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 $>38^\circ$C or $<36^\circ$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 Mark 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 of the first step of EGDT – adequate preload.

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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 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’s 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].

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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 that a goal-directed protocol still led to greater fluid administration, 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].

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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 5713 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 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


