CHAPTER 1
GENERAL INTRODUCTION AND OUTLINE OF THIS THESIS
INTRODUCTION

Sepsis is a common, life-threatening illness affecting millions of people globally, causing more deaths than AIDS, breast cancer and prostate cancer put together (1-3). Colloquially it is known as a form of “blood poisoning”, although public awareness is poor (4). Despite the fact that the mortality of (severe) sepsis is ten times higher than myocardial infarction and up to five times higher than stroke, relatively little attention is given to sepsis in the media and by policymakers (5-7). In recent years, successful clinical care management pathways have been developed for patients suffering from a myocardial infarction, stroke and trauma. This has not been the case for sepsis although there is strong evidence in scientific literature to support that prompt recognition and treatment are extremely important for improving survival.

DEFINITIONS

Sepsis is a complex syndrome rather than a disease with a golden diagnostic standard. It is difficult to identify in early stages, where treatment is still possible, while in later stages it may be easier to recognize but more difficult to treat. Hence the major variations in the reported incidence and mortality rates.

The definition of sepsis was first established in an international consensus meeting in the early 1990s by the American College of Chest Physicians (ACCP) and the Society of Critical Care Medicine (SCCM) (8). Sepsis was defined as a proven or suspected infection associated with a generalized inflammatory response, the “systemic inflammatory response syndrome” (SIRS).

Sepsis is divided into three categories according to the severity in this definition:

1. uncomplicated (non-severe) sepsis,
2. severe sepsis with failure of one or more organ systems and
3. septic shock if severe sepsis is associated with circulatory failure which manifests as persistent low blood pressure despite adequate resuscitation (Table 1).

For two decades, the definitions of sepsis, severe sepsis and septic shock remained virtually the same, except for modest changes in 2001, by expanding the diagnostic criteria (9).

Systemic Inflammatory Response Syndrome (SIRS)

Two of the following
- Temperature >38 °C or <36 °C
- Heart rate > 90/min
- Respiratory rate > 20/min or PaCO2<32 mmHg (4.3 kPa)
- White blood cell count <4x10⁹/L (<4000/mm³), >12x10⁹/L (>12,000/mm³), or 10% bands

Ref: Bone et al 1992(8)
In early 2016, the new Sepsis-3 Taskforce, consisting of members of the European Society of Intensive Care Medicine and the Society of Critical Care Medicine proposed the new definition for sepsis (10). Apart from the criticism on the specificity of the SIRS criteria, there was also a need to adapt the definition according to a better understanding of the pathophysiology of sepsis (11).

The most important changes compared to the conventional definition were that the terms ‘SIRS’ and ‘severe sepsis’ have become redundant. According to the SEPSIS-3 criteria, sepsis is defined as ‘a life threatening organ dysfunction caused by a disordered host response to an infection’. Organ dysfunction is determined based on changes in the Sequential Organ Failure Assessment (SOFA) score. In patients not known to have pre-existing organ dysfunction, it can be assumed that the baseline SOFA score is zero. A SOFA score of 2 or more, is associated with an in hospital mortality rate of approximately 10% and in septic shock seen as a part of sepsis where underlying circulatory, cellular or metabolic abnormalities, the mortality can be significantly higher (>40%).

The taskforce also constructed a simplified version of the SOFA score, the so-called quick SOFA (qSOFA). The qSOFA functions as an easy prompt to identify patients with
a suspected infection who are at risk of a poor prognosis. It is useful as a prognostic tool but not as a screening tool for early sepsis and is not intended as a replacement of SIRS (12-14).

Redefining the criteria for sepsis and septic shock has profound implications for the epidemiology of sepsis. As the SEPSIS-3 definition is relatively new, its use is not widely implemented throughout the acute care chain or in critical literature yet. In addition, qSOFA criteria has not been properly validated in the ED setting. Therefore, in this thesis we have used the conventional definition of sepsis.

**EPIDEMIOLOGY**

While mortality rates have fallen in the last few decades, the total deaths from sepsis has increased (15, 16). This is due to an increase in the incidence of sepsis, which may have several causes (1, 2). Firstly, due to a growing number of patients who have a high susceptibility for infection such as the elderly, patients with chronic illnesses such as AIDS, chronic obstructive pulmonary disease, transplant patients and those suffering from malignancies. Secondly, due to an increased use of immunotherapy, cytotoxic agents and invasive medical devices rendering patients more prone for an infection. In addition, there is better recognition and coding of patients with (mild) sepsis due to increased awareness, which leads to increase in the incidence and reduction in the mortality (coding artefact).

Reported incidence estimates are highly variable ranging from 50 to 100 cases per 100,000 individuals (1, 17, 18), while the real incidence is probably much higher, partly due to under-reporting and the absence of incidence rates from countries where adequate hospital and intensive care (IC) is scarce (17).

The case fatality rates depend on the setting, severity of disease, patient-specific characteristics and the definition that is being used. For young patients without comorbidity, reported mortality is less than 5% and for intensive care patients with severe sepsis or septic shock mortality ranges from 25% to 45% (16). The cause of discrepancies found in reported incidence and case fatality rates can be related to the use of different terminology and multiple and inconsistent ways of coding of sepsis.

Almost half of the patients with septic shock are in need of urgent care and must be admitted to the intensive care unit (ICU). The costs associated with these admissions together with long lengths of stay is considerable. Total hospital expenses per year in the United States for severe sepsis increased from 15.4 billion in 2003 to 24.3 billion in 2007 (19). Sepsis is the most expensive reason for hospitalization (20). The average direct cost is estimated around $20,000 per patient. Despite the improvement in survival, long-term mortality is high for patients who have experienced severe sepsis (21, 22). Moreover, sepsis has long-term negative effects on the quality of life, both in the physical functioning and in the mental wellbeing of patients (21, 23). The likelihood and severity of these complications depends on a number of factors including age, comorbidities, and the severity of sepsis and the length of stay in hospital and in ICU. Overall, sepsis has a profound impact, not only on the individual patient but also on health care in general.
MANAGEMENT OF SEPSIS

In 2002, the ‘Surviving Sepsis Campaign’ (SSC) was launched by a collaboration of international experts from numerous specialties, with the aim of reducing sepsis mortality (24) by improving awareness, improving diagnosis and recognition and developing guidelines for appropriate treatment and care. The cornerstones of therapy for the septic patient include source control, administering broad-spectrum antibiotics, antibiotic stewardship, aggressive resuscitation and, if necessary, administering vasopressors and mechanical ventilation.

Early antibiotics

The first hour of presentation in the emergency room, also known as the ‘Golden Hour’ is thought to be the most critical one in the treatment of a septic patient. In the much-cited retrospective study by Kumar et al. (25), the authors found that delays in the administration of antibiotics in patients with septic shock caused an increase in mortality rate with 7.6% every hour. Retrospective studies have shown that rapid antibiotic administration could mean better chance of survival as well as a reduction in the chance of lasting physical problems. Rapid intervention can lead to a shorter hospital stay and even prevent the need for ICU admission (12, 18, 26-28).

Based on SSC’s recommendations, national guidelines for early diagnosis and treatment of patients with sepsis were implemented throughout hospitals in the Netherlands. This was done as part of a patient safety agency (VMS) programme that had the aim to reduce the unintentional and avoidable damage in patients, with sepsis being one of its main topics. Implementing this programme containing these guidelines indeed resulted in a sharp fall in sepsis related mortality (29). However, in daily practice, it is not always easy to implement this directive and there are delays in initiating treatment in the emergency department (ED) for several reasons (25, 30). One of the reasons is that recognizing sepsis remains a challenge, as symptoms are often non-specific and may be attributable to various other diseases. Secondly, the acute healthcare chain is not functioning optimally with fragmented health care processes and stagnation in care (31).

Recognition

Timely recognition and rapid initiation of treatment in sepsis is thus crucial in improving (clinical) outcomes for patients with sepsis (32). The recognition of sepsis among different healthcare providers however is suboptimal. A survey wherein a clinical case was presented to 917 physicians from different disciplines, showed that the recognition of SIRS, infection, sepsis, severe sepsis and septic shock was 78.2%, 92.6%, 27.3%, 56.7%, and 81.0% respectively (33). In particular, the recognition of sepsis and severe sepsis was poor, which may be caused by the difficulty in recognizing organ dysfunction. Another reason is that “sepsis” and “severe sepsis” are sometimes used as synonyms. The authors did not investigate what the possible effect on treatment would be if a particular diagnosis (sepsis, severe sepsis, etc.) was chosen. Recognition of sepsis is also difficult. Suffoletto et al. (34) investigated how accurately emergency medical services
(EMS) personnel were able to recognize a serious infection, the negative predictive value was 93%. In contrast, 69% of the patients with a severe infection were missed. Another survey amongst EMS personnel found that the majority of respondents believe sepsis is not recognized "some" or a "lot of the time" (76%, 596/786) (35).

**EARLY WARNING SCORES**

The inability to accurately recognize and initiate treatment of the critically unwell patient not only leads to higher levels of morbidity but also to an excessive utilization of costly resources such as increased ICU usage and longer inpatient stay, a pressing issue in a climate of intense financial constraint and increased demands. The acute healthcare chain needs tools to help recognize patients at risk of deterioration in order to give the right care at the right moment.

Early warning scores (EWS) may be the solution; they are simple scoring systems, consisting of a predetermined set of vital parameters such as respiratory rate and heart rate. They are easy to use prompts, designed for the timely recognition of critically ill patients, such as sepsis patients, who are at high risk of sudden clinical deterioration and poor outcomes. Evidence of acute deterioration is namely often present for hours prior to the occurrence of serious adverse events (SAEs) such as cardiac arrest, death and intensive care unit admission, leading to the conclusion that many of these SAEs might be preventable. Factors contributing to ‘preventable’ SAEs frequently include poor clinical monitoring, inadequate interpretation of changes in physiological parameters and failure to undertake appropriate action.

**EMERGENCY MEDICAL SERVICES**

EMS personnel are next to general practitioners (GPs), the first healthcare providers, patients with sepsis encounter. Around half of patients with sepsis presenting to the emergency department are transported by the EMS (36, 37). This is a seriously ill population with a high mortality. Nevertheless, more than half of this group of patients is transported with non-urgent rides (37) and only in a minority of the transported patients important vital signs are assessed and initial treatment in the form of oxygen and intravenous fluids administered. EMS personnel have already made a significant contribution in improving care for patients with acute coronary syndrome, stroke and trauma (38, 39). Patients with severe sepsis or septic shock can also benefit from early pre-hospital care (35, 39).

Pre-hospital care is the initial medical care, which is given by GPs or EMS personnel once they reach the patient. Since time plays a crucial role in the treatment of sepsis, early recognition and initiation of treatment by the EMS personnel may help to reduce mortality. The provision of pre-hospital care is associated with a shorter start-up time of initiation of therapy in the hospital (35, 40-42). One can postulate that early recognition of sepsis in the pre-hospital setting and administering antibiotics in the ambulance, may lead to improved survival. Therefore, much can be gained by training EMS personnel in proper recognition of sepsis.
To date no randomized controlled trials (RCTs) on the effect of antibiotics in the pre-hospital settings on adults had been conducted. Some early uncontrolled studies have been performed in children with meningitis. The results however were divergent, in the studies by Strang (43) and Cartwright (44), a clear beneficial effect on survival was seen after pre-hospital administration of antibiotics by general practitioners. While Harnden (45) and Sorensen (46) showed that administration of antibiotics in the pre-hospital setting was associated with worse outcomes. A possible explanation for these divergent results is that there was a strong selection bias. The group of children receiving pre-hospital antibiotics could be in a more critical stage of illness.

An important point to note is that all the studies which state that early in-hospital antibiotic administration is associated with improved survival, were retrospective and uncontrolled studies, making occurrence of selection bias probable. One of the reasons why doctors may not be very keen on initiating the antibiotics early (before a definitive diagnosis is made) may be the fact that they consider current evidence insufficient and incomplete. In order to investigate the optimal timing of antibiotic administration, prospective randomized controlled studies should be performed at the emergency department. However, at present it may be considered unethical to randomize patients and delay initiation of antibiotic therapy at the ED. An alternative and perhaps a better option was to perform a prospective randomized trial in the pre-hospital setting, i.e. in the ambulances. In current practice, antibiotic therapy is initiated at the ED and not in the ambulances. Pre-hospital antibiotic administration on the one hand may be a solution to avoid delays in treatment at the ED and on the other hand a way to finally perform a prospective randomised trial to examine the effect of onset to needle time on clinical endpoints such as improved survival, shorter hospital stays and better quality of life.

AIMS AND OUTLINE OF THE THESIS

The aim of this thesis was to investigate how we could improve the health for critically ill patients such as patients with sepsis by bringing separate links of the acute care chain to closely work together and thereby strengthening the acute care chain to function as one.

In Chapter 2 of this thesis, we performed a systematic review to investigate the impact of using early warning scores on patient outcomes, such as mortality and length of stay. In Chapter 3, we used a specific early warning score, namely the National Early Warning Score (NEWS) to explore its performance in an ED setting with regard to predicting adverse outcomes, such as ICU admission and death. The study also aimed to assess the feasibility of the use of NEWS as a structural monitoring tool in a Dutch ED. Chapter 4 describes the epidemiology of sepsis and the recognition thereof by EMS personnel in the Netherlands. In Chapter 5, we investigated the recognition of sepsis by GPs and EMS personnel and evaluated associations between recognition of sepsis in the pre-hospital setting and patient outcomes. EMS personnel were trained beforehand in recognizing sepsis as part of our other study discussed in chapter 7.

In Chapter 6, we emphasize the importance for the need for a RCT investigating the effect of early antibiotic therapy on mortality. In Chapter 7, we present the results of
the first nationwide RCT comparing the effects of training EMS personnel in recognizing and initiating treatment in the prehospital setting together with early administration of antibiotics against usual care in patients suspected of (severe) sepsis and septic shock. Chapter 8 gives an overview of long-term health related quality of life in patients with sepsis after an ICU stay.
REFERENCES


INTRODUCTION AND GENERAL OUTLINE AND AIMS OF THESIS


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