Chapter 1

General introduction and outline of the thesis

General Introduction

Introduction

Despite significant technological advances and improvement in care of critically ill patients, sepsis remains a common cause of death in patients with community-acquired and nosocomial infections.[1] In the Netherlands, it is estimated that 15.500 patients with severe sepsis and 6,000 patients suffering from septic shock each year are admitted to an intensive care.[2] In fact, sepsis is the leading cause of death in non-coronary intensive care units (ICUs), with a Dutch mortality rate of 26 % in severe sepsis and septic shock in 2014.[1] Sepsis is recently defined as a life-threatening organ dysfunction caused by a dysregulated host response to infection according to the third International consensus definitions for sepsis and septic shock. Septic shock is nowadays defined as a subset of sepsis in which underlying circulatory and cellular metabolism abnormalities are profound enough to substantially increase mortality. The new definitions highlight the importance of the potential lethality and the need for early recognition.[2] So, it is of utmost importance to recognize septic patients promptly and it is advised to start antibiotics as soon as possible since delayed antibiotic therapy is strongly associated with a worse outcome for these patients.[3]

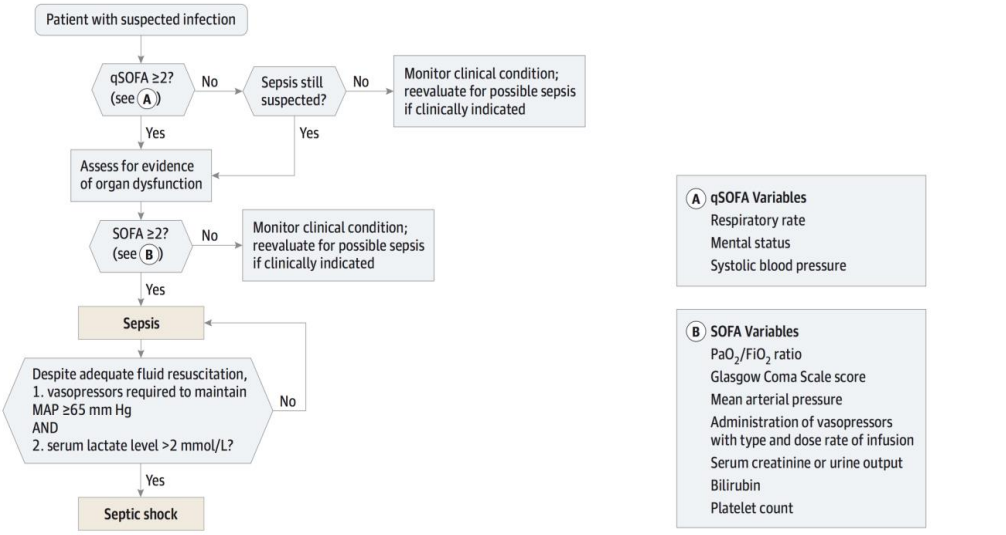

Figure 1: Operationalization of clinical criteria identifying patients with sepsis and septic shock

Conventional clinical signs nor laboratory parameters, including white blood cell count or CRP have proven to be neither specific nor sensitive for the diagnosis of sepsis in ICU patients.[4,5] Even a recently proposed clinical model qSOFA, which incorporates altered mentation, systolic blood

pressure of 100 mmHg or less and a respiratory rate of 22/min or greater, showed a limited predictive validity.[6] So the search for markers and indices of sepsis continues in order to provide this additional objective information in regard to early recognition of sepsis.

Contrary to the importance of rapid and adequate antibiotic therapy, it is generally recognized that aggressive strategies can also lead to a high consumption of broad-spectrum antimicrobial agents. However, as no objective measure exists on how long antibiotics should be applied and given the fear of under treatment, liberal antimicrobial treatment has been an accepted practice. Then again with the worldwide upcoming bacterial resistance, we are obliged to critically overlook the duration of antibiotic treatment, even in septic patients. Decision rules based on clinical severity scores or biomarkers to identify criteria for antibiotic initiation and discontinuation can be helpful for the physician, particularly in the critically ill patient. Procalcitonin (PCT) has shown to be one of the most promising among the bacterial infection related biomarkers studied sofar.[7-12]

In this thesis we are analyzing promising tools, like indices of infection and biomarkers in the work-up and treatment of sepsis in the ICU.

Part I Microbiological Outcome in the critically ill patient

Over the past decade antimicrobial resistance has emerged as a major factor affecting patient outcomes and overall resources in intensive care units.[13] The loss of effectiveness against common pathogens has headed towards the use of more expensive antibiotic drugs in high-income countries, but also to increased morbidity and mortality in low-income and middle-income countries.[14] Especially among gram-negative bacilli drug resistance is rapidly increasing.[13,15,16] It is, therefore, of vital importance to prescribe appropriate antibiotic therapy as early as possible. Furthermore, it is necessary to optimize the duration of antibiotic therapy for each individual patient and to have appropriate measures for infection surveillance by e.g. infection-prevention practitioners (IP).

Part II Respiratory viral infections in the critically ill: marker or mediator?

Viruses are abundant in the environment and common causes of respiratory tract infections in children and the outpatient setting, but less prevalent in the ICU setting.[17] However, a limited number of viral agents cause respiratory tract disease in the intensive care unit. There are viruses, such as influenza, respiratory syncytial virus (RSV) and Herpes Simplex Virus (HSV), which are more common than others like severe acute respiratory syndrome (SARS)-coronavirus, which is rare, but have a huge public health impact.[18] Data regarding pulmonary pathogenicity of respiratory viruses in the adult critically ill patient are limited and an understanding of the basic viral pathogenesis, along with the host response, is needed for a foundation in treatment within the ICU.[19,20] With polymerase chain reaction (PCR), viral detection has been intensely improved, which hopefully will provide more insight in the prevalence and role of viral pathogens in the respiratory tract. Molecular screening with

PCR is a fast and a highly specific diagnostic tool for identification of pathogen presence in a lower-respiratory-tract sample. Overall, PCR-based methods are between two and five times more sensitive than conventional virus diagnostic methods (culture, antigen detection, and serological assays) and a specificity of 99% for detection of respiratory viruses.[21]

The important question arises: when a viral pathogen is detected by PCR in the respiratory tract, is it a marker of more severe illness leading to depression of the immune system and viral replication, rather than a direct contributor to morbidity and death, in the critically ill?[22]

Part III Biomarkers of sepsis in the critically ill

A biomarker is defined as 'a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention'.[23] There is a need for an ideal biomarker, which can help in the early diagnosis of infectious diseases with definite cut-off ranges, predicts prognosis with a high sensitivity and specificity and is cost effectiveness. More than 170 biomarkers have been identified as useful for evaluating infectious diseases and sepsis, including C-reactive protein, procalcitonin, various cytokines, and cell surface markers.[23]

The biomarkers which we explore in this thesis are Cluster of Differentiation 64 protein (CD64) and procalcitonin (PCT). CD64 is a membrane glycoprotein expressed on monocytes and macrophages. It is the neutrophil FcγRI receptor which is weakly expressed by neutrophils at physiological levels, but is upregulated within 4-6 hours in the presence of sepsis by cytokines such as Interferon-alpha (INF-α) and Granulocyte Colony Stimulating Factor (G-CSF) which are produced in sepsis.[24-26] The difference in expression in resting and activated neutrophils is much higher for FcRI than for FcγRII (CD32) and FçRIII (CD16), which potentially makes CD64 antigen upregulation the most useful reflection of neutrophil activation. [24,27]

Procalcitonin has been extensively described in literature as a serum marker of systemic infection and sepsis. Procalcitonin is produced in the thyroid gland and is the precursor of the active hormone, calcitonin, is a 116 amino-acid peptide. PCT is expressed in all tissues throughout the body in response to sepsis.[28] After injection of endotoxins, PCT values rise within 6–8 hours. This is a faster response than that seen in C-reactive protein (CRP), which reaches maximal values after approximately 48 h.[29] Unlike cytokines, PCT's unique kinetics help physicians detect sepsis over a much wider time window than IL-6, IL-10, and TNF-α.[30]

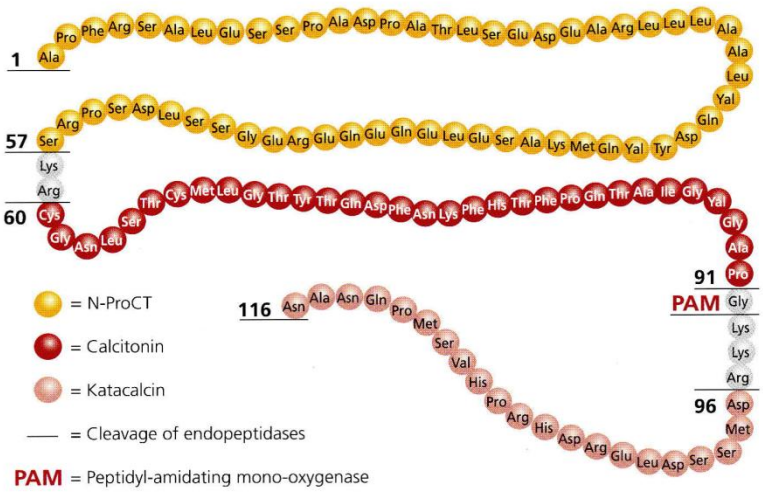

Figure 2: Procalcitonin is composed of three structures: the amino-terminus (N-ProCT), calcitonin and katacalcin

Outline of this thesis

This dissertation focuses on indices and markers of infectious diseases in critically ill patients and its implications on outcome. Early diagnosis and timely treatment of sepsis will improve patients' outcome.

Part 1 depicts methods to predict and detect infections. In **chapter 2** we investigated risk factors in patients with a drowning-associated pneumonia and we hypothesized, when decided to start antibiotic treatment in submersion victims, it should at least be directed against the same micro-organisms cultured from water samples where the patient was submersed. In **chapter 3** we designed and evaluated an Electronic Surveillance System with decision making capabilities in the Intensive Care Unit (ICU), a so-called trigger screening. Catheter related sepsis (CRS) and ventilator associated pneumonia (VAP) are the most predominant hospital infections in an ICU setting, therefore we chose CRS and VAP as outcome parameters.

Part II focuses on several aspects of respiratory viral infections in the critically ill patients. In **chapter 4** the role of viral pathogens detected by polymerase chain reaction (PCR) assays in the lower respiratory tract is explored with regard to incidence, clinical characteristics and route of infection. In **chapter 5** it is hypothesized that a high HSV-1 load in the lower respiratory tract in critically ill patients relates to severe underlying disease, clinical pulmonary infection and an unfavorable clinical course. The pathogenicity of HSV-1 in these patients is explored.

Part III focuses on promising biomarkers for sepsis in the critical ill population. Quantitation of neutrophil CD64 expression and procalcitonin (PCT) levels in blood samples have been proposed as useful tools for early detection of sepsis.

Chapter 6 we aim to determine whether CD64 is useful as a biomarker for bacterial infection in adult critically ill patients. We studied longitudinal expression patterns of CD64 on neutrophils with regard to outcome and sepsis severity. **Chapter 7** describes an observational cohort study, in which procalcitonin is valued as a diagnostic marker for predicting the presence of an infection in patients with SIRS who are admitted to the ICU. In **Chapter 8** a trial design is proposed based upon the concept to use a PCT algorithm as a guide to stop antimicrobial chemotherapy in critically ill patients. If the PCT-values have dropped to less than 20% of the maximum PCT value antibiotics are advised to be stopped. Additionally, if PCT levels reach values below 0.5 ug/ml antibiotics are stopped as well. The primary aim was to investigate whether such an approach would safely reduce the total consumption of antimicrobial chemotherapy and reduce the duration of antimicrobial treatment. **Chapter 9** presents the results of this large randomized, controlled, open multi-center intervention trial focusing on the additional value of PCT in responsibly discontinuing antibiotic treatment and provides insights in the optimization of antibiotic therapy in Dutch ICU's.

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