Current controversies in the support of sepsis

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Purpose of review
Sepsis has a high morbidity, with a mortality rate of over 50% in the septic shock patient. This review provides a comprehensive summary of the latest Surviving Sepsis Campaign and the recent evidence since its publication. The guidelines reflect literature from the past 5 years to optimize outcomes in patients with severe sepsis and septic shock.

Recent findings
The most relevant changes in the latest Surviving Sepsis Campaign include the use of a protocolized resuscitation with specific physiologic targets, preference of crystalloids for volume resuscitation, preferential use of norepinephrine as the initial vasopressor, addition of lactate and its clearance as a marker of tissue hypoperfusion, reduced emphasis on corticosteroids, and removal of activated protein C therapy. Since these latest guidelines, there have been many trials published to address the various measures that are advocated. We review the recent data on fluid resuscitation, targets of resuscitation, vasopressors, and trials of protocolized care versus usual care.

Summary
Severe sepsis remains a significant cause of morbidity and mortality in hospitalized patients. The International Surviving Sepsis Guidelines provide a framework for early recognition and treatment of this condition, with the goal of an improved outcome and mortality in severe sepsis. The recent evidence suggests that early identification, adequate volume resuscitation, and assessment of adequate circulation may be the key elements to decrease morbidity from severe sepsis and septic shock.

Keywords
controversy, infection, sepsis, severe sepsis, Surviving Sepsis Campaign

INTRODUCTION

Sepsis is one of the oldest syndromes in medicine. It continues today to be a worldwide health condition associated with high mortality rates despite improvements in the management of infections. It remains among the most common reasons for utilization of ICU resources. Over 1.6 million cases of sepsis occur in the United States each year, with a mortality ranging from 20 to 50% [1]. There is a continuum of disease ranging from sepsis, to severe sepsis, and septic shock. Even with optimal treatments including antimicrobial agents and life support, the mortality due to severe sepsis and septic shock remains quite high, at approximately 40% to greater than 50% [2–5].

FLUID RESUSCITATION AND MONITORING TARGETS

Administration of intravenous fluid, in quantitated amounts, remains a cornerstone of care in the ICU for sepsis, as well as many other disorders. The 2012 Surviving Sepsis Campaign recommends protocolized resuscitation of the patient in septic shock with intravenous fluids to overcome the sepsis-induced tissue hypoperfusion [6▪▪]. The hypoperfusion is quantitated as hypotension that remains after the initial fluid challenge, or a serum lactate greater than or equal to 4 mmol/l. It is also recommended to initiate the fluid therapy without any delay. There are several targets of the fluid therapy listed in the guidelines including central venous pressure (CVP) of 8–12 mmHg, mean arterial pressure (MAP) at least 65 mmHg, urine output at least 0.5 ml/kg/h, mixed venous oxygen saturation at

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Curr Opin Crit Care 2014, 20:681–684
DOI:10.1097/MCC.0000000000000154

KEY POINTS

- Severe sepsis and septic shock remain a disorder with a high mortality rate.
- Early recognition of severe sepsis still remains a challenge to the clinician.
- Use of protocolized quantitative resuscitation with specific physiologic targets for treatment is being studied.
- Early antibiotics and adequate fluid resuscitation are essential components of care for patients with severe sepsis and septic shock.

least 65%, or central venous oxygen saturation at least 70%. It is also suggested to normalize the elevated lactate level. These recommendations are based on the work of Rivers *et al.* [7] and their early goal-directed therapy (EGDT), which showed a 15.9% reduction in 28-day absolute mortality when the resuscitation was initiated in the first 6 h.

Following these recommendations often results in an aggressive fluid resuscitation, of 5–10 l, particularly early in the patient's course [8▪▪]. One of the hallmarks of sepsis is the break in the endothelial barrier that results in a 'leaky vasculature' [9]. There is currently no specific therapy that targets reversing this extravasation of fluid. Even administration of such large volumes of fluid for resuscitation is not consistently effective at maintaining adequate intravascular volume, and pressors are required in cases that progress to septic shock. Despite the ineffectiveness of fluids at maintaining tissue perfusion in the septic shock patient, they have the potential for harm. In a secondary retrospective analysis of the VASST trial, which originally studied the role of vasopressin in septic shock, it was shown that patients with a more positive fluid balance, at both 12 h and on day 4, had a significant correlation with increased mortality [10].

The 2012 Surviving Sepsis Campaign only specifies that crystalloid should be the initial fluid for resuscitation. It does not specify which crystalloid should be used for the initial resuscitation, nor for the maintenance fluid, although it does suggest that albumin can be substituted for a portion of the crystalloid. Clinicians need to be aware that use of 0.9% isotonic saline as their resuscitation fluid can result in a hyperchloremic acidosis, which increases the risk of renal failure [11▪].

The endpoints of resuscitation in the Surviving Sepsis Campaign 2012 are based on urine output, CVP, and surrogates of oxygen delivery looking at clearance of lactate and central or mixed venous saturation. None of these endpoints are ideal, and each has its own limitations. When urine output is present, it is useful to follow for fluid status; however, there is a high incidence of acute tubular necrosis in sepsis, resulting in acute kidney injury. In fact, with severe sepsis the incidence of acute kidney injury is 23%, and in septic shock with positive blood cultures, the incidence is 51% [12], which means in some patients they may be resuscitated, but still be oliguric.

CVP is another emphasized endpoint of resuscitation in the Surviving Sepsis Campaign. However, it is a static parameter, and the current trend is for dynamic measures of fluid status. CVP, when looked at in a literature review, was found to have a poor correlation with fluid status [13]. Unfortunately, the Surviving Sepsis Campaign does not recommend a dynamic index of fluid status, such as inferior vena cava distensibility with respiratory variation [14].

Finally, serum lactate measurements, as well as mixed and central venous oxygen saturation, when normalized, do indicate an adequate resuscitation. However, an elevated lactate or low venous saturation can be due to other causes, such as hypoxia or a component of cardiac shock, and clinicians need to be cognizant that these other causes do not indicate a fluid deficiency.

EMPIRIC ANTIBIOTIC THERAPY

The Surviving Sepsis Campaign 2012 recommends early, empiric antibiotic treatment. This involves not waiting for culture results to initiate antibiotic therapy. Previous research has shown that delays in administration of appropriate antibiotics when septic patients develop hypotension are associated with decreased survival [15]. In a recent retrospective analysis [16▪▪] of 28 150 patients with severe sepsis and septic shock, it was shown that an increase in the probability of death could be correlated with the hours of delay to the patient receiving their antibiotic. Treatment of severe sepsis and septic shock requires timely administration of the correct antibiotic [17]. Given the challenges of choosing the correct antibiotic, a meta-analysis of administering combination antimicrobial therapy to high-risk critically ill patients favored the multiple agents [18].

VASOPRESSOR THERAPY

There remain many unanswered questions regarding vasopressors, including target MAP, optimal time to initiate, and duration of therapy.

The target of MAP remains unchanged from the prior 2008 version of the guidelines. A large ICU database review determined that risk of kidney

injury and death was increased if the MAP was below 60 mmHg [19]. The Assessment of Two Levels of Arterial Pressure on Survival in Patients with Septic Shock was a randomized, controlled trial that studied patients in septic shock [20▪]. The patients were randomized to a target MAP of 65–70 or 80–85 mmHg. The primary endpoint was mortality. Secondary endpoints were 90-day mortality and end organ failure. There was no significant difference between the two groups in primary or secondary endpoints. Subgroup analysis was performed on patients with chronic hypertension, which demonstrated increased renal dysfunction in the patients in the lower MAP target. The time patients were below an MAP of 65 mmHg was an independent predictor of mortality.

Norepinephrine remains the first-choice vasopressor for use in patients with septic shock. Norepinephrine increases MAP primarily through vasoconstriction-improving cardiac output, and cerebral, renal, and splanchnic systems with little effect on heart rate.

Norepinephrine and dopamine have been compared directly in at least six randomized trials, and most recently in a meta-analysis. These trials showed a relative risk for death of 0.91 (0.83–0.99) with the use of norepinephrine compared with dopamine as vasopressor therapy for septic shock. A 2012 meta-analysis, including randomized and observational trials, concluded that dopamine brings an increased risk for death compared with norepinephrine as a first-line vasopressor for septic shock. Patients with septic shock on dopamine demonstrated increased risks of cardiac arrhythmias [21]. Therefore, dopamine is not recommended for patients with septic shock.

Epinephrine is suggested as the next-line vasopressor after norepinephrine for septic shock, to be added or substituted if norepinephrine is not adequate to achieve the target MAP. Epinephrine has been compared to norepinephrine in several randomized trials, with no increase in the risk for death.

Vasopressin is another useful agent for the patient with septic shock. Low-dose vasopressin as an addition to norepinephrine with intent to decrease norepinephrine dose or increase MAP with a maximum dosage of 0.03 U/min is to be considered. In the VASST trial [22], patients with septic shock were randomized to receive norepinephrine alone or norepinephrine and vasopressin at dose of 0.03 U/min. There was no difference in outcome with norepinephrine with intention to treat analysis (VASST trial). There still remains the question as to the best time to initiate use of vasopressin, as well as, any vasopressor support.

PROTOCOLIZED-BASED CARE FOR SEPSIS

Many of the recommendations of the Surviving Sepsis Guidelines are based on a single-center emergency room-based trial that revealed decreased mortality in patients treated with a 6-h protocol of EGDT. The individual components of the bundles included intravenous fluids, vasopressors, inotropes, and transfusion of blood, which were adjusted to meet targets of resuscitation. Other multicenter trials conducted since EGDT have not been able to reproduce these results.

The ProCESS Investigators [23▪▪] conducted a randomized trial to assess difference in mortality with protocolized care versus usual care. In 31 academic centers across the United States, they randomized 1341 patients with severe sepsis or septic shock into three arms. The first group was a protocol based on EGDT that included targets of resuscitation of CVP 8–12 mmHg, ScVO2 greater than 70%, MAP greater than 65 mmHg using 500 cm^3 boluses of fluids as needed. Patients in the first group received central lines to monitor these targets. The second group was standard protocolized care that included adequate peripheral intravenous access. This group received boluses of fluid to target shock index and systolic blood pressure (>100 mmHg). The third group received usual care that was at the discretion of the treating provider without a study-mandated protocol. There was no difference in the primary outcome of 60-day, 90-day, and 1-year mortality between the groups.

Post-hoc analysis revealed that the patients in the EGDT arm had a greater than two-fold increase in central-line placement. This was mandated as part of this protocol group. These patients also had increase in dobutamine infusions and increased transfusion requirements as compared with the other two arms.

Overall fluid requirements in the first 6 h showed that the early goal-directed group received 3.3 l, the protocol group received 2.8 l, and the usual-care group received on average 2.3 l. Despite this difference in average fluid amount, there were no differences in serious adverse events between the groups. All the study groups received greater than 2 l of fluid prior to randomization. More than 75% also received antibiotics prior to randomization. Both of these are elements of the 3-h bundle from the Surviving Sepsis Guidelines. In the 2001 EGDT trial, septic shock mortality was 46.5% as compared with 18% mortality in the usual care group, which reveals that there have been improvements made in sepsis recognition or intervention since.

There are two other large, international, multicenter trials, Australian Resuscitation In Sepsis

Evaluation Randomised Controlled Trial (ARISE) and The Protocolised Management in Sepsis Trial (ProMISe), that are investigating the role of CVP and ScvO2 as targets for resuscitation in patients with severe sepsis and septic shock.

CONCLUSION

Although severe sepsis and septic shock remain a common problem worldwide, the latest recommendations from the Surviving Sepsis Campaign summarize the latest evidence. However, since ProCESS, a new era of management of severe sepsis and septic shock may be on the horizon. We await the results of the ARISE and ProMISe trials. The ProCESS trial did help identify early recognition of sepsis with early fluid and antibiotic administration as well as clinical assessment of adequacy of circulation as key components of the management of sepsis. Much evidence remains to be obtained on how best to guide fluid resuscitation, timing of vasopressors, and utility of lactate. Future directions for research and implementation in this area include computer-driven algorithms for the earlier identification of the sepsis patient, both upon initial presentation in the emergency department, as well as when sepsis subsequently develops as an inpatient, in or out of the ICU. In addition, computer-driven algorithms can also be used to drive the protocol of care and enhance data collection of compliance with the elements of the bundle. With continued efforts, the disease of sepsis can be positively and significantly impacted.

Acknowledgements

None.

Conflicts of interest

There are no conflicts of interest.

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