

## Sepsis and the Heart

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**Abstract**—Sepsis is generally viewed as a disease aggravated by an inappropriate immune response encountered in the afflicted individual. As an important organ system frequently compromised by sepsis and always affected by septic shock, the cardiovascular system and its dysfunction during sepsis have been studied in clinical and basic research for more than 5 decades. Although a number of mediators and pathways have been shown to be associated with myocardial depression in sepsis, the precise cause remains unclear to date. There is currently no evidence supporting global ischemia as an underlying cause of myocardial dysfunction in sepsis; however, in septic patients with coexistent and possibly undiagnosed coronary artery disease, regional myocardial ischemia or infarction secondary to coronary artery disease may certainly occur. A circulating myocardial depressant factor in septic shock has long been proposed, and potential candidates for a myocardial depressant factor include cytokines, prostanoids, and nitric oxide, among others. Endothelial activation and induction of the coagulatory system also contribute to the pathophysiology in sepsis. Prompt and adequate antibiotic therapy accompanied by surgical removal of the infectious focus, if indicated and feasible, is the mainstay and also the only strictly causal line of therapy. In the presence of severe sepsis and septic shock, supportive treatment in addition to causal therapy is mandatory. The purpose of this review is to delineate some characteristics of septic myocardial dysfunction, to assess the most commonly cited and reported underlying mechanisms of cardiac dysfunction in sepsis, and to briefly outline current therapeutic strategies and possible future approaches. (*Circulation*. 2007;116:793-802.)

**Key Words:** immune system ■ infection ■ inflammation ■ shock ■ sepsis

Sepsis, defined by consensus conference as “the systemic inflammatory response syndrome (SIRS) that occurs during infection,”<sup>1</sup> is generally viewed as a disease aggravated by the inappropriate immune response encountered in the affected individual (for review, see Hotchkiss and Karl<sup>2</sup> and Riedemann et al.<sup>3</sup>). The Table gives the current criteria for the establishment of the diagnosis of systemic inflammatory response syndrome, sepsis, and septic shock.<sup>1,4</sup> Morbidity and mortality are high, resulting in sepsis and septic shock being the 10th most common cause of death in the United States.<sup>5</sup> The incidence of sepsis and sepsis-related deaths appears to be increasing by 1.5% per year.<sup>6</sup> In a recent study,<sup>6</sup> the total national hospital cost invoked by severe sepsis in the United States was estimated at approximately \$16.7 billion on the basis of an estimated severe sepsis rate of 751 000 cases per year with 215 000 associated deaths annually. A recent study from Britain documented a 46% in-hospital mortality rate for patients presenting with severe sepsis on admission to the intensive care unit.<sup>7</sup>

As an important organ system frequently affected by sepsis and always affected by septic shock, the cardiovascular system and its dysfunction during sepsis have been studied in clinical and basic research for more than 5 decades. In 1951, Waisbren was the first to describe cardiovascular dysfunction

due to sepsis.<sup>8</sup> He recognized a hyperdynamic state with full bounding pulses, flushing, fever, oliguria, and hypotension. In addition, he described a second, smaller patient group who presented clammy, pale, and hypotensive with low volume pulses and who appeared more severely ill. With hindsight, the latter group might well have been volume underresuscitated, and indeed, timely and adequate volume therapy has been demonstrated to be one of the most effective supportive measures in sepsis therapy.<sup>9</sup>

Under conditions of adequate volume resuscitation, the profoundly reduced systemic vascular resistance typically encountered in sepsis<sup>10</sup> leads to a concomitant elevation in cardiac index that obscures the myocardial dysfunction that also occurs. However, as early as the mid-1980s, significant reductions in both stroke volume and ejection fraction in septic patients were observed despite normal total cardiac output.<sup>11</sup> Importantly, the presence of cardiovascular dysfunction in sepsis is associated with a significantly increased mortality rate of 70% to 90% compared with 20% in septic patients without cardiovascular impairment.<sup>12</sup> Thus, myocardial dysfunction in sepsis has been the focus of intense research activity. Although a number of mediators and pathways have been shown to be associated with myocardial depression in sepsis, the precise cause remains unclear.

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**Current Criteria for Establishment of the Diagnosis of SIRS, Sepsis, and Septic Shock<sup>1,4</sup>**

SIRS	Two or more of the following: Body temperature $>38.5^{\circ}\text{C}$ or $<35.0^{\circ}\text{C}$ Heart rate $>90$ bpm Respiratory rate $>20$ breaths per minute or arterial $\text{CO}_2$ tension $<32$ mm Hg or need for mechanical ventilation White blood cell count $>12\,000/\text{mm}^3$ or $<4000/\text{mm}^3$ or immature forms $>10\%$
Sepsis	SIRS and documented infection (culture or Gram stain of blood, sputum, urine, or normally sterile body fluid positive for pathogenic microorganism; or focus of infection identified by visual inspection, eg, ruptured bowel with free air or bowel contents found in abdomen at surgery, wound with purulent discharge)
Severe sepsis	Sepsis and at least 1 sign of organ hypoperfusion or organ dysfunction: Areas of mottled skin Capillary refilling time $\geq 3$ s Urinary output $<0.5$ mL/kg for at least 1 h or renal replacement therapy Lactates $>2$ mmol/L Abrupt change in mental status or abnormal electroencephalogram Platelet counts $<100\,000/\text{mL}$ or disseminated intravascular coagulation Acute lung injury—acute respiratory distress syndrome Cardiac dysfunction (echocardiography)
Septic shock	Severe sepsis and 1 of the following: Systemic mean blood pressure $<60$ mm Hg ( $<80$ mm Hg if previous hypertension) after 20–30 mL/kg starch or 40–60 mL/kg serum saline, or pulmonary capillary wedge pressure between 12 and 20 mm Hg Need for dopamine $>5\ \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ or norepinephrine or epinephrine $<0.25\ \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ to maintain mean blood pressure above 60 mm Hg (80 mm Hg if previous hypertension)
Refractory septic shock	Need for dopamine $>15\ \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ or norepinephrine or epinephrine $>0.25\ \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ to maintain mean blood pressure above 60 mm Hg (80 mm Hg if previous hypertension)

SIRS indicates systemic inflammatory response syndrome.

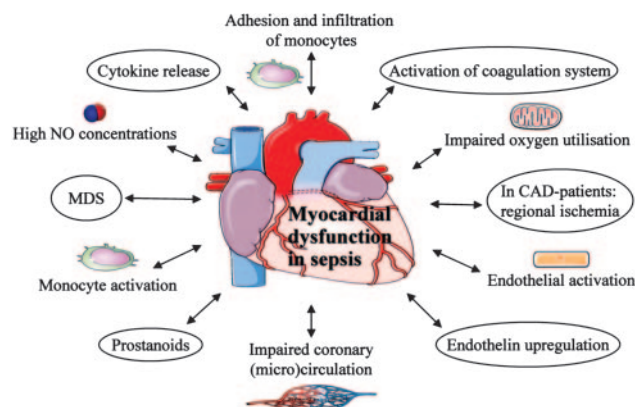
The purpose of the present review is to delineate some characteristics of septic myocardial dysfunction, to assess the most commonly cited and reported underlying mechanisms of cardiac dysfunction in sepsis, and to briefly outline current therapeutic strategies and possible future approaches. This review is not intended to be all inclusive.

### Characteristics of Myocardial Dysfunction in Sepsis

Using portable radionuclide cineangiography, Calvin et al<sup>13</sup> were the first to demonstrate myocardial dysfunction in adequately volume-resuscitated septic patients with decreased ejection fraction and increased end-diastolic volume index. Adding pulmonary artery catheters to serial radionuclide cineangiography, Parker and colleagues<sup>11</sup> extended these observations with the 2 major findings that (1) survivors of septic shock were characterized by increased end-diastolic volume index and decreased ejection fraction, whereas non-survivors typically maintained normal cardiac volumes, and (2) these acute changes in end-diastolic volume index and ejection fraction, although sustained for several days, were reversible. More recently, echocardiographic studies have demonstrated impaired left ventricular systolic and diastolic function in septic patients.<sup>14–16</sup> These human studies, in conjunction with experimental studies ranging from the cellular level<sup>17</sup> to isolated heart studies<sup>18,19</sup> and to in vivo animal models,<sup>20–22</sup> have clearly established decreased contractility and impaired myocardial compliance as major factors that cause myocardial dysfunction in sepsis.

Notwithstanding the functional and structural differences between the left and right ventricle, similar functional alterations, as discussed above, have been observed for the right ventricle, which suggests that right ventricular dysfunction in sepsis closely parallels left ventricular dysfunction.<sup>23–26</sup> However, the relative contribution of the right ventricle to septic cardiomyopathy remains unknown.

Myocardial dysfunction in sepsis has also been analyzed with respect to its prognostic value. Parker et al,<sup>27</sup> reviewing septic patients on initial presentation and at 24 hours to determine prognostic indicators, found a heart rate of  $<106$  bpm to be the only cardiac parameter on presentation that



Synopsis of potential underlying mechanisms in septic myocardial dysfunction. MDS indicates myocardial depressant substance.

predicted a favorable outcome. At 24 hours after presentation, a systemic vascular resistance index  $>1529 \text{ dyne} \cdot \text{s}^{-1} \cdot \text{cm}^{-5} \cdot \text{m}^{-2}$ , a heart rate  $<95 \text{ bpm}$  or a reduction in heart rate  $>18 \text{ bpm}$ , and a cardiac index  $>0.5 \text{ L} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$  suggested survival.<sup>27</sup> In a prospective study, Rhodes et al<sup>28</sup> demonstrated the feasibility of a dobutamine stress test for outcome stratification, with nonsurvivors being characterized by an attenuated inotropic response. The well-established biomarkers in myocardial ischemia and heart failure, cardiac troponin I and T, as well as B-type natriuretic peptide, have also been evaluated with regard to sepsis-associated myocardial dysfunction. Although B-type natriuretic peptide studies have delivered conflicting results in septic patients (for review, see Maeder et al<sup>29</sup>), several small studies have reported a relationship between elevated cardiac troponin T and I and left ventricular dysfunction in sepsis, as assessed by echocardiographic ejection fraction<sup>30–33</sup> or pulmonary artery catheter-derived left ventricular stroke work index.<sup>34</sup> Cardiac troponin levels also correlated with the duration of hypotension<sup>35</sup> and the intensity of vasopressor therapy.<sup>34</sup> In addition, increased sepsis severity, measured by global scores such as the Simplified Acute Physiology Score II (SAPS II) or the Acute Physiology And Chronic Health Evaluation II score (APACHE II), was associated with increased cardiac troponin levels,<sup>31,33</sup> as was poor short-term prognosis.<sup>32,33,35,36</sup> Despite the heterogeneity of study populations and type of troponin studied, the mentioned studies were univocal in concluding that elevated troponin levels in septic patients reflect higher disease severity, myocardial dysfunction, and worse prognosis. In a recent meta-analysis of 23 observational studies, Lim et al<sup>37</sup> found cardiac troponin levels to be increased in a large percentage of critically ill patients. Furthermore, in a subset of studies that permitted adjusted analysis and comprised 1706 patients, this troponin elevation was associated with an increased risk of death (odds ratio, 2.5; 95% CI, 1.9 to 3.4,  $P<0.001$ )<sup>37</sup>; however, the underlying mechanisms clearly require further research.

Thus, it appears reasonable to recommend inclusion of cardiac troponins in the monitoring of patients with severe sepsis and septic shock to facilitate prognostic stratification and to increase alertness to the presence of cardiac dysfunction in individual patients. However, it remains to be shown whether risk stratification based on cardiac troponins can identify patients in whom aggressive therapeutic regimens might reap the greatest benefit and so translate into a survival benefit.

### Mechanisms Underlying Myocardial Dysfunction in Sepsis

Cardiac depression during sepsis is probably multifactorial (Figure). Nevertheless, it is important to identify individual contributing factors and mechanisms to generate worthwhile therapeutic targets. As a consequence, a vast array of mechanisms, pathways, and disruptions in cellular homeostasis have been examined in septic myocardium.

#### Global Ischemia

An early theory of myocardial depression in sepsis was based on the hypothesis of global myocardial ischemia; however,

septic patients have been shown to have high coronary blood flow and diminished coronary artery–coronary sinus oxygen difference.<sup>38</sup> As in the peripheral circulation, these alterations can be attributed to disturbed flow autoregulation or disturbed oxygen utilization.<sup>39,40</sup> Coronary sinus blood studies in patients with septic shock have also demonstrated complex metabolic alterations in septic myocardium, including increased lactate extraction, decreased free fatty acid extraction, and decreased glucose uptake.<sup>41</sup> Furthermore, several magnetic resonance studies in animal models of sepsis have demonstrated the presence of normal high-energy phosphate levels in the myocardium.<sup>42,43</sup> It has also been proposed that myocardial dysfunction in sepsis may reflect hibernating myocardium.<sup>44</sup> To reach this conclusion, Levy et al<sup>44</sup> studied a murine cecal ligation and double-puncture model and observed diminished cardiac performance, increased myocardial glucose uptake, and deposits of glycogen in a setting of preserved arterial oxygen tension and myocardial perfusion. Although all of the above-mentioned findings reflect important alterations in coronary flow and myocardial metabolism, mirroring effects observed in peripheral circulation during sepsis, there is no evidence supporting global ischemia as an underlying cause of myocardial dysfunction in sepsis. However, in septic patients with coexistent and possibly undiagnosed coronary artery disease (CAD), regional myocardial ischemia or infarction secondary to CAD may certainly occur. The manifestation of myocardial ischemia due to CAD might even be facilitated by the volatile hemodynamics in sepsis, as well as by the generalized microvascular dysfunction so frequently observed in sepsis.<sup>45</sup> Additional CAD-aggravating factors encountered in sepsis encompass generalized inflammation and the activated coagulatory system. Furthermore, the endothelium plays a prominent role in sepsis (see below), but little is known of the impact of preexisting, CAD-associated endothelial dysfunction in this context. In a postmortem study of 21 fatal cases of septic shock, previously undiagnosed myocardial ischemia at least contributed to death in 7 of the 21 cases (all 21 patients were males, with a mean age of 60.4 years).<sup>46</sup> It certainly appears prudent to remain wary of CAD complications while treating sepsis, especially in patients with identifiable risk factors and in view of the ever-increasing mean age of intensive care unit patients and including septic patients.

#### Myocardial Depressant Substance

A circulating myocardial depressant factor in septic shock was first proposed more than 50 years ago.<sup>47</sup> Parrillo et al<sup>48</sup> quantitatively linked the clinical degree of septic myocardial dysfunction with the effect the serum, taken from respective patients, had on rat cardiac myocytes, with clinical severity correlating well with the decrease in extent and velocity of myocyte shortening. These effects were not seen when serum from convalescent patients whose cardiac function had returned to normal was applied or when serum was obtained from other critically ill, nonseptic patients.<sup>48</sup> In extension of these findings, ultrafiltrates from patients with severe sepsis and simultaneously reduced left ventricular stroke work index ( $<30 \text{ g} \cdot \text{m}^{-1} \cdot \text{m}^{-2}$ ) displayed cardiotoxic effects and contained significantly increased concentrations of interleu-

kin (IL)-1, IL-8, and C3a.<sup>49</sup> Recently, Mink et al<sup>50</sup> demonstrated that lysozyme c, a bacteriolytic agent believed to originate mainly from disintegrating neutrophilic granulocytes and monocytes, mediates cardiodepressive effects during *Escherichia coli* sepsis and, importantly, that competitive inhibition of lysozyme c can prevent myocardial depression in the respective experimental sepsis model. Additional potential candidates for myocardial depressant substance include other cytokines, prostanoids, and nitric oxide (NO). Some of these will be discussed below.

### Cytokines

Infusion of lipopolysaccharide (LPS, an obligatory component of Gram-negative bacterial cell walls) into both animals and humans<sup>51</sup> partially mimics the hemodynamic effects of septic shock.<sup>51,52</sup> However, only a minority of patients with septic shock have detectable LPS levels, and the prolonged time course of septic myocardial dysfunction and the chemical characteristics of LPS are not consistent with LPS representing the sole myocardial depressant substance.<sup>48,53</sup> Tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) is an important early mediator of endotoxin-induced shock.<sup>54</sup> TNF- $\alpha$  is derived from activated macrophages, but recent studies have shown that TNF- $\alpha$  is also secreted by cardiac myocytes in response to sepsis.<sup>55</sup> Although application of anti-TNF- $\alpha$  antibodies improved left ventricular function in patients with septic shock,<sup>56</sup> subsequent studies using monoclonal antibodies directed against TNF- $\alpha$  or soluble TNF- $\alpha$  receptors failed to improve survival in septic patients.<sup>57–59</sup> IL-1 is synthesized by monocytes, macrophages, and neutrophils in response to TNF- $\alpha$  and plays a crucial role in the systemic immune response. IL-1 depresses cardiac contractility by stimulating NO synthase (NOS).<sup>60</sup> Transcription of IL-1 is followed by delayed transcription of IL-1 receptor antagonist (IL-1-ra), which functions as an endogenous inhibitor of IL-1. Recombinant IL-1-ra was evaluated in phase III clinical trials, which showed a tendency toward improved survival<sup>61</sup> and increased survival time in a retrospective analysis of the patient subgroup with the most severe sepsis<sup>62</sup>; however, to date, this initially promising therapy has failed to deliver a statistically significant survival benefit. IL-6, another proinflammatory cytokine, has also been implicated in the pathogenesis of sepsis and is considered a more consistent predictor of sepsis than TNF- $\alpha$  because of its prolonged elevation in the circulation.<sup>63</sup> Although cytokines may very well play a key role in the early decrease in contractility, they cannot explain the prolonged duration of myocardial dysfunction in sepsis, unless they result in the induction or release of additional factors that in turn alter myocardial function, such as prostanoids or NO.<sup>64,65</sup>

### Prostanoids

Prostanoids are produced by the cyclooxygenase enzyme from arachidonic acid. The expression of cyclooxygenase enzyme-2 is induced, among other stimuli, by LPS and cytokines (cyclooxygenase enzyme-1 is expressed constitutively).<sup>66</sup> Elevated levels of prostanoids such as thromboxane and prostacyclin, which have the potential to alter coronary autoregulation, coronary endothelial function, and intracoro-

nary leukocyte activation, have been demonstrated in septic patients.<sup>67</sup> Early animal studies with cyclooxygenase inhibitors such as indomethacin yielded very promising results.<sup>68,69</sup> Along with other positive results, these led to an important clinical study involving 455 septic patients who were randomized to receive intravenous ibuprofen or placebo.<sup>70</sup> Unfortunately, that study did not demonstrate improved survival for the treatment arm. Similarly, a more recent, smaller study on the effects of lornoxicam failed to provide evidence for a survival benefit through cyclooxygenase inhibition in sepsis.<sup>71</sup> Animal studies aimed at elucidating possible benefits of isotype-selective cyclooxygenase inhibition have so far produced conflicting results.<sup>72,73</sup>

### Endothelin-1

Endothelin-1 (ET-1; for an in-depth review of endothelin in sepsis, see Gupta et al<sup>74</sup>) upregulation has been demonstrated within 6 hours of LPS-induced septic shock.<sup>75</sup> Cardiac overexpression of ET-1 triggers an increase in inflammatory cytokines (among others, TNF- $\alpha$ , IL-1, and IL-6), interstitial inflammatory infiltration, and an inflammatory cardiomyopathy that results in heart failure and death.<sup>76</sup> The involvement of ET-1 in septic myocardial dysfunction is supported by the observation that tezosentan, a dual endothelin-A and endothelin-B receptor antagonist, improved cardiac index, stroke volume index, and left ventricular stroke work index in endotoxemic shock.<sup>77</sup> However, higher doses of tezosentan exhibited cardiotoxic effects and led to increased mortality.<sup>77</sup> Although ET-1 has been demonstrated to be of pathophysiological importance in a wide array of cardiac diseases through autocrine, endocrine, or paracrine effects, its biosynthesis, receptor-mediated signaling, and functional consequences in septic myocardial dysfunction warrant further investigation to assess the therapeutic potential of ET-1 receptor antagonists.

### Nitric Oxide

NO exerts a plethora of biological effects in the cardiovascular system.<sup>78</sup> It has been shown to modulate cardiac function under physiological and a multitude of pathophysiological conditions. In healthy volunteers, low-dose NO increases LV function, whereas inhibition of endogenous NO release by intravenous infusion of the NO synthase (NOS) inhibitor *N*<sup>G</sup>-monomethyl-L-arginine reduced the stroke volume index.<sup>79</sup> Higher doses of NO have been shown to induce contractile dysfunction by depressing myocardial energy generation.<sup>80</sup> The absence of the important NO scavenger myoglobin (Mb) in Mb knockout mice results in impaired cardiac function that is partially reversible by NOS inhibition.<sup>81</sup> Endogenous NO contributes to hibernation in response to myocardial ischemia by reducing oxygen consumption and preserving calcium sensitivity and contractile function.<sup>82</sup> NO also represents a potent modulator of myocardial ischemia/reperfusion injury. However, as in sepsis-related NO research, the reported effects of NO on ischemia/reperfusion injury are inconsistent owing to a multitude of confounding experimental factors.<sup>83</sup>

Sepsis leads to the expression of inducible NOS (iNOS) in the myocardium,<sup>84,85</sup> followed by high-level NO production,



which in turn importantly contributes to myocardial dysfunction, in part through the generation of cytotoxic peroxynitrite, a product of NO and superoxide (for an excellent review, see Pacher et al<sup>86</sup>). In iNOS-deficient mice, cardiac function is preserved after endotoxin challenge.<sup>87</sup> Nonspecific NOS inhibition restores cardiac output and stroke volume after LPS injection.<sup>88</sup> Strikingly, in septic patients, infusion of methylene blue, a nonspecific NOS inhibitor, improves mean arterial pressure, stroke volume, and left ventricular stroke work and decreases the requirement for inotropic support but, unfortunately, does not alter outcome.<sup>89</sup> An interesting study comparing the inhibition of NO superoxide and peroxynitrite in cytokine-induced myocardial contractile failure found peroxynitrite to indeed be the most promising therapeutic target.<sup>90</sup> It has also been proposed that the constitutively expressed mitochondrial isoform of NOS (mtNOS), the expression of which can be augmented by induction, controls rates of oxidative phosphorylation by inhibiting various steps of the respiratory chain.<sup>91</sup> Although this hypothesis would provide a plausible explanation for the reduced coronary oxygen extraction observed during sepsis (see above), the effects of sepsis on expression of mtNOS and NO generation remain to be explored. Furthermore, the constitutively expressed endothelial NOS (eNOS), previously neglected in the context of sepsis, has been shown to be an important regulator of iNOS expression, resulting in a more stable hemodynamic status in eNOS-deficient mice after endotoxemia.<sup>92</sup> Very recently, a functional NOS in red blood cells (rbcNOS) was identified that regulates deformability of erythrocyte membranes and inhibits activation of platelets.<sup>93</sup> With both effect targets thus far demonstrated for rbcNOS lying at the core of microvascular dysfunction in sepsis, this discovery opens a whole new window to NO-related sepsis research. Given the existence of different NOS isoforms and their various modulating interactions, dose-dependent NO effects, and the precise balance of NO, superoxide, and thus peroxynitrite generated in subcellular compartments, further advances in our understanding of the complex NO biology and its derived reactive nitrogen species hold the promise of revealing new, more specific and effective therapeutic targets.

### Adhesion Molecules

Surface-expression upregulation of intercellular adhesion molecule-1 and vascular cell adhesion molecule-1 has been demonstrated in murine coronary endothelium and cardiomyocytes after LPS and TNF- $\alpha$  stimulation.<sup>94</sup> After cecal ligation and double puncture, myocardial intercellular adhesion molecule-1 expression increases in rats.<sup>95</sup> Vascular cell adhesion molecule-1 blockade with antibodies has been shown to prevent myocardial dysfunction and decrease myocardial neutrophil accumulation,<sup>94,96</sup> whereas both knockout and antibody blockade of intercellular adhesion molecule-1 ameliorate myocardial dysfunction in endotoxemia without affecting neutrophil accumulation.<sup>94</sup> In addition, neutrophil depletion does not protect against septic cardiomyopathy, which suggests that the cardiotoxic potential of neutrophils infiltrating the myocardium is of lesser importance in this context.<sup>94</sup> Other aspects of adhesion molecules are discussed in conjunction with possible statin effects below.

### Therapeutic Approaches: The Present and the Future

A detailed discussion of therapeutic options in septic patients would clearly be beyond the scope of this review, and readers are kindly referred to the multiple excellent reviews published on the subject (eg, Hotchkiss and Karl,<sup>2</sup> Annane et al,<sup>4</sup> and Dellinger et al<sup>97</sup>). Although a number of preventive measures, such as prophylactic antibiotics, maintenance of normoglycemia, selective digestive tract decontamination, vaccines, and intravenous immunoglobulin, have shown benefit in distinct patient populations, preventive strategies with a broader aim remain elusive. Once sepsis is manifest (see the Table for criteria), prompt and adequate antibiotic therapy accompanied by surgical removal of the infectious focus, if indicated and feasible, is the mainstay and also the only strictly causal line of therapy. In the presence of severe sepsis and septic shock, supportive treatment in addition to causal therapy is mandatory. Supportive therapy encompasses early and goal-directed fluid resuscitation,<sup>9</sup> vasopressor and inotropic therapy, red blood cell transfusion, mechanical ventilation, and renal support when indicated. It is very likely beneficial to monitor cardiac performance in these patients. A wide array of techniques are available for this purpose, ranging from echocardiography to pulmonary catheters, thermolulution techniques, and pulse pressure analysis.<sup>98</sup> Because none of these techniques have demonstrated superiority, physicians should use the method with which they are most familiar. Whichever method is chosen, it should be applied frequently to tailor supportive therapy to the individual patient and to achieve the “gold standard” of early goal-directed therapy. In recent years, several attempts have been made to therapeutically address myocardial dysfunction in sepsis. Although the combination of norepinephrine as vasopressor and dobutamine as inotropic agent is probably the most frequently applied in septic shock, there is currently no evidence to recommend one catecholamine over the other.<sup>97</sup> In human endotoxemia, epinephrine has been demonstrated to inhibit proinflammatory pathways and coagulation activation, as well as to augment antiinflammatory pathways,<sup>99,100</sup> whereas no immunomodulatory or coagulant effects could be demonstrated for dobutamine in a similar setting.<sup>101</sup> Isoproterenol has recently been applied successfully in a small group of patients with septic shock, no known history of CAD, and inappropriate mixed venous oxygen concentration despite correction of hypoxemia and anemia.<sup>102</sup> In a cecal ligation and double-puncture model of sepsis, the  $\beta$ -blocker esmolol given continuously after sepsis induction improved myocardial oxygen utilization and attenuated myocardial dysfunction,<sup>103</sup> which suggests that therapeutic strategies proven in ischemic heart failure might also hold promise in septic cardiomyopathy. However, the optimal mode of  $\beta$ -receptor stimulation (or indeed inhibition) to limit myocardial dysfunction remains a wide-open field for inspired investigation.

Given the generally accepted view of sepsis as a disease largely propelled by an inappropriate immune response, numerous basic research and clinical trials have been undertaken to curb the lethal toll of sepsis through modulation of this uncontrolled immune response.<sup>2,3</sup> To date, activated

protein C<sup>104</sup> and low-dose hydrocortisone<sup>105</sup> have emerged as the only inflammation-modulating substances that have been confirmed to be of benefit in patients with severe sepsis and septic shock. Over the past years, increasing evidence has accumulated that suggests that inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A reductase, or statins, have therapeutic benefits independent of cholesterol lowering, termed “pleiotropic” effects. These have added a wide scope of potential targets for statin therapy that range from decreasing renal function loss<sup>106</sup> and lowering mortality in patients with diastolic heart failure<sup>107</sup> to prevention and treatment of stroke,<sup>108</sup> to name just a few. These pleiotropic effects include antiinflammatory and antioxidative properties, improvement of endothelial function, and increased NO bioavailability and thus might contribute to the benefit observed with statin therapy. Notably, these important immunomodulatory effects of statins have been demonstrated to be independent of lipid lowering<sup>109</sup> and appear to be mediated via interference with the synthesis of mevalonate metabolites (nonsteroidal isoprenoid products). Blockade of the mevalonate pathway has been shown to suppress T-cell responses,<sup>110</sup> reduce expression of class II major histocompatibility complexes on antigen presenting cells,<sup>109</sup> and inhibit chemokine synthesis in peripheral blood mononuclear cells.<sup>111</sup> Furthermore, CD11b integrin expression and CD11b-dependent adhesion of monocytes have been found to be attenuated by the initiation of statin treatment in hypercholesterolemic patients.<sup>112</sup> In this context, Yoshida et al<sup>113</sup> have reported that statins reduce the expression of both monocytic and endothelial adhesion molecules, eg, the integrin leukocyte function-associated antigen-1 (LFA-1), via an inhibition of Rho GTPases, in particular their membrane anchoring by geranylation. In addition, mechanisms for antiinflammatory actions of statins have been revealed that are not related to the isoprenoid metabolism. For instance, Weitz-Schmidt et al<sup>114</sup> have identified that some statins act as direct antagonists of LFA-1 owing to their capacity to bind to the regulatory site in the LFA-1 i-domain. In addition to these multifaceted antiinflammatory effects, statins may interfere with activation of the coagulation cascade, as illustrated by the suppression of LPS-induced monocyte tissue factor in vitro.<sup>115</sup> Beyond their immunomodulatory functions, statins have been shown to exert direct antichlamydial effects during pulmonary infection with *Chlamydia pneumoniae* in mice,<sup>116</sup> and a recent report suggests the benefit of statins may also extend to viral pathogens.<sup>117</sup>

Given the strong impact of statins on inflammation, statins might represent a welcome enforcement in the battle against severe infectious diseases such as sepsis. Consequently, several investigators have evaluated the role of statins in the prevention and treatment of sepsis. In a retrospective analysis, Liappis et al<sup>118</sup> demonstrated a reduced overall and attributable mortality in patients with bacteremia who were treated concomitantly with statins. Pretreatment with simvastatin has been shown to profoundly improve survival in a polymicrobial murine model of sepsis by preservation of cardiovascular function and inhibition of inflammatory alterations.<sup>19</sup> Encouraged by these findings, the same model was used to successfully treat sepsis in a clinically feasible fashion, ie, treatment was initiated several hours after the

onset of sepsis. With different statins (atorvastatin, pravastatin, and simvastatin) being effective, the therapeutic potential of statins in sepsis appears to be a class effect.<sup>22</sup> Recently, Steiner et al<sup>119</sup> observed that pretreatment with simvastatin can suppress the inflammatory response induced by LPS in healthy human volunteers. Furthermore, in a prospective observational cohort study in patients with acute bacterial infections performed by Almog et al,<sup>120</sup> previous treatment with statins was associated with a considerably reduced rate of severe sepsis and intensive care unit admissions. A total of 361 patients were enrolled in that study, and 82 of these patients had been treated with statins for at least 4 weeks before their admission. Severe sepsis developed in 19% of patients in the no-statin group compared with only 2.4% in patients who were taking statins. The intensive care unit admission rates were 12.2% for the no-statin group and 3.7% for the statin group. Because of the number of patients enrolled, the study was not powered to detect differences in mortality, although the large effect on sepsis rate and intensive care unit admission were at least suggestive. As the most recent development in this field, Hackam et al<sup>121</sup> have produced an impressive observational study by initial evaluation of 141 487 cardiovascular patients, which resulted in a well-paired and homogenous study cohort of 69 168 patients after propensity-based matching. Drawing from this solid base, Hackam and coauthors were able to support the conclusion that statin therapy is associated with a considerably decreased rate of sepsis (hazard ratio, 0.81; 95% CI, 0.72 to 0.90), severe sepsis (hazard ratio, 0.83; 95% CI, 0.70 to 0.97), and fatal sepsis (hazard ratio, 0.75; 95% CI, 0.61 to 0.93). This protective effect prevailed at both high and low statin doses and for several clinically important subpopulations, such as diabetic and heart failure patients.

As has been suggested previously,<sup>122</sup> statins might provide cumulative benefit by reducing mortality from cardiovascular and infectious diseases such as sepsis. However, statins may have detrimental effects in distinct subsets of patients. Therefore, caution should prevail, and the use of statins in patients with sepsis must be accompanied by meticulous monitoring of unexpected side effects and well-designed randomized, controlled clinical trials.

Beyond an apparent rationale for randomized trials on statins in sepsis, it is notable that the results with other immunomodulatory approaches in sepsis have yielded rather limited success. For instance, use of the anti-TNF antibody F(ab')<sub>2</sub> fragment afelimomab led to a significant but rather modest reduction in risk of death and to improved organ-failure scores in patients with severe sepsis and elevated IL-6 levels.<sup>123</sup> Moreover, a selective inhibitor of group IIA secretory phospholipase A2 failed to improve clinical outcome for patients with severe sepsis, with a negative trend most pronounced among patients with cardiovascular failure.<sup>124</sup> Hence, because none of the available strategies proven to be effective in sepsis are designed specifically to target myocardial dysfunction, one might conclude that strategies that preferentially address cardiac morbidity in sepsis may be a promising area for investigation. For instance, lipoteichoic acid, a major virulence factor in Gram-positive sepsis, causes cardiac depression by activating myocardial TNF- $\alpha$  synthesis

via CD14 and induces coronary vascular disturbances by activating thromboxane 2 synthesis. It thus contributes to cardiac depression and may therefore be a worthwhile and cardiac-specific target.<sup>125</sup> The implications of intensified efforts in the search for successful novel approaches to the treatment of myocardial dysfunction in sepsis may be considerable with regard to improved patient care that results in reduced mortality. This is of major significance in view of the substantial economic consequences of increasing sepsis morbidity in an aging population.

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### Disclosures

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