Endotoxin Attacks the Cardiovascular System

Black Death at the Tollgate*

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Bacteria have attacked the cardiovascular system since time immemorial. The propensity for pathogenic bacteria to effect cardiovascular collapse and death has shaped human history. Black Death, caused by Yersinia pestis, killed tens of millions in China, the Middle East, and decimated one-third of the European population in the 14th century. More recently, fatalities from toxic Escherichia coli and the sinister threat of bio-weapons serve as poignant reminders of the dangers of severe bacterial infections.

The propinquity of bacteria as part of the normal flora poses an ever-present threat. Bacteria colonize humans in symbiotic and commensal relationships that are neither beneficial nor detrimental. However, disruption of normal barriers (e.g., skin or gastrointestinal tract) permits bacteria to invade into the bloodstream (bacteremia) and release toxins (endotoxemia). Severe infections induce systemic inflammatory responses (sepsis) that predispose to multiorgan failure, hypotension (septic shock), and death.

See page 1656

Severe sepsis causes as many deaths as does acute myocardial infarction (MI) in the U.S., with an annual cost of $16.7 billion (1). The incidence rates of sepsis and deaths related to sepsis have increased significantly over the past 20 years (2). This has been related to an increase in invasive procedures and predisposing conditions, such as aging, chronic diseases, and immunosuppression (e.g., cancer, HIV, transplants). The high mortality from sepsis and septic shock (e.g., 30% to 50%) has motivated a search for more effective treatments based on pathogenesis (3,4).

In 1892, Richard Peiffer related the pathogenicity of bacteria to endotoxins, which others subsequently characterized as lipopolysaccharide (LPS) (5,6); LPS is the major component comprising 75% of the outer cell wall of gram-negative bacteria (6). Lysis of a single gram-negative bacterium releases approximately 10^6 LPS molecules. Minute amounts of LPS activate coagulation and complement cascades and effector cells of innate immunity to release a cascade of mediators that neutralize invading bacteria. The transmembrane receptor responsible for LPS sensing and signal transduction remained elusive until this past decade, when it was identified as toll-like receptor 4 (TLR-4) in mammals. The TLR-4 resembles Toll proteins of Drosophila, an ancient, evolutionarily conserved antimicrobial system in vertebrates, invertebrates, and plants. These pattern recognition receptors identify and defend against invasion by foreign pathogens, such as LPS.

The LPS activates innate immune-response cells through TLR-4 (e.g., monocytes, macrophages, neutrophils, and endothelial cells) with exuberant production of cytotoxic mediators that may contribute to organ damage in sepsis (3,7). Cells that express TLR-4, such as cardiac myocytes, are susceptible to direct damage by LPS, independently of mediators. Low levels of LPS depress cardiac myocyte contractility, impair beta-adrenergic responsiveness, and induce cell death by apoptosis to contribute to cardiac depression in sepsis (8,9).

Key mediators have been targeted for therapy to improve survival in sepsis. Based on the success of preclinical studies, clinical trials have evaluated inhibitors of LPS, cytokines (e.g., TNFα and IL-1), oxygen radicals, platelet activating factor, prostaglandins, bradykinin, and nitric oxide (7,10,11). Unfortunately, the majority of clinical trials failed to improve mortality, creating a “graveyard for pharmaceutical companies” (although recent novel approaches such as activated protein C have shown promise) (11). The widespread failure of therapeutic trials has been disheartening, raising concerns that survival has improved little since the introduction of antibiotics over 50 years ago. This despair may be unwarranted because the causes, context, and definition of sepsis have undergone major transformations. Epidemiologic data have documented advances in therapy with decreased in-hospital mortality in the U.S. over the past 20 years (from 28% to 18%), even though the total number of deaths has increased (2).

It is important to understand why favorable results from experimental models have not translated into improved outcomes in therapeutic trials. The approach of identifying and inhibiting specific immune mediators warrants critical reappraisal. It may be unrealistic to expect that a “magic bullet” targeting a single pathway can abrogate the sequelae of sepsis. Early therapy that interrupts proximal pathways can be successful in preclinical studies, but this is difficult to achieve in clinical sepsis. Patients are often in the later stages of sepsis before the diagnosis is established and therapy is contemplated. By this time, LPS has activated a cascade of interacting mediators with redundant pathways that induce tissue damage (3). Organ failure adds another dimension of complexity with additional mechanisms for inducing tissue damage. At this stage, it may be too late to alter the clinical course by blocking a single or few branches in this complex network.

Preclinical studies utilize homogeneous models of sepsis with controlled timing and dose of the insult, treatment,

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host factors (e.g., age and genetics), and mortality. This uniformity does not exist in clinical trials. Including patients at low risk for death makes it more difficult to prove that therapy improves mortality (10). In fact, inhibiting normal innate immune mechanisms in low-risk patients may have deleterious effects. In the clinical setting, few criteria exist for titrating doses or determining if therapy is contraindicated.

Heterogeneity of the target population makes it difficult to evaluate the effectiveness of therapy (7). Patients vary in their susceptibility, etiology, and severity of sepsis and responses to therapy. Elderly patients are more prone to severe sepsis, with potential racial and gender differences (1,2). Genetic polymorphisms of TLR-4 predispose to more severe infections (12). Risk stratification schemes that take into account the cause, severity, and host responses are needed to identify patients who are most likely to benefit from specific therapies. This approach has been employed with success in other complex conditions, such as cancer and coronary artery disease.

In this issue of the Journal, Pleiner et al. (13) examined LPS effects on vascular responsiveness. Low doses of LPS injected into normal subjects impaired forearm blood flow responses to vasoconstrictors (norepinephrine, angiotensin II, and vasopressin) and lowered vitamin C levels after 4 h. These abnormalities were corrected by infusing high doses of the antioxidant, vitamin C. This suggests that LPS impairs vasoconstrictor responses by inducing oxidative stress.

These results may add to the armamentarium to treat vasodilation with endotoxemia in conditions such as sepsis. Sepsis is the most common cause of vasodilatory shock, with refractoriness to vasoconstrictors a harbinger of death (14). Optimizing hemodynamics and tissue oxygenation early in sepsis decreases multorgan failure and improves survival (15). However, several issues need to be addressed before the results from this model can be applied to sepsis. This cautious approach is not unique for the Pleiner et al. (13) study but is mandated by the frequent failure to extrapolate favorable preclinical results into improved outcomes in therapeutic trials.

First, infusing low doses of endotoxin into normal volunteers is not a model of sepsis. This mimics subacute endotoxemia, which occurs with low circulating levels of LPS in conditions such as decompenated heart failure (16), cardiopulmonary bypass surgery (17), chronic infections (e.g., respiratory, gastrointestinal, genitourinary), and smoking (18). It is unknown whether oxidative stress with impaired vasoconstrictor response occurs in these conditions, but that would be an interesting implication of these results.

Second, oxidative stress in sepsis involves several reactive oxygen species (e.g., superoxide, hydrogen peroxide, hydroxyl radicals) and antioxidative defense mechanisms (e.g., superoxide dismutase, catalase, vitamins C and E, and glutathione) (19). Scant clinical data prove that antioxidant therapy improves survival. This may relate to the need to identify the specific type and source of reactive oxygen species involved and/or requirement to use multiple antioxidants.

Third, impairments were measured 4 h after LPS exposure in healthy subjects. Oxidative stress may impair vasoconstrictor responses early after LPS, but this may not be the sole or dominant mechanism with higher levels of LPS or in sepsis. Sepsis activates multiple pathways that induce vasodilatory shock, including nitric oxide (14). Nitric oxide is not involved in this model, but that does not exclude an important role in sepsis. Antioxidant therapy that is effective in normal subjects with normal endothelial function may not be beneficial in patients with preexisting and/or acquired endothelial dysfunction in sepsis.

Fourth, refractory vasodilation and oxidative stress may be important in some, but not all, cases of sepsis. Cardiovascular dysfunction is present in 25% of patients with severe sepsis (1). The broad application of antioxidant therapy for all patients with sepsis may not improve outcome or adequately test the hypothesis that reducing oxidative stress effectively treats refractory hypotension. The subgroup most likely to benefit from therapy needs to be defined along with appropriate endpoints (e.g., use of pressors and mortality).

Finally, there is a potential for treatment to worsen outcome. For example, a phase III clinical trial was aborted when it was found that inhibiting nitric oxide increased mortality in sepsis (despite promising preclinical results) (20). Nitric oxide and reactive oxygen species are protective in controlling the proliferation of invading bacteria. These mediators may cause tissue damage, but routine inhibition might increase mortality. Oxidative stress impairs vasoconstrictor responses, but it may be undesirable to subvert this defense mechanism except in cases of refractory hypotension.

Bacterial attacks on the cardiovascular system have had a storied history. It required five centuries after the Black Death to establish the role of endotoxin, several decades to relate this to LPS, and recent developments to understand how LPS activates cells through Toll-like receptors. Reductionist models have provided invaluable insights, but translating these results into improving survival from sepsis poses unresolved challenges. However, advances in supportive care and adjunctive therapies provide encouragement that progress is being made in solving these complex problems.

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REFERENCES

1. Angus DC, Linde-Zwirble WT, Clermont G, Carcillo J, Pinsky MR. Epidemiology of severe sepsis in the United States: