CHAPTER 9

SUMMARY OF MAIN FINDINGS AND GENERAL DISCUSSION
This final chapter summarises and discusses the findings of the work presented in this thesis. The aim of this thesis was to investigate how to improve the care for critically ill patients, especially sepsis patients, by bringing separate links of the acute care chain (pre-hospital and hospital) to closely work together.

Sepsis is associated with high mortality and morbidity, especially when not recognized and treated early (1-5). The inability to accurately recognize and initiate early treatment of critically ill patients not only leads to higher levels of morbidity (6-14), but also to excessive utilization of costly resources (15). The acute healthcare chain needs tools such as warning scores to help recognize patients at risk of deterioration in order to give the right care at the right moment before any serious adverse events (SAEs) arise. Moreover, there is a strong need for uniformity to make collaboration between different healthcare providers in the acute care chain easier.

SUMMARY OF MAIN FINDINGS

In chapter 2, we performed a systematic literature review evaluating the impact of the use of the Early Warning Score (EWS) on patient outcomes, such as in-hospital mortality and unexpected intensive care unit admission. We found that the EWS itself is a simple and easy to use prompt, which may be of help in identifying patients with potential for acute deterioration. If the EWS is coupled with an outreach service, they may be used to timely initiate appropriate therapy upon identification of the seriously ill patient. Although most of the included studies found a positive impact on clinical outcomes (8-10, 13, 16, 17), we cannot make definite conclusions as all included studies used specific subgroups of patients. Since its development, the EWS has gone through much iteration and its modified forms have widely been used throughout many hospitals across the world. The use of adapted forms of the EWS together with different thresholds, poor or inadequate methodology makes it difficult to draw comparisons. A general conclusion can thus not be generated due to the lack of use of a single standardized score and the use of different populations.

In chapter 3, we studied the utility of the NEWS in an ED. This was the first prospective study performed in an ED evaluating the performance of the NEWS. We documented the NEWS at three time points: on arrival (T0), an hour after arrival (T1) and at transfer to the general ward/ICU (T2). We found that the NEWS was a good predictor of patient outcomes, including 30-day mortality, hospital admission, and length of stay at all measured time points. The NEWS can be of additional value in the ED to longitudinally monitor patients during their stay in the ED and in the hospital.

In chapter 4, we aimed to determine epidemiological characteristics of sepsis and the recognition of sepsis by EMS personnel in an urban area in the Netherlands. From all patients with confirmed sepsis, more than half were transported by EMS. Sepsis was poorly diagnosed and documented by EMS personnel as well as GPs. Only 13.7% of the patients were diagnosed and documented by EMS personnel. Sepsis went unrecognized in 45.8% of the cases (n=60) although enough SIRS criteria were present at initial presentation. We
conclude that recognition of sepsis by EMS personnel in the Netherlands is low, probably due to a lack of awareness of the syndrome and infrequent measurement of temperature and respiratory rate. As early initiation of therapy is important much can be gained by providing more training in recognizing and treating sepsis in the prehospital setting.

In chapter 5 we describe the recognition of sepsis by GPs and EMS personnel and the association between recognizing sepsis in the prehospital setting and patient outcomes. GPs and EMS personnel correctly identified and documented 31.6% and 41.4% of all sepsis patients respectively. EMS personnel were trained in recognizing sepsis as part of the RCT presented in chapter 9. Recognition and documentation of sepsis improved with increasing severity. The mean time to administration of antibiotics (TTA) was nearly halved for the group of patients where sepsis was documented compared to the group in which sepsis was not documented. There is room for improvement in the recognition and documentation of sepsis amongst EMS personnel and GPs. Documentation of sepsis prior to arrival in hospital led to a reduced time delay in administration of antibiotics.

In chapter 6 we comment on the systematic review by Sterling et al. (18) in which they investigated the association between timing of antibiotics and mortality in severe sepsis and septic shock. The authors concluded that in patients with severe sepsis and septic shock, antibiotic administration within 3 hours ED triage and/or within 1 hour of shock recognition is not associated with significant improvement in mortality. An answer to the question what the best timing of antibiotic administration is can only be obtained by a prospective randomized controlled trial that avoids selection bias. However, as authors mentioned, it is unethical to randomize patients and delay initiation of antibiotic therapy at the ED. Therefore, we stress the need for a prospective randomized trial in the prehospital setting, that is, in the ambulances. In current practice, initiation of antibiotic therapy starts at the ED and not in the ambulances.

Prehospital antibiotic administration may be a solution to avoid delays in treatment at the ED and a way to finally perform a prospective randomized trial to examine the effects of timing of antibiotics on clinical endpoints, such as improved survival.

Chapter 7 describes the results of the first randomized controlled trial comparing the effects of early antibiotic therapy against usual care in patients suspected of sepsis. Prior to the start of the trial, members of the research team trained EMS personnel in recognizing sepsis and initiating treatment in the prehospital setting. The primary outcome was 28-day mortality. To assess the effect of training, average time to antibiotics (TTA) in the emergency department (ED) and recognition of sepsis by EMS personnel before and after the training were determined. A total of 2672 patients were enrolled in this trial. The intervention group received antibiotics 26 minutes (IQR 19-34) before arriving at the ED. Median TTA after arriving at the ED in the usual care group was 70 minutes (IQR 36-128) compared to 92.5 (IQR 39 -140) before personnel was trained (P=0.142). This means a shortening of the TTA with 22.5 minutes after training. At day 28, 120 patients (7.8%) had died in the intervention and 93 (8.2%) in the usual care group [RR=0.95, 95% CI: 0.74-1.24]. Only 1,4% patients in the intervention and 1,7% in the usual care group received an alternative diagnosis during the retrospective chart review by panel
of experts at discharge from the hospital. In conclusion, training the EMS personnel in early recognition does seem to have benefits by improving the care in the whole acute care chain in patients with sepsis. However, we do not advice antibiotic administration in the ambulances to all patients with suspected sepsis.

In chapter 8, we provide a systematic literature overview focusing on long-term outcomes of sepsis. Sepsis survivors are often confronted with long-term complications after admission to the intensive care unit (ICU), which may negatively influence their health related quality of life (HRQOL). The majority of the included studies (81.3%) reported that survivors of sepsis suffer from an impaired HRQOL in both physical and mental domains of life. Although some recovery was seen, the decline in HRQOL could still persist months until years after an episode of sepsis. Those who survived and were discharged, still had a risk for death in the years following an episode of sepsis. Mortality rates reached up to 67% within 5 years after discharge. More focus on improving long-term outcomes for patients surviving sepsis and the ICU are needed.

GENERAL DISCUSSION

The acute care chain has faced many challenges in the last decade, from an increase in the complexity of the problems in patients presenting to the ED leading to overcrowding and congestion in patient flows. Excessive crowding compromises patient safety and time to appropriate treatment, while in time-dependent illnesses such as sepsis, time to treatment is probably a crucial factor in survival.

In the United states, the Institute of Medicine (IOM) has characterized ED crowding as a national crisis (19). Also in the Netherlands, there is increasing pressure on EDs, regularly leading to closure of EDs for ambulances (‘stops’) (20). Although there was a slight decrease in the total number of ED presentations, the number of admissions from the ED has increased; more patients are referred to the ED and are brought in by the ambulance. This number is likely to rise in the upcoming years due to changing demographics. Healthcare professionals throughout the whole acute care chain provide care to patients with a high severity of illness, consisting mainly of an aging population with multiple chronic diseases and in need of complex care. Immediate assessment of all patients presenting to the ED is not possible or realistic. When resources are limited, patients who are in need or urgent care need to be prioritized by means of triage.

IMPORTANCE OF TRAIGHT

The concept of triage dates back to the Napoleonic wars (21) and has become a well-established system in the acute care chain. The goal of triage is to optimize waiting times according to severity of medical condition in order to rapidly treat the most urgent symptoms and reduce the negative impact related to delays in appropriate treatment. Most of the modern triage scales were developed since the early nineties and the Manchester Triage System (MTS)(22, 23) and Emergency Severity Index (ESI) (24, 25) are two of the most frequently used scores and have had major influence on modern ED
Although triage systems help to optimize waiting times, crowding at the ED’s still occur. One of the most common causes of recurrent and persistent crowding is an exit block from the ED. An exit block is the situation where patients who have been assessed in the ED are unable to leave the ED due to a lack of capacity in the downstream system (e.g. no bed capacity in the admitting hospital). Although virtually all EDs use triage systems to determine treatment priority, less attention is paid to longitudinal monitoring once patients are in the ED (9). No widely used scores are specifically designed to detect patient deterioration during their sometimes-lengthy stay at the ED. When crowding at the ED occurs, deteriorating patients are at risk of going undetected during their stay and vulnerable to develop serious adverse events, such as avoidable intensive care admissions and unnecessary patient death.

**EARLY WARNING SCORES**

Clinical deterioration is often preceded by deterioration in physical parameters. Considering that early warning scores were developed to timely detect this deterioration, they may be useful to monitor patients during their sometimes-lengthy stay at the ED. In chapter 3 we found that the NEWS when measured at different time points at the ED was a good predictor of patient’s outcomes such as admission and mortality. While, triage systems such as the MTS or ESI may provide useful prognostic information as a predictor of admission or 24 h mortality, they have not been evaluated across different triage levels for outcomes such as hospital admission. Moreover, wide variation exists between different triage scales (26). In our explorative study we found that the NEWS can be used as a structural monitoring system in the ED, analogous to its use in the ward. Within higher triage categories, NEWS could risk stratify patients for mortality, the need for admission but also length of stay. This finding implies that patients with high NEWS should not only be seen more urgently by medical staff but there is potential to fast track these patients for admission once they are stabilized.

An early warning score, such as the NEWS can therefore be used together with existing triage systems, expediting admission to medicals wards and intensive care and thereby smoothing patient flow through the ED.

Early warning scores are already widely used on the wards, sometimes coupled with an outreach service. The review performed in chapter 2 investigating the effect of EWS systems, showed mixed results, but in general there was a positive trend towards better clinical outcomes including survival, lower ICU mortality and a decrease in SAE. The studies included in the review looked at different subpopulations while using different types of early warning scores with different thresholds, making it difficult to draw a general conclusion. The NEWS has a big advantage over other early warning scores, namely the standardization of the score. This offers many opportunities for nationwide implementation such as uptake in existing curriculum of nurses and EMS personnel. The use of one early warning score throughout the whole acute care chain would improve continuity of care by improving communication and handovers between
different healthcare personnel. While the NEWS is useful in detecting deteriorating patients, its effect on clinical outcomes remains to be investigated.

There are also some aspects of an EWS that should be taken into consideration before implementation. Compared to other scoring systems, the EWS is a simple and easy to use tool, however the coupled outreach service is not. Vital parameters needed to calculate an EWS are still not consequently and completely documented (27). Before an early warning score system can be successfully implemented anywhere in the acute care chain, it is necessary to properly train staff and increase awareness about the importance of structural patient monitoring and documentation. The NICE guidelines (28) also have put emphasis on the importance of a full clinical assessment together with a tailored written monitoring and management plan based on clinical circumstances of the patient. The importance of training medical staff herein is also emphasized: only if the clinical relevance of an action, like measuring the respiratory rate is understood, will there be proper uptake and implementation.

AWARENESS FOR SEPSIS

For critically ill patients and especially those with sepsis, prognosis can be improved by early recognition and early intervention. However awareness amongst the public for sepsis as a medical emergency is low (29-31).

Sepsis is a syndrome, which is difficult to recognize. While medical conditions such as heart attacks or a stroke often have a typical presentation, sepsis does not have very distinct features. Patients with sepsis may therefore delay in coming to the hospital. Patients who develop sepsis can vary in their response and clinical course depending on virulence of the infecting microorganism and patient related factors such as comorbidities, genetic characteristics and race. Depending on the aforementioned factors some patients with sepsis may deteriorate rapidly and develop multi-organ failure within a few hours, while for other deterioration may occur late in the illness. Timely recognition of sepsis, its deterioration and starting treatment is the key in improving outcomes for patients with sepsis.

As general practitioners and EMS personnel are often the first healthcare providers for patients with sepsis, they play a crucial role in the early recognition and initiation of treatment. However in Chapter 4 we showed that recognition and awareness of sepsis was poor amongst EMS personnel, only 13.7% of the transported patients were recognized as having severe sepsis or septic shock. These findings were in accordance with another study conducted in the Netherlands (32). Nearly 40% of sepsis patients went unrecognized, which was probably due to an incomplete survey. Measuring vital signs is crucial for recognising the early signs of sepsis, however vital signs were documented completely in only 7.6% of the EMS forms, with body temperature and respiratory rate frequently left out. Suboptimal documentation can lead to important information loss during handovers, leading to insufficient care. This study illustrated the need for training EMS personnel in early recognition of sepsis as well as the importance of proper documentation.
With more than half of sepsis patients arriving with the ambulance, it is of paramount importance to raise awareness for sepsis amongst the EMS personnel and actively involve them in the care pathway for sepsis. Screening prompts such as the EWS or the qSOFA may be helpful in assessing the severity of illness in order to identify patients most at risk of deterioration and for a structured handover, however these scores are yet to be validated in the prehospital setting.

**RECOGNITION AND IDENTIFICATION OF SEPSIS CAN IMPROVE BY TRAINING**

Training EMS personnel in recognising and initiating treatment was one part of our prospective randomised controlled multicentre trial, the second part being the comparison of usual care with early prehospital administration of antibiotics after obtaining blood cultures.

The observational study conducted in chapter 5, conducted a year after start of the PHANTASi trial and after training EMS personnel, showed remarkable improvement (from 13.7% to 41.4%) in recognition and documentation of sepsis by EMS personnel. Documentation of sepsis prior to arrival in hospital also led to a reduced TTA in de ED, although this was not directly associated with improved patient outcomes.

**ANTIBIOTICS AND SEPSIS**

Early antibiotic administration and adequate source control have always been the mainstays in the treatment of sepsis. The time-sensitivity of antibiotic therapy to the septic patient and with it the relation to prognosis came to the forefront since the publication of the much-cited study of Kumar et al(33). Since then several prospective and retrospective studies were carried out, although with conflicting results. Studies finding a positive effect of early antibiotic treatment on mortality included mainly patients with more severe illness and a TTA of more than 5-6 hours (34, 35). Studies with shorter TTA (2-3 hours) found that early antibiotic therapy had no mortality benefit (36-41). A systematic review with meta-analysis by Sterling and colleagues(18) showed no improvement in survival when antibiotic administration occurred within 3 hours of ED triage or within 1 hour of severe sepsis and septic shock recognition.

Prior to the PHANTASi trial, no randomized controlled trial has been performed investigating the effects of early antibiotic therapy in patients with sepsis. In this trial we found that giving prehospital antibiotics led to a time gain of 96 minutes but did not lead to a difference in mortality or in other secondary outcomes. However unplanned readmission with significantly lower in the intervention group, a clear explanation for this was not found.

It must be noted that compliance with SSC guidelines regarding antibiotic therapy in our participating centres was much better than other studies: most patients in our usual care group received antibiotics within 1 hour of presentation to the ED compared to the reported average of 115-360 min.
Whereas previous studies had focused mainly on ICU populations, with patients having septic shock, our study included patients with varying degrees of sepsis who were brought in by ambulance to the ED. Although this makes our study less comparable with other study, it is a better reflection of the overall ED population. The proportion of septic shock patients in our study was small and our population had a much lower mortality than anticipated and a relative short TTA in the usual care group compared other sepsis studies performed. It is therefore possible that the time-benefit of early antibiotics may have only applied for patients with a higher severity of illness with longer TTA.

Another point is that the usual care may have improved drastically due to the raised awareness by the study itself. Awareness for sepsis was increased by not only training EMS personnel but also by promoting the study amongst health care workers in the whole acute care chain through blogs in national medical journals, regular briefings and site visits to participating EDs. Additionally the EMS as well as the primary care services in the Netherlands are robustly organized with short arrival response times and arrival times to the ED. In addition most patients are first seen, treated and referred by general practitioners. Moreover the EMS personnel consists of nurses with years of experience in critical care, who had additional specialised training before being able to qualify as a registered ambulance nurse. This makes comparison to communities with different health care settings (e.g. less organised primary care services, training of EMS nurses and long response and arrival times) difficult. Whether including more patients with septic shock and performing the study in a setting with long response and arrival times would have led to improved patients outcomes is unclear. This study however did show that even in a setting such as ours, EMS personnel were able to recognise sepsis, obtain blood cultures, administer antibiotics and shorten delays in care in the hospital. Only a small proportion of the patients diagnosed with sepsis in the ambulance by the EMS personnel had an alternative diagnosis during chart review after hospital discharge. During the planning of the trial the qSOFA criteria was not yet introduced. The EMS used the SIRS criteria to diagnose sepsis, had we used the qSOFA criteria, many patients would not have been eligible for inclusion in the study. However the usefulness of the qSOFA in the prehospital and ED setting is still a matter of debate.

**CLINICAL RELEVANCE AND FUTURE IMPLICATIONS**

The studies described in this thesis have shown the importance of a well-organized acute care chain. Organizing acute care in an efficient and effective way is a challenging task. Good communication and collaboration between healthcare providers throughout the whole acute care chain is essential and can improve patient safety. Whereby tools such as the early warning score may be utilized, not only in the wards but also at the ED, in order to timely recognize critically ill patients at risk of deterioration.

Furthermore, in this thesis we have shown:

1. the importance of sepsis as a serious healthcare problem;
2. the essential role EMS personnel play as one of the first healthcare providers, patients with sepsis encounter;
3. the recognition and documentation of sepsis is poor, but that it can improve with proper training;
4. training EMS personnel also helps in improving care further in the clinical pathway,
5. more focus should be paid to long term outcomes of sepsis, as many sepsis survivors suffers from impaired HRQOL.

Fortunately, the tremendous burden of sepsis is also increasingly being recognized globally. Organizations such as the Global Sepsis Alliance and national institutions such as the UK Sepsis Trust have successfully been raising awareness for sepsis in the last decade. On 13 September 2012, the first ‘World Sepsis Day’ was held with as main objective: “to increase awareness for sepsis as a potentially lethal condition, which should be considered a medical emergency” (42). In May 2017, the World Health Assembly (WHA) and the World Health Organization (WHO) finally established sepsis as a global priority. They adopted the resolution to improve, prevent, diagnose, and manage sepsis through a series of actions directed at developed and developing countries around the world. The adopted principles state among others:

1. Sepsis is an emergency that requires time-critical actions, improved training of health care professionals and laypeople.
2. Public awareness needs to be raised and encouraged, for example by using the term ‘sepsis’ when communicating with patients, relatives, and other parties, or by supporting World Sepsis Day, every year on September 13.
3. Integrated approaches to the prevention and clinical management of sepsis are urgently needed, including access to appropriate health care for survivors.
4. The International Classification of Diseases (ICD) system needs to be applied and improved to establish the prevalence and profile of sepsis and the development of specific epidemiologic surveillance systems.
5. The work presented throughout this thesis supports these objectives.

In the last several years, we have worked in close collaboration with healthcare providers working in different areas of the acute care chain. Together we have effectively worked in raising awareness for sepsis as an important health care issue as well as worked towards a better understanding of sepsis through training. We are currently active with acute care workgroups to implement regional and nationwide training for EMS personnel in recognizing and managing sepsis. An international study to investigate the effects of early antibiotics in patients with septic shock alone is also being initiated.

Although we have made a decent start in bringing the separate links of the acute care chain together along with putting care for sepsis patients as a pressing matter on the healthcare agenda, we still have a long and challenging road ahead of us in improving and keeping up the quality of care of acute clinical pathways.
REFERENCES


