Clinical relevance of the serum level of IL-6 and of its genes' polymorphism during sepsis

PhD Student: Dr. Iudita Maria Hodász (Badea)

PhD Coordinator: Prof. Dr. Leonard Azamfirei

Diagnosing and treating a patient with severe systemic infection is always a challenge for the intensivist. The pathology in case has a large spectrum of aetiologies and severity therefore strict diagnostic criteria and treatment guidelines are problematic.

Early diagnosis and intervention are essential for a good outcome. Until recently, the physicians used to rely on clinical manifestations, fever monitoring, white cells count and bacteriological exams in order to diagnose an infection. Clinical manifestations, despite being instrumental in recognising an organ disfunction, are nonspecific markers for a bacterial infection. Modern molecular biology technologies may shorten the time for the microbiological diagnosis, but they cannot differentiate between colonisation and infection, which is a clinically relevant dissimilarity.

Clinical frame of sepsis varies greatly with the site of infection, the germ involved, the medical history of the patient and last but not least the time until therapy initiation.

Sepsis is the end result of an array of factors linked to the germ and immune status of the human host. Early sepsis is defined by inflammation – sometimes accompanied by the "cytokine storm" – followed by catastrophic dysfunction of the immune system. Evolution of sepsis is linked to the nature, severity and length of the infection and it has multiple repercussions on the host.

Bacterial virulence is determined by factors – like glycocalyx or adesynes – that allow for the colonisation and progression of the infection at organ level. The endotoxin or Lipid A, part of the lipopolysaccharides freed by gram negative bacteria, is one of the main causes of sepsis, while the gram positive bacteria's effect on the host is mediated through the lipoteichoic acid. These are also known as superantigens and are linked to the histocompatibility complexes and the T cells' receptors, causing the release of the inflammatory cytokines by the T cells.

The host's initial response to a pathogen is the activation of the immune system's cells – mainly the NK cells, monocytes, macrophages and neutrophils – followed by the Damage Associated Molecular Patterns – DAMP – released by the apoptotic or damaged cells, such as ATP and mitochondrial DNA.

The activation of the intracellular signals induces the transcription and release of the inflammatory cytokines, like IL-6, IL-1 and TNF alfa.

IL-6 is released promptly but briefly as a response to an infection or tissue damage and is a contributor to the host's defence mechanisms through the initiation of acute phase responses, haematopoiesis and immune responses. While its expression is strictly regulated during transcription and post transcription, irregular but continue synthesis of IL-6 has a pathological effect on chronic inflammation and self-immunity.

General objective of this thesis is the evaluation of the diagnostic and prognostic role of IL-6 during systemic infections, starting from the hypothesis that IL-6's serum levels are corelated with the clinical severity and also that IL-6's genetic polymorphisms have a clinical importance in the evolution of sepsis.

Study 1 – Diagnostic and prognostic value of the serum level of IL-6

The Objective of this study was to establish a serum profile of IL-6 in a septic patient, corelated with the severity of clinical forms – sepsis/septic shock – in order to asses IL-6's usefulness as an early diagnostical and prognostical marker.

Patients with at least one organ disorder had significantly higher IL-6 serum levels while there are also statistic significant relationships between ICU stay days and the need for vasopressor drug. These results are highly suggestive for a possible IL-6 role in the prognostic of sepsis.

Regarding the patients' distribution among the two sexes, we found that the males are more often affected, while age and BMI do not appear to influence the IL-6 serum levels, regardless the clinical severity of infection.

The presence of infection has an effect on the white cells' levels, lactate levels and hemoglobinemia, even without an organ disorder. APACHE II and SOFA had significantly different values between groups.

All the patients that died had higher serum values of IL-6 suggesting a possible use for it as a prognostic marker in patients with severe infections with organ disorders.

Study 2: IL-6's genetic polymorphism in sepsis

The Objective of this study was to evaluate if IL-6's genetic variability has an implication in host's receptivity to sepsis and also to evaluate the effect of genetic polymorphisms on its serum levels.

The IL-6-174 G/C polymorphism has no statistical significance regarding the risk to develop sepsis, while IL-6-572 G/C polymorphism is a possible prognostic marker for sepsis.

Study 3: The relationship between blood IL-6 and its tissue expression in experimental sepsis

The Objective of this study was to assess the relationship between the serum level of IL-6 and its cellular expression in various organs of an animal representation of sepsis.

During early stages of infection, the IL-6 serum levels had no correlation with tissue level inflammation, while after five and 24 hours after inoculation, serum cytokine levels were higher than the baseline, despite only mild clinical symptoms. High tissue levels were present since the start of inflammation.

During a mild inflammation IL-6 serum level does not have a significant rise despite a remarkable expression at tissue level. This find does not recommend its use as an early predictor for sepsis, at least at an experimental level.