



**Karolinska
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**Centrum för infektionsmedicin
Institutionen för medicin, Huddinge**

Clinical and pathophysiological aspects of sepsis

AKADEMISK AVHANDLING

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ABSTRACT

Severe sepsis and septic shock represent challenging problems for the health care system. Despite adequate antibiotics and modern intensive care, severe sepsis is associated with a substantial mortality rate of around 30%, which rises even higher if exacerbated by septic shock, and the incidence continues to increase. In severe sepsis and septic shock, the normally tightly controlled balance between the inflammatory, coagulatory and neuroendocrine systems is lost. Our understanding of the causes, mitigating factors and mediators of severe sepsis has advanced in the last number of years. However, immunomodulatory interventions specifically directed against cytokines that all appeared promising in animal studies, did not translate well into human clinical trials. It has been suggested that the failure of many sepsis trials may in part be due to enrollment of diverse patients with sepsis of varying severity and different causative microorganisms. We, and others, believe that successful clinical trials of immunotherapeutic agents in sepsis require well defined patient cohorts with respect to severity and microbiological aetiology. This thesis project aimed to document clinical presentation and outcome of severe sepsis and septic shock, to evaluate clinical efficacy of adjunctive polyspecific intravenous immunoglobulin therapy (IVIG) in streptococcal toxic shock syndrome (STSS) and to define pathogenic mechanisms in sepsis, with a specific emphasis on the role of heparin-binding protein (HBP) and resistin; recently identified markers of severity in sepsis.

In **paper I** we conducted a prospective observational study of 101 patients with severe sepsis and septic shock. We reported a relatively low mortality in severe sepsis/septic shock, in aspects of both short- and long-term mortality, compared to studies outside Scandinavia. A troubling finding was that women received delayed antibiotics as compared to men.

In **paper II**, we documented clinical efficacy of IVIG therapy in a comparative observational study of 67 patients with STSS. This study demonstrated a significantly reduced mortality rate among STSS patients receiving IVIG as compared to patients who did not. Also clindamycin therapy was identified as an important factor for survival. The IVIG-group had a higher degree of NF as compared to the non-IVIG group.

In **paper III** and **IV**, the role of novel biomarkers in sepsis, i.e. HBP and resistin was explored *in vitro* and *in vivo*. Paper III focuses on resistin responses in STSS and necrotizing fasciitis (NF). The results demonstrate that STSS and NF are characterized by hyperresistinemia in circulation as well as at the local site of infection. Importantly, neutrophils were identified as a novel and dominant source of resistin in bacterial septic shock. *In vitro* assays using primary neutrophils showed that resistin release was readily triggered by streptococcal cell wall components and by the streptococcal M1 protein, but not by the potent streptococcal superantigens or LPS. In paper IV we explored whether neutrophil responses, in particular the release of sepsis-associated factors HBP and resistin, vary depending on bacterial stimuli and how this relates to sepsis of different aetiology. Fixed streptococcal strains induced significantly higher release of HBP and resistin, compared to *S. aureus* or *E. coli*. *In vivo* analyses of HBP and resistin in plasma of septic patients revealed elevated levels as compared to non-infected critically ill patients. HBP and resistin correlated significantly in septic patients, with the strongest association seen in group A streptococcal cases. The study reveals pronounced differences in neutrophil responses to various bacterial stimuli, and shows that streptococcal strains are particularly potent inducers of HBP and resistin.

In summary, this thesis provides new insight concerning mortality of sepsis patients in intensive care units and further supports the adjunctive treatment with IVIG in STSS patients. It also adds to the understanding of the complex pathophysiology of sepsis and our observations on bacterial induced neutrophil activation underscore the need for personalized medicine in sepsis.