Journal of
Blood Disorders & Transfusion

Tannehill, J Blood Disord Transfus 2012, S4
DOI: 10.4172/2155-9864.S4-002

Rapid Communication Open Access

Treating Severe Sepsis & Septic Shock in 2012

David Tannehill*

Department of Critical Care Medicine, Saint Louis University, Mercy Hospital, USA

Severe sepsis and septic shock are common, complicated & deadly conditions within the same pathophysiologic spectrum. As defined by the American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference in 1992, this spectrum begins with the Systemic Inflammatory Response Syndrome or SIRS. SIRS is defined as the presence of two of four abnormal findings: temperature >38°C or <36°C, white blood cell count >12,000/cu mm or <4,000/cu mm or >10% immature "band" forms, heart rate >90 beats per minute, respiratory rate >20 breaths per minute or partial pressure of arterial carbon dioxide <32 mmHg. If a clinician feels that a patient is exhibiting SIRS secondary to infection, that patient has sepsis. If that same patient has signs or symptoms of organ dysfunction, then that patient has Severe Sepsis. Septic Shock is then characterized by global tissue hypoperfusion, tissue hypoxia or frank hypotension defined as a mean arterial pressure less than 65 mmHg or systolic blood pressure less than 90 mmHg that fails to respond to a 20 mL/kg fluid bolus of crystalloid or colloid [1].

Severity of illness and the inherent mortality risk escalate from SIRS, through sepsis, severe sepsis and septic shock to multi-organ failure. Mortality estimates vary, but Severe Sepsis and Septic Shock carry high potential mortality rates, possibly up to 46% [2]. The number of sepsis-related ICU admissions is steadily increasing over time [3,4]. Since 2001, treatment of this condition has evolved and we continue to learn more about strategies to help save more patients. The Surviving Sepsis Campaign (SSC) [5,6], first described in 2004, updated in 2008 and the soon to be released 2012 update, provide a uniform set of guidelines to help clinicians care for these patients utilizing the best evidence-based approach to improve outcomes. Healthcare organizations, hospitals, professional organizations, the Institute for Healthcare Improvement, industry, etc. have all adopted elements, if not the entire Surviving Sepsis Campaign Guidelines to formulate a blueprint for standards to which hospitals, departments and even individual physicians can be measured.

Therefore, it seems that the process of caring for these patients has become just as, if not more important than the intravenous fluids & antibiotics that are prescribed. This multidisciplinary & incredibly complex process of care should receive the kind of attention given to the processes of care for acute myocardial infarction, stroke & trauma, because the impact on outcomes is potentially just as striking. This review will describe the various elements of the initial management strategies described by the SSC, as well as potential areas of controversy and investigation. Articles were selected by the author after reviewing the title and/or abstracts from a list of articles derived from a PubMed search using the MeSH terms *sepsis or septic shock*. Additional articles were selected because they have been referenced by the *Surviving Sepsis Campaign* or by articles selected in the original search. The primary focus of this review is on data that has been published since 2001 and since the 2008 update to the SSC guidelines.

Early Goal-Directed Therapy (Figure 1)

The cornerstone of The Surviving Sepsis Campaign and one of the key tools for improving outcomes is Early Goal-Directed Therapy (EGDT), as described by Dr. Rivers [7]. This step-wise resuscitation algorithm was shown in the original paper to have a number needed to treat of six, and an absolute risk reduction for mortality of 16% [7]. However, compliance with not only completing the various steps in the algorithm, but with using EGDT at all is not good [8,9]. The reason for this is simple– it is difficult to do, and even more difficult to complete within the requisite six hours as described in the original paper.

However, there may be other reasons why compliance is poor. The primary measure of the first goal to be achieved, a Central Venous Pressure (CVP) of 8-12 mmHg, is felt by some to be flawed. As described by Marik et al. [10,11], CVP is a poor overall marker of volume status and volume responsiveness. The intent, of course, of achieving this goal CVP is to ensure adequate preload to optimize hemodynamics. Using this goal CVP in the first six hours the treatment group did end up receiving, on average, 1.5 L more IVF than the standard therapy group in Dr. Rivers et al. [7] original study. At 72 hours, the two groups had received an equal amount of total volume. This suggests some benefit of using CVP as a "preload marker" during initial resuscitation.

The main reason why CVP is still referenced in the Surviving Sepsis Campaign guidelines is because no other preload marker has been adequately studied in this context. But that is not to say that there are no alternatives. One could argue that any number of surrogate markers for potentially inadequate preload, or persistent volume responsiveness, could be substituted for CVP. Pulse pressure variation is one tool that may have merit; however, it is complicated by the requirement that the patient be receiving controlled mechanical ventilation without spontaneous respiratory efforts and at tidal volumes not typically used in today's ICUs [9]. Of similar utility, but also with similar restrictions is various parameters observed with bedside echocardiography, including respiratory variability of both the inferior and superior vena cava [12-19] and collapsibility of the left ventricle at the level of the papillary muscles [20]. Passive leg raising is a simple maneuver that does not require specialized equipment or expertise and has been shown to reliably predict fluid responsiveness [21,22]. Newly available devices have been shown to accurately predict volume responsiveness by utilizing noninvasive bioreactance [23,24]. Any one or a combination of these tools could certainly be utilized for helping to achieve the goal of the first step of EGDT – adequate preload.

The next step, achieving a Mean Arterial Pressure (MAP) of 65-90 mmHg, is fairly straightforward. When hypotension is present, this goal should be achieved with IVF if hypovolemia or preload responsiveness persists, but vasopressor support may be needed as

***Corresponding author:** David Tannehill, DO, Assistant Clinical Professor of Medicine, Physician, Department of Critical Care Medicine, Saint Louis University, Mercy Hospital, St. Louis, 625 S. New Ballas Road, Suite 2020, St. Louis, MO 63141, USA, Tel: (314) 402-8244; E-mail: dtannehill87@gmail.com

Received July 16, 2012; **Accepted** August 07, 2012; **Published** August 09, 2012

Citation: Tannehill D (2012) Treating Severe Sepsis & Septic Shock in 2012. J Blood Disord Transfus S4:002. doi:10.4172/2155-9864.S4-002

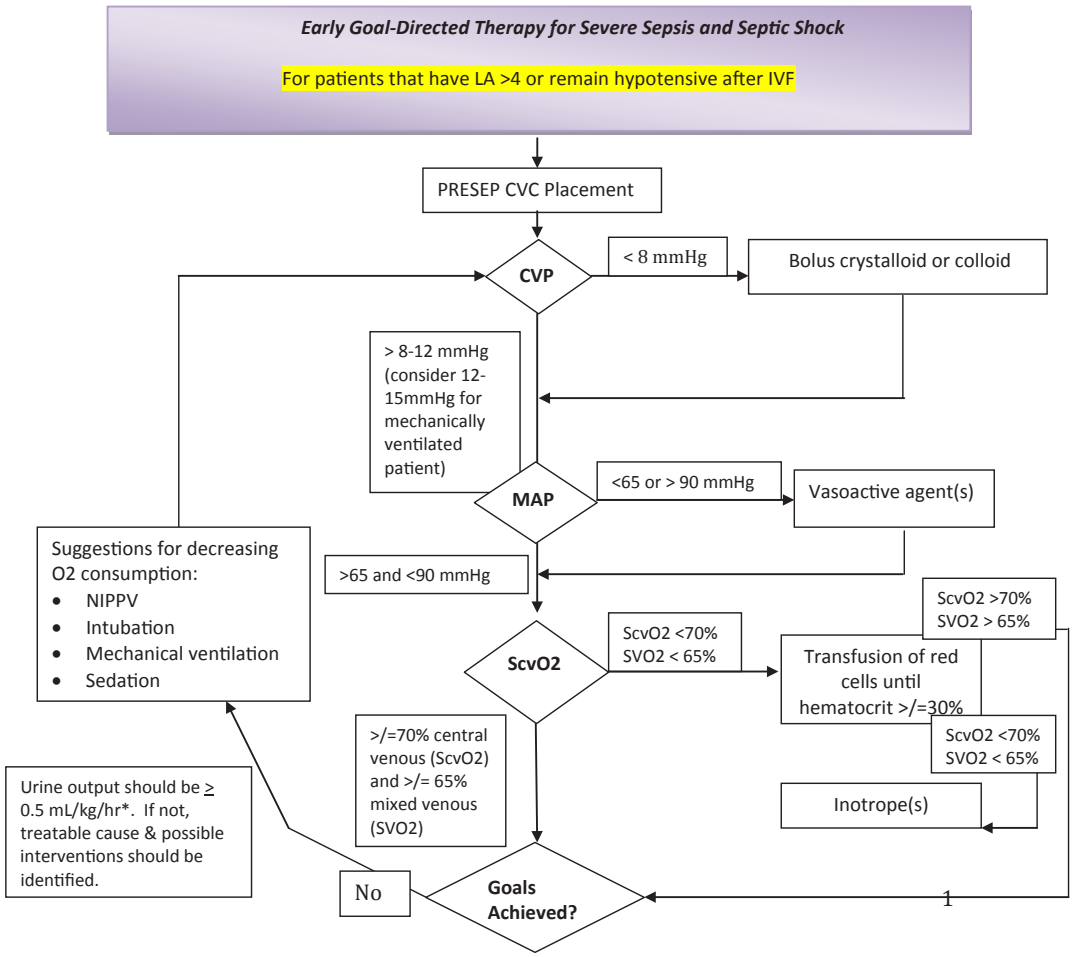

Figure 1: Early Goal-Directed Therapy for Severe Sepsis and Septic Shock.

well. Generally, the options are norepinephrine or dopamine with epinephrine, phenylephrine and vasopressin being second line agents [25]. In 1993, Martin et al. [26] suggested that norepinephrine was three times better at achieving certain hemodynamic and oxygen transport goals within six hours. The SSC guidelines favor norepinephrine [6] and there have been studies since the 2008 update to bolster that preference. De Backer et al. and Patel et al. in separate studies, demonstrated that when compared to norepinephrine, dopamine use lead to a higher rate of adverse events and a nonsignificant trend toward higher mortality [27,28]. De Backer et al. [29] again looked at this question in a meta-analysis, focusing only on those patients with septic shock and again showed that dopamine was associated with more arrhythmias, confirming a suggestion from a Cochrane Review [30]. But importantly, the data from the randomized trials analyzed in De Backer's meta-analysis suggested dopamine was also associated with higher mortality [29]. A similar systematic review published online a year earlier yielded similar results [31]. The editorialist for De Backer et al. [29] meta-analysis wrote, "In practice, physicians should take into account the evidence accumulated from the six randomized trials and should consider using norepinephrine as the first choice vasopressor for sepsis" [32]. This editorialist does suggest that dopamine could be useful if the septic patient has a low cardiac index or inappropriately low heart rate, as dopamine does provide more β-agonist activity [32].

Rarely, a patient with severe sepsis will actually be hypertensive and have a mean arterial pressure greater than 90 mmHg. It is important to note that this does happen and requires intervention, just the same as the hypotensive patient. 23 patients (9%) in the original EGDT trial presented in this way [7,33] and all of these patients had a preexisting cardiac history and were treated with intravenous nitroglycerin to lower their MAP below 90 mmHg [7,33]. Intravenous nitroglycerin was shown in one study by Spronk et al. [34] to recruit microvascular beds in septic and cardiogenic shock patients, providing physiologic evidence supporting a positive benefit of this therapy. However, a study by Boerma et al. [35] has cast some doubt on this idea. It should be remembered that severe sepsis patients who presented with hypertension had a higher mortality rate [33].

Once CVP and MAP are at goal, the clinician's attention should then turn to the central venous oxygen saturation, ScvO2 [6,7]. This intervention decision point is between the additions of dobutamine versus transfusing blood if the ScvO2 is less than 70%. For a hematocrit less than 30%, blood is to be transfused. Transfusion guidelines in critical care suggest an overall conservative approach to blood transfusion; however, within those guidelines, no specific recommendations are offered for the septic patient [36]. Those same guidelines suggest that blood transfusions are associated with increased nosocomial infections, higher rates of multi-organ failure and SIRS, longer ICU and hospital

length of stay as well as an association with acute lung injury– so called Transfusion Related Acute Lung Injury [36]. Therefore, there may be reason to be skeptical about the role of transfused blood in sepsis resuscitation. Lastly, there is a suggestion that at least some of the benefit of transfused blood in EGDT may have been secondary to the volume bolus it represented, rather than the physiologic effect of the transfused red blood cells. 35.9% of patients in the original study only required further fluid to get the ScvO2 above 70%. Overall, 50.4% of the patients required a blood transfusion to achieve this goal [33]. It may be that results would be similar if the resuscitation algorithm were altered so that the hematocrit goal was decreased, or even removed and replaced with an assessment of volume responsiveness or possible need for inotropic support. In the original trial, only 13.7% of patients reached an adequate CVP and had a hematocrit >30%, thus requiring dobutamine to achieve a ScvO2>70% [7].

Dobutamine is a β-agonist that results in a positive inotropic effect leading to improved contractility, ejection fraction and cardiac output [37]. De Backer demonstrated dobutamine might have a positive effect on the microcirculation as well [38]. If the CVP, MAP and hematocrit are adequate, its use is recommended as part of the resuscitation algorithm endorsed by the SSC [5,6]. The primary rationale for its inclusion is to improve cardiac output and thus, oxygen delivery. But monitoring ScvO2, especially continuously, is technically difficult and can be resource-intensive. Lin et al. [39] published an unblinded study evaluating a goal-directed resuscitation protocol that did not include continuous ScvO2 monitoring versus a non goal-directed approach for septic shock patients admitted to the ICU. They did not have the capability to continuously monitor this target. Their results suggest that a goal-directed protocol still led to greater fluid administration, faster administration of vasopressors & faster shock reversal that likely contributed to reducing ICU LOS & importantly, mortality. In a study by Jones et al. [40], targeting therapy toward lactic acid clearance was found to be noninferior to ScvO2 normalization, offering a potential alternative, or certainly an additional metabolic target of resuscitation.

Echocardiography

A growing body of evidence and a growing number of physicians are using bedside, real-time echocardiography to guide their hemodynamic management [12,13]. Some ICUs have nearly abandoned invasive hemodynamic measurements altogether [13]. First described by Parker et al. [41], myocardial depression or "global left ventricular hypokinesia" may have an incidence as high as 60% in septic shock patients [42]. It is often associated with elevated levels of cardiac biomarkers, such as cardiac Troponin I [43]. Paradoxically, this myocardial depression is described as reversible and also associated with a better prognosis overall [41,42]. There is evidence to support a simple subjective evaluation of echocardiographic images for determining normal versus abnormal ejection fraction [44]. This measurement-subjective or with formal objective measurements – can then be used to determine the possible benefit of inotropic therapy. Importantly, it can then be used in real time to visualize such therapy's effect. Less is known about impaired diastolic function in sepsis, but it has been described as well and was also associated with increased cardiac troponin I [45]. As mentioned earlier, echocardiographic assessment of the septic shock patient is a potentially valuable tool for assessing filling pressures and more importantly, volume responsiveness. Reassessment after any intervention, be it more IVF or the addition of vasoactive medications allows for confirmation of the presumed positive effect [12,13].

Antibiotics

There is compelling data on the use of early, broad-spectrum antibiotics and their potential impact on outcomes. The SSC suggests that antibiotics should be given within one hour of the diagnosis of severe sepsis or septic shock [6]. Since then, Dr. Gaieski et al. [46] have demonstrated that patients who received antibiotics in less than one hour from either triage or qualification for early goal-directed therapy had a lower odds ratio for mortality. While Puskarich et al. [47] failed to demonstrate similar benefits for time to antibiotics from triage; they did demonstrate a significant mortality benefit if those antibiotics were given before a patient developed shock. In a retrospective, propensity-matched analysis cohort study, Kumar et al. [48] describe data suggesting a mortality benefit of early combination antibiotic therapy compared with monotherapy. A similar benefit has been shown for combination therapy, particularly if it includes an aminoglycoside, in the setting of severe sepsis or septic shock secondary to gram-negative bacteremia [49]. All things considered, the most important factor as it pertains to mortality, more so than the speed with which those agents are administered, is to avoid inappropriate initial antibiotics. In 1999, Kumar et al. published a retrospective review of 5715 septic shock patients. They describe an approximately 20% rate of inappropriate initial antibiotics for coverage of the subsequently identified source of infection. This initial inappropriate antibiotic coverage resulted in a greater than five-fold decrease in rates of survival [50].

Of course another important element is source control. As suggested in the studies above, it is not rare that physicians might be incorrect in selecting appropriate antibiotics for the offending pathogen. Therefore, broad-spectrum combination antibiotic therapy should be employed. The source of infection should be elucidated and eliminated as soon as possible, so as to remove the nidus of infection [51]. Of over five thousand patients admitted to ICUs in Israel from 2002-2008, source of infection was 34% pulmonary, 12% urinary tract, 12% peritoneal cavity, 5% soft tissue infection, 4% gastrointestinal and the source was unidentified in one third of the patients [3]. This large proportion of patients in which a causative organism is not identified can make the use of broad-spectrum combination therapy tricky, because the decision to deescalate antimicrobial therapy can be difficult. In a recent study published by Heenen et al. [52] examining a one-year period in the authors' ICU, microbiologic data was only available in 77% of severe sepsis cases during that year. There was a 16% rate of inappropriate initial antibiotics and de-escalation was only applied 43% of the time. The authors concluded that there were only 4 cases where the chance to de-escalate may have been missed. While antimicrobial de-escalation is complicated, the increased risk of death attributed to inappropriate initial antibiotics may tilt the risk/benefit ratio back toward early, aggressive, broad-spectrum antibiotics.

Process Improvement

Rivers has described the strikingly similar results of no fewer than twenty follow-up early goal-directed therapy studies and their consistent findings supporting the mortality benefits of EGDT [53]. He writes, "… {stroke, major trauma or acute myocardial infarction} were rapidly recognized and treated by a multidisciplinary team upon hospital arrival," and that the same emphasis on early detection and multidisciplinary intervention should be in place for severe sepsis [53,54]. In his counterpoint article and subsequent rebuttal, Dr. Gregory Schmidt [55,56] outlines many of the criticisms of EGDT, many of them discussed above. But, he also touches on an important point; that is, that many of the subsequent studies evaluating EGDT are

broader in scope than the original 2001 trial [56]. These studies involve not just utilizing a resuscitation algorithm, but often times involve a complete reworking of an institution's approach to the septic patient. This approach has been shown to be not only feasible, but also lead to decreased mortality [57], similar to the original trial. A multidisciplinary approach to severe sepsis and septic shock has also been described as cost effective [58,59]. Schramm et al. was able to demonstrate that a gradual introduction of various changes to the process of care for severe sepsis and septic shock, including education, introduction of a sepsis order set, implementation of a sepsis rapid response team, finally combined with feedback to physicians regarding performance, led to stepwise improvements in sepsis bundle compliance from 12.7% to 37.7% and ultimately up to 53.7% over three years. This improvement then lead to lower mortality rates, from 30.3%, down to 28.3% and ultimately to 22% [60].

So to care for patients with severe sepsis, maximizing an institution's resources to develop an efficient multidisciplinary approach to the process of care for these patients is likely as important as the patient-specific steps involved in doing so. Attention to various aspects of the initial care of these patients is important and continuing to strive for these treatment goals may yield a mortality benefit beyond six hours, possibly out as far as eighteen [61].

Few would argue that it would be ideal if we could simply identify these patients quickly and intervene sooner. With increasing technology, real-time patient monitoring will likely become easier. With the expansion of Electronic Health Records (EHR) and then the combination of EHR data with electronic patient monitoring, earlier diagnosis & treatment of septic patients may be possible. Sawyer et al. were able to demonstrate that electronic sepsis alerts for patients not in the ICU lead to an increased number of early diagnostic and therapeutic interventions [62]. It remains to be seen if these strategies will significantly change outcomes in all settings. Research for the appropriate venue for such a tool is still needed as the idea holds intuitive merit, but the data lacks consistency. Recently, it was shown that a similar electronic surveillance system used for patients already in the ICU did not influence interventions or outcomes [63]. As more of these systems are developed, more study shall hopefully bring further insight.

Summary

Rivers et al. first introduced early goal-directed therapy over 10 years ago [7] and the original Surviving Sepsis Campaign guidelines are more than eight years old [5]. Mortality, LOS and costs seem to be decreasing [4], suggesting that something is working. However, this task is not easy and poor levels of compliance are commonly quoted [64]. Further research is needed to help clinicians optimize a patient's hemodynamics, preferably with speedy, efficient, inexpensive and noninvasive means such as echocardiography and the use of other devices. These noninvasive strategies need to be evaluated within the context of a specific, team-oriented, multidisciplinary resuscitation algorithm and process of care. More guidance is needed regarding what metabolic markers of tissue perfusion should be followed and how they should be followed. Research is ongoing to evaluate the appropriate role and spectrum of antibiotics, as well as biomarkers suggestive of infection, such as procalcitonin [66]. A potential role for statin therapy in the prevention and treatment of sepsis deserves further study [67]. Lastly, research into the potential role of electronic surveillance is in its infancy and may someday shed light on appropriate ways to more quickly identify septic patients sooner and intervene more quickly. All of these questions have to be answered in a way that will efficiently maximize our healthcare systems' limited resources. Research in severe sepsis is continually expanding and it is unlikely that any one-size-fits-all strategy will be appropriate for all patients in all hospitals. It seems clear that using a multidisciplinary approach to be aggressive in identifying and then appropriately intervening early in severe sepsis and septic shock will save lives.

References

1. Bone RC, Balk RA, Cerra FB, Dellinger RP, Fein AM, et al. (1992) 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 101: 1644-1655.
2. Rangel-Frausto MS, Pittet D, Costigan M, Hwang T, Davis CS, et al. (1995) The natural history of the systemic inflammatory response syndrome (SIRS). A prospective study. JAMA 273: 117-123.
3. Dreiher J, Almog Y, Sprung CL, Codish S, Klein M, et al. (2012) Temporal trends in patient characteristics and survival of intensive care admissions with sepsis: a multicenter analysis. Crit Care Med 40: 855-860.
4. Lagu T, Rothberg MB, Shieh MS, Pekow PS, Steingrub JS, et al. (2012) Hospitalizations, costs, and outcomes of severe sepsis in the United States 2003 to 2007. Crit Care Med 40: 754-761.
5. Dellinger RP, Carlet JM, Masur H, Gerlach H, Calandra T, et al. (2004) Surviving Sepsis Campaign guidelines for management of severe sepsis and septic shock. Crit Care Med 32: 858-873.
6. Dellinger RP, Levy MM, Carlet JM, Bion J, Parker MM, et al. (2008) Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock: 2008. Crit Care Med 36: 296-327.
7. Rivers E, Nguyen B, Havstad S, Ressler J, Muzzin A, et al. (2001) Early goal-directed therapy in the treatment of severe sepsis and septic shock. N Engl J Med 345: 1368-1377.
8. Levy MM, Dellinger RP, Townsend SR, Linde-Zwirble WT, Marshall JC, et al. (2010) The Surviving Sepsis Campaign: results of an international guideline-based performance improvement program targeting severe sepsis. Crit Care Med 38: 367-74.
9. Ferrer R, Artigas A, Levy MM, Blanco J, González-Díaz G, et al. (2008) Improvement in process of care and outcome after a multicenter severe sepsis educational program in Spain. JAMA 299: 2294-2303.
10. Marik PE, Baram M, Vahid B (2008) Does central venous pressure predict fluid responsiveness? A systematic review of the literature and the tale of seven mares. Chest 134: 172-178.
11. Marik PE, Cavallazzi R, Vasu T, Hirani A (2009) Dynamic changes in arterial waveform derived variables and fluid responsiveness in mechanically ventilated patients: a systematic review of the literature. Crit Care Med 37: 2642-2647.
12. Vieillard-Baron A, Prin S, Chergui K, Dubourg O, Jardin F (2003) Hemodynamic instability in sepsis: bedside assessment by Doppler echocardiography. Am J Respir Crit Care Med 168: 1270-1276.
13. Beaulieu Y (2007) Bedside echocardiography in the assessment of the critically ill. Crit Care Med 35: S235-249.
14. Jardin F, Fourme T, Page B, Loubières Y, Vieillard-Baron A, et al. (1999) Persistent preload defect in severe sepsis despite fluid loading: a longitudinal echocardiographic study in patients with septic shock. Chest 116: 1354-1359.
15. Kircher BJ, Himelman RB, Schiller NB (1990) Noninvasive estimation of right atrial pressure from the inspiratory collapse of inferior vena cava. Am J Cardiol 66: 493-496.
16. Jue J, Chung W, Schiller NB (1992) Does inferior vena cava size predict right atrial pressure in patients receiving mechanical ventilation? J Am Soc Echocardiogr 5: 613-619.
17. Nagueh SF, Kopelen HA, Zoghbi WA (1996) Relation of mean right atrial pressure to echocardiographic and Doppler parameters of right atrial and right ventricular function. Circulation 93: 1160-1169.
18. Jardin F, Vieillard-Baron A (2006) Ultrasonographic examination of the venae cavae. Intensive Care Med 32: 203-206.

19. Feissel M, Michard F, Faller JP, Teboul JL (2004) The respiratory variation in inferior vena cava diameter as a guide to fluid therapy. Intensive Care Med 30: 1834-1837.

20. Vieillard-Baron A, Prin S, Chergui K, Dubourg O, Jardin F (2003) Hemodynamic instability in sepsis: bedside assessment by Doppler echocardiography. Am J Respir Crit Care Med 168: 1270-1276.

21. Boulain T, Achard JM, Teboul JL, Richard C, Perrotin D, et al. (2002) Changes in BP induced by passive leg raising predict response to fluid loading in critically ill patients. Chest 121: 1245-1252.

22. Teboul JL, Monnet X (2008) Prediction of volume responsiveness in critically ill patients with spontaneous breathing activity. Curr Opin Crit Care 14: 334-339.

23. Benomar B, Ouattara A, Estagnasie P, Brusset A, Squara P (2010) Fluid responsiveness predicted by noninvasive bioreactance-based passive leg raise test. Intensive Care Med 36: 1875-1881.

24. Squara P, Denjean D, Estagnasie P, Brusset A, Dib JC, et al. (2007) Noninvasive cardiac output monitoring (NICOM): a clinical validation. Intensive Care Med 33: 1191-1194.

25. Beale RJ, Hollenberg SM, Vincent JL, Parrillo JE (2004) Vasopressor and inotropic support in septic shock: an evidence-based review. Crit Care Med 32: S455-S465.

26. Martin C, Papazian L, Perrin G, Saux P, Gouin F (1993) Norepinephrine or dopamine for the treatment of hyperdynamic septic shock? Chest 103: 1826-1831.

27. De Backer D, Biston P, Devriendt J, Madl C, Chochrad D, et al. (2010) Comparison of dopamine and norepinephrine in the treatment of shock. N Engl J Med 362: 779-789.

28. Patel GP, Grahe JS, Sperry M, Singla S, Elpern E, et al. (2010) Efficacy and safety of dopamine versus norepinephrine in the management of septic shock. Shock 33: 375-380.

29. De Backer D, Aldecoa C, Njimi H, Vincent JL (2012) Dopamine versus norepinephrine in the treatment of septic shock: A meta-analysis*. Crit Care Med 40: 725-730.

30. Havel C, Arrich J, Losert H, Gamper G, Müllner M, et al. (2011) Vasopressors for hypotensive shock. Cochrane Database Syst Rev 5: CD003709.

31. Vasu TS, Cavallazzi R, Hirani A, Kaplan G, Leiby B, et al. (2012) Norepinephrine or dopamine for septic shock: systematic review of randomized clinical trials. J Intensive Care Med 27: 172-178.

32. Annane D (2012) Physicians no longer should consider dopamine for septic shock!* Crit Care Med 40: 981.

33. Otero RM, Nguyen HB, Huang DT, Gaieski DF, Goyal M, et al. (2006) Early goal-directed therapy in severe sepsis and septic shock revisited: concepts, controversies, and contemporary findings. Chest 130: 1579-1595.

34. Spronk PE, Ince C, Gardien MJ, Mathura KR, Oudemans-van Straaten HM, et al. (2002) Nitroglycerin in septic shock after intravascular volume resuscitation. Lancet 360: 1395-1396.

35. Boerma EC, Koopmans M, Konijn A, Kaiferova K, Bakker AJ, et al. (2010) 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 38: 93-100.

36. Napolitano LM, Kurek S, Luchette FA, Corwin HL, Barie PS, et al. (2009) Clinical practice guideline: red blood cell transfusion in adult trauma and critical care. Crit Care Med 37: 3124-3157.

37. Dellinger RP (2003) Cardiovascular Management of Septic Shock. Crit Care Med 31: 946-955.

38. De Backer D, Creteur J, Dubois MJ, Sakr Y, Koch M, et al. (2006) The effects of dobutamine on microcirculatory alterations in patients with septic shock are independent of its systemic effects. Crit Care Med 34: 403-408.

39. Lin SM, Huang CD, Lin HC, Liu CY, Wang CH, et al. (2006) A modified goal-directed protocol improves clinical outcomes in intensive care unit patients with septic shock: a randomized controlled trial. Shock 26: 551-557.

40. Jones AE, Shapiro NI, Trzeciak S, Arnold RC, Claremont HA, et al. (2010) Lactate clearance vs central venous oxygen saturation as goals of early sepsis therapy: a randomized clinical trial. JAMA 303: 739-746.

41. Parker MM, Shelhamer JH, Bacharach SL, Green MV, Natanson C, et al. (1984) Profound but reversible myocardial depression in patients with septic shock. Ann Intern Med 100: 483-490.

42. Vieillard-Baron A, Caille V, Charron C, Belliard G, Page B, et al. (2008) Actual incidence of global left ventricular hypokinesia in adult septic shock. Crit Care Med 36: 1701-1706.

43. Bouhemad B, Nicolas-Robin A, Arbelot C, Arthaud M, Féger F, et al. (2009) Acute left ventricular dilatation and shock-induced myocardial dysfunction. Crit Care Med 37: 441-447.

44. Mueller X, Stauffer JC, Jaussi A, Goy JJ, Kappenberger L (1991) Subjective visual echocardiographic estimate of left ventricular ejection fraction as an alternative to conventional echocardiographic methods: comparison with contrast angiography. Clin Cardiol 14: 898-902.

45. Bouhemad B, Nicolas-Robin A, Arbelot C, Arthaud M, Féger F, et al. (2008) Isolated and reversible impairment of ventricular relaxation in patients with septic shock. Crit Care Med 36: 766-774.

46. Gaieski DF, Mikkelsen ME, Band RA, Pines JM, Massone R, et al. (2010) Impact of time to antibiotics on survival in patients with severe sepsis or septic shock in whom early goal-directed therapy was initiated in the emergency department. Crit Care Med 38: 1045-1053.

47. Puskarich MA, Trzeciak S, Shapiro NI, Arnold RC, Horton JM, et al. (2011) Association between timing of antibiotic administration and mortality from septic shock in patients treated with a quantitative resuscitation protocol. Crit Care Med 39: 2066-2071.

48. Kumar A, Zarychanski R, Light B, Parrillo J, Maki D, et al. (2010) Early combination antibiotic therapy yields improved survival compared with monotherapy in septic shock: a propensity-matched analysis. Crit Care Med 38: 1773-1785.

49. Micek ST, Welch EC, Khan J, Pervez M, Doherty JA, et al. (2010) Empiric combination antibiotic therapy is associated with improved outcome against sepsis due to gram-negative bacteria: a retrospective analysis. Antimicrob Agents Chemother 54: 1742-1748.

50. Kumar A, Ellis P, Arabi Y, Roberts D, Light B, et al. (2009) Initiation of inappropriate antimicrobial therapy results in a fivefold reduction of survival in human septic shock. Chest 136: 1237-1248.

51. Marshall JC, Maier RV, Jimenez M, Dellinger Pa (2004) Source control in the management of severe sepsis and septic shock: an evidence-based review. Crit Care Med 32: S513-526.

52. Heenen S, Jacobs F, Vincent JL (2012) Antibiotic strategies in Severe nosocomial sepsis: why do we not de-escalate more often? Crit Care Med 40: 1404-1409.

53. Rivers EP (2010) Point: adherence to early goal-directed therapy: does it really matter? Yes. After a decade, the scientific proof speaks for itself. Chest 138: 476-480.

54. Rivers EP (2010) Rebuttal from Dr. Rivers. Chest 138: 483-484.

55. Schmidt GA (2010) Counterpoint: adherence to early goal-directed therapy: does it really matter? no. both risks and benefits require further study. Chest 138: 480-483.

56. Schmidt GA (2010) Rebuttal from Dr. Schmidt. Chest 138: 484-485.

57. Nguyen HB, Corbett SW, Steele R, Banta J, Clark RT, et al. (2007) Implementation of a bundle of quality indicators for the early management of severe sepsis and septic shock is associated with decreased mortality. Crit Care Med 35: 1105-1112.

58. Jones AE, Troyer JL, Kline JA (2011) Cost-effectiveness of an emergency department-based early sepsis resuscitation protocol. Crit Care Med 39: 1306-1312.

59. Huang DT, Clermont G, Dremsizov TT, Angus DC (2007) Implementation of early goal-directed therapy for severe sepsis and septic shock: a decision analysis. Crit Care Med 35: 2090-2100.

60. Schramm GE, Kashyap R, Mullon JJ, Gajic O, Afessa B (2011) Septic shock: a multidisciplinary response team and weekly feedback to clinicians improve the process of care and mortality. Crit Care Med 39: 252-258.

61. Coba V, Whitmill M, Mooney R, Horst HM, Brandt MM, et al. (2011) Resuscitation bundle compliance in severe sepsis and septic shock: improves survival, is better late than never. J Intensive Care Med.

62. Sawyer AM, Deal EN, Labelle AJ, Witt C, Thiel SW, et al. (2011) Implementation of a real-time computerized sepsis alert in nonintensive care unit patients. Crit Care Med 39: 469-473.

63. Hooper MH, Weavind L, Wheeler AP, Martin JB, Gowda SS, et al. (2012) Randomized trial of automated, electronic monitoring to facilitate early detection of sepsis in the intensive care unit*. Crit Care Med 40: 2096-2101.

64. O'Neill R, Morales J, Jule M (2012) Early goal-directed therapy (EGDT) for severe sepsis/septic shock: which components of treatment are more difficult to implement in a community-based emergency department? J Emerg Med 42: 503-510.

65. Bochud PY, Bonten M, Marchetti O, Calandra T (2004) Antimicrobial therapy for patients with severe sepsis and septic shock: an evidence-based review. Crit Care Med 32: S495-512.

66. PTang BM, Eslick GD, Craig JC, McLean AS (2007) Accuracy of procalcitonin for sepsis diagnosis in critically ill patients: systematic review and meta-analysis. Lancet Infect Dis 7: 210-217.

67. Kouroumichakis I, Papanas N, Proikaki S, Zarogoulidis P, Maltezos E (2011) Statins in prevention and treatment of severe sepsis and septic shock. Eur J Intern Med 22: 125-133.

This article was originally published in a special issue, **Sepsis: Pathophysiology & Management** handled by Editor(s). Dr. Farid Sadaka, PMercy Hospital St Louis, USA.