Host response and outcome of sepsis in the critically ill
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Chapter 1

General introduction and outline of this thesis
CHAPTER 1

GENERAL INTRODUCTION

Sepsis is a severe clinical condition resulting from an inadequate host response to infection. Sepsis is a frequent reason for intensive care unit (ICU) admission worldwide and contributes substantially to mortality and (long-term) morbidity. Here, we describe different aspects of sepsis, starting with a paragraph on epidemiology. The complex host response during sepsis will be portrayed thereafter. Next, we give insight into patient characteristics, including comorbidities and chronic medication, influencing sepsis severity and outcome, followed by a paragraph on the study cohort. The chapter closes with an outline of this thesis.

Epidemiology of sepsis

Sepsis is an old and intriguing syndrome. Hippocrates (460 – 375 BC) described septicis (sepsis) as a process of rotting flesh; however, sepsis was not clinically defined until the early 1990s, when a consensus statement was developed by the American College of Chest Physicians and the Society of Critical Care Medicine that defined systemic inflammatory response syndrome (SIRS), sepsis, severe sepsis, and septic shock. Sepsis was diagnosed when 2 or more criteria of the SIRS syndrome (temperature >38°C or <36°C, heart rate >90 beats/min, respiratory rate >20 breaths/min or arterial carbon dioxide pressure <32 mm Hg, white blood cell count >12x10^9/L or <4x10^9/L) and a presumed or proven infection were present; severe sepsis included sepsis with evident organ failure; septic shock was defined as sepsis with persistent hypotension after fluid resuscitation. In 2001, these definitions were modestly revised. Almost a quarter of a century, sepsis research and trials were based on these definitions. Nevertheless, the SIRS criteria appeared not as robust as previously thought, lacking sensitivity and specificity. In addition, variations between studies were attributed to differences in the used definition of sepsis. In February 2016, a Task Force installed by the European Society of Intensive Care Medicine and the Society of Critical Care Medicine published a new definition for sepsis: a life threatening organ dysfunction caused by a dysregulated host response to infection, which is assessed by an acute change of 2 or more in the Sequential Organ Failure Assessment score.

Globally, likely more than 19 million severe sepsis cases occur annually. Restricted to the last decade, the incidence rate is estimated at 270 per 100,000 person-years in high-income countries. The incidence of sepsis has increased over the past decades and this trend is expected to continue due to aging of the population, increased burden of comorbidities, cumulative use of immunosuppressive drugs, chemotherapy, transplantation and invasive procedures. Mortality rates vary across studies; a recent meta-analysis reported sepsis-associated hospital mortality between 17-26% during the most recent 10 years. Despite the repeated failure to demonstrate survival benefits for many promising therapeutic agents for the treatment of sepsis, early diagnosis and rapid administration of antibiotics have likely contributed to improved sepsis survival over the past 2 decades. In addition, advances in supportive care, such as implementation of bundled care processes and low tidal volume ventilation in patients with acute respiratory distress syndrome, have led to declined case-fatality rates among critically ill patients with severe sepsis. Severe sepsis aggravates cognitive and physical
imperfections, and can worsen chronic illnesses, such as chronic kidney disease and cardiovascular disease; changes that may persist for several years after the initial episode of severe sepsis. Hence, sepsis represents a major health burden worldwide.

Sepsis can arise from various sites of infections, yet the most frequent cause of sepsis is pneumonia, accounting for approximately half of all sepsis cases, followed by abdominal and urinary tract infections. The source of infection can influence mortality risk, where abdominal infections are associated with higher and urinary tract infections with lower risk for in-hospital mortality in patients with septic shock. In addition, a wide range of pathogens can cause sepsis. Staphylococcus aureus, Streptococcus pneumoniae, Escherichia coli, Klebsiella species and Pseudomonas aeruginosa are the most common isolates. Of importance, in only one third of sepsis cases blood cultures are positive, whereas in up to a third of cases, no pathogen is detected from any site.

The clinical diagnosis of sepsis is not straightforward; patients present with highly variable symptoms, many of which are not specific for sepsis. Manifestation of sepsis depends on the initial site of infection, causative organism, presence and type of acute organ dysfunction, premorbid conditions and the interval before treatment was initiated. Symptoms may include, but are not limited to, tachycardia, increased respiratory rate, hypotension and altered mental status. Fever and hypothermia are both hallmark characteristics of sepsis, with hypothermia being observed in 9%-35% of septic patients.

Sepsis pathogenesis
Pathogens are detected by the innate immune system via a number of pathogen-recognition receptors (PRRs). PRRs recognize conserved motifs, expressed by pathogens, known as pathogen-associated molecular patterns. An adequate reaction to infection is a balanced host response, in which the interplay between pro and anti-inflammatory components, vascular endothelium and coagulation system is important, and which leads to effective pathogen elimination and tissue repair. The essence of sepsis pathogenesis lies in the failure of the body to maintain or reconstitute homeostasis upon infection. This dysregulated host response is characterized by concurrent immune suppressive and hyperinflammatory features that harm host tissues and organ function. In this thesis a variety of host response biomarkers providing insight into dysregulation of pathways and organ systems implicated in sepsis pathogenesis is reported.

The proinflammatory response during sepsis consists of multiple components among which activation of the cytokine network, the vascular endothelium and the coagulation system. In Chapters 3-7 and 9 we measured plasma biomarkers reflecting activation of these pathways. Cytokines are small proteins that orchestrate inflammatory processes by a complex interaction between proinflammatory and anti-inflammatory mediators. Activation and dysfunction of the vascular endothelium plays a large role in the homeostatic imbalance in sepsis. Aberrant endothelial function contributes to the coagulopathy commonly observed in sepsis, associated with microvascular thrombosis due to simultaneous activation of coagulation and impairment of anticoagulation mechanisms. Coagulation is regulated by three main anticoagulant mechanisms: antithrombin,
Host factors, such as comorbidity and chronic medication, can influence the outcome of sepsis, some of which were studied in Chapters 3-5 and 7. 

In sepsis, proinflammatory reactions as described above are accompanied by concurrent anti-inflammatory and immune suppressive responses. Immune suppression in sepsis patients has been a large focus in the sepsis field during the past years. A hallmark characteristic of sepsis is a reduced capacity of blood leukocytes (monocytes in particular) to release pro-inflammatory cytokines upon stimulation with endotoxin (lipopolysaccharide) and other bacterial components, which we used as a readout for immune suppression in Chapter 8. Sepsis is also characterized by apoptosis of CD4+ and CD8+ T cells, B cells and dendritic cells in various organs of patients dying of sepsis, and post-mortem analysis of patients who had died from sepsis showed a profound loss of both innate and adaptive immune cells in the spleen. Persistent immune suppression has been postulated to be associated with enhanced susceptibility towards secondary infections, thereby contributing to late mortality of sepsis.

Host factors influencing sepsis

Host factors, such as comorbidity and chronic medication, can influence the outcome of sepsis, some of which were studied in Chapters 3-5 and 7.

Risk factors for sepsis and sepsis-related mortality can broadly be divided into risk factors for infection and risk factors for organ dysfunction. Individuals with chronic obstructive pulmonary disease, cancer, chronic renal failure, diabetes, and patients with immune disorders are more vulnerable to acquire infections. Likewise immunosuppressive therapy, presence of prosthetic devices, malnutrition and residence in long-term care facilities increase the risk of sepsis.

Yet, why some patients develop acute organ dysfunction is not well understood. Virulence, type and microbial load of the causative pathogen have shown to influence the severity of infection; nevertheless, host factors have a strong influence on sepsis severity and outcome. Genetic factors may be involved; children whose biological parents died of infections had a 5.8 fold increase risk of death due to infection. In addition, specific gene variants, such as alterations in toll-like receptors genes, have been associated with enhanced severity of sepsis. Moreover, age and comorbidities are predictors of sepsis-induced organ dysfunction. In Australia and New Zealand, sepsis mortality was less than 5% in the absence of comorbidity and older age. Although decreasing over the past years, patients with cancer have a higher risk of dying from sepsis.

The epidemiology of sepsis in patients infected with the Human Immunodeficiency Virus (HIV) has changed dramatically since the introduction of combination antiretroviral therapy.
incidence of opportunistic infections decreased and long-term survival improved, however, invasive bacterial infections and sepsis remain an important cause of morbidity and mortality in HIV patients\textsuperscript{34,35}. Notably, HIV infection is associated with activation and dysregulation of several cellular and mediator pathways also implicated in the pathogenesis of sepsis.

Cardiovascular disease is among the most common comorbid diseases in sepsis patients\textsuperscript{36,37}. In patients with cardiovascular disease, statin and aspirin use is common, often in combination with antihypertensive drugs. Numerous clinical and preclinical studies have demonstrated that certain cardiovascular drugs can influence host responses involved in sepsis pathogenesis, including inhibition of proinflammatory cytokine release and endothelial cell activation, and attenuation of coagulation activation\textsuperscript{23,38-42}. Hence, the interaction between host and pathogen can be influenced by a variety of patient characteristics, all potentially interfering with the outcome and host response in sepsis.

**Molecular diagnosis And Risk stratification of Sepsis**

A major factor contributing to the failure of many clinical sepsis trials probably lies in the heterogeneity of the patient population enrolled, resulting from the lack of tools that allow an effective classification of the patient’s immune status. The Molecular Diagnosis and Risk Stratification of Sepsis (MARS) project was a collaboration of multiple partners (ClinicalTrials.gov identifier NCT01905033). The aim of the MARS consortium was to develop tools that can provide rapid and accurate information on pathogen and host immune response or status. These tools should be easy to use, at or close to the bedside, aiding the clinician in the determination of the optimal treatment in an individual patient.

From 2011 until 2013 all consecutive patients of 18 years and older admitted to the mixed ICUs of two tertiary teaching hospitals in the Netherlands, the Academic Medical Center in Amsterdam and the University Medical Center Utrecht, with a suspected length of stay of more than 24 hours, were included in the MARS cohort. In this observational study, clinical data were prospectively collected from all patients including demographics, comorbidities, chronic medication use, ICU admission characteristics, daily physiological measurements, severity scores, incidence of sepsis complications such as acute kidney injury and acute lung injury, antibiotic use, and culture results. The plausibility of infection was post-hoc scored based on all available evidence and classified on a 4-point scale (none, possible, probable or definite) according to Center for Disease Control and Prevention and International Sepsis Forum consensus definitions\textsuperscript{43}. Mortality data were recorded up to one year after ICU admission. From all patients, daily plasma was stored for protein biomarker analysis and whole blood was collected within 24 hours after ICU admission and at sepsis complications during ICU admission for genome wide RNA expression profiling of leukocytes.

During the 3-year study period, 6984 unique patients were enrolled in the MARS study, responsible for 8305 admissions in total. This thesis describes results of studies with specific research questions within this large cohort, designed to further untangle the host response of critically ill patients with sepsis.
CHAPTER 1

OUTLINE OF THIS THESIS

This thesis focuses on the host response, disease severity, and outcome of sepsis patients enrolled in the MARS cohort. The general aim of this thesis is to obtain more insight into factors that influence the outcome and host response of sepsis. In Chapter 2 we determined the association of the biomarker fractalkine with severity of disease and mortality in patients with sepsis and compared fractalkine with the endothelial marker soluble E-selectin, the latter also in healthy volunteers intravenously injected with lipopolysaccharide. Several drugs, used in patients with cardiovascular disease possess immune modulatory properties. We therefore aimed to investigate the impact of such drugs in patients who were admitted to the ICU with sepsis. Chapter 3 describes the association of chronic use of antiplatelet therapy with disease severity, host response and outcome. In Chapter 4, we determined the association of the use of calcium channel blockers and other cardio protective medication with outcome, and studied the host response in patients with and without calcium channel blockade. We examined the host response in patients on statin therapy in Chapter 5. We then studied risk factors, host response and outcome of sepsis patients displaying hypothermia versus patients without hypothermia (Chapter 6). Chapter 7 describes the impact of concurrent HIV infection on sepsis presentation and outcome, and on plasma host response biomarkers in patients with sepsis due to pneumonia. In Chapter 8 we assessed the relationship between reduced responsiveness of blood leukocytes and the subsequent development of ICU-acquired infections. Chapter 9 further evaluates the host response in critically ill sepsis patients who do or do not develop an ICU-acquired infection. Finally, the main results and implications of this thesis are discussed in Chapter 10.
REFERENCES