CRITICAL CARE

COMMENTARY

Gram-negative versus Gram-positive bacteremia: what is more alarmin(g)?

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See related research by Abe *et al.*, http://ccforum.com/content/14/2/R27

Abstract

Gram-negative bacteremia has been associated with severe sepsis, although the exact mechanism and pathophysiological 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.

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 pathophysiology and potential clinical outcomes [1]. The study participants were adults admitted to the intensive care unit of a university hospital in Japan over an 8-year period. Eligible patients (n = 259) had at least one blood culture drawn during hospitalization, met the criteria for sepsis, and had a white cell count, a CRP level and an IL-6 level drawn. Participants were evaluated according to severity of sepsis (sepsis, severe sepsis and septic shock) and according to the type of bacteremia (Gram-positive (GP), GN, and mixed (GP/GN)). The white cell count, CRP level, IL-6 blood level and mortality were compared among the different pathogenic bacterial species and patient groups.

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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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