CHAPTER 91

Recommendations for Sepsis Management

Jean-Sebastien Rachoin and R. Phillip Dellinger

Objective

This chapter will:
1. Present key evidence pertaining to the treatment of sepsis.

Infection is a common occurrence in the intensive care unit (ICU), as a reason for ICU admission and when acquired in the ICU, and results in significant morbidity and mortality. In the United States the annual incidence of infection-induced organ dysfunction is estimated to be more than 750,000 cases a year, resulting in more than $24 billion in costs, which is more than the gross domestic product of some European countries, such as Estonia, Iceland, or Malta.[1,2] Despite significant advances in our understanding of infection-induced organ dysfunction, the mortality rates remain unacceptably high, with rates ranging from 10% to 50% based on definition and population used for extraction.[3–6]

However, first we begin with a discussion of the challenges of defining infection-induced systemic perturbations with a focus on organ dysfunction.

DEFINITIONS

The American College of Chest Physicians and the Society of Critical Care Medicine held the first sepsis definitions consensus conference in 1991 with the creation of the term *systemic inflammatory response syndrome (SIRS).*[10] The criteria for SIRS were based on heart rate, respiratory rate, temperature, and white blood cell count. Infection associated with abnormalities (specific defined thresholds) of two of these four criteria was called *sepsis.* SIRS was recognized to occur in noninfectious conditions as well. *Severe sepsis* was the recommended term to characterize patients with sepsis-induced organ dysfunction or tissue hypoperfusion.

The second sepsis definitions consensus conference was held in 2001 with minor modifications to the 1991 definitions.[11] There was an expansion of clinical and laboratory parameters that would define sepsis, which were additive to the SIRS criteria. The definition of severe sepsis remained unchanged. Septic shock was defined as hypotension characterized by either a systolic blood pressure less than 90 mm Hg or mean arterial pressure (MAP) less than 70 mm Hg despite adequate fluid resuscitation. The third sepsis definitions consensus conference was published in 2015 with major revisions in the sepsis terminology recommended.[12] This committee recommended abandoning the term *severe sepsis* and using *sepsis* to describe infection-induced organ dysfunction or tissue hypoperfusion. The previous use of the word *sepsis,* infection with systemic manifestations, no longer had a specific name, and the word *infection* was recommended regardless of whether systemic manifestations of infection were present. This most recent document recommended de-emphasizing the SIRS criteria.

Because the 2001 definitions currently are used in the United States for both ICD-10 codes and are the reference standard for the Centers for Medicare and Medicaid Services (CMS) quality metrics, any movement to adopt these definitions likely will be slow and will require planning and coordination with these agencies.

ANTIBIOTICS ADMINISTRATION

Antibiotics administration is a cornerstone in the treatment of sepsis. There are three issues pertaining to this important therapy: mode of administration, type of antibiotics, and timing of treatment.

Mode of Administration

In the setting of severe sepsis and septic shock the administration of antibiotics should be done intravenously to ensure adequate bioavailability and prompt delivery of the medication to the blood stream and affected organs of the diseased patient.

Type of Antibiotics

In the absence of a definitive microbe as the cause of severe sepsis, broad-spectrum antimicrobials must be administered to cover a wide range of potential pathogens. This approach is supported by retrospective studies in which inappropriate antibiotic treatment was associated with higher mortality.[13,14] An additional issue that sometimes arises is whether antifungal agents should be added up front. The decision to cover broadly must be linked to the commitment to de-escalate antibiotics based on culture results. De-escalation therapy is safe and results in improved outcomes.[15]

It would seem reasonable that in a patient with appropriate risk factors (such as cancer on chemotherapy or chronic TPN) that clinicians consider upfront treatment with an antifungal, because if unrecognized, it can be associated with substantial mortality.[16] Another controversial topic is using combination treatment for high index of suspicion of having pseudomonal infection. Recent data suggest that this approach could result in better outcomes.

Timing of Antibiotics Administration

This has been the topic of several studies and one recent meta-analysis. In a large retrospective study of 2731 patients with septic shock in 14 intensive care units (ICUs) from

1998 until 2004 in the United States and Canada, Kumar showed that earlier administration of antibiotics, hour after hour from diagnosis of hypotension improved survival. Delaying the administration beyond the first hour had an exponential impact on mortality. After adjusting for other factors, timing of administration of antibiotics was the most powerful predictor of survival in this patient population.[17] In another study from Europe done in 165 ICUs that included almost 18,000 patients between 2005 and 2010, Ferrer showed similarly that delay in antibiotics administration was associated with a worsening of survival.[18] Not all studies confirm these findings.[19,20]

In a recent meta-analysis, Sterling et al. combined the results of 11 trials[21] and concluded that there was no definitive evidence to support that early antibiotics treatment was associated with improved outcomes.[21] This study had several notable limitations. As the authors point out, the trials included were heterogeneous. In addition, correctly identifying a time "zero" can be challenging. It has been shown that in the emergency department a significant portion of patients (15% to 23%) with documented severe sepsis are misclassified at triage; thus correctly deciding on an accurate start time for shock is daunting because of the unpredictable and changing clinical course of the disease.[22,23] Finally, there was little information about appropriateness of the antibiotics (broad vs. narrow spectrum) and results of microbiology testing. Argument for early administration of antibiotics is the earliest possible attempt to limit bacterial growth and spread. In the absence of any possibility of doing a prospective randomized study (because equipoise could not be obtained for the trail that randomized patients to earlier versus later antibiotics) effective antibiotics should be administered as soon as possible and preferably within 1 hour of hypotension or detection of other infection induced organ dysfunction.

Vasopressor Agents

Regarding vasopressor therapy of persistent infection-induced hypotension, important questions to consider are the following: What should the patient's blood pressure goal be? Which vasopressor agent(s) should be used? When should vasopressors be initiated?

Blood Pressure Goal

The target blood pressure is paramount because it is chosen to optimize tissue perfusion and can also serve as a measure of quality of care. The current recommendation is to aim for a mean arterial pressure (MAP) of 65 mm Hg. Patients with chronic hypertension or with severe atherosclerosis may need higher MAP to maintain adequate organ function. On the other hand, healthy younger patients or patients with cirrhosis could do well with lower blood pressure goals because their baseline is already low. The question of optimal MAP target in septic shock has been the subject of numerous research studies: In studies that looked at hemodynamic endpoints, raising MAP goals from 65 to 85 mm Hg resulted in an increase in cardiac output and oxygen delivery; the impact on lactic acid level was insignificant, and on the mixed venous saturation was inconsistent.[24,25]

There is only one randomized clinical trial that compared targeting higher versus lower MAP targets on clinical outcome. In a study of 776 patients, Asfar et al. randomized patients to a goal MAP of 65 to 70 mm Hg or 80 to 85 mm Hg. This study found no difference in the 28-day mortality when comparing groups, but when their analysis included only patients with chronic hypertension, those with higher MAP goals had better renal outcomes (need for dialysis, or doubling of serum creatinine). The findings of this trial would suggest that in the majority of patients a goal MAP of 65 mm Hg is sufficient, but in patients with baseline hypertension a higher MAP goal of 80 to 85 may result in better renal outcomes. In that study, aiming for higher MAP resulted in a higher rate of atrial fibrillation.[26]

Selection of Vasopressor

Patients who fail to normalize blood pressure after initial fluid resuscitation require vasopressors. Because hypotension that persists after adequate fluid resuscitation is due to some combination of arteriolar vasodilation and inotropic suppression, a combined inotrope/vasopressor drug should be used. Norepinephrine (along with epinephrine and dopamine, one of the three combined inotrope vasopressors) is the vasopressor of choice in septic shock (see discussion below). A second vasopressor typically is added when norepinephrine doses exceed 30 to 40 ug/min, although considerably higher doses of norepinephrine are used by some. Choices for a second vasopressor include epinephrine or low-dose vasopressin (up to 0.03–0.04 units/min). (See discussion later in chapter.) Epinephrine is chosen because it is also a combined inotrope/vasopressor. Vasopressin, although a pure vasoconstrictor, is an alternative because the dose is targeted as physiologic replacement. Studies have shown that vasopressin levels are unexpectedly lower than anticipated in many patients with septic shock. Phenylephrine is a pure vasoconstrictor and is not recommended for empiric use, although niche uses for phenylephrine include (1) difficulty raising mean arterial pressure in the presence of high cardiac output as well as (2) serious tachyarrhythmias induced by norepinephrine (not usually an issue). Dopamine, although not recommended as initial empiric therapy because of its association with arrhythmias, has a niche usage in patients with septic shock and sinus bradycardia. In 2010, De Backer et al. published the results of a large multicenter trial in which 1679 patients were randomized, to either dopamine or norepinephrine. Although there were no statistically significant between-group differences in the rate of death at 28 days in the populations studied, survival was better with norepinephrine in all subgroups of shock studied, including septic shock. There were more arrhythmias in the dopamine group.[27]

In the VASST study, 778 critically ill patients were randomized to either norepinephrine (NE) plus low-dose vasopressin or norepinephrine only.[26] There was no significant mortality difference between the vasopressin and norepinephrine groups. The conclusion was that the addition of low-dose vasopressin (0.03 units/min) to NE was safe and produced similar outcomes as NE alone. In a rigorous systematic review and meta-analysis, Avni et al. reviewed results from 32 trials (3544 patients).[27] Their analysis found that NE was associated with less mortality compared with dopamine and less major adverse events RR 0.89 (95% CI 0.81–0.98), corresponding to an absolute risk reduction of 11% and number needed to treat of 9. Few trials reported end points such as urine output and blood lactate levels, and when reported, norepinephrine was superior in that regard. Studies included in this systematic review were published in a time span ranging from 1989 to 2012 with very different practice patterns. The current evidence would support the use of norepinephrine over dopamine, with epinephrine and vasopressin as second-line choices.

Timing of Vasopressor Initiation

Few studies have looked into this important issue. In one retrospective cohort study using data from 213 adult septic shock patients there was association between delayed administration of pressor and mortality. Every 1-hour delay in norepinephrine initiation during the first 6 hours after the onset of septic shock onset was associated with an increase of 5.3% in mortality. This could represent earlier recognition of severity of illness and thus indicate the early initiation of salvaging treatments (although the timing of antibiotics was similar in both groups).[27a]

Intravenous Fluids

Important questions to address are the following: What is the type of fluid (crystalloid vs. colloid) to be used in critically ill patients? Is there any difference between different crystalloids? What is the amount needed?

Type of Fluid to Use in Critically Ill Patients

In the more modern era of critical care medicine, three major trials analyzed outcomes differences between albumin and crystalloids therapy. In a substudy from the SAFE trial, the morbidity difference (measured by renal failure, SOFA score) between the patients receiving albumin or crystalloids was similar, but mortality rates were lower for colloids group OR-0.7.[28] In the CRYSTAL Study Annane et al. conducted a multicenter, randomized clinical trial and stratified by case mix (sepsis, trauma, or hypovolemic shock without sepsis or trauma) 2857 sequential ICU patients. The authors found that among ICU patients with hypovolemia, the use of colloids versus crystalloids did not result in a significant difference in 28-day mortality. The 90-day mortality, however, was lower in patients receiving colloids.[29] Finally in the ALBIOS study, 1818 patients with severe sepsis were assigned randomly to receive either 20% albumin and crystalloid or crystalloid alone. Albumin replacement, in addition to crystalloids, did not improve the rate of survival at 28 and 90 days.[30] However, there was a significant difference observed in a posthoc subgroup analysis that included 1121 patients with septic shock, as compared with 660 without septic shock, at the time of enrollment (relative risk with septic shock, 0.87; relative risk without septic shock, 1.13).

The results of these three trials were combined in a meta-analysis with the following conclusions.[31] Compared with crystalloid, a trend toward reduced 90-day mortality was observed in severe sepsis patients resuscitated with albumin (odds ratio [OR] 0.88; 95% CI, 0.76 to 1.01; p = .08). However, the use of albumin for resuscitation significantly decreased 90-day mortality in septic shock patients (OR 0.81; 95% CI, 0.67 to 0.97; p = .03). Compared with saline, the use of albumin for resuscitation slightly improved outcome in severe sepsis patients (OR 0.81; 95% CI, 0.64 to 1.08; p = .09). Starches (hydroxyethyl starch as well as pentastarch) are no longer recommended for fluid resuscitation after multiple studies showed either increased mortality or increased renal failure.[31–33]

Difference Between Crystalloids

The potential harm of chloride-rich fluids has been the impetus for some experts to advocate for the use of more balanced intravenous solution. The impact of such a practice on organ function and mortality has been analyzed in several studies.

In a prospective study, Yunos et al. compared the outcomes of patients treated with a chloride-liberal or a chloride restrictive fluid strategy.[34] The authors did not find any differences in mortality or length of stay (LOS), but there was a significantly less risk, injury, failure, loss, and end-stage renal disease (RIFLE)-defined acute kidney injury (AKI) as well as in-hospital need to RRT in the chloride-restricted group.[35] In a follow-up study the authors extended their observation period to 12 months, and their results were sustained with less AKI (20.5 vs. 15.7%) and less need for RRT (9.8% vs. 6.8 %).[36]

In another retrospective cohort study 53,000 outcomes in septic patients were compared based on whether or balanced fluids were administered. Receipt of balanced fluids was associated with lower in-hospital mortality (19.6% vs. 22.8%; relative risk, 0.86; 95% CI, 0.78, 0.94), and there was a proportional response with patients receiving larger amount of balanced fluids having an even lower mortality.[37]

Finally, in a retrospective cohort study of 60,734 patients in 360 ICUs across the United States, outcomes of patients treated with different fluid combinations were compared. Patients were categorized into four groups: those who received isotonic saline alone, those receiving saline in combination with balanced crystalloids, those receiving saline in combination with colloids, and those receiving saline in combination with balanced crystalloids and colloids. Hospital mortality was the lowest in the saline and balanced crystalloid group (17.7%), followed by the saline in combination with balanced crystalloids and colloid (19.2%), the exclusive saline (20.2%), and finally the saline plus colloid (24.2%). The administration of isotonic saline exclusively yielded a higher mortality than the coadministration of balanced solutions.[34]

When systematically reviewed, these findings were confirmed in a meta-analysis.[38]

Amount of Fluid and Potential Harm

In the initial phase of treatment, rapid infusion of fluid is usually needed, but overzealous and uncontrolled administration in patients at risk can result in adverse events such as hypoxemia respiratory failure. In the FACTT study the authors compared a conservative (central venous pressure (CVP) 4 mm Hg or less) and a liberal strategy (CVP 10-14) of fluid management in 1000 patients with acute lung injury. There was no significant difference in the primary outcome of 60-day mortality, but the conservative strategy of fluid management resulted in a lower duration of mechanical ventilation and length of stay in the intensive care.[39] In another analysis from the same cohort, the authors focused on the renal impact of such a practice. Of the 306 patients that developed AKI in the first 2 study days, 137 were in the fluid-liberal arm and 169 in the fluid-conservative arm (p = .04). In addition, a positive fluid balance in those patients was significantly associated with mortality in crude and adjusted analysis.[40]

In addition to its negative effect on lung and kidney, excessive fluid can increase intraabdominal pressure and increase postoperative complications after major surgery.[41]

A review of the consequences on specific organ consequences has been summarized by others.[42]

In addition to the direct effect of fluid accumulation, worsening renal function can be masked by diluting the creatinine level and therefore delaying recognition by the clinician. In a fascinating study, Liu et al. analyzed the classification and outcomes of critically ill patients

before and after adjustment for fluid balance. In that study the authors identified a group of patients who met acute kidney injury criteria after adjustment of creatinine for fluid balance (but not before). These patients had a significantly higher mortality than patients without renal failure.[43]

In a cohort study of 1453 patients from 35 ICUs in Australia and New Zealand, Bellomo et al. analyzed the association between daily fluid balance and clinical outcomes. Patients who survived the ICU stay had a lower mean daily and cumulative fluid balance (–234 mL/day, –1941 mL) compared with the nonsurvivors (+560 mL/day, +1755 mL). A negative mean daily fluid balance during study treatment was independently associated with improved clinical outcomes: mortality, length of stay, and less need for dialysis.[44]

In another study, after correcting for age and Acute Physiology and Chronic Health Evaluation II (APACHE II) score, a more positive fluid balance at both 12 hours and day 4 of ICU stay correlated significantly with increased mortality.[45]

During the early course of septic shock, traditional therapy has included aggressive fluid resuscitation to minimize vasopressors. However, the association of poor outcome with high input/output (I/O) ratios has been reported. Although some would link this association to poor outcome with overly aggressive fluid administration, patients with more severe sepsis would be predicted to need more fluid to maintain optimum intravascular volume in the presence of more severe venodilation and more severe capillary leak. Whether higher I/O ratios represent an association or cause and effect is unknown. It is likely that too much fluid resuscitation and too little fluid resuscitation are both possible in this patient population. There is likely a right combination of fluid and vasopressors to maintain mean arterial pressure in each patient. Currently we have very little in our armamentarium to know the correct combination of these two therapies in an individual patient. Although aggressive fluid resuscitation may save lives early by preventing cardiovascular deaths and increasing tissue perfusion to organs at risk, there is likely a price to pay once the patient is stabilized as fluid remains in the extravascular spaces and lingers there after the bacteria and toxins are cleared. Beyond that initial phase of fluid administration, the clinician constantly should reassess whether patients would benefit from fluid administration using dynamic indices such as passive leg raising test, end-expiratory occlusion test, fluid challenge, or pulse pressure variation analysis.[46]

Fluid Administration Regimen

The basic tenet of critical care in the first hours of sepsis is to improve cardiac output to ensure oxygen delivery and fluid administration must be given as bolus. Past the initial phase, need for fluid must be constantly reassessed. The ROSE model for fluid management was proposed by Hoste et al. as they divided resuscitation into four phases: a resuscitation phase, optimization phase, stabilization phase, and evacuation phase (Fig. 91.1). In the first phase (R for resuscitation) characterized by low cardiac output, capillary leak, and venodilation, the aim would be to achieve adequate rapid correction of macrodynamic parameters: MAP ≥ 65, and optimization of cardiac output using rapid administration of fluids. In the second phase (O for optimization phase) the goal is to improve tissue perfusion and carefully administer fluids. In that phase fluid administration should be considered as a marker of severity of illness.[47] The clinician must optimize macrodynamic end points, but fluid balance, urine output, and intraabdominal pressure should be monitored as well. The optimization ("unstable") phase is followed by a stabilization phase, during which the clinician needs to aim for even fluid balance. Finally in the evacuation phase the goal is to remove excess fluid. This can be achieved by the patient, using diuretics or even dialysis as needed (Table 91.1).[48]

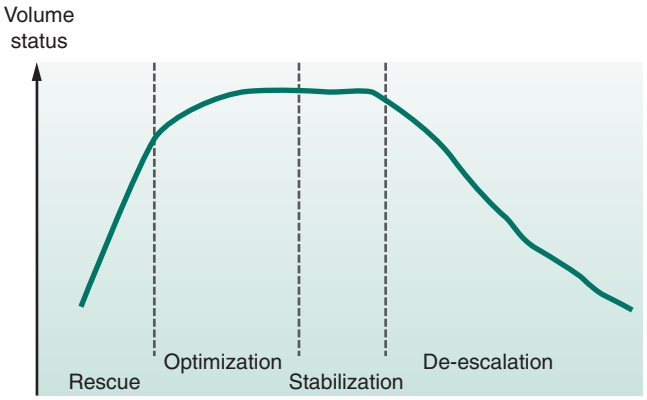

FIGURE 91.1 Phases of the ROSE model of resuscitation. (From Hoste EA, Maitland K, Brudney CS, Mehta R, Vincent JL, Yates D, Kellum JA, Mythen MG, Shaw AD. Four phases of intravenous fluid therapy: A conceptual model. *Br J Anaesthes.* 2014;113[5]:740–747, with permission.)

STEROIDS IN THE TREATMENT OF SEPSIS

Treatment with corticosteroids for sepsis has been advocated by some but remains a controversial topic. Although an earlier trial from France showed a decrease in mortality in some patients, these findings were not confirmed in a large multicenter study.[49,50] Meta-analyses including different trials concluded that even though the impact on mortality was unclear, there is some evidence to support its use for shock reversal in patients on high-dose/multiple pressor.[51,52]

RESUSCITATION END POINTS

In the first minutes to hours of management of sepsis, clinicians should aim to improve macrodynamic parameters such as mean arterial pressure and cardiac output. As time passes, however, the focus should shift toward other end points that are more indicative of adequacy of tissue perfusion. In the initial "early goal-directed therapy" study from Rivers, resuscitation end points that must be optimized were central venous pressure and $ScvO_2$.[53]

Over the last decade targeting these measures was shown to be nonessential for successful resuscitation. The CVP initially was used as a surrogate measure of adequate fluid resuscitation. Unfortunately owing to the static nature of this measure as well as its poor discrimination regarding patients who would or would not benefit from additional fluids, this end point is less preferred than more dynamic assessment of fluid responsiveness.[54–57] The $ScVO_2$ has been used as a surrogate marker for adequacy of perfusion and a normal value of 70% or greater was considered an appropriate resuscitation endpoint. A low $ScVO_2$ would identify a group of patients in whom an increase in cardiac output (improved oxygen delivery) would be expected to raise central venous oxygen saturation ($ScvO_2$). However, $ScvO_2$ is not a good marker for fluid responsiveness.[58] Findings from

TABLE 91.1

Characteristics of Different Stages of Resuscitation: 'Fit for Purpose Fluid Therapy'. GDT, Goal Directed Therapy; DKA, Diabetic Keto Acidosis; NPO, Nil Per Os; ATN, Acute Tubular Necrosis; SSC, Surviving Sepsis Campaign

	RESCUE	OPTIMIZATION	STABILIZATION	DE-ESCALATION
Principles	Lifesaving	Organ rescue	Organ support	Organ recovery
Goals	Correct shock	Optimize and maintain tissue perfusion	Aim for zero or negative fluid balance	Mobilize fluid accumulated
Time (usual)	Minutes	Hours	Days	Days to weeks
Phenotype	Severe shock	Unstable	Stable	Recovering
Fluid therapy	Rapid boluses	Titrate fluid infusion conservative use of fluid challenges	Minimal maintenance infusion only if oral intake inadequate	Oral intake if possible Avoid unnecessary i.v. fluids
Typical clinical scenario	• Septic shock • Major trauma	• Intraoperative GDT • Burns • DKA	• NPO postoperative patient • 'Drip and suck' management of pancreatitis	• Patient on full enteral feed in recovery phase of critical illness • Recovering ATN
Amount	Guidelines, for example, SSC, pre-hospital resuscitation, trauma, burns, etc.			

Process, ARISE, and PROMISE show that resuscitation can be just as successful without the use of $ScvO_2$. We believe that $ScVO_2$ still has a place in management of critically ill patients in conjunction with other markers (such as lactate or dynamic measures of fluid responsiveness).

Targeting a hematocrit goal of 30% has been shown to have no impact on mortality or ischemic events, and findings from the TRICC and the TRISS trial indicate that using a threshold of 7 g/dL for blood transfusion is adequate for septic patients.[59,60]

Other alternative targets also were studied during the last decade. In a multicenter randomized, noninferiority trial patients with severe sepsis or septic shock were assigned randomly to resuscitation protocols of either an $ScVO_2$ of 70% or greater or a lactate clearance of 10% or more. The authors enrolled 300 patients, and the outcomes in each group were similar.[61]

Microvascular dysfunction when assessed using sublingual imaging has been shown to be a strong mortality predictor in septic patients. [62] Microcirculation assessment is a sophisticated bedside skill and to date is limited to research trials. Furthermore, attempts to use treatments (such as nitroglycerin) aimed at optimizing microcirculation have failed to be successful. [63]

Protocolized Versus Usual Care

Since the launch of the first Surviving Sepsis Campaign (SSC) guidelines (2004) in the aftermath of the landmark Rivers trial, an associated improvement in outcomes on all continents has been observed. A study that looked at data from 165 centers across United States, Europe, and South America found that over time, compliance with SSC sepsis performance improvement bundles increased while mortality rates decreased with 5.4% less mortality for centers that implemented the program over 2 years.[64]

In a meta-analysis of 50 observational studies from multiple countries over an extensive period of time, Damiani et al. showed that adherence to SSC guidelines via a performance improvement process resulted in lower mortality.[65] In their analysis the authors found that those institutions with increased compliance with sepsis bundles had an associated reduction in mortality (OR = 0.66 [0.61–0.72]).[65]

Three major randomized controlled studies have compared combinations of protocolized care and "usual care."

PROCESS Study

In 31 emergency departments in the United States, 1341 patients were assigned to one of three treatment groups: protocol-based traditional Early Goal Directed Therapy (EGDT), protocol-based standard therapy, and to usual care. There were significant differences in regard to amount of fluid and blood transfusion administered, and use of vasopressors and inotropic agents. However, mortality end points were no different.[66]

ARISE Trial

Peake et al. randomly assigned septic patients presenting to the emergency department in one of the 51 centers (mainly in Australia and New Zealand) to receive either traditional EGDT or usual care. 1600 patients were included in the trial and similarly to the PROCESS trial the patients assigned to the EGDT group received more IV fluids, vasopressors, inotropes, and transfusions. Also similarly, mortality was not different.[67]

PROMISE Study

1260 patients from 56 hospitals in England were assigned randomly to receive either EGDT or usual care. Again like the two previous trials, more resources were used in the EGDT group with mortality outcome not different.[68]

How do we reconcile the findings of those three major studies with that of the results from the quality improvement project?

First, it is possible that, when analyzed in the rigorous context of a research study, results may not be translatable to real world practice. The story of glycemic control is a prime example in which strict blood sugar control was found beneficial in controlled studies but detrimental when applied to real world situations.[69]

Second, it is possible that parts of the SSC sepsis bundle may not be as useful as others, but taken together, the overall adherence to the bundle does lead to improved outcomes.

Third, a one-size-fits-all approach in the care of critically ill patients is not ideal, and what possibly would work in some may not be good for others. This would point to the

importance of individualizing care with the use of dynamic variables and bedside clinical evaluation.

Finally, since the publication of the Rivers study as well as the SSC guidelines there has been a huge increase in public and healthcare teams' awareness of the importance of early aggressive therapy to avoid dire consequences of sepsis. There is little doubt that practitioners feel more familiar with the concepts and methodology and reasoning in treating septic patients over the last 10 years, and this may be a primary determinant of improved outcomes.

Key Points

1. Early antibiotics administration (within 1 hour of identification) may improve survival of septic patients.
2. In patients with septic shock, clinicians should use norepinephrine as the preferred vasopressor and should aim for a mean arterial pressure of 65 mm Hg in most patients.
3. Administration of crystalloids confers similar outcomes compared with colloids in most patients with sepsis with the exception of patients with septic shock, in whom colloids may provide an advantage. After the initial phase of resuscitation, needs for fluids should be reassessed frequently to minimize side effects.
4. Resuscitation should be individualized with the use of dynamic variables and bedside clinical evaluation.

Key References

9. Dellinger RP, Levy MM, Rhodes A, et al. Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock, 2012. *Intensive Care Med*. 2013;39(2): 165-228.
17. Kumar A, Roberts D, Wood KE, et al. Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock. *Crit Care Med*. 2006;34(6):1589-1596.
45. Boyd JH, Forbes J, Nakada TA, et al. Fluid resuscitation in septic shock: a positive fluid balance and elevated central venous pressure are associated with increased mortality. *Crit Care Med*. 2011;39(2):259-265.
48. Hoste EA, Maitland K, Brudney CS, et al. Four phases of intravenous fluid therapy: a conceptual model. *Br J Anaesth*. 2014;113(5):740-747.

A complete reference list can be found online at ExpertConsult.com.

References

1. Angus DC, Linde-Zwirble WT, Lidicker J, et al. Epidemiology of severe sepsis in the United States: analysis of incidence, outcome, and associated costs of care. *Crit Care Med*. 2001;29(7): 1303-1310.
2. Lagu T, Rothberg MB, Shieh MS, et al. Hospitalizations, costs, and outcomes of severe sepsis in the United States 2003 to 2007. *Crit Care Med*. 2012;40(3):754-761.
3. Winters BD, Eberlein M, Leung J, et al. Long-term mortality and quality of life in sepsis: a systematic review. *Crit Care Med*. 2010;38(5):1276-1283.
4. Danai P, Martin GS. Epidemiology of sepsis: recent advances. *Curr Infect Dis Rep*. 2005;7(5):329-334.
5. Angus DC, van der Poll T. Severe sepsis and septic shock. *N Engl J Med*. 2013;369(9):840-851.
6. Dombrovskiy VY, Martin AA, Sunderram J, et al. Rapid increase in hospitalization and mortality rates for severe sepsis in the United States: a trend analysis from 1993 to 2003. *Crit Care Med*. 2007;35(5):1244-1250.
7. Deleted in review.
8. Deleted in review.
9. Deleted in review.
10. Bone RC, Balk RA, Cerra FB, et al. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. The ACCP/SCCM Consensus Conference Committee. American College of Chest Physicians/Society of Critical Care Medicine. *Chest*. 1992;101(6):1644-1655.
11. Levy MM, Fink MP, Marshall JC, et al. 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. *Crit Care Med*. 2003;31(4):1250-1256.
12. Singer M, Deutschman CS, Seymour CW, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *JAMA*. 2016;315(8):801-810.
13. Ibrahim EH, Sherman G, Ward S, et al. The influence of inadequate antimicrobial treatment of bloodstream infections on patient outcomes in the ICU setting. *Chest*. 2000;118(1): 146-155.
14. Garnacho-Montero J, Garcia-Garmendia JL, Barrero-Almodovar A, et al. Impact of adequate empirical antibiotic therapy on the outcome of patients admitted to the intensive care unit with sepsis. *Crit Care Med*. 2003;31(12):2742-2751.
15. Garnacho-Montero J, Gutierrez-Pizarraya A, Escoresca-Ortega A, et al. De-escalation of empirical therapy is associated with lower mortality in patients with severe sepsis and septic shock. *Intensive Care Med*. 2014;40(1):32-40.
16. Ng K, Schorr C, Reboli AC, et al. Incidence and mortality of sepsis, severe sepsis, and septic shock in intensive care unit patients with candidemia. *Infect Dis (Lond)*. 2015;47(8):584-587.
17. Kumar A, Roberts D, Wood KE, et al. Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock. *Crit Care Med*. 2006;34(6):1589-1596.
18. Ferrer R, Martin-Loeches I, Phillips G, et al. Empiric antibiotic treatment reduces mortality in severe sepsis and septic shock from the first hour: results from a guideline-based performance improvement program. *Crit Care Med*. 2014;42(8):1749-1755.
19. Puskarich MA, Trzeciak S, Shapiro NI, et al. Association between timing of antibiotic administration and mortality from septic shock in patients treated with a quantitative resuscitation protocol. *Crit Care Med*. 2011;39(9):2066-2071.
20. Vilella AL, Seifert CF. Timing and appropriateness of initial antibiotic therapy in newly presenting septic patients. *Am J Emerg Med*. 2014;32(1):7-13.
21. Sterling SA, Miller WR, Pryor J, et al. The Impact of Timing of Antibiotics on Outcomes in Severe Sepsis and Septic Shock: A Systematic Review and Meta-Analysis. *Crit Care Med*. 2015; 43(9):1907-1915.
22. Venkatesh AK, Avula U, Bartimus H, et al. Time to antibiotics for septic shock: evaluating a proposed performance measure. *Am J Emerg Med*. 2013;31(4):680-683.
23. Villar J, Clement JP, Stotts J, et al. Many emergency department patients with severe sepsis and septic shock do not meet diagnostic criteria within 3 hours of arrival. *Ann Emerg Med*. 2014;64(1):48-54.
24. Correa TD, Vuda M, Takala J, et al. Increasing mean arterial blood pressure in sepsis: effects on fluid balance, vasopressor load and renal function. *Crit Care*. 2013;17(1):R21.
25. LeDoux D, Astiz ME, Carpati CM, et al. Effects of perfusion pressure on tissue perfusion in septic shock. *Crit Care Med*. 2000;28(8):2729-2732.
26. Asfar P, Meziani F, Hamel JF, et al. High versus low blood-pressure target in patients with septic shock. *N Engl J Med*. 2014;370(17):1583-1593.
27. De Backer D, Biston P, Devriendt J, et al. Comparison of dopamine and norepinephrine in the treatment of shock. *N Engl J Med*. 2010;362(9):779-789.

27a. Bai X, Yu W, Ji W, et al. Early versus delayed administration of norepinephrine in patients with septic shock. *Crit Care*. 2014;18:532.

28. Finfer S, McEvoy S, Bellomo R, et al. Impact of albumin compared to saline on organ function and mortality of patients with severe sepsis. *Intensive Care Med*. 2011;37(1):86-96.
29. Annane D, Siami S, Jaber S, et al. Effects of fluid resuscitation with colloids vs crystalloids on mortality in critically ill patients presenting with hypovolemic shock: the CRISTAL randomized trial. *JAMA*. 2013;310(17):1809-1817.
30. Caironi P, Tognoni G, Masson S, et al. Albumin replacement in patients with severe sepsis or septic shock. *N Engl J Med*. 2014;370(15):1412-1421.
31. Brunkhorst FM, Oppert M. Nephrotoxicity of hydroxyethyl starch solution. *Br J Anaesth*. 2008;100(6):856, author reply 856-857.
32. Perner A, Haase N, Guttormsen AB, et al. Hydroxyethyl starch 130/0.42 versus Ringer's acetate in severe sepsis. *N Engl J Med*. 2012;367(2):124-134.
33. Brunkhorst FM, Engel C, Bloos F, et al. Intensive insulin therapy and pentastarch resuscitation in severe sepsis. *N Engl J Med*. 2008;358(2):125-139.
34. Raghunathan K, Bonavia A, Nathanson BH, et al. Association between Initial Fluid Choice and Subsequent In-hospital Mortality during the Resuscitation of Adults with Septic Shock. *Anesthesiology*. 2015;123(6):1385-1393.
35. Yunos NM, Bellomo R, Hegarty C, et al. Association between a chloride-liberal vs chloride-restrictive intravenous fluid administration strategy and kidney injury in critically ill adults. *JAMA*. 2012;308(15):1566-1572.
36. Yunos NM, Bellomo R, Glassford N, et al. Chloride-liberal vs. chloride-restrictive intravenous fluid administration and acute kidney injury: an extended analysis. *Intensive Care Med*. 2015;41(2):257-264.
37. Raghunathan K, Shaw A, Nathanson B, et al. Association between the choice of IV crystalloid and in-hospital mortality among critically ill adults with sepsis*. *Crit Care Med*. 2014;42(7):1585-1591.
38. Rochwerg B, Alhazzani W, Sindi A, et al. Fluid resuscitation in sepsis: a systematic review and network meta-analysis. *Ann Intern Med*. 2014;161(5):347-355.
39. Wiedemann HP, Wheeler AP, Bernard GR, et al. Comparison of two fluid-management strategies in acute lung injury. *N Engl J Med*. 2006;354(24):2564-2575.
40. Grams ME, Estrella MM, Coresh J, et al. Fluid balance, diuretic use, and mortality in acute kidney injury. *Clin J Am Soc Nephrol*. 2011;6(5):966-973.
41. Brandstrup B, Tonnesen H, Beier-Holgersen R, et al. Effects of intravenous fluid restriction on postoperative complications: comparison of two perioperative fluid regimens: a randomized assessor-blinded multicenter trial. *Ann Surg*. 2003;238(5): 641-648.
42. Marik PE. Iatrogenic salt water drowning and the hazards of a high central venous pressure. *Ann Intensive Care*. 2014; 4:21.
43. Liu KD, Thompson BT, Ancukiewicz M, et al. Acute kidney injury in patients with acute lung injury: impact of fluid accumulation on classification of acute kidney injury and associated outcomes. *Crit Care Med*. 2011;39(12):2665-2671.
44. Bellomo R, Cass A, Cole L, et al. An observational study fluid balance and patient outcomes in the Randomized Evaluation of Normal vs. Augmented Level of Replacement Therapy trial. *Crit Care Med*. 2012;40(6):1753-1760.

45. Boyd JH, Forbes J, Nakada TA, et al. Fluid resuscitation in septic shock: a positive fluid balance and elevated central venous pressure are associated with increased mortality. *Crit Care Med*. 2011;39(2):259-265.
46. Monnet X, Teboul JL. Assessment of volume responsiveness during mechanical ventilation: recent advances. *Crit Care*. 2013;17(2):217.
47. Bagshaw SM, Brophy PD, Cruz D, et al. Fluid balance as a biomarker: impact of fluid overload on outcome in critically ill patients with acute kidney injury. *Crit Care*. 2008;12(4):169.
48. Hoste EA, Maitland K, Brudney CS, et al. Four phases of intravenous fluid therapy: a conceptual model. *Br J Anaesth*. 2014;113(5):740-747.
49. Annane D, Sebille V, Charpentier C, et al. Effect of treatment with low doses of hydrocortisone and fludrocortisone on mortality in patients with septic shock. *JAMA*. 2002;288(7):862-871.
50. Sprung CL, Annane D, Keh D, et al. Hydrocortisone therapy for patients with septic shock. *N Engl J Med*. 2008;358(2):111-124.
51. Annane D, Bellissant E, Bollaert PE, et al. Corticosteroids in the treatment of severe sepsis and septic shock in adults: a systematic review. *JAMA*. 2009;301(22):2362-2375.
52. Sligl WI, Milner DA Jr, Sundar S, et al. Safety and efficacy of corticosteroids for the treatment of septic shock: A systematic review and meta-analysis. *Clin Infect Dis*. 2009;49(1):93-101.
53. Rivers E, Nguyen B, Havstad S, et al. Early goal-directed therapy in the treatment of severe sepsis and septic shock. *N Engl J Med*. 2001;345(19):1368-1377.
54. Marik PE, Baram M, Vahid B. Does central venous pressure predict fluid responsiveness? A systematic review of the literature and the tale of seven mares. *Chest*. 2008;134(1):172-178.
55. Nagdev AD, Merchant RC, Tirado-Gonzalez A, et al. Emergency department bedside ultrasonographic measurement of the caval index for noninvasive determination of low central venous pressure. *Ann Emerg Med*. 2010;55(3):290-295.
56. Muller L, Toumi M, Bousquet PJ, et al. An increase in aortic blood flow after an infusion of 100 ml colloid over 1 minute can predict fluid responsiveness: the mini-fluid challenge study. *Anesthesiology*. 2011;115(3):541-547.
57. Duus N, Shogilev DJ, Skibsted S, et al. The reliability and validity of passive leg raise and fluid bolus to assess fluid responsiveness in spontaneously breathing emergency department patients. *J Crit Care*. 2015;30(1):217.e211-217.e215.
58. Teboul JL, Hamzaoui O, Monnet X. SvO2 to monitor resuscitation of septic patients: let's just understand the basic physiology. *Crit Care*. 2011;15(6):1005.
59. Holst LB, Haase N, Wetterslev J, et al. Lower versus higher hemoglobin threshold for transfusion in septic shock. *N Engl J Med*. 2014;371(15):1381-1391.
60. Hebert PC, Wells G, Blajchman MA, et al. A multicenter, randomized, controlled clinical trial of transfusion requirements in critical care. Transfusion Requirements in Critical Care Investigators, Canadian Critical Care Trials Group. *N Engl J Med*. 1999;340(6):409-417.
61. Jones AE, Shapiro NI, Trzeciak S, et al. Lactate clearance vs central venous oxygen saturation as goals of early sepsis therapy: a randomized clinical trial. *JAMA*. 2010;303(8):739-746.
62. Trzeciak S, Dellinger RP, Parrillo JE, et al. Early microcirculatory perfusion derangements in patients with severe sepsis and septic shock: relationship to hemodynamics, oxygen transport, and survival. *Ann Emerg Med*. 2007;49(1):88-98, 98.e81-82.
63. Boerma EC, Koopmans M, Konijn A, et al. Effects of nitroglycerin on sublingual microcirculatory blood flow in patients with severe sepsis/septic shock after a strict resuscitation protocol: a double-blind randomized placebo controlled trial. *Crit Care Med*. 2010;38(1):93-100.
64. Levy MM, Dellinger RP, Townsend SR, et al. The Surviving Sepsis Campaign: results of an international guideline-based performance improvement program targeting severe sepsis. *Crit Care Med*. 2010;38(2):367-374.
65. Damiani E, Donati A, Serafini G, et al. Effect of performance improvement programs on compliance with sepsis bundles and mortality: a systematic review and meta-analysis of observational studies. *PLoS ONE*. 2015;10(5):e0125827.
66. Yealy DM, Kellum JA, Huang DT, et al. A randomized trial of protocol-based care for early septic shock. *N Engl J Med*. 2014;370(18):1683-1693.
67. Peake SL, Delaney A, Bailey M, et al. Goal-directed resuscitation for patients with early septic shock. *N Engl J Med*. 2014;371(16):1496-1506.
68. Mouncey PR, Osborn TM, Power GS, et al. Trial of early, goal-directed resuscitation for septic shock. *N Engl J Med*. 2015;372(14):1301-1311.
69. Preiser JC. NICE-SUGAR: the end of a sweet dream? *Crit Care*. 2009;13(3):143.