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Early management of adult sepsis and septic shock: Korean clinical practice guidelines

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Background: Despite recent advances and global improvements in sepsis recognition and supportive care, mortality rates remain high, and adherence to sepsis bundle components in Korea is low. To address this, the Korean Sepsis Alliance, affiliated with the Korean Society of Critical Care Medicine, developed the first sepsis treatment guidelines for Korea based on a comprehensive systematic review and meta-analysis.

Methods: A *de novo* method was used to develop the guidelines. Methodologies included determining key questions, conducting a literature search and selection, assessing the risk of bias, synthesizing evidence, and developing recommendations. The certainty of evidence and the strength of recommendations were determined using the Grading of Recommendations, Assessment, Development, and Evaluations approach. Draft recommendations underwent internal and external review processes and public hearings. The development of these guidelines was supported by a research grant from the Korean Disease Control and Prevention Agency.

Results: In these guidelines, we focused on early treatments for adult patients with sepsis and septic shock. Through the guideline development process, 12 key questions and their respective recommendations were formulated. These include lactate measurement, fluid therapies, target blood pressure, antibiotic administration, use of vasopressors and dobutamine, extracorporeal membrane oxygenation, and echocardiography.

Conclusions: These guidelines aim to support medical professionals in making appropriate decisions about treating adult sepsis and septic shock. We hope these guidelines will increase awareness of sepsis and reduce its mortality rate.

Key Words: guidelines; outcome; sepsis; septic shock; treatment

Guideline

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INTRODUCTION

Sepsis is a life-threatening condition characterized by a dysregulated host response to infection, leading to organ dysfunction. It is a significant global health issue, affecting approximately 50 million individuals annually and causing at least 11 million deaths worldwide [1,2]. In recent decades, advances in sepsis recognition and supportive care have led to improved

outcomes. However, studies indicate that mortality rates in Korea remain higher than in Western countries, and compliance with sepsis bundle components is notably low across Asia [3,4]. Specifically, a Korean Sepsis Alliance (KSA) report highlights significant regional and hospital-level variations in sepsis mortality and bundle compliance within Korea [5]. This underscores the growing awareness of the need for standardized sepsis treatment protocols and performance improvements.

Two decades ago, the European Society of Intensive Care Medicine and the Society of Critical Care Medicine consortium developed the Surviving Sepsis Campaign (SSC) international guidelines, which are revised every 4 years [6]. The United Kingdom also has the National Institute for Health and Care Excellence guidelines on sepsis management [7]. Among Asian countries, Japan developed a version of sepsis guidelines in 2016 and 2020 [8,9]. However, sepsis guidelines incorporating comprehensive systematic review and meta-analysis had yet to be developed in Korea. Hence, in recognition of the clinical circumstances in Korea, the KSA, an organization affiliated with the Korean Society of Critical Care Medicine (KSCCM), applied for research funding from the Korean Disease Control and Prevention Agency and developed the first sepsis treatment guidelines with a comprehensive systematic review and meta-analysis, involving multidisciplinary departments.

The present guidelines comprise 12 key questions (KQs) and their recommendations, focusing mainly on early sepsis treatments such as fluids, vasopressors, and prompt antibiotic administration. Diagnostic methods, management after initial resuscitation, and adjunctive therapies are not covered. Early recognition is crucial, but the topic could not be covered in these guidelines because of constraints. These guidelines are intended to support medical professionals in making appropriate decisions for treating sepsis and septic shock. The original Korean version of the guidelines obtained approvals from the KCDA and KSCCM and was subsequently endorsed by seven academic societies. The Korean version was first released on the official website of the KSCCM (https://www.ksccm.org/html/).

MATERIALS AND METHODS

For development of the guidelines, we employed a *de novo* method to account for the unique epidemiological and clinical characteristics of sepsis patients in Korea. Supplementary Material 1 provides detailed processes, and Table 1 summarizes the recommendations.

Organization of Committee Members

The guideline committees consisted of a steering committee (n=9), a working committee (n=24 from 9 departments), an advisory committee (external consultants, n=2; from the National Evidence-based Healthcare Collaborating Agency [NECA] and Korean Society of Anesthesiologists), and external reviewers (n=9). Guideline development was carried out through regular online meetings.

Key Questions and PICO

After an initial survey of landmark articles and international guidelines, the working committee identified 14 candidate KQs deemed most urgent and essential for treating sepsis and septic shock in the Korean clinical context. The 12 KQs with the highest votes from the working group members were selected from these. In a single working group, two members were assigned to each KQ and established the PICO (patients, intervention, comparator, and outcomes). For each PICO, the working group classified outcomes as either "critical" or "important."

Literature Search and Selection

We collaborated with a professional literature search agency for a comprehensive literature search. A literature search was performed using PubMed, Embase, Cochrane Library, and KMbase and was supplemented by a manual search and reference assessment. The literature search was performed through December 2022. The inclusion and exclusion criteria for study selection was based on the PICO elements and study design of each KQ. Screening was initially performed using titles and abstracts by two members of each KQ group. Thereafter, the two members independently conducted a full-text review and reached a consensus. Disagreements were resolved by a third member or by discussion with the steering committee.

Assessment of Risk of Bias (Quality)

For the selected articles, two working members independently assessed the risk of bias and reached a consensus. In the event of disagreements, an external consultant (e.g., a NECA methodologist) was involved. For randomized controlled trials (RCTs), the Cochrane risk of bias (RoB) tool was used, and for non-RCTs, RoB for nonrandomized studies 2.0 (RoBANS 2.0) was used.

Level of Evidence and Grade of Recommendations

A meta-analysis was performed if quantitative synthesis was

Table 1. Summary of recommendations

KQ	Subject	Recommendation	Recommendation strength	Quality of evidence
1	Lactate clearance	When performing fluid resuscitation in patients with sepsis or septic shock, the use of lactate clearance is suggested as an indicator rather than central venous oxygen saturation ($ScvO_2$).	B, conditional recommendation for intervention	Moderate
2	Fluid resuscitation	In adult patients with sepsis or septic shock accompanied by hypotension or hypoperfusion, administration of 30 ml/kg of crystalloid fluids within the first 3 hours is suggested.	B, conditional recommendation for intervention	Low
3	Fluid types	Balanced crystalloids or saline (0.9% saline) can be used during fluid resuscitation in sepsis patients.	B, conditional recommendation for intervention	Moderate
4	Target blood pressure	In adult patients with septic shock, we suggest a target MAP be ≥65 mm Hg over higher MAP targets.	B, conditional recommendation for intervention	Moderate
5	Dynamic parameters	If additional fluids are required after the initial fluid resuscitation in adult patients with sepsis or septic shock, fluid therapy using dynamic parameters is suggested.	B, conditional recommendation for intervention	Moderate
6-1	Antibiotics	In adult patients with septic shock, we suggest administering antibiotics within 1 hour of septic shock recognition.	B, conditional recommendation for intervention	Low
6-2	Antibiotics	In adult patients with sepsis, we suggest administering antibiotics within 3 hours of sepsis recognition.	E, expert consensus	Very low
7	Timing of vasopressors	In adult patients with septic shock, early administration of vasopressors is suggested if necessary to ensure hemodynamic stability during the initial fluid therapy.	B, conditional recommendation for intervention	Moderate
8	Vasopressor types	We recommend that norepinephrine be used in preference to other vasopressors in adult patients with septic shock.	A, strong recommendation for intervention	High (vs. dopamine)
9	Vasopressin	In adult patients with septic shock, when appropriate MAP is not maintained despite the use of the usual dose of norepinephrine, we suggest adding vasopressin rather than increasing norepinephrine dose.[b]	B, conditional recommendation for intervention	Moderate
10	Dobutamine	In adult septic shock patients with decreased cardiac function and hypoperfusion, the use of dobutamine may be considered.	E, expert consensus	Very low
11-1	VV-ECMO	In patients with acute respiratory distress syndrome due to sepsis who do not respond to existing standard treatments, we suggest performing veno-vneous ECMO.[c]	E, expert consensus	None
11-2	VA-ECMO	In patients with septic shock and decreased cardiac function who does not respond to existing standard treatments, venous-arterial ECMO can be applied.[c]	B, conditional recommendation for intervention	Low
12	ECHO	We suggest performing echocardiography to assess cardiac function and hemodynamics in adult patients with sepsis.	B, conditional recommendation for intervention	Very low

KQ: key question; MAP: mean arterial pressure; VV: veno-venous; ECMO: extracorporeal membrane oxygenation; VA: veno-arterial; ECHO: echocardiography.
a) In clinical practice, the recommendation to administer antibiotics within 1 hour may still be difficult to apply. However, it is advisable to administer empiric antibiotics as soon as possible after recognizing sepsis or septic shock, and when the causative organisms are identified, it is necessary to adjust antibiotics according to susceptibility results; b) Additional research is needed on the timing of vasopressin administration, but based on the results of past randomization studies, it seems appropriate to consider adding vasopressin when the norepinephrine administration concentration exceeds 0.25 μg/kg/min; c) (1) Before performing ECMO, the benefits and risks to the patient must be considered. (2) ECMO is not recommended for patients with septic shock accompanied by multi-organ failure.

possible, and qualitative description was used if meta-analysis was not possible. A random-effects model was applied when heterogeneity was high. Publication bias was assessed using Egger's test and the trim-and-fill method when the number of included studies was 10 or more. In these guidelines, Review Manager (RevMan) version 5.4 (The Nordic Cochrane Center) was used for meta-analyses [10]. The certainty of evidence was assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach, where the level was rated as "high," "moderate," "low," or "very low" [11]. The direction and strength of the recommendations were determined from four factors: "certainty of evidence," "magnitude

of effects (benefits and harms)," "patient values and preferences," and "resources used." Definitions for the certainty of evidence and grade of recommendations are summarized in Tables 2 and 3.

Drafting of Recommendation and Consensus Process

The working group members in each KQ drafted the recommendations. Subsequently, consensus was reached through online meetings attended by the majority of working group members. In cases of disagreement, the steering committee intervened to make the final decision. After internal (peer) and external review and a public hearing, some minor modifications were made to the recommendations (Supplementary Material 1).

Table 2. Significance of the four levels of evidence by GRADE

Level of evidence	Recommendations
High	We are very confident that the true effect lies close to that of the estimated effect.
Moderate	We are moderately confident in the estimated effect. The true effect is likely to be close to the estimated effect, but there is a possibility that it is substantially different.
Low	There is limited confidence in the estimated effect: the true effect might be substantially different from the estimated effect.
Very low	We have very little confidence in the estimated effect: the true effect is likely to be substantially different from the estimated effect.

GRADE: Grading of Recommendations Assessment, Development and Evaluation.

KEY QUESTIONS AND RECOMMENDATIONS

The guidelines present 12 KQs along with their respective recommendations. For each recommendation, background information, a summary of evidence, and relevant comments are provided. However, due to space constraints, the summary of findings (tables), the assessment of RoB, and the meta-analyses (e.g., forest plots), are presented in Supplementary Material 1. Some data accompanying KQ 7 (e.g., timing of vasopressors) were previously reported in another article [12].

KQ 1. Lactate clearance

When performing fluid resuscitation in patients with sepsis or septic shock, is the use of lactate clearance recommended as an indicator rather than central venous oxygen saturation ($ScvO_2$)?

Recommendation

When performing fluid resuscitation in patients with sepsis or septic shock, the use of lactate clearance is suggested as an indicator rather than $ScvO_2$ (Recommendation strength B,

Table 3. Grade of recommendation by GRADE approach

Grade of recommendation			Definition
Evidence-based	A	Strongly recommended	We strongly recommend this intervention under most clinical situations considering the benefits and harms of the intervention, level of evidence, patients' values and preferences, and resources used.
	B	Conditionally recommended	We recommend selective or collective use since this intervention may vary depending on the clinical situations or patient/social values.
	C	Conditionally against	We recommend against this intervention under some situations or conditions since this intervention may result in more harms than benefits and when considering the clinical situations or patient/social values.
	D	Strongly against	We recommend against this intervention under most clinical situations since this intervention yields more harms than benefits and when considering the clinical situations or patient/social values.
	I	Inconclusive	Considering the benefits and harms of the intervention, level of evidence, patients' values and preferences, and resources used, we cannot decide whether this intervention should be implemented or not due to the low level of evidence, uncertainty in the balance between benefits and harms, and large variability. This means that the recommendation can be for or against this intervention, and we recommend that you follow the decision made by the clinician.
Expert consensus	E	Expert consensus	Despite the lack of clinical evidence in literature, we recommend the use of this intervention based on clinical experience and expert consensus considering the benefits and harms of the intervention, level of evidence, patients' values and preferences, and resources used.

GRADE: Grading of Recommendations Assessment, Development and Evaluation.

conditional recommendation for intervention; Certainty of evidence: moderate).

Background

Lactate is a marker of metabolic stress and tissue hypoxia, while $ScvO_2$ reflects the balance between oxygen delivery and consumption (e.g., the amount of oxygen remaining in the blood after circulating through the tissues). Previously, $ScvO_2$ was used as a target for quantitative resuscitation of sepsis patients in the early SSC international guidelines [13]. However, there are some barriers to using $ScvO_2$ as a quantitative resuscitation goal, such as time, technology, and need for measurement equipment [14,15]. Of note, protocoled quantitative resuscitation, known as early goal-directed therapy (EGDT), failed to show a reduction in mortality in subsequent large multicenter RCTs and was removed from the recommendations when the SSC guidelines were revised in 2016 [16-18]. However, the relationship between lactate concentration and mortality in sepsis patients is well known [19,20], and lactate measurement is recommended as a component of the Hour-1 bundle by the SSC guideline. Elevated levels of lactate (>2 mmol/L) are also included as a criterion for septic shock in the Sepsis-3 definition [21].

Summary of Evidence

Of 16,822 articles found through the initial literature search, 12,462 were screened. Seventy-five full-text articles were reviewed, and four RCTs were finally selected [15,22-24]. All four studies looked at in-hospital mortality as the primary clinical outcome, and the lengths of intensive care unit (ICU) days and mechanical ventilation (MV) were confirmed in two studies each. In the studies, the lactate clearance and $ScvO_2$ measurement groups were compared during initial fluid resuscitation. The meta-analysis showed that the lactate clearance group, compared to the $ScvO_2$ group, had a significantly lower in-hospital mortality rate (risk ratio [RR], 0.74; 95% CI, 0.59–0.93). No significant differences were observed between the two groups in the periods of MV application and length of ICU stay, but the period of MV application tended to be lower in the lactate clearance group (mean difference [MD], 10.74 hours; 95% CI, 23.86 to 2.38). Despite unclear information about the concealment of group allocation in two studies, the RoB in other areas was low, and the level of evidence was moderate in all four RCTs. The overall level of evidence was determined as moderate, considering the level of in-hospital mortality, which is a crucial outcome indicator. The benefits are higher than the risks because lactate levels can be measured quickly without inserting a central venous catheter.

Comments

In a KSA survey on obstacles to performing the sepsis bundle, the most common reason for difficulty or delay in measuring lactate levels was a shortage of doctors or nurses (43.6%). The second most common reason was a lack of awareness among medical staff regarding the importance of lactate measurement (21.5%) [25]. Therefore, continuous promotion and education on the importance of lactate measurement remain essential. Emphasis should be placed on lactate clearance, rather than just measuring lactate levels. Additionally, clinicians should be aware of other conditions involving increase in lactate levels, such as medications (metformin, epinephrine, etc.), excessive exercise, alcohol, convulsions, liver disease, and tumors. Interestingly, recent studies on resuscitation using capillary refill time showed a trend toward a lower 28-day mortality rate and improvement in major organ function at three days compared to lactate levels [26,27]. Thus, capillary refill time may be helpful in resource-limited countries where a prompt lactate measurement is not feasible.

KQ 2. Fluid resuscitation

Should at least 30 ml/kg of crystalloid fluids be administered within 3 hours of starting resuscitation in adult patients with sepsis or septic shock and hypoperfusion?

Recommendation

In adult patients with sepsis or septic shock accompanied by hypotension or hypoperfusion, administration of 30 ml/kg of crystalloid fluids within the first 3 hours is suggested (Recommendation strength B, conditional recommendation for intervention; Certainty of evidence: low).

Background

Fluid therapy is essential to early sepsis resuscitation, increasing circulating blood volume and cardiac output. The 2021 SSC international guidelines recommend administering 30 ml/kg of crystalloid fluids within 3 hours in patients with tissue hypoperfusion due to sepsis [20]. That dosage was based on the amount of fluid administered in previous sepsis studies. However, excessive fluid treatment carries the risk of complications such as fluid overload, pulmonary edema, and prolonged MV. In studies by Boyd et al. [28] and Sakr et al. [29], positive fluid balance was associated with increased mortality. In a study

by Marik et al. [30], fluid treatment of greater than 5 L on the first day was associated with a high mortality rate. However, many studies were not limited to sepsis patients but covered a broad range of critically ill patients. In observational studies, it is essential to consider that greater severity may correlate with a higher likelihood of receiving larger fluid volumes early in treatment.

To date, no prospective study has examined the association between fluid dose and treatment outcomes in sepsis patients. Specifically, the timing of fluid administration (early vs. delayed fluid administrations) and treatment results differed from study to study. The presently considered guideline reviewed and analyzed studies that specified the initial fluid dose and administration time for patients with sepsis or septic shock.

Summary of Evidence

From 3,720 papers retrieved through the literature search strategy, 2,948 studies were initially screened, excluding duplicates. Among them, 20 full-text articles were reviewed, and finally, five RCTs and two retrospective cohort studies were selected. In a retrospective cohort study by Kuttab et al. [31], sepsis or septic shock was defined using International Classification of Diseases (ICD) codes. That study found that, compared to patients who received 30 ml/kg crystalloids within the first 3 hours of sepsis (509 patients), the in-hospital mortality rate (odds ratio [OR], 1.52; 95% CI, 1.03–2.24) and the length of ICU stay were significantly increased in patients who did not that treatment (523 patients) [31]. Since no other articles addressing the PICO were identified, the scope was extended to secure as much evidence as possible for the clinical question by including one observational study and five RCTs as indirect evidence.

Seymour et al. [32] analyzed 26,978 patients who received 30 ml/kg of fluid within 12 hours among 49,331 patients with sepsis or septic shock who visited the emergency rooms of 149 hospitals. The mortality rate did not increase when the completion time of 30 ml/kg fluid administration was delayed (OR, 1.01; 95% CI, 0.99–1.02). Additionally, no significant difference was found between patients who received 30 ml/kg fluid within 6 hours and those who experienced it between 6 and 12 hours (OR, 1.02; 95% CI, 0.92–1.14) [32]. However, because no accurate data on the number of patients were available, our meta-analysis did not include that study. In the meta-analysis using the five RCTs on the EGDT (Rivers et al. [33], ProCESS [17], ARISE [16], ProMISe [18], and Andrews et al. [34]), the risk for in-hospital mortality and 28-day mortality was 1.17 (0.91–1.51) and 1.10 (0.92–1.32), respectively. A non-significant difference occurred between the early resuscitation and the control groups. In one of these studies, the mortality rate was higher in the resuscitation group [34]. However, since the EGDT study by Rivers et al. [33], early fluid therapy has been considered important and is included in the usual care of patients with sepsis or septic shock. In RCTs, such as ARISE, ProCESS, and ProMISe, approximately 2.0 L of fluids was administered within the first 6 hours, even in the usual care group [35]. In particular, the dose-response relationship between the amounts of initial fluids and outcomes in a retrospective study by Kuttab et al. [31] may emphasize the importance of early fluid administration. Based on this evidence, the recommendation grade for treatment was determined as conditional, and the level of evidence was judged to be low due to the lack of related research.

Comments

There is insufficient evidence to determine if at least 30 ml/kg of crystalloid fluids should be administered within the first 3 hours for management in adults with sepsis or septic shock accompanied by hypoperfusion. However, the CLASSIC trial used four noteworthy conditions (e.g., conditions for intravenous fluid administration in the restrictive fluid group): severe hypoperfusion, which was defined as lactate levels of at least 4 mmol/L; a mean arterial pressure (MAP) below 50 mm Hg despite infusion of a vasopressor or an inotropic agent; mottling beyond the edge of the kneecap (mottling score >2); and a urine output < 0.1 ml/kg/hr for the first 2 hours [36,37]. Again, although fluid therapy is critical for increasing cardiac output and tissue perfusion, the disadvantages should be considered. Excessive fluid administration can cause worsening pulmonary edema, a decrease in cardiac function, and increases in the duration of MV or ICU stay. Therefore, the decision to administer fluids should be made with caution, considering the risks and benefits.

KQ 3. Fluid type

When performing fluid resuscitation in patients with sepsis, does the use of balanced crystalloid, compared to 0.9% saline, reduce mortality rates and incidence of acute kidney injury?

Recommendation

Balanced crystalloids or saline (0.9% saline) can be used

during fluid resuscitation in patients with sepsis (Recommendation strength B, conditional recommendation for intervention; Certainty of evidence: moderate)

Background

Crystalloid fluids are recommended during fluid resuscitation in sepsis patients [20]. However, recent studies have reported that intravenous 0.9% saline promotes hyperchloremic metabolic acidosis, increases the possibility of acute kidney injury (AKI) [38-40], and increases mortality [41-43]. Therefore, more attention has been given to the usefulness of balanced solutions with electrolyte components more closely resembling those of plasma-Ringer's Lactate solution and Plasma-Lyte A solution [42]. However, conclusive evidence on the choice of crystalloid fluids on patient outcomes is lacking [44,45]. Therefore, the present guideline analyzed and compared the effects of the two fluid types on patient outcomes.

Summary of Evidence

Through the literature search, a total of 23,338 articles was identified. After excluding duplicate studies, the titles and abstracts of 19,788 studies were assessed, and the full texts of 11,312 studies were reviewed. Among these, six RCTs were finally selected [40,46-50]. Of the six studies, only one targeted patients with sepsis, while the other five targeted those admitted to ICUs, although the number of participating patients was more significant. In the analysis, mortality (in-hospital, 28-, 30-, and 90-day mortality) was considered the critical outcome, and the incidence of AKI was analyzed as an essential outcome. Among the six selected studies, that by Semler et al. (SALT trial) [47] reported death and renal damage as a composite outcome. Therefore, we performed a meta-analysis on mortality using five studies. There was no significant difference in mortality between the two fluid therapies (RR, 0.95; 95% CI, 0.87–1.02). For the incidence of AKI, our meta-analysis was conducted using two studies (by Young et al. [46] and Kumar et al. [48]), and no significant difference was found between the two fluids (RR, 0.71; 95% CI, 0.47–1.06). In an open-label study by Kumar et al. [48] (also published by Golla et al. in 2022), the concentration of chloride ion and the incidences of AKI at 24 and 48 hours were significantly increased in the group receiving 0.9% saline compared to those receiving balanced crystalloids. However, during the entire hospitalization period, there was no difference in the chloride ion concentration, AKI incidence, and mortality rate [48]. In the SMART study by Semler et al. [40], which targeted 7,942 critically ill patients admitted to ICUs, balanced crystalloids reduced mortality, use of renal replacement therapy (RRT), and persistent renal function decline in all enrolled patients with no statistical significance, but there was a tendency favoring balanced crystalloids in sepsis patients. In a study by Brown et al. [43], a secondary analysis of the SMART trial, balanced crystalloids significantly reduced the 30-day in-hospital mortality rate (adjusted OR, 0.74; 95% CI, 0.59–0.93; P=0.01) with improved renal outcomes. However, this was a single-center study, and fluid resuscitation was not assigned using a blinded method. There is also a possibility of misclassification due to the use of ICD-10 codes. In a 2015 study by Young et al. [46] of patients in medical ICUs, no differences were identified either in the incidence of AKI or the use of RRT between the two fluid groups. In our meta-analysis, no significant differences were identified between 0.9% saline and balanced crystalloid groups; except for the study by Seymour et al. [32], there was no significant difference in primary outcomes. Therefore, the level of evidence was lowered by one grade due to inconsistency. Additionally, since meta-analysis was conducted using data from subgroup populations, it is difficult to rule out RoB. Based on this, the evidence level of the recommendation was judged as moderate.

Comments

Despite no significant difference in the critical outcomes in the meta-analysis, the results from recent analyses by Zampieri et al. [51,52] are noteworthy. In their secondary analyses of the original BaSICS (Balanced Solutions in Intensive Care Study) trial, the beneficial effects of balanced solution over 0.9% saline were more apparent in septic patients likely to have unplanned ICU admission and the need for higher fluid volumes. Based on their results, a balanced solution may be preferred to 0.9% saline in septic conditions where a large volume of fluids is needed, such as peritonitis or pancreatitis. However, it is important to consider the association of volume overload with worse outcomes regardless of the type of fluid, especially in septic patients. In addition, the use of balanced crystalloids may exert detrimental effects in patients with traumatic brain injury [49]. Finally, given the statistically significant increase in chloride ion concentration (or hyperchloremic acidosis) in the 0.9% saline group [48], the choice of crystalloid fluids can depend on the circumstances, especially when the patient has hyperkalemia, hyperchloremia, or AKI [46,48].

KQ 4. Target blood pressure

In adult patients with septic shock, can a target MAP ≥65 mm Hg improve the outcomes of patients compared to targeting a higher MAP?

Recommendation

In adult patients with septic shock, we suggest a target MAP ≥65 mm Hg over higher MAP targets (Recommendation strength B, conditional recommendation for intervention; Certainty of evidence: moderate).

Background

The 2021 SSC international guidelines recommend maintaining the initial target MAP above 65 mm Hg in adult patients with septic shock using vasopressors as a strong recommendation with moderate quality of evidence [20]. MAP is the primary determinant of systemic filling pressure and the main driver of venous return and cardiac output. Thus, as MAP increases, tissue blood flow also increases. Specific organs, such as the brain and kidneys, can autoregulate blood flow, but when MAP falls below approximately 60 mm Hg, tissue perfusion decreases proportionally. Therefore, an adequate MAP is crucial in patients with septic shock.

Summary of Evidence

A total of 8,386 studies was identified; after excluding duplicates, we reviewed the titles and abstracts of 6,750 studies. Among these, after excluding 6,736 articles, we reviewed the full texts of 14 articles. Finally, three RCTs were selected to compare patients who maintained MAP above 65 mm Hg (control) with those who targeted an MAP higher than 65 mm Hg (intervention). In a prospective, open-label RCT by Asfar et al. [53], 776 patients with septic shock were divided into a high-target group (n=338, MAP target 80 to 85 mm Hg) and a low-target group (n=338, MAP target 65 to 70 mm Hg). On day 28, 142 people (36.6%) in the higher MAP group and 132 people (34.0%) in the lower MAP group had died, with no significant difference between the two groups (hazard ratio [HR], 1.07; 95 % CI, 0.84–1.38; P=0.57). The 90-day mortality rate also showed no significant difference between the two groups. However, atrial fibrillation was more frequent and use of RRT was less frequent in the higher MAP group. In a prospective, multicenter RCT, Lamontagne et al. [54] investigated 118 patients with septic shock, with 58 in the high MAP group (MAP target 75 to 80 mm Hg) and 60 in the lower MAP group (MAP target 60 to 65 mm Hg). The primary outcome was the separate measurement of MAPs in each group, and secondary outcomes were in-hospital, 28-day, and 6-month mortality rates. The 28-day mortality rate did not differ significantly between the higher and lower MAP groups (46% vs. 44%, P=0.21). In a study by 65 clinical trial investigators (Mouncey et al. [55]), a prospective multicenter pragmatic RCT, 1,291 patients in the permissive hypotension group (MAP of 60–65 mm Hg) were compared to 1,307 patients in the usual care group. The average MAP up to 7 days after the application of vasopressors was 67.6 mm Hg in the permissive hypotension group and 72.9 mm Hg in the usual care group. At 90 days, the mortality rate was not different between the two groups (41.0% vs. 43.8%, P=0.154). After controlling for pre-specified variables, the OR for 90-day mortality was 0.82, favoring the permissive hypotension group more than the usual care group. Our meta-analysis found no significant benefit of maintaining a target MAP higher than 65 mm Hg (e.g., a higher MAP group). In the RCTs included, there were no significant problems with random sequence generation, allocation concealment, or blinding of participants and personnel. However, in some studies, blinding of interventions was incomplete, and missing data were identified. Additionally, the underlying conditions of the enrolled patients varied, and the criteria for low and high MAPs differed slightly. Considering this, the overall recommendation strength for this clinical question was assessed as conditional for the intervention (e.g., target MAP ≥65 mm Hg), and the evidence level was moderate.

Comments

Currently, there is no evidence that a higher MAP target, compared to maintaining an MAP ≥65 mm Hg, improves patient outcomes. In the SEPSISPAM study by Asfar et al. [53], the incidence of atrial fibrillation was higher but renal replacement therapy was less frequent in the higher MAP target group. Importantly, it is necessary to consider the accuracy of measurements because the value of 65 mm Hg measured with invasive methods may differ from that measured with non-invasive methods. Large-scale comparative studies on the currently suggested level of MAP (65 mm Hg) are needed.

KQ 5. Dynamic parameters

In adult patients with sepsis or septic shock, can fluid therapy using dynamic parameters compared to static parameters or usual treatments reduce mortality rate?

Recommendation

If additional fluids are required after initial fluid resuscitation in adult patients with sepsis or septic shock, fluid therapy using dynamic parameters is suggested (Recommendation strength B, conditional recommendation for intervention; Certainty of evidence: moderate).

Background

In clinical practice, parameters that represent the filling pressure of the heart, such as central venous pressure (CVP) or pulmonary artery pressure, have been widely used as static parameters. This hypothesis assumes that, as ventricular volume increases, heart-filling pressure increases proportionally. However, this is only true if ventricular compliance, which determines the pressure-volume relationship in the heart, remains constant. The actual compliance of the ventricles varies from patient to patient because it is affected by myocardial ischemia or infarction, myocardial hypertrophy, or cardiomyopathy. Even in the same patient, compliance of the ventricles varies depending on positive end-expiratory pressure and changes in cardiac function [56]. As a result, heart-filling pressure may remain the same despite varying volume states [56,57]. Additionally, changes in filling pressure can differ with increasing preload, highlighting a limitation of static parameters. Conversely, representative dynamic parameters include pulse pressure variation (PPV) and stroke volume variation (SVV), with larger values indicating a hypovolemic state and more significant variation in the respiratory cycle [58,59]. However, these dynamic parameters may not be accurate when an arrhythmia or increased intra-abdominal pressure is present, when vascular tension significantly changes, when tidal volume is low, or when there is spontaneous breathing effort [60-63]. In patients with spontaneous breathing, the passive leg raising (PLR) test is especially helpful in predicting responsiveness to fluid therapy. When a patient's leg is lifted to 45°, approximately 300 ml of blood moves from the periphery to the heart, and cardiac output changes accordingly.

Summary of Evidence

Among a total of 20,463 documents found through a literature search strategy, 18,502 were selected after excluding 1,961 duplicates. Among these, 67 full-text articles were reviewed (among 68 selected papers), and four RCTs were ultimately selected [64-67]. In an RCT by Richard et al. [65], the intervention group (n=30) received fluid therapy using SVV with PLR test or PPV (for patients on MV), and the control group (n=30) was given fluid therapy using CVP. Chen et al. [64] conducted a study of patients with septic shock who had received vasopressors for more than 12 hours and used the changes in PPV, inferior vena cava distension index, and stroke volume index after PLR (41 patients in each group). A study by Kuan et al. [66] targeted patients with sepsis with serum lactate levels of 3.0 mmol/L or higher and examined the changes in stroke volume index after PLR (61 vs. 61 patients in intervention vs. control groups). Finally, Douglas et al. [67] performed a PLR test in sepsis patients with persistent refractory hypotension or expected to be admitted to the ICU. They compared fluid therapy using changes in cardiac output with usual care (83 vs. 41 patients).

In this guideline, the critical outcomes were overall mortality and 28- or 30-day mortality rates, and other important outcomes were duration of MV and fluid balance on day 3. Of the four RCTs, three reported 28- or 30-day mortality rates [65-67], but one study only reported in-hospital mortality [64]. When combining all four studies, the risk of mortality was lower in the group that used dynamic parameters (intervention group) than the group that did not (usual care group), with no significant difference (RR, 0.81; 95% CI, 0.59–1.11). Regarding 28- or 30-day mortality (after exclusion of the study reporting in-hospital mortality), the risk of mortality in the intervention group was lower than in the usual care group, with statistical significance (RR, 0.62; 95% CI, 0.39–0.99). The duration of MV was shorter by 2.48 days in the intervention group than the usual care group (MD, –2.48 days; 95% CI, –3.61 to –1.35) [64,67], and fluid balance on day 3 was no different between the two groups (MD, –0.62 L; 95% CI, –1.31 to 0.08 L) [64,65,67]. As the four studies were RCTs, heterogeneity was not high. The level of evidence, which was lowered by one step due to imprecision, was finally determined to be moderate.

Comments

According to a study by Richard et al. [65], there was no difference in time to shock resolution when comparing fluid therapy using dynamic parameters with usual care (median [interquartile range]: 2.3 days [1.4–5.6] vs. 2.0 days [1.2–3.1], P=0.29). However, in our meta-analysis of subgroups (three RCTs), a significant reduction in 28- 30-day mortality rates and the period of MV was found. Therefore, fluid therapy using dynamic parameters can be considered beneficial to patients. Douglas et al. [67] compared major cardiovascular endpoints, including cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke, between the two groups and found

no significant difference. Therefore, compared to usual care or fluid therapy using static parameters, fluid therapy using dynamic parameters has no obvious harm, and the benefits may be more significant [65,67]. However, the primary obstacle to using dynamic parameters may be the absence of equipment monitoring cardiac output or PPV (due to its high costs). Additionally, healthcare insurance does not cover the PLR test, which may be another barrier.

KQ 6-1. Antibiotics

In adult septic shock patients, does administering antibiotics within 1 hour of sepsis recognition improve mortality compared to administering antibiotics at 1 hour or later?

Recommendation

In adult patients with septic shock, we suggest administering antibiotics within 1 hour of septic shock recognition (Recommendation strength B, conditional recommendation for intervention; Certainty of evidence: low).

KQ 6-2. Antibiotics

In adult sepsis patients, does administering antibiotics within 3 hours of sepsis recognition improve mortality compared to administering antibiotics at 3 hours or later?

Recommendation

In adult patients with sepsis, we suggest administering antibiotics within 3 hours of sepsis recognition (Recommendation strength E, expert consensus; Certainty of evidence: very low).

Background

Early administration of appropriate antibiotics is one of the most effective treatments for lowering the mortality rate of sepsis patients [32,68,69]. However, there are controversies about the relationship between timing of antibiotic administration and mortality in patients with sepsis or septic shock [70,71]. The 2016 SSC international guidelines were not approved by the Infectious Diseases Society of America (IDSA) because of concerns about antibiotic overuse, overdiagnosis of sepsis, lack of data to support time-to-antibiotic administration goals, and difficulty in distinguishing between patients with sepsis and septic shock [72]. In 2018, the SSC committee consolidated the 3-hour and 6-hour bundles into a 1-hour bundle and recommended that the Hour-1 bundle be implemented promptly [73]. However, concerns were raised about insufficient evidence to support these changes in emergency room care. The Society of Critical Care Medicine (SCCM) and the American College of Emergency Physicians (ACEP) issued a joint statement and announced that the Hour-1 bundle will not be immediately applied to hospitals in the United States [74]. In 2020, the IDSA highlighted the lack of evidence to support early antibiotic administration in patients with suspected sepsis without shock, the risk of antibiotic overuse, and the complexity of the "time zero" definition. They recommended modifications to the Severe Sepsis and Septic Shock Early Management (SEP-1) bundle, suggesting that sepsis without shock excluded from the bundle treatment, broad-spectrum antibiotics should be started within 1 hour of time zero in septic shock, and the definition of time zero should be clear and reproducible [75].

In 2021, the ACEP issued guidelines for the initial treatment of sepsis in emergency settings, which the IDSA and SCCM endorsed. Although antibiotics should be administered promptly when sepsis is diagnosed, there is insufficient evidence to recommend a specific time standard for antibiotic administration [76]. Accordingly, the SSC committee received feedback from other expert groups and distributed a new version of the guidelines in 2021. In the revised guidelines, the antibiotic administration time is divided according to the presence of shock and the possibility of sepsis. In patients with septic shock or sepsis with a high risk of infection, antibiotics are administered within 1 hour. However, diagnostic tests should be conducted promptly in sepsis with a low risk of infection, and antibiotics should be treated within 3 hours if infection concerns persist [20].

Summary of Evidence

The literature search strategy initially found 14,670 articles. Of these articles, 12,257 were screened, and 65 full-text articles were reviewed. For this guideline, 33 cohort studies were ultimately selected, with no RCTs identified.

When "time zero" is defined as the moment when sepsis or septic shock is recognized

Thirteen articles defined "time zero" as the moment of sepsis or septic shock recognition [68,77-88]. In our meta-analysis of patients with sepsis or septic shock, there was no significant difference in mortality between those who were given antibiotics within 1 hour of recognition of sepsis or septic shock and those given antibiotics after 1 hour (RR, 0.87; 95% CI, 0.75–1.01). However, in a subgroup analysis targeting only patients with septic shock, the mortality rate was significantly lower in

those who were given antibiotics within 1 hour than in those given antibiotics after 1 hour (RR, 0.89; 95% CI, 0.88–0.90). In patients with sepsis or septic shock, the mortality rate was significantly lower in those who were given antibiotics within 3 hours of sepsis or septic shock recognition than in those given antibiotics after 3 hours (OR, 0.67; 95% CI, 0.53–0.86). In a subgroup analysis targeting only patients with septic shock, the mortality rate was significantly lower in those given antibiotics within 3 hours than those given antibiotics after 3 hours (OR, 0.65; 95% CI, 0.51–0.83).

Since only two observational studies were included in the analysis of antibiotic administration within 3 hours in patients with septic shock, it was inappropriate to recommend antibiotics within 3 hours in this group. Therefore, in adult patients with septic shock, we recommend administering antibiotics within 1 hour of recognizing septic shock (Recommendation strength B, conditional recommendation for intervention; Certainty of evidence: low). Regarding antibiotic administration within 3 hours of time zero, no articles targeted only sepsis patients. However, among the observational studies in the meta-analysis, which included both sepsis and septic shock cases, sepsis accounted for most of the cases. Considering an increased mortality rate due to delayed administration of antibiotics, we can assume that the beneficial effects of antibiotics within 3 hours will also be greater than their harmful effects in patients with sepsis (Recommendation strength E, expert consensus; Certainty of evidence: very low).

When "time zero" is defined as the moment of emergency department triage

A total of 20 papers defined the "time zero" as the time of emergency department triage [32,70,89-106]. In our meta-analysis on patients with sepsis or septic shock, there was no significant difference in mortality rate in those who were given antibiotics within 1 hour of the triage compared to those given antibiotics after 1 hour (OR, 0.92; 95% CI, 0.85–1.00). This was also the case in a subgroup analysis targeting only patients with septic shock (OR, 0.91; 95% CI, 0.60–1.39). In patients with sepsis or septic shock, mortality was not significantly different in those who were given antibiotics within 3 hours of the triage compared to those given antibiotics after 3 hours (OR, 0.90; 95% CI, 0.76–1.07). This was also the case in a subgroup analysis targeting only patients with septic shock (OR, 1.08; 95% CI, 0.54–2.12).

Comments

In our meta-analyses, when "time zero" was defined as the time of triage, no significant differences were found in mortality rates according to the timing of antibiotic administration among patients with sepsis or septic shock. Therefore, it seems better to define "time zero" as the time of sepsis or septic shock recognition rather than the time of emergency department triage. However, as described above, unconditional rapid administration of antibiotics can cause various problems, such as antibiotic overuse, overdiagnosis of sepsis, and increased burden on medical staff and costs. Hence, sufficient effort is needed to make an accurate diagnosis and find the source of infection. Conversely, in patients who require antibiotics, maximum effort and improved performance are needed to ensure that antibiotic administration is not delayed after recognition of septic shock. Given the absence of large-scale RCTs on this topic, there is a need for additional well-designed large-scale RCTs.

KQ 7. Timing of vasopressors

When should vasopressors be administered to adult patients with septic shock?

Recommendation

In adult patients with septic shock, early administration of vasopressors is suggested if necessary to ensure hemodynamic stability during initial fluid therapy (Recommendation strength B, conditional recommendation for intervention; Certainty of evidence: moderate).

Background

Vasopressors can increase blood perfusion of organs and correct hypotension. They are essential for treating septic shock, along with fluid and antibiotic therapies [20]. The 2021 SSC international guidelines recommend administering fluids and vasopressors with an MAP ≥65 mm Hg as the initial hemodynamic goal. They also recommend administering vasopressors using a peripheral venous catheter rather than delaying the treatment for CVC insertion [20]. However, the appropriate timing of vasopressor administration in patients with septic shock is controversial, with conflicting research results [107-109].

Summary of Evidence

Through the literature search strategy, four RCTs [110-113] and eight cohort studies [109,114-120] were ultimately selected.

The RCTs included two studies using restrictive fluid and early vasopressor strategies [110,113]. In the meta-analysis, the mortality rate tended to be lower in the early vasopressor group versus the late group, regardless of whether they only included RCTs (RR, 0.76; 95% CI, 0.53–1.09) or observational studies (RR, 0.84; 95% CI, 0.66–1.07), with no statistical significance. In the RCTs, there was no significant difference in the length of ICU stay, duration of MV, vasopressor-free days, RRT-free days, or incidence of arrhythmia. However, the incidence of pulmonary edema was significantly lower in the early treatment group [110,112,113]. In the observational studies, although no difference was found in the length of ICU stay, a significantly shorter period was reported in MV, use of vasopressors, and RRT in the early vasopressor group compared to the late group. However, the number of studies included in the analysis was limited. In terms of fluid volume, there was a tendency for the 6-hour and 24-hour fluid doses to be lower in the early group, with no significant difference. In a subgroup analysis of two RCTs that implemented a restrictive fluid strategy, no significant difference was found in mortality rate [110,113]. However, in the two studies not using a fluid restriction strategy, the mortality rate was significantly lower in the early vasopressor group [111,112], consistent with the results of a previous meta-analysis [108].

Among the studies included in the analysis, the overall level of evidence from RCTs was assessed as moderate, while that for observational studies was very low. Accordingly, the overall level of evidence for this clinical question was moderate according to the level of evidence in RCTs.

Comments

Considering the following, we recommend early administration of vasopressors for adult patients with septic shock. First, although no significant difference was found in mortality between the early and delayed vasopressor administration groups, some results suggest a therapeutic benefit in early administration in secondary endpoints such as pulmonary edema. Second, a reduction in mortality was observed in a subgroup analysis including two RCTs in which a fluid restriction strategy was not implemented. Third, no significant worsening prognosis or side effects were observed in the group receiving the early administration of vasopressors. Finally, the correlation between the duration of hypotension and increased mortality has been well established [121].

However, the effects of early vasopressor use might differ depending on certain factors such as vasopressor dose, volume status (or fluid volume administered), severity of sepsis, and corticosteroids (e.g., hydrocortisone). In particular, fluid volume and vasopressor timing may have interactions with mortality. In all the studies included in our analysis, initial fluid therapy was administered before vasopressor infusions. Hence, early administration of vasopressors alone without fluid therapy is not recommended. In most studies, the difference in timing of vasopressor administration between the early and delayed groups was not remarkable, and it did not specify an optimal time for vasopressor initiation. Therefore, an individualized approach that depends on the severity and clinical course of the septic shock is needed.

KQ 8. Vasopressor type

Should norepinephrine be used preferentially over other vasopressors in adult patients with septic shock?

Recommendation

We recommend that norepinephrine be used in preference to other vasopressors in adult patients with septic shock (Recommendation strength A, strong recommendation for intervention).

Quality of evidence:

- Norepinephrine vs. dopamine: high quality
- Norepinephrine vs. vasopressin: moderate quality
- Norepinephrine vs. epinephrine: low quality
- Phenylephrine: very low quality
- Norepinephrine vs. terlipressin: low quality

Background

According to international guidelines, norepinephrine is recommended as the first-line vasopressor to maintain the target MAP of 65 mm Hg [20]. If norepinephrine is 0.25–0.5 μg/kg/min and the target MAP is not reached, vasopressin is recommended as the second-line drug. When norepinephrine is not available, dopamine or epinephrine can be used as a substitute [20]. Norepinephrine is a powerful α1 adrenergic receptor agonist with moderate β-agonist activity, exerting strong vasoconstriction but less direct cardiac contractility. Therefore, norepinephrine primarily increases systolic and diastolic pressure and has a minimal effect on heart rate.

Dopamine is an endogenous central neurotransmitter precursor of norepinephrine and acts on dopamine and adrenergic receptors. Low doses (<3 μg/kg/min) stimulate dopamine receptors in the coronary arteries, kidneys, and cerebrum, promoting vasodilation and increased blood flow to tissues.

At medium doses (5–10 μg/kg/min), dopamine binds to β1 adrenergic receptors and promotes the release of norepinephrine, increases cardiac contractility and heart rate (chronotropic), and slightly increases systemic vascular resistance (SVR). High doses (10–20 μg/kg/min) act on α1 adrenergic receptors, resulting in dominant vasoconstriction. However, dose-dependent activation of β1 adrenergic receptors may cause arrhythmia.

Vasopressin is an endogenous peptide hormone produced in the hypothalamus and stored and released in the posterior pituitary gland. Vasopressin binds to the V1 receptor of the vascular smooth muscle and the V2 receptor of the renal collecting duct. Hence, it induces vascular smooth muscle contraction through V1 stimulation, increasing arterial blood pressure and water reabsorption through the V2 receptor. Vasopressin also causes less direct coronary and cerebral vascular constriction than catecholamines while increasing SVR dose-dependently.

Epinephrine is an endogenous catecholamine with a high affinity for β1, β2, and α1-receptors in cardiac and vascular smooth muscles. It has the characteristics of more pronounced β1 adrenergic effects at low doses but more pronounced α1 adrenergic effects at high doses. At low doses, it mainly acts on β1 adrenergic receptors to increase cardiac output and reduce SVR, whereas at high doses it increases cardiac output and SVR. Potential side effects of epinephrine include arrhythmia and disruption of the splanchnic blood circulation.

Summary of Evidence

The literature search strategy identified 10,926 studies. After excluding 1,993 duplicates, 8,933 studies were screened. A total of 40 full-text articles was reviewed, and 16 RCTs and 6 cohort studies were ultimately selected.

Norepinephrine vs. dopamine

There was no significant difference in overall mortality between the norepinephrine and dopamine groups from the analysis of six RCTs (RR, 0.93; 95% CI, 0.84–1.02) [122-127]. However, a significant reduction was found in the norepinephrine group in one cohort study (RR, 0.67; 95% CI, 0.55–0.82) [128]. Additionally, when analyzing four RCTs, the ICU mortality rate was significantly reduced in the norepinephrine group compared to the dopamine group (RR, 0.90; 95% CI, 0.82–0.99) [122,124,125,129]. In the analysis of three RCTs, the incidence of arrhythmia was significantly lower in the norepinephrine group than in the dopamine group (RR, 0.49; 95% CI, 0.40–0.59) [125-127]. However, no significant difference was found in the length of ICU stay between the two groups in the analysis of two RCTs [125,126].

Norepinephrine vs. vasopressin

There was no significant difference in overall mortality between the norepinephrine and vasopressin groups in all four RCTs (RR, 1.09; 95% CI, 0.94–1.26) [129-132] and in three cohort studies (RR, 1.14; 95% CI, 0.79–1.65) [133-135]. There was no statistically significant difference in ICU mortality between the norepinephrine and vasopressin groups in three RCTs (RR, 0.94; 95% CI, 0.71–1.24) [129,131,132]. Regarding AKI, no difference was found between the norepinephrine and vasopressin groups in two RCTs, but the use of RRT was less frequent in the vasopressin group (RR, 1.44; 95% CI, 1.09–1.90) [129,132]. However, in the analysis of two cohort studies [133,135], no difference was found in the rate of RRT between the two groups. In terms of the length of ICU stay, it was shorter in the norepinephrine group compared to the vasopressin group in the three RCTs (MD, −1.55 days; 95% CI, −2.52 to −0.58) [129,131,132], but no difference was found in the analysis of two cohort studies [133,135].

Norepinephrine vs. epinephrine

In one RCT, overall mortality between the norepinephrine and epinephrine groups was not significantly different (RR, 1.13; 95% CI, 0.80–1.60) [136]. Vasopressin-free days were also not different between the two groups in the study.

Norepinephrine vs. phenylephrine

The overall mortality rate was not different between the norepinephrine and phenylephrine groups in one RCT [137]. However, the incidence of arrhythmia was significantly lower in the phenylephrine group compared to the norepinephrine group in a cohort study (RR, 1.20; 95% CI, 1.09–1.33) [138].

Norepinephrine vs. terlipressin

The overall mortality rate was not different between the norepinephrine and terlipressin groups in three RCTs (RR, 1.02; 95% CI, 0.74–1.42) [131,139,140]. Additionally, no differences were noted between the two groups in the RCT for both length of ICU stay and vasopressor-free days. Regarding the selection of the first vasopressor to be used in adult patients with septic shock, studies comparing norepinephrine with five other vasopressors (dopamine, vasopressin, epinephrine, phenylephrine, and terlipressin) were analyzed, and recommendations

for each drug are given in this guideline. The overall level of RCTs comparing norepinephrine with the five other vasopressors varied: high for dopamine, moderate for vasopressin, low for epinephrine and terlipressin, and very low for phenylephrine. However, unlike the RCTs, the evidence for cohort studies comparing norepinephrine with five other vasopressors was all confirmed as very low.

Comments

Dopamine mainly increases cardiac output and MAP by increasing stroke volume (SV) and heart rate, while norepinephrine increases MAP through vasoconstriction without significant changes in SV and heart rate. In an RCT by the SOAP (The Sepsis Occurrence in Acutely Ill Patients) II investigators, more arrhythmic events were observed in the dopamine group compared to the norepinephrine group, and a higher 28-day mortality was also noted in the former group among patients with cardiogenic shock [125]. The results of our meta-analysis showed that norepinephrine reduced the rates of ICU mortality and arrhythmia compared to the use of dopamine. Therefore, we recommend that norepinephrine be preferred to dopamine in patients with septic shock. When used at low doses, vasopressin increases blood pressure in patients who do not respond to other vasopressors. Conversely, high-dose vasopressin can be associated with ischemia in the heart, extremities, and intestine [141]. Our meta-analysis showed that norepinephrine, compared to vasopressin, reduced the length of ICU stay despite no difference in mortality. However, the incidence of RRT was lower in the vasopressin group. The VASST (Vasopressin and Septic Shock Trial) study, which examined the effect of co-administering low-dose vasopressin (0.01 to 0.03 units/min) with norepinephrine, found in subgroup analysis that adding low-dose vasopressin to norepinephrine (5–14 μg/min) improved survival rates compared to using norepinephrine alone [142]. This suggests that vasopressin should be initiated at an early stage of septic shock, particularly in less severe cases.

Epinephrine is associated with side effects such as arrhythmia, lactic acidemia, and splanchnic circulation disorders [143]. However, there was no significant difference in mortality in studies comparing the drug with norepinephrine, and the results of our meta-analysis also showed no difference between the two drugs. The 2021 SSC international guidelines suggest using epinephrine when the optimal blood pressure is not achieved despite the combined use of norepinephrine and vasopressin in patients with septic shock [1]. Epinephrine may be useful in patients with refractory septic shock and cardiac dysfunction. Phenylephrine results in less frequent tachycardia (compared to norepinephrine) but can induce splanchnic vasoconstriction. Given that only one RCT with a small number of patients (n=32) was included in our analysis, it was not possible to draw any conclusions about the effects of the drug on clinical outcomes. Regarding the use of terlipressin, no differences were found in our meta-analysis between the norepinephrine and terlipressin groups in terms of mortality, length of ICU stay, and vasopressor-free days. However, serious adverse events occurred more significantly with terlipressin use.

KQ 9. Vasopressin

In adult patients with septic shock, when appropriate MAP is not maintained despite the use of norepinephrine, is the addition of vasopressin better than increasing norepinephrine dose?

Recommendation

In adult patients with septic shock, when appropriate MAP is not maintained despite the usual dose of norepinephrine, we suggest adding vasopressin rather than increasing norepinephrine dose (Recommendation strength B, conditional recommendation for intervention; Quality of evidence: moderate).

Clinical Considerations

Additional research is needed on the timing of vasopressin administration. However, based on the results of previous RCTs, it seems appropriate to consider adding vasopressin when the norepinephrine concentration exceeds 0.25 μg/kg/min.

Background

In adult septic shock, when it is difficult to maintain a target MAP, even with appropriate fluid therapy, the use of vasopressors should be considered. Norepinephrine is an α1, β1, and β2 adrenergic receptor agonist that constricts blood vessels, increasing MAP. Based on many RCTs, it is recommended as a first-line vasopressor in adult sepsis [144]. When it is difficult to achieve an appropriate MAP with norepinephrine, addition of epinephrine or vasopressin can be considered. Several physiological advantages can be anticipated regarding the use of vasopressin. First, previous studies reported a relatively low concentration of endogenous vasopressin in patients with septic shock [145]. Second, when administering norepinephrine, the adrenergic receptors are probably already saturated. Finally,

catecholamine-saving effects can be obtained using vasopressin [146]. Therefore, vasopressin is prioritized as a secondary vasopressor [20].

Summary of Evidence

For this clinical question, a three-step strategy literature search recovered 6,789 articles. After excluding 1,364 duplicates, 5,425 documents were selected using titles and abstracts. A full-text review was performed on seven RCTs [129,130,132,142,147-149], five of which were selected for our analysis [129,130,132,142,148]. Most studies used first-line vasopressors to correct blood pressure after diagnosis of septic shock and before randomization [129,132,142,148]. After randomization, the study drug dose was increased if the MAP did not achieve the target value. The studies included in the meta-analysis are summarized in Table 4.

A meta-analysis was conducted on 28-day and ICU mortality rates, the incidence of AKI, and the application of RRT. In four RCTs where 28-day mortality was addressed, vasopressin plus norepinephrine showed no significant difference in 28-day mortality rate compared to norepinephrine alone (RR, 0.98; 95% CI, 0.86–1.12) [129,132,142,148]. Additionally, ICU mortality was not different in three of those studies [129,130,148]. Regarding AKI, no difference was found between the combination treatment and norepinephrine alone [129,132,142]. However, the incidence of RRT was significantly lower with the combination treatment (RR, 0.69; 95% CI, 0.89–1.06) [129,132,148].

Among all studies included in the meta-analysis, the primary endpoints varied (e.g., hemodynamic variables, 28-day mortality, AKI-free day, and lactate clearance). The baseline characteristics and disease severity of the enrolled patients were also different. In addition, because several studies did not include critical outcome variables, the meta-analyses were performed using subgroups of the studies that reported each outcome. For the three RCTs included in the analysis of ICU mortality, the level of evidence decreased due to the imprecision caused by the small number of events [129,130,148]. Therefore, the overall level of evidence for the clinical questions was downgraded to moderate.

Comments

In the meta-analysis, the combined use of norepinephrine plus vasopressin showed no significant difference in mortality rate compared to norepinephrine alone but significantly reduced the rate of RRT. However, the timing of vasopressin initiation needs to be noted. In an RCT (the VASST trial) by Russell et al. [142], vasopressin administration was associated with lower mortality in the low-severity group of patients in whom norepinephrine concentration was <15 μg/min (<0.25 μg/min/kg for 60 kg). In another RCT (by Gordon et al. [129]), the norepinephrine concentration when vasopressin was initiated was 0.1 to 0.3 μg/kg/min. The 2021 SSC international guidelines recently recommended the concurrent use of vasopressin when the norepinephrine dose reaches 0.25 to 0.5 μg/kg/min [20]. Additionally, they suggested that intravenous corticosteroids (hydrocortisone, 200 mg/day) be commenced at a dose of norepinephrine ≥0.25 μg/kg/min at least 4 hours after initiation.

Since most previous studies used vasopressin as a second-line drug in addition to the use of other vasopressors [129,132,142,148], additional research is needed to determine

Table 4. Summary of included studies for KQ9

Study	Country	Study design	Numbers of patients (intervention/control)	Intervention	Control	Primary outcome
Lauzier et al. (2006) [130]	France, Canada	Open-labeled RCT	Vasopressin (n=13) NEPI (n=10)	Vasopressin	NEPI	Hemodynamics
Russell et al. (2008) [142]	Canada, Australia, and USA	Multi-center double-blind RCT	Vasopressin (n=396) NEPI (n=382)	Vasopressin	NEPI	28-Day mortality
Barzegar et al. (2016) [148]	Iran	Open-labeled RCT	NEPI and fixed-dose vasopressin (n=15) NEPI (n=15)	NEPI and fixed-dose vasopressin	NEPI	Clearance of lactate
Gordon et al. (2016) [129]	UK	Multi-center double-blind RCT	Vasopressin (n=204) NEPI (n=204)	Vasopressin	NEPI	AKI-free days
Hajjar et al. (2019) [132]	Brazil	Single-center double-blind RCT	Vasopressin (n=125) NEPI (n=125)	Vasopressin	NEPI	28-Day mortality

KQ: key question; RCT: randomized controlled trial; NEPI: norepinephrine; AKI: acute kidney injury.

the benefits of combination therapy and the appropriate dose of norepinephrine when vasopressin infusion is started.

KQ 10. Dobutamine

In adult patients with septic shock accompanied by decreased cardiac function, does adding dobutamine to existing treatments reduce mortality?

Recommendation

In adult septic shock patients with decreased cardiac function and hypoperfusion, the use of dobutamine may be considered (Recommendation strength E, expert opinion; Quality of evidence: very low).

Background

In patients with septic shock, cardiac dysfunction is a major cause of hemodynamic instability and is associated with worsening prognosis [150]. Dobutamine can increase cardiac output, increasing visceral perfusion and tissue oxygenation and improving intramucosal metabolic acidosis and hyperlactatemia. However, this effect is difficult to predict, and hypotension may occur due to vasodilation. Additionally, there are cases where the heart rate increases without the expected increase in cardiac output. The 2021 SSC guidelines suggest the use of dobutamine in patients with persistent hypoperfusion accompanied by acute myocardial dysfunction despite appropriate fluid therapy, but the level of evidence is very low [20]. In particular, most studies have focused on physiological variables rather than clinical indicators, resulting in a very limited number of studies on which the guidelines are based, with no relevant RCTs. However, several retrospective observational studies have emerged since the guidelines were published [151-153], and an RCT is in progress (NCT04166331) [154].

Summary of Evidence

A total of 8,049 articles was found through the literature search. After excluding duplicates, 1,363 articles were screened, and 65 full-text articles were reviewed. However, no studies addressed the key question (patients with septic shock and decreased cardiac function). As an alternative, studies targeting patients with sepsis and septic shock were selected (16 studies), with 4 RCTs [155-158] and 12 non-RCTs (9 prospective before-after studies [159-167] and 3 retrospective cohort studies [152,153,168]).

To date, there are no RCTs examining the effect of dobutamine use on mortality in patients with sepsis or septic shock. In a retrospective study by Wilkman et al. [168], among 420 patients with septic shock, the mortality rate was significantly higher in the dobutamine group than in the non-administration group (44.0% vs. 24.2%, P<0.001). However, our meta-analysis, including 4 non-RCTs, showed that dobutamine did not affect mortality in patients with sepsis or septic shock (RR, 1.22; 95% CI, 0.86–1.73). The length of ICU stay was no different between the two groups when using two retrospective studies [152,153]. For tissue perfusion, a meta-analysis was conducted on renal (urine output), gastrointestinal, and peripheral tissue perfusion indices, using data from one RCT and three non-RCTs [158,159,162,166]. There was no significant difference in urine output between the dobutamine and non-dobutamine groups (MD, –11.60 ml/hr; –24.93 to 1.74 ml/hr). In terms of gastrointestinal perfusion, there were no significant differences in gastric mucosal pH [156,157,165] or gastric mucosal-arterial blood carbon dioxide partial pressure difference ($\Delta PaCO_2$) between the two groups [155,156,158,161].

A recently published network meta-analysis showed that, among various drug combinations, that of norepinephrine and dobutamine was associated with lower 28-day mortality in patients with septic shock accompanied by decreased cardiac function [169]. Despite being small RCTs, the data on use of dobutamine showed some positive results on tissue perfusion [155,161]. Given that the network meta-analysis shows the best results from the combination of norepinephrine and dobutamine [169], we may consider using dobutamine while carefully monitoring patients with septic shock. However, the RCTs included in the meta-analysis had a high RoB, and they investigated physiological indicators rather than clinical parameters. Additionally, the risk of inconsistency and imprecision was high considering the different patient groups and insufficient subjects. In this guideline, the level of evidence was very low, and the recommendation grade was expert opinion.

Comments

Despite the improved tissue perfusion mentioned above, several studies have reported a higher mortality rate or increased length of ICU stay in the dobutamine group. Dobutamine can sometimes lower blood pressure due to its vasodilation effect. It can also destabilize the vital signs of sepsis patients by increasing heart rate without increasing SV. To date, no RCTs have included the effect of dobutamine administration on mortality or length of ICU stay. However, the results of our meta-analysis showed that the use of dobutamine had no influence on the mortality rate or length of ICU stay in patients

with sepsis or septic shock. Therefore, it is advisable to make decisions on the use of the drug after carefully reviewing the condition of the patient. Additionally, these recommendations may change depending on the results of a large-scale RCT currently in progress [154].

KQ 11. Extracorporeal membrane oxygenation (ECMO)

Is ECMO treatment effective in adult patients with septic shock?

Recommendation

1. In patients with acute respiratory distress syndrome due to sepsis who do not respond to existing standard treatments, we suggest performing venovenous (VV) ECMO (Recommendation strength E, expert opinion; Quality of evidence: none).
2. In patients with septic shock and decreased cardiac function who do not respond to existing standard treatments, venous arterial (VA) ECMO can be applied (Recommendation strength B, conditional recommendation for intervention; Quality of evidence: low).

Clinical Considerations

ECMO is not recommended for patients with septic shock accompanied by multi-organ failure. When ECMO treatment is considered in these patients, the benefits and risks of the treatment should be assessed.

Background

ECMO is a method of treatment that supports cardiopulmonary function through an extracorporeal circulation device consisting of an artificial oxygenator and a blood pump. It is used in patients with severe heart failure or severe acute respiratory failure who do not respond to standard treatments and have no other treatment options. A recent multicenter international report published by the Extracorporeal Life Support Organization found that the number of ECMO applications is increasing every year. The discharge rate of live patients after ECMO treatment is 45% and 58% in adults with acute heart failure and acute respiratory failure, respectively [170]. However, because ECMO is an invasive treatment and serious life-threatening complications occur at a considerable rate, the choice of ECMO treatment must be made carefully.

Summary of Evidence

Through a literature search strategy, 6,776 studies were retrieved. In the literature selection process, 4,975 studies were screened using titles and abstracts, with duplicates excluded. Afterward, 504 original texts were reviewed, and three cohort studies were ultimately selected. A study by Takauji et al. [171] included both patients with septic shock due to severe respiratory failure without respiratory infections and those with respiratory infections. Their multicenter retrospective observational study used propensity score matching (conservative treatment group, n=239; VV-ECMO group, n=65). A publication by Bréchot et al. [172] also involved an international multicenter retrospective observational study. They included 212 patients with sepsis-induced cardiogenic shock and compared 90-day mortality rates between the conservative treatment (n=130) and VA-ECMO groups (n=82) after propensity score weighting. A study by Zha et al. [173] conducted a propensity score matching analysis among 255 patients with septic shock, respiratory infection, or respiratory failure. They compared 30- and 90-day mortality rates between conservative treatment (n=31) and VV-ECMO treatment groups (n=31).

Among the selected studies (n=3), the ECMO treatment group had a lower risk of death than the conservative treatment group (RR, 0.69; 95% CI, 0.51–0.93). Two studies reported serious adverse reactions (AKI, RRT, stroke, bleeding, etc.), and bleeding complications were more likely to occur in the ECMO treatment group than in the conservative treatment group (RR, 2.60; 95% CI, 1.64–4.14) [171,173]. In three studies reporting critical outcomes, the heterogeneity was high, so the recommendation grade was lowered by one step due to inconsistency and publication bias. Another step reduction was due to imprecision and effect size related to the small number of subjects and events. Additionally, the criteria for selecting ECMO treatment were diverse among the studies (e.g., selection bias). Based on these factors, the level of evidence for this clinical question was evaluated as low.

Comments

Since all the studies included in this guideline were not RCTs but retrospective observational studies, evaluating benefits and risks is subject to major limitations. However, given the results of a recent large-scale RCT (EOLIA [Extracorporeal Membrane Oxygenation for Severe Acute Respiratory Syndrome]) [174], VV-ECMO can be considered in patients with acute respiratory distress syndrome due to sepsis refractory to standard treatments if they have no multi-organ failures. Although there are no RCTs on patients with refractory septic shock, an international retrospective analysis by Ling et al.

[175] showed that VA-ECMO significantly improved survival in patients with sepsis-induced cardiogenic shock. Moreover, in an individual participant data meta-regression analysis by Ling et al. [175], VA-ECMO showed improved survival in adults with septic shock and sepsis-induced myocardial depression. However, the treatment was associated with poor outcomes among those with septic shock without severe left ventricular depression. Therefore, VA-ECMO may be a viable treatment option in selected adult patients with refractory septic shock and left ventricular dysfunction.

In Korea, the influenza pandemic and the Middle East respiratory syndrome (MERS) epidemic have led to accumulated and widely shared knowledge and experience in the managing of ECMO cases of various causes among healthcare providers. ECMO has also been recognized as an important treatment option for severe cases of coronavirus disease 2019 (COVID-19). However, no RCTs have evaluated the effect of ECMO in patients with refractory septic shock. Therefore, the treatment should be carefully considered in the ICU.

KQ 12. Echocardiography

Is echocardiography recommended to assess cardiac function in adult patients with sepsis?

Recommendation

We suggest echocardiography to assess cardiac function and hemodynamics in adult patients with sepsis (Recommendation strength B, conditional recommendation for intervention; Quality of evidence: very low).

Background

Reduced or hyperdynamic LV systolic function is a risk factor for increased mortality in patients with sepsis [176]. Sepsis-induced cardiomyopathy (SICM) or sepsis-induced myocardial dysfunction can be expressed as a temporary cardiac dysfunction in sepsis patients. Although its importance in determining the prognosis of sepsis patients continues to evolve, there is no widely accepted definition. Transthoracic echocardiography (TTE) is a commonly used instrument in many clinical fields because it is non-invasive and easily accessible. The 2021 SSC international guidelines recommend echocardiography as a dynamic indicator to evaluate fluid responsiveness during the initial fluid treatment in sepsis patients. However, there is no specific mention of its use to evaluate cardiac function [20].

Summary of Evidence

Of the 8,795 articles found through the literature search strategy, 8,776 were excluded using the title and abstract, and a full-text review was performed on 19 articles. Given that the existing sepsis treatment guidelines did not cover the topic in detail, it was difficult to find studies that provided evidence related to the PICO. Finally, four retrospective cohort studies were selected and reviewed (Table 5) [177-180].

In a study using the Medical Information Mart for Intensive Care (MIMIC) III database by Feng et al., when comparing two propensity-matched cohorts (1,626 patients in each group), the 28-day mortality rate was significantly lower in the TTE group than the non-TTE group (OR, 0.78; P<0.001). In addition, the former group was able to stop vasopressors earlier than the latter (vasopressor-free days, 21 vs. 19; P=0.004) [177]. Lan et al. [178] also used the MIMIC-III database and a propensity score matched analysis (1,289 patients in each group). They found that the 28-day mortality rate in the TTE group was significantly lower than in the non-TTE group (HR, 0.83; P=0.005). Hanumanthu et al. [179] conducted a single-center retrospective cohort study using data on patients with sepsis but without acute coronary syndrome. When comparing the SICM group (n=19) and the non-SICM group (n=340), with TTE used for diagnosis

Table 5. Summary of included studies for KQ12

Study	Country	Study design	Population	Intervention	Comparator	Primary outcomes
Feng et al. (2018) [177]	USA	Retrospective cohort study (PSM), MIMIC-III	TTE, 1,626; no TTE, 1,626	TTE	No TTE	28-Day mortality
Lan et al. (2019) [178]	USA	Retrospective cohort study (PSM), MIMIC-III	TTE, 1,289; no TTE, 1,289	TTE	No TTE	28-Day mortality
Hanumanthu et al. (2021) [179]	USA	Retrospective cohort study	SICM 19 by TTE; non-SICM 340 by TTE	SICM	Non-SICM	All-cause in-hospital mortality
Zheng et al. (2022) [180]	USA	Retrospective cohort study (PSM), MIMIC-III	Early TTE, 544; delayed TTE, 2,720	Early TTE	Delayed TTE	28-Day mortality

KQ: key question; PSM: propensity-score matching; MIMIC: Medical Information Mart for Intensive Care; TTE: transthoracic echocardiography; SICM: sepsis-induced cardiomyopathy.

confirmation, the in-hospital mortality rate was significantly higher in the SICM group (OR, 4.46; P=0.03). Another retrospective cohort study using the MIMIC-III database by Zheng et al. [180] compared 28-day mortality rates between an early TTE group (within 10 hours of admission to the ICU, n=544) and a delayed TTE group (>10 hours of admission to the ICU, n=2,027). They found that the early TTE group had a significantly lower 28-day mortality rate compared to the delayed TTE group (HR, 0.73–0.78; P<0.05) [180].

In the meta-analysis of the three observational studies that reported critical outcomes, a significantly lower 28-day mortality rate was noted in the TTE group compared to the non-TTE group (RR, 0.79; 95% CI, 0.71–0.88) [175-177]. However, there is a high RoB because only retrospective observational studies were used in the meta-analysis. Additionally, the study period and inclusion criteria differ in two of the three studies that used the MIMIC-III database [177,178]. Due to these limitations, the current level of evidence was determined as very low.

Comments

TTE is a non-invasive test that can be performed at the bedside with no serious complications. Although the 2021 SSC international guidelines recommend echocardiography as a dynamic indicator to evaluate fluid responsiveness, we analyzed the role of TTE from a different perspective, and the results indicate that the 28-day mortality rate is significantly lower in the group who underwent TTE compared to those who did not. Therefore, TTE itself might be beneficial in adult patients with sepsis or septic shock. This implies that TTE can affect treatment strategies or help predict prognosis in patients with sepsis. However, echocardiography is operator-dependent, and the accuracy of results can vary based on the clinician's skill and experience. Additionally, further research is warranted since the evidence remains unclear on the indicators to be used as references in echocardiography.

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CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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SUPPLEMENTARY MATERIALS

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