EDITORIALS

Septic Shock — Vasopressin, Norepinephrine, and Urgency

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Septic shock is one of the most challenging problems in critical care medicine. Shock due to sepsis accounts for many of the deaths in medical and surgical intensive care units.[1-4] It is estimated that septic shock results in approximately 215,000 deaths per year in the United States, a number similar to the number of deaths from acute myocardial infarction. However, the two disorders are not similar with respect to the approach to evaluation and management. Myocardial infarction is easier to diagnose and usually presents with characteristic chest pain and electrocardiographic changes. The presentation of septic shock is much more nonspecific and ambiguous, requiring the clinician to recognize a constellation of symptoms and signs that include a likely source of infection; fever, tachycardia, tachypnea or abnormal peripheral white-cell count; and hypotension as a sign of circulatory dysfunction.[3-6]

Clinicians also do not feel the same sense of urgency to initiate therapy in cases of septic shock that they do in cases of myocardial infarction. Yet, two studies suggest that initiating therapy rapidly may play a critical role in reducing mortality associated with septic shock. First, in a randomized, controlled trial, Rivers et al. demonstrated that early cardiovascular support initiated in the emergency department, consisting of a protocol-driven, goal-directed regimen of fluids, inotropic agents, and blood transfusions, was associated with a substantial reduction of in-hospital mortality, from 46.5% to 30.5%.[7] Another study has confirmed that early, goal-directed therapy can be implemented in medical centers by means of teamwork between emergency and critical care services.[8] In a large, observational database study of septic shock, the duration of hypotension before the administration of effective antimicrobial therapy was found to be a critical determinant of survival.[9] A patient who received antimicrobial agents within the first hour after hypotension began had a much higher rate of survival than one treated 6 hours after hypotension (80% vs. 42%), yet at 6 hours, 49% of patients had not yet been treated. These studies show that avoiding delays and rapidly instituting cardiovascular support and antimicrobial agents in patients with septic shock have an important effect on the likelihood of survival. It thus appears that the concept of a golden hour — a critical period during which therapy must be applied (similar to that for volume resuscitation for trauma patients or coronary reperfusion for myocardial infarction) — may also apply in cases of septic shock.[4,10] However, such goal-directed therapy requires initiation of treatment rapidly, within minutes, and implementing this process is a logistical challenge.

One of the key components of cardiovascular support in septic shock is to maintain an adequate mean arterial blood pressure (>65 mm Hg) to ensure tissue perfusion. Recent guidelines[5] have advocated the use of aggressive fluid resuscitation and, if hypotension persists, administration of either norepinephrine or dopamine. However, catecholamines such as norepinephrine and dopamine have adverse effects and may occasionally increase mortality rates.[11]

Vasopressin is a peptide hormone released from the pituitary gland that has multiple physiological effects. It induces vasoconstriction by activating V1 receptors on vascular smooth muscle, a mechanism distinct from that of adrenergic vasoconstriction. Several small trials have suggested that vasopressin may represent an attractive alternative to norepinephrine or dopamine in the management of sepsis. Vasopressin levels are reduced dur-

ing septic shock, and exogenous administration of vasopressin has been associated with potent vasopressor effects in several observational studies.[12-14]

In this issue of the *Journal*, Russell et al.[15] report the results of a well-conducted, randomized, multicenter, controlled trial involving 778 patients with septic shock that evaluated low-dose vasopressin (0.01 to 0.03 U per minute) added to norepinephrine as compared with norepinephrine alone, used in addition to open-label vasopressors. They found no difference between the vasopressin and norepinephrine groups in the primary end point of 28-day mortality (35% and 39%, respectively; P=0.26) or 90-day mortality. Somewhat paradoxically, the study suggested that patients with less severe septic shock (those with a requirement for 5 to 14 μg of norepinephrine per minute at baseline) had a significant reduction in mortality with vasopressin therapy. The authors had predicted that, because of its potency as a vasoconstrictor, vasopressin would be more efficacious in the stratum of patients with more severe septic shock (≥15 μg of norepinephrine per minute at baseline); however, the therapeutic groups had similar mortality rates in the more severe stratum. The authors conclude — correctly, in my opinion — that these subgroup findings should be hypothesis-generating and should not be used as a basis for conclusions about therapy.

A number of other observations from this large clinical trial are noteworthy. First, the rates of adverse events were similar in the two groups. However, the authors appropriately and carefully excluded any patients with either acute ischemic heart disease or heart failure. The equivalence in the rate of adverse events seen in the two groups probably resulted, in part, from ensuring that patients with underlying heart disease were not entered into the trial. Without these exclusions, it is possible that vasopressin might have increased the mortality rate.

Second, the overall mortality rate associated with septic shock in this study was 37%, below the reported range of 50 to 60%.[2,4] The low mortality rate may have resulted from excluding many of the high-risk patients, which represents a selection bias that commonly occurs in randomized, controlled trials. A more "real-world" population might have different results.

Third, the mean arterial pressure at baseline in the study was 72 to 73 mm Hg during catecholamine therapy alone. This makes the trial an evaluation of low-dose vasopressin as a catecholamine-sparing agent, not an evaluation of vasopressin in septic shock that was unresponsive to catecholamines. No randomized, controlled data are available to determine the best agent to treat patients with septic shock that is unresponsive to norepinephrine, but my experience and several observational studies suggest that vasopressin will restore adequate blood pressure in a substantial number of such patients.

Fourth, the average time from meeting the diagnostic criteria to infusion of the study drug was approximately 12 hours (the maximum was 24 hours, according to the entry criteria). Studies by Rivers et al.[7] and Kumar et al.[9] suggest that cardiovascular and antimicrobial therapies initiated earlier (within 6 hours after the onset of septic shock, and preferably within 1 or 2 hours) result in the highest survival rates. Treatment initiated at an average of 12 hours after the onset of septic shock may be too late for any vasopressor agent to show a significant effect on mortality.

What are the lessons from this study for the practicing clinician? Although adding vasopressin to norepinephrine therapy in patients with septic shock appears to produce similar mortality rates and is safe, there is no compelling advantage to using vasopressin rather than norepinephrine. Thus, the data in this field to date suggest that it is the timing of vasopressor (and other) therapy, rather than the specific agent, that is decisive. In both clinical practice and clinical trials, once hypotension occurs in septic shock, we need to initiate immediate antimicrobial therapy, cardiovascular support, and other effective therapies recommended by current guidelines.[5]

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Collaboration, Genetic Associations, and Lupus Erythematosus

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Systemic lupus erythematosus (SLE), a disease that preferentially targets women during the reproductive years, is considered by many clinicians and investigators to be the prototypic autoimmune disease. Among clinicians, this status is based on the characteristic involvement of multiple organ systems — most notably, skin, kidneys, joints, central nervous system, and cardiovascular system — with the deposition of immune complexes and complement, inflammation, and vascular damage noted by pathologists. From the perspective of the immunologist, SLE is a model disease that has provided important insights into immune-system function. As is characteristic of most complex diseases, genetic and environmental factors determine the development of SLE and what its clinical manifestations will be.

Recent technological advances have allowed rapid and increasingly cost-efficient analysis of single-nucleotide polymorphisms (SNPs) in patients with complex diseases and appropriate control subjects. This week, important new data from two complementary genomewide association studies of patients with SLE,[1,2] from a third genomewide study that focused on nonsynonymous DNA variations,[3] and an analysis of an attractive candidate gene[4] are published in the *Journal* and in *Nature Genetics*. Results from these ambitious projects involving international collaborations expand a growing compendium of genetic data that implicate many components of the immune system in the pathogenesis of SLE (Table 1).

Recognition of the essential role of innate immune-system activation in SLE and other immune-mediated diseases has followed the characterization of toll-like receptors and their environmental and endogenous stimuli. Production of type I interferon in patients with SLE is now recognized as a central pathogenic mechanism,[5] and increased serum interferon activity is a heritable trait in families with a history of lupus (Fig. 1).[6] Analysis of genes encoding components of the interferon pathway has led to extensive support for an association of polymorphic variants of interferon regulatory factor 5 (*IRF5*) with SLE.[7] The *IRF5* association is replicated in both genomewide association studies reported this week,[1,2] although a functional link between the *IRF5* risk haplotype and increased production of type I interferon has yet to be made.

The central contribution of the adaptive immune response to SLE is represented by characteristic autoantibodies specific for nucleic-acid–containing particles (Fig. 1). The HLA locus that generates the strongest statistical association with SLE has been associated with the production of particular autoantibodies,[8] suggesting that MHC class II molecules promote the expansion of autoantigen-specific T cells and the production of T-cell–dependent autoantibodies. Moreover, variations in other lupus-associated genes encode proteins expressed in T and B cells that are associated with altered activation or function of those cells. Protein tyrosine phosphatase, nonreceptor type 22 (*PTPN22*), for example, encodes a cytoplasmic lymphoid phosphatase expressed