Sepsis and Septic Shock Part II:

Resuscitation and hemodynamic support

of the patient with sepsis

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Intended Learning Outcomes

Sepsis and Septic Shock Part II: Resuscitation and hemodynamic support of the patient with sepsis

1. Discuss a physiology-based approach to the endpoints of resuscitation of the septic patient
2. Discuss a physiology-based approach to fluid resuscitation of the septic patient
3. Describe vasopressor/inotropic agents used in the treatment of septic shock, and understand when they should be initiated
4. List treatment options for the treatment of refractory septic shock

eModule Information

Relevant Competencies from CoBaTrICE

Sepsis and Septic Shock Part II: Resuscitation and hemodynamic support of the patient with sepsis

- **1.1** Adopts a structured and timely approach to the recognition, assessment and stabilisation of the acutely ill patient with disordered physiology
- **2.9** Monitors and responds to trends in physiological variables
- **3.3** Recognises and manages the patient with circulatory failure
- **3.9** Recognises and manages the septic patient
- **11.6** Critically appraises and applies guidelines, protocols and care bundles

1. Resuscitation and Haemodynamic Support of the Septic Patient

Sepsis is a life-threatening condition caused by a dysregulated host response to infection that results in organ dysfunction. Septic shock refers to a subset of sepsis characterized by profound circulatory and cellular metabolism abnormalities and is associated with higher mortality rates than sepsis alone. In high-income countries, contemporary large cohort data show decreasing mortality in high-income countries, with septic shock mortality more commonly reported between 30 and 40 percent. The septic shock definition has evolved over time, and although septic shock characterization was initially coupled to the need for vasopressor support, more recent definitions have highlighted the importance of metabolic abnormalities. To date, circulatory failure is defined as the evidence of inadequate tissue perfusion with impaired oxygen utilization by the cells, independently of the presence of arterial hypotension.

Recent epidemiological data from high income countries indicate a gradual reduction in overall sepsis related mortality over the past decade, likely reflecting improvements in early recognition, antimicrobial therapy, and organ support. However, septic shock remains associated with substantial mortality, commonly reported between 30 and 40 percent, with marked variability according to age, comorbidities, infection source, and organ dysfunction burden. Importantly, despite improved survival, septic shock continues to represent a major cause of long term morbidity and resource utilization, emphasizing the need for optimized and physiology driven resuscitation strategies.

The purpose of hemodynamic support is to detect, monitor and guide the resuscitation process of the failing circulation.

1. 1. Detection of septic shock

The initial approach to evaluating the adequacy of tissue perfusion comprises the assessment of clinical signs, hemodynamic alterations and laboratory blood tests. Clinical signs include the assessment of what has been called the three "physical windows" to hypoperfusion: the skin (mottling/prolonged capillary refill time), the kidneys (low urinary output), and the brain (altered mentation). However, clinical signs alone are insufficient for detecting circulatory shock due to their lack of sensitivity and specificity.

The main hemodynamic alteration observed in shock states is hypotension, defined as: (1) Mean arterial pressure (MAP) < 65 mmHg; (2) systolic arterial pressure (SAP) < 90 mmHg; or (3) a decrease from baseline blood pressure > 40 mmHg. Hypotension will be considered pathological, since the inadequacy of perfusion pressure will surely cause tissue hypoperfusion, but tissue hypoperfusion might be present also in

situations with preserved, or even elevated, blood pressure. Therefore, blood pressure also lacks sensitivity, and we should not rely only on blood pressure for detecting shock states.

While arterial hypotension is a common manifestation of circulatory shock, it should be emphasized that normal or even elevated blood pressure values do not exclude the presence of severe tissue hypoperfusion. Septic patients may exhibit preserved arterial pressure as a result of compensatory vasoconstriction or early vasopressor use, despite ongoing impairment in oxygen delivery or utilization at the cellular level. This so-called occult or cryptic shock is associated with delayed recognition and worse outcomes, reinforcing the need for systematic assessment of tissue perfusion beyond blood pressure alone.

Since what truly defines shock is the inadequate oxygen utilization by the cells, the detection of shock will rely on the utilization of metabolic markers of tissue dysoxia. The most commonly used marker is lactate. Lactate kinetics can provide insights on potentially ongoing anaerobic metabolism in the setting of acute circulatory failure. In septic patients, elevated or rising levels of serum lactate should be interpreted as an early marker of imbalance between oxygen consumption (VO_2) and delivery (DO_2) to the tissues. Although some other metabolic markers will be discussed later on, blood lactate is the widely used screening test for detecting shock in septic patients.

Given the limited sensitivity and specificity of individual clinical or laboratory markers, early detection of septic shock should rely on a multimodal assessment integrating bedside clinical examination, metabolic markers such as lactate, peripheral perfusion indicators including capillary refill time, and dynamic hemodynamic evaluation when available. This integrated approach allows earlier identification of circulatory failure, facilitates timely escalation of therapy, and reduces the risk of both under resuscitation and unnecessary interventions.

1. 2. Mechanisms of septic shock

Septic shock can be the result of a complex interaction between several hemodynamic and/or cellular abnormalities, such as:

Septic shock can be the result of a complex interaction between several hemodynamic and/or cellular abnormalities, such as:

- Diminished venous return, either as results of absolute or relative hypovolemia.
    - Absolute hypovolemia, due to water losses from fever, fasting, vomiting, diarrhea and/or capillary leak causing extravasation of fluid into the interstitial space.
    - Relative hypovolemia due to vasoplegia. Vasoplegia may be present at the time of initial presentation or develop later in the course of hemodynamic decline.

- Diminished cardiac contractility. Myocardial dysfunction is often present in sepsis, even at earlier stages. In addition, many patients suffering from sepsis might have baseline impaired cardiac function, worsening the hemodynamic performance in the septic episode.
- Altered vasomotor tone. In addition to the relative hypovolemia resulting from the converting from stressed to unstressed blood volume, vasoplegia causes a drop in perfusion pressure and blood flow maldistribution as results of impaired vascular autoregulation.
- Alterations in oxygen utilization in the tissues. Oxygen extraction might be impaired due to diffusion alterations (capillary leak), capillary shunting (heterogeneous microcirculation), and mitochondrial dysfunction.

It is important to recognize that correction of macrocirculatory variables such as mean arterial pressure and cardiac output does not necessarily translate into restoration of effective microcirculatory flow or cellular oxygen utilization. Persistent microcirculatory dysfunction and mitochondrial impairment may coexist despite normalization of conventional hemodynamic targets, contributing to ongoing organ dysfunction. This dissociation underscores the limitations of relying solely on global hemodynamic parameters and supports the use of complementary perfusion and metabolic endpoints during resuscitation.

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1. 3. Endpoints of resuscitation

The purpose of the hemodynamic resuscitation process is to correct the imbalance of oxygen at the cellular level in order to meet the metabolic demands and doing so, avoiding cellular dysfunction and progression to organ failure and death. The hemodynamic resuscitation process will pivot on two sequential (but overlapping) steps: (1) restoring sufficient tissue perfusion pressure; and (2) normalizing markers of tissue metabolism.

While the conceptual framework of restoring perfusion pressure followed by normalization of tissue metabolism remains valid, recent evidence emphasizes that these processes frequently overlap and must be continuously reassessed rather than addressed sequentially. Early correction of hypotension may improve macrocirculatory flow, yet persistent abnormalities in tissue perfusion and cellular metabolism may remain despite apparently adequate global hemodynamic variables. Therefore, resuscitation should be viewed as a dynamic and iterative process guided by both pressure based and perfusion based endpoints.

1. 3. 1. Mean arterial pressure

As already mentioned, mean arterial pressure (MAP) is a key component of the driving pressure for tissue perfusion. Blood flow to the tissues depends not only on cardiac output, but also on the adequacy of a pressure gradient between upstream and downstream pressure. This latter issue is highly significant in septic shock, where vascular tone is impaired. In clinical practice, initial resuscitation usually consists of administering fluids, which can produce both an increase in perfusion pressure and in cardiac output. However, when vascular tone is impaired, despite increases in cardiac output as a result of fluid expansion, intravascular volume might remain unstressed (unable to generate increases in the mean filling pressure of the vascular system due to its high compliance) leading to a lack of response in arterial pressure. Accordingly, early vasopressor use may be necessary when blood pressure does not improve after initial fluid administration.

Current international guidelines recommend an initial mean arterial pressure target of 65 mmHg during septic shock resuscitation. This recommendation is supported by randomized trials demonstrating no survival benefit from routinely targeting higher arterial pressures in unselected populations. However, emerging evidence supports an individualized approach, particularly in patients with chronic hypertension, where higher perfusion pressures may be required to ensure adequate organ blood flow. Importantly, increasing arterial pressure through escalating vasopressor doses may carry deleterious effects related to excessive catecholamine exposure, reinforcing the need to balance perfusion targets against potential harm. Some studies have tested the use of higher targets of MAP, but no benefits have been detected in terms of survival. On the other hand, the burden of catecholamines has also been independently associated with negative outcomes, and therefore increasing MAP values might not be free of consequences. To date, no strong recommendation can be specified, and further research to better define an optimal or even individualized blood pressure target is still required.

In addition to absolute mean arterial pressure values, diastolic arterial pressure provides relevant physiological information regarding vascular tone. A markedly reduced diastolic pressure may indicate profound vasoplegia and has been associated with worse outcomes. In such cases, earlier initiation of vasopressor therapy may be

justified even before completion of fluid resuscitation, particularly when signs of ongoing hypoperfusion are present. This approach reflects a shift toward earlier restoration of vascular tone to prevent prolonged exposure to hypotension.

1. 3. 2. Tissue hypoxia markers

Markers of tissue hypoxia and perfusion are central to guiding resuscitation once minimal perfusion pressure has been achieved. No single variable adequately reflects the complexity of tissue oxygen delivery and utilization in sepsis. Consequently, reliance on a single endpoint may lead to inappropriate escalation or premature cessation of resuscitative interventions. A multimodal strategy integrating metabolic, oxygenation, and perfusion parameters is therefore recommended.

We have three main physiological parameters informing about global tissue perfusion at the bedside: lactate, venous oxygen saturations (either central or mixed), and carbon dioxide-derived variables (Figure 1). The utilization of physiological hemodynamic and/or metabolic endpoints in the resuscitation process is known as quantitative, or Goal-Directed, resuscitation. Although quantitative resuscitation strategies have proven superior to qualitative strategies, choosing the adequate endpoint/s that drive the whole process is still a matter of debate. Since the publication in 2001 of Rivers' Early Goal-Directed Therapy (EGDT) study, where the use of central venous oxygen saturation ($ScvO_2$) as the ultimate goal was associated with dramatic mortality reductions, $ScvO_2$ has been one of the most widely advocated resuscitation endpoints. However, subsequent studies trying to replicate the EGDT study have failed to demonstrate such an impact on clinical outcomes. More recent data from three large international multicenter RCTs comparing $ScvO_2$-driven protocols versus usual care did not show any survival benefits, thus challenging the recommendation of guiding the resuscitation process by $ScvO_2$. Some criticisms to the RCTs were that only 20-30% of the studied patients had values of $ScvO_2$ below the normal range at inclusion, and that mortality was significantly lower in the control group as compared to Rivers' EGDT study. Independently of the debate on the limitations of the trials, $ScvO_2$ is still a physiological parameter that provides information on the global status of tissue oxygenation of the patient.

Although central venous oxygen saturation provides insight into the balance between oxygen delivery and consumption, normal or elevated values do not exclude persistent tissue hypoperfusion. In septic shock, impaired oxygen extraction and microcirculatory shunting may result in misleadingly high $ScvO_2$ values despite ongoing cellular dysoxia. In such situations, complementary parameters such as lactate kinetics and venous to arterial carbon dioxide gradients may help identify inadequate blood flow states and guide further resuscitative efforts.

Lactate has repeatedly demonstrated its prognostic value in septic shock patients. Although hyperlactatemia interpretation might be complex, and it does not directly preclude tissue hypoxia, guiding the resuscitation process according to lactate kinetics

has also demonstrated its favorable impact on survival. In a non-inferiority study including 300 septic shock patients, a resuscitation strategy driven by lactate clearance showed comparable mortality rates than the usual strategy driven by $ScvO_2$.

Although elevated lactate levels have traditionally been interpreted as a marker of anaerobic metabolism secondary to tissue hypoxia, contemporary evidence indicates that hyperlactatemia in sepsis reflects a complex interplay of mechanisms. These include adrenergic driven aerobic glycolysis, impaired hepatic and renal lactate clearance, microcirculatory shunting, and mitochondrial dysfunction. Consequently, lactate should be regarded as a global marker of illness severity and metabolic stress rather than a direct or isolated indicator of tissue hypoxia. Serial lactate measurements and lactate kinetics provide more clinically meaningful information than isolated values.

The combination of lactate kinetics and $ScvO_2$ provides a wider clinical picture of global metabolic status (Figure 1). In acute illness, the presence of elevated lactate and low $ScvO_2$, tissue hypoperfusion must be suspected. However, the interpretation of hyperlactatemia combined with high $ScvO_2$ values is much more complex. Such situations might correspond to alterations in the utilization of oxygen as results of mitochondrial dysfunction, for instance, but it is also difficult to rule out the persistence of local tissue hypoperfusion, with abnormally elevated $ScvO_2$ as results of microcirculatory shunting phenomena. In these latter situations, carbon dioxide parameters might provide additional information. Central venous-to-arterial carbon dioxide difference (Pcv-aCO_2 gap) is highly linked to tissue perfusion, and its elevations reflect low blood flow situations. In septic patients with apparently normalized $ScvO_2$ and persistent hyperlactatemia, Pcv-aCO_2 gap > 6 mmHg discriminates those patients with worse outcomes. These observations have resulted in the recommendation of further increasing cardiac output when high lactate and Pcv-aCO_2 gap values coexist, despite normal or elevated $ScvO_2$ values. However, no prospective data on the impact of including the Pcv-aCO_2 gap in a resuscitation protocol is currently available

In addition to these metabolic markers, some authors have advocated for the utilization of parameters informing specifically of peripheral perfusion, such as the capillary refill time (CRT). Recently, in a large multicenter trial, CRT-guided resuscitation proved to be non-inferior to lactate-guided resuscitation in terms of mortality, while less amounts of fluids were administered in the CRT group. Such findings may be partially explained by a relevant limitation of lactate, such as its inability to differentiate between low perfusion states and impaired oxygen utilization in high flow states, where perfusion is not the key problem anymore.

To date, there is an ongoing debate on whether a multimodal approach combining perfusion variables and metabolic parameters will result in improved outcomes. In fact, using a single parameter-based approach might be very limited in the framework of current knowledge. An adequate physiological reasoning is mandatory not only in order

to further increase oxygen delivery to the tissues when tissue hypoperfusion is presumed, but also to avoid unnecessary and potentially deleterious interventions when tissue dysoxia does not depend on oxygen availability.

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1. 4. Haemodynamic monitoring

Hemodynamic monitoring in septic shock aims to guide interventions that improve oxygen delivery while avoiding harm from unnecessary fluids, excessive vasopressors, or inappropriate inotropes. Contemporary guidance emphasizes integrating clinical examination, perfusion markers, echocardiography, and dynamic tests of preload responsiveness rather than relying on static pressure based surrogates. Hemodynamic assessment should be repeated frequently because the circulatory phenotype in sepsis is dynamic and can shift rapidly during the first hours and days of critical illness.

The resuscitation process is based upon the optimization of oxygen delivery (DO_2) to the tissues to match the metabolic demands. Since DO_2 depends on arterial oxygenation, hemoglobin concentration and cardiac output (CO), in most of the cases of septic shock the key to the whole process is the manipulation of stroke volume (SV). Accordingly, hemodynamic monitoring tools can either be used to estimate cardiac output and its changes in response to a given intervention, or to predict whether SV will increase as results of fluid administration ("fluid responsiveness").

1. 4. 0. 1. Fluid-responsiveness

Fluid administration is considered the first step in the resuscitation process of septic shock patients. Fluid expansion aims at increasing venous return, cardiac preload and, if the patient is in the preload-responsive area of the Frank-Starling curve of cardiac performance, ultimately CO and DO_2. This is of utmost importance, since hemodynamic benefits would only be expected when the patient is situated in the fluid-responsive area; otherwise fluid will only be detrimental. A robust body of evidence shows that fluid overload is associated with increased morbidity and mortality, particularly in septic patients. Therefore, the current approach to fluid administration relies fundamentally on the conceptual framework of the Frank-Starling curve of cardiac performance.
Accordingly, for a given contractility, one should define two separated zones:

1. A preload-dependence zone, where increases in preload will cause increases in stroke volume (SV); and
2. a preload-independence zone, where SV will not increase as results of volume expansion.

In the assessment of preload-dependence, the so-called fluid challenge is a simple method based on infusing a fluid bolus and evaluating its effect on SV. This approach is still considered the gold standard for evaluating fluid responsiveness at the bedside. However, this approach implies that the effect of volume expansion will be only evaluated once the volume has been administered. Unfortunately, since in shock states fluid-responsiveness might account for approximately 50% of the cases, no positive benefits are expected in half of the fluid challenges. Of note, fluid-responsiveness will vary in the time course of septic shock, and fluid-responsive patients might rapidly become non-responders, and in aggressive fluid loading scenarios, downstream harmful effects will largely overcome the minimal impact on stroke volume. Therefore, it seems reasonable to use bedside tools to predict the hemodynamic effect of a fluid bolus prior to its administration.

1. 4. 0. 2. Fluid-responsiveness predictors

Several hemodynamic parameters have been evaluated in order to predict the response to a fluid challenge. We can divide these tools into two main groups:

1. Static parameters; and
2. Dynamic parameters.

Static parameters of fluid-responsiveness prediction consist in steady-state measurements of cardiovascular pressures, volumes, or areas in an attempt to estimate the absolute value of ventricular preload. In this group we have left ventricular end-diastolic area (LVEDA) and inferior vena cava diameter (IVCd), obtained by echocardiography, global end diastolic volume (GEDV) by transpulmonary thermodilution (TTD), or central venous pressure (CVP) measured with a central venous line. While such static parameters were previously widely used, evidence has repeatedly shown that CVP and other static parameters fail to predict fluid responsiveness, even in its extreme values. Therefore, fluid administration guided by static parameters is strongly discouraged.

Dynamic parameters are based on the evaluation of the cardiovascular response to a temporary and reversible change in preload (Table 1; Figure 1). In that regard, pulse pressure variation (PPV) and stroke volume variation (SVV) have been shown to be excellent fluid-responsiveness predictors in mechanically ventilated patients. Unfortunately, these parameters have certain limitations that have restricted its widespread use: namely, the patient has to be in regular cardiac rhythm, fully adapted to mechanical ventilation (MV), with no spontaneous efforts, and receiving tidal volumes > 8ml/kg of ideal body weight. This last limitation is particularly relevant in the era of protective MV, with the widespread use of low tidal volumes, but it also might be overcome by the incorporation of a tidal volume challenge maneuver. Furthermore, the End-Expiratory Occlusion Test (EEOT) has also been proposed as a reliable fluid responsiveness predictor in critically ill patients, and interestingly it is also useful in patients with cardiac arrhythmias, spontaneously breathing, and low pulmonary compliance. Finally, the passive leg raising (PLR) maneuver is a standardized test that, if induces an increase of CO >10%, predicts fluid responsiveness. Such test requires continuous CO monitoring. Interestingly, PLR may be used in patients with cardiac arrhythmias, spontaneous breathing efforts, or low pulmonary compliance. Its main limitation is that some specific populations of critically ill patients may not tolerate the maneuver. Of note, except for PPV, all dynamic parameters need a continuous CO monitoring technology in place for its calculation.

Table 1: Methods for predicting the CO response to fluid administration.

Method	Variable	Threshold	Considerations

• Pulse pressure variation (PPV) or • Stroke volume variation (SVV)	• Pulse pressure or Stroke volume	12%	Patients must be deeply sedated and require paralysis. Not interpretable in the setting of: • Cardiac arrhythmia • Poor lung or thoracic wall compliance • Spontaneous respiratory activity Potential false negatives: • Low tidal volumes (≤ 6 mL/kg) Potential false positives: • Right ventricular failure
Inferior vena cava (IVC) variation	Diameter	12%	Respiratory induced variations in vena cava assessed by ultrasonography Skill and experience are needed Not interpretable in the setting of: • Poor lung or thoracic wall compliance • Spontaneous respiratory activity • Right ventricular failure
Superior vena cava (SVC) variation	Diameter	36%	Respiratory induced variations in vena cava assessed by ultrasonography Skill and experience are needed Not interpretable in the setting of: • Poor lung or thoracic wall compliance • Spontaneous respiratory activity • Right ventricular failure
Passive leg raising test (PLR)	Cardiac output	10%	Assessed by changes in cardiac output/index (CO/CI) Patients might not tolerate the maneuver, or it might not be indicated (increased intracranial pressure, i.e.)

End-expiratory occlusion test (EEOT)	Cardiac output	5%	Only in intubated patients and must tolerate a 15 second pause in ventilation. May be invalid at a tidal volume of 6 mL/kg.
“Mini” fluid challenge: infusion of 50-100 ml of fluid.	Cardiac output	6%	Not robustly validated Requires a very precise technique for evaluating CO
Tidal volume challenge	Pulse pressure or stroke volume variation	3.5%	Useful to overcome tidal volume or grey zone limitations in PPV/SVV
Pleth variability index (PVI)	Pleth index	20%	Weak predictor of fluid responsiveness in patients receiving norepinephrine

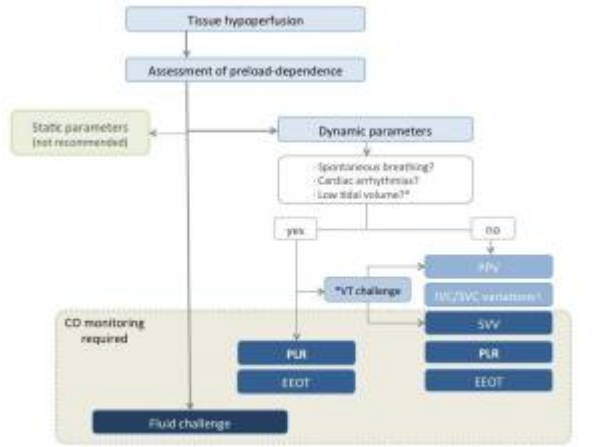

Figure 1: Preload-responsiveness assessment. Adapted from Mesquida et al, 2017.

It is very important to bear in mind that monitoring of CO may be necessary in many circumstances where the response to volume expansion cannot be predicted. This may be especially relevant in those situations where fluid overload is associated with potential deleterious effects, such as pulmonary edema. In addition, in many circumstances, and especially in septic patients, the response to fluids cannot be inferred from the response in blood pressure. As previously mentioned, alterations in vascular tone might limit the impact on blood pressure of significant increases in stroke volume after a fluid challenge (Figure 2). Therefore, when PPV is not reliable, monitoring CO would be desirable in order to properly assess fluid-responsiveness.

Peripheral perfusion monitoring should be incorporated into bedside hemodynamic assessment because it provides information that may not be captured by global macrocirculatory variables. Capillary refill time is a rapid and reproducible measure that can be used repeatedly during early septic shock resuscitation and integrated with

dynamic preload tests to guide fluid and vasopressor decisions. Recent randomized evidence has evaluated personalized hemodynamic resuscitation protocols targeting capillary refill time, supporting its inclusion as part of a multimodal monitoring strategy in early shock.

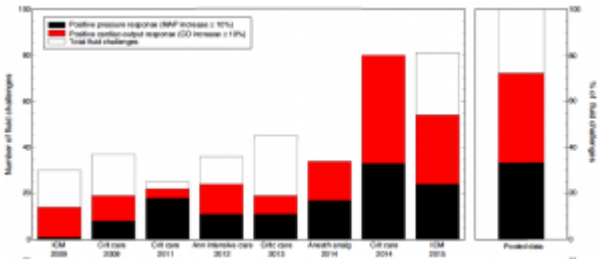

Figure 2: Response in MAP and CO after a fluid challenge. Positive responses in CO might not be accompanied by positive responses in MAP in almost half the cases.

In text References

(Marik and Cavallazzi. 2013; Monnet and Teboul. 2018; Angus et al. 2015; Hjortrup et al. 2016; Mesquida, Gruartmoner and Ferrer. 2017; Monge García and Barrasa González. 2017; Liu et al. 2019; Monnet et al. 2013; Alvarado Sánchez et al. 2023; Monnet et al. 2025; Chaves et al. 2024; Mulder et al. 2025; Hernandez et al. 2025)

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1. 5. Treatments

1. 5. 1. Fluids

When giving fluid therapy, four questions must be addressed: 1) When to start? 2) When to stop? 3) When to start the de-resuscitation? and, 4) When to stop the de-resuscitation? Recently the four-hit model of septic shock has tried to answer these questions by separating the fluid administration into four phases, these phases are Resuscitation, Optimization, Stabilization and Evacuation, most known by the acronym ROSE.

The ROSE framework should be interpreted as a conceptual guide rather than a strictly sequential algorithm. In clinical practice, patients may transition back and forth between phases depending on evolving hemodynamics, organ perfusion, and response to therapy. Recent evidence emphasizes the importance of early reassessment and timely limitation of fluid administration once signs of adequate perfusion are achieved, in order to reduce the risk of fluid accumulation and associated organ dysfunction.

The first phase (Resuscitation) occurs during the “ebb” phase of sepsis during the first 4-6 hours, after the first hit. This phase is characterized by strong vasodilation leading to microcirculatory impairment. In this phase, fluid resuscitation is commonly administered according to an early, adequate, goal-directed, fluid management strategy; however, the modalities of fluid administration at this early phase have been a matter of great debate.

Fluid bolus should be differentiated from fluid challenge, fluid challenge is a dynamic test to assess fluid responsiveness by giving a fluid bolus and simultaneously monitoring the hemodynamic effect and fluid bolus is given to correct hypovolemia, hypotension, inadequate blood flow or impaired microcirculatory perfusion. The volume of fluid bolus given in this phase is heterogeneous among publications, varying from 500 to 2000mL.

A fluid challenge should be regarded as a diagnostic intervention rather than a therapeutic goal. Its purpose is to assess whether an increase in preload results in a meaningful improvement in stroke volume and tissue perfusion. Importantly, a positive hemodynamic response does not mandate further fluid administration unless accompanied by evidence of ongoing hypoperfusion. This distinction is critical to avoid unnecessary fluid loading once perfusion goals have been achieved.

However, excessive amounts of fluid may be harmful and increase mortality. The RIFTS trial demonstrated that a restrictive resuscitation strategy can successfully reduce the amount of IV fluid administered to patients with severe sepsis and septic shock compared to usual care.

More recent large, randomized trials have evaluated restrictive versus liberal fluid strategies in sepsis and septic shock. In the CLASSIC trial, a restrictive intravenous fluid strategy after initial resuscitation did not reduce ninety-day mortality compared with standard care in ICU patients with septic shock, but resulted in lower cumulative fluid volumes. Similarly, the CLOVERS trial demonstrated no mortality difference between a restrictive strategy with earlier vasopressor use and a liberal fluid strategy in patients with sepsis induced hypotension treated in the emergency department. These findings indicate that restrictive approaches are feasible and safe, but do not support a universal restrictive or liberal strategy, reinforcing the need for individualized, physiology guided fluid management.

All of the following points should be considered:

- No predictor of fluid responsiveness has perfect sensitivity or specificity.
- Ancillary data points such as heart rate, urine output, improvement in tissue pallor, and lactate levels may also be useful in assessing the response to resuscitation.
- Fluid overload can be associated with a rise in mortality. Careful fluid management and “de-resuscitation” of septic patients (potentially as early as 24-48 hours following the success of early resuscitation efforts) can save lives and at a minimum, decrease the incidence of acute kidney failure and number of days in the ICU.

How should fluids be administered?

- Fluid administration should be individualized.
- The SSC guidelines recommend the administration of an initial fixed bolus of at least 30 mL/kg of fluid within the first 3 hours with frequent reassessments of hemodynamic status
- Fluid overload is strongly associated with an increase in mortality.
- After initial resuscitation additional fluid administration should be carefully weighed against detrimental effects, and guided by frequent reassessments of hemodynamic status.

Although international guidelines suggest an initial fluid bolus of approximately 30 mL per kilogram, this recommendation is based on low quality evidence and should not be interpreted as a mandatory or universal target. Current guidance emphasizes early initiation of fluid resuscitation accompanied by frequent reassessment of perfusion, hemodynamics, and fluid responsiveness. In patients with conditions predisposing to fluid intolerance, such as cardiac dysfunction or chronic kidney disease, smaller initial volumes with earlier reassessment may be appropriate.

The ideal fluid for septic patients is one that can expand the intravascular volume increasing cardiac output and tissue perfusion without leading to tissue edema and that contains the most similar chemical composition of plasma. However, this fluid is not currently available for our daily practice which makes the choice of the most appropriate fluid more challenging.

Table 2 summarizes the current available fluids in our daily practice and their composition. **Crystalloids** are solutions of ions that can pass through semipermeable membranes such as capillaries. Isotonic crystalloids may be categorized as “balanced” or “unbalanced.” Saline (NaCl 0.9%) is the prototypical “unbalanced” crystalloid, with a chloride concentration around 50% greater than the chloride content of extracellular fluid. In contrast, balanced crystalloids such as lactated Ringer’s, Hartmann’s solution, Plasmalyte, or Normosol contain a chloride concentration more like that of plasma. To achieve this, most balanced crystalloids substitute an organic anion such as bicarbonate, lactate, acetate, or gluconate in place of chloride resulting in a more neutral pH and a greater strong ion difference. Large data provided from recent randomized controlled trials, such as SPLIT, SALT, SMART and SALT-ED compared

the use of balanced crystalloids versus saline among critical ill patients and these trials demonstrated a reduction in the outcome of death, new renal replacement therapy or persistent renal dysfunction with the use of balanced crystalloids compared to saline. Given the widespread use of isotonic crystalloids for patients with sepsis, and the similar costs of saline and balanced crystalloids, these new data suggest balanced crystalloids may represent the first-line fluid therapy for adults with sepsis or septic shock.

Colloid solutions contain large molecules such as starches and proteins that cannot permeate healthy capillary membranes and may have a theoretical benefit of such colloid solutions is improved volume expansion due to retention in the intravascular space. Colloids can be classified as human or semisynthetic colloids. Albumin is a human plasma derivate colloid, recent data from the ALBIOS or the SAFE randomized trials suggest that the use of human albumin may reduce the total volume of fluid administration, shorter time on vasopressors and might decrease mortality.

Semisynthetic colloids or Gelatins are prepared by hydrolysis of bovine collagen, dextrans are biosynthesized from sucrose by bacteria, and hydroxyethyl starch (HES) is synthesized from the maize-derived d-glucose polymer amylopectin. Each individual colloid has different rates of loss from the circulation determined by its molecular weight, and different metabolism determined by individual chemical properties which influence the duration of volume expansion.

These individual properties also result in unique adverse event profiles: increased risk of acute kidney injury (HES, gelatin), allergic reactions (gelatins, dextrans), and bleeding (dextrans, HES). Recent guidelines recommend against the use of starches and suggest avoiding gelatins and dextrans due to an increase in the risk of anaphylaxis, mortality, renal failure, and bleeding. Unless future research demonstrates a conclusive outcome benefit to a specific semisynthetic colloid among patients with sepsis, the use of all semisynthetic colloids should be avoided in sepsis management due to their risks.

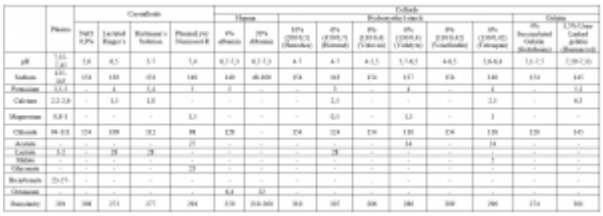

Table 2: Composition of common sepsis resuscitation fluids. Modified from Brown and Semler, 2019

Principles behind fluid selection are presented in Table 3. The superiority of colloids over crystalloids in terms of effectiveness is no longer accepted, and initial resuscitation is now based on the use of crystalloids. The optimal crystalloid is not presently clear however. Concerns have been raised from observational studies and a

meta-analysis over the association between the use of normal (0.9%) saline and hyperchloremic renal injury (and potentially a rise in mortality). However, such concerns have yet to be borne out in a randomized trial.

Although the SSC guidelines presently do not recommend the use of balanced salt solutions (e.g. Ringer's lactate or Plasmalyte®) over normal saline, hyperchloremia should be avoided and appropriate attention paid to serum chloride levels irrespective of the fluid solution selected.

Table 3: The Optimal Fluid in Sepsis

The Optimal Fluid in Sepsis
Crystalloids are preferred over colloids. The ratio of effectiveness is not 1:6 as previously thought, but 1:1 to 1:1.8.
Irrespective of crystalloid solution selected, hyperchloremia should be avoided.
Human albumin can be considered for patients requiring substantial amounts of crystalloids.
The place of gelatin solutions is presently unknown (quality studies on use in sepsis are lacking).
Hydroxyethyl starch (HES) should not be used due to higher rates of mortality and RRT as compared to crystalloid.
If anemia warrants correction, post-transfusion hemoglobin concentrations should be kept between 7-9 g/dL (i.e. there is no demonstrated benefit of transfusing to hemoglobin levels >9 g/dL) **unless active bleeding is present**.

The place of human albumin is still a matter of debate. However, when a colloid is considered in septic shock patients, albumin is the preferred choice and serum albumin concentration target of 3 g/dL is usually used. The SSC guidelines suggest the addition of albumin to crystalloids for intravascular volume replacement when patients are requiring substantial volumes of crystalloids for resuscitation, though this is a recommendation with low quality of supporting evidence (Table 4).

Table 4: Summary of the SSC recommendations regarding fluid therapy (SSC 2016)

Summary of the SSC recommendations regarding fluid therapy (SSC 2016)
We recommend that a fluid challenge technique be applied where fluid administration is continued as long as hemodynamic factors continue to improve.
We recommend crystalloids as the fluid of choice for initial resuscitation and subsequent intravascular volume replacement in patients with sepsis and septic shock (strong recommendation, moderate quality of evidence).

We suggest using either balanced crystalloids or saline for fluid resuscitation of patients with sepsis or septic shock (weak recommendation, low quality of evidence).
We suggest using albumin in addition to crystalloids for initial resuscitation and subsequent intravascular volume replacement in patients with sepsis and septic shock when patients require substantial amounts of crystalloids (weak recommendation, low quality of evidence).
We recommend against using hydroxyethyl starches (HESs) for intravascular volume replacement in patients with sepsis or septic shock (strong recommendation, high quality of evidence).
We suggest using crystalloids over gelatins when resuscitating patients with sepsis or septic shock (weak recommendation, low quality of evidence).

In text References

(Rhodes et al. 2017; Hjortrup et al. 2016; Brown and Semler 2019; Finfer et al. 2004; Serpa Neto et al. 2017; Caironi et al. 2014; Holst et al. 2014; Martin 2019; Malbrain et al. 2018; Monnet et al. 2025; Meyhoff et al. 2022; Self et al. 2018)

1. 5. 2. Vasopressors

Presently, the SSC guidelines recommend the initiation of vasopressor therapy when fluid resuscitation has proven unsuccessful and there are some data to support norepinephrine initiation within 60 minutes of fluid resuscitation failure. An additional consideration for the early initiation of vasopressor therapy is a diastolic arterial pressure (DAP) <40 mmHg. A diastolic pressure this low suggests a markedly decreased arterial tone, and these patients may benefit from the earlier initiation of vasopressor therapy, potentially as fluid resuscitation is ongoing. Studies to address the optimal timing of vasopressor initiation in relationship to fluid resuscitation are anticipated in the near future.

There is a large variety of vasopressor options with different mechanisms of actions that are actually available for the clinician in Table 5 and recommended doses in Table 6. Recent systematic reviews and meta-analyses have established norepinephrine as the vasopressor of first choice. Dopamine is now recommended as an alternative to norepinephrine only in a highly selected patient population (e.g. those with absolute or relative bradycardia and a low risk of tachyarrhythmia). Vasopressin and epinephrine are adjunctive agents to norepinephrine; either to decrease high norepinephrine dosages or to raise MAP to the targeted goal should norepinephrine alone prove insufficient. Terlipressin remains, where available, as an alternative to vasopressin.

Table 5: Vasopressors and major effects

Agent	Receptor	Major effects	Major side-effects

Norepinephrine	a1,B1	↑Venous and arterial tone ↑preload and contractility	Cardiac arrhythmia, peripheral ischemia, inadvertent immunomodulation
Epinephrine	a1,B1,B2	↑ contractility and preload ↑ venous and arterial tone ↑ heart rate	Tachycardia, tachyarrhythmia, splanchnic ischemia, increased myocardial oxygen consumption, lactic acidosis, hyperglycemia
Dopamine	a1,B1,D1,D2	↑ contractility and heart rate ↑Venous and arterial tone ↑Renal and mesenteric vasodilation	Tachycardia, tachyarrhythmia
Angiotensin II	ATR1,ATR2	↑venous and arterial tone ↑ACTH, ADH, aldosterone reabsorption	Tachycardia, peripheral ischemia, thrombotic events
Vasopressin	V1,V2,V1b	↑venous and arterial tone, platelet aggregation ↑water retention, release of coagulation factors ↑corticotropic axis stimulation, insulin secretion	Peripheral ischemia, mesenteric ischemia, cardiac arrhythmia
Terlipressin	V1ab>V2	↑ venous and arterial tone, platelet aggregation. ↑ water retention, release of coagulation factors	Peripheral ischemia, mesenteric ischemia, cardiac arrhythmia
Selepressin	V1a	↑venous and arterial tone, platelet aggregation ↓vascular leakage	Peripheral ischemia, cardiac arrhythmia

Methylene Blue	Inhibitor NO–cGMP	↑venous and arterial tone	Paradoxical induction of methemoglobinemia, acute hemolytic anemia, and detrimental effects on pulmonary function

The SSC guideline recommends the start of vasopressors within the first hour when fluid resuscitation is not enough to achieve the target MAP. However, this statement may contradict the previous pathophysiological statements discussed about the hemodynamic changes and dynamics in sepsis and septic shock; because of these, a group of 35 experts from the European Society of Intensive Care Medicine (ESICM) recently published a recommendation statement for the early initiation of vasopressors, even before the completion of fluid resuscitation.

Several RCTs suggest that the early initiation of vasopressors may help to achieve perfusion goals in less time and reduce the amount of fluid administered. Another argument presented to support the early use of vasopressors suggests that Norepinephrine (NE) may increase cardiac preload and reduce preload dependency in the early phase of shock by increasing the mean systemic filling pressure and redistributing the blood from a state of abnormally increased unstressed volume to a state of stressed volume by reduction of venous capacitance mediated by a-adrenergic receptors.
Another benefit of early administration of NE is related to recruitment of microvessels that may improve microcirculation and mean organ perfusion.

Table 6: Vasopressor doses.

Agent	Initial dose	Maximum dose
Norepinephrine	0.1 mcg/kg/min	3 mcg/kg/min
Epinephrine	0.05 mcg/kg/min	1 mcg/kg/min
Phenylephrine	0.1 mcg/kg/min	1 mcg/kg/min
Dopamine alpha dose	10 mcg/kg/min	20 mcg/kg/min
Angiotensin II	20 ng/kg/min	80 ng/kg/min
Vasopressin	0,1 mU/kg/min	2 mU/kg/min
Terlipressin	1.3 mcg/kg/h	20 mcg/kg/h
Selepressin	1.25 ng/kg/min	3.75 ng/kg/min

Numerous retrospective and prospective single-center RCT have been studied the effect of early initiation of vasopressors observing a reduction in mortality, volume of fluid administered and consequently lowered the risk of fluid overload compared with the SSG suggested initiation. However, no definitive recommendation re: the timing of vasopressor initiation in sepsis can presently be given.

In text References

(Rhodes et al. 2017; De Backer et al. 2010; Russell et al. 2008; Asfar et al. 2014; Khanna et al. 2017; Shi et al. 2020; Ospina-Tascón et al. 2020; Ramirez. et al. 2020; Ospina-Tascón et al. 2020; Guarracino, Bertini and Pinsky. 2019; Jang, Nelson and Hoffman. 2013)

1. 5. 3. Inotropes

Sepsis induced myocardial dysfunction is a frequent and often early manifestation of septic shock, characterized by reversible impairment of systolic and diastolic function. This phenomenon is dynamic and may evolve rapidly during the course of illness, with ventricular dilation and reduced ejection fraction representing adaptive mechanisms that help maintain stroke volume rather than irreversible myocardial injury. Recognition of this reversible nature is essential, as aggressive attempts to normalize ejection fraction may be unnecessary or harmful if tissue perfusion is preserved.

A major mechanism of direct cardiac depression in sepsis is the attenuation of the adrenergic response at the cardiomyocyte level due to down-regulation of B-adrenergic receptors and depression of post-receptor signaling pathways. Another mechanism of direct cardiac depression in sepsis is cardiomyocyte injury or death, which can be induced by toxins, complements, Damage-Associated Molecular Patterns (DAMPs), and as-yet unidentified myocardial depressants. Hemodynamically, at the very early phase of sepsis, left ventricular ejection fraction (LVEF) is not impaired, usually higher that 55%, but stroke volume (SV) is low because of insufficient cardiac preload due to a high vascular permeability and vasodilation.

The compensatory increase in HR is often insufficient to maintain adequate CO. After fluid resuscitation, SV can be recovered in preload-responders while LVEF is temporarily decreased in part due to high left ventricular end diastolic volume (LVEDV). This indicates that low LVEF may represent preload adaptation to increased LVEDV (Figure 3).

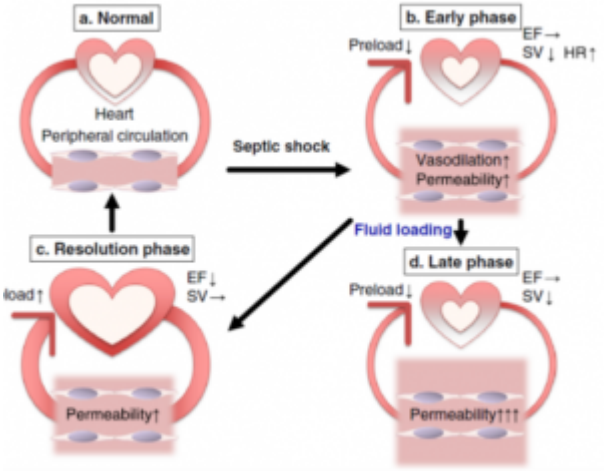

Figure 3: Pathophysiology of septic shock and secondary myocardial dysfunction. From DOI 10.1186/s40560-016-0148-1

Inotropic support should be considered in septic shock patients with evidence of persistent hypoperfusion despite adequate preload optimization and restoration of perfusion pressure. The decision to initiate inotropes should be guided by integrated assessment of cardiac output, tissue perfusion markers, and echocardiographic findings rather than ejection fraction alone. Importantly, a reduced ejection fraction in the presence of adequate cardiac output and preserved perfusion does not mandate inotropic therapy.

Dobutamine is the most commonly used inotropic agent in septic shock due to its predominant beta one adrenergic effects, which increase myocardial contractility and cardiac output. However, randomized data have not demonstrated a clear survival benefit associated with routine dobutamine use. Its administration should therefore be limited to patients with documented low cardiac output and ongoing hypoperfusion, and titrated carefully to avoid excessive tachycardia, arrhythmias, and increased myocardial oxygen consumption.

From a clinical point of view, the use of dobutamine for the correction of systolic dysfunction should be titrated to a target cardiac index. Targeting a cardiac index of 3.0-3.5 L/min/m^2 is reasonable, but has no evidence base. Targets should be assessed in the hemodynamic/perfusion context, integrating additional data such as lactate levels and the $ScvO_2$. Of note, markedly elevated cardiac indices or $ScvO_2$ are associated with poor outcomes and should be avoided when possible. Consequently, dobutamine is best used with a continuous assessment of cardiac index and measurements of $ScvO_2$.

Levosimendan and phosphodiesterase three inhibitors such as milrinone exert inotropic effects while reducing ventricular afterload through vasodilation. Despite favorable physiological effects, randomized trials and meta analyses have not demonstrated consistent outcome benefits for levosimendan in septic shock, and its use may be associated with hypotension and arrhythmias. These agents should be reserved for selected patients with low cardiac output and high systemic vascular resistance, with close monitoring for vasodilatory adverse effects.

On the other hand, short acting beta blockers may be considered in carefully selected septic shock patients with persistent tachycardia despite adequate resuscitation and restored perfusion pressure. Controlled trials suggest that heart rate reduction using ultra short acting agents such as esmolol may improve ventricular filling, reduce myocardial oxygen consumption, and stabilize hemodynamics without compromising tissue perfusion. This strategy requires advanced monitoring and should not be applied in patients with ongoing hypoperfusion or severe ventricular dysfunction.

Table 7: Inotropes and major effects.

Agent	Receptor	Major effects	Major side-effects
Dobutamine	B1,a1,B2	↑ contractility and heart rate, mostly B1 and B2 effects. At higher doses but offset by B2.	Cardiac arrhythmia, Cardiac ischemia, hypotension related to B2 effect in high doses.
Levosimendan	Phosphodiesterase inhibitor	↑ contractility Do not increase myocardial oxygen demand Inodilator ↓Venous and arterial tone	Tachyarrhythmia, Headaches, hypotension
Dopamine	a1,B1,D1,D2	↑ contractility and heart rate ↑Venous and arterial tone ↑Renal and mesenteric vasodilation	Tachycardia, tachyarrhythmia. Low Dopa-doses NOT RECOMMENDED FOR renal perfusion or protection
Milrinone	Blocks PDE3 degradation of cAMP, equivalent to B1 and B2 activity	↑ contractility and heart rate, Decreases pulmonary vascular resistance Inodilator ↓Venous and arterial tone	Profound vasodilatory effects mediated through PDE3 inhibition, torsades and other ventricular arrhythmias.

In text References

(Rhodes et al. 2017; Guarracino, Bertini and Pinsky. 2019; Stratton, Berlin and Arbo. 2017; Scheeren et al. 2021; Manolopoulos et al. 2020; L'Heureux et al. 2020; Lin et al. 2020; Kakihana et al. 2016; Cecconi et al. 2014; L'Heureux et al. 2020; Gordon et al. 2016; Morelli et al. 2013; Zangrillo et al. 2015)

1. 5. 4. Rescue options for refractory shock

Refractory septic shock refers to a state of persistent hypotension and tissue hypoperfusion despite adequate fluid resuscitation, high dose vasopressor therapy, and correction of reversible factors such as hypoxemia and acidosis. Although no universally accepted vasopressor dose threshold exists, refractory shock is commonly considered when escalating doses of norepinephrine fail to restore adequate perfusion pressure. This condition is associated with extremely high mortality and requires timely consideration of adjunctive and rescue therapies alongside reassessment of diagnosis and goals of care.

There are 2 main pathways in the development of refractory shock (Figure 4), the first one is related to a metabolic disarray caused by hypoxia, acidemia, lactic acidosis and the systemic inflammatory response syndrome, leading to endothelial and mitochondrial dysfunction. The second one is related to absolute or relative deficiency of vasopressin.

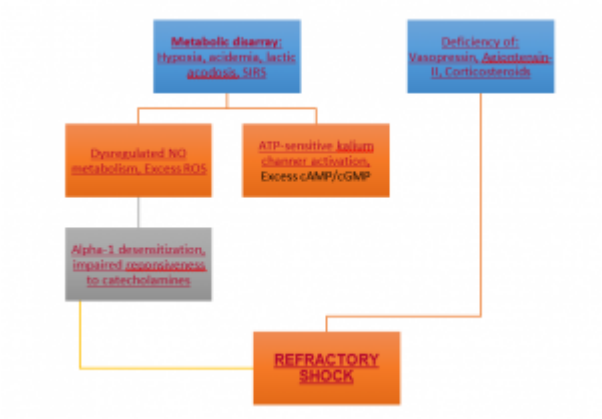

Figure 4: Development of refractory shock.
Adapted from Jacob Jenzer 2021.

A possible schema to characterize septic shock in terms of the NE requirements (albeit not SSC supported or widely adopted) is below:

- Mild: NE <0.1mcg/kg/min
    - Patients usually only requires NE
- Moderate: NE 0.1-0.19mcg/kg/min
    - Check $ScvO_2$, echo, ionized calcium, arterial pH.
    - Consider whether to add second vasopressor
- Severe: NE 0.2-0.29mcg/kg/min.
    - Consider addition of a second vasopressor
    - Consider adjunctive stress-dose corticosteroids
- Resistant: NE 0.3-0.9mcg/kg/min, or 2 vasopressors at < mcg/kg/min norepinephrine equivalent
- Refractory: 2 vasopressors at >1mcg/kg/min norepinephrine equivalent.

When septic shock remains refractory to standard therapies, several options are presented in Table 8. As first supportive therapy, low dose corticosteroids may be considered in patients with septic shock who remain hypotensive despite adequate fluid resuscitation and vasopressor therapy. Hydrocortisone administered at a total daily dose of 200 mg has been shown to shorten the duration of shock and reduce vasopressor requirements, although consistent mortality benefit has not been demonstrated. Current evidence supports the use of corticosteroids as adjunctive therapy to facilitate shock reversal rather than as a primary resuscitative intervention.

On the other hand, Methylene blue has emerged as a potential adjunctive therapy in refractory septic shock characterized by profound vasoplegia. By inhibiting nitric oxide mediated vasodilation and restoring vascular responsiveness to catecholamines, methylene blue may increase arterial pressure and reduce vasopressor requirements.

Systematic reviews suggest potential short term hemodynamic benefits, although robust evidence demonstrating improved survival is lacking. Its use should therefore be restricted to highly selected patients with refractory vasodilatory shock and implemented within a structured rescue strategy.

Angiotensin II represents an alternative vasopressor pathway that may be effective in catecholamine resistant vasodilatory shock. By acting on the renin angiotensin aldosterone system, angiotensin II increases vascular tone and may reduce requirements for other vasopressors. Randomized trial data demonstrate effective blood pressure restoration, though concerns remain regarding thromboembolic complications. Angiotensin II should be reserved for refractory shock after standard vasopressor therapy, with careful patient selection and monitoring.

Extracorporeal blood purification techniques have been proposed to modulate the dysregulated inflammatory response in septic shock. Despite promising physiological effects, randomized trials and meta analyses have not demonstrated consistent improvements in patient centered outcomes. Current evidence does not support routine use of hemoadsorption or endotoxin removal devices in septic shock, and their application should be limited to clinical trials or highly selected cases within experienced centers.

Table 8: Potential Options for Refractory Septic Shock

1. Hydrocortisone (200mg IV/day) +/- Fludrocortisone
2. Calcium-sensitizing agents (i.e.: levosimendan)
3. Methylene blue
4. Angiotensin II
5. Extracorporeal purification techniques
6. VA ECMO, depending on mechanism of hemodynamic compromise

After 12 to 24 hours, if hemodynamic stabilization has been achieved, catecholamine weaning should be considered.

1. 5. 4. 1. Veno-arterial extracorporeal membrane oxygenation (VA ECMO)

The use of extracorporeal life support in adult patients with refractory septic shock remains controversial. Few case reports describe the use of this technique in this population, with highly variable clinical outcomes. Best results are reported in patients with severe cardiac dysfunction, in which ECMO may help to restore adequate tissue perfusion to reverse multiple organ failures and to buy time to achieve infection control.

Large high-quality studies are needed before VA ECMO becomes standard of care in this setting. Nevertheless, it might be considered a valuable option in selected unresponsive patients, particularly in patients with severe cardiac systolic dysfunction and end-organ hypoperfusion, however, it should not be used for isolated vasodilatory septic shock without significant myocardial dysfunction.

In patients with refractory septic shock unresponsive to escalating therapy, ongoing reassessment of prognosis and alignment of treatment intensity with patient values and goals of care is essential. Early involvement of multidisciplinary teams and transparent communication with patients and families support ethically appropriate decision making. Recognition of the limits of rescue therapy is a critical component of high quality sepsis care and should occur alongside maximal physiological support.

In text References

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1. 6. Summary

Hemodynamic management of septic shock should be individualized, dynamic, and guided by repeated assessment of perfusion rather than fixed protocols. Initial priorities include rapid infection control, early antimicrobial therapy, restoration of minimal perfusion pressure, and correction of hypovolemia when present. Subsequent management should integrate clinical examination, peripheral perfusion, metabolic markers, echocardiography, and dynamic tests of fluid responsiveness to guide fluids, vasopressors, and inotropes while minimizing treatment related harm.

1. 6. 1. Take Home Points

1. Septic shock is a dynamic and heterogeneous syndrome requiring individualized management.
2. Restoration of perfusion pressure should occur early, but normalization of blood pressure alone does not guarantee adequate tissue perfusion.
3. Fluid responsiveness does not equate to fluid requirement and fluid administration should be guided by perfusion and reassessment.
4. Norepinephrine is the first line vasopressor and may be initiated early in selected patients.
5. Vasopressin is the preferred adjunctive vasopressor to limit catecholamine exposure.
6. Inotropes should be reserved for patients with persistent hypoperfusion and low cardiac output.
7. Rescue therapies may restore hemodynamics in refractory shock but do not replace reassessment of prognosis and goals of care.