EXPERT OPINION

Hemodynamic management of septic shock

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ABSTRACT

We present a review of the hemodynamic management of septic shock. Although substantial amount of evidence is present in this area, most key decisions on the management of these patients remain dependent on physiological reasoning and on pathophysiological principles rather than randomized controlled trials. During primary (early) resuscitation, restoration of adequate arterial pressure and cardiac output using fluids and vasopressor and/or inotropic drugs is guided by basic hemodynamic monitoring and physical examination in the emergency department. When more advanced level of monitoring is present in these patients, *i.e.* during secondary resuscitation (later phase in the emergency department and in the ICU), hemodynamic management can be guided by more advanced measurements of the macrocirculation. Our understanding of the microcirculation in septic shock is limited and reliable therapeutic modalities to optimize it do not yet exist. No specific hemodynamic treatment strategy, be it medications including fluids, monitoring devices or treatment algorithms has yet been proved to improve outcome. Moreover, there is virtually no data on the optimal management of the resolution phase of septic shock. Despite these gaps in knowledge, the data from observational studies and trials suggests that mortality in septic shock has been generally decreasing during the last decade. *(Minerva Anestesiol 2015;81:1262-72)*

Key words: Shock, septic - Fluid therapy - Catecholamines - Vasoconstrictor agents - Hemodynamics.

Everything we hear is an opinion, not a fact. Everything we see is a perspective, not the truth.
Marcus Aurelius

The principles of septic shock treatment have been very similar for decades, however, the mortality of sepsis appears to have declined as suggested by epidemiological studies,[1-3,4] although mortality is still high in certain subgroups.[5, 6] Early recognition and timely implementation of treatment have probably contributed to improved outcomes and management of these patients relies on optimization of the circulation (hemodynamic management).[7] Such hemodynamic management of can be difficult, because initial resuscitation has to be started with basic hemodynamic monitoring. In addition, other issues also need to be simultaneously addressed, in parallel with the hemodynamic optimization.

The first hour: primary resuscitation

Ethics and non-hemodynamic management

In developed countries, many patients with septic shock carry several serious comorbidities. Thus, discussions regarding the level of intervention are necessary.[8] This can be a logistic challenge since major decisions, regarding limitations of care, are preferably handled at a senior level. The initial management of such patients is summarized in Table I.

Table I.—*Immediate management of patients with septic shock.*[14]

Assessment	Action to be taken
Level of consciousness	Secure airway, exclude other causes than septic encephalopathy
A – Compromised airway	Secure airway
B – Respiratory failure	Improve oxygenation and increase ventilation by supplementation of oxygen by nasal cannula, mask, and non-invasive ventilation or invasive ventilation
C – Circulatory failure	Begin fluid resuscitation as soon as intravenous access is available
Sepsis focus	Samples for cultures, immunological and molecular biological diagnostics during intravenous catheter insertion, then broad, high dose, empiric antibiotic treatment should be started immediately. Surgical source control when appropriate.

Hemodynamic management – targets

Blood pressure and heart rate

A summary of the pathophysiologic changes in septic shock is presented in Figure 1 and therapeutic strategies in Figure 2. These pathophysiologic changes are similar in different diseases triggering the syndrome of septic shock. Thus, supportive measures are similar, but specific treatment should be tailored to the underlying disease. The first phase of management can be termed primary resuscitation. During such primary resuscitation only heart rate (HR), arterial blood pressure (ABP) and physical examination are available to clinicians. HR is a sign of illness severity and should only be treated directly except for major myocardial damage or life threatening arrhythmias. Apart from being a sign of disease, a low ABP, however, may affect other organ systems. Thus, treating hypotension is a priority. Some would argue that ABP gives no information on cardiac output, which is central for estimating tissue oxygen delivery. However, there are physiologic, logistic and pragmatic arguments against this. The physiological argument is that, independent of cardiac output, vital organs may not auto-regulate their blood flow if

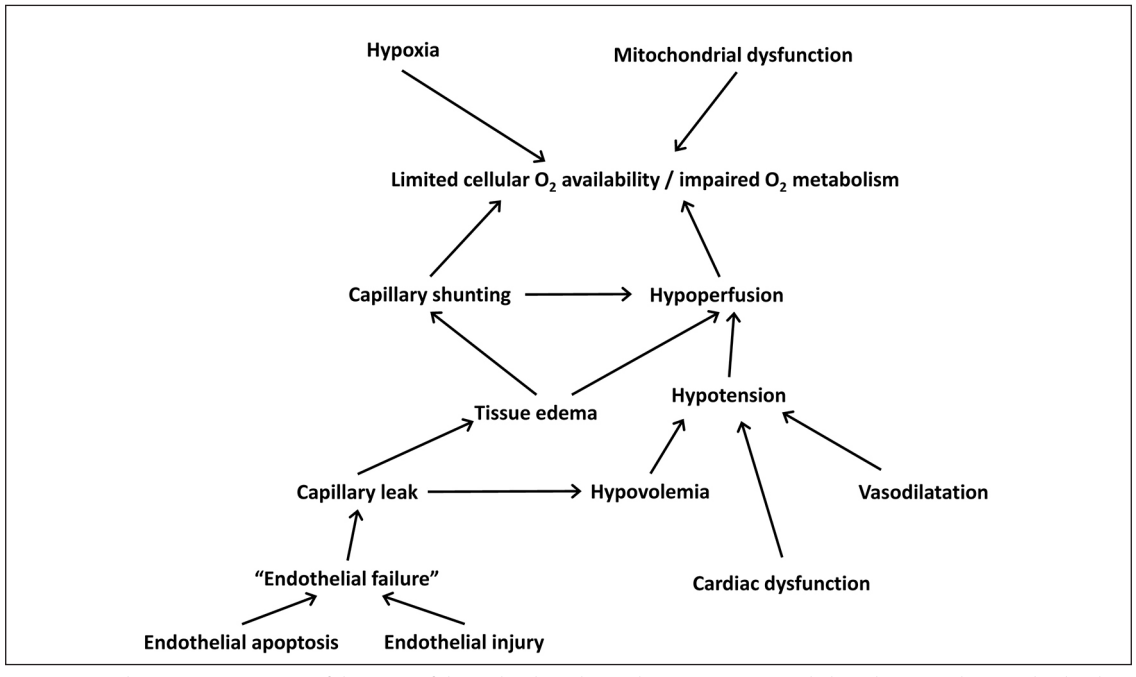

Figure 1.—Schematic presentation of the some of the pathophysiologic phenomena in sepsis believed to contribute to the development of shock.

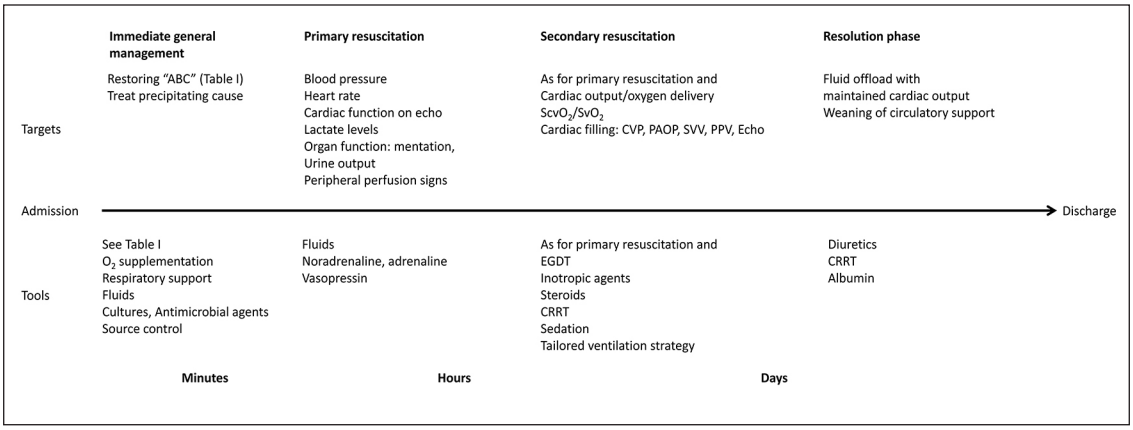

Figure 2.—An overview of the key steps in management of patients with septic shock, with special reference to hemodynamic targets and means of achieving these. CRRT: continuous renal replacement therapy; CVP: central venous pressure; Echo: echocardiography; EGDT: early goal directed therapy; NIV: non-invasive ventilation; PaoP: pulmonary artery occlusion pressure; PPV: pulse pressure variation; $ScvO_2/SvO_2$: central/mixed venous oxygen saturation; SVV: stroke volume variation.

the ABP is too low.[9] The logistic argument is that ABP is easily and immediately measured. Finally, the pragmatic argument is that an *adequate* ABP with normal mentation and urine output and warm peripheries signals that an inadequate cardiac output is unlikely.

A low (<60 mmHg) mean arterial pressure (MAP) is associated with mortality in the ICU.[10] Moreover, in hospitalized patients a decrease in MAP from premorbid levels is associated with development of acute kidney injury (AKI).[11] So, a MAP at least above 60 mmHg seems a reasonable initial target. Modification of MAP target based on premorbid MAP could impact on the incidence of AKI.[12] However, a recent randomized controlled trial (RCT) in ICU patients with septic shock comparing MAP targets of 65-70 mmHg or 80-85 mmHg found no difference in mortality except for patients with pre-admission hypertension.[13] No RCT has yet addressed the issue of MAP targets in the emergency department (ED). However, the Surviving Sepsis Campaign recommends that MAP should be maintained above 65 mmHg in this setting.[14]

Other circulation targets

Other targets available for immediate hemodynamic management are less easily quantified. Monitoring organ function such as level of consciousness or urine output is relatively easy. However, the presence of altered consciousness may reflect the consequences of a high fever or toxemia or events that preceded presentation. Such events cannot be immediately reversed by hemodynamic optimization, especially in the elderly. Similarly, a low urinary output and renal injury may reflect events prior to presentation, which cannot be reversed by the restoration of renal perfusion or the injurious renal effects of inflammation *per se*. Thus, their continued presence does not necessarily indicate that hemodynamic management has been inadequate.[15, 16]

A convenient method for the rapid assessment of the presence of hypovolemia and/or impaired cardiac function is transthoracic echocardiography.[17] The major limitations of this method are the intermittent nature of the assessment, and that technology and skill must both be available. Several protocols for rapid echocardiographic assessment are available.[18, 19]

A simple tool for identifying fluid responsiveness might also be the leg raising test. However, cardiac output monitoring is required for its evaluation.[20] Such monitoring is generally not available during primary resuscitation.

Plasma lactate levels and lactate clearance have been suggested as possible targets of resuscitation. However, already plasma lactate levels close to the reference range signal increased mortality.[21] Including lactate clearance in the resuscitation algorithm of patients with sepsis in the ED

has given diverging results.[22, 23] Possible reasons for the complex picture are that lactate clearance is influenced by several factors [24] and that the half time of lactate in plasma is in hours in this group of patients [22] and this relatively slow response rate makes lactate less useful in primary resuscitation beyond its role as a marker of illness severity.

Microcirculation as a hemodynamic target

Assessing the circulation at tissue level is appealing. However, there are many obstacles with monitoring the microcirculation at the bedside in the ED and the meaning and therapeutic implications of changes in the circulation of the skin or tongue are unclear.

The skin can be easily studied but circulatory failure in the skin is seldom of major concern. However, a mottled and cold skin can be a feature of fulminant septic shock. Skin temperature and capillary refill time have been for many years used in the pediatric population.[25, 26] In the last decade, several publications have investigated skin temperature and capillary refill time in septic shock patients. These are related to the severity of shock,[27, 28] and can be used to signal adequate resuscitation.[29] However, treatment of macrocirculatory failure may not necessarily normalize the perfusion of the skin [30] and skin temperature may not reflect the circulation of more central capillary beds.[31]

Several complex techniques have been developed to assess the peripheral circulation of which two are presented in Table II.[28-101] However the role of these techniques is yet to be found.

In summary, primary resuscitation still relies on basic hemodynamic tools such as blood pressure and heart rate and imperfect clinical findings (*e.g.* skin temperature in hands and feet, capillary refill time of fingers and toes, appearance of the skin, urinary output, adequate filling of neck veins, pulse pressure, mentation), although echocardiography and other techniques are becoming more common.

Hemodynamic management – tools

The two mainstays of hemodynamic treatment have been increasing intravascular volume with fluids or counteracting hypotension and low cardiac output with vasoactive drugs with varying inotropic properties.

Fluids

Fluid therapy to counteract circulatory failure is simple and cheap and is recommended in the Surviving Sepsis Guidelines as a part of the initial management.[14] However, fluids should be carefully prescribed to maximize their impact and limit their side-effects.

The amount of fluid administered has been reported at values under [32] and over [33] the current sepsis guidelines.[14] Interestingly, limited fluid administration in sepsis patients does not seem to lead high mortality [32, 34-36] and a positive fluid balance is associated with increased mortality in septic patients.[37-40] Critics of these observational studies would argue that illness severity is a major confounder. A large randomized trial in African children, however, found that generous fluid therapy increased mortality under resource poor circumstances.[41] The relevance of such findings to developed countries is unclear. Importantly, the role of fluid boluses in primary resuscitation

Table II.—*Examples of different techniques to assess the peripheral microcirculation.*

Method	Principle	Comments
Near infrared spectroscopy (NIRS) of the thenar muscles	Measures tissue hemoglobin oxygen saturation with or without a temporary occlusion of blood flow at the upper arm.	Tissue oxygen saturation in septic shock in the thenar muscle has been investigated in several studies.[98] The rate of changes in the thenar muscle saturation after vascular occlusion is linked to disease severity.[99, 100]
Sidestream dark field imaging (SDF)	Visualizes capillary circulation of blood cells in mucosal capillaries. Computer algorithms quantify the state of the microcirculation.	Visualizing the capillaries can be difficult.[101] Also, it is difficult to interpret the visual information bedside, assess its relevance to the clinical scenario and convert it to medical interventions.

Table III.—*Characteristics of fluids used in treatment of septic shock.*

Fluid type	Safety data	Recommendation	Cost
Saline	Risk of metabolic acidosis,[102] AKI [43] and increased mortality [103] vs. balanced solutions	Use with caution especially in metabolic acidosis.	Cheap
Hypertonic saline	Sodium and chloride load are of concern. Minimal safety data in sepsis patients.	Use with caution especially in metabolic acidosis.	Relatively expensive
Balanced solutions	Less harm than saline [43, 103] and HES solutions [104, 105]	Electrolyte constitution resembles plasma. Currently probably optimal fluids.	Cheap
Gelatin solutions	Colloid effect questioned due to relatively small molecule size Minimal safety data in critically ill patients [106]	Limited of safety data. Use of gelatins cannot be recommended in septic shock.	Cheapest colloid
Dextrane solutions	Minimal safety data in critically ill patients [106]	Given the limited safety data. Use of dextranes cannot be recommended in septic shock.	Relatively expensive
Hydroxyethyl starch (HES) solutions	Increased risk of AKI and mortality in critically ill patients [104, 105, 107]	Risk of harm with these solutions. Use of HES solutions cannot be recommended in septic shock.	Relatively expensive
Albumin solutions	Outcome similar as for treatment with saline for 4% [45, 108] and 20% [5] albumin	Albumin offers no clear advantage compared to saline. Can be considered in septic shock if substantial amounts of fluids have been given.	Expensive in many countries

is insufficiently investigated. Moreover, in the post primary resuscitation phase the hemodynamic effect of fluid boluses is clearly questionable.[42] Until further evidence is available, amount and mode of fluid administration is based on clinical judgment.

More evidence is available on the type of fluids in the resuscitation of sepsis patients. The characteristics of different fluids are presented in Table III. Although firm evidence is lacking, balanced crystalloid solutions could have an advantage over saline.[43] Among colloid solutions available on the market only albumin has an acceptable safety profile.[44] This colloid appears to have a post-hoc relationship with better outcomes in the SAFE trial and ALBIOS trial.[5, 45] Albumin also has many characteristics that would logically support a beneficial effect. However, it lacks a definitive trial showing a survival advantage. In the absence of such convincing data and given the high cost of albumin in some countries, its use for fluid resuscitation and/or supplementation should be based on clinical judgment.

Vasoactive agents

Although hypotension or suspected hypoperfusion are not obligate features of septic shock,[46] one or both are usually present. The general notion is that hypotension is partly caused by hypovolemia,[20] low systemic vascular resistance and myocardial dysfunction.[47] Although ICU patients with septic shock typically have a high cardiac output,[48] no data describe the cardiac output state of unresuscitated patients with septic shock when they present to the ED.

A simplified approach to hemodynamic optimization would be to treat suspected hypovolemia with fluids, vasodilatation with vasopressors and myocardial dysfunction with inotropic agents. However, most vasopressors have inotropic properties and many "pure" inotropic agents induce vasodilatation. The vasopressor with essentially no inotropic effect is phenylephrine. However, phenylephrine may adversely affect the hepato-splanchnic circulation [49] and its safety is not fully tested.[50] Noradrenaline, as a vasopressor with mild inotropic effect, is most commonly used. In a small study noradrenaline did not change outcome in a mixed intensive care population when compared to adrenaline, but hyperglycemia and hyperlactatemia were decreased.[51] The addition of dobutamine to noradrenaline does not appear to change outcome compared to adrenaline.[52] Additionally, adding low dose vasopressin to noradrenaline did not

decrease mortality compared with norepinephrine alone among patients with septic shock.[53] Dopamine has been associated with more adverse effects, primarily arrhythmias compared with noradrenaline [54, 55] and is not recommended. Low dose dopamine does not prevent AKI in these patients.[56] In patients with severe hypotension (MAP<50 mmHg), vasopressor support should be started simultaneously with fluids via peripheral vein as central venous access is obtained. Inotropic agents have generally a limited role in the acute treatment of septic shock unless they are combined with demonstrable cardiac dysfunction and/or a low cardiac output. Minimal data are available on levosimendan in septic shock [57] and no human data are available on milrinone.

Based on pathophysiologic reasoning, both fluids and vasoactive agents may be required in the hemodynamic management of some patients with septic shock. However, at the bedside one may ask whether hemodynamic optimization should be achieved by using more fluids or more vasopressors. Currently there are no data to guide clinicians on this issue.

The first 24 hours and beyond: secondary resuscitation

After the initial stabilization and treatment, some patients improve rapidly (especially. those with a urinary focus of sepsis). Others, however, remain unwell and require continuous vasopressor infusion. These patients typically receive treatment in an ICU, where advanced monitoring becomes possible and can guide the optimization of the circulation.

Hemodynamic management – targets

The rationale behind establishing more advanced monitoring is to be able to assess the macro-circulation and ensure hemodynamic stability. Yet, increasing the level of monitoring has not been convincingly shown to improve outcome.[58]

The main hemodynamic determinant of global oxygen delivery is cardiac output.[59] The measurement of which is most commonly obtained by pulmonary artery catheter,[60] calibrated [61, 62] and non-calibrated pulse contour analysis,[63] as well as Doppler techniques.[64] All of these techniques have their advantages and disadvantages. Given that high cardiac output is a feature of septic shock after initial resuscitation [48], it is not surprising that the use of inotropic agents in sepsis (which marks patients with a lower cardiac output) is associated with increased mortality.[65] Nevertheless, improving low cardiac output in sepsis could decrease mortality.[66] A more specific measure of hemodynamic efficiency, oxygen delivery, has been of interest because in perioperative management supra normal levels, seemed to be of benefit.[67] However, although normalizing oxygen delivery could have a positive impact on outcome,[66] increasing oxygen delivery to supra normal levels does not appear to improve outcome in patients with sepsis.[68] Increased tissue oxygen extraction can be estimated by central venous ($ScvO_2$) or mixed venous saturation (SvO_2).[69] $ScvO_2$ has been a key resuscitation target in septic shock for over decade after an initial single center study;[33] however, the utility of this parameter has been challenged by two recent multicenter studies.[70, 71] More RCTs on the role of $ScvO_2$ are being conducted.[72] To date, no investigation has shown any benefit for SvO_2 as resuscitation target compared to cardiac output monitoring in sepsis or critically ill patients.[73]

As the administration of fluids is common, several methods have been suggested to assess fluid responsiveness, *i.e.* that fluid administration leads to a clinically significant increase in cardiac output by increasing ventricular end diastolic volume and stroke volume.[74] Fluid responsiveness in not uncommon in the sepsis patients;[75] however one must remember that fluid responsiveness does not imply that fluid administration is necessarily desirable.

Traditional hemodynamic measures such as right and left ventricular filling pressures,[86, 76-78] or pulmonary artery occlusion pressure in patients with septic shock [75, 79] do not perform well in predicting fluid responsiveness. Similarly, right ventricular end-diastolic volume index performed poorly in a mixed intensive care cohort.[80] Techniques assessing right ventricular fluid responsiveness have been suggested,[81] but

clinical studies investigating the value of such technology are current not available. Assessment of left ventricular filling with echocardiography is a quick and non-invasive method. However, it requires at least basic echocardiographic skills, is an intermittent method and its ability to predict fluid responsiveness has not been adequately validated.[77] On the other hand, respiratory changes in the diameter of the inferior caval vein measured with 2 dimensional echocardiography requires minimal training and can help predict fluid responsiveness in mechanically ventilated sepsis patients.[82, 83] Other good predictors of fluid responsiveness in mechanically ventilated patients with septic shock are pulse pressure variation [75] and stroke volume variation.[75, 84] Limitation of these two methods of fluid responsiveness are that need to be free of arrhythmias and spontaneous breaths as well as the need for mechanical ventilation with tidal volumes over 8 mL/kg.[85]

Hemodynamic management – tools

During secondary resuscitation, the tools of hemodynamic management do not differ from those of primary resuscitation. Yet, with more advanced monitoring, more complex treatment algorithms can be introduced. The early goal directed therapy (EGDT) concept has dominated this area for more than a decade.[33] The results of the original EGDT study, however, could not be reproduced in two recent large multi-center studies.[70, 71] An additional study investigating the role of the EGDT is underway.[72] Although the name of the concept suggests "early treatment", what was actually investigated in these studies was the role of $ScvO_2$ and an associated specific algorithm, implemented several hours after ED presentation. Algorithms may improve outcome in patients with sepsis,[86] but the rationale for implementing "successful" algorithms is limited.[87] Finally, the use of corticoids in sepsis has been a matter of debate [88] for at least three decades. Robust evidence suggests, that low dose corticosteroids can help restore hemodynamic stability and thus can be considered in patients with high noradrenaline requirements.[89, 90] However, the increased risk of superinfections is a concern [90] and the overall effect mortality unclear.[89, 90] At least one large randomized trial is currently underway to assess the effect of glucocorticoids in septic shock,[91] and in due time our understanding of the benefits vs. risks with glucocorticoid treatment will improve. Until more data is available steroid treatment should be based on clinical judgment. Other measures for hemodynamic optimization relate to sedation, continuous renal replacement therapy (CRRT) or different ventilation strategies.

The role of sedation and/or paralysis in the hemodynamic management of severe sepsis/septic shock has not been studied in RCTs. Whether the advantages that might derive from such interventions (decreased oxygen consumption, easier ventilation) outweigh the side effects (lower blood pressure, neuromuscular weakness) remains uncertain.

The role of CRRT in the management of hemodynamics in septic shock is not supported by randomized controlled trials. However, CRRT can lower body temperature effectively and can help correct severe acidosis/acidemia.[92] Both effects can help decrease vasopressor requirements and may improve hemodynamics.[93] The decision to deploy CRRT for hemodynamic improvement purposes should be based on clinical judgment.

Finally, there are no randomized controlled trials to assess how different approaches to mechanical ventilation may affect the outcome of septic patients. However, mechanical ventilation strategies (high peep, recruitment maneuvers, choice of tidal volume) can all profoundly affect blood pressure and cardiac output. Such effects must be taken into account when initiating and or maintaining or targeting specific ventilatory and oxygenation goals in the setting of septic shock. Given the complexity of possible interactions, benefits and risks, decisions on how to mechanically ventilate septic shock patients should be individualized and supervised by an experienced clinician.

During secondary resuscitation, the aim of ongoing treatment is to use more sophisticated monitoring tools to maintain hemodynamic adequacy or achieve it, if primary resuscitation failed to do so. Fluid management of sepsis pa-

tients at this time is focused on adjusting the rate of fluid maintenance to cover ongoing losses. Vasoactive drugs and fluids are adjusted in response to continuous invasive hemodynamic monitoring, biochemical assessment and organ function assessment, while treatment of sepsis continues with antibiotics and/or surgical intervention and/or both.

The resolution phase

The hemodynamic management in the late (resolution) phase of sepsis is not well investigated. One RCT investigating the effects of conservative or liberal fluid management strategies in ARDS patients (of whom about 70% had infection as the precipitating factor) shortened the length of ventilator therapy and intensive care stay with conservative fluid strategy.[94] Another study showed less fluid gain with daily albumin infusions in critically ill patients.[95]

In the resolution phase of sepsis, the removal of excess fluid is a challenge for many clinicians. The general concept is to keep cardiac filling pressures low and increase low plasma oncotic pressure whilst maintaining cardiac output. One way of achieving this is to give hyperoncotic albumin solutions and loop diuretics.[96] This concept is under investigation for the general intensive care population.[97] Similarly, vasoactive drugs are weaned in response to improving clinical status and MAP. The use of CRRT for fluid removal in the resolution phase of critical illness, or septic shock, has not been investigated, and therefore cannot be recommended. No information, however, is available to guide clinicians to best practice aimed as accelerating recovery at this time.

Conclusions

Although there is much evidence on the hemodynamic features and management of septic shock, most of it is observational and no multicenter randomized controlled trials exist to demonstrate that a particular approach leads to better patient outcomes. In the absence of such data, physiological reasoning and key principles of applied pathophysiology can be used to guide treatment and monitoring. At this time, during primary resuscitation, restoration of adequate MAP by fluids and vasopressor drugs and restoration of adequate cardiac output, as assessed by physical examination and/or echocardiography, are key goals. Similar goals apply during secondary resuscitation but monitoring is by continuous MAP and, if appropriate, by invasive cardiac output and central pressure monitoring with or without dynamic assessment of fluid responsiveness. There is great uncertainty and essentially no data on how best to accelerate recovery in the resolution phase of sepsis.

Key messages

— Initial hemodynamic management of patients with septic shock should target restoration of adequate blood pressure.

— Echocardiography can provide valuable non-invasive information on cardiac filling and cardiac output in patients with septic shock.

— Once advanced hemodynamic monitoring has been established, oxygen delivery/extraction targeted hemodynamic management is possible. However, its benefits are uncertain.

— The mainstay of hemodynamic management of patients with septic shock is optimizing intravascular volume, counteracting vasodilatation with vasopressor agents, maintaining an adequate cardiac output and, when indicated, commencing adjuvant therapies such as glucocorticoids and renal replacement therapy.

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Conflicts of interest.—The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

Received on September 23, 2014. - Accepted for publication on October 31, 2014. - Epub ahead of print on November 4, 2014.

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