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SPECIAL ARTICLE

SBA Recommendations for Anesthetic Management of Septic Patient

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Method and evidence collection

Our search included studies regarding anesthesia, anesthetics, strategy and anesthetic management (induction, maintenance, and adjuvants), cardiovascular support, mechanical ventilation, and monitoring, whether or not related to clinical outcome (mortality, length of stay, duration of mechanical ventilation, and vasopressor or inotropic support). We also selected articles on specific drugs (etomidate, ketamine, corticosteroids, and others) and applied the following strategy using the PubMed system to search Medline database, with unlimited publication date:

"Sepsis" [Mesh] OR "Shock, Septic" [Mesh]) AND

a. "Anesthesia" [Mesh] OR "Anesthesia, Inhalation" [Mesh] OR "Balanced Anesthesia" [Mesh] OR "Anesthesia, Intravenous" [Mesh] OR "Anesthesia, General" [Mesh] OR "Adjuvants, Anesthesia" [Mesh] OR "Anesthetics, Inhalation" [Mesh] OR "Anesthetics, General" [Mesh] OR "Anesthetics" [Mesh] OR "Anesthetics, Combined" [Mesh] OR "Midazolam" [Mesh] OR "Ketamine" [Mesh] OR "Intraoperative Care" [Mesh] OR "Etomidate" [Mesh]);
b. "dopamine", "noradrenaline", "norepinephrine", "vasopressor agent", "outcome" and "mortality";
c. "Fluid" [Mesh]) AND "colloids" [Mesh] OR "starch" [Mesh] OR "hypertonic solution" [Mesh] OR "saline" [Mesh];
d. "early goal direct therapy" OR "EGDT" AND (outcome)
e. "methylene blue" [Mesh];
f. "cardiac output" OR "cardiac index" OR "stroke volume variation" OR "pulse pressure variation".

Level of evidence and grade of recommendation

The level of evidence (LE) and grade of recommendation (GR) of each study were assigned according to the Centre of Evidence Based Medicine (CEBM) classification.[1]

A. Experimental or observational studies of better consistency, meta-analyses with randomized controlled trials homogeneity (LE = 1);
B. Experimental or observational studies with less consistency (LE = 2 or 3) or extrapolations of studies (LE = 1);
C. Case report or series (non-controlled studies) (LE = 4); or extrapolations of studies (LE = 2 or 3);
D. Opinion without critical evaluation, based on consensus, expert opinions, physiological studies or animal models, meta-analyzes with high coefficient of heterogeneity (LE = 5) or inconsistent or non-conclusive studies of any level.

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Introduction

Sepsis is the leading cause of death in the intensive care unit (ICU).[2] However, there are few studies assessing the epidemiology of systemic inflammatory response syndrome (SIRS), sepsis, severe sepsis, and septic shock, according to the American College of Clinical Pharmacy (ACCP) and Society of Critical Care Medicine (SCCM) consensus criteria.[3] Throughout the present investigation, we identified some studies demonstrating the increased incidence[4] (8.7%/year)[5] and only a small reduction in mortality.[4] Mortality rate in the United States was 27.8% in the late 1970s versus 17.9% in 2000.[5] A study estimated the annual incidence of 3:1,000 sepsis cases in the United States,[6] with an annual growth of 1.5%/year and overall mortality of 28.6%. A European study[7] of patients with septic shock also found increased incidence of 7 to 9.7 of 100 admissions and mortality reduction from 62.1% to 55.9% between 1993 and 2000. In Brazil, according to DataSUS,[8] there were 232,679 hospitalizations between January 2008 and August 2012, with the international code of diseases 10th version (ICD-10): septicemia. Mean hospital stay was 11.6 days, with 121,103 deaths (52.5%). According to the study Bases,[9] the first prospective epidemiological cohort of sepsis in a developing country, which included 1,383 patients hospitalized in five intensive care units, the incidence-density of sepsis was 57.9 (95% CI: 51.5-65.3) per 1,000 patients.day.$^{-1}$ Mortality rates attributed to SIRS, sepsis, severe sepsis, and septic shock were 24.2%, 33.9%, 46.9%, and 52.2%, respectively. The Sequential Organ Failure Assessment (SOFA) maximum scores for sepsis, severe sepsis, and septic shock were 5, 8.8, and 11, respectively. Most sepsis diagnoses of (67.7%) were made during admission of patients to the ICU and the remaining 32.3% in the following days. The study also showed that the incidence of severe sepsis and mortality at intensive care units of public hospitals is higher than at private hospitals (16% versus 35% and 28.9% versus 12.5%; $p < 0.005$).

One multicenter prospective cohort study,[10] which included 3,128 patients admitted to 75 ICUs in 65 Brazilian hospitals, found 16.7% incidence of sepsis, severe sepsis or septic shock. Mortality rates for sepsis, severe sepsis, septic shock, and overall mortality in 28-day were estimated at 16.7%, 34.4%, 65.3%, and 46.6%, respectively. The average length of stay in the ICU was 15 days.

Finally, another prospective, multicenter and observational study,[2] with 560 patients admitted to three ICUs, found sepsis, severe sepsis, and septic shock incidences of 31.9%, 24.4%, and 31.4%, respectively, and mortality rates of 10.1%, 22.6%, and 64.8%, respectively.

Septic patients are often undergoing urgent or emergency surgical procedures and, necessarily, an anesthesiologist sees these patients.

The anesthesiologist is a professional whose training gives him skills for rapid management of critical conditions. The knowledge of physiology and pathophysiology of the various organ systems makes him able to meet the multifaceted therapeutic challenge of sepsis, surgery, and anesthesia.[11]

The anesthesiologist priority is to improve the patient's condition to get maximum benefit from the surgical procedure and achieve short-term survival.[12] Therefore, predicting a greater susceptibility of these patients to anesthetic drugs is fundamental. Another key point is the management of hemodynamic and respiratory variables affected by the sepsis process and worsened by surgery, anesthesia, bleeding, loss of fluid, hypothermia, and other critical events. Anesthesiologists need to apply their knowledge to predict the pharmacodynamic and pharmacokinetic behavior in septic patients, with varying degrees of organ dysfunction, such as increased extravascular space, hypoalbuminemia, and increased levels of acid glycoprotein (AGP).[13]

Objective

Several clinical predictors and organ dysfunction scores were created to aid the physician in assessing the degree of severity, risk and prognosis in the short and long term such as Multiple Organ Dysfunction Score (MODS), Logistic Organ Dysfunction Score (LODS), Sequential Organ Failure Assessment (SOFA); cytokine levels, and various sepsis severity assessment score such as Mortality Probability Model Score (MPMS), Simplified Acute Physiology Score II (SAPS II), Acute Physiology and Chronic Health Disease Classification (Apache II and III). In this study, we have given utmost importance to indicators of short-term outcome, due to the short time the anesthesiologist spends with the septic patient. The morbidity and mortality indicators chosen by clinical trials are reported by the articles of greatest impact (days of hospitalization and mechanical ventilation and 28-day mortality) and repeated in less impact articles, in order to better compare data obtained.

Based on the best current evidence (2012) resulting from qualitative systematic review, this recommendation aims to answer the following clinical questions:

1. Does the use of etomidate as an induction agent increase the morbidity and mortality indicators in septic patients undergoing tracheal intubation?
2. Is midazolam superior to etomidate regarding morbidity and mortality indicators in septic patients undergoing tracheal intubation induction?
3. Is ketamine superior to etomidate regarding morbidity and mortality rates in septic patients undergoing tracheal intubation induction?
4. Is cardiovascular support with norepinephrine superior to dopamine regarding septic patient's morbidity and mortality?
5. Is cardiovascular support with the combination of norepinephrine and dobutamine superior to epinephrine regarding septic patient's morbidity and mortality?
6. Is cardiovascular support with phenylephrine superior to norepinephrine regarding septic patient's morbidity and mortality?
7. Is there benefit in the use of methylene blue regarding morbidity and mortality indicators in septic patients?
8. Is there a difference between volatile and intravenous anesthetics for general anesthesia maintenance regarding mortality in septic patients?
9. Is there influence on MAC Values of inhaled anesthetics in septic patients?
10. Is fluid resuscitation with albumin superior to crystalloid infusion regarding morbidity and mortality indicators in septic patients?

11. Is volume replacement with hydroxyethyl starch superior to crystalloid infusion regarding morbidity and mortality indicators in septic patients?
12. Is hypertonic saline infusion superior to normal saline regarding morbidity and mortality indicators in septic patients?
13. Is the early goal-directed therapy implementation superior to other approaches of septic patients?
14. Is cardiac output monitoring by uncalibrated pulse power analysis accurate in septic patients?

Does the use of etomidate as an induction agent increase the morbidity and mortality indicators in septic patients undergoing tracheal intubation?

A retrospective cohort study (B)[14] that included 224 patients with severe sepsis or septic shock compared tracheal intubation performed after hypnotic induction with etomidate or other drugs. Apache II, MPM II, vasopressors, corticosteroids, and adrenal suppression were measured (assessed by tests of cortisol alone or corticotropin test).

Among patients who received etomidate, the relative risk for mortality, use of vasopressors and corticosteroids were: a) relative risk (RR): 0.92, CI: 0.74-1.14, p = 0.51; b) RR: 1.16, CI: 0.9-1.51, p = 0.31; and c) RR: 1.34, CI: 1.11-1.61, p = 0.003.

There was no statistically significant difference in the outcomes: length of ICU stay (days), mechanical ventilation (days), APACHE II, and MPM II.

A meta-analysis (D)[15] compared the effects of a single dose of etomidate with other agents in critically ill patients. Mortality rate at 28 days (primary outcome) and incidence of adrenal insufficiency (secondary endpoint assessed by the corticotrophin or serum cortisol test) were recorded. The 28-day mortality outcomes and adrenal insufficiency were: a) RR: 1.19; extreme 1.10-1.30, n = 3,516, p = 0.0001; coefficient of heterogeneity (I^2) = 64% (values greater than 30% indicate heterogeneity of studies); and b) RR: 1.64, extremes: 1.52-1.77, n = 2,854, p = 0.0001; I^2 = 88%. A reanalysis including only septic patients (n = 1,767) showed the same trend (RR: 1.22, extremes: 1.11-1.35; I2 = 74%, p = 0.0001), but not non-septic patients (RR: 1.15, extremes: 0.97-1.35, n = 1,749, I^2 = 53%, p = 0.1). The study also found that cortisol levels of patients exposed to etomidate were 50% lower than in non-exposed patients and adrenal suppression persisted for 12 to 24 hours after single injection.

Another systematic review with meta-analysis (A)[16] of randomized controlled and observational trials of patients with severe sepsis or septic shock evaluated mortality and adrenal suppression (by corticotropin test) after a dose of etomidate for rapid sequence intubation. Relative risk for overall mortality, mortality in randomized controlled trials, and at 28 days were respectively: a) RR: 1.20, 95% CI: 1.02-1.42; Q: 20, I^2 = 4, 9%, n = 865; b) RR: 1.26, 95% CI: 1.06-1.50; Q: 3.39, I^2: 11.6%, n = 795; and c) RR: 1.28, 95% CI: 1.06-1.54; Q: 3.70; I^2: 46%. Relative risks for general adrenal insufficiency and in randomized controlled trials were: a) RR: 1.33, 95% CI: 1.22-1.46; Q: 10.7; I^2: 43.9%; n = 1,303, and b) RR 1.35, 95% CI: 1.24-1.47; Q: 1.24; I^2: 0%.

Recommendations: The use of etomidate for septic patients tracheal intubation was associated with adrenal suppression (A) persisting for 12 to 24 hours after administration (D), increased mortality (A), and corticosteroids consumption (B).

Therefore, etomidate is contraindicated for tracheal intubation in patients with sepsis.

Is midazolam superior to etomidate regarding morbidity and mortality rates in septic patients undergoing tracheal intubation induction?

Another prospective, double-blind, randomized study (A)[17] compared etomidate and midazolam as induction agents for endotracheal intubation of 122 patients with a presumptive diagnosis of sepsis in the intensive care unit. No difference was found between midazolam and etomidate groups in the following outcomes: mean time of hospital stay (9.5 versus 7.3 days), ICU stay (4.2 versus 3.1 days), and on mechanical ventilation (2.8 versus 2.1 days). Mortality was assessed as a secondary outcome and there was no significant difference.

Recommendations: There is no evidence in the literature reporting differences between length of hospital or ICU stay, duration of mechanical ventilation, and mortality between the use of midazolam or etomidate for intubation in patients with severe sepsis or septic shock (A).

Midazolam is recommended as an alternative to etomidate as hypnotic agent for tracheal intubation in patients with a presumptive diagnosis of sepsis.

Is ketamine superior to etomidate regarding morbidity and mortality indicators in septic patients undergoing tracheal intubation induction?

A multicenter prospective, randomized, blinded controlled study (A)[18] involving 469 patients (180 with sepsis) compared the use of etomidate or ketamine (single dose) for tracheal intubation. The primary endpoint was the maximum SOFA index in the first three days. Secondary endpoints were: SOFA index variation, mortality, days out of intensive care, and days without mechanical ventilation or vasoactive drugs in the following 28 days. In the septic group with patients exposed to etomidate or ketamine, the mean maximum SOFA index was respectively: 12.4 (SD: 3.8) and 10.8 (SD: 4.5), with an absolute difference of 1.6 (95% CI: -0.3-3.4), and mortality (OR: 0.8, 95% CI: 0.5-3.5). The other endpoints showed no difference with respect to exposure to ketamine or etomidate. Adrenal suppression was assessed by corticotropin test, and etomidate group was associated with a higher incidence of adrenal suppression (OR: 6.7, 95% CI 3.5-12.7, p = 0.01).

Recommendations: Ketamine is associated with similar mortality rates and lower incidence of adrenal suppression compared to etomidate for intubation of patients with sepsis (A).

Ketamine is recommended as an alternative to etomidate for intubation of patients with sepsis.

Is cardiovascular support with norepinephrine superior to dopamine regarding septic patient's morbidity and mortality?

A systematic review (A)[19] of observational (n = 1,360) and randomized (n = 1,408) articles compared the use of norepinephrine or dopamine in patients with septic shock. Observation group (after the exclusion of one study, which improved the homogeneity of the population) and randomized group showed significant increase in 28-day mortality with the use of dopamine (RR: 1.23, 95% CI: 1,05-1.43, p < 0.01; I^2 = 32.3% and RR: 1.12, 95% CI: 1.01-1.20, p < 0.35; I^2 = 0%, respectively). In two of the interventional studies, dopamine has been linked with increased risk of arrhythmias (RR: 2.34, 95% CI: 1.46-3.77, p = 0.001).

These results are in line with another systematic review of randomized trials[20] with 2,043 patients in which norepinephrine was superior to dopamine regarding 28-day mortality (RR: 0.91, 95% CI: 0.83-0.99; p = 0.028, I^2 = 0.0%).

Recommendations: Norepinephrine is associated with lower incidence of arrhythmia and mortality compared to dopamine for hemodynamic support of septic patients.

Noradrenaline is recommended as the agent of choice for hemodynamic support of septic patients (A).

Is cardiovascular support with the combination of norepinephrine-dobutamine superior to epinephrine regarding septic patient's morbidity and mortality?

A prospective, multicenter, randomized, double-blind study[21] with 330 adults admitted to the ICU compared the combination of norepinephrine and dobutamine with epinephrine. The primary endpoint was 28-day mortality. The secondary endpoints were mortality at 7 and 14 days, up to ICU and hospital discharge, survival at 90 days, hemodynamic parameters, arterial pH and lactate, SOFA score, time to successful hemodynamic stabilization, and time to weaning of vasoactive drugs. The result was not significant for 28-day mortality (RR: 0.86, 95% CI: 0.65-1.14), or for the other secondary endpoints, except for pH (p = 0.01) and lactate (p = 0.001) being higher in the adrenaline group.

Recommendations: There is no evidence of a statistically significant difference in mortality outcomes, duration of vasopressor support, and 90-day survival with the use of norepinephrine-dobutamine compared with adrenaline (A). However, the levels of lactate are significantly higher and pH is significantly lower in patients treated with adrenaline (A).

The combined use of dobutamine and norepinephrine is recommended for hemodynamic support of septic patients, when indicated.

Is cardiovascular support with phenylephrine superior to norepinephrine regarding septic patient's morbidity and mortality?

A prospective, randomized controlled study[22] compared equipotent doses of phenylephrine and noradrenaline for hemodynamic support of 32 patients with septic shock. There were no statistically significant differences in the primary endpoint mortality (RR: 1.11, 95% CI: 0.63-1.97) and secondary endpoints: systolic volume index (49 ± 19, 50 ± 11, p = 0.963), pH (7.37 ± 0.08, 7.34 ± 0.08, p = 0.435), base excess (0.2 ± 6.3, -3.0 ± 6.4, p = 0.228), mixed venous saturation (67 ± 9, 67 ± 10, p = 0.431), and length of ICU stay (16 days, extreme: 7-25; 16 days, extreme: 10-24).

Recommendations: The only level-1 evidence study comparing norepinephrine and phenylephrine for hemodynamic support of septic patients found no difference between norepinephrine and phenylephrine regarding mortality and hemodynamic and metabolic indices (A). However, because the study involved a small sample size in order to detect differences equal to or greater than 30%, the choice of norepinephrine is recommended due to the already demonstrated advantages over other vasopressors.

Is there benefit in the use of methylene blue regarding morbidity and mortality indicators in septic patients?

A qualitative systematic review[23] assessed the use of methylene blue associated with vasoactive drugs in septic shock treatment. It included 14 studies (2 prospective and randomized studies). Meta-analysis was not possible due to the great heterogeneity. The study concluded that the use of methylene blue significantly reduced the need for norepinephrine (87%), epinephrine (81%), and dopamine (40%), in addition to being associated with increased peripheral and pulmonary vascular resistance. Heterogeneity of studies prevented conclusions about mortality. Survival at 28 days was 50% in the methylene blue group and 30% in the control group; however, without statistical significance.

Recommendations: Methylene blue is associated with increased systemic vascular resistance and blood pressure, without evidence of improving oxygen delivery to tissue or death (D).

Until there is better evidence, methylene blue should not be used as an adjuvant for hemodynamic support of patients with sepsis.

Is there a difference between volatile and intravenous anesthetics for general anesthesia maintenance regarding septic patients' morbidity and mortality?

In animal models, volatile anesthetics have anti-inflammatory properties and reduce oxidative stress, lipid peroxidation, and inflammatory response. This effect is more marked with sevoflurane compared to isoflurane. There is also evidence that sevoflurane is associated with lower mortality rates compared to isoflurane.[24] In the animal sepsis model, isoflurane for maintenance of general anesthesia provides increased survival and reduced pulmonary injury and inflammatory reaction compared to pentobarbital,[25,26] in addition to being related to renal, hepatic, and anti-inflammatory effect protection and mortality reduction (D).[27] On the other hand, there is evidence that isoflurane may trigger deleterious effects on the endocrine-metabolic response in animal models of sepsis, with increased lung and inflammatory

cascade injury, compared to animals not submitted to anesthesia (D).[28] In animal model of sepsis, comparison between ketamine, alfentanil, isoflurane, and halothane showed that ketamine is associated with better laboratory, metabolic, and hemodynamic profiles, compared with the other agents. In this study, halothane, compared with the other agents, was related to the worse laboratory and metabolic hemodynamic profiles (D).[29] There is also evidence from studies in animal models of sepsis that compared with propofol, isoflurane has protective lung effects according to histological criteria and capillary permeability tests (D).[30]

Recommendations: There is no evidence of any agent superiority for maintenance of anesthesia in humans. Considering that animal studies have no sufficient level of evidence for a recommendation, it is concluded that there is no scientific support for recommending the use of anesthetics for maintenance of general anesthesia in patients with sepsis (D).

Is there influence on MAC values of inhaled anesthetics in septic patients?

A study (D)[31] evaluated the effect of septic status on the MAC of isoflurane in rodent model of sepsis. The isoflurane MAC in normotensive rats was estimated at 0.81% (SD = 0.3%) in the group of rats subjected to sepsis and 1.4% (SD: 0.12%) in the control group ($p < 0.003$). Secondary endpoints showed no significant differences: heart rate, blood pressure, except metabolic acidosis (pH of control group: 7.35; SD: 0.02 and pH of septic group: 7.28; SD = 0.02; $p < 0.05$). In another study (D),[32] the MAC of sevoflurane in normotensive pigs was estimated at 1.35% (95% CI: 1.2-1.45, $p < 0.05$) for septic group and 2,4% (95% CI: 2.1-2.55, $p < 0.05$) for control group.

Recommendations: Although evidence suggest that the MAC of inhalational anesthetics is lower in septic animals than in non-septic animals, it is not possible to extrapolate these results to humans (D).

Is fluid resuscitation with albumin superior to crystalloid infusion regarding morbidity and mortality indicators in septic patients?

A systematic review with meta-analysis (A),[33] which included 1,977 adult and pediatric patients with severe sepsis or septic shock (Safe test subgroup), compared the mortality outcome between groups receiving solutions containing albumin and groups receiving other solutions for parenteral hydration. The authors concluded that in septic patients albumin replacement is associated with lower mortality rates (OR: 0.82; 95% CI: 0.67-1; I^2: 0%; $p < 0.047$). However, data re-evaluation according to a random-effects model showed that effects are not significant on mortality (OR: 0.84; 95% CI: 0.69-1.02; $p = 0.08$), and the reviewed articles reporting albumin benefits were those comparing it with crystalloids (1,441 patients, OR: 0.78; 95% CI: 0.62-0.99; $p = 0.04$) (A).[34]

Another meta-analysis (A)[35] compared several strategies for volume replacement in a population of critically ill pediatric and adult patients from different causes (burns, sepsis, trauma). A sub-analysis of 7,754 patients undergoing replacement with albumin or plasma compared with crystalloid found no significant difference (RR: 1.01; 95% CI 0.92-1.10; $p = 0.87$).

Recommendations: There is no evidence that volume replacement with albumin is superior to crystalloids in septic patients (A).

Is volume replacement with hydroxyethyl starch superior to crystalloid infusion regarding morbidity and mortality indicators in septic patients?

In a prospective, multicenter, controlled, randomized, double-blind study (A)[36] (Scandinavian starch for severe sepsis/septic shock - 6S), 6% hydroxyethyl starch infusion (HES 130/0.42) was compared with Ringer's lactate infusion up to 33 $mL.kg^{-1}$ in 798 patients with septic shock. The primary endpoints analyzed were mortality and terminal renal injury (dialysis-dependence), both at 90 days. The results found were mortality (HES/Ringer: RR: 1.17; 95% CI: 1.01-1.36; $p = 0.03$) and one patient in each group progressed to end-stage renal failure. Secondary endpoints were need for renal replacement therapy during intensive care stay (RR: 1.35; 95% CI: 1.01-1.80; $p = 0.04$) and severe bleeding (RR: 1.52; 95% CI: 0.94-2.48; $p = 0.09$).

Another multicenter study (VISEP) (A)[37] included 537 randomized patients with severe sepsis for intensive or conventional interventions with insulin therapy and volume replacement with 10% HES 200/0.5 or Ringer's lactate. The study was stopped early for safety reasons (nocturnal hypoglycemia in the intensive insulin group). The primary endpoints were mortality and SOFA index. The secondary endpoints were acute renal failure (baseline creatinine increased by 100%), length of hospital stay, time on mechanical ventilation, blood transfusion, hemodynamic stabilization, vasopressor use, and mortality at 90 days. There was no difference between HES and Ringer's groups regarding mortality rates (26.7% and 24.1%; $p = 0.48$), but there was a trend towards increased 90-day mortality (41% and 33.9%; $p = 0.09$). There was no difference in mean SOFA index (8 and 7.5, $p = 0.16$). There was an increase in the incidence of acute renal failure (34.9% versus 22.8%; OR: 1.81; 95% CI: 1.22-2.71; $p = 0.002$)[38] and more days on renal replacement therapy (18.3% versus 9.2%). After multivariate analysis of subgroups, researchers found increased 90-day mortality in subgroup receiving high dose of HES compared with the low-dose group (57.6% versus 30.9%; OR: 3.08; 95 %: 1.78-5.37; $p = 0.001$) (A)[38] and increased 90-day renal failure and need for renal replacement therapy in HES group with low-dose compared with Ringer's group (30.9% vs 21.7%; $p = 0.04$ and 25.9% vs 17.3%; $p = 0.03$). Patients in HES group received less volume ($p < 0.04$) and more rapidly achieved CVP over 8 ($p < 0.008$).

Recommendations: There are evidences that starch solution infusion of various molecular weights is associated, in a dose-dependent manner, with a higher incidence of renal injury compared to Ringer's lactate. Given the positive aspects of starch solution administration, including the lowest amount

needed to maintain intravascular volume and more rapid fluid resuscitation, monitoring renal function when using these agents in patients with sepsis is recommended (A).

Is hypertonic saline infusion superior to normal saline regarding morbidity and mortality indicators in septic patients?

A prospective, controlled, randomized, and double-blind study[39] with 24 adults in intensive care compared isotonic and hypertonic saline solution infusions. Patients were monitored with PiCCO (*Pulse Contour Cardiac Output Monitoring*) and gastric tonometry. Treatment group received 250 mL solution of 6% HES/200 in 7.2% sodium chloride and control group received 500 mL solution of 6% HES/200 in 0.9% sodium chloride. The primary endpoint was gastric tonometry and secondary endpoints were mean blood pressure (MAP), noradrenaline infusion, central venous pressure (CVP), cardiac index (CI), CO, stroke volume variation (SVV), intrathoracic blood volume index (ITBVI), and diuresis. Among hemodynamic parameters, there was no statistically significant difference for ITBVI, SVV, CVP, and CI. Norepinephrine infusion rate was lower in treatment group ($p < 0.008$), as well as the infusion volume (hypertonic: 2.8; SD: 1.5 L/24h, isotonic: 4.1, SD: 1.6 L/24h, $p = 0.46$); diuresis was higher in treatment group ($p = 0.19$). Among cardiac effects; contractility was higher in treatment group with increased blood volume index (BVI) ($p = 0.0012$). Gastric tonometry showed hypoperfusion in both groups ($p = 0.17$), without significant differences between groups after volume infusion ($p = 0.31$), as there was no difference in CO_2 between fluid responsive and non-responsive patients ($p = 0.64$). The evaluation of sublingual microcirculation showed no difference between treatment and control groups, in which the comparison of initial parameters showed difference only for fluid responsive patients in each group (baseline: 2.32; IQR: 1.63 to 2.79; after treatment: 2.90; IQR: 2.43 to 2.98, $p = 0.04$). Among metabolic parameters, lactate levels were higher in treatment group before ($p = 0.09$) and after infusion ($p = 0.04$). Sodium and chloride levels become higher in treatment group 30 minutes after infusion, but without affecting pH levels.

Recommendation: There is evidence that infusion of 6% HES/200 with 7.2% sodium chloride is associated (in metabolism and lingual microcirculation) with increased myocardial contractility and other hemodynamic variables, regardless of the positive effect on plasma expansion; however, without demonstrating superiority to isotonic solution.

Is the implementation of early goal-directed therapy superior to other approaches in septic patients?

A qualitative systematic review (D)[40] assessed the impact evidence of the early goal-directed therapy (EGDT) implementation. This review recorded 5,998 patients with severe sepsis or septic shock (3,042 before and 2,956 after EGDT implementation). There was no difference in sex, age, APACHE II, and mortality parameters of the studied population. Mean relative risk reduction (RRR) and absolute risk reduction (ARR) were 26% ± 0.46 and 20.3 ± 12.7%, respectively. These data were superior to the original 2001, which found 34% and 16%, respectively. This review also identified a decrease in hospital costs and hospital stay (up to 23.4%, four days or 32.4%; $p = 0.03$ in one study).

In another review by the same author (D),[41] the impact of EGDT implementation was evaluated 10 years after the classic study publication in 2001.[42] The revised population comprised 19,411 patients with severe sepsis or septic shock (9,527 before and 9,884 after EGDT implementation). APACHE II score was comparable between groups, but higher than that of the classic study. The conclusions also differed from those in the 2001 article, with a RRR of 0.37 and ARR of 18.3% and a reduction of 20% in hospital costs, mainly because of shorter ICU stay (five days per patient).

Recommendations: There are evidences that in septic patients the early goal-directed therapy approach is associated with lower mortality, shorter hospital stay, and reduced hospital costs compared with other fluid resuscitation approaches. However, this evidence was derived from reviews that were not systematic or meta-analytic, not indicating the degree of heterogeneity between studies, albeit providing cumulative analysis, which included the reduction of absolute and relative risk based on results from prospective randomized clinical trials.

The authors recommended that EGDT be used as a strategy for early fluid resuscitation of patients with severe sepsis or septic shock (D).

Is cardiac output monitoring by uncalibrated pulse power analysis accurate in septic patients?

A study (B)[43] including 24 septic patients compared the measurements of cardiac output by pulse wave analysis systems (FloTrac/Vigileo, 1.07) and transpulmonary thermodilution (PiCCO plus) before and after the increased MAP with norepinephrine infusion. There was significant correlation between measurements.

Another study (B)[44] compared the newest version (3:02) of the FloTrac/Vigileo system with thermodilution system before and after volume expansion and increasing or reducing the dose of norepinephrine in 60 patients (48 septic). The coefficients of determination r^2: 0.26, 0.0025, 0.16; measure of bias 0.11, 0.36, 0.17; and limits of agreement -1.2 to 0.98, -1.25 to 1.98, -1.26 to 0.92 found for the three study procedures, respectively, indicate that the third generation FloTrac system was not reliable in detecting changes in CO induced by norepinephrine, not even by volume expansion, and that the higher the systemic vascular resistance the greater the bias.

Another study (1B)[45] compared estimates of cardiac index by uncalibrated pulse wave analysis (FloTrac) or thermodilution-calibrated pulse contour analysis (PiCCO) in 80 septic patients undergoing interventions with volume expansion or norepinephrine dose introduction/increase. The respective results were: a) CI bias: -0.23 ± 0.95 L.min.$^{-1}$m^{-2}, -0.01 ± 1.75 L.min.$^{-1}$.m^{-2}; b) percentage variation: $r = 0.33$ ($p < 0.05$), -0.03 ($p = 0.65$); c) ability to detect CI increase > 15% by thermodilution: 56% sensitivity and 71% specificity; 23% sensitivity and 96% specificity. These results repeat the previous study findings.[44]

Another prospective, observational, multicenter study (1B)[46] involving 58 septic patients compared the thermodilution method (TD) in pulmonary artery with the FloTrac algorithm second and third generation (G2, and G3, respectively). The results found for CI in the comparison were: a) mean bias with 95% CI: -10 (-15 to -5)% [-0.8 (-1.1 to - 0.4) L.min.$^{-1}$] 0 (-4 to 4)% [0 (-0.3 to 0.3) L.min.$^{-1}$]); b) error percentage: 29% (20-37), 30% (24-37). The difference between CI measurements by TD and G2 were strongly correlated with the total systemic vascular resistance ($r^2 = 0.37$, $p < 0.0001$) and weakly correlated with G3 ($r^2 = 0.05$). In conclusion, the third generation FloTrac is more accurate and less influenced by total systemic vascular resistance (SVR) than the second generation.

Recommendations: The measurements obtained by the FloTrac/Vigileo system have low correlation, high percentage of disagreement, significant bias, and wide limits of agreement compared to cardiac output invasive measurements.

The authors recommended that the cardiac output monitoring by uncalibrated pulse wave analysis not be used in septic patients (A).

Conflicts of interest

The authors declare no conflicts of interest.

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