The Final thesis

Scoping Research of Fluid Infusion Volumes During Initial Management of Septic Shock

Institute of Clinical Medicine, Clinic of Anaesthesiology and Intensive Care

Yuliya Aheyeva, VI year, group 4

Supervisor: Assoc. Prof. Saulius Vosylius

Consultant _____

The Head of Department/Clinic Prof. dr. Jūratė Šipylaitė

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Email of the student: yuliya.aheyeva@mf.stud.vu.lt

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Summary

Early detection and treatment of septic shock are critical for a patient's prognosis. Even with the Surviving Sepsis Campaign guidelines, there are many unanswered questions about initial infusion therapy in septic shock. More emphasis in this thesis is being placed on the fact that each patient is unique, and that his management and monitoring should be personalized and implemented based on the shock phase.

Keywords

Septic shock, infusion therapy, management of septic shock, initial infusions in septic shock, personalized septic shock treatment, phase-dependent treatment of shock

Introduction

Septic shock is defined as a subset of sepsis in which underlying circulatory, cellular, and metabolic abnormalities are associated with a greater risk of mortality than sepsis alone (1).

Sepsis and septic shock are major healthcare issues that affect millions of people worldwide each year, killing up to one in every four patients (and often more) (2). Despite guideline-based treatment and the best efforts of healthcare providers, mortality from septic shock remains quite high at nearly 35% to 40% (3). As a result, early identification in the first hours after sepsis development is critical.

Clinical criteria identifying septic shock include persisting hypotension requiring vasopressors to maintain mean arterial blood pressure (MAP) ≥65 mm Hg and blood lactate >2 mmol/L despite adequate volume resuscitation (4).

Even though Surviving Sepsis Campaign (SSC) guidelines provide excellent management of septic patients there is always a possibility for personalization for several reasons (4). First, while these guidelines are evidence-based, they are primarily based on randomized controlled trials (RCTs) that investigate the response of large groups of patients to an intervention. These trials are generally negative, demonstrating no differences in mortality. However, it is critical to recognize that individual patient characteristics may influence response or tolerance to a given intervention. Second, many aspects of resuscitation remain debatable, and research gaps persist (5). As a result, guidelines frequently fail to provide strong and precise recommendations in

specific areas. Third, there are different stages in shock management, each requiring a unique approach (6).

Individualizing therapeutic options based on the patient's condition may be reasoned in this way. In this study, I discuss personalizing various options for managing patients in the initial stages of septic shock and their hemodynamic monitoring. In contrast to standard treatment options, the general principle of personalized shock management is to measure, interpret, apply therapy, evaluate its effects, and respond.

Literature search strategy

For this review, a systemic literature search was performed using “PubMed” scientific database, which is supported by the “National Center for Biotechnology and Information” at the “National Library of Medicine” and “The UpToDate” system. English-language studies published from 2000 to 2022, including the following terms: septic shock, shock phases, initial management of septic shock, infusion therapy, vasopressors in septic shock, glucocorticoids, and fluid resuscitation, were considered. Relevant clinical data, including controlled trials, observational studies, review articles, and guidelines, were summarised, with a concentration on particular questionable issues concerning the initial infusion in septic shock. Even though the evidence of identified citations was contentious, there was a consistent interest in reporting recommendations for the personalization of existing treatment.

Clinical presentation and pathophysiology of septic shock

Septic shock is a potentially fatal circulatory disorder that causes tissue hypoxia and microcirculation disruption due to fluid redistribution. As a result, it is categorized as a distributive shock.

Patients who progress to septic shock will present with altered mental status, oliguria or anuria, hypoxia, and hypotension. Notably, blood pressure may be maintained at an early "compensated" stage of shock, with other signs of distributive shock, such as warm extremities, flash capillary refill (less than one second), and bounding pulses, also known as warm shock. This stage of shock can be reversed if treated aggressively. Hypotension develops as septic shock progresses into the uncompensated stage, and patients may present with cool extremities, delayed capillary refill (more than three seconds), and thready pulses, also known as cold shock. With continued tissue

hypoperfusion, shock may become irreversible, rapidly progressing into multiorgan dysfunction syndrome and death (7).

The pathophysiology of septic shock is not fully understood yet, but it is considered to involve a complex interaction between the pathogen and the host's immune system. A normal response to localized infection involves the activation of host defence mechanisms, resulting in the influx of activated neutrophils and monocytes, the release of inflammatory mediators, local vasodilation, increased endothelial permeability, and activation of coagulation pathways. These response mechanisms occur on a systemic scale during septic shock (8).

When a pathogen meets with a macrophage it causes the release of various cytokines such as TNF, IL-1,2,6,8,12, and platelet-activating factor. In turn, the cytokines affect the hypothalamus and evoke symptoms such as fever, tachycardia, and tachypnea. In addition, these signal proteins act on a vessel wall increasing the production of nitric oxide (NO) which results in vasodilation. Changes in endothelial function which lead to increased neutrophil migration, platelet adherence, and disseminated intravascular coagulation (DIC) with clinical thromboses and/or haemorrhage can affect intravascular volume leading to its depletion. Vasodilation and endothelial cell dysfunction result in cellular hypoxia and low systemic vascular resistance consecutively causing lactic acidosis and death. Endothelial damage can activate inflammatory and coagulation cascades, resulting in a positive feedback loop, the profound release of various inflammatory mediators, and further endothelial and end-organ damage (8, 9). Cardiovascular, pulmonary, renal, gastrointestinal, endocrine, and nervous systems are most often involved.

The hemodynamic changes in septic shock include a decrease in vascular tone, a hypovolemic component resulting from the accumulation of blood in capacitance veins due to diminished venous tone (relative or central hypovolemia) as well as fluid losses caused by the vascular leak (absolute hypervolemia), a variable degree of myocardial dysfunction, dysregulation of regional blood flow distribution and microvascular changes (Fig. 1).

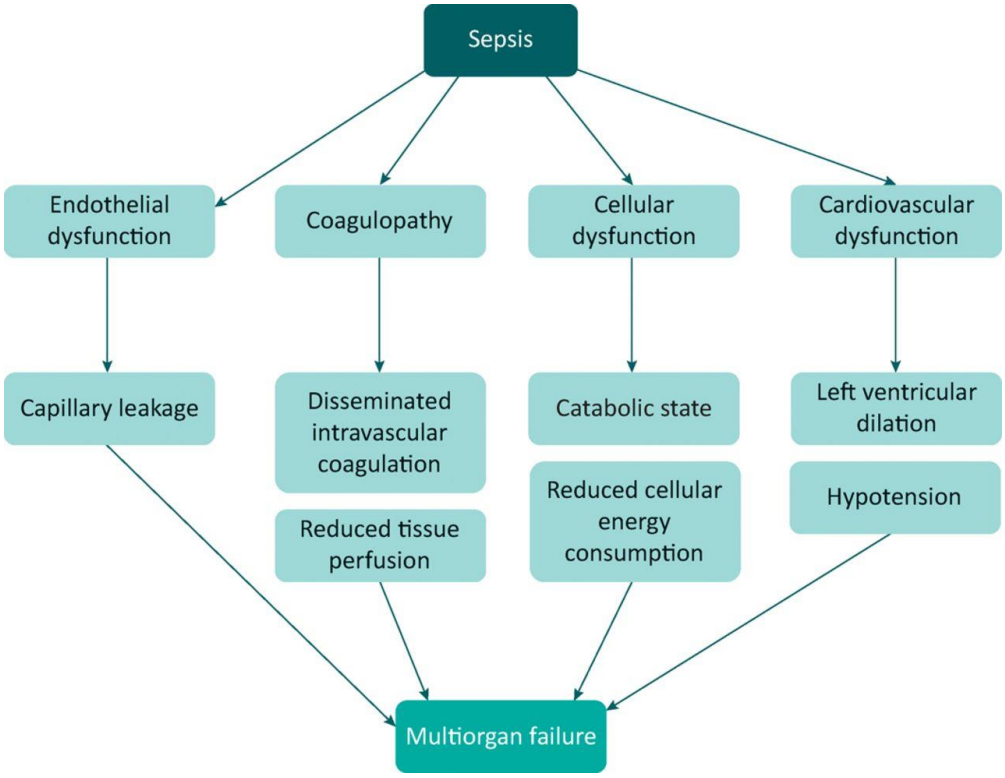

Fig. 1 The key pathophysiological changes of sepsis and how these combine to produce multiorgan failure.

Endothelial dysfunction plays important role in microvascular changes. Several experimental studies demonstrated that alterations in microvascular perfusions are characterized by a decrease in the density of perfusion between regions that are only a few microns apart. The increase in the intercapillary distance caused by diminished capillary density leads to an increase in oxygen diffusion distance which could result in hypoxia (10).

Even though the traditional resuscitation strategies are based on vasopressors, fluids, and in some cases, inotropic agents to maintain perfusion pressure and cardiac output (11), tissue perfusion abnormalities frequently remain even after resuscitation targets were achieved, which contributes to the development of organ dysfunction (12). Preserved tissue perfusion abnormalities might be present due to unrestored microcirculation (10). Experimental research has emphasized the potential significance of microvascular perfusion alterations in septic shock.

The most recent assessment methods are veno-arterial differences in pCO2 (PvaCO2), lactate levels, and direct microcirculatory evaluation by handheld microscopes (10).

The improvement in microvascular perfusion is associated with a decrease in lactate levels (13) and PvaCO2— gradients (14). What is a more important improvement in microvascular perfusion is associated with improved organ function (15, 16, 17). Changes in microvascular perfusion during early resuscitation procedures were associated with inverse changes in organ function score the next day (15). In patients receiving fluid administration, organ function improved in patients who improved their microvascular perfusion but not in the others (16).

Numerous studies have demonstrated a connection between the severity of microvascular changes and the prognosis for septic shock patients (18, 19, 20, 21). Even though the majority of studies examine differences in microvascular perfusion between survivors and non-survivors at admission, the evolution of microvascular perfusion also varied between them over time: microvascular alterations improved over time in survivors but remained stable in non-survivors (20).

Salvage, optimization, stabilization, and de-escalation (SOSD) phases in the treatment of Septic Shock

Vincent and DeBacker proposed a framework for resuscitating a patient in septic shock, according to which shock can be divided into four stages, with specific therapeutic goals and monitoring required in each stage (Fig.1) (6). The "salvage, optimization, stabilization, and de-escalation" (SOSD) mnemonic should be used as a general guide to fluid resuscitation, and fluid administration should be adapted according to the course of the disease (80). Initial resuscitation should be conducted in the salvage and optimization phases. During the initial salvage phase, the lifesaving fluid should be administered liberally with the addition of vasopressors when it is essential for the achievement of minimum blood pressure and cardiac output compatible with immediate survival. In this stage basic monitoring should be carried out and if circumstances permit continuous arterial pressure monitoring. Once hemodynamic monitoring is available, fluid administration should be optimized by determining the patient's fluid status and the need for additional fluid (22).

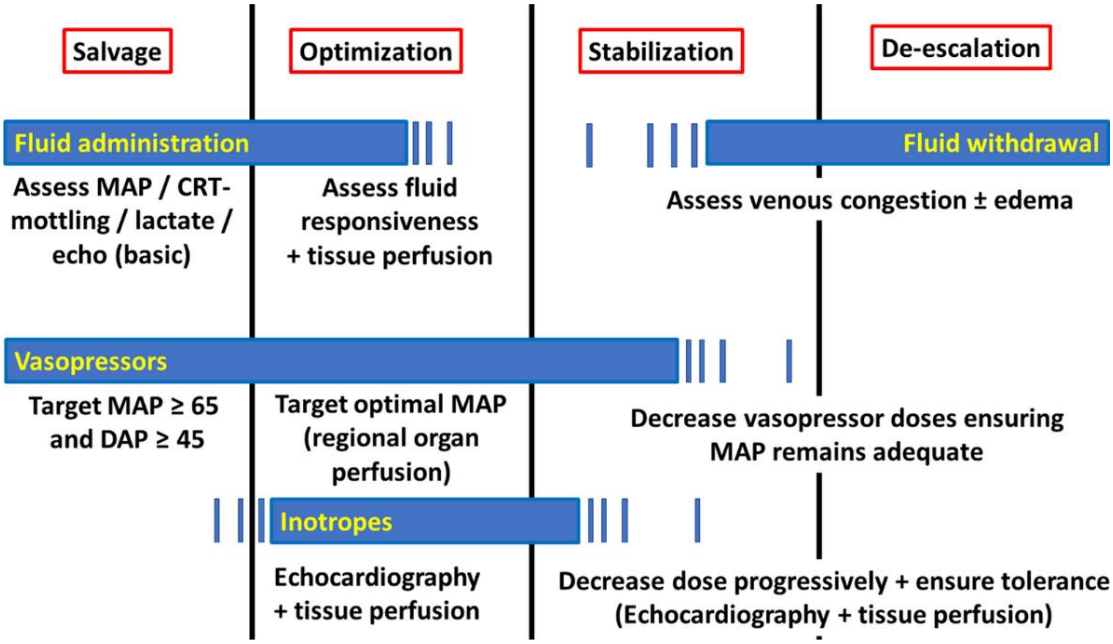

Fig. 2 Suggestions for monitoring and interventions at various stages of shock. At each stage of septic shock, therapeutic options (yellow in blue rectangles) and monitoring techniques and goals are shown. MAP stands for mean arterial pressure, CRT stands for capillary refill time, echo stands for echocardiography, and DAP stands for diastolic blood pressure.

Initial resuscitative therapy

The core elements of initial resuscitation are the rapid restoration of perfusion and the early start of antibiotic therapy. Tissue perfusion is primarily accomplished through the liberal administration of intravenous fluids. Empiric antibiotic therapy is administered within the first hour and is directed at the suspected organism and site of infection. A database study of nearly 50,000 patients with sepsis and septic shock who were treated with various types of protocolized treatment bundles (which included antibiotics and fluids infusions, blood cultures, and serum lactate measurements) demonstrated the importance of timely treatment, particularly with antibiotics. When compared to those who completed a three-hour bundle (blood cultures before broad-spectrum antibiotics, serum lactate level) within the three-hour time frame, those who completed a three-hour bundle later than three hours had a higher in-hospital mortality (odds ratio 1.04 per hour). Increased mortality was linked to delayed antibiotic administration but not to a longer time to complete a fluid bolus (23).

Fluids infusion during the initial management of a septic shock

According to the international guideline of SSC 2021, septic shock is a medical emergency and it is recommended to start resuscitation and treatment immediately. The treatment of sepsis-induced hypoperfusion starts with infusion therapy (4). Fluids are cardinal in the hemodynamic resuscitation of septic shock. Hypovolemia and preload dependence are associated with microcirculatory alterations (24). Fluids may improve microvascular perfusion, but the effect is quite variable and may depend on the timing at which these are administered: fluids improve microvascular perfusion within 12–24 hours of sepsis recognition, while these have limited or even detrimental impact on the microcirculatory perfusion at later stages (25).

Surviving Sepsis Compagnie 2016 gave a strong recommendation for the initial infusion therapy of septic shock at least 30 ml/kg crystalloid fluid IV within the first 3 hours (10). Based on the low quality of evidence this recommendation was downgraded from a strong recommendation to a weak recommendation in SSC 2021 (4).

It is important to emphasize that fluids can be administered liberally during the salvage phase. At this phase, in fluid-responsive patients infusion therapy and MAP optimization improve microcirculatory, regional, and macrocirculatory blood flow which complies with maintained hemodynamic coherence and is associated with more benefits than risks. At more advanced stages, the treatment is questionable. The predominance of adrenergic tone and endothelial inflammation leads to non-responsiveness to systemic blood flow optimization. As a result, hemodynamic coherence is lost, and attempts to increase stroke volume or MAP with fluids or vasoactive agents may result in fluid overload or catecholamine toxicity (Fig. 3)(65).

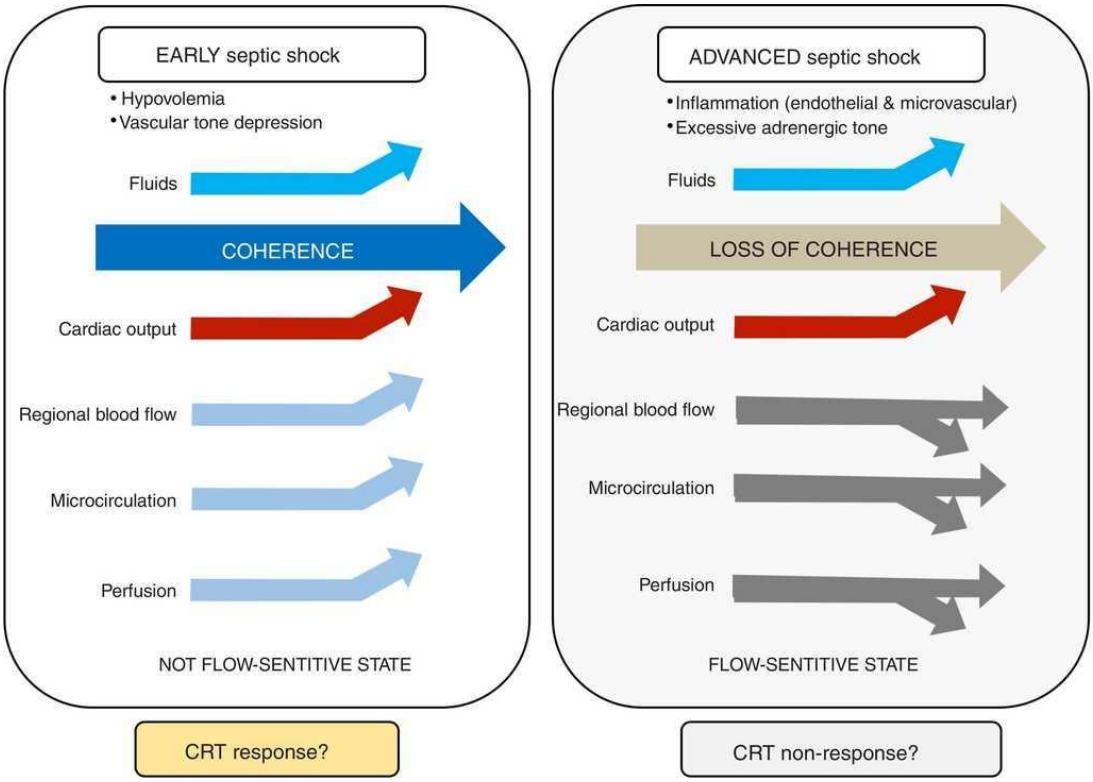

Fig. 3 Concept of hemodynamic coherence in septic shock.

There have been no prospective intervention studies comparing different volumes of resuscitation in sepsis or septic shock. A retrospective study of adults who presented to an emergency department with sepsis or septic shock found that failure to receive 30 mL/kg of crystalloid fluid therapy within 3 hours of sepsis onset was associated with higher in-hospital mortality (13). Furthermore, in the PROCESS, PROMISE, and ARISE trials, the average volume of fluid received before randomization was in the range of 30 mL/kg, indicating that this fluid volume has been adopted in routine clinical practice (4).

The situation becomes more complicated during the optimization stage. The proportion of patients responding to fluids decreases progressively, while the risk of adverse events rises (26).

Other studies revealed that the amount of administrated fluid doesn't correlate with improvement in microvascular perfusion (27, 28). It appeared that the administration of a limited amount of fluids at the initial stage improves the microcirculation, whereas further fluid administration is ineffective even when cardiac output increases. In particular, when fluids improve microcirculation they also improve the organ's

function. However, not every organ reacts similarly. Sublingual microcirculation improved with fluid administration in patients with abdominal sepsis, but gut microcirculation did not (29). These variations could be caused by several variables, such as a local inflammatory reaction and increased intraabdominal pressure. Although fluid withdrawal may result in an improvement in microvascular perfusion by decreasing interstitial edema, rapid fluid removal may worsen microvascular perfusion (9).

Despite the obvious benefits of IV fluid therapy, excessive fluid administration can result in several complications. In general, significantly positive fluid balances are associated with poorer outcomes for critically ill patients (**Error! Reference source not found.**). Fluid retention in the interstitial space could result in interstitial edema, impaired organ perfusion, and possibly acute pulmonary edema. A globally increased permeability syndrome (GIPS) may develop in terms of persistent systemic inflammation (i.e., high capillary leak) and positive cumulative fluid balance (i.e., edema formation and poly-compartment syndromes) with resistant organ failure (30, 32). It is critical to carefully tailor fluid therapy. Whether dry or wet, per-formula strategies are inappropriate, and personalized strategies are preferred (33). Personalized fluid administration consists of several steps. First, a clear indication for fluids should be present, such as perfusion impairment that is expected to respond to fluids with the increase in cardiac output. Second, the patient's response and assessment of the potential benefits and risks of fluids should be made. Prediction of fluid responsiveness is better achieved with dynamic tests over static measurements of preload (34). Third, using the fluid challenge technique, the response to fluids should be carefully evaluated (35).

There are no strong recommendations for the assessment of fluid resuscitation according to the stage of shock in SSC guidelines. Generally, they recommend using dynamic measures such as passive leg rising combined with cardiac output (CO) measurement and fluid challenges against stroke volume (SV), systolic pressure or pulse pressure, lactate levels, and capillary refill time to guide fluid resuscitation (4).
In the salvage stage, basic clinical monitoring plays a major role in identifying and assessing a patient’s response to fluids (36).

Ideally, there should be a carefully chosen indicator that would represent tissue hypoperfusion that responds quickly to infusion. By now, fluid resuscitation is triggered by prolonged capillary refill time (CRT), skin mottling, decreased venous oxygen saturation, and increased veno-arterial PCO2 gradients. Increased lactate levels alone are insufficient because hyperlactatemia can take time to resolve and can be influenced by other factors. Besides CRT can be used to guide the need for additional fluid administration (**Error! Reference source not found.**). Because a positive response is less likely to occur if the patient received several liters of fluid infusion, the amount of already administered fluid must be considered when evaluating the benefits and risks of infusion as well as potential risks (right ventricular dysfunction, severe hypoxemia, venous congestion, and intra-abdominal hypertension). Fluid responsiveness should be evaluated before fluid administration whenever possible when there is an indication based on an appropriate indicator and a potentially positive benefit/risk ratio.

Administering a fluid bolus and measuring its effect on CO is the simplest way to detect preload responsiveness, but if boluses are repeated, this technique can lead to fluid overload. The passive leg-raising test is reversible and replicates the hemodynamic effects of approximately 300 ml of fluid load (66). The effects of the test can be measured as the response in CO, in pulse wave\contour analysis, or CRT (37, 39, 67). End-tidal carbon dioxide may be used to assess changes in CO during passive leg rising tests and fluid infusion in intubated patients if ventilation is stable (68, 69). These tests, however, are difficult to perform during the salvage phase, when many interventions are being used at the same time. Fluid responsiveness prediction and fluid effect assessment should be started as soon as technically possible, especially in patients with poor cardiac function. Preload responsiveness may be reflected in cyclic variations in stroke volume during ventilation. Several indices that reflect respiratory variations in stroke volume have been reported. The first of these indices is arterial pulse pressure variations (PPV) which are measured by the majority of bedside monitors. The primary limitation of PPV is that it cannot be used in many clinical situations that result in false positives (spontaneous ventilation, cardiac arrhythmia, right ventricular failure) and false negatives (low tidal volume, low lung compliance, extremely high respiratory rate) (70). The Vt challenge, a transient increase in Vt from 6 to 8 mL/Kg whose effects on PPV and stroke volume variation (SVV) are evaluated, was superior to PPV and SVV in predicting fluid responsiveness in the presence of low Vt (75).

Stroke volume variations can be assessed using techniques that measure stroke volumes beat by beat, such as pulse wave analysis and echocardiography. Due to unavoidable measurement errors, the benefit of direct estimation of stroke volume outweighs the benefit of PPV in adults (71).

The respiratory occlusion test used for an assessment of fluid responsiveness involved briefly interrupting mechanical ventilation and measuring CO response. The effects of the test on pulse pressure are difficult to quantify because the variations are small and transient. Initially, CO was measured using pulse wave contour analysis in this test (72). Variations in vena cava size affected by respiration cause fluctuations in venous return. Echocardiography can easily estimate respiratory variations in superior and inferior vena cava diameters. The diagnostic prediction of fluid responsiveness of superior vena cava respiratory variations is superior to that of inferior vena cava, but superior vena cava required transoesophageal echocardiography (73). IVC variations, given their limitations, should be used in combination with other approaches.

Regrettably, CO monitoring may be challenging to use regularly because it is expensive and invasive. Luckily, such monitoring techniques as capnography, plethysmography, bioreactance, or simple changes in PPV, may replace invasive CO measures during passive leg raising tests.

Furthermore, when a central venous catheter is in place, central venous O2 saturation (ScvO2) and the gradient of carbon dioxide partial pressure (pCO2) between central venous and arterial blood (PvaCO2) may be useful in guiding resuscitation.

After determining the likelihood of a significant CO response to fluid, the results of volume expansion should be assessed using a fluid bolus. The fluid challenge is the most secure method of administering fluids. A limited amount of fluid is administered over a short time frame (4ml/kg over 10 min) to assess the initial response in terms of increases in stroke volume and CO, fluid tolerance during administration, and diffusion of the preliminary effect. Standardization of this technique is required (74).

While guidelines recommend balanced crystalloids (4), individual patient factors such as chloride and albumin levels, as well as the presence of edema, should be taken into account when choosing between albumin and crystalloids, and 0.9% saline versus balanced crystalloids (based on chloride levels).

Saline has been shown in preclinical studies to cause hyperchloremic metabolic acidosis, inflammation, coagulopathy, greater need for blood transfusions, impaired peripheral perfusion and microcirculation, hypotension, acute kidney injury, and death. Studies on patients and healthy human volunteers indicate that even small amounts of saline can have physiological effects (79). Randomized clinical trials have shown that using balanced crystalloids instead of saline prevents the development of hyperchloremic metabolic acidosis and may minimize the need for vasopressors. Observational studies in critically ill adults have linked the administration of balanced crystalloids to lower rates of complications, such as acute kidney injury and death (77).

According to the secondary analysis of a clinical trial of the Isotonic Solutions and Major Adverse Renal Events Trial (SMART) data set, the effect of balanced crystalloids (lactated Ringer's, Plasma-Lyte) vs saline on sepsis mortality appeared to be greater among patients whose fluid choice was determined by the trial starting in the emergency department (ED) compared to patients whose fluid choice was determined by the trial only after intensive care unit (ICU) admission. These findings suggest that using balanced crystalloids early in sepsis resuscitation may have a greater impact on survival than later in the illness fluid selection. The results were similar for ventilator-, vasopressor, and ICU-free days—beneficial effects with balanced crystalloids were observed only in patients for whom fluid choice was controlled by the trial in the ED before ICU admission (76).

A systematic review and meta-analysis discovered that administration of Plasmalyte leads to decreased post-infusion serum chloride and lactate concentrations, as well as a higher base excess when compared to other balanced crystalloids. The certainty of these findings is low because the studies included heterogeneous populations, resulting in inconsistency for some outcomes and the risk of bias among the included studies. There was insufficient data to investigate the impact of various balanced crystalloids on patient-important outcomes such as mortality and hospitalization length (78).

A retrospective cohort study analysed data of patients hospitalized with sepsis/septic shock who developed acute kidney injury (AKI) and had human albumin infusions. The use of albumin within 24 hours of hospital admission was associated with a shorter duration of hospital stay and a higher rate of discharge with clinical stability, among

patients with sepsis/septic shock who developed stage 3 AKI during hospitalization (40). Thus, albumin may be a beneficial solution for patients with septic shock and acute kidney injury. Further investigations are needed to evaluate albumin as a first-line solution in septic shock.

Vasoactive therapy

Patients who present with persistent hypoperfusion despite adequate initial fluid and antimicrobial therapy should be reassessed for fluid responsiveness, antimicrobial adequacy, diagnosis correctness, and the probability of unexpected complications (such as pneumothorax following central venous catheter insertion).

While some patients benefit from fluid therapy alone, others require vasopressor support. The first-choice vasopressor in septic shock is norepinephrine (4).
Norepinephrine causes vasoconstriction acting on adrenergic receptors α -1 and α -2 and increasing cardiac output due to the action on the β -1 receptor. Norepinephrine, like most vasopressor drugs, can cause excessive vasoconstriction and decrease vital organ perfusion, resulting in peripheral, myocardial, cerebral, and gastrointestinal ischemia (41). Furthermore, norepinephrine may have adverse immunosuppressive effects, limiting its use in septic shock (42).

Other treatment options are Dopamine, Vasopressin, and Epinephrine. When norepinephrine is unavailable, epinephrine or dopamine can be used as a substitute, however, the use of norepinephrine should still dominate when it is available (4). Epinephrine usage as a first-line agent was discouraged due to concerns about splanchnic vasoconstriction, tachyarrhythmias, and production of lactate which may interfere with lactate-guided resuscitation management (2).
In low dosages dopamine act on D1 and D2 receptors, which vasodilate splanchnic and renal vasculature increasing perfusion of the organs. Initially, it was thought that potentially beneficial increased renal perfusion would improve renal function in patients with sepsis. However, a large randomized controlled trial found no difference in renal replacement rates, urine output, time to renal recovery, or survival in patients who received dopamine versus placebo (43). In medium doses, dopamine stimulates the β-1 receptor and leads to an increase in heart rate (HR) and contractility. A

vasoconstrictive effect is caused by high dosages. Dopamine tends to provoke tachyarrhythmias and should be used with caution.

Norepinephrine increases MAP due to its vasoconstrictive effects, with little change in HR and less increase in stroke volume compared with dopamine. Dopamine increases MAP and cardiac output, primarily due to an increase in stroke volume and heart rate. Recommended initial target mean arterial pressure (MAR) for patients on vasopressors 65mmHg (4). Norepinephrine is more potent than dopamine and may be more effective at reversing hypotension in patients with septic shock. Dopamine may be particularly useful in patients with compromised systolic function but causes more tachycardia than norepinephrine (44).

Vasopressin is another treatment option due to its stimulating effect on V1a receptors which are responsible for vasoconstriction. Moreover, it acts on V1b for adrenocorticotrophic hormone release stimulation, V2 for antidiuretic effects, and oxytocin. V1a receptor activation on vascular smooth muscle causes vasoconstriction via a catecholamine-independent pathway. In septic shock, there is a vasopressin deficiency, and low-dose vasopressin therapy has been shown to decrease norepinephrine requirements, maintain blood pressure, and increase urine output in small groups of patients (45, 46). Surviving Sepsis Guidelines recommend vasopressin to reduce catecholamine dose or achieve target mean arterial pressure in patients who do not respond to norepinephrine. It usually started when the dose of norepinephrine is in the range of 0.25−0.5 μg/kg/min (4).

Selepressin and Angiotensin II have low-quality evidence according to SSC 2021 (5). Selepressin is a new drug a highly selective V1a receptor agonist. It has been proposed as a non-adrenergic vasopressor when high doses of catecholamines are required. A blinded, placebo-controlled, randomized, controlled trial of selepressin versus placebo in septic shock found that selepressin reduced positive fluid balance and resulted in faster norepinephrine discontinuation (47).
Selepressin decreases vascular leakage and limits sepsis-induced vasoplegia (48).
In phase 2b/3, a multicentre, double-blinded, randomized clinical trial investigated the efficacy and safety of selepressin at different dosages on vasopressor-dependent septic shock. Selepressin was administered for a median of 37.8 hours. A significant

difference between the two groups was found in terms of higher MAP and lower norepinephrine requirement in patients receiving selepressin over the first 6 hours. Besides, in the first 24 hours, the selepressin group had significantly less cardiovascular dysfunction, higher urine output, and lower net fluid balance than the placebo group. In conclusion, despite its norepinephrine-sparing effect without increasing adverse events, the trial appears to show no benefit in terms of ventilator- and vasopressor-free days in the selepressin group when compared to placebo (49).

In the treatment of vasodilatory shock, angiotensin II has emerged as a novel pressor. When compared to a placebo, it is effective at raising blood pressure and has a catecholamine-sparing effect (50). A post hoc analysis of patients with replacement renal therapy (RRT) revealed that patients who were randomized to angiotensin II had better survival and were free of RRT sooner (51).

Briefly assessing all the above I can conclude that norepinephrine still stays the first option for vasoactive treatment, despite its immunosuppressive adverse effects. In patients with septic shock receiving high doses of norepinephrine, the addition of vasopressin enhances microvascular perfusion (52). Selepressin has a selective action on V1a receptors, and it decreases vascular leakage. It also decreases the required amount of norepinephrine and lowers the cardiovascular dysfunction rate. Despite a favourable profile in preclinical studies, selepressin administration in patients with septic shock without blood flow assessment failed to demonstrate a beneficial impact on the outcome. Dopamine and Epinephrine are alternatives used in patients with low risk of tachyarrhythmias and absolute or relative bradycardia. There are still important questions about optimal vasopressor selection, the role of combination therapy, and the most effective and safest escalation method in different patient cohorts (53). More tools are needed to reveal the most effective vasopressors in specific situations and how to avoid harm from using them.

The SSC guidelines recommend maintaining mean arterial pressure (MAP) at $\geq$ 65 mmHg but do not specify when or how fluids should be prioritized over vasopressors. Some patients with severe hypotension may require the administration of vasopressors early, i.e., without waiting for the fluid effects, to accelerate arterial pressure restoration. Delaying the correction of hypotension is linked to a poor outcome (54).

Furthermore, norepinephrine may help to increase cardiac preload by recruiting unstressed blood volume (55), which may reduce fluid requirements. In an observational study that used propensity matching, early start of norepinephrine was associated with a less positive fluid balance and lower 28-day mortality (**Error! Reference source not found.**). In cases of severe hypotension, starting vasopressors early seems logical, though no precise MAP cutoff can be given. Diastolic pressure (DAP) may also play a role in the decision. DAP is determined by vascular tone and aortic blood volume decay time. A low DAP in sepsis often indicates severe vasodilation and is associated with increased mortality (56). When DAP is very low, such as < 45 mmHg, it seems logical to start vasopressors. The diastolic shock index (DSI) is a ratio of DAP and HR. Its high values are associated with a higher risk of death in tachycardic patients with septic shock (56). It is unknown whether DSI > 2 should be used to activate vasopressors.

Additional treatment options

Additional therapies such as glucocorticoids and inotropic agents are not routinely indicated in patients with sepsis or septic shock, but they may be useful in refractory cases of septic shock or special circumstances.

The routine use of glucocorticoids in sepsis patients is discouraged by guidelines. Corticosteroid therapy, on the other hand, may be appropriate in patients with septic shock who are resistant to adequate fluid resuscitation and vasopressor administration. The reasoning for glucocorticoid administration in sepsis and septic shock patients is based on evidence that critical illness causes absolute or relative adrenal insufficiency, which may contribute to shock. The goal of giving glucocorticoids to sepsis patients is to restore balance to the altered hypothalamic-pituitary-adrenal (HPA) axis to improve significant clinical outcomes such as mortality.

Both hydrocortisone and fludrocortisone administration resulted in faster shock resolution and a mortality benefit in two large, randomized trials. In the French study, 300 patients with vasopressor-dependent septic shock were randomly assigned to receive either a placebo or hydrocortisone (50 mg intravenously every six hours) plus fludrocortisone (50 mcg enterally once a day). Treatment began eight hours after the onset of septic shock and lasted seven days. Administration of

hydrocortisone/fludrocortisone reduced 28-day mortality and resulted in faster shock reversal. These benefits were maintained in patients with insufficient adrenal reserve while no benefit was shown in those with adequate adrenal reserve. The trial was chastised for having a high placebo-group mortality rate (58).
In another trial, 1241 patients with severe septic shock on vasopressors were randomized to receive a placebo or hydrocortisone (200 mg per day in four divided doses) plus fludrocortisone (50 micrograms via nasogastric tube daily) for seven days without tapering. Administration of hydrocortisone/fludrocortisone reduced 90-day and 180-day mortality and increased vasopressor-free days. ICU discharge, hospital discharge, and organ failure-free days were all improved by hydrocortisone/fludrocortisone administration. There was no increase in superinfection or neurologic sequelae, but corticosteroids increased the rate of hyperglycaemia (59).

According to David A Kaufman's article published in 2022, glucocorticoid therapy can help patients with refractory shock (defined as a systolic blood pressure less than 90 mmHg for more than one hour after adequate fluid resuscitation and vasopressor administration). They recommend hydrocortisone alone (400 mg per day in divided doses) as therapy rather than combined therapy with fludrocortisone (60). Based on trials that showed a mortality benefit, the addition of fludrocortisone (50 mcg via gastric tube once daily) is a reasonable alternative (58,59). Therapy duration is usually from five to seven days and a tapered withdrawal approach that is guided by clinical response is used. Potential side effects of steroid administration in patients with septic shock include hypernatremia, hyperglycaemia, and neuromuscular weakness. In studies, the risk of superinfection does not appear to be consistently elevated (60).

Inotropic agents are good for patients who failed to respond to adequate fluids and vasopressors, particularly those with decreased cardiac output (61, 62). Cardiac depression with impaired left ventricular function is a well-recognized manifestation of septic shock, reported in up to 60% of patients (63). Patients presented with low cardiac output (CO) related to left or right ventricular dysfunction may benefit from inotropic agents (64). Dobutamine and epinephrine are recommended treatment options (4). Harmful impacts (tachycardia, arrhythmias) and associated risks in certain patient groups (hypertrophic cardiomyopathies, myocardial ischemia) should be carefully

evaluated, as should the risks/benefits of the intervention. Therapy should not be used to raise the cardiac index above normal.

Conclusion

Fluid therapy is a vital treatment for septic shock patients. Because of the risk of interstitial edema, impaired organ perfusion, and acute pulmonary edema in critically ill patients, widespread early and aggressive fluid therapy has been thrown into doubt. A more individualized approach is required because there is a risk of insufficient resuscitation when using a fixed volume infusion, the late addition of vasopressors, or the usage of crystalloid-balanced solution on all patients. At the salvage phase, it is recommended to use liberal IV infusion therapy with vasopressors to achieve minimum blood pressure and compatible cardiac output (mean arterial blood pressure ≥ 65, diastolic arterial blood pressure ≥ 45). Selection of the solution type should be based on the individual patient's parameters: levels of chloride, lactate, albumin, and the presence of edema. Privilege is given for balanced solutions such as lactated Ringer's, and Plasma-Lyte due to decreased rate of mortality, and complications. As soon as hemodynamic monitoring is available, conduction of optimization of fluid volumes by defining fluid status and subsequent fluid needs. In the optimization phase continuation of vasopressor therapy targeting optimal mean arterial blood pressure with the administration of inotropes for patients with decreased cardiac output. It is important to note that monitoring and support must be tailored to the stages of shock, and the effectiveness of interventions must be evaluated regularly.

List of abbreviations

MAP – mean arterial blood pressure.
HR – heart rate
SSC – Surviving Sepsis Campaign
RCTs – randomized controlled trials
NO – nitric oxide
SOSD – salvage, optimization, stabilization, and de-escalation
CRT – capillary refill time
DAP – diastolic blood pressure.
CO – cardiac output
SV – stroke volume

ScvO2 – central venous O2 saturation

pCO2 – carbon dioxide partial pressure

PvaCO2 – veno-arterial differences in pCO2, gradient of pCO2 between central venous and arterial blood

GIPS – globally increased permeability syndrome

AKI – acute kidney injury

MAR – mean arterial resistance

RRT – replacement renal therapy

DSI – diastolic shock index

RBC – red blood cell

ICU – intensive care unit

HPA – hypothalamic-pituitary-adrenal axis

DIC – disseminated intravascular coagulation

NO – nitric oxide

PPV – pulse pressure variations

SVV – stroke volume variation

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