Gram-negative (GN) bacteria have often been implicated in the pathogenesis of severe sepsis and septic shock, although the exact mechanism is uncertain [1]. There is evidence to support two different theories on how GN bacteria induce harmful systemic responses. The intravascular stimulus hypothesis posits that bacteria invade through a normal or damaged epithelium and enter the bloodstream, inducing systemic inflammatory responses (for example, increased vascular permeability, leukocyte–endothelial adhesion, and activation of complement and clotting pathways) and resulting in multiorgan failure. A second theory suggests that the multiorgan dysfunction and shock result from neuroendocrine dysregulation and mediators released into the bloodstream from the infected tissues; circulating bacteria or endotoxin are not needed as direct stimuli for intravascular inflammation [2].

Previous studies have shown that proinflammatory cytokines (TNFα, IL-1β, IL-6, and IL-8) are elevated in patients with acute respiratory distress syndrome and septic shock. Measuring blood levels of these cytokines may help in evaluating the severity and predicting the outcome in patients with sepsis [3,4]. IL-6 is induced by TNF, and appears in the circulation after the initial TNF response, making it a good surrogate marker of localized TNFα activity. IL-6 has a longer half-life than TNFα and its blood levels remain elevated in the presence of various diseases [5,6].

C-reactive protein (CRP), an acute-phase protein, has been used as a sepsis marker, although blood levels may be elevated in response to non-infectious conditions (trauma, ischemia, and burns). Definite correlation has not been documented between infection and high serum concentrations of CRP [7]. Some authors have reported that elevated CRP plasma levels correlate with an increased risk of organ failure and death while persistently high CRP concentrations have been associated with a poor outcome [8,9]. Procalcitonin is another sepsis marker with kinetic characteristics that may allow anticipation of diagnosis of sepsis 24 to 28 hours before the CRP level [10].

Abe and colleagues investigate the relationship between the type of bacteremia and its relationship to pathophysiologic differences among bacterial species are not well understood. In the previous issue of Critical Care, Abe and colleagues report results of a retrospective study that show a significantly higher incidence of Gram-negative bacteremia among adult intensive care unit patients with septic shock than in those with sepsis or severe sepsis. In this study, C-reactive protein and IL-6 levels were significantly higher in Gram-negative bacteremia than in Gram-positive bacteremia. These observations suggest a distinct immunopathophysiologic behavior of sepsis in patients with Gram-negative bacteremia that may influence clinical outcomes. Future research exploring new biomarkers and danger signals and further characterizing differences in the virulence mechanisms between Gram-negative and Gram-positive bacteria appears promising and could lead to new therapeutics and to improved clinical outcomes.
The rate of GN bacteremia was significantly higher in patients with septic shock than in patients with severe sepsis or with sepsis (43.0% vs. 22.7% vs. 22%, respectively). Patients with severe sepsis also had higher rates of mixed bacteremia than patients with severe sepsis or with sepsis (12.3% vs. 5.3% vs. 3.1%, respectively). By contrast, the rate of GP bacteremia was greater in patients with sepsis and with severe sepsis than in those with septic shock (72.4% vs. 68% vs. 43.9%, respectively).

Corresponding to these findings, CRP and IL-6 levels and mortality were significantly higher in patients with septic shock when compared with either sepsis patients or severe sepsis patients. Mortality was not significantly higher in patients with GN (40%) when compared with GP (28%) and with mixed bacteremia (33.3%). The point estimates do differ, however, suggesting that the sample was underpowered. The authors demonstrated statistically significant higher levels of CRP and IL-6 in patients with GN bacteremia than in patients with GP bacteremia.

The authors chose IL-6 and CRP as biomarkers. Both have been challenged as markers of infection considering that they are relatively nonspecific. Newer sepsis markers such as procalcitonin might be more appealing. Comparison of CRP and IL-6 between the GN and GP bacteremias is important, although the appearance of these cytokines in the circulation is not as predictable as in experimental models of sepsis. Interfering therapeutic agents, compromised response mechanisms and a variable temporal relationship to the onset of infection make the interpretation of both the frequency and magnitude of these cytokines difficult. The study could be strengthened by further evaluating responses of individual pathogens, resistance patterns and trends, and their possible associations with comorbidities, source of bacteremia, length of stay, and mortality.

Abe and colleagues discuss the danger signals that alert the immune system and trigger defensive immune responses [1]. These inflammatory responses may be generated in response to exogenous pathogen-associated molecular patterns and to endogenous signals of tissue and cell injury (alarmins). Among the alarmins, high mobility group box 1 has been described as a mediator of sepsis that could potentially be a target for anti-inflammatory therapy.

These observations support a distinct immunopathophysiologic behavior of sepsis in patients with GN bacteremia that may influence clinical outcomes. The results of the study are limited by its retrospective nature, which can introduce selection bias. For instance, sepsis patients were statistically significantly younger (54.7 years) than severe sepsis patients (61.7 years). Additionally, the study is limited by observations from just one hospital in Japan. Nonetheless, differences in the virulence mechanisms between GN bacteria and GP bacteria identified in Abe and colleagues’ study could be further explored and characterized at the molecular level. Better understanding of these processes will make sepsis less alarmin(g) and its clinical course and outcome more predictable [11-14].

Abbreviations
CRP, C-reactive protein; GN, Gram-negative; GP, Gram-positive; IL, interleukin; TNF, tumor necrosis factor.

Competing interests
The authors declare that they have no competing interests.

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References
1. Abe R, Oda S, Sadahiro T, Nakamura M, Hisayama Y, Tateishi Y, Shinozaki K, Hirayama H. Gram-negative bacteremia induces greater magnitude of inflammatory response than Gram-positive bacteremia. Crit Care 2010, 14:R27.
2. Munford RS. Severe sepsis and septic shock: the role of gram-negative bacteremia. Annu Rev Pathol 2006, 1:467-496.
3. Damas P, Canivet JL, de Groote D, Vrindts Y, Albert A, Franchimont P, Lamy M. Sepsis and serum cytokine concentrations. Crit Care Med 1997, 25:405-412.
4. Meduri GU, Headley S, Kohler G, Stentz F, Tolley E, Umberger R, Leeper K. Persistent elevation of inflammatory cytokines predicts a poor outcome in ARDS. Plasma IL-1 beta and IL-6 levels are consistent and efficient predictors of outcome over time. Chest 1995, 107(1):1062-1073.
5. Panacek EA, Kaul M. IL-6 as a marker of excessive TNF-α activity in sepsis. Sepsis 1999, 2:65-73.
6. Dinarello CA. Proinflammatory and anti-inflammatory cytokines as mediators in the pathogenesis of septic shock. Chest 1997, 112(6 Suppl):321S-329S.
7. Marson A, Soni N, Sheldon J. C-reactive protein as a diagnostic test of sepsis in the critically ill. Anaesth Intensive Care 1991, 19:182-186.
8. Poovoa P, Almeida E, Moreira P, Fernandes A, Mealha R, Aragao A, Sabino H. C-reactive protein as an indicator of sepsis. Intensive Care Med 1998, 24:1052-1056.
9. Lobo SM, Lobo FR, Bota DP, Lopes-Ferreira F, Soliman HM, Melot C, Vincent JL. C-reactive protein levels correlate with mortality and organ failure in critically ill patients. Chest 2003, 123:2043-2049.
10. Castelli GP, Pognani C, Mesiner M, Stuani A, Belloni D, Sparsi L. Procalcitonin and C-reactive protein during systemic inflammatory response syndrome, sepsis and organ dysfunction. Crit Care 2004, 8(R234-R242).
11. Oppenheim JJ, Yang D: Alarmins: chemotactic activators of immune responses. Curr Opin Immunol 2005, 17:359-365.
12. Harris HE, Raucci A: Alarmin(g) news about danger: workshop on innate danger signals and HMGB1. EMBO Rep 2006, 7:774-778.
13. Finlay BB, McFadden G: Anti-immunology: evasion of the host immune system by bacterial and viral pathogens. Cell 2006, 124:767-782.
14. Bunchi ME: DAMPs, PAMPs and alarmins: all we need to know about danger. J Leukoc Biol 2007, 81:1-5.