Commentary

Meningococcal disease: identifying high-risk cases

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Abstract

In the previous issue of *Critical Care*, Vermont and colleagues presented a simple but well-executed observational study describing the levels of chemokines in the serum of 58 children with meningococcal sepsis. The chemokine levels correlated with disease severity and outcome. Significant correlations were demonstrated between admission chemokine levels and the Paediatric Risk of Mortality score, the Disseminated Intravascular Coagulopathy score, the Sequential Organ Failure Assessment score and laboratory parameters of disease severity. Additionally, nonsurvivors had much higher levels of chemokines compared with survivors, and the chemokine levels predicted mortality with a high degree of sensitivity and specificity. The findings are important as they indicate a possible mechanism for risk stratification in future trials of novel therapies in human sepsis, which as yet have not been successful.

Injection of lipopolysaccharide into volunteers is followed by acute rises of monocyte-derived proinflammatory cytokines, including tumour necrosis factor [1], IL-1, and IL-6 [2]. Although the concentration of these cytokines falls to normal within a few hours, the secondary effects of their release can be devastating. These effects include fever, leukocyte and endothelial activation, leukocyte margination and transmigration, leukocyte maturation, metabolic and endocrine effects, and enhanced procoagulant activity at the endothelial surface – all features of sepsis syndrome. Cytokines are released into the circulation in human septic shock, and the levels in both septic shock [3] and meningococcaemia [4,5] correlate with disease severity and mortality.

Chemoattractant cytokines, or chemokines, also play an important role in the recruitment and regulation of the leukocyte traffic during acute inflammatory responses [6]. Chemokines are structurally homologous proteins with a molecular mass between 6 kDa and 14 kDa, divided into four subfamilies (CC, CXC, CX_3C, and C) on the basis of the arrangement and number of cysteine motifs. The CC chemokines monocyte chemoattractant protein 1 (MCP-1) and macrophage inflammatory protein 1α (MIP-1α) are chemoattractant for monocytes, whereas the CXC chemokines IL-8 and growth-related ongogenes alpha are chemoattractant for neutrophils. Chemokine production is induced in monocytes by lipopolysaccharide from Gram-negative bacteria such as the meningococcus [7].

There has so far been only one published account of the chemokine response in meningococcal disease [8]. This investigation demonstrated that in patients with fulminant meningococcal septicaemia, MCP-1, MIP-1α, and IL-8 levels were significantly higher than in cases of distinct meningitis or mild systemic meningococcal disease and correlated with plasma lipopolysaccharide concentrations. However, more formal descriptions of disease severity or outcome were not provided.

In the previous issue of *Critical Care*, Vermont and colleagues presented a simple but well-executed observational study describing the levels of the chemokines MIP-1α, MCP-1, IL-8 and growth-related ongogenes alpha in the serum of 58 children with meningococcal sepsis [9]. The authors correlated the level of these chemokines to both disease severity and outcome. Significant correlations were demonstrated between admission chemokine levels and the Paediatric Risk of Mortality score, the Disseminated Intravascular Coagulopathy score, the Sequential Organ Failure Assessment score and laboratory parameters of disease severity. Additionally, nonsurvivors had much higher levels of chemokines compared with survivors, and chemokine levels predicted mortality with a high degree of sensitivity and specificity. Prediction of mortality with chemokine levels was vastly superior to the prediction with tumour necrosis factor alpha levels.

IL = interleukin; MCP-1 = monocyte chemoattractant protein 1; MIP-1α = macrophage inflammatory protein 1α.

There are some limitations of the study; no control group of other critically ill children was included and, of the 58 patients included, 38 were involved in a placebo-controlled dose-finding study of protein C concentrate [10]. Although the involvement of patients in the protein C study may have had some impact on the chemokine levels measured at 24 hours, most of the paper is taken up with an investigation of chemokine levels at admission to the paediatric intensive care unit, which will have been unaffected by protein C administration. Additionally, the extent of the changes in chemokine concentrations and the correlations seen were so impressive as to mitigate against the absence of a control group of cases of children without meningococcal disease.

The findings are important because they are consistent with the current view of the pathophysiology of severe sepsis and of the redundancy built into the inflammatory response. They also indicate another potential mechanism for risk stratification in future trials of novel therapies in sepsis.

Previous trials of immunomodulatory therapy in sepsis, performed in the 1990s, were not successful. Trials of recombinant bactericidal/permeability-increasing protein and recombinant human activated protein C have more recently also failed to demonstrate any benefit [11,12]. Inclusion of too many low-risk patients may have contributed to the failure of these trials.

Risk stratification should ideally include considerations of timing, disease severity and of the proinflammatory or anti-inflammatory state but should also be immediately available at the bedside [13]. Standard tests such as neutropaenia and thrombocytopaenia may currently offer the best risk stratification [14], but the study of Vermont and colleagues raises the potential for specific risk assessment by looking at levels of chemokines.

The search for specific groups of patients likely to benefit from novel therapies will be critical for future trials. As Grau and Maennel stated in the 1990s, the key will be to 'inject the right inhibitor, at the right dose, in the right patient subgroup and most importantly in the right time window' [15]. To do this effectively, it is necessary to define who will benefit from therapy by elucidating the basic mechanisms of the host response to infection and the subgroups of patients most likely to respond to therapy. Only then will a logical approach to reducing the mortality from sepsis, both meningococcal and otherwise, be possible.

Competing interests

The authors declare that they have no competing interests.

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