İSTANBUL ÜNİVERSİTESİ
CERRAHPAŞA

YOĞUN BAKIMDA SEPSİS TAKİBİ

DR.GÜNİZ KÖKSAL

CERRAHPAŞA TIP FAKÜLTESİ

İÇ HASTALIKLARI YOĞUN BAKIM BİLİM DALI

Yeni Sepsis Tanımları

JAMA, Şubat 2016

- Enfeksiyona karşı konak yanıtının disregülasyonu sonucu organ işlevlerinin bozulması
- Vücudun enfeksiyona karşı yanıtı kendi organ ve dokularına zarar vermeye başladığında ortaya çıkan hayatı tehdit edici durum
- Organ işlevlerinin bozulması SOFA skorunun 2'nin üzerine çıkması ile tespit edilebilir
- Septik şok, yeterli sıvı replasmanına rağmen OAB < 65 mmHg ve/veya laktat > 2 mmol/L veya vazopresör gereksinimi

QSOFA


Hypotension
Systolic BP
<100 mmHg
Altered
Mental
Status
Tachypnea
RR >22/Min
Score of ≥2 Criteria Suggests a Greater Risk of a Poor Outcome

Table 1 Modified Early Warning Score

Score	3	2	1	0	1	2	3
Respiratory rate (min^{-1})		≤ 8		9–14	15–20	21–29	> 29
Heart rate (min^{-1})		≤ 40	41–50	51–100	101–110	111–129	> 129
Systolic BP (mmHg)	≤ 70	71–80	81–100	101–199		≥ 200	
Urine output (ml/kg/h)	Nil	< 0.5					
Temperature (°C)		≤ 35	35.1–36	36.1–38	38.1–38.5	≥ 38.6	
Neurological				Alert	Reacting to voice	Reacting to pain	Unresponsive

The scores for each parameter are recorded at the time that observations are taken. If the total is 4 or more then the ward doctor is informed.

Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

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

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

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

IMPORTANCE Septic shock currently refers to a state of acute circulatory failure associated with infection. Emerging biological insights and reported variation in epidemiology challenge the validity of this definition.

OBJECTIVE To develop a new definition and clinical criteria for identifying septic shock in adults.

DESIGN, SETTING, AND PARTICIPANTS The Society of Critical Care Medicine and the European Society of Intensive Care Medicine convened a task force (19 participants) to revise current sepsis/septic shock definitions. Three sets of studies were conducted: (1) a systematic review and meta-analysis of observational studies in adults published between January 1, 1992, and December 25, 2015, to determine clinical criteria currently reported to identify septic shock and inform the Delphi process; (2) a Delphi study among the task force comprising 3 surveys and discussions of results from the systematic review, surveys, and cohort studies to achieve consensus on a new septic shock definition and clinical criteria; and (3) cohort studies to test variables identified by the Delphi process using Surviving Sepsis Campaign (SSC) (2005-2010; n = 28 150), University of Pittsburgh Medical Center (UPMC) (2010-2012; n = 1 309 025), and Kaiser Permanente Northern California (KPNC) (2009-2013; n = 1 847 165) electronic health record (EHR) data sets.

MAIN OUTCOMES AND MEASURES Evidence for and agreement on septic shock definitions and criteria.

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

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

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

Editorial page 757

Author Audio Interview at jama.com

Related articles pages 762 and 801

Supplemental content at jama.com

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Group Information: Members of the Sepsis Definitions Task Force are listed at the end of this article.

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Journal of Intensive Care

GUIDELINE Open Access

The Japanese Clinical Practice Guidelines for Management of Sepsis and Septic Shock 2016 (J-SSCG 2016)

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the SSCG 2016. New topics not covered in the first edition of the J-SSCG [1, 2] include controlling of the origin of infection, blood transfusion preparations, management of analgesia, sedation and delirium, acute kidney injury, body temperature regulation, venous thromboembolism countermeasures, intensive care unit (ICU)-acquired weakness, and post-intensive care syndrome. Moreover, there are few pediatric ICUs in Japan, and as healthcare professionals handling adult patients will inevitably need to treat pediatric sepsis cases as well, new CQs related to pediatric sepsis patients were also added to this edition. As a result, these guidelines ultimately comprised a large-scale reference material covering a total of 19 clinical areas and 87 CQs. However, therapy administration to patients in the prone position during respiratory management has been recently addressed by the Japanese Acute Respiratory Distress Syndrome (ARDS) Clinical Practice Guidelines. As

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REVIEW ARTICLE

Intra-abdominal sepsis: new definitions and current clinical standards

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Purpose The abdomen is the second most common source of sepsis and is associated with unacceptably high morbidity and mortality. Recently, the essential definitions of sepsis and septic shock were updated (Third International Consensus Definitions for Sepsis and Septic Shock, Sepsis-3) and modified. The purpose of this review is to provide an overview of the changes introduced by Sepsis-3 and the current state of the art regarding the treatment of abdominal sepsis.

Results While Sepsis-1/2 focused on detecting systemic inflammation as a response to infection, Sepsis-3 defines sepsis as a life-threatening organ dysfunction caused by a dysregulated host response to infection. The Surviving Sepsis Campaign (SSC) guideline, which was updated in 2016, recommends rapid diagnosis and initiating standardized therapy. New diagnostic tools, the establishment of antibiotic stewardship programs, and a host of new-generation antibiotics are new landmark changes in the sepsis literature of the last few years. Although the "old" surgical source control consisting of debridement, removal of infected devices, drainage of purulent cavities, and decompression of the abdominal cavity is the gold standard of surgical care, the timing of gastrointestinal reconstruction and closure of the abdominal cavity ("damage control surgery") are discussed intensively in the literature. The SSC guidelines provide evidence-based sepsis therapy. Nevertheless, treating critically ill intensive care patients requires individualized, continuous daily re-evaluation and flexible therapeutic strategies, which can be best discussed in the interdisciplinary rounds of experienced surgeons and intensive care medicals.

PLOS ONE

RESEARCH ARTICLE

Vasopressors for the Treatment of Septic Shock: Systematic Review and Meta-Analysis

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International guidelines recommend dopamine or norepinephrine as first-line vasopressor agents in septic shock. Phenylephrine, epinephrine, vasopressin and terlipressin are considered second-line agents. Our objective was to assess the evidence for the efficiency and safety of all vasopressors in septic shock.

Systematic review and meta-analysis. We searched electronic database of MEDLINE, CENTRAL, LILACS and conference proceedings up to June 2014. We included randomized controlled trials comparing different vasopressors for the treatment of adult patients with septic shock. Primary outcome was all-cause mortality. Other clinical and hemodynamic measurements were extracted as secondary outcomes. Risk ratios (RR) and mean differences with 95% confidence intervals (CI) were pooled.

Thirty-two trials (3,544 patients) were included. Compared to dopamine (866 patients, 450 events), norepinephrine (832 patients, 376 events) was associated with decreased all-cause mortality, RR 0.89 (95% CI 0.81-0.98), corresponding to an absolute risk reduction of 11% and number needed to treat of 9. Norepinephrine was associated with lower risk for major adverse events and cardiac arrhythmias compared to dopamine. No other mortality benefit was demonstrated for the comparisons of norepinephrine to epinephrine, phenylephrine and vasopressin / terlipressin. Hemodynamic data were similar between the different vasopressors, with some advantage for norepinephrine in central venous pressure, urinary output and blood lactate levels.

Conclusions

Evidence suggests a survival benefit, better hemodynamic profile and reduced adverse events rate for norepinephrine over dopamine. Norepinephrine should be regarded as the first line vasopressor in the treatment of septic shock.

ORIGINAL ARTICLE

Early Use of Norepinephrine in Septic Shock Resuscitation (CENSER)

A Randomized Trial

Chairat Permpikul[1], Surat Tongyoo[1], Tanuwong Viarasilpa[1], Thavinee Trainarongsakul[1], Tipa Chakorn[2], and Suthipol Udompanturak[3]

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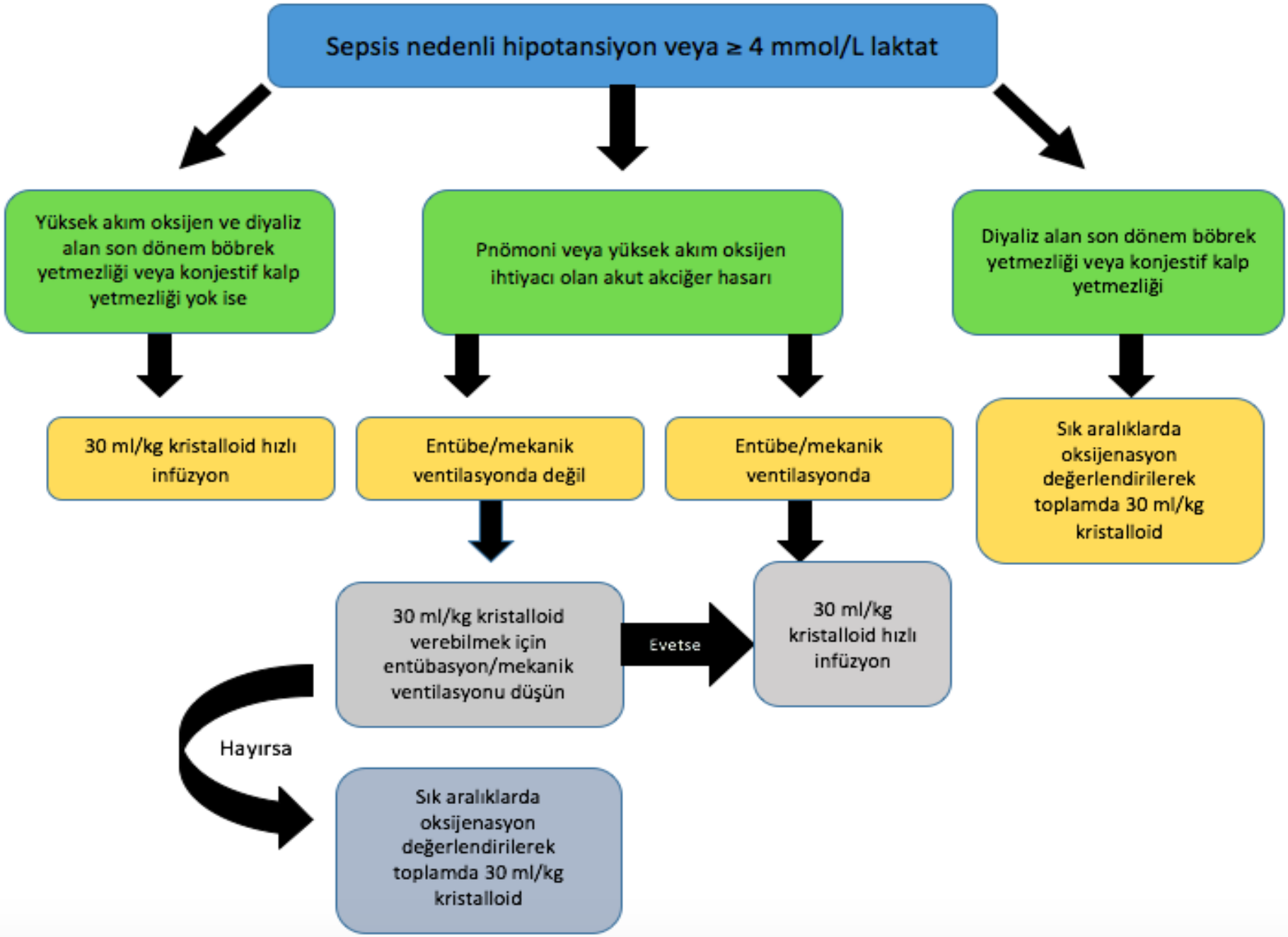
Rationale: Recent retrospective evidence suggests the efficacy of early norepinephrine administration during resuscitation; however, prospective data to support this assertion are scarce.

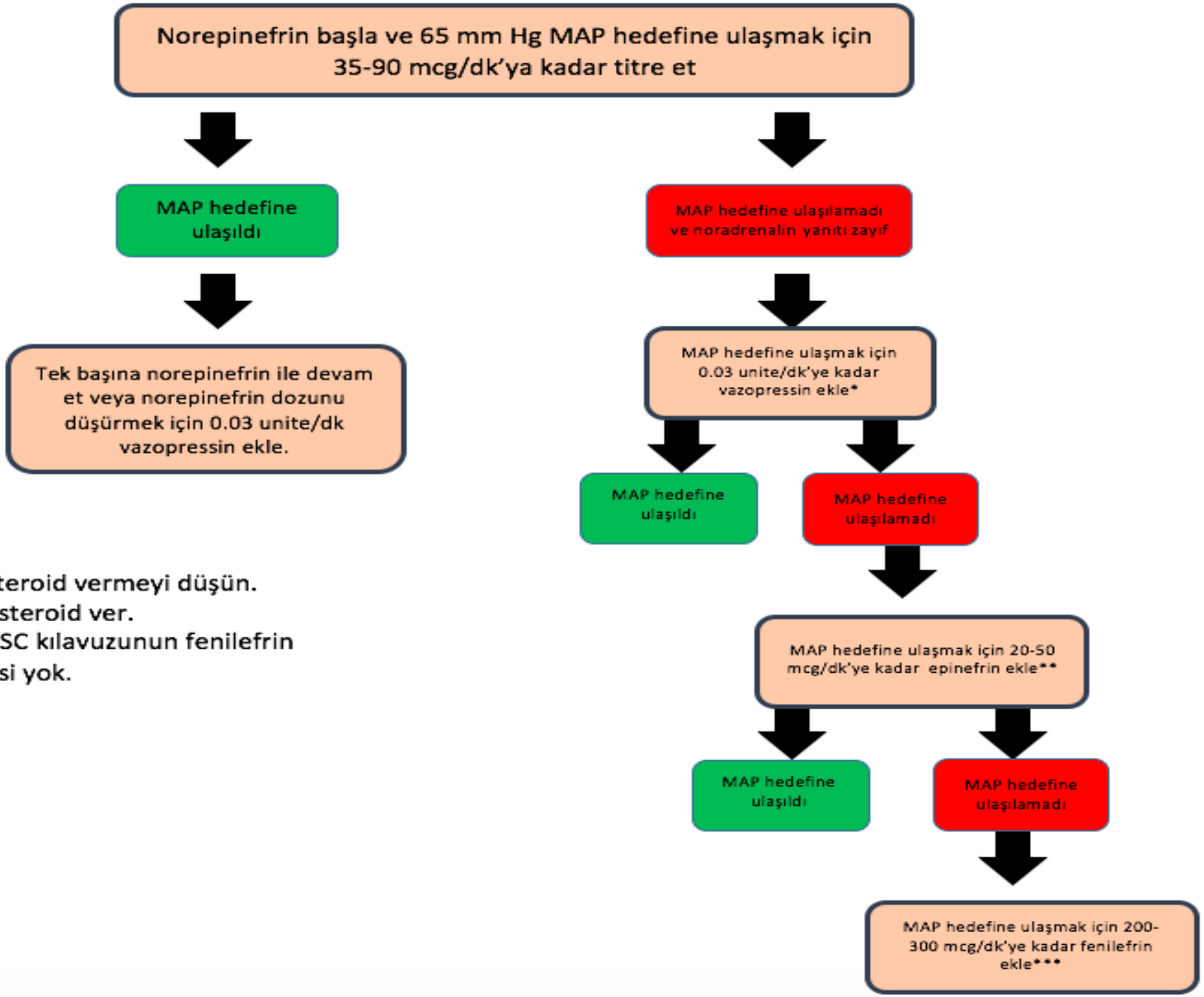
Objectives: To conduct a phase II trial evaluating the hypothesis that early low-dose norepinephrine in adults with sepsis with hypotension increases shock control by 6 hours compared with standard care.

Methods: This single-center, randomized, double-blind, placebo-controlled clinical trial was conducted at Siriraj Hospital, Bangkok, Thailand. The study enrolled 310 adults diagnosed with sepsis with hypotension. The patients were randomly divided into two groups: early norepinephrine ($n = 155$) and standard treatment ($n = 155$). The primary outcome was shock control rate (defined as achievement of mean arterial blood pressure $\geq$65 mm Hg, with urine flow $\geq$0.5 ml/kg/h for 2 consecutive hours, or decreased serum lactate $\geq$10% from baseline) by 6 hours after diagnosis.

Conclusions: Early norepinephrine was significantly associated with increased shock control by 6 hours. Further studies are needed before this approach is introduced in clinical resuscitation practice.

Erişkin Septik Şokta Sıvı Resüsitasyon Uygulaması





* iv steroid vermeyi düşün.
** iv steroid ver.
*** SSC kılavuzunun fenilefrin önerisi yok.

Hernández and Teboul *Critical Care* (2017) 21:133
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Critical Care

EDITORIAL Open Access

Fourth Surviving Sepsis Campaign's hemodynamic recommendations: a step forward or a return to chaos?

Glenn Hernández[1] and Jean-Louis Teboul[2*]

Fluids

It is now recommended to infuse at least 30 mL/kg of IV crystalloids within the first 3 h of resuscitation of sepsis-induced hypoperfusion. We are concerned by both the predefined volume and timeframe. First, all septic patients do not exhibit the same degree of hypovolemia. For instance, abdominal sepsis inducing massive internal or external fluid losses is generally not equivalent to community-acquired pneumonia in terms of volume deficit. Deliberate administration of 30 mL/kg of fluids in patients with pneumonia with cardiovascular comorbidities might eventually result in pulmonary edema and hasten the need for mechanical ventilation.

Vasopressors

From the last version of the SSC publication [5], it is unclear when norepinephrine should be initiated. The reader could understand that the decision should be made only at the time of the first reassessment (3 h). One major characteristic of septic shock is vasoplegia, where the need of a vasopressor is mandatory since fluid resuscitation alone cannot restore vascular tone and thus cannot completely correct profound hypotension [8], which is an event associated with mortality [9]. In addition, sepsis-induced vasoplegia results in a dramatic fall in diastolic arterial pressure (DAP), which represents the upstream pressure for perfusion of the left ventricle. A low DAP, especially in the context of tachycardia, can be an easy bedside tool to identify patients who need early initiation of a vasopressor. This was mentioned in the previous publication of the SCC [10] but disappeared inexplicably in the most recent one [5]. Early initiation of a vasopressor not only can rapidly correct hypotension in case of low vascular tone but also can avoid harmful fluid overload.

Perfusion monitoring

After several recent negative trials testing the use of central venous oxygen saturation ($ScvO_2$) as a target for early resuscitation of septic shock [4], the SSC has abandoned its initial recommendation to include $ScvO_2$ as part of standard monitoring. This could lead to a loss of confi-

Lactate normalization as a resuscitation target

Normalization of lactate is recommended by the SSC as a resuscitation goal since it is assumed that tissue hypoxia is the main source of lactate production. However, there are several unresolved concerns about the role of lactate as an appropriate resuscitation target. First, be-

Conclusions

Important knowledge on the pathophysiology of septic shock has been built up over decades of experimental and clinical research. Translation of these scientific foundations into clinical practice has, however, been slow and erratic. For such a condition with a mortality risk of at least 30–40%, we should expect the rationale of consensus recommendations to be firmly grounded on pathophysiology. Our opinion is that some of the recent SSC's hemodynamic recommendations move far away from this objective and might not constitute a valuable contribution to improve septic shock morbidity or mortality.

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Annals of Intensive Care

RESEARCH Open Access

Current use of inotropes in circulatory shock

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Abstract

Background: Treatment decisions on critically ill patients with circulatory shock lack consensus. In an international survey, we aimed to evaluate the indications, current practice, and therapeutic goals of inotrope therapy in the treatment of patients with circulatory shock.

Methods: From November 2016 to April 2017, an anonymous web-based survey on the use of cardiovascular drugs was accessible to members of the European Society of Intensive Care Medicine (ESICM). A total of 14 questions focused on the profile of respondents, the triggering factors, first-line choice, dosing, timing, targets, additional treatment strategy, and suggested effect of inotropes. In addition, a group of 42 international ESICM experts was asked to formulate recommendations for the use of inotropes based on 11 questions.

Results: A total of 839 physicians from 82 countries responded. Dobutamine was the first-line inotrope in critically ill patients with acute heart failure for 84% of respondents. Two-thirds of respondents (66%) stated to use inotropes when there were persistent clinical signs of hypoperfusion or persistent hyperlactatemia despite a supposed adequate use of fluids and vasopressors, with (44%) or without (22%) the context of low left ventricular ejection fraction. Nearly half (44%) of respondents stated an adequate cardiac output as target for inotropic treatment. The experts agreed on 11 strong recommendations, all of which were based on excellent (> 90%) or good (81–90%) agreement. Recommendations include the indications for inotropes (septic and cardiogenic shock), the choice of drugs (dobutamine, not dopamine), the triggers (low cardiac output and clinical signs of hypoperfusion) and targets (adequate cardiac output) and stopping criteria (adverse effects and clinical improvement).

Conclusions

In conclusion, the use of inotropes in critically ill patients is quite heterogeneous as reported by individual caregivers. International experts recommend the use of inotropes in septic and cardiogenic shock (but not in hypovolemia), using an inadequate CO and signs of tissue hypoperfusion as triggers and targets for treatment, and adverse effects and clinical improvement as stopping/weaning criteria. While experts recommend using dobutamine as the first-line agent, they recommend against the use of dopamine. Future studies reporting patient-centred outcomes should focus on specific subpopulations based on prespecified and measurable triggers, targets, and with clear stopping criteria in order to ensure comparability across trials. This would allow a better summary of the evidence and its implementation in future guidelines.

Antibiyotik Kullanımı

REVIEW

Curr Opin Crit Care 2020, 26:473–477

Culture-negative sepsis

Jonathan Thorndike and Marin H. Kollef

Purpose of review

The traditional approach to sepsis treatment utilizes broad-spectrum antibiotics. Unfortunately, a significant proportion of infected patients have 'culture-negative' sepsis despite appropriate microbiologic assessment.

Recent findings

There has been increased interest in the past decade on the treatment of culture-negative sepsis. Outcome data comparing culture-negative sepsis with culture-positive sepsis are mixed and it is unclear if culture-negative sepsis is a distinct entity. Recent recommendations promoting antibiotic de-escalation in culture-negative sepsis can be difficult to implement. A variety of strategies have been suggested for limiting antibiotic courses among patients with negative cultures, including limiting antibiotic durations, use of antibiotic stewardship programs, early consideration of narrow antibiotics, rapid diagnostic technology, and eliminating anti-MRSA therapy based on surveillance swabs.

Summary

Owing to the difficulty inherent in studying the lack of positive data, and to the uncertainty surrounding diagnosis in patients with culture-negative sepsis, prospective data to guide antibiotic choices are lacking. However, antibiotic de-escalation in culture-negative sepsis is both recommended and feasible in patients showing clinical signs of improvement. Increased use of rapid diagnostics, careful consideration of antibiotic necessity, and antibiotic stewardship programs may result in less antibiotic days and better outcomes.

Jouffroy and Vivien *Crit Care* (2021) 25:293
https://doi.org/10.1186/s13054-021-03651-0

Critical Care

LETTER Open Access

Comparison of culture-negative and culture-positive sepsis or septic shock: outcomes are more influenced by the nature of the infectious agent itself than by the samples' positivity

Romain Jouffroy[1] and Benoît Vivien[2*]

To the editor,

Recently in the Journal, Li et al. [1] reported that culture positivity or negativity was not associated with differences in mortality, intensive care unit length of stay (LOS), mechanical ventilation requirements and renal replacement requirements of sepsis or septic shock patients. Conversely, hospital length of stay and mechanical ventilation duration of culture-positive septic patients were longer than those of culture-negative patients. While the authors must be congratulated for this systematic review and meta-analysis, we believe that their interpretation of the results requires caution. Firstly, we are surprised that for a major issue of interest such as blood culture positivity during sepsis, only seven studies were included by the authors in the final analysis. For example, the study by Vincent et al. [2], which is a 1-day, prospective, multicenter point reporting the prevalence of ICU infection, has not been included here, where 70% of their patients had positive microbial isolates. Secondly, despite international guidelines [3] on sepsis management, we cannot exclude heterogeneity between strategies and cares directly influencing outcomes. Thirdly, two studies [4, 5] include approximatively 19,000 patients, i.e., 85% of all cases, which could noticeably influence the results of this meta-analysis. Last but not least, we believe that more than the positivity or negativity of blood sampling, it is more the infectious agent itself that influences the outcomes, especially since the broad spectrum of the initial antibiotic therapy may be responsible for culture negativity.

Nevertheless, beyond all these limitations, we fully agree with Li et al. [1] that larger-scale studies are required to confirm or infirm their results.

Response to: Comparison of culture-negative and culture-positive sepsis or septic shock: outcomes are more influenced by the nature of the infectious agent itself than by the samples' positivity

Yuting Li[3], Jianxing Guo[3], Hongmei Yang[3], Hongxiang Li[3], Yangyang Shen[3] and Dong Zhang[3]*

We agree with Dr. Jourffroy et al. that the infectious agent itself influences the outcomes of septic patients. We attempted to convey the message that culture positivity or negativity was not associated with mortality of sepsis or septic shock patients. A positive culture does not mean a severe infection, and a negative culture does not mean a mild infection. The clinical outcomes may be associated with not only the infection sources but also the management of the sepsis and septic shock.

van Oers et al. Critical Care (2018) 22:83
https://doi.org/10.1186/s13054-018-2008-y

Critical Care

LETTER Open Access

Do we need new trials of procalcitonin-guided antibiotic therapy? A response

Jos A. H. van Oers[1*], Maarten W. Nijsten[2] and Dylan W. de Lange[3]

See related Commentary by Lisboa et al., https://ccforum.biomedcentral.com/articles/10.1186/s13054-018-1948-6

and populations. As authors of the largest study included in this meta-analysis, the Stop Antibiotics on Procalcitonin guidance Study (SAPS) [3], we want to respond. SAPS was a pragmatic randomized controlled trial in the Netherlands with 1546 adult ICU patients with antibiotics for a presumed infection. We demonstrated a highly significant reduction in initial antibiotic duration (5.0 vs 7.0 days). The median duration of antibiotic treatment (DOT) in the control group of the total population was 7 days (interquartile range (IQR) 4–11 days). Of these patients, 65% had a presumed pulmonary

believe it is necessary. Moreover, physicians may perform even better in clinical trials, because they know they are being watched, commonly referred to as the "Hawthorne effect". In SAPS the patients were already on antibiotics. When a PCT-stopping criterion was reached antibiotics were stopped in 53% of the patients within 48 h. It was a stopping advice. Sensitivity and specificity are not high enough to withhold antibiotics on PCT alone. And indeed, PCT is no holy grail. Like other biomarkers, there are numerous non-infectious inflammatory processes, i.e., trauma, surgery, and acute kidney injury, in which PCT can be elevated. But such conditions were well balanced between both groups.

Steroid Kullanımı

Steroids for sepsis and ARDS: this eternal controversy remains with COVID-19

In the past 50 years, the potential benefit of corticosteroids in treating sepsis or acute respiratory distress syndrome (ARDS) has been evaluated in many randomised controlled trials (RCTs). Corticosteroids have contradictory effects on mortality, leading to a profound and still active controversy. Low doses of corticosteroids have been shown to decrease mortality from septic shock in patients who also receive mineralocorticoids.[1] However, the effect of corticosteroids has been negative in other studies.[2] In one RCT,[3] corticosteroids were efficacious for ARDS of various origin. This modest hope for corticosteroids has been heightened from findings in patients with severe COVID-19.

Most of the initial therapeutic studies of corticosteroids for COVID-19 have been of very poor quality. The RECOVERY trial was one of the most robust studies.[4] In this large, open-labelled RCT, 2104 patients treated with corticosteroids were compared with 4321 patients receiving standard therapy. The study used different compounds, at different time courses, and in patients with COVID-19 symptoms of varying severity. Corticosteroids (dexamethasone, 6 mg per day) caused a moderate but significant 11% reduction in mortality. Mortality was significantly reduced in patients who were mechanically ventilated (29%) or received oxygen (11%), but not in patients without any respiratory failure. These results were considered credible proof of corticosteroid efficacy, particularly by WHO, which announced prematurely that corticosteroid was the gold standard for treating severe COVID-19.[5] However, the methodology in this study was very questionable, in particular (but not only) because no severity markers were recorded, making highly questionable the comparability of the two treatment groups at the time of study inclusion.

Results of four additional studies have since been published,[6–9] one of which was a meta-analysis promoted by WHO.[6] In this meta-analysis of pooled data from seven studies, corticosteroids were associated with a decrease in mortality from severe COVID-19. However, this effect disappeared when data from the RECOVERY trial[4] were excluded from the meta-analysis, suggesting an overweight of these data in the meta-analysis. The substantial heterogeneity within the remaining six trials limits the validity of the interpretation of the meta-analysis results. Furthermore, in the RECOVERY trial,[4] various compounds and dosages of corticosteroids were used.

Among the three other studies,[7–9] the CAPE COVID study[7] was stopped after publication of the RECOVERY trial[4] results. In CAPE COVID,[7] a well designed study that enrolled 149 patients with severe COVID-19, no benefit of corticosteroids was found. In the REMAP trial,[8] which included 903 treated patients, hydrocortisone (40 mg intravenous every 6 h) significantly reduced mortality from severe COVID-19 by 26%. Although not double-blinded, REMAP was the first robust trial to show a very clear-cut positive effect on mortality. The CoDEX trial,[9] with an excellent methodology, included 299 patients with mild or severe ARDS. Corticosteroids significantly increased ventilator-free days during the first 28 days, but there was no benefit on 28-day mortality or length of stay in intensive care units, both tested as secondary endpoints. Finally, in Metcovid,[10] a large phase 2b double-blind RCT with 416 patients with COVID-19, corticosteroids had no effect on mortality.

The above scientific limits and the contradicting results of the various studies ought to impose caution before adoption of corticosteroids as the master drug to save lives from COVID-19 (appendix). Although the medical community and citizens worldwide are impatient for efficient therapies, enthusiasm after the first positive results should be tempered until studies with a better design are completed, demonstrating clearly the efficacy of corticosteroids. We do not think there is any equipoise or ethical problem in planning further double-blind RCTs.

We declare no competing interests.

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1 Annane D, Renault A, Brun-Buisson C, et al. Hydrocortisone plus fludrocortisone for adults with septic shock. *N Engl J Med* 2018; **378:** 809–18.
2 Venkatesh B, Finfer S, Cohen J, et al. Adjunctive glucocorticoids therapy in patients with septic shock. *N Engl J Med* 2018; **378:** 797–808.
3 Vilar J, Ferrando C, Martinez D et al. Dexamethasone treatment for ARDS: a multicentric randomized controlled trial. *Lancet Respir Med* 2020; **8:** 267-76.
4 The RECOVERY Collaborative Group. Dexamethasone in hospitalized patients with COVID-19—preliminary report. *N Engl J Med* 2020; published online July 17. https://doi.org/10.1056/NEJMoa2021436.
5 Lamontagne F, Agoritsas T, Macdonald H. A living WHO guideline on drugs for COVID-19. *BMJ* 2020; **370:** m3379.
6 The WHO Rapid Evidence Appraisal for COVID-19 therapies (REACT) working group. Association between systemic corticosteroids administration and mortality among critically ill patients with Covid-19: a meta-analysis. *JAMA* 2020; published online Sept 2. https://doi.org/10.1056/JAMAoa2021436.
7 Dequin PF, Heming N, Meziani F et al. Effect of hydrocortisone on 21-day mortality or respiratory support among critically ill patients with COVID-19. *JAMA* 2020; published online Sept 2. https://doi.org/10.1001/jama.2020.16761.
8 The Writing Committee for REMAP-CAP Investigators. Effect of hydrocortisone on mortality and organ support in patients with severe COVID-19. *JAMA* 2020; published online Sept 2. https://doi.org/10.1001/jama.2020.17022.
9 Tomasini BM, Maia IS, Cavalcati AB, et al. Effect of dexamethasone on days alive and ventilator-free in patients with moderate or severe acute respiratory distress syndrome and COVID-19: The CoDEX randomized clinical trial. *JAMA* 2020; published online Sept 2. https://doi.org/10.1001/jama.2020.17021.

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See Online for appendix

JAMA Internal Medicine | Original Investigation

Association of Corticosteroid Treatment With Outcomes in Adult Patients With Sepsis
A Systematic Review and Meta-analysis

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IMPORTANCE Although corticosteroids are widely used for adults with sepsis, both the overall benefit and potential risks remain unclear.

OBJECTIVE To conduct a systematic review and meta-analysis of the efficacy and safety of corticosteroids in patients with sepsis.

DATA SOURCES AND STUDY SELECTION MEDLINE, Embase, and the Cochrane Central Register of Controlled Trials were searched from inception until March 20, 2018, and updated on August 10, 2018. The terms *corticosteroids*, *sepsis*, *septic shock*, *hydrocortisone*, *controlled trials*, and *randomized controlled trial* were searched alone or in combination. Randomized clinical trials (RCTs) were included that compared administration of corticosteroids with placebo or standard supportive care in adults with sepsis.

DATA EXTRACTION AND SYNTHESIS Meta-analyses were conducted using a random-effects model to calculate risk ratios (RRs) and mean differences (MDs) with corresponding 95% CIs. Two independent reviewers completed citation screening, data abstraction, and risk assessment.

MAIN OUTCOMES AND MEASURES Twenty-eight–day mortality.

RESULTS This meta-analysis included 37 RCTs (N = 9564 patients). Eleven trials were rated as low risk of bias. Corticosteroid use was associated with reduced 28-day mortality (RR, 0.90; 95% CI, 0.82-0.98; I^2 = 27%) and intensive care unit (ICU) mortality (RR, 0.85; 95% CI, 0.77-0.94; I^2 = 0%) and in-hospital mortality (RR, 0.88; 95% CI, 0.79-0.99; I^2 = 38%). Corticosteroids were significantly associated with increased shock reversal at day 7 (MD, 1.95; 95% CI, 0.80-3.11) and vasopressor-free days (MD, 1.95; 95% CI, 0.80-3.11) and with ICU length of stay (MD, −1.16; 95% CI, −2.12 to −0.20), the sequential organ failure assessment score at day 7 (MD, −1.38; 95% CI, −1.87 to −0.89), and time to resolution of shock (MD, −1.35; 95% CI, −1.78 to −0.91). However, corticosteroid use was associated with increased risk of hyperglycemia (RR, 1.19; 95% CI, 1.08-1.30) and hypernatremia (RR, 1.57; 95% CI, 1.24-1.99).

CONCLUSIONS AND RELEVANCE The findings suggest that administration of corticosteroids is associated with reduced 28-day mortality compared with placebo use or standard supportive care. More research is needed to associate personalized medicine with the corticosteroid treatment to select suitable patients who are more likely to show a benefit.

Supplemental content

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Sepsis-Associated Acute Kidney Injury: A Problem Deserving of New Solutions

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Sepsis-associated acute kidney injury (S-AKI) significantly worsens patient prognosis, and recent evidence suggests that the injury process begins early and may be sustained by therapies used to treat the sepsis (e.g., fluids resuscitation, antibiotics). While efforts to develop less-injurious treatments are making progress, some degree of secondary injury is to be expected. So too is the inevitable nature of organ injury, which is often present at the time the patient seeks medical attention. We recently found that most patients presenting with septic shock and developing AKI had evidence of kidney damage at the time of, or within 24 h of their ad-

Since S-AKI patients are at increased risk of developing chronic kidney disease, a fundamental target for interventions in S-AKI is to prevent fibrosis (maladaptive repair) while stimulating regeneration (proliferation of viable epithelial cells). Using a pathway-agnostic, proliferation-based phenotypic assay, we discovered phenylthiobutanoic acid, a small molecule histone deacetylase inhibitor, that enhances renal recovery and reduces fibrosis in both zebrafish and mouse models of AKI.

Hindawi
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Review Article

Biomarkers of Sepsis-Induced Acute Kidney Injury

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AKIN criteria definition and classification of AKI.

Stage	Serum creatinine and urine output criteria
1	Serum creatinine increase of ⩾26.4 umol/L (0.3 mg/dl) or to 150–200% of baseline or urine output < 0.5 ml/kg/h for >6 h
2	Serum creatinine increases to >200–300% of baseline or urine output < 0.5 ml/kg/h for >12 h
3	Serum creatinine increases to >300% of baseline or serum creatinine ⩾354 umol/L (4 mg/dl) with an acute rise of at least 44 umol/L (0.5 mg/dl) or urine output < 0.3 ml/kg/h for 24 h or anuria for 12 h

Table 2: KDIGO criteria definition and classification of AKI.

Stage	Serum creatinine and urine output criteria
1	Serum creatinine increased 1.5–1.9 times baseline or increase >26.4 umol/L (0.3 mg/dl) or urinary output < 0.5 ml/kg/h during a 6 hour block
2	Serum creatinine increased 2.0–2.9 times baseline or urinary output < 0.5 ml/kg/h during two 6 hour blocks
3	Serum creatinine increased >3 times baseline or increased to >353 umol/L (4 mg/dl) or initiation of renal replacement therapy or urinary output < 0.3 ml/kg/h during more than 24 hours or anuria for more than 12 hours

Different renal injury mechanisms and biomarkers.

Kidney injury mechanism	Biomarkers
Ischemia	Kim-1, NGAL, MCP-1, and cyr61
Hypoxia	L-FABP
cell-cycle arrest	IGFBP 7, TIMP-2

3.1. Biomarkers of Acute Kidney Injury. The KDIGO guidelines highlight early AKI diagnosis and treatment, and the diagnostic marker remains at serum creatinine level. Because the serum creatinine test is convenient and inexpensive, it provides a practical clinical indicator. However, some limitations exist. Renal hypoperfusion due to a prerenal cause may lead to an increase of creatinine, despite noninjured renal parenchyma [19]. When the renal parenchyma is injured, renal compensation may lead to a lag in the creatinine increase; moreover, injury of 50% of the kidney may occur without an increase in creatinine levels [20, 21], resulting in delayed diagnosis and intervention [22]. Thus, new markers

Different renal injury site and biomarkers.

Kidney injury site	Biomarkers
Glomerular	Urine: TP (total protein), β2-microglobulin, Albumin, and α1-microglobulin Blood: creatinine, cystatin C, and NGAL
Proximal tubules	Kim-1, NAG, netrin-1, IL-18, L-FABP, NET-3, HGF, IGFBP 7, and TIMP-2
Distal tubules	NGAL, GST-α/π, cystatin C, Cyr61, and NET-3
Collecting duct	Calbindin D28

Mekanik Ventilasyon

SHOCK, Vol. 47, Supplement 1, pp. 41–46, 2017

Review Article

MECHANICAL VENTILATION IN SEPSIS: A REAPPRAISAL

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ABSTRACT—Sepsis is the main cause of close to 70% of all cases of acute respiratory distress syndromes (ARDS). In addition, sepsis increases susceptibility to ventilator-induced lung injury. Therefore, the development of a ventilatory strategy that can achieve adequate oxygenation without injuring the lungs is highly sought after for patients with acute infection and represents an important therapeutic window to improve patient care. Suboptimal ventilatory settings cannot only harm the lung, but may also contribute to the cascade of organ failure in sepsis due to organ crosstalk. Despite the prominent role of sepsis as a cause for lung injury, most of the studies that addressed mechanical ventilation strategies in ARDS did not specifically assess sepsis-related ARDS patients. Consequently, most of the recommendations regarding mechanical ventilation in sepsis patients are derived from ARDS trials that included multiple clinical diagnoses. While there have been important improvements in general ventilatory management that should apply to all critically ill patients, sepsis-related lung injury might still have particularities that could influence bedside management. After revisiting the interplay between sepsis and ventilation-induced lung injury, this review will reappraise the evidence for the major components of the lung protective ventilation strategy, emphasizing the particularities of sepsis-related acute lung injury.

REVIEW

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Mechanical ventilation in septic shock

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Purpose of review
The aim of this study was to review the most recent literature on mechanical ventilation strategies in patients with septic shock.

Recent findings
Indirect clinical trial evidence has refined the use of neuromuscular blocking agents, positive end-expiratory pressure (PEEP) and recruitment manoeuvres in septic shock patients with acute respiratory distress syndrome. Weaning strategies and devices have also been recently evaluated. The role of lung protective ventilation in patients with healthy lungs, while recognized, still needs to be further refined. The possible detrimental effects of spontaneous breathing in patients who develop acute respiratory distress syndrome is increasingly recognized, but clinical trial evidence is still lacking to confirm this hypothesis. A new concept of lung and diaphragm protective is emerging in the critical care literature, but its application will need a complex intervention implementation approach to allow adequate scrutiny of this concept and uptake by clinicians.

Summary
Many advances in the management of the mechanically ventilated patient with sepsis and septic shock have occurred in recent years, but clinical trial evidence is still necessary to translate new hypotheses to the bedside and find the right balance between benefits and risks of these new strategies.

Original Research

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Effects of Early Enteral Nutrition on Immune Function and Prognosis of Patients With Sepsis on Mechanical Ventilation

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Abstract

Objective: To explore the therapeutic effects of early enteral nutrition (EEN) on patients with sepsis on mechanical ventilation. **Methods:** Patients with sepsis on mechanical ventilation in the medical intensive care unit (ICU) from January 2013 to March 2016 were treated with enteral nutrition. Patients treated within 48 hours of initiation of mechanical ventilation were assigned to the EEN group, and the rest were assigned to the delayed enteral nutrition (DEN) group. Peripheral blood Th17 cells and Treg cells, endotoxin (ET) level, 28-day mortality, duration of mechanical ventilation, lengths of ICU stay and hospital stay, and incidence of ICU-acquired weakness (ICU-AW) were analyzed between the 2 groups. **Results:** The proportion of Th17 cells and ET levels in the EEN group were significantly lower than those in the DEN group, whereas the proportion of Treg cells in the EEN group was remarkably higher than that in the DEN group ($P < .05$). The duration of mechanical ventilation, lengths of ICU stay and hospital stay, and incidence of ICU-AW were higher in the DEN group than in the EEN group ($P < .05$), but there was no significant difference in the 28-day mortality between the 2 groups. **Conclusion:** Patients with sepsis mainly present with an increased proportion of Th17 cells in the early stage, manifesting as enhanced immune response. Early enteral nutrition can inhibit the excessive immune response, shorten the duration of mechanical ventilation, lengths of ICU stay and hospital stay, and reduce the incidence of ICU-AW, but it has no obvious effect on 28-day mortality.

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GUIDELINES

Surviving sepsis campaign: international guidelines for management of sepsis and septic shock 2021

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Recommendation

2. We **recommend against** using qSOFA compared to SIRS, NEWS, or MEWS as a single screening tool for sepsis or septic shock

Strong recommendation, moderate-quality evidence

Recommendation

3. For adults suspected of having sepsis, we **suggest** measuring blood lactate

Weak recommendation, low-quality evidence

Initial resuscitation

Recommendations

4. Sepsis and septic shock are medical emergencies, and we **recommend** that treatment and resuscitation begin immediately

Best Practice Statement

5. For patients with sepsis induced hypoperfusion or septic shock we **suggest** that at least 30 mL/kg of intravenous (IV) crystalloid fluid should be given within the first 3 h of resuscitation

Weak recommendation, low-quality evidence

6. For adults with sepsis or septic shock, we **suggest** using dynamic measures to guide fluid resuscitation, over physical examination or static parameters alone

Weak recommendation, very low-quality evidence

Remarks

Dynamic parameters include response to a passive leg raise or a fluid bolus, using stroke volume (SV), stroke volume variation (SVV), pulse pressure variation (PPV), or echocardiography, where available

7. For adults with sepsis or septic shock, we **suggest** guiding resuscitation to decrease serum lactate in patients with elevated lactate level, over not using serum lactate

Weak recommendation, low-quality evidence

Remarks

During acute resuscitation, serum lactate level should be interpreted considering the clinical context and other causes of elevated lactate

8. For adults with septic shock, we **suggest** using capillary refill time to guide resuscitation as an adjunct to other measures of perfusion

Weak recommendation, low-quality evidence

Mean arterial pressure

Recommendation
9. For adults with septic shock on vasopressors, we **recommend** an initial target mean arterial pressure (MAP) of 65 mm Hg over higher MAP targets *Strong recommendation, moderate-quality evidence*

Admission to intensive care

Recommendation
10. For adults with sepsis or septic shock who require ICU admission, we **suggest** admitting the patients to the ICU within 6 h *Weak recommendation, low-quality evidence*

Infection

Diagnosis of infection

Recommendation
11. For adults with suspected sepsis or septic shock but unconfirmed infection, we **recommend** continuously re-evaluating and searching for alternative diagnoses and discontinuing empiric antimicrobials if an alternative cause of illness is demonstrated or strongly suspected *Best Practice statement*

Time to antibiotics

Recommendations
12. For adults with possible septic shock or a high likelihood for sepsis, we **recommend** administering antimicrobials immediately, ideally within 1 h of recognition *Strong recommendation, low quality of evidence (Septic shock)* Strong recommendation, very low quality of evidence (Sepsis without shock)
13. For adults with possible sepsis without shock, we **recommend** rapid assessment of the likelihood of infectious versus non-infectious causes of acute illness *Best Practice Statement* **Remarks** Rapid assessment includes history and clinical examination, tests for both infectious and non-infectious causes of acute illness and immediate treatment for acute conditions that can mimic sepsis. Whenever possible this should be completed within 3 h of presentation so that a decision can be made as to the likelihood of an infectious cause of the patient's presentation and timely antimicrobial therapy provided if the likelihood of sepsis is thought to be high
14. For adults with possible sepsis without shock, we **suggest** a time-limited course of rapid investigation and if concern for infection persists, the administration of antimicrobials within 3 h from the time when sepsis was first recognised *Weak recommendation, very low quality of evidence*
15. For adults with a low likelihood of infection and without shock, we **suggest** deferring antimicrobials while continuing to closely monitor the patient. *Weak recommendation, very low quality of evidence*

Antibiotic Timing

	Shock is present	Shock is absent
Sepsis is definite or probable	Administer antimicrobials **Immediately**, ideally within 1 hour of recognition	
Sepsis is possible	Administer antimicrobials **Immediately**, ideally within 1 hour of recognition	Rapid assessment* of infectious vs noninfectious causes of acute illness Administer antimicrobials **within 3 hours** if concern for infection persists

*Rapid assessment includes history and clinical examination, tests for both infectious and non-infectious causes of acute illness and immediate treatment for acute conditions that can mimic sepsis. Whenever possible this should be completed within 3 hours of presentation so that a decision can be made as to the likelihood of an infectious cause of the patient's presentation and timely antimicrobial therapy provided if the likelihood is thought to be high.

Antimicrobial choice

Recommendations
17. For adults with sepsis or septic shock at high risk of methicillin resistant staph aureus (MRSA), we **recommend** using empiric antimicrobials with MRSA coverage over using antimicrobials without MRSA coverage *Best Practice statement*
18. For adults with sepsis or septic shock at low risk of methicillin resistant staph aureus (MRSA), we **suggest against** using empiric antimicrobials with MRSA coverage, as compared with using antimicrobials without MRSA coverage *Weak recommendation, low quality of evidence*

Antifungal therapy

Recommendations
22. For adults with sepsis or septic shock at high risk of fungal infection, we **suggest** using empiric antifungal therapy over no antifungal therapy *Weak recommendation, low quality of evidence*
23. For adults with sepsis or septic shock at low risk of fungal infection, we **suggest against** empiric use of antifungal therapy *Weak recommendation, low quality of evidence*

Antiviral therapy

Recommendation
24. We make **no recommendation** on the use of antiviral agents

Delivery of antibiotics

Recommendation
25. For adults with sepsis or septic shock, we **suggest** using prolonged infusion of beta-lactams for maintenance (after an initial bolus) over conventional bolus infusion *Weak recommendation, moderate quality of evidence*

Pharmacokinetics and pharmacodynamics

Recommendation
26. For adults with sepsis or septic shock, we **recommend** optimising dosing strategies of antimicrobials based on accepted pharmacokinetic/pharmacodynamic (PK/PD) principles and specific drug properties *Best Practice Statement*

Source control

Recommendation
27. For adults with sepsis or septic shock, we **recommend** rapidly identifying or excluding a specific anatomical diagnosis of infection that requires emergent source control and implementing any required source control intervention as soon as medically and logistically practical *Best Practice Statement*

Recommendation
28. For adults with sepsis or septic shock, we **recommend** prompt removal of intravascular access devices that are a possible source of sepsis or septic shock after other vascular access has been established *Best Practice Statement*

Haemodynamic management

Fluid management

Recommendations

32. For adults with sepsis or septic shock, we **recommend** using crystalloids as first-line fluid for resuscitation
Strong recommendation, moderate quality of evidence

33. For adults with sepsis or septic shock, we **suggest** using balanced crystalloids instead of normal saline for resuscitation
Weak recommendation, low quality of evidence

34. For adults with sepsis or septic shock, we **suggest** using albumin in patients who received large volumes of crystalloids over using crystalloids alone
Weak recommendation, moderate quality of evidence

35. For adults with sepsis or septic shock, we **recommend against** using starches for resuscitation
Strong recommendation, high quality of evidence

36. For adults with sepsis and septic shock, we **suggest against** using gelatin for resuscitation
Weak recommendation, moderate quality

Vasoactive agents

Recommendations

37. For adults with septic shock, we **recommend** using norepinephrine as the first-line agent over other vasopressors. *Strong recommendation*
Dopamine. *High quality evidence*
Vasopressin. Moderate-quality evidence
Epinephrine. Low-quality evidence
Selepressin. *Low-quality evidence*
Angiotensin II. *Very low-quality evidence*

Remark

In settings where norepinephrine is not available, epinephrine or dopamine can be used as an alternative, but we encourage efforts to improve the availability of norepinephrine. Special attention should be given to patients at risk for arrhythmias when using dopamine and epinephrine

38. For adults with septic shock on norepinephrine with inadequate MAP levels, we **suggest** adding vasopressin instead of escalating the dose of norepinephrine
Weak recommendation, moderate-quality evidence

Remark

In our practice, vasopressin is usually started when the dose of norepinephrine is in the range of 0.25–0.5 ug/kg/min

39. For adults with septic shock and inadequate MAP levels despite norepinephrine and vasopressin, we **suggest** adding epinephrine
Weak recommendation, low-quality evidence

40. For adults with septic shock, we **suggest against** using terlipressin
Weak recommendation, low quality of evidence

Vasoactive Agent Management

- Use norepinephrine as first-line vasopressor

For patients with septic shock on vasopressor

- Target a MAP of 65mm Hg
- Consider invasive monitoring of arterial blood pressure

If central access is not yet available

- Consider initiating vasopressors peripherally*

If MAP is inadequate despite low-to-moderate-dose norepinephrine

- Consider adding vasopressin

If cardiac dysfunction with persistent hypoperfusion is present despite adequate volume status and blood pressure

- Consider adding dobutamine or switching to epinephrine

Strong recommendations Weak recommendations

*When using vasopressors peripherally, they should be administered only for a short period of time and in a vein proximal to the antecubital fossa.

Inotropes

Recommendations

41. For adults with septic shock and cardiac dysfunction with persistent hypoperfusion despite adequate volume status and arterial blood pressure, we **suggest** either adding dobutamine to norepinephrine or using epinephrine alone

Weak recommendation, low quality of evidence

42. For adults with septic shock and cardiac dysfunction with persistent hypoperfusion despite adequate volume status and arterial blood pressure, we **suggest against** using levosimendan

Weak recommendation, low quality of evidence

Fluid balance

Recommendation

45. There is **insufficient evidence to make a recommendation** on the use of restrictive versus liberal fluid strategies in the first 24 h of resuscitation in patients with sepsis and septic shock who still have signs of hypoperfusion and volume depletion after initial resuscitation

Remarks

Fluid resuscitation should be given only if patients present with signs of hypoperfusion

Monitoring and intravenous access

Recommendations

43. For adults with septic shock, we **suggest** using invasive monitoring of arterial blood pressure over non-invasive monitoring, as soon as practical and if resources are available

Weak recommendation, very low quality of evidence

44. For adults with septic shock, we **suggest** starting vasopressors peripherally to restore MAP rather than delaying initiation until a central venous access is secured

Weak recommendation, very low quality of evidence

Remark

When using vasopressors peripherally, they should be administered only for a short period of time and in a vein in or proximal to the antecubital fossa

Ventilation

Oxygen targets

Recommendation
46. There is **insufficient evidence to make a recommendation** on the use of conservative oxygen targets in adults with sepsis-induced hypoxemic respiratory failure

High-flow nasal oxygen therapy

Recommendation
47. For adults with sepsis-induced hypoxemic respiratory failure, we **suggest** the use of high flow nasal oxygen over non-invasive ventilation *Weak recommendation, low quality of evidence*

Non-invasive ventilation

Recommendation
48. There is **insufficient evidence to make a recommendation** on the use of non-invasive ventilation in comparison to invasive ventilation for adults with sepsis-induced hypoxemic respiratory failure

Protective ventilation in acute respiratory distress syndrome (ARDS)

Recommendation
49. For adults with sepsis-induced ARDS, we **recommend** using a low tidal volume ventilation strategy (6 mL/kg), over a high tidal volume strategy (> 10 mL/kg) *Strong recommendation, high quality of evidence*

Recommendation
50. For adults with sepsis-induced severe ARDS, we **recommend** using an upper limit goal for plateau pressures of 30 cm H_2O, over higher plateau pressures *Strong recommendation, moderate quality of evidence*

Extracorporeal membrane oxygenation (ECMO)

Recommendation
57. For adults with sepsis-induced severe ARDS, we **suggest** using veno-venous (VV) ECMO when conventional mechanical ventilation fails in experienced centers with the infrastructure in place to support its use *Weak recommendation, low quality of evidence*

Blood Purification

Recommendations
59. For adults with sepsis or septic shock, we **suggest against** using polymyxin B haemoperfusion *Weak recommendation; low quality of evidence*
60. There is **insufficient evidence to make a recommendation** on the use of other blood purification techniques

Red blood cell (RBC) transfusion targets

Recommendation
61. For adults with sepsis or septic shock, we **recommend** using a restrictive (over liberal) transfusion strategy *Strong recommendation; moderate quality of evidence* **Remark** A restrictive transfusion strategy typically includes a haemoglobin concentration transfusion trigger of 70 g/L; however, RBC transfusion should not be guided by haemoglobin concentration alone. Assessment of a patient's overall clinical status and consideration of extenuating circumstances such as acute myocardial ischaemia, severe hypoxemia or acute haemorrhage is required

Additional therapies

Corticosteroids

Recommendation
58. For adults with septic shock and an ongoing requirement for vasopressor therapy we **suggest** using IV corticosteroids *Weak recommendation; moderate quality of evidence* **Remark** The typical corticosteroid used in adults with septic shock is IV hydrocortisone at a dose of 200 mg/day given as 50 mg intravenously every 6 h or as a continuous infusion. It is suggested that this is commenced at a dose of norepinephrine or epinephrine ≥ 0.25 mcg/kg/min at least 4 h after initiation

Immunoglobulins

Recommendation
62. For adults with sepsis or septic shock, we **suggest against** using intravenous immunoglobulins *Weak recommendation, low quality of evidence*

Stress ulcer prophylaxis

Recommendation
63. For adults with sepsis or septic shock, and who have risk factors for gastrointestinal (GI) bleeding, we **suggest** using stress ulcer prophylaxis *Weak recommendation, moderate quality of evidence*

Venous thromboembolism (VTE) prophylaxis

Recommendations
64. For adults with sepsis or septic shock, we **recommend** using pharmacologic VTE prophylaxis unless a contraindication to such therapy exists *Strong recommendation, moderate quality of evidence*
65. For adults with sepsis or septic shock, we **recommend** using low molecular weight heparin (LMWH) over unfractionated heparin (UFH) for VTE prophylaxis *Strong recommendation, moderate quality of evidence*
66. For adults with sepsis or septic shock, we **suggest against** using mechanical VTE prophylaxis in addition to pharmacological prophylaxis, over pharmacologic prophylaxis alone *Weak recommendation, low quality of evidence*

Renal replacement therapy

Recommendations
67. In adults with sepsis or septic shock and AKI who require renal replacement therapy, we **suggest** using either continuous or intermittent renal replacement therapy *Weak recommendation, low quality of evidence*
68. In adults with sepsis or septic shock and AKI, with no definitive indications for renal replacement therapy, we **suggest against** using renal replacement therapy *Weak recommendation, moderate quality of evidence*

Glucose control

Recommendation
69. For adults with sepsis or septic shock, we **recommend** initiating insulin therapy at a glucose level of ≥ 180 mg/dL (10 mmol/L) *Strong recommendation; moderate quality of evidence* **Remark** Following initiation of an insulin therapy, a typical target blood glucose range is 144–180 mg/dL (8–10 mmol/L)

Vitamin C

Recommendation
70. For adults with sepsis or septic shock, we **suggest against** using IV vitamin C *Weak recommendation, low quality of evidence*

Bicarbonate therapy

Recommendations
71. For adults with septic shock and hypoperfusion-induced lactic acidemia, we **suggest against** using sodium bicarbonate therapy to improve haemodynamics or to reduce vasopressor requirements *Weak recommendation, low quality of evidence*
72. For adults with septic shock, severe metabolic acidemia (pH ≤ 7.2) and AKI (AKIN score 2 or 3), we **suggest** using sodium bicarbonate therapy *Weak recommendation, low quality of evidence*

Cognitive therapy

Recommendation
90. There is **insufficient evidence to make a recommendation** on early cognitive therapy for adult survivors of sepsis or septic shock

Nutrition

Recommendation
73. For adult patients with sepsis or septic shock who can be fed enterally, we **suggest** early (within 72 h) initiation of enteral nutrition *Weak recommendation; very low quality of evidence*

Post-discharge follow-up

Recommendations
91. For adult survivors of sepsis or septic shock, we **recommend** assessment and follow-up for physical, cognitive, and emotional problems after hospital discharge Best Practice Statement
92. For adult survivors of sepsis or septic shock, we **suggest** referral to a post-critical illness follow-up programme if available *Weak recommendation, very low-quality evidence*
93. For adult survivors of sepsis or septic shock receiving mechanical ventilation for > 48 h or an ICU stay of > 72 h, we **suggest** referral to a post-hospital rehabilitation programme *Weak recommendation, very low-quality evidence*

Kılavuzlar gerekli, çünkü yapılan çalışmalar toplanıyor, yorumlanıyor okuyucuya sunuluyor

Kılavuzlar “sofistike” değil kolay uygulanabilir olmalıdır

Kılavuzların *ilk sayfaları* mutlaka okunmalı

Kılavuzların sadece *şematik kısımları değil tüm kılavuz okunmalı* 74 sayfa 655 literatürden oluşsa dahi

Kılavuzlar klinikte hekim bilgisinin ve tecrübesinin önüne geçmemelidir. Hiçbir kılavuz bunun sorumluluğunu almamaktadır

Kılavuzların sık sık yenilenmesi anlaşılması ve yaygınlaşmasını zorlaştırmaktadır


THINK
TREAT
STOP!
sepsis