Differences Between Murine and Human Sepsis

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KEYWORDS

• Sepsis • Systemic inflammatory response syndrome • Proinflammatory
• Anti-inflammatory • Cytokines • Leukocytes

KEY POINTS

- Murine models do not accurately reflect human sepsis.
- Detection of clinical sepsis usually occurs during the late phases of the disease progression, and is often associated with irreversible damage to patients.
- Most of the existing mouse models of sepsis reflect only the immunologic aspect of the disease, and this xenogeneic comparison is suitable only when comparing the early phases of this clinical disorder.
- Instead of the conventional biphasic approach to modeling sepsis, sepsis should be perceived as a triphasic phenomenon by incorporating a preinfected state as a part of the pathologic simulation.
- Progression of sepsis may be foreshadowed by the immunologic state of the patient before infection, which is determined by the net effect of proinflammatory and anti-inflammatory modulators.

INTRODUCTION

Sepsis and severe sepsis continue to burden the health care system and are among the greatest medical concerns, with a mortality rate ranging from 30% to 50% in North America.[1] Sepsis is the most common cause of death in intensive care units and has

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been shown to result in an annual health care cost of $14 to $16 billion.[1,2] Between 1979 and 2000, sepsis accounted for an incidence rate of 500,000 cases in the United States. More recently, that figure has increased to onward of 750,000 cases annually.[3] Sepsis can be defined as a systemic inflammatory response syndrome (SIRS) occurring in the presence of an infectious source.[4] The most frequently observed gram-positive and gram-negative bacteria in septic patients include *Staphylococcus aureus*, *Streptococcus pyogenes*, *Escherichia coli*, *Klebsiella* species, and *Pseudomonas aeruginosa*.[5–7] It has long been understood that gram-negative bacteria are the most common sources of bacteremia in sepsis; however, Martin and colleagues[8] showed that the last 25 years has witnessed a shift in gram-positive dominance, with an average annual increase of 26% in cases within the study period.

In 1992, as part of an international effort to standardize the classification process, the American College of Chest Physicians and Critical Care Consensus Conference proposed diagnostic guidelines for SIRS, sepsis, severe sepsis, and septic shock.[9] Generally speaking, the SIRS response is triggered by nontraumatic causes; sepsis can be considered the activation of SIRS inflicted by microbial infections (eg, bacterial, fungal, viral); severe sepsis has the inclusion of multiple organ dysfunction; and the manifestation of hypotension with a lack of responsiveness to fluid resuscitation is septic shock. The specific criteria for each condition are listed later in this article. In 2003, another consensus panel revisited these in an attempt to clarify categorical ambiguity. It was determined that some of the symptoms of SIRS, such as tachycardia, manifest in other septic and nonseptic conditions, and are poor at differentiating it from other conditions. Thus, the terms sepsis and severe sepsis can be used interchangeably when there are organ complications present as a result of infection.[10] More recently, the Surviving Sepsis Campaign produced updated guidelines in an effort to improve the management of sepsis.[11] Suggestions were noted for all categories of sepsis, with an emphasis placed on early quantitative resuscitation of the septic patient within the first 6 hours of positive blood cultures. In light of these multiple paradigm shifts in defining clinical sepsis, this review attempts to provide a summation of the innate immunologic alterations that manifest during sepsis, establish and compare mouse models of sepsis with the clinical course, and discuss the authors' views on additional elements that should be considered in modeling and predicting clinical sepsis from a basic research setting.

Systemic Inflammatory Response Syndrome

A patient must demonstrate at least 2 of the following criteria:

- Temperature less than 36°C or greater than 38.3°C
- Heart rate greater than 90 beats/min
- Respiratory rate greater than 20 breaths/min or $Paco_2$ (partial pressure of arterial carbon dioxide) less than 32 mm Hg
- White blood cell counts less than 4000 cells/μL, greater than 12,000 cells/μL, or more than 10% bands

Sepsis

SIRS with the inclusion of an infection.

Severe Sepsis

Sepsis with the association of hypotension, hypoperfusion, or multiple organ dysfunction.