | 0.374 |
| McCabe class II % | 6 (9) | 14.7 (12.9) | 0.02 (0.00) | 0.948 |
| McCabe class III % | 4 (6) | 16.2 (15.0) | 0.71 (0.50) | 0.120 |
| Diabetes mellitus % | 23 (36) | 24.4 (6.88) | 0.01 (0.00) | 0.856 |
| Heart failure or coronary disease % | 26 (40) | 20.7 (8.7) | 0.33 (0.11) | 0.133 |
| Chronic obstructive pulmonary disease % | 25 (39) | 15.1 (6.3) | 0.04 (0.00) | 0.911 |
| Chronic renal disease % | 21 (33) | 7.6 (5.0) | 0.06 (0.00) | 0.773 |
| Chronic liver disease % | 17 (26) | 5.5 (2.8) | 0.25 (0.06) | 0.320 |
| Cancer % | 20 (31) | 21.2 (8.1) | 0.19 (0.03) | 0.426 |
| Severity of illness scores | | | | |
| APACHE II score | 33 (51) | 22.5 (3.65) | 0.21 (0.05) | 0.376 |
| APACHE III score | 1 (2) | – | – | – |
| APACHE IV score | 1 (2) | – | – | – |
| SAPS II score | 24 (37) | 55.7 (4.42) | 0.36 (0.13) | 0.079 |
| SAPS III score | 3 (4) | 77.6 (1.91) | 0.01 (0.00) | 0.644 |
| SOFA score | 37 (58) | 9.59 (2.47) | 0.57 (0.33) | 0.007** |
| Characteristics of acute illness | | | | |
| Medical (non-surgical) % | 22 (34) | 69.7 (13.1) | 0.26 (0.07) | 0.314 |
| Time from diagnosis to randomization, hours | 13 (20) | 13.77 (8.84) | 0.47 (0.22) | 0.069 |
| Mechanical ventilation % | 33 (51) | 78.1 (28.3) | 0.61 (0.38) | 0.0005*** |
| Heart rate, 1/min | 39 (60) | 104 (8.8) | 0.13 (0.02) | 0.435 |
| Mean arterial pressure, mmHg | 43 (66) | 70.7 (6.65) | 0.06 (0.00) | 0.561 |
| Central venous pressure, mmHg | 22 (34) | 11.2 (2.21) | 0.17 (0.03) | 0.425 |
| Vasopressor support % | 38 (58) | 84.6 (30.0) | 0.57 (0.32) | 0.0019** |
| Serum lactate, mmol/l | 52 (80) | 4.00 (1.28) | − 0.13 (0.02) | 0.389 |
| Serum creatinine, µmol/l | 26 (40) | 168 (31.1) | 0.48 (0.23) | 0.007** |
| Fluids before randomization, ml | 19 (30) | 3209 (1637) | 0.31 (0.10) | 0.194 |
| Infection site characteristics | | | | |
| Respiratory % | 53 (82) | 42.6 (13.7) | 0.27 (0.08) | 0.087 |
| Abdominal % | 51 (78) | 24.0 (15.0) | 0.06 (0.00) | 0.686 |
| Urogenital % | 41 (63) | 11.3 (5.7) | − 0.27 (0.07) | 0.094 |
| Central nervous system % | 19 (30) | 1.2 (1.6) | 0.03 (0.00) | 0.885 |
| Skin and soft tissue % | 28 (43) | 6.8 (3.6) | − 0.09 (0.01) | 0.803 |
| Bloodstream % | 32 (49) | 12.9 (8.2) | − 0.11 (0.01) | 0.487 |
| Pathogen characteristics | | | | |
| Gram-negative % | 25 (39) | 32.0 (16.1) | 0.41 (0.17) | 0.0573 |
| Gram-positive % | 22 (34) | 24.6 (7.12) | − 0.41 (0.17) | 0.083 |
| Other pathogen % | 22 (34) | 44.0 (23.3) | − 0.13 (0.02) | 0.473 |
| Culture negative % | 18 (28) | 29.4 (8.3) | − 0.38 (0.14) | 0.085 |

Univariate associations between control group mortality rate and commonly reported mean baseline characteristics. Associations were estimated using a weighted random-effects model with mortality on the log-odds scale. Some baseline characteristics were reported by a minority of trials, which resulted in low power to detect a significant association. $R^2$ can be interpreted as the proportion of heterogeneity that is explained by the population characteristic for the n trials that report that characteristic

*APACHE* Acute Physiology and Chronic Health Evaluation score, *SAPS* Simplified Acute Physiology score, *SOFA* Sequential Organ Failure Assessment score

reported in only 28–39% of trials. This compromised the power of our analysis to detect associations across all trials, but, more importantly, it also prevents readers of trial reports from evaluating and comparing populations among trials and from judging to what extent a trial population corresponds to the population under their care.

Another source of heterogeneity is the imprecise definition of many variables. It is unclear whether a variable like 'pre-existing kidney disease' in one trial has the same meaning as 'chronic renal insufficiency' in another trial. Minor variations in variable definitions and data capture methods have been shown to lead to significantly different septic shock populations and to inter-observer variability in severity-of-illness scoring systems [5, 87, 88]. The importance of this 'fine print' in defining a population does not receive due attention in the methods section of most trials.

The time of inclusion may be an additional source of heterogeneity. Patients recruited later after the diagnosis of septic shock have not responded to treatment in an earlier phase and are therefore likely to have a worse prognosis. Only 13 trials reported the time from diagnosis to randomization, and for those trials it explained 22% of the heterogeneity.

While we have focused on inclusion criteria and baseline characteristics, the prognosis of septic shock may be largely influenced by post-randomization standards of care and co-interventions. Unfortunately, co-interventions and (control group) treatment standards are often described as 'according to the Surviving Sepsis Campaign guidelines' or not discussed at all in trial reports. Variables describing important post-randomization interventions, such as red blood cell transfusions, vasopressor dose, or fluid balance were recently found to be reported in only 33, 17, and 13% of large septic shock trials, respectively [89].

We did not analyze the association between trial countries and the mortality rate because many countries are represented by a single trial in the present sample. Nevertheless, between-country differences in standards of care or access to early healthcare may account for part of the residual heterogeneity. Large international observational studies are a more appropriate instrument for the investigation of differences in mortality rates among countries.

#### Implications for investigators and clinicians

Clinicians demand of clinical trials that they are relevant, reproducible, and generalizable to a clearly defined patient population. The results of this study indicate that many of the baseline characteristics upon which clinicians rely to gauge the applicability of trial results to their practice are in fact only weakly or not at all associated with mortality outcomes across trials.

The association between the number of exclusion criteria and mortality suggests that many seemingly inconsequential criteria together may have a significant effect on the composition of a trial population. Investigators should therefore be aware of this phenomenon in the design phase of a trial, as it affects the generalizability and external validity of trial results.

The wide prediction limits of control-group mortality have consequences for sample size calculations. Detecting a relative risk reduction of 25% with 80% power requires 245 patients if mortality is estimated to be 71.7%, while it requires 795 patients if control group mortality is 38.6% or 2980 patients if mortality is 13.5%. In practice, misestimation of the mortality rate by more than 7.5% occurred in 65% of critical care trials [11]. We therefore suggest that sample size calculations should not be based on the mean of reported control-group mortality rates in the literature but should be robust towards a wider range of expected event rates.

Reproducibility and generalizability also require a common phenomenological structure with respect to diagnostic definitions, inclusion criteria, patient characteristics, concomitant treatment, and outcomes. A recent review of large septic shock trials found that only half of the information deemed necessary for evaluation of the control group was reported in the investigated trials [89]. In the present study, we now find that many of the reported characteristics are not associated with control-group mortality rates, possibly due to variations in variable definitions.

The third consensus definitions for sepsis and septic shock were partly developed to harmonize the inclusion criteria for clinical studies [3]. We were unable to analyze a subset of trials with populations that might fit the Sepsis-3 septic shock definition, as none of the included trials employed both delta SOFA score and vasopressor inclusion criteria. We do note that SOFA score is independently associated with mortality rates, although baseline SOFA explains only 33% ($R^2$) of the variation in mortality rates in the 37 trials that report it. Furthermore, we found significant heterogeneity within subsets of trials employing similar inclusion criteria (Fig. 2).

We suggest that an international consensus is necessary to standardize variable definitions, data collection, and reporting of patient characteristics and outcomes for sepsis trials, as has been proposed before [89–92]. The feasibility of harmonizing study protocols has been demonstrated in three large trials investigating early goal-directed therapy [93]. The present results indicate that SOFA score, the proportion of ventilated patients, and creatinine independently reflect baseline risk across trials and should therefore be reported for each trial.

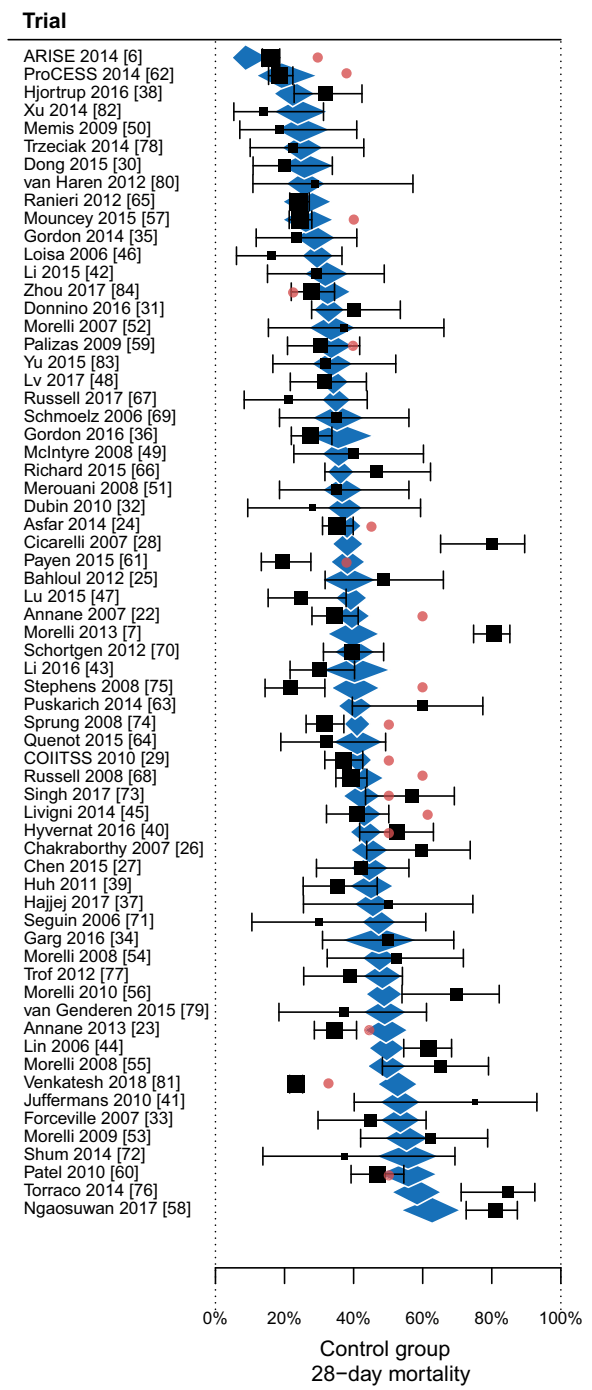


**Fig. 3** Included trials ordered by predicted control group mortality rate (diamonds). The predicted mortality rates were based on a multivariate weighted random-effects regression model with baseline mean Sequential Organ Failure Assessment (SOFA) score, the proportion of patients on mechanical ventilation, and mean serum creatinine as significant independent variables. The squares and brackets are the observed control-group mortality rates with 95% confidence interval. The figure illustrates that the model explained ($R^2$) 41% of the variability in mortality rates, with significant residual heterogeneity ($P < 0.0001$). The red dots are the reported a-priori expected mortality rates used for sample size calculations

The results from this study also support the practice of data sharing, as we have shown that aggregated population characteristics are less informative than expected. Sharing individual patient data will not only increase the power to detect treatment effects across multiple studies but can also be used to test the generalizability of trial results vis-à-vis large cohorts with septic shock.

### Strengths and limitations

This study was performed with a prospectively registered protocol and analysis plan. We chose to include only trials published between 2006 and 2018 to minimize the influence of long-term secular trends in septic shock diagnosis, treatment, and mortality [94, 95]. The search strategy was broad and comprehensive, but we excluded 40 trial reports not written in English, which compromised power and generalizability. We excluded trials that recruited only septic shock patients with specific organ dysfunction (such as kidney or liver failure) to rule out this source of between-trial heterogeneity.

For 20 trials, 28-day mortality was estimated using another reported mortality rate. Although the prediction equations were very precise ($R^2$ values $\geq 0.98$), we cannot rule out the possibility that this influenced the results. Excluding these 20 trials would have eroded the power of the study.

Importantly, using study-level data means that, to avoid the ecological fallacy, we cannot make inferences about predictive characteristics at the individual patient level, although several predictor variables are known to be individually associated with mortality (e.g. high SOFA score as a risk factor [96, 97]).The fact that there was substantial variation in the reporting of baseline variables was an important finding in itself, but also limited our power to detect associations across trials. A more in-depth investigation into the heterogeneity among trial populations would require individual patient data, but we think that obtaining such data would lead to significant selection bias.

## Conclusion

Septic shock is a syndrome with various etiologies, biochemical characteristics, and phenotypes [9, 98]. Onto this inherently heterogeneous syndrome, a layer of investigator-induced heterogeneity is added when trials employ different inclusion criteria, report different variables, and use different variable definitions. This compounded complexity causes heterogeneity among trial populations that may go unnoticed. We have shown that control-group mortality rates are very dissimilar across trials, and that the majority of this heterogeneity remains unexplained after accounting for reported population characteristics. The lack of standardized reporting

limits the usefulness of the variables explaining the mortality differences found in this study. In all, the substantial between-trial heterogeneity limits the reproducibility and generalizability of septic shock research and may inhibit the discovery of beneficial therapies for specific (sub)populations. The findings of this study therefore strongly support the argument for profound standardization and harmonization of septic shock trial reporting as well as data-sharing policies to test the external validity of trial populations.

**Electronic supplementary material**
The online version of this article (https://doi.org/10.1007/s00134-018-5134-8) contains supplementary material, which is available to authorized users.

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**Author contributions**
HJdG and AG designed the study. HJdG and JP performed the study screening and extracted the data. HJdG performed the statistical analyses. SL, HO, and AG provided technical, material, and administrative support. HJdG drafted the manuscript. JP, SL, JJP, HO and AG revised the manuscript for important intellectual content.

**Compliance with ethical standards**

**Conflicts of interest**
All authors declare that they have no conflicts of interest.



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**References**

1. Bone RC, Balk RA, Cerra FB et al (1992) Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. The ACCP/SCCM Consensus Conference Committee. American College of Chest Physicians/Society of Critical Care Medicine. Chest 101:1644–1655
2. Levy MM, Fink MP, Marshall JC et al (2003) 2001 SCCM/ESICM/ACCP/ATS/SIS international sepsis definitions conference. Intensive Care Med 29:530–538. https://doi.org/10.1007/s00134-003-1662-x
3. Singer M, Deutschman CS, Seymour CW et al (2016) The third international consensus definitions for sepsis and septic shock (sepsis-3). JAMA 315:801–810. https://doi.org/10.1001/jama.2016.0287
4. Dellinger RP, Carlet JM, Masur H et al (2004) Surviving sepsis campaign guidelines for management of severe sepsis and septic shock. Intensive Care Med 30:536–555. https://doi.org/10.1007/s00134-004-2210-z
5. Shankar-Hari M, Phillips GS, Levy ML et al (2016) Developing a new definition and assessing new clinical criteria for septic shock: for the third international consensus definitions for sepsis and septic shock (sepsis-3). JAMA 315:775–787. https://doi.org/10.1001/jama.2016.0289
6. ARISE Investigators, ANZICS Clinical Trials Group, Peake SL et al (2014) Goal-directed resuscitation for patients with early septic shock. N Engl J Med 371:1496–1506. https://doi.org/10.1056/nejmoa1404380
7. Morelli A, Ertmer C, Westphal M et al (2013) Effect of heart rate control with esmolol on hemodynamic and clinical outcomes in patients with septic shock: a randomized clinical trial. JAMA 310:1683–1691. https://doi.org/10.1001/jama.2013.278477
8. Vincent J-L, Hall JB, Slutsky AS (2015) Ten big mistakes in intensive care medicine. Intensive Care Med 41:505–507. https://doi.org/10.1007/s00134-014-3570-7
9. Marshall JC (2014) Why have clinical trials in sepsis failed? Trends Mol Med 20:195–203. https://doi.org/10.1016/j.molmed.2014.01.007
10. Opal SM, Dellinger RP, Vincent J-L et al (2014) The next generation of sepsis clinical trial designs: what is next after the demise of recombinant human activated protein C? Crit Care Med 42:1714–1721. https://doi.org/10.1097/CCM.0000000000000325
11. Harhay MO, Wagner J, Ratcliffe SJ et al (2014) Outcomes and statistical power in adult critical care randomized trials. Am J Respir Crit Care Med 189:1469–1478. https://doi.org/10.1164/rccm.201401-0056CP
12. de Grooth HJ, Oudemans-van Straaten HM, Girbes AR (2016) Heterogeneity in a decade of septic shock RCTs: a systematic analysis of mortality outcomes. PROSPERO 2016 CRD42016049330. https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=49330. Accessed 3 Nov 2016
13. Moher D, Liberati A, Tetzlaff J et al (2009) Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ 339:b2535
14. Jadad AR, Moore RA, Carroll D et al (1996) Assessing the quality of reports of randomized clinical trials: is blinding necessary? Control Clin Trials 17:1–12. https://doi.org/10.1016/0197-2456(95)00134-4
15. Deeks JJ, Higgins JPT, Altman DG (2011) Section 9.5: heterogeneity. Cochrane handbook for systematic reviews of interventions version 5.1.0 (updated March 2011)
16. IntHout J, Ioannidis JPA, Rovers MM, Goeman JJ (2016) Plea for routinely presenting prediction intervals in meta-analysis. BMJ Open 6:e010247. https://doi.org/10.1136/bmjopen-2015-010247
17. Breiman L, Friedman J, Olshen R, Stone C (1984) Classification and regression trees. CRC Press, Boca Raton, Florida, USA
18. Atkinson EJ, Therneau TM (2017) An introduction to recursive partitioning using the RPART routines. Mayo Found, Rochester, Minnesota, USA
19. Viechtbauer W (2010) Conducting meta-analyses in R with the metafor package. J Stat Softw. https://doi.org/10.18637/jss.v036.i03
20. Van Buuren S, Groothuis-Oudshoorn K (2011) mice: Multivariate imputation by chained equations in R. J Stat Softw 45:1–67. https://doi.org/10.18637/jss.v045.i03
21. Therneau T, Atkinson B, Ripley B (2017) rpart: recursive partitioning and regression trees. R Packag. version 4.1-11
22. Annane D, Vignon P, Renault A et al (2007) Norepinephrine plus dobutamine versus epinephrine alone for management of septic shock: a randomised trial. Lancet (London, England) 370:676–684. https://doi.org/10.1016/s0140-6736(07)61344-0
23. Annane D, Timsit J-F, Megarbane B et al (2013) Recombinant human activated protein C for adults with septic shock: a randomized controlled trial. Am J Respir Crit Care Med 187:1091–1097. https://doi.org/10.1164/rccm.201211-2020OC
24. Asfar P, Meziani F, Hamel J-F et al (2014) High versus low blood-pressure target in patients with septic shock. N Engl J Med 370:1583–1593. https://doi.org/10.1056/NEJMoa1312173
25. Bahloul M, Chaari A, Ben Mbarek MN et al (2012) Use of heptaminol hydrochloride for catecholamine weaning in septic shock. Am J Ther 19:e8–e17. https://doi.org/10.1097/MJT.0b013e3181e9b630
26. Chakraborty A, Mathur S, Dhunna R (2007) Comparison of norepinephrine and dopamine in the management of septic shock using impedance cardiography. Indian J Crit Care Med 11:186. https://doi.org/10.4103/0972-5229.37713
27. Chen C, Kollef MH (2015) Targeted fluid minimization following initial resuscitation in septic shock: a pilot study. Chest 148:1462–1469. https://doi.org/10.1378/chest.15-1525
28. Cicarelli DD, Vieira JE, Benseñor FEM (2007) Early dexamethasone treatment for septic shock patients: a prospective randomized clinical trial. São Paulo Med J (Rev Paul Med) 125:237–241

29. COIITSS Study Investigators, Annane D, Cariou A et al (2010) Corticosteroid treatment and intensive insulin therapy for septic shock in adults: a randomized controlled trial. JAMA 303:341–348. https://doi.org/10.1001/jama.2010.2
30. Dong W, Zhang G, Qu F (2015) Effects of Ringer's sodium pyruvate solution on serum tumor necrosis factor-α and interleukin-6 upon septic shock. Pak J Med Sci 31:672–677. https://doi.org/10.12669/pjms.313.7170
31. Donnino MW, Andersen LW, Chase M et al (2016) Randomized, double-blind, placebo-controlled trial of thiamine as a metabolic resuscitator in septic shock: a pilot study. Crit Care Med 44:360–367. https://doi.org/10.1097/CCM.0000000000001572
32. Dubin A, Pozo MO, Casabella CA et al (2010) Comparison of 6% hydroxyethyl starch 130/0.4 and saline solution for resuscitation of the microcirculation during the early goal-directed therapy of septic patients. J Crit Care 25:659.e1–659.e8. https://doi.org/10.1016/j.jcrc.2010.04.007
33. Forceville X, Laviolle B, Annane D et al (2007) Effects of high doses of selenium, as sodium selenite, in septic shock: a placebo-controlled, randomized, double-blind, phase II study. Crit Care 11:R73. https://doi.org/10.1186/cc5960
34. Garg M, Sen J, Goyal S, Chaudhry D (2016) Comparative evaluation of central venous pressure and sonographic inferior vena cava variability in assessing fluid responsiveness in septic shock. Indian J Crit Care Med 20:708–713. https://doi.org/10.4103/0972-5229.195706
35. Gordon AC, Mason AJ, Perkins GD et al (2014) The interaction of vasopressin and corticosteroids in septic shock: a pilot randomized controlled trial. Crit Care Med 42:1325–1333. https://doi.org/10.1097/CCM.0000000000000212
36. Gordon AC, Mason AJ, Thirunavukkarasu N et al (2016) Effect of early vasopressin vs norepinephrine on kidney failure in patients with septic shock: the VANISH randomized clinical trial. JAMA 316:509–518. https://doi.org/10.1001/jama.2016.10485
37. Hajjej Z, Meddeb B, Sellami W et al (2017) Effects of levosimendan on cellular metabolic alterations in patients with septic shock: a randomized controlled pilot study. Shock 48:307–312. https://doi.org/10.1097/SHK.0000000000000851
38. Hjortrup PB, Haase N, Bundgaard H et al (2016) Restricting volumes of resuscitation fluid in adults with septic shock after initial management: the CLASSIC randomised, parallel-group, multicentre feasibility trial. Intensive Care Med 42:1695–1705. https://doi.org/10.1007/s00134-016-4500-7
39. Huh JW, Choi H-S, Lim C-M et al (2011) Low-dose hydrocortisone treatment for patients with septic shock: a pilot study comparing 3 days with 7days. Respirology 16:1088–1095. https://doi.org/10.1111/j.1440-1843.2011.02018.x
40. Hyvernat H, Barel R, Gentilhomme A et al (2016) Effects of increasing hydrocortisone to 300 mg per day in the treatment of septic shock: a pilot study. Shock 46:498–505. https://doi.org/10.1097/SHK.0000000000000665
41. Juffermans NP, Vervloet MG, Daemen-Gubbels CRG et al (2010) A dose-finding study of methylene blue to inhibit nitric oxide actions in the hemodynamics of human septic shock. Nitric Oxide 22:275–280. https://doi.org/10.1016/j.niox.2010.01.006
42. Li M-Q, Pan C-G, Wang X-M et al (2015) Effect of the shenfu injection combined with early goal-directed therapy on organ functions and outcomes of septic shock patients. Cell Biochem Biophys 72:807–812. https://doi.org/10.1007/s12013-015-0537-4
43. Li Y, Zhang X, Lin P et al (2016) Effects of shenfu injection in the treatment of septic shock patients: a multicenter, controlled, randomized, open-label trial. Evid Based Complement Alternat Med 2016:2565169. https://doi.org/10.1155/2016/2565169
44. Lin S-M, Huang C-D, Lin H-C et al (2006) A modified goal-directed protocol improves clinical outcomes in intensive care unit patients with septic shock: a randomized controlled trial. Shock 26:551–557. https://doi.org/10.1097/01.shk.0000232271.09440.8f
45. Livigni S, Bertolini G, Rossi C et al (2014) Efficacy of coupled plasma filtration adsorption (CPFA) in patients with septic shock: a multicenter randomised controlled clinical trial. BMJ Open 4:e003536. https://doi.org/10.1136/bmjopen-2013-003536
46. Loisa P, Parviainen I, Tenhunen J et al (2007) Effect of mode of hydrocortisone administration on glycemic control in patients with septic shock: a prospective randomized trial. Crit Care 11:R21. https://doi.org/10.1186/cc5696
47. Lu N-F, Zheng R-Q, Lin H et al (2015) Improved sepsis bundles in the treatment of septic shock: a prospective clinical study. Am J Emerg Med 33:1045–1049. https://doi.org/10.1016/j.ajem.2015.04.031
48. Lv Q, Gu X, Chen Q et al (2017) Early initiation of low-dose hydrocortisone treatment for septic shock in adults: a randomized clinical trial. Am J Emerg Med 35:1810–1814. https://doi.org/10.1016/j.ajem.2017.06.004
49. McIntyre LA, Fergusson D, Cook DJ et al (2008) Fluid resuscitation in the management of early septic shock (FINESS): a randomized controlled feasibility trial. Can J Anaesth (J Can d'anesthésie) 55:819–826. https://doi.org/10.1007/bf03034053
50. Memiş D, Kargi M, Sut N (2009) Effects of propofol and dexmedetomidine on indocyanine green elimination assessed with LIMON to patients with early septic shock: a pilot study. J Crit Care 24:603–608. https://doi.org/10.1016/j.jcrc.2008.10.005
51. Merouani M, Guignard B, Vincent F et al (2008) Norepinephrine weaning in septic shock patients by closed loop control based on fuzzy logic. Crit Care 12:R155. https://doi.org/10.1186/cc7149
52. Morelli A, Lange M, Ertmer C et al (2007) Glibenclamide dose response in patients with septic shock: effects on norepinephrine requirements, cardiopulmonary performance, and global oxygen transport. Shock 28:530–535. https://doi.org/10.1097/shk.0b013e3180556a3c
53. Morelli A, Ertmer C, Rehberg S et al (2009) Continuous terlipressin versus vasopressin infusion in septic shock (TERLIVAP): a randomized, controlled pilot study. Crit Care 13:R130. https://doi.org/10.1186/cc7990
54. Morelli A, Ertmer C, Rehberg S et al (2008) Phenylephrine versus norepinephrine for initial hemodynamic support of patients with septic shock: a randomized, controlled trial. Crit Care 12:R143. https://doi.org/10.1186/cc7121
55. Morelli A, Ertmer C, Lange M et al (2008) Effects of short-term simultaneous infusion of dobutamine and terlipressin in patients with septic shock: the DOBUPRESS study. Br J Anaesth 100:494–503. https://doi.org/10.1093/bja/aen017
56. Morelli A, Donati A, Ertmer C et al (2010) Levosimendan for resuscitating the microcirculation in patients with septic shock: a randomized controlled study. Crit Care 14:R232. https://doi.org/10.1186/cc9387
57. Mouncey PR, Osborn TM, Power GS et al (2015) Trial of early, goal-directed resuscitation for septic shock. N Engl J Med 372:1301–1311. https://doi.org/10.1056/NEJMoa1500896
58. Ngaosuwan K, Ounchokdee K, Chalermchai T (2017) Clinical outcomes of minimized hydrocortisone dosage of 100 mg/day on lower occurrence of hyperglycemia in septic shock patients. Shock. https://doi.org/10.1097/SHK.0000000000001061
59. Palizas F, Dubin A, Regueira T et al (2009) Gastric tonometry versus cardiac index as resuscitation goals in septic shock: a multicenter, randomized, controlled trial. Crit Care 13:R44. https://doi.org/10.1186/cc7767
60. Patel GP, Grahe JS, Sperry M et al (2010) Efficacy and safety of dopamine versus norepinephrine in the management of septic shock. Shock 33:375–380. https://doi.org/10.1097/SHK.0b013e3181c6ba6f
61. Payen DM, Guilhot J, Launey Y et al (2015) Early use of polymyxin B hemoperfusion in patients with septic shock due to peritonitis: a multicenter randomized control trial. Intensive Care Med 41:975–984. https://doi.org/10.1007/s00134-015-3751-z
62. Investigators ProCESS, Yealy DM, Kellum JA et al (2014) A randomized trial of protocol-based care for early septic shock. N Engl J Med 370:1683–1693. https://doi.org/10.1056/NEJMoa1401602
63. Puskarich MA, Kline JA, Krabill V et al (2014) Preliminary safety and efficacy of L-carnitine infusion for the treatment of vasopressor-dependent septic shock: a randomized control trial. JPEN J Parenter Enter Nutr 38:736–743. https://doi.org/10.1177/0148607113495414
64. Quenot J-P, Binquet C, Vinsonneau C et al (2015) Very high volume hemofiltration with the Cascade system in septic shock patients. Intensive Care Med 41:2111–2120. https://doi.org/10.1007/s00134-015-4056-y
65. Ranieri VM, Thompson BT, Barie PS et al (2012) Drotrecogin alfa (activated) in adults with septic shock. N Engl J Med 366:2055–2064. https://doi.org/10.1056/NEJMoa1202290
66. Richard J-C, Bayle F, Bourdin G et al (2015) Preload dependence indices to titrate volume expansion during septic shock: a randomized controlled trial. Crit Care 19:5. https://doi.org/10.1186/s13054-014-0734-3

67. Russell JA, Vincent J-L, Kjølbye AL et al (2017) Selepressin, a novel selective vasopressin V1A agonist, is an effective substitute for norepinephrine in a phase IIa randomized, placebo-controlled trial in septic shock patients. Crit Care 21:213. https://doi.org/10.1186/s13054-017-1798-7
68. Russell JA, Walley KR, Singer J et al (2008) Vasopressin versus norepinephrine infusion in patients with septic shock. N Engl J Med 358:877–887. https://doi.org/10.1056/NEJMoa067373
69. Schmoelz M, Schelling G, Dunker M, Irlbeck M (2006) Comparison of systemic and renal effects of dopexamine and dopamine in norepinephrine-treated septic shock. J Cardiothorac Vasc Anesth 20:173–178. https://doi.org/10.1053/j.jvca.2005.10.016
70. Schortgen F, Clabault K, Katsahian S et al (2012) Fever control using external cooling in septic shock: a randomized controlled trial. Am J Respir Crit Care Med 185:1088–1095. https://doi.org/10.1164/rccm.201110-1820OC
71. Seguin P, Laviolle B, Guinet P et al (2006) Dopexamine and norepinephrine versus epinephrine on gastric perfusion in patients with septic shock: a randomized study [NCT00134212]. Crit Care 10:R32. https://doi.org/10.1186/cc4827
72. Shum HP, Leung YW, Lam SM et al (2014) Alteco endotoxin hemoadsorption in Gram-negative septic shock patients. Indian J Crit Care Med 18:783–788. https://doi.org/10.4103/0972-5229.146305
73. Singh RK, Agarwal V, Baronia AK et al (2017) The effects of atorvastatin on inflammatory responses and mortality in septic shock: a single-center, randomized controlled trial. Indian J Crit Care Med 21:646–654. https://doi.org/10.4103/ijccm.IJCCM_474_16
74. Sprung CL, Annane D, Keh D et al (2008) Hydrocortisone therapy for patients with septic shock. N Engl J Med 358:111–124. https://doi.org/10.1056/NEJMoa071366
75. Stephens DP, Thomas JH, Higgins A et al (2008) Randomized, double-blind, placebo-controlled trial of granulocyte colony-stimulating factor in patients with septic shock. Crit Care Med 36:448–454. https://doi.org/10.1097/01.CCM.0B013E318161E480
76. Torraco A, Carrozzo R, Piemonte F et al (2014) Effects of levosimendan on mitochondrial function in patients with septic shock: a randomized trial. Biochimie 102:166–173. https://doi.org/10.1016/j.biochi.2014.03.006
77. Trof RJ, Beishuizen A, Cornet AD et al (2012) Volume-limited versus pressure-limited hemodynamic management in septic and non-septic shock. Crit Care Med 40:1177–1185. https://doi.org/10.1097/CCM.0b013e31823bc5f9
78. Trzeciak S, Glaspey LJ, Dellinger RP et al (2014) Randomized controlled trial of inhaled nitric oxide for the treatment of microcirculatory dysfunction in patients with sepsis. Crit Care Med 42:2482–2492. https://doi.org/10.1097/CCM.0000000000000549
79. van Genderen ME, Engels N, van der Valk RJP et al (2015) Early peripheral perfusion-guided fluid therapy in patients with septic shock. Am J Respir Crit Care Med 191:477–480. https://doi.org/10.1164/rccm.201408-1575LE
80. van Haren FMP, Sleigh J, Boerma EC et al (2012) Hypertonic fluid administration in patients with septic shock: a prospective randomized controlled pilot study. Shock 37:268–275. https://doi.org/10.1097/SHK.0b013e31823f152f
81. Venkatesh B, Finfer S, Cohen J et al (2018) Adjunctive glucocorticoid therapy in patients with septic shock. N Engl J Med NEJMoa1705835. https://doi.org/10.1056/nejmoa1705835
82. Xu Q, Yan J, Cai G et al (2014) Effect of two volume responsiveness evaluation methods on fluid resuscitation and prognosis in septic shock patients. Chin Med J (Engl) 127:483–487. https://doi.org/10.3760/cma.j.issn.0366-6999.20131830
83. Yu T, Peng X, Liu L et al (2015) Propofol increases preload dependency in septic shock patients. J Surg Res 193:849–855. https://doi.org/10.1016/j.jss.2014.08.050
84. Zhou X, Liu D, Su L et al (2017) Use of stepwise lactate kinetics-oriented hemodynamic therapy could improve the clinical outcomes of patients with sepsis-associated hyperlactatemia. Crit Care 21:33. https://doi.org/10.1186/s13054-017-1617-1
85. Kaukonen K-M, Bailey M, Suzuki S et al (2014) Mortality related to severe sepsis and septic shock among critically ill patients in Australia and New Zealand, 2000–2012. JAMA 311:1308–1316. https://doi.org/10.1001/jama.2014.2637
86. Gaieski DF, Edwards JM, Kallan MJ, Carr BG (2013) Benchmarking the incidence and mortality of severe sepsis in the United States. Crit Care Med 41:1167–1174. https://doi.org/10.1097/CCM.0b013e31827c09f8
87. Klein Klouwenberg PMC, Ong DSY, Bonten MJM, Cremer OL (2012) Classification of sepsis, severe sepsis and septic shock: the impact of minor variations in data capture and definition of SIRS criteria. Intensive Care Med 38:811–819. https://doi.org/10.1007/s00134-012-2549-5
88. Féry-Lemonnier E, Landais P, Loirat P et al (1995) Evaluation of severity scoring systems in ICUs—translation, conversion and definition ambiguities as a source of inter-observer variability in Apache II, SAPS and OSF. Intensive Care Med 21:356–360. https://doi.org/10.1007/BF01705416
89. Pettilä V, Hjortrup PB, Jakob SM et al (2016) Control groups in recent septic shock trials: a systematic review. Intensive Care Med 42:1912–1921. https://doi.org/10.1007/s00134-016-4444-y
90. Porter ME, Larsson S, Lee TH (2016) Standardizing patient outcomes measurement. N Engl J Med 374:504–506. https://doi.org/10.1056/NEJMp1511701
91. Myles PS, Grocott MPW, Boney O et al (2016) Standardizing end points in perioperative trials: towards a core and extended outcome set. Br J Anaesth 116:586–589. https://doi.org/10.1093/bja/aew066
92. Vincent J, Martin-Loeches I, Annane D (2016) What patient data should be collected in this randomized controlled trial in sepsis? Intensive Care Med 42:2011–2013. https://doi.org/10.1007/s00134-016-4560-8
93. Investigators PRISM, Rowan KM, Angus DC et al (2017) Early, goal-directed therapy for septic shock—a patient-level meta-analysis. N Engl J Med 376:2223–2234. https://doi.org/10.1056/NEJMoa1701380
94. Shankar-Hari M, Harrison DA, Rowan KM (2016) Differences in impact of definitional elements on mortality precludes international comparisons of sepsis epidemiology—a cohort study illustrating the need for standardized reporting. Crit Care Med 44:2223–2230. https://doi.org/10.1097/CCM.0000000000001876
95. Martin GS, Mannino DM, Eaton S, Moss M (2003) The epidemiology of sepsis in the United States from 1979 through 2000. N Engl J Med 348:1546–1554. https://doi.org/10.1056/NEJMoa022139
96. Ferreira FL, Bota DP, Bross A et al (2001) Serial evaluation of the SOFA score to predict outcome in critically ill patients. JAMA 286:1754–1758. https://doi.org/10.1001/jama.286.14.1754
97. Minne L, Abu-Hanna A, de Jonge E (2008) Evaluation of SOFA-based models for predicting mortality in the ICU: a systematic review. Crit Care 12:R161. https://doi.org/10.1186/cc7160
98. Kempker JA, Martin GS (2016) Does sepsis case mix heterogeneity prevent outcome comparisons? Crit Care Med 44:2288–2289. https://doi.org/10.1097/CCM.0000000000001933

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ORIGINAL ARTICLE

FREE PREVIEW

# Hydrocortisone plus Fludrocortisone for Adults with Septic Shock

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## Abstract

**BACKGROUND** Septic shock is characterized by dysregulation of the host response to infection, with circulatory, cellular, and metabolic abnormalities. We hypothesized that therapy with hydrocortisone plus fludrocortisone or with drotrecogin alfa (activated), which can modulate the host response, would improve the clinical outcomes of patients with septic shock.

**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).

**RESULTS** Among the 1241 patients included in the trial, the 90-day mortality was 43.0% (264 of 614 patients) in the hydrocortisone-plus-fludrocortisone group and 49.1% (308 of 627 patients) in the placebo group (P=0.03). The relative risk of death in the hydrocortisone-plus-fludrocortisone group was 0.88 (95% confidence interval, 0.78 to 0.99). Mortality was significantly lower in the hydrocortisone-plus-fludrocortisone group than in the placebo group at ICU discharge (35.4% vs. 41.0%, P=0.04), hospital discharge (39.0% vs. 45.3%, P=0.02), and day 180 (46.6% vs. 52.5%, P=0.04) but not at day 28 (33.7% and 38.9%, respectively; P=0.06). The number of vasopressor-free days to day 28 was significantly higher in the hydrocortisone-plus-fludrocortisone group than in the placebo group (17 vs. 15 days, P<0.001), as was the number of organ-failure–free days (14 vs. 12 days, P=0.003). The number of ventilator-free days was similar in the two groups (11 days in the hydrocortisone-plus-fludrocortisone group and 10 in the placebo group, P=0.07). The rate of serious adverse events did not differ significantly between the two groups, but hyperglycemia was more common in hydrocortisone-plus-fludrocortisone group.

**CONCLUSIONS** In this trial involving patients with septic shock, 90-day all-cause mortality was lower among those who received hydrocortisone plus fludrocortisone than among those who received placebo. (Funded by Programme Hospitalier de Recherche Clinique 2007 of the French Ministry of Social Affairs and Health; APROCCHSS ClinicalTrials.gov number, NCT00625209.)

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A complete list of investigators in the APROCCHSS trial is provided in the Supplementary Appendix, available at NEJM.org.