Sepsis: Clinical Dilemmas

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Sepsis, manifested by systemic inflammatory response syndrome (SIRS), septic shock and multiple organ dysfunction syndrome (MODS), remains the leading cause of morbidity and mortality in critically ill patients. Despite advances and our knowledge of sepsis, there remain clinical dilemmas that impact how we treat patients. These clinical dilemmas include hypotension, cardiac dysfunction and altered oxygen consumption. There is increasing recognition that treatment of these problems does not necessarily improve outcome. As we improve our understanding of sepsis, there is increased recognition that improvement in morbidity and survival will come not only from treating the manifestations of sepsis but also the endogenous mediators responsible for the development of these clinically important conditions. This manuscript discusses the clinical dilemmas associated with sepsis, current therapy and future directions for managing sepsis.

INTRODUCTION

The American College of Chest Physicians and the Society of Critical Care Medicine published their definitions for sepsis and organ failure in 1992, definitions to which many subscribe (Table 1) [1]. This definition of sepsis and organ failure correlates with the development of morbidity (multiple organ dysfunction syndrome [MODS]) and mortality [2].

The incidence of sepsis is increasing in the United States and presumably in other countries. Data from a decade ago demonstrate that the incidence rose 139 percent over a nine-year interval [3], an increase that is thought not only to be due to an increased improvement in reporting but also to an increase in predisposing factors, i.e., an aging population, presence of comorbidities (human immunodeficiency virus), transplantation (immunosuppression) and the increased use of invasive devices leading to iatrogenic infections. A more recent study indicates that the incidence of sepsis is even higher than that reported by the Morbidity and Mortality Weekly Report [3]. The incidence may be two to three times higher, at approximately 400 to 500 patients per 100,000 population per year [4].

Despite improved understanding of the pathogenesis of sepsis and of new therapies, the mortality not only remains high but is thought to be increasing [5]. It is imperative that current therapies of sepsis be assessed and evaluated and new treatments designed. In this context, it is clear that there are a number of dilemmas that face the healthcare provider when caring for a patient with systemic inflammatory response syndrome (SIRS), sepsis or septic shock.

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b Abbreviations: MODS, multiple organ dysfunction syndrome; SIRS, systemic inflammatory response syndrome; SVR, systemic vascular resistance; LVEDV, left ventricular-end diastolic volume; ICU, intensive care unit.
CLINICAL DILEMMAS

Hypotension

A decrease in blood pressure is one of the characteristics of Gram-negative sepsis. In animal models of sepsis, after an intravenous injection of endotoxin or live bacteria, there is actually an increase in blood pressure initially, an increase that lasts for approximately 20 to 30 minutes before the animal becomes hypotensive. This increase and subsequent decrease in systemic vascular resistance (SVR) is thought to be secondary to the interaction of a number of endogenous vasoactive compounds [6], often on the vascular endothelium [7]. At the arteriolar level, arterioles are maximally vasodilated, others vasoconstricted, in an attempt to elevate perfusion pressure. In fact, this is one of the paradoxes of hypotension. A number of shunts through the vascular beds of organs are open so that if blood flow to that organ is measured, it can be normal to high. When one examines capillary blood flow, though, evidence of vasoconstriction and lack of perfusion exist. The dilemma then is how to augment flow using a vasoconstrictor that does not worsen capillary perfusion but raises the SVR within those vessels that are vasodilated and shunting blood through the organ.

Not all studies have identified alterations in organ blood flow in sepsis. Finley and colleagues found that the average muscle blood flow was greater in septic than nonseptic patients as was skeletal capillary muscle blood flow [8]. If the latter is truly the case, then the defect in tissue oxygenation, if such a defect exists, is not secondary to a decrease in flow, but may be related to a block in oxygen transport either within the cell or at some level within the mitochondria. The conundrum the physician faces is whether to increase blood pressure or increase flow; if the findings of Finley and colleagues are reliable, then no increase in flow or pressure will alter the potential block at the mitochondrial level.

Hyperdynamic cardiac function

Historical accounts of septic shock describe a warm and cold phase of septic shock: the “warm phase” characterized by an increase in cardiac output. Two decades ago, the prevailing belief was that when patients first became septic, they were in a hyperdynamic phase manifested by high cardiac outputs, increased peripheral perfusion and warming of the extremities and skin. It was only later, in the irreversible phase of shock, that patients

| Table 1. Definitions. |
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| **Systemic inflammatory response syndrome (SIRS)** | Activation of the immune system by an infectious agent with release of cytokines and a number of vasoactive substances. Their response is characterized by alterations in temperature (>38°C or <36°C), elevated heart rate (>90 beats/min), tachypnea (>20 breaths/min) and leukocytosis (>12,000/m³). |
| **Sepsis** | Sepsis is the SIRS with the presence of an identifiable infectious source—be it an abscess or an infected lime. The same criteria as in sepsis applies, but a recognized infectious source must be present. Severe sepsis is sepsis associated with the presence of organ dysfunction. |
| **Septic shock** | Septic shock is a severe sepsis with presence of hypotension (systolic blood pressure <90 mmHg or a >44 mmHg decrease from baseline) despite adequate filling pressure (pulmonary artery occlusion pressure at 12 to 18 mmHg). |
became cool, acidosis developed and cardiac output fell, to the point that it was inadequate to perfuse and oxygenate the extremities. This was usually a premorbid event.

Parker and colleagues were surprised when they studied 28 patients with septic shock to find that the majority had evidence of myocardial dysfunction, despite the fact that the majority also had high cardiac outputs [9]. This same group of investigators believed that the myocardial depression was related to a circulating myocardial depressant factor [10]. They also speculated that the myocardial dysfunction was actually a protective event. In a subsequent analysis of their 20 patients, they found that those patients who were survivors had left ventricular dilation, and a reduction in ejection fraction, but maintenance of stroke volume. These same patients had high cardiac outputs due to an associated tachycardia.

Nonsurvivors did not have an increase in their left ventricular end-diastolic volume (LVEDV). Parker and colleagues at the National Institutes of Health speculated that in the survivors, the increase in LVEDV with a decrease in stroke volume decreased the workload on the left ventricle and was somehow protective. Survivors eventually decreased their LVEDV to normal, with a return to normal in their ejection fraction, with stroke volume staying essentially the same. Nonsurvivors, however, may have maintained their LVEDV, their stroke volume and the ejection fraction at the expense of an increase in left ventricular work (Figure 1) [11].

**Oxygen delivery/oxygen consumption**

In the 1960s, investigators recognized that there was defective oxygen consumption in septic shock [12]. More recently, with the understanding of what was happening at the

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**Figure 1.** A schematic representation of the reversible myocardial depression seen in the survivors of septic shock. Reprinted with permission from: Parker, M.M., Shelhamer, J.H., Bacharach, S.L., Green, M.V., Natanson, C., Frederick, T.M., Damske, B.A., and Parrillo, J.E. Profound but reversible myocardial depression in patients with septic shock. Ann. Intern. Med. 100:488, 1984.
capillary level in terms of blood flow, investigators speculated that improving oxygen delivery might increase survival in septic patients. Support for this hypothesis was generated from studies conducted by Shoemaker and colleagues in several groups of patients [13]. A recent consensus conference concluded that although there was a general belief that whole body and organ-specific oxygen availability were important to monitor in sepsis, there were no good data to support the concept that titrating therapy to specific hemodynamic and oxygen transport value improves outcome [14]. Part of the problem in understanding the relationship of oxygen delivery to oxygen consumption may come from the fact that there is mathematical coupling of data [15]. In calculating the relationship of oxygen consumption to oxygen delivery, it is important to understand that commonly the Fick equation is used to help calculate both variables, i.e., the cardiac index as measured by thermodilution techniques using a pulmonary artery catheter, is used in both the data on the abscissa and the ordinate. Perhaps a better way to assess a relationship is to use indirect calorimetry to measure oxygen consumption and the Fick equation to measure oxygen delivery. Under those circumstances, if a relationship exists, then the contribution of mathematical coupling of data would be eliminated [15].

TREATMENTS

Most studies of promising therapies to treat septic shock have failed to demonstrate an improvement in outcome [16-18]. As already stated, a recent consensus conference found that there were little data demonstrating an improvement in outcome for many of the therapies that are currently used in treating patients with sepsis [14]. Prevention of sepsis from iatrogenic injuries and nosocomial infection is, therefore, extremely important [19]. In fact, simple hand washing in the intensive care unit (ICU) and attention to detail in handling urinary catheters, pulmonary hygiene, and use of parenteral nutrition only when necessary, is as or more important than any other modality in decreasing the incidence of sepsis and subsequent mortality in the ICU [20].

Although a great deal of attention in managing patients with sepsis is devoted to discussions of the appropriate use of antibiotics, fluid therapy and inotropes, Natanson and colleagues at the National Institutes of Health demonstrated in an elegant study in a canine model that these interventions, even when carefully titrated, did not improve survival of septic animals [21]. Septic dogs given no therapy had a 100 percent mortality at four days, animals given antibiotics alone had a 90 percent mortality, and animals given cardiovascular support to include fluid therapy and inotropes after volume resuscitation, likewise, had 90 percent mortality. It was a combination of antibiotics and appropriate cardiovascular support that lead to improvement in survival to 50 percent. We currently have some of the most potent, well-designed antibiotics available and yet the mortality rate is still high. Likewise, we understand the adrenergic mechanisms that are active during septic shock. Therapy to impact outcome and improve survival in patients with septic shock, however, has failed despite studies of multiple new therapies. When choosing antibiotic therapy for patients with sepsis and who are non-neutropenic, there is good evidence that a single agent is probably as good as combination therapy [22]. Institution of appropriate antibiotic therapy early in the course of sepsis is important, but it is ethically impossible to demonstrate benefit to antibiotic therapy in the majority of patients with sepsis and septic shock.

Though a decrease in SVR and hypotension correlates well with mortality [23], improvement in SVR and in blood pressure does not necessarily correlate with an improvement in outcome. Hypotension is probably a marker of severity of illness and of mortality, but not necessarily the causative factor [24]. However, a long-standing tenet of
therapy for septic shock is to increase SVR and raise blood pressure using catecholamines. Unfortunately, blood pressure is often refractive to vasoconstrictor therapy, primarily because of down regulation of the adrenergic receptors and of the interaction of other endogenous mediators. Using nitric oxide synthase inhibitors, it is possible to improve blood pressure, but no one has yet demonstrated an improvement in outcome. A great deal of attention has been given to choosing appropriate inotropes and vasopressors in septic shock [25]. We already have potent inotropes and vasopressors, improving outcome will likely not come from the development of new inotropes or vasopressors. In patients with profound hypotension, if vasoconstrictor therapy is used, norepinephrine with its alpha-adrenergic effects is better than beta-adrenergic agents [26]. But to avoid excessive vasoconstriction, it is probably best to use a combination of norepinephrine and an agent such as dopamine, which will maintain renal perfusion and urine output. There is evidence that if a beta-adrenergic agent is used, that dobutamine works as well as any other agent [27].

Many of the manifestations of sepsis and septic shock are markers of the severity of comorbid disease and not the causative factor in mortality. Since these effects come not necessarily from bacteria themselves or from bacteria-derived products but from endogenous mediators, new therapies are targeted at manipulating these endogenous mediators [28]. It is naive to assume though that there is a single agent or a "magic bullet" that will improve outcome [29]. A better understanding of the interplay between these endogenous mediators and the host organism is important, and perhaps a multimodel therapy will ultimately be the treatment that improves outcome in patients with a systemic reaction to an infectious agent. These issues are discussed in other articles in this issue.

CONCLUSION

The clinician managing the patient with SIRS/sepsis/septic shock is faced with a number of clinical dilemmas. The patient may be hypotensive, but raising blood pressure does not necessarily improve perfusion in peripheral vascular beds. Likewise, though the patient may have an elevated cardiac output, this does not necessarily imply that cardiac function is normal or adequate. Improving perfusion pressure and cardiac output, however, which will improve oxygen delivery and in some circumstances oxygen consumption, does not necessarily lead to an improvement in survival. However, if one ignores the cardiac dysfunction and hypotension, certainly mortality can be in excess of 50 percent.

When managing patients in the hospital or in an ICU environment, it is important to avoid iatrogenic injury and to prevent infection, particularly in those who are at the extremes of age and who are immunocompromised for whatever reason. The appropriate antibiotics given early in the course of the infection, fluid therapy (either colloid or crystalloid) to improve left ventricular filling pressure, and inotropes and vasoconstrictors when judged to be clinically necessary are important in managing septic patients. However, even with the best of care, the mortality rate remains approximately 50 percent. Improvement in outcome will most likely depend on a better understanding of the pathophysiology of the endogenous mediators that underlie the systemic response to infection and appropriate interventions, perhaps more than one, to nullify or modify this over-exuberant release of endogenous cytokines and inflammatory agents.

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