

# CONGRESS REVIEW



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Physicians should claim credit commensurate with the extent of their participation in the activity.

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## THE SCIENCE AND MEDICINE OF SEPSIS MANAGEMENT

Current understanding of sepsis is marked by a variety of theories on the pathophysiology of sepsis and an expanded number of implicated mediators. Of particular interest are Toll-like receptors (TLR), which play a critical role in inflammation and represent promising potential targets for antisepsis therapy.

### The Immunopathophysiological State of Sepsis H. Shaw Warren, MD

First described by Hippocrates in 400 B.C., sepsis is a controversial topic eliciting various hypotheses as to its immunopathophysiology. The first crucial steps in understanding the pathophysiology occurred in the late 1800s at the Pasteur Institute in France, where landmark experiments demonstrated that heat-killed bacteria injected into animals induce fever and death. "From those experiments, the concept eventually grew into what we know today: that it isn't the replication of bacteria in animals or humans that kills us, but rather the consequences related to the inflammatory response," said H. Shaw Warren, MD, from Massachusetts General Hospital in Boston, Massachusetts, USA.

Another milestone in understanding the pathophysiology of sepsis took place in the 1980s, when recombinant technology made it possible to purify secondary mediators such as cytokines and inject them into animals to induce inflammation. Widespread clinical trials on sepsis treatments, most of which failed, followed in the 1990s. The most recent significant advance in understanding emerged in the late 1990s and early 2000s with the discovery of TLRs and signaling mechanisms used by immune cells to identify microbial threats.

Sepsis is defined according to a disease continuum based on the experiments of Bone and colleagues (*Chest*. 1992;101:1644). The continuum proceeds from infection/trauma to systematic inflammatory response syndrome (SIRS) to sepsis to severe sepsis. In this model, sepsis is characterized as SIRS with a presumed or confirmed infectious process. Severe sepsis, the focus of most research thus far, consists of SIRS and sepsis with one or more signs of organ failure.

"It seems to me that the controversy surrounding sepsis comes from the way it is defined. As defined, sepsis syndrome is a challenge to study," remarked Warren. Sepsis, according to the current definition, is associated with a high, variable mortality rate, encompasses a heterogeneous patient population, and has an unpredictable disease progression. Sepsis also is challenging to investigate because its etiology and pathogenesis remain unclear, and because it is defined by inflammation, regardless of the source.

"Also, very importantly, our knowledge base has expanded tremendously since 1992, when the definition was agreed upon," said Warren. "We now know that sepsis involves more mediators than previously thought, and that Toll-like receptors play an important role. Thus, I think it is time to begin to think about a narrower definition of sepsis." Warren discussed a few theories of sepsis that have surfaced in the past two decades. According to the coagulopathic theory, sepsis represents microbe-induced disseminated intravascular coagulation, as occurs in *Neisseria meningitidis* infection. Similar clotting problems have been linked to ancient organisms (e.g., *Limulus polyphemus* or horseshoe crabs), and knowledge derived from this link has evolved into use of the *Limulus* Amebocyte Lysate test to detect endotoxin. The coagulopathic theory has led to the clinical use of heparin and activated protein as anticoagulation therapies.

The cytokine theory of sepsis rests on the concept that soluble proinflammatory mediators are released in response to a microbial challenge, amplify the host response (inflammation), and can cause death. In animal models, neutralization of some cytokine mediators protects against high-dose bacterial infusion. "This theory emerged in the mid-1980s, with studies demonstrating that tumor necrosis factor (TNF) was a necessary mediator of acute septic shock, and that bacterial-induced death could be blocked by anti-TNF antibodies," explained Warren.

Research over the past 15 or 20 years has also revealed that sepsis can be treated by blocking mediators other than TNF, including various interleukins, leukotrienes, prostaglandins and others. "Our understanding now includes evidence that macrophages get their signal through Toll-like receptors that all converge in a complex signaling system," Warren said. Eventually, the signaling cascade is amplified and modified, inducing inflammation. Clinical response is determined by combi-

nations of receptors and the temporal history of each receptor's activation, making it possible for a limited number of receptors to generate a multitude of clinical syndromes.

Scientists also have discovered that many immune cell agonists have synergistic properties, which can exist between different microbial TLR agonists and between microbial and endogenous agonists. Such synergy creates the potential for interrupting proinflammatory response by blocking either the TLR mechanism or endogenous agonists themselves.

Another theory of sepsis is the anti-inflammatory hypothesis, which purports that sepsis is a biphasic syndrome. The initial phase (i.e., the systemic inflammatory response syndrome) is pro-inflammatory. This is followed by the compensatory anti-inflammatory response syndrome, characterized by an influx of anti-inflammatory molecules such as TNF, interleukin-4 and interleukin-10. "It has also been proposed that these different responses may occur simultaneously, with proinflammatory signals in the tissue and anti-inflammatory signals in the blood trying to control systemic spread," said Warren. "In addition, some have proposed that the anti-inflammatory response is due to apoptosis of cells."

The apoptotic theory of sepsis, based on experiments by Hotchkiss and colleagues, reflects the observation that massive apoptosis of lymphocytes is seen in lymphoid tissues of animals and humans with sepsis. "Hotchkiss proposed that the later phase of immunosuppression may be due, in part, to apoptosis," explained Warren. "He reasoned that, therefore, the secondary nosocomial infections we see, and perhaps viral reactivation, is one of the root causes of sepsis in our intensive care units."

Warren completed his discussion of sepsis hypotheses by explaining the neuroendocrine theory of sepsis. Although much is known about the adrenergic pathways, epinephrine and the role of the adrenal gland, less is understood about the cholinergic pathways and cholinergic anti-inflammatory reflex. "In a remarkable series of experiments, Tracey revealed a reflex arch that shows immune modulation occurs not through humeral mechanisms, but through nerve endings," noted Warren. An afferent arc of the reflex, consisting of nerves that sense injury and infection, activates efferent neural circuits such as the cholinergic anti-inflammatory pathway that modulates immune responses and progression of inflammatory diseases (Tracey KJ. *Nat Rev Immunol*. 2009;9:418). "We can think about this as the vagus nerve providing a constant brake on the inflammatory system, and there are at least two potential implications of this system," said Warren. "One is that a root cause of sepsis could be due to decreased braking, resulting in too much inflammation. The other is the possibility that this pathway could be manipulated either neurologically or pharmacologically to provide treatment."

After discussing these various sepsis theories, Warren asked: "Is inflammation really essential for host defense? Is microbial-induced inflammation always in proportion to what is required?" According to the current paradigm, inflammation has evolved to the right proportion for host defense. "Using the metaphor of walking a tightrope, the person who doesn't have enough inflammation would be immunocompromised or have acute and chronic infection," Warren said. "On the flip side, the person who has too much inflammation would have sepsis or chronic inflammatory disease. Thus, our current paradigm holds that health consists of just the right balance of inflammation to maintain host defense but not cause disease."

Summing up what is known about the immunopathophysiology of sepsis, Warren noted that an all-encompassing single mechanism remains elusive. Host inflammation is believed to be the cause of the syndrome, yet no single component of the immune system is solidly implicated. He added that the natural resistance of mice to inflammation relative to humans might suggest a potential role for blockage of TLRs without compromising host defense.

## The Role of Toll-Like Receptors in Sepsis Judith Hellman, MD

Sepsis is induced by interactions between components of microorganisms and host cells that lead to the upregulation of inflammation pathways, complex coagulation disturbances, problems with oxygen delivery and utilization, and vascular leak; TLRs play a central role in these interactions and the downstream inflammatory effects. "TLRs are critical in the early inflammatory responses to infection and are involved in the development of 'adaptive immunity,'" stated Judith Hellman, MD, from the University of California in San Francisco, California, USA.

"We know that TLR agonists circulate in the bloodstream in sepsis, and that TLR polymorphisms have been identified," Hellman continued, pointing to the higher incidence of TLR4 polymorphism noted in patients with meningococemia (Smirnova I, et al. *Proc Natl Acad Sci USA*. 2003;100:6075) and the increased susceptibility to *Legionella* observed in patients with common TLR5 mutation (Hawn TR, et al. *J Exp Med*. 2003;198:1563). TLRs also are postulated to participate in SIRS from endogenous processes and have been implicated in a broad range of human disease, including ischemia-reperfusion injury, neurologic processes such as neurodegenerative disease, autoimmune diseases and allergies, allograft rejection and atherosclerosis.

The basic structure of TLRs consists of two domains. The extracellular domain contains amino-terminal leucine-rich repeats that interact with the TLR agonists. The cytoplasmic carboxy-terminal Toll interleukin-1 receptor (TIR) domain is responsible for interacting with adapter molecules, inducing the downstream effects of TLR activation and ultimately the production of cytokines and other mediators. There are many different TLRs. Unlike the receptors of the adaptive immune system, which recognize very specific ligands, the TLRs more broadly recognize conserved molecular motifs rather than specific antigens.

The complex TLR signaling system can be simplified conceptually by using two broad categories to describe the different pathways: those that mediate through myeloid differentiation primary response gene (MyD88) and those that mediate through TIR domain-containing adapter-inducing interferon- $\beta$  (TRIF), as shown in Figure 1. "Most of the TLRs mediate inflammation through the adapter protein MyD88," said Hellman. "TLR2 recognizes bacterial lipoproteins, while TLR4 is unique in that it activates both TRIF and MyD88, so it has two different pathways to induce inflammation. That may explain, in part, why TLR4 is such a potent activator of inflammation."

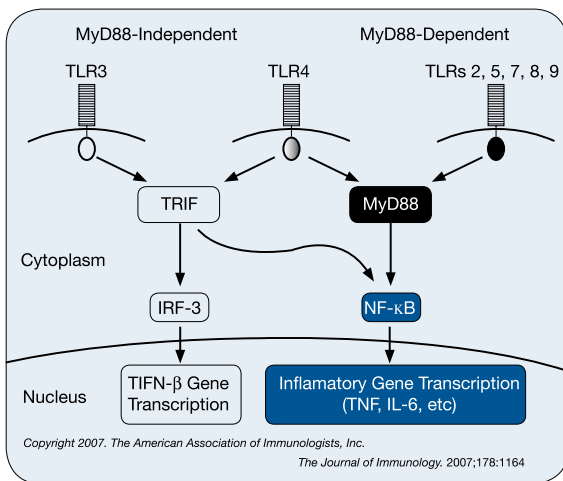


Figure 1. Toll-Like Receptors Signaling System

Research indicates that TLR agonists circulate in the bloodstream both attached to microorganisms, and also separately from microorganisms. Multiple studies have detected lipopolysaccharide (LPS), an agonist for TLR4, in the blood of septic humans and rodents and found TLR2 agonists in septic rodents. "A vast number of studies over the

decades indicate that LPS induces inflammation and other classic septic responses," reported Hellman, "and growing evidence suggests the involvement of bacterial lipoproteins (TLR2) in Gram-positive, fungal, and most recently Gram-negative infection."

There are many reasons why TLR2 should be the focus of interest in sepsis, Hellman stressed. "First, TLR2 agonists are present in all of the major classes of microorganisms that cause sepsis. Second, TLR2 agonists are shed by Gram-negative bacteria into human serum, and they circulate in sepsis models. Third, TLR2 agonists induce inflammation, and fourth, TLR2 activation profoundly modulates inflammatory responses to other Toll-like receptors." The latter point is likely to be important in the clinical context, because patients usually have more than one type of TLR agonist circulating in the bloodstream.

Researchers have observed that TLR2 induces a septic-like process in the lung. TLR2 agonists have been shown to induce lung inflammation, and TLR activation impairs hypoxic pulmonary vasoconstriction and decreases blood oxygenation (Petersen B, et al. *Am J Physiol Lung Cell Mol Physiol*. 2008;294:L300; Hellman J, et al. *J Biol Chem*. 2002; 277:14274).

The endothelium is also important in sepsis and other inflammation-driven processes seen in intensive care unit patients. Endothelial cells actively participate in inflammation through cytokine production, expression of adhesion molecules, activation and trafficking of white blood cells, and expression of other inflammatory mediators. The endothelium contributes to the balance between coagulation and anticoagulation. Endothelial leak occurs in sepsis and other similar inflammation-driven disorders. Interestingly, endothelial cells are activated by TLR agonists. Both TLR2 and TLR4 agonists have been shown to lead to activation of endothelial cells.

"Derangements of coagulation and thrombosis are common during sepsis," noted Hellman. "Coagulation disturbances are believed to be important in the complications of sepsis and SIRS states, with some data linking a coagulation cascade to poor outcomes in sepsis." Such research observed that elevated levels of plasminogen activator inhibitor-1 (PAI-1), an agent involved in inhibiting fibrinolysis, were associated with increased incidences of organ failure and death in sepsis (Mesters RM, et al. *Thromb Haemost*. 1996;75:902; Madoiwa S, et al. *Int J Hematol*. 2006;84:398). "This suggests a role for a hypercoagulable state in the pathogenesis of sepsis-induced organ failure." Activation of TLRs and pathways also has been shown to induce coagulation abnormalities, although the mechanism is not well understood.

In light of the critical role of TLRs in sepsis, can TLR signaling pathways be considered good potential targets for antiseptic therapies? "There's substantial logic supporting targeting Toll-like receptors," stated Hellman. Much of the data involve TLR4, whose agonist is LPS. TLR4-deficient mice have been shown to be LPS-hyporesponsive and yet they do worse with infection, suggesting they require the inflammatory response to help combat infection. "Preclinical studies support targeting TLR4 or MyD88, which are both somewhat required in conjunction for LPS signaling," Hellman said.

TLR2 is also a potential target in sepsis. Among its agonists are lipoproteins, lipoteichoic acid (LTA), lipoarabinomannan and possibly peptidoglycan. Because TLR2 recognizes many different microorganisms, it may be particularly useful in treating early sepsis before pathogen identification. Studies have demonstrated that TLR2 knockout mice are more susceptible to infection (Takeuchi O, et al. *J Immunol*. 2000;165:5392; Puliti M, et al. *Infect Immun*. 2009;77:1524; Echchannaoui H, et al. *J Infect Dis*. 2002;186:798), and some data suggest that TLR2 deficiency is protective against bacterial infection (Wiersinga WJ, et al. *PLoS Med*. 2007;4:e248). Strategies targeting TLR2 have shown promise in preclinical studies (Meng G, et al. *J Clin Invest*. 2004;113:1473; O'Brien GC, et al. *J Immunol*. 2005;174:1020).

Hellman concluded her remarks by emphasizing that TLR4 is the most extensively studied therapeutic target and has shown promise in preclinical studies. "Modulation of TLR4 ligands may represent a therapeutic strategy for sepsis treatment," she said. "Agents directed at TLR4 ligands currently are being investigated for their efficacy and safety in severe sepsis."

## Clinical Trials of Anti-TLR4 Agents for Sepsis Mitchell P. Fink, MD, FCCM

“Translating favorable preclinical sepsis findings obtained in animal models into results that are positive in human beings is a daunting task,” said Mitchell P. Fink, MD, from the University of California Los Angeles, California, USA. Further complicating this situation is the fact that one of the preclinical models involves challenging animals or humans with LPS, and this is a model of systemic inflammation but not a model of human sepsis.

Fink noted that the elucidation of TLR4 signaling pathway over the past 15 years represents an important advance in immunology and inflammation research. TLR4 is a receptor for both pathogen-associated pattern molecules (e.g., LPS and lipoarabinomannan) and danger-associated pattern molecules (e.g., HMGB1, heat shock proteins, hyaluronan, biglycans, and fibronectin). Of these substances, LPS (endotoxin) is the most important exogenous ligand for TLR4.

Several clinical trials have been conducted to evaluate the use of anti-TLR4 agents that target LPS (antibodies against LPS, polymyxin B, and bactericidal/permeability-increasing protein) or TLR4 and the TLR signalosome (TAK-242 and eritoran). Although disappointing mortality outcomes have emerged from the trials investigating antibody-based therapies aimed at the core region of LPS, another therapeutic approach – that of detoxifying endotoxin with a small or mid-sized molecule that binds to endotoxin and neutralizes it – may have promise. The classic compound for accomplishing this in the laboratory is the antibiotic polymyxin B.

“The question is: Can you take advantage of the ability of polymyxin B to neutralize endotoxin and use it therapeutically in the clinic? The answer is: Maybe by using a special cartridge designed for hemofiltration,” said Fink. Favorable results have been reported with the use of the polymyxin B hemoperfusion cartridge, which is approved in Japan for the adjuvant treatment of severe sepsis and septic shock. In a multicenter, unblinded controlled trial, 64 patients with severe sepsis or septic shock who underwent surgery for intra-abdominal infection were randomized to receive either standard therapy or two treatments (24 and 48 hours postsurgery) of hemoperfusion using the endotoxin-binding cartridge (Cruz DN, et al. *JAMA*. 2009;301:2445). “The results were encouraging, and indicated a statistically significant difference in survival,” noted Fink. Furthermore, a meta-analysis of the many trials investigating the cartridge yielded positive data regarding the use of this device (Cruz DN, et al. *Crit Care*. 2007;11:R47).

Another molecule that binds to and neutralizes endotoxin is bactericidal/permeability-increasing (BPI) protein, an endogenous protein found in the granules of neutrophils. In both *in vitro* and preclinical models, BPI is capable of neutralizing the pro-inflammatory effects of LPS. A recombinant form, rBPI-21, was evaluated in a randomized controlled trial involving 393 patients with severe meningococcal sepsis (Giroir B et al. *Lancet*. 356:961). Although no significant difference was observed in overall mortality, the therapy was associated with reduced incidences of amputation or long-term residual neurologic dysfunction. “Unfortunately, because the study failed to meet its primary endpoint, development of BPI-21 stopped,” stated Fink. “As far as I’m aware, this protein is no longer being developed.”

A third molecule of interest in the treatment of sepsis is TAK-242, a small molecule that is highly specific for TLR4 and does not block any other TLRs. In a concentration-dependent fashion, TAK-242 blocks the secretion of cytokines from macrophages stimulated with LPS and  $\gamma$ -interferon. Survival is improved markedly with administration of TAK-242, either given as a pretreatment or as a post-treatment, in mice challenged with a lethal dose of endotoxin. “The results of preclinical studies were dramatic,” said Fink. “TAK-242 appeared to be nontoxic, it’s not expensive to manufacture, and I thought it had great promise. However, despite these favorable preclinical data, the results in a phase 2 trial of patients with severe sepsis were very disappointing.” Thus, development of TAK-242 also has ceased.

“That leaves us with eritoran, which is a modified form of lipid A,” Fink stated. “Eritoran binds to the Toll-like receptor and prevents the binding of lipid A or LPS. However, eritoran is not an agonist and does not activate downstream signaling via the TLR4 pathways. Rather, eritoran is a classic competitive antagonist of the TLR4 signaling system.” In human volunteers challenged with LPS, 100 and 250  $\mu$ g doses of eritoran blocked all clinical signs and symptoms of LPS-induced toxicity (chills, fever, headache, myalgia, and tachycardia) as well as all biochemical effects of an LPS challenge.

Data from a phase 2 study of eritoran in patients with severe sepsis recently were published (Tidswell M, et al. *Crit Care Med*. 2010;38:72). Patients received either 45 mg or 105 mg of eritoran over six days. Results showed a trend toward a lower mortality rate among patients treated with eritoran versus placebo, particularly with the dose of 105 mg. An analysis of prospectively defined subgroups indicated that eritoran tended to have a greater effect among sicker patients, but the results were not statistically significant (see Figure 2). Trends toward improved survival occurred in patients with shock versus without shock and in patients with gram-positive infection versus gram-negative infection. No demonstrable effect on circulating levels of interleukin-6, a classic marker of systemic inflammation, was observed.

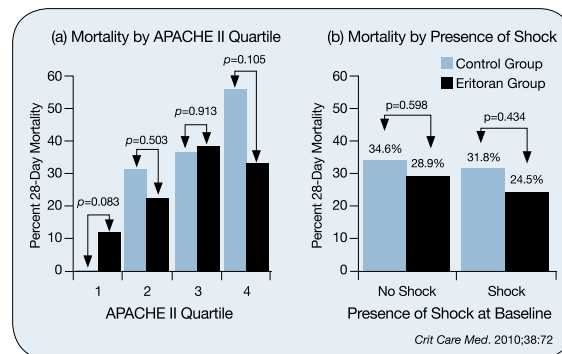


Figure 2. Mortality by APACHE II Quartile Versus Mortality by Presence of Shock

“We will soon hear the results of the phase 3 trial of eritoran, which has enrolled 2,000 patients in almost 160 centers worldwide,” reported Fink. “At this time, we don’t know whether the results will be favorable or not.”

In closing, Fink emphasized that TLR4 is an attractive target for the treatment of severe sepsis, in part because it is specific not only for LPS but also for a number of endogenous ligands involved in orchestrating the inflammatory response. Two strategies that target TLR4 signaling – polymyxin B cartridges and eritoran – appear to be promising and are under investigation.

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### Continuing Education Self-Assessment

#### THE SCIENCE AND MEDICINE OF SEPSIS MANAGEMENT

- Which one of the following theories is explained by a reflex arch involved in modulating the immune responses and progression of inflammatory disease?
  - Anti-inflammatory theory of sepsis
  - Apoptotic theory of sepsis
  - Cytokine theory of sepsis
  - Neuroendocrine theory of sepsis
- Endothelial cells are important in sepsis and are activated by both TLR2 and TLR4 agonists.
  - True
  - False