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Institutionen för medicin, Huddinge

Diagnostic and prognostic markers in sepsis

AKADEMISK AVHANDLING
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ABSTRACT

Sepsis is a life-threatening disease affecting millions of people globally. The more severe forms are considered to be a consequence of an unbalanced systemic inflammatory response to infection, causing organ dysfunction, vascular leakage and hypotension. An early diagnosis followed by appropriate antimicrobial therapy is critical for the outcome. Conversely, inappropriate antibiotic use will escalate antibiotic resistance. Therapeutic guidance from microbiological cultures is lacking in the early hospital course, and better tools are needed for prompt identification and severity stratification of sepsis patients.

The aim of this thesis was to assess the clinical impact of severe sepsis and the diagnostic properties of clinical and biological markers in patients with a suspected or established serious infection.

The diagnostic value of clinical and laboratory variables in predicting infections that require antibiotic treatment was evaluated in a prospective observational study of adult patients with suspected severe infections. We also analyzed the relations between severe sepsis, systemic inflammatory response syndrome (SIRS), and the clinical course.
We concluded that increased C-reactive protein, white blood cell count, respiratory rate and a decreased hemoglobin level contributed independently to an accurate selection of patients for antibiotic therapy. Procalcitonin did not provide guidance on antibiotic decisions, but was associated with bacteremia and severe sepsis. In addition, severe sepsis was a common condition (42%), but mortality was low (5%), suggesting that severe sepsis is a more benign condition than earlier reported. SIRS did not exhibit discriminative ability in the classification of sepsis.

We used the enzyme-linked immunospot (ELISpot) assay to study the spontaneous as well as the lipopolysaccharide (LPS)-induced secretion of a number of pro- and anti-inflammatory cytokines from leukocytes of septic patients and healthy controls. We concluded that circulating leukocytes did not appear to be the source of the increased plasma levels of cytokines observed in sepsis. A selective sepsis-induced downregulation of cytokine secretion in response to LPS was found: while the numbers of IL-6 and TNF-α secreting cells remained similar, significantly fewer IL-1β, IL-10, IL-12p40 and GM-CSF secreting cells were seen in samples from septic patients as compared to healthy controls. The reduced number of cytokine secreting cells in response to LPS stimulation correlated with disease severity.

LPS-induced cytokine secretion from polymorphonuclear cells (PMN) and peripheral blood mononuclear cells (PBMC) from healthy donors was analyzed by ELISpot. PMN were found to secrete the two chemokines IL-8 and MIP-1β in response to LPS. Also TNF was secreted but by significantly fewer cells. PBMC had a broader cytokine secreting repertoire and released considerably larger amounts of the investigated cytokines, with CD14+ monocytes being the primary source of production.

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