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IDENTIFICATION OF THE ADULT SEPTIC PATIENT IN THE PREHOSPITAL AND EMERGENCY DEPARTMENT SETTING

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Identification of the adult Septic Patient in the Prehospital and Emergency Department Setting

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To my aunt Margareta, who passed away in sepsis when her life was just about
to begin, and to my grandparents Allan and Karin and my father Bosse
who have missed her ever since

“Suddenly, I felt so strange. I couldn´t dress myself and I felt that something was seriously wrong. I called the ambulance, but I obviously gave them an address where I used to live fifty years ago. After that I don´t remember anything more”

Lolita

PROLOGUE

My aunt died from sepsis at the age of 22 years. She was previously healthy. Despite repeated contacts with the health care system during her last days, no one realized she was suffering from sepsis until it was too late, and the condition was irreversible. My grandparents felt frustrated as they understood that their daughter was seriously ill, but they did not manage to convince the health care personnel how sick she was.

Many years have passed since then; but has the identification of sepsis improved? During my years within emergency care, as a former resident in emergency medicine, and during my research over the last years, I have encountered many patients who have reminded me of my aunt. The patient and the relatives often understand that there is something seriously wrong and they express anxiety and a fear of death. Furthermore, they frequently express a feeling of not being understood or believed when they try to convince health care personnel that this is not an ordinary gastroenteritis/ flu/ lumbago. This suggests that sepsis identification remains as a challenge within health care and raises the question; how can we improve?

My motivation during this project has always been the septic patients who are not timely identified.

ABSTRACT

Sepsis is one of the most urgent conditions encountered within emergency care but is often difficult to recognize due to its non-specific presentations. One third of the patients lack the classic sign of infection; i.e. fever, and it is often not obvious that the patient suffers from an underlying infection, which is a prerequisite for sepsis. Identification of sepsis within emergency care is today mainly based on clinical judgment, which is known to have a low sensitivity. Timely identification and treatment influence patient outcome. We believe that screening tools may increase the identification of septic patients, which may in turn improve outcome. The problem is that current screening tools designed for emergency care are based on vital signs despite one third of the patients with severe infections present with normal vital signs. The general aim of the current thesis was to study the presentation of adult septic patients within emergency care and to find a way to improve identification of the septic patient. The thesis builds upon four studies;

Study I was a retrospective cross-sectional study of 353 septic Emergency Medical Services (EMS) patients. Two previously unvalidated screening tools were compared to clinical judgment by EMS with respect to sepsis identification. The Robson screening tool (including temperature, heart rate, respiratory rate, altered mental status, plasma glucose, and a history suggestive of a new infection) surpassed both BAS 90-30-90 (refers to the vital signs systolic blood pressure, respiratory rate and oxygen saturation) and clinical judgment with respect to sensitivity for identification of septic patients in the ambulance.

Study II was a retrospective cross-sectional study where time to treatment and mortality among 61 septic Emergency Department (ED) patients with ED chief complaint decreased general condition (DGC) was compared with that of 516 septic patients with other ED chief complaints. Furthermore, the sensitivity and specificity of the Robson screening tool was compared with that of clinical judgment by the ED physician among 122 patients presenting to the ED with chief complaint DGC, of which 61 were discharged with ICD-code sepsis. Septic patients with non-specific presentations, here exemplified as the chief complaint DGC, had a longer time to treatment and a higher mortality. A larger proportion of these patients was identified as septic if the Robson screening tool was applied. Clinical judgment was more specific than the Robson screening tool.

In **Study III** the presentation of septic patients within the prehospital setting was explored and keywords relating to symptom presentation were identified. A mixed-methods analysis was conducted, starting with a content analysis of 80 EMS records from septic patients, followed by quantification of the identified keywords, among 359 septic EMS patients admitted the following year. Keywords related to patients´ symptom presentation recurred, so that a pattern was discernible, and some symptoms were particularly frequent. Furthermore, certain keywords were associated with a high mortality.

Study IV was a prospective cohort study of 878 EMS patients. Symptoms, vital signs and POC variables were associated with outcome sepsis/ infection/ no infection. Variables with the strongest association to sepsis among the 551 patients with suspected infection were used

to create a screening tool; the Predict Sepsis screening tool. The predictive accuracy of the Predict Sepsis screening tool exceeded that of prior proposed prehospital screening tools.

Conclusions:

In general, our findings indicate a low sensitivity of emergency care providers´ clinical judgment and support the use of a screening tool, with respect to sepsis identification within emergency care. However, neither earlier proposed tools nor the Predict Sepsis screening tool identifies all septic patients, and addition of novel variables such as symptoms in the screening process were not as important as we had expected. Nevertheless, this approach may be of greater benefit if tested among unselected emergency care patients, i.e. not only among those with a suspected infection, to identify septic patients with non-specific presentations. Sepsis identification remains a challenge within emergency care, mainly due to the diversity of its presentations. Increased education would most likely increase sepsis identification. However, an enhanced understanding of the underlying pathophysiology to explain the diversity in sepsis presentation is of major concern to improve identification. Future identification and management of sepsis may require consideration of delineated sub-populations of septic patients.

LIST OF SCIENTIFIC PAPERS

I. Identification of adult septic patients in the prehospital setting: a comparison of two screening tools and clinical judgment.
Wallgren UM, Castrén M, Svensson AE, Kurland L.
Eur J Emerg Med. 2014 Aug;21(4):260-5. doi: 10.1097/MEJ.0000000000000084.

II. Longer time to antibiotics and higher mortality among septic patients with non-specific presentations--a cross sectional study of Emergency Department patients indicating that a screening tool may improve identification.
Wallgren UM, Antonsson VE, Castrén MK, Kurland L.
Scand J Trauma Resusc Emerg Med. 2016 Jan 6;24:1. doi: 10.1186/s13049-015-0193-0.

III. Presentations of adult septic patients in the prehospital setting as recorded by emergency medical services: a mixed methods analysis.
Wallgren UM, Bohm KEM, Kurland L.
Scand J Trauma Resusc Emerg Med. 2017 Mar 3;25(1):23. doi: 10.1186/s13049-017-0367-z.

IV. Sepsis identification in the ambulance and the predictive value of parameters measurable bedside: the Predict Sepsis study.
Wallgren UM, Sjölin J, Järnbert-Pettersson H, Kurland L.
Manuscript

CONTENTS

LIST OF ABBREVIATIONS

AISAB	ambulanssjukvården i storstockholm AB
ARDS	acute respiratory distress syndrome
AUC	area under the receiver operating characteristic curve
BAS	Swedish acronym: blodtryck andningsfrekvens saturation
C3b	complement component 3b
C5a	complement component 5a
CD64	cluster of differentiation 64
CHAID	chi-squared automatic interaction detection
CI	confidence interval
CNS	central nervous system
CRF	case report form
CV	coefficient of variation
DGC	decreased general condition
DIC	disseminated intravascular coagulation
ED	emergency department
EGDT	early goal directed therapy
ELISA	enzyme-linked immunosorbent assay
EMCC	emergency medical communication centre
EMD	emergency medical dispatcher
EMS	emergency medical services
EMT	emergency medical technician
ETCO2	end-tidal carbon dioxide
FiO2	fraction of inspired oxygen
GCS	Glasgow coma scale
HCAI	healthcare-associated infections
HPA	hypothalamic-pituitary-adrenal
HBP	heparin binding protein
ICD	international classification of diseases
ICU	intensive care unit

IL	interleukin
iRISC	Inflammatory Response and Infection Susceptibility Centre
LR	likelihood ratio
MAP	mean arterial pressure
NLRs	NOD-like receptors
NO	nitric oxid
NPV	negative predictive value
PaCO2	partial pressure of carbon dioxide
PAMPs	pathogen-associated molecular patterns
PaO2	partial pressure of oxygen
POC	point-of-care
PPV	positive predictive value
PRESEP	prehospital sepsis score
PRESS	prehospital severe sepsis score
qSOFA	quickSOFA
RN	registered nurse
ROC	receiver operating characteristic
SAE	sepsis-associated encephalopathy
SIRS	systemic inflammatory response syndrome
SPSS	statistical package for the social sciences
SOFA	sequential organ failure assessment
StO2	tissue oxygenation
sTREM	soluble triggering receptor expressed on myeloid cells
suPAR	soluble urokinase plasminogen activator receptor
TNF	tumor necrosis factor alpha
TLR	toll-like receptors

1 INTRODUCTION

Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection[1], and is frequently the cause of death in pneumonia, urinary tract infections and post-surgical infections. Sepsis is one of the most urgent conditions encountered within emergency care but is often difficult to recognize due to its non-specific presentations[1]. It has been called “the most complicated disease in Emergency Medicine”, and it certainly is, due to a complex pathophysiology and a wide range of clinical presentations. Sepsis is the chameleon within emergency care as it may mimic nearly all other conditions[2], and it is frequently mistaken as stroke, gastroenteritis and myocardial infarction[3]. The course of the onset may vary from a rapid progress within a few hours, to a more insidious onset evolving over days to weeks[4]. Sepsis is common and affects more than 70.000 people annually in Sweden[5]. The mortality is considerable; 10% for sepsis and 40% for its most severe form; septic shock[1], which means that the mortality exceeds that of myocardial infarction[1,6]. Despite the high mortality of sepsis, chest pain and stroke has traditionally received more attention within emergency care and sepsis has been identified as an area within health care in need of special attention[3].

Recently, sepsis fast tracks have been introduced in some emergency departments. These fast tracks are mainly based on vital signs. Sepsis-specific presentations such as fever, low blood pressure and a decreased level of consciousness have been shown to be associated with an increased identification of sepsis[7]. However, despite fast tracks, patients with non-specific presentations are at risk of being overlooked.

Timely treatment with antibiotics remains as a cornerstone within sepsis care, even though the urgency of treatment has been debated recent years[8,9]. An early identification enables rapid treatment which may, in turn, improve the outcome of septic patients.

Sepsis identification is a challenge. This may have several reasons except for the diversity of clinical presentations. A low awareness of sepsis and its presentations both in public[10], and within emergency care likely contributes. Only one in five persons in Sweden has heard of sepsis, whereas 95% has heard of stroke[10]. This may delay the patient´s contact with health care. Also among health care providers the rate of identification is poor[11-14], and the often non-specific presentations among septic patients is thought to be an obstacle to identification.

Figure 1. The need for a structured approach

A large number of patients are managed within emergency care. Time is often limited and results of examinations e.g. blood tests included in the sepsis definition are frequently unavailable. Identification predominantly depends on clinical judgment, which has been shown to be inadequate[15,16]. There is a need for a structural approach to enable identification of septic patients within emergency care and we believe that screening tools may be useful.

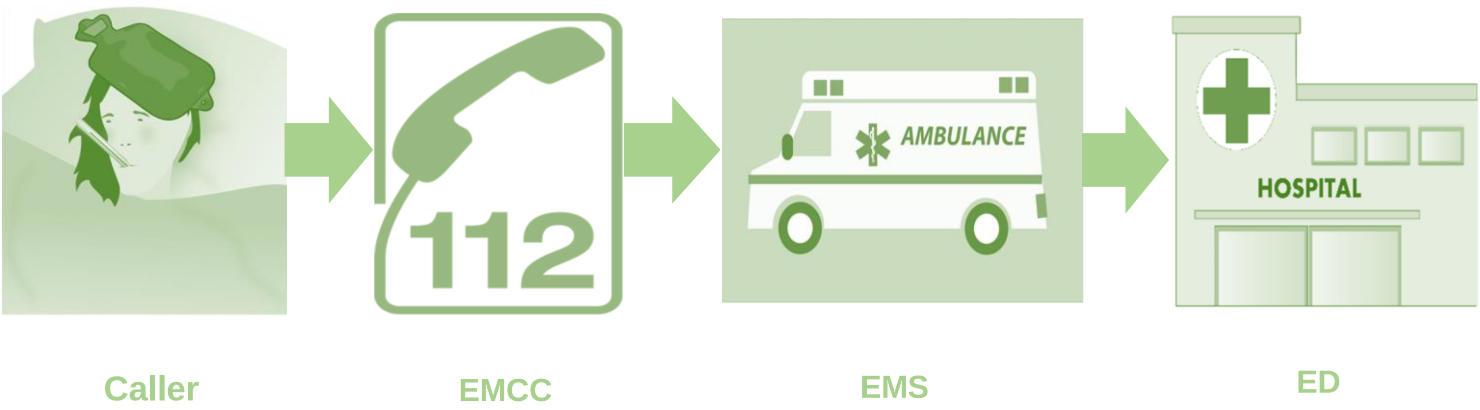
In the current thesis we investigated whether screening tools were beneficial as compared to clinical judgment by health care providers, with respect to sepsis identification within emergency care. Furthermore, we assessed how the presentation of sepsis may be associated with time to treatment and mortality, i.e. if the outcome of septic patients with non-specific presentations differed from that of septic patients who presented with more obvious signs of infection/sepsis. Moreover, we used a combination of qualitative and quantitative methods to obtain a deeper understanding of sepsis presentation within prehospital care. As the last part of the thesis, the association between variables measurable in the ambulance and sepsis was analyzed and a screening tool including symptom-variables and a point-of-care blood test was created.

2 BACKGROUND

2.1 THE CHAIN OF EMERGENCY CARE

The chain of emergency care constitutes the first part of care for many patients admitted to the hospital and includes both a prehospital and a hospital-based component. The prehospital part involves the emergency medical services (EMS), in turn including the emergency medical communication centre (EMCC) and the ambulance and helicopter services. In the current thesis the in-hospital part refers to the receiving emergency department (ED) and EMS refers to the ambulance services.

Figure 2. The chain of emergency care



Pictures obtained from Pixabay and PNGimage.net

In medical emergencies the caller may be a patient or a relative, but the caller may also be someone working in a nursing home, primary health care center or a bystander. The emergency medical dispatcher (EMD) who receives the call at the EMCC responds by dispatching adequate resources, e.g. an ambulance. The EMD may also provide medical advice and may instruct the caller, e.g. to provide chest compressions as part of cardiopulmonary resuscitation.

In Sweden, the emergency medical communication centre (EMCC) is predominantly operated by the publicly owned company SOS Alarm. There are in total 14 SOS centrals in Sweden, receiving approximately 3.2 million 112-calls annually[13], of which 907,000 calls involve medical emergencies. The SOS Alarm is staffed by personnel with a 16-week course in medical dispatching. Some of these are registered nurses and nurse assistants, some do not have a medical background[14]. Recently, the cooperation between SOS Alarm and

"Sjukvårdens larmcentral"[15] has increased, and in some regions of Sweden the medical dispatching is handled by Sjukvårdens larmcentral which is run by the local county councils and staffed by nurses with at least three years of experience from emergency care[15].

In Stockholm county there are three ambulance providers; Samariten Ambulans AB, Falck Ambulans AB and Ambulanssjukvården i Storstockholm AB (AISAB), and they account for almost 183,000 annual ambulance assignments[16]. Every ambulance is staffed with two health care personnel. It is regulated by law that at least one of the two must be a registered nurse (RN), but preferably a nurse specialized in prehospital emergency medicine. The second person can be either another nurse or an emergency medical technician (EMT).

In 83,5 percent of the cases, the EMS transports the patient to the ED of a hospital[17]. In the current thesis, the ED refers to a hospital-bound emergency department for somatic care of adult patients, open 24 hours a day, all days of the year. The EDs are staffed by nurse specialists, RNs, nurses' assistants and both junior and senior physicians. Some of the senior physicians are specialized within emergency medicine, which is a supraspecialty in Sweden since 2008, and a primary specialty since 2015. There are seven hospitals in the Stockholm County Council (Södersjukhuset, Karolinska Huddinge, Karolinska Solna, St Göran, Danderyd, Norrtälje, Södertälje). Together, they account for approximately 480.000 annual visits[18].

Emergency care constitutes an environment that in many ways differs from the rest of the health care system. Patients typically present with signs and symptoms to emergency care and not with a diagnosis. Assessment of the patient is often performed during limited time with limited resources. Results of blood tests, radiology and other examinations are often not available. This is most pronounced in the ambulance. For the emergency physician in the ED a structured approach, based on symptom presentation, and the ability to perform a likelihood assessment based on probabilities and differential diagnosis, is of utter importance. When encountering instable patients focus is often set on stabilizing function of vital organs rather than identifying a definite diagnosis. However, there are some time critical conditions that benefit from a timely identification to improve the patient´s outcome, and sepsis is one of them, just like myocardial infarction, stroke and trauma.

2.2 WHAT IS SEPSIS?

2.2.1 Sepsis-1 and Sepsis-2

In 1991, a consensus conference was held by the American College of Chest Physicians and Society of Critical Care Medicine[19], to establish diagnostic criteria for sepsis, and the definition is referred to as the Sepsis-1 definition.

The Sepsis-1 definition focused on the prevailing view that sepsis resulted from a host's systemic inflammatory response syndrome (SIRS) to an infection[17], and sepsis was defined as *the systemic response to infection, manifested by two or more of the following SIRS criteria* *as a result of infection: temperature >38°C or <36°C; heart rate >90 beats per minute; respiratory rate >20 breaths per minute or partial pressure of carbon dioxide (PaCO2) < 4 kPa; white blood cell count >12 x 10^9/L, or <4x10^9/L, or >10% immature forms*[19]. Severe sepsis was defined as *sepsis associated with organ dysfunction, hypoperfusion (including lactic acidosis, oliguria, or an acute alteration in mental status), or hypotension*[19].

A new consensus conference was held 2001[20] by several North American and European intensive care societies to revisit the definitions for sepsis and related conditions. The sepsis criteria were updated with a list of signs and symptoms that may accompany sepsis[20]. However, the definitions from 1991 remained otherwise unrevised. The definition from 2001 is further on referred to as Sepsis-2.

2.2.2 Sepsis-3 definitions of sepsis and septic shock

The sensitivity and specificity of the SIRS criteria with respect to sepsis has been shown to be low[21,22]. Advances into the pathobiology, management and epidemiology of sepsis and the insight that sepsis is not only caused by an excessive inflammatory response led to a reexamination of the sepsis definition during a third consensus conference held in 2016. Sepsis is now recognized to involve activation of both pro- and anti-inflammatory responses, along with modifications in nonimmunologic pathways[1]. Accordingly, sepsis was redefined as *a life-threatening organ dysfunction caused by a dysregulated host response to infection*, referred to as the Sepsis-3 definition[1]. The sepsis criteria are based on the *presence of infection and an increase in the SOFA (Sequential Organ Failure Assessment) score of 2 points or more*[1], see Appendix 1. The SOFA score is used to assess and monitor organ failure within critical care and it is based on mortality[23]. Variables included in the SOFA score are: partial pressure of oxygen divided with fraction of inspired oxygen (PaO2/FiO2) ratio, Glasgow coma scale (GCS) score, mean arterial pressure (MAP), administration of vasopressors with type and dose rate of infusion, serum creatinine or urine output, bilirubin and platelet count, see Appendix 1. Septic shock is defined as *vasopressor requirement to maintain a mean arterial pressure of 65mmHg or greater and serum lactate level greater than 2 mmol/L (>18mg/dL) in the absence of hypovolemia*[1]. The problem with SOFA score is that results of the variables required in the criteria are frequently not available during the first hour of care, which limits its usefulness within emergency care.

2.2.3 Definition of infection, included in the sepsis definition

Infection has traditionally been defined as *the presence of micro-organisms in a normally sterile body cavity or fluid, or as an inflammatory response to a micro-organism in a body cavity or fluid that may normally contain micro-organisms*[24]. Unfortunately, this definition is not useful within emergency care, where results of antimicrobial testing are often not available. According to the Surviving Sepsis Campaign´s Evaluation for Severe Sepsis Screening Tool[25], some examples of “history or signs suggestive of a new infection” are listed. However, the definitions for those examples remain unclear and the origin of the infection may not be obvious in the acute setting.

Furthermore, only 50-60% of septic patients demonstrate positive blood cultures[26,27] and positive blood cultures are not required for the sepsis diagnosis.

2.3 EPIDEMIOLOGY

2.3.1 Incidence and short-term mortality of sepsis

Sepsis affects 19 million individuals world-wide annually[28]. It is the 10th leading cause of death overall in the United States[29] and claimed almost 2,000 lives in Sweden in 2013[30]. Septic shock is the second most common cause of death among patients in Swedish intensive care units (ICUs)[31].The incidence is high[3] and increasing[29,32]. The Swedish incidence of sepsis, according to the Sepsis-3 definition, is estimated to be 780/100,000 citizens/year which corresponds to more than 70.000 annual cases[5]. Correct diagnostic coding constitutes a problem[33], and identification by discharge diagnoses underestimates the prevalence of sepsis[34]. Henriksen et al demonstrated a seven times higher incidence rate of community-acquired severe sepsis when comparing the incidence rate identified by assessment of symptoms and clinical findings at arrival to the hospital with the incidence rate according to international classification of diseases (ICD) discharge diagnoses[35]. The main reasons for the increased incidence of sepsis are an increasingly older population with multiple comorbidities and a greater use of invasive procedures and immunosuppressive treatment[36-40]. However, a greater awareness of sepsis among clinicians and an improvement of ICD-coding may also have contributed[41,37].

Sepsis is a time critical condition associated with a high mortality; 10% for patients with sepsis defined in accordance with the Sepsis-3 definition, and approximately 40% for patients with septic shock[1]. The case fatality rate of sepsis has decreased by at least one percent per year[42,43] over the last decades, but still exceeds that of acute myocardial infarction (8%)[1,6], and is of the same magnitude as that of stroke (26%)[44].

2.3.2 Causes

Sepsis may be caused by bacteria, viruses or fungi. However, approximately 90 % of all sepsis is of bacterial origin[29]. The incidence of fungal infections is increasing, particularly among immune compromised patients[24,29]. The most common underlying infections of sepsis are: pneumonia (50-60%)[24,45], intra-abdominal infections (20-25%)[24], urinary tract infections (7-10%)[24], infections in soft tissue/bone/joints (5–10%)[24], endocarditis (<5%)[24] and meningitis (<5%)[24]. However, according to some studies[46,47], urinary tract infections constitute the second leading cause of sepsis.

2.3.3 Risk factors

Sepsis may affect anyone at any time but there are certain risk factors. A high age is a major risk factor, with an incidence of 26/1000 citizens above 85 years of age. Infancy is another susceptible period of life, with an incidence of 5/1000 for infants below the age of one year. This can be compared with the incidence of approximately 2/1000 for the ages 1-50 years[48]. Other risk factors include advanced cancer, diabetes, end-stage renal disease, congestive heart failure and chronic obstructive pulmonary disease[49] and male gender[40]. Sepsis is a well-known complication after invasive procedures such as injections, hemodialysis and surgery and may complicate primary surgical conditions (e.g. diverticulitis and pancreatitis).

2.3.4 Long-term complications

For patients who have survived an episode of sepsis the risk to die is still increased, and furthermore, these patients have an increased risk of long-term cognitive and functional deficits[49]. Approximately 40% of the patients are re-hospitalized within 90 days of discharge[28], whereof approximately 12% for infection or sepsis[28]. The one-year post-discharge mortality for patients hospitalized due to sepsis (44%) is more than ten percent higher than that of patients hospitalized due to other causes[50]. Also long-term mortality, (i.e. 1- to 10-year mortality) is increased, as compared to patients who survived non-septic critical illness and as compared to the general population[51]. Results by Linder et al indicate that the effect of surviving an episode of sepsis is equivalent to adding approximately 14 years of age[51]. Long-term complications of sepsis include an increased prevalence of cognitive impairment, mental health problems (anxiety, depression and posttraumatic stress disorder)[28] and muscle weakness[52]. Furthermore, sepsis-survivors have an increased risk of recurrent acute renal failure and cardiovascular events[28], but it should be mentioned that the absolute risks are low[28]. Reasons for deterioration of health after hospital care due to sepsis is considered multifactorial and to include accelerated progression of preexisting chronic diseases, persistent organ damage, and an impaired immune function[28]. Hence, sepsis is a syndrome associated with considerable long-term mortality and morbidity except for the high mortality during acute illness. Early recognition and treatment may be of benefit to counteract the development of these complications.

2.4 PATHOPHYSIOLOGY

Sepsis covers a wide spectrum of host responses. The location of the primary infection, as well as microbial and host factors (e.g. underlying age, comorbidity and genetic factors) may affect the clinical presentation[3,53]. The pathophysiology of sepsis is complicated, and its mechanisms are still not fully understood.

Until recently sepsis was considered to be a strong, body-wide inflammatory response causing alterations in microvascular flow, endothelial leakage, and impaired parenchymal cell function, in turn manifesting as tissue hypoperfusion and multi organ dysfunction[28]. Such a hyperactive proinflammatory response can be triggered by outer cell membrane products of the bacteria binding to and activating, toll-like receptors (TLRs)[54]. TLRs are found on white blood cells, macrophages, and endothelial cells, included in the innate immune system. NOD-like receptors (NLRs) act synergistically with TLRs in the initiation of the innate immune system and they respond to various pathogen-associated molecular patterns (PAMPs)[55]. The innate immune system is the “front line” of the immune system including natural barriers such as epithelium of the skin/gastrointestinal tract, antimicrobial peptides, humoral factors (complement and coagulation systems) and cellular factors such as neutrophils, monocytes, natural killer cells and macrophages[54,56,57]. Activation of this system stimulates the release of nitric oxide (NO) and proteases, aimed to kill the bacteria[54], and increases the release of pro-inflammatory cytokines (e.g. TNF-α and IL-1, IL-6)[54,57]. Unfortunately, some of these released mediators may also injure the hosts’ cells[54]. NO, produced by the activated endothelium, leads to vascular smooth muscle relaxation, in turn resulting in vasodilatation and the shunting of blood from capillary beds to collaterals[54]. Activation of the endothelium allows adhesion and migration of stimulated white blood cells, but may also lead to leakage of larger molecules into the tissue, in turn causing tissue oedema[54]. Shunting of blood from capillary beds, in combination with the development of microthrombi, results in a reduced capillary perfusion, which contributes to hypoperfusion and tissue hypoxia[54]. Furthermore, NO disturbs mitochondrial function, which may contribute to organ failure[54]. The complement cascade is activated by bacterial surfaces and factors (C3b, C5a) attracting white blood cells, maintaining the inflammatory response[54].

However, more recent evidence demonstrates that the pathophysiological response is more complex and variable[28,58]. Both pro- and anti-inflammatory responses are involved[59], and the patient´s immune system may be either severely suppressed (immunoparalysis) or hyperactive[57], which may be related to the immunological phenotype of the host[57]. Immunoparalysis is associated with a high mortality and morbidity in sepsis[57] and involves an impaired capacity of leukocytes to release proinflammatory cytokines and an increased apoptotic immune cell death, in turn stimulating production of anti-inflammatory cytokines and causing anergy of immune cells[57]. The reason why some patients exhibit a hyperinflammatory response while others display immunoparalysis is currently unknown but both host-related factors (such as age, gender, comorbidities and genetic predisposition) as well as pathogen-related factors are thought to contribute[57]. Due to multiple changes it is sometimes difficult to classify an individual´s immune response as proinflammatory or immunosuppressed[53].

Besides the aspects of a hyperactive immune response and immunoparalysis, a new model has been introduced to describe the host response to infection, i.e. “tolerance”. Tolerance is a form of defense strategy within the host to preserve homeostasis without exerting negative effects on the microbe[60]. Disruption of tolerance can be triggered by pathogens or indirectly by host immune-driven mechanisms[61], and the course of the infection can then have a more dramatic course and sepsis may develop[62]. The metabolism of nutrients such as iron and glucose have been shown to play an essential role for regulation of tolerance[60,61].

Finally, alterations in multiple non-immunological pathways in the host such as metabolic, autonomic and bioenergic pathways are involved in sepsis[1,53,63], further complicating the pathophysiology.

In summary, the pathophysiology of sepsis is complex and not fully understood. Sepsis is a consequence of an immune response and numerous non-immunological responses to an infection. The response is dysregulated in sepsis; the response may be excessive in some individuals and inadequate in others. Variations in pathophysiology may reflect the diversity of presentations and the varied response to treatment in sepsis, where some patients seem to recover almost by themselves without adequate treatment while others have a rapid and fatal course despite timely management. The immune response may affect all organs of the body and can be devastating to the host[57]. The most commonly affected organs in sepsis are the lungs, kidneys, and the cardiovascular system[64].

2.5 EFFECT ON ORGAN SYSTEMS AND CLINICAL FEATURES

The heart is affected in several ways. Biventricular dilatation may occur as well as myocardial depression, due to cardiotoxic effects of cytokines[49,54,65]. Shock may occur as a consequence of both hypovolemia and cardiac depression[49,54]. Sepsis is frequently associated with a mild increase in the classic marker of myocardial infarction, i.e.troponin, which sometimes leads to a misdiagnosis of atherosclerotic myocardial infarction[66]. Sepsis-associated myocardial depression can be profound, necessitating therapy with inotropic agents[49].

The lungs: Leakage of fluids and molecules due to cytokine-mediated endothelial damage and disruption of the alveolar walls in the lungs may lead to pulmonary edema and acute respiratory distress syndrome (ARDS)[49,54,65]. Chest X-ray imaging usually shows an increased level of pulmonary fluid with bilateral infiltrates[49]. Respiratory failure is present in 18-38% of all patients with sepsis[65], making it one of the most common sepsis manifestations. Early signs of sepsis may be an increasing respiratory rate and hypoxia presenting as a low oxygen saturation[3].

Acute *kidney* failure is a frequent complication of sepsis and affects approximately one fourth of the septic patients[65]. The exact mechanisms responsible for sepsis-induced renal failure are unknown[49], but loss of intravascular volume due to capillary leakage and hypotension due to myocardial depression likely contribute. Surprisingly, kidney histology seldom shows overt signs of damage despite the facts that the patient is anuric and laboratory markers are deranged[54]. The development of severe renal failure in sepsis may be prevented by aggressive and appropriate volume resuscitation[49].

Coagulation. An imbalance between thrombogenesis and thrombolysis within the coagulation system may occur in sepsis, causing disseminated intravascular coagulation; DIC[65]. The clinical manifestations of DIC depend on which part of the coagulation system that predominates. The patient may present with bleeding from multiple sites if thrombolysis predominates and with thrombosis causing cyanotic and gangrenous fingers or toes if thrombogenesis predominates[49]. DIC is most commonly seen in gram-negative sepsis[65]. Purpura, due to cutaneous bleeding and necrosis, is most frequently seen in meningococcal and pneumococcal sepsis[65].

The central nervous system (CNS). More than two thirds of all patients with sepsis demonstrate signs of affected mental status[65]. The etiology of sepsis-associated encephalopathy (SAE) is incompletely understood but possible causes include disruption of the blood brain barrier and cerebral blood flow abnormalities[65]. SAE covers a spectrum of stages from altered behavior to loss of consciousness[65]. Neurological examination is typically without focal neurological findings[49]. However, septic patients with previous cerebrovascular lesions may present with aggravation of previous neurological deficits, without demonstrating a new stroke.

Gastrointestinal dysfunction. Hypoperfusion of the bowels is a common feature of sepsis[65], and leads to an increased intestinal permeability and, sometimes, to upper gastrointestinal bleeding[65]. Vomiting and diarrhea are frequent among septic patients, and may be mistaken for viral gastroenteritis[3].

Liver dysfunction, as indicated by increased levels of serum alanine transaminase and bilirubin, is common in sepsis[49]. The exact etiology of liver dysfunction in sepsis is unknown, but poor hepatic perfusion is thought to contribute[49].

Neuromuscular dysfunction. Critical-illness polyneuropathy is a well-known problem among ICU-patients and is present in approximately two thirds of all patients with sepsis[65]. It is caused by axonal degeneration and is characterized by a flaccid weakness of the limbs and absence of deep tendon reflexes[65]. Furthermore, sepsis induces a myopathy of skeletal muscle due to proinflammatory cytokines, increases in free-radical generation, activation of proteolytic pathways and mitochondrial dysfunction[67]. Weakness of the limb muscles and respiratory muscles is common[67]. Both sepsis-induced polyneuropathy and myopathy may affect the patient´s ability to stand and walk and the weakness of respiratory muscles may delay weaning from mechanical ventilation among septic ICU-patients[68].

Stress induced hyperglycemia. The increased release of stress hormones results in multiple effects; both metabolic, cardiovascular and immunological[69]. The hypothalamic-pituitary-adrenal (HPA) axis, sympathoadrenal system and proinflammatory cytokines (TNF-α, IL-1 and IL-6) act synergistically to induce stress hyperglycemia[69]. This mechanism seems to be physiological and it has been demonstrated that patients with septic shock who express stress hyperglycemia have a lower mortality than those with normal blood glucose levels[70].

Elevated lactate. The lactate level in sepsis is a sensitive but non-specific indicator of cellular dysfunction rather than "shock"[1,71]. The mechanism of lactate elevation in sepsis is complex and multiple factors such as insufficient tissue oxygen delivery, impaired aerobic respiration, accelerated aerobic glycolysis, and reduced hepatic clearance may contribute[1]. Two main mechanisms contribute to lactic acid accumulation in sepsis and low-flow states according to Kraut et al: tissue hypoxia and epinephrine-induced stimulation of aerobic glycolysis[71,72]. Regardless of the cause, elevated lactate levels correlate to an increased mortality among septic patients[73].

2.6 MANAGEMENT OF SEPSIS

2.6.1 The urgency of treatment

Time to treatment affects outcome in sepsis. However, the urgency of treatment has been debated. In a frequently cited study by Kumar et al in 2006, a survival rate of 80% was demonstrated among patients with septic shock receiving the first dose of antibiotics within one hour[74]. Moreover, Kumar demonstrated that the mortality increases almost 8% for every hour antibiotic administration is delayed[74]. These findings have been supported in more recent studies; in 2014 Ferrer et al showed an increase in mortality of almost 1% for every hour antibiotic treatment was delayed[75], and in 2017 Seymour et al demonstrated a relative increase in mortality rate of 5% per hour antibiotics were delayed among vasopressor-requiring patients with severe sepsis or septic shock. The benefit of early antibiotic treatment has however been questioned, especially after the publication of a systematic review and meta-analysis by Sterling et al 2015[8], indicating that treatment may be most urgent for patients with septic shock. Nevertheless, a recalculation of the data by Yokee et al[76] and several sepsis authorities[77,78] have questioned the conclusions made by Sterling et al, and early antibiotic treatment remains as a fundamental recommendation[1,79,80]. The debate regarding the urgency of treatment continues and Singer in 2017 questioned this issue again, warning against overtreatment of non-sepsis[9]. This was based on the fact that noninfectious conditions account for 18% of all ED patients initially diagnosed and treated as septic, according to a study by Heffner et al[81]. Furthermore, Singer referred to deficient quality of the supporting studies, claiming that the benefit of treatment within specifically one hour is not always obvious[9].

Nevertheless, early identification and immediate treatment remains as the cornerstone of sepsis treatment[3,79,82].

2.6.2 Antibiotics

Antibiotics constitute the foundation of sepsis management. According to the guidelines, intravenous antibiotics should be initiated "*as soon as possible after recognition and within 1 hour for both sepsis and septic shock*"[3,79,82]. In Sweden, antibiotic treatment is traditionally initiated after ED arrival despite the fact that EMS transports may be long.

2.6.3 Hemodynamic stabilization

-the value of protocolized treatment

Due to loss of intravascular volume caused by leaking capillary membranes and vasodilation, septic patients typically require volume resuscitation to replace these losses[49]. In 2001, Rivers et al published the results of a standardized protocol for early and invasive monitoring of central venous oxygen saturation, timely hemodynamic stabilization and intensive efforts to overcome tissue hypoxia; Early Goal Directed Therapy (EGDT)[83]. EGDT was shown to reduce the mortality in severe sepsis and septic shock with 16%[83] compared with non-protocol-based sepsis care. However, three later published multicenter studies[84-86] showed no significant difference in mortality between patients with septic shock receiving EGDT compared to patients obtaining usual-care. This may reflect that usual sepsis resuscitation has evolved during the last decade, including protocol-based administration of intravenous fluids, vasoactive drugs and improved monitoring. Hence, usual care during the latter three studies to a higher extent consisted of protocolized treatment. The results indicate that the monitoring of central venous pressure and central venous oxygen saturation through a central venous catheter were not the main factors explaining the success of EGDT, but rather that the breakthrough was attributed to the introduction of protocolized treatment in sepsis.

2.6.4 Sepsis bundles and adherence to guidelines

Surviving Sepsis Campaign was initiated 2002 with the primary aim to reduce the mortality of severe sepsis[87], through standardizing care by the development and publication of evidence-based guidelines[79,87-89]. To facilitate the implementation of evidence based care, ”sepsis bundles” were created which summarized the guidelines; the ”6-hour resuscitation bundle” (including a 3 h bundle) for emergency care and the ”24-h management bundle” mainly focusing on intensive care[38,90,91]. An update of the sepsis bundles was presented by the Surviving Sepsis Campaign in 2018, where the original 3 h and 6 h bundles were restructured and combined into a 1-h bundle, focusing on immediate actions[80], see Appendix 2.

Another bundle strategy was developed by Robson et al in 2008, as a reaction to the adherence to sepsis bundles being so poor; the Sepsis Six[38,91] (see Appendix 3). Sepsis Six was developed with nurses in mind with the expectation that this would increase bundle compliance.

Application of the Surviving Sepsis Campaign sepsis bundles has led to increased quality of sepsis care and reduced mortality[87,92]. However, despite improved sepsis care, not all septic patients are managed in accordance to guidelines. The time to administration of antibiotics is often too long[93,94] and there are studies demonstrating that septic patients are still not identified[5,35]. As described above, this may in part be explained by difficulties in the identification of sepsis, in turn explained by the diversity in sepsis presentation[95]. Another possible explanation of the low compliance may be ED crowding and a demonstrated poor knowledge of sepsis among health care personnel[11,96,97]. Finally, the competence in the entire chain of emergency care is not utilized in an optimal way. Despite the fact that more than half of the patients with sepsis are initially transported by EMS[98], guidelines focus on in-hospital care[3,79,82]. Prehospital identification has been shown to almost halve the time to in-hospital treatment[16]. Accordingly, the prehospital setting constitutes an important opportunity for early identification and care of septic patients.

2.7 IDENTIFICATION OF SEPSIS

2.7.1 Sepsis is a clinical diagnosis

Both prehospital and ED identification of sepsis is in general still based on clinical judgment, which is, in turn, based on diagnostic criteria according to guidelines and clinical experience[1]. The specificity of clinical judgment has been shown to be high[14]. However, the sensitivity of clinical judgment is low[13-16] and septic patients are not identified[15,16,35]. To increase the identification of sepsis within emergency care efforts have been made to improve triage systems and sepsis fast tracks have been introduced. However, these efforts predominantly favor patients with specific presentations and deviation of vital signs.

2.7.2 Sepsis biomarkers

No single biomarker has been identified with which to diagnose sepsis[99,53,100]. Procalcitonin, Presepsin, CD64, suPAR, and sTREM-1 are to date the best biomarkers for sepsis diagnosis and prognostication[101]. Procalcitonin and C-reactive protein are the two markers most frequently used clinically for sepsis identification. However, biomarkers all have their limitations in the lack of differentiation between infectious and non-infectious illness[100,102,101], which limits their usefulness. Nevertheless, biomarkers may play an important role in combination with other variables, to aid sepsis identification.

2.7.3 Sepsis screening tools

Screening tools have been shown to increase sepsis identification as compared to clinical judgment within emergency care[13,14]. There are a few screening tools for prehospital[103-109], ED[110-114], and in-hospital identification of sepsis[114,115], in addition to quickSOFA (qSOFA)[1]. qSOFA is proposed by the Sepsis-3 task force to be used in out-of-hospital/ ED/ hospital ward settings (i.e. outside the ICU). Typically, most of the proposed screening tools are based on the presence of infection in combination with deviant vital signs (often SIRS criteria). Some tools also include lactate. Recently, automatized screening algorithms[113] and machine learning methods[114] have been introduced within emergency care to identify septic patients and to develop new screening algorithms, respectively. These algorithms are also predominantly based on vital signs. The problem is that more than one third of the patients with severe infections have been shown to present with normal vital signs[116]. Furthermore, more than a quarter of bacteraemic patients and one of eight patients with the former severe sepsis do not fulfil SIRS criteria[21,102]. This indicates that the inclusion of variables other than vital signs in a screening tool is needed.

Prehospital sepsis screening tools

Robson et al. presented a prehospital screening tool for severe sepsis in 2009[103], which includes temperature, heart rate, respiratory rate, altered mental status, glucose and a history suggestive of a new infection. The second part of the tool screens for severe sepsis and includes blood pressure, oxygen saturation, lactate, assessment of urinary production and bleeding tendency. During 2012 to 2015, Swedish sepsis care guidelines[117-119] and Swedish prehospital guidelines[120,121] referred to a Swedish screening tool; “BAS 90-30-90”[3,104], for identification of the septic patient. The acronym refers to the vital signs systolic blood pressure, respiratory rate and oxygen saturation. Deviation of any one of these parameters should alert health care personnel that the patient could suffer from a severe bacterial infection. The Robson screening tool and BAS 90-30-90 were, until 2015, the only tools described for prehospital sepsis identification. In 2015, a score based on temperature, heart rate, respiratory rate, oxygen saturation and systolic blood pressure, referred to as the PRESEP score[105], was presented by Bayer et al. In addition, Polito et al presented an EMS screening tool (The PRESS score)[106] for identification of severe sepsis in 2015. This was the first screening tool including variables other than vital signs. Six EMS characteristics were found to be predictors of severe sepsis: older age, transport from nursing home, emergency medical dispatch (EMD) chief concern "sick person", hot tactile temperature assessment, low systolic blood pressure, and low oxygen saturation[106]. Still, the Robson screening tool had the highest sensitivity (95%[13] as compared to 85% for the PRESEP score[105] and 86% for the PRESS score[106]). However, the specificity of the Robson screening tool (43%[105]) was inferior to that of the PRESEP score (86%[105]) and to that of the PRESS score (47%[106]). None of these tools have been validated prospectively. In 2016, Baez et al presented the prehospital sepsis project score (PSP-S) including temperature, shock index, respiratory rate in combination with lactate. High-risk population (≥ 3 points) resulted in a post-test probability of 72%[107]. The same year, Hunter et al presented a screening tool based on two or more SIRS criteria in combination with ETCO2 (end-tidal carbon dioxide), demonstrating a 90% sensitivity and a 58% specificity[108]. Johansson et al presented a Swedish decision support system in 2018[109], with the aim to enable the identification and to steer patients with critical infectious conditions (including sepsis) to a specialized ED for infectious diseases. Clinical suspicion of sepsis, fever/chills, and ≥1 of the following was required for sepsis alert: respiratory rate ≥30/min, systolic blood pressure <90 mmHg, saturation <90% (based on BAS 90-30-90). The sensitivity and specificity of this system has not been evaluated.

ED sepsis screening tools

With respect to ED use, Singer et al presented an ED sepsis screening tool in 2014, including vital signs and bedside lactate[110]. The same year Goerlich et al presented an ED sepsis screening tool based on heart rate, respiratory rate, temperature and a spot check tissue oxygenation (StO2) device[111]. The sensitivity of these two tools varied between 34%[110] and 85.7%[111] and the specificity between 78.4%[111] and 82%[110]. Furthermore, in 2014 Alsolamy et al presented an electronic sepsis alert system aimed to screen ED patients for SIRS and organ dysfunction criteria (hypotension, hypoxemia or lactic acidosis), and found the sensitivity of this model to be 93% and the specificity 98% for severe sepsis/septic shock[112]. Outcome sepsis was defined as clinical judgment severe sepsis/septic shock by an ED or ICU physician[112], which may have affected the diagnostic characteristics of this tool. In 2016, Brown et al presented an automated method to identify sepsis/severe sepsis in the ED setting, including vital signs in addition to age and white blood cell count[113], demonstrating a sensitivity of 76% and a false alert rate of 4.7%[113]. Moreover, an algorithm developed by using machine learning was introduced by Mao et al 2018, including six vital signs. This model demonstrated an AUC of 0.92 for sepsis and 0.87 for severe sepsis[114].

qSOFA

The Sepsis-3 task force proposed a new score termed; qSOFA[1] which is suggested to be used outside the intensive care unit, to identify adult patients with suspected infection, likely to have a poor outcome typical of sepsis. This model incorporates altered mentation, systolic blood pressure of 100 mm Hg or less, and respiratory rate of 22/min or greater[1]. It is based on a model developed by by Seymour et al[122], demonstrating a high predictive validity outside the ICU (AUC = 0.81; 95% CI, 0.80-0.82), if two or more criteria are fulfilled. However, the accuracy of qSOFA has been questioned in several studies, demonstrating a low sensitivity for sepsis[123-125], failing to identify at least two thirds of the patients admitted to an ED with the former severe sepsis[123,125].

In summary, few of the proposed screening tools have been prospectively validated. A low specificity constitutes a general weakness of several of the existing tools, leading to false alarms which may in turn cause unnecessary antibiotic administration to non-septic patients. The sensitivity of screening tools has been shown to be superior to clinical judgment with respect to sepsis identification, but current screening tools do not identify patients with normal vital signs and patients without a distinct history of infection. Hence, inclusion of variables other than vital signs may increase the sensitivity of a sepsis screening tool for emergency care.

Variables which could be used in a screening tool for emergency care:

1. Components derived from the patient´s medical history

The possibility to include information on symptoms as variables predictive of sepsis has recently gained interest[126]. In 2016, Edman-Wallér et al demonstrated in a retrospective study of Swedish ED patients that symptoms could predict sepsis[126]. It is unlikely that there are unique keywords pathognomonic for sepsis as the presentation is so diverse, but we do believe in the predictive value of combinations of symptoms together with other variables measurable bedside within emergency care.

2. Point-of-care blood tests

Point-of-care (POC) blood tests are rapid, bedside laboratory tests not requiring a laboratory setting for analysis[127]. POCs make testing outside the hospital i.e. in the ambulance, possible and could therefore be part of bedside clinical decision tools[127].

Four possible point-of-care blood tests were studied in the current thesis: glucose, lactate, heparin-binding protein (HBP) and soluble urokinase plasminogen activator receptor (suPAR).

Glucose

Glucose is currently measured by the Swedish EMS[128]. An increased level of glucose is a consequence of the stress hormone cortisol and catecholamines. Glucose has been incorporated in a previous prehospital sepsis screening tool by Robson et al[103], but the predictive value of increased glucose levels with respect to sepsis has not been studied previously.

Lactate

Lactate testing is standard procedure in Swedish EDs, but not within EMS care. Elevated lactate is one of the two required criteria for septic shock according to the Sepsis-3 definition[1]. Lactate levels have been shown to be more sensitive in identifying patients at risk of death than both systolic blood pressure and heart rate[129], and lactate is used to monitor sepsis care. However, the problem is that an increased lactate level alone is not specific for sepsis. According to the Sepsis-3 consensus document, Singer et al state that addition of lactate to the qSOFA is not justified since this has not been proven to increase the predictive validity as compared to two or more qSOFA criteria for septic patients outside the ICU. However, according to the original study by Seymour et al, lactate may help to identify patients at intermediate risk, defined as qSOFA score = 1, where addition of a lactate level of 2.0 mmol/L or higher indicated in-hospital mortality rate similar to that of 2 qSOFA points[122].

suPAR

suPAR is the soluble form of the membrane bound protein urokinase plasminogen activator receptor, present on immunologically active cells. Elevated suPAR levels indicate activation of the immune system and have been shown to be a sensitive and specific prognostic marker for bacteremia[130], and a biomarker for sepsis with promising results[130]. A number of publications have established suPAR as a valuable prognostic marker in conditions such as streptococcal pneumonia, septicaemia and myocardial infarction in the acute setting[130-132]. However, despite its promise, there are still no studies demonstrating the added value of suPAR, alone, or in combination with other POC tests, in the prehospital setting with respect to sepsis identification.

HBP

A biomarker which has recently attracted interest is HBP (heparin-binding protein), a neutrophil-derived mediator of vascular leakage[133] shown to be a predictor of sepsis in ED patients with infections[133], and an early marker of circulatory failure in sepsis[134]. HBP is not currently used clinically. To date, no studies have demonstrated the added value of HBP alone, or in combination with other analysis within prehospital care.

3 AIMS

The general aim of the current thesis was to study the presentation of adult septic patients within emergency care and to find a way to improve identification of the septic patient.

Specific aims of the included studies:

Study I

The aim of the first study was to compare the sensitivity of two prehospital sepsis screening tools (Robson and BAS 90-30-90) with that of regular care (EMS clinical judgment) with respect to identification of septic patients in the prehospital setting.

Study II

The primary aim was to assess the time to antibiotics and the in-hospital mortality rate among septic patients with non-specific ED presentations, as compared with septic patients with other presentations. Chief complaint decreased general condition (DGC) upon ED arrival was chosen as an example of a non-specific ED presentation. The second aim was to determine whether a screening tool (Robson) would increase the identification of sepsis among patients presenting to the ED with chief complaint DGC.

Study III

The primary aim was to explore the presentations of adult septic patients in the prehospital setting as documented in EMS medical records and to identify and quantify keywords related to septic patients' symptom presentation according to EMS documentation. The secondary aims were to compare keywords in relation to in-hospital mortality and the distribution of keywords in relation to age categories, survivors/ deceased and severe/ non-severe sepsis.

Study IV

Our primary aim was to identify variables predictive of sepsis among patients with suspected infection in the ambulance, with the purpose of designing a screening tool adapted to the prehospital setting that could be compared with the earlier proposed PRESEP and Robson tools. The second aim was to compare variables in relation to in-hospital mortality.

4 MATERIAL AND METHODS

4.1 DESIGN, SETTING AND STUDY POPULATION

Summary of study design, setting, study population and participants for the four studies included in this thesis:

Study	Design	Setting	Study population	Participants
Study I	Retrospective cross-sectional	Prehospital	Adult (≥18 years) patients with ICD-code sepsis	353
Study II	Retrospective cross-sectional	Emergency Department	Adult (≥18 years) patients with ICD-code sepsis	638 61 with ED chief complaint decreased general condition, 516 with other ED chief complaints 61 patients with ED chief complaint decreased general condition but no ICD-code sepsis
Study III	Retrospective mixed methods-analysis	Prehospital	Adult (≥18 years) patients with ICD-code sepsis	439 Content analysis: 80 patients Quantification of keywords: 359 patients
Study IV	Prospective observational cohort study	Prehospital	Adult (≥18 years), non-trauma EMS patients with suspected infection / no suspected infection	878 553 patients with suspected infection, whereof 551 had sufficient documentation to determine outcome 318 patients with no suspected infection 7 patients lacked documentation whether EMS suspected infection or not.

Study setting of Stockholm

All studies included in the current thesis were conducted in Stockholm county. The population of Stockholm county is approximately 2.3 million inhabitants[135] and there are approximately 480.000 annual visits to the seven hospital-bound EDs of the county (Södersjukhuset, Karolinska Huddinge, Karolinska Solna, St Göran, Danderyd, Norrtälje, Södertälje)[18]. Three ambulance providers serve the Stockholm county; Samariten Ambulans AB, Falck Ambulans AB and Ambulanssjukvården i Storstockholm AB (AISAB), with a total of approximately 183.000 annual ambulance assignments[17].

Study I and III included patients from all three ambulance providers admitted to Södersjukhuset. Södersjukhuset is an urban, 571-bed teaching hospital with more than 129 000 adult ED visits annually[136].

All four studies included adult (≥18 years) patients with community-acquired sepsis, in the current thesis defined as onset of sepsis outside an emergency hospital and admission of the patient via the ED.

Study I

Design and setting

Retrospective cross-sectional study in the prehospital setting.

Study population

Inclusion criteria: adult (≥18 years) patients transported by EMS and admitted to Södersjukhuset, with a principal hospital discharge ICD-code compatible with sepsis. For ICD-10-codes consistent with sepsis, see Appendix 4. All patients were admitted between January 1st, 2007 and May 18th, 2008. Only patients demonstrating signs and symptoms compatible with an ongoing infection according to manual EMS and ED chart review were included.

Exclusion criteria were healthcare-associated infections, defined as onset of infection 48 h or more after ED admission[137], patients already treated for sepsis or infection transported from other hospitals, and patients lacking an EMS record or a Swedish personal identification number. Only the first EMS transport for patients with sepsis was included for those with repeated EMS transports to the ED during the study period.

Study II

Design and setting

Retrospective cross-sectional study in the ED setting.

Study population

Inclusion criteria: adult (≥18 years) septic patients presenting to the ED with chief complaint decreased general condition (DGC), according to the triage nurse and predefined triage categories documented in the ED electronical ledger (this group is referred to as septic patients presenting with ED chief complaint DGC), and adult septic patients presenting to the ED with other chief complaints (referred to as the sepsis reference group). Only patients demonstrating signs and symptoms compatible with an ongoing infection according to manual ED chart review were included in the two groups with outcome sepsis. Outcome sepsis was defined in accordance to hospital discharge ICD-code (bi- or principal), see Appendix 4. In addition, adult non-septic patients randomly selected by SPSS were included, among all patients admitted to the hospital with ED chief complaint decreased general condition (referred to as the DGC reference group). The size of the latter group was selected to be equal to the group of septic patients presenting with ED chief complaint DGC. All patients were admitted to in-hospital care via the ED of Södersjukhuset during the period January 15th to December 31st, 2008.

Exclusion criteria: patients with healthcare-associated infections (HCAI), defined as onset of infection ≥48 h after ED admission[138] were excluded from the two groups with outcome sepsis. Exclusion criteria in all groups were: lack of ED admission record/ Swedish personal identification number/ ED ledger data, and transport from another general hospital of a patient already under treatment for sepsis.

Study III

Design and setting

Mixed methods analysis[139,140] in the prehospital setting, using a sequential exploratory design[139], comprised of both a qualitative (content analysis) and a quantitative part (quantification of identified keywords).

Study population

Content analysis

Inclusion criteria: adult (≥18 years) patients, arriving by the EMS to Södersjukhuset through the ED and discharged from in-hospital care during 2012 with an ICD-10-code (bi- or principal) compatible with sepsis (See Appendix 4) were candidates for inclusion. The included patients were selected with the maximum variation sampling method[141], to achieve maximal variation regarding arrival time, gender, season and age. The first and the last male and female patient every month within the following age categories: <65 years, 65–74 years and 75 years or older[29] were included. To obtain a spread of patients over day and night, patients that arrived daytime (>8:00 am - ≤20:00 pm) were included uneven months and patients that arrived at night (>20:00 pm - ≤8:00 am) were included even months. The aim was to include patients until the point where collecting additional data did not yield new information[142], a condition referred to as "saturation" within qualitative research[142 143]. There is no predefined sample size for qualitative studies, as it depends on richness of data[142].

Quantification of keywords

Inclusion criteria: adult (≥18 years) patients arriving by the EMS to Södersjukhuset through the ED and discharged from in-hospital care during 2013 with an ICD-10-code (bi- or principal) compatible with sepsis (see Appendix 4) were candidates for inclusion.

Exclusion criteria for both the content analysis and the quantification of keywords were healthcare-associated infections (HCAI), defined as onset of infection ≥48 h after ED admission[137], subjects already admitted and treated for sepsis or infections transported from other general hospitals, EMS records with insufficient information, lack of EMS records and patients with no information in the electronical ED ledger.

Study IV

Design and setting

Prospective observational cohort study in the prehospital setting.

Study population

Inclusion criteria: Two groups of adult (≥18 years) non-trauma EMS patients were included 1) patients considered to suffer from a new onset infection according to clinical judgment by the EMS personnel, 2) patients not considered to suffer from an infection. Patients included in the second group were initially planned to be the patients immediately following patients suspected to have an infection, but this approach was not logistically feasible, and a decision of not requiring consecutive patients was taken during the study. All patients were enrolled by EMS during the period of April 3rd, 2017 and August 30th, 2018 and transported to the ED of one of the seven general hospitals of Stockholm city county.

Exclusion criteria: lack of written consent, trauma other than fall at home, patient leaving ED prior to physician's assessment, direct admission to geriatric hospital i.e. bypassing the ED, missing hospital records and missing personal identification number.

4.2 DATA COLLECTION

Study I

Data collection

As a first step, patients discharged with the principal ICD-code consistent with sepsis according to the in-hospital record system (Pasett, Sweden, Version 1.61) were identified. Subsequently, the patients were matched to the electronic ED ledger (AkuSys, Sweden, Version 5.0f) and only patients initially transported by EMS and admitted to in-hospital care from the ED were included. EMS records were retrieved from CAK-NET database (version 5.3, Stockholm County Council IT), and from a database for scanned patient-related documents (KoVis, Version 5.0, Global 360, Inc) when EMS records could not be found through the CAK-NET. Primarily, the EMS records and ED admission records (from hospital medical records: Melior, Version 1.5, Siemens AB) were screened for signs consistent with infection (defined in Appendix 5). Data related to age and gender was retrieved from the ED ledger and in-hospital mortality was retrieved from hospital medical records. EMS vital signs, level of consciousness, plasma glucose (Breeze 2 Glucose Meter, Bayer Ascensia ®) and documentation of primary impression by EMS were acquired from EMS records. Documentation of referrals, or a previous assessment by a medical doctor for the same symptoms within the 24 hours prior to EMS arrival without referral, was acquired from hospital medical records and EMS records. The applied definition of severe sepsis is described in Appendix 6.

Study II

Data collection

First, we identified all patients, 18 years or older, discharged from in-hospital care with an ICD-10-code compatible with sepsis (Pasett, Sweden, Verson. 1.61). Septic patients presenting with DGC were identified in accordance to the electronic ED ledger (AkuSys, Sweden, Version 5.5b).

Second, patients in the DGC reference group were identified as follows: first, all patients 18 years or older, presenting to the ED during the study period with chief complaint DGC (according to AkuSys), were identified. Second, a sample was randomly selected among those without an ICD-10-code compatible with sepsis by SPSS (Statistical Package for the Social Sciences, Inc., Chicago IL, version 21, 2012).

Data related to ED arrival, age, triage priority, gender and chief complaint were retrieved from the electronic ED ledger. The first triage priority that the patient received upon arrival to the ED was used.

Information regarding ED doctor clinical judgment and preexisting comorbidity was acquired from the ED admission records (Melior,Version 1.5, Siemens AB), which were also screened for signs consistent with infection (defined in Appendix 5).

Vital signs and time of initiation of antibiotics were obtained primarily from the, by a nurse handwritten and scanned, ED arrival chart (KoVis, Version 5.0, Global 360, Inc, via Melior).

If missing there, vital signs were obtained from the, by a physician documented ED admission record and time of antibiotics from the list of medications for the care episode, reached through KoVis or Melior. In-hospital mortality rates were acquired from the in-hospital medical record system Pasett.

Study III

Data collection

Medical records were obtained through the in-hospital record system (Pasett, Sweden, Version 1.61). All patients were screened for signs of suspected infection (see Appendix 5) during EMS transport or ED stay. Deceased was defined as in-hospital death in accordance with the in-hospital record system. The applied definition of severe sepsis is described in Appendix 6.

Content analysis

The maximum variation sampling method was used for inclusion patients to the content analysis of patients admitted during 2012, for details see 4.1.

Quantification of keywords

All EMS patients admitted through the ED and discharged with ICD-code sepsis during 2013 were screened, and patients fulfilling eligibility criteria were included. For the quantification of keywords identified in the content analysis of patients admitted during 2012, the narrative section of EMS records from septic patients admitted during 2013 was analyzed.

Study IV

Data collection

A Case Report Form (CRF) applied by EMS included eight keywords relating to medical history and six vital signs. Vital signs not recorded in the CRFs were extracted from the ambulance records (amPHI® Prehospital ambulance record, Amphi Systems A/S, Aalborg, Denmark, achievable through the hospital medical record (TakeCare®, v. 18.3.10, CompuGroup Medical, Stockholm, Sweden) and the digital IT-support for prehospital care in Stockholm; FRAPP® (Framtida IT-plattform för prehospital vård i Stockholms läns landsting).

Data related to ED arrival time, age, gender, in-hospital vital signs/ laboratory tests/ mortality and discharge ICD-code, in addition to information on comorbidity, were retrieved from the hospital medical records.

A standardized data extraction protocol was used for registration of data from EMS and hospital records, including the following variables: age, EMS/ in-hospital vital signs and laboratory parameters, pre-existing comorbidity, level of priority, criteria for suspicion of a new-onset infection, variables for SOFA score/ qSOFA score/ SIRS and criteria for severe sepsis according to our previously published definition adapted to prehospital care (see Appendix 6), treatment, hospital discharge ICD-code and in-hospital mortality.

Predictive variables

A total of 21 variables were measured, as follows:

1. Keywords related to medical history

Eight keywords related to medical history, with a prevalence exceeding 20% among septic patients in the prehospital setting[95] were measured in the ambulance; “abnormal/ suspected abnormal temperature”, “pain”, “acute altered mental status”, “weakness of the legs”, “breathing difficulties”, “loss of energy”, “gastrointestinal symptoms” and “risk factors for sepsis”[95].

2. Vital signs

Six vital signs were registered in the ambulance: the first measured values of respiratory rate, oxygen saturation, heart rate, systolic blood pressure, Glasgow coma scale; GCS and temperature, in accordance with current Swedish EMS guidelines[128].

3. POC-tests

Blood for four POC-tests was taken in the ambulance; P-Glucose, P-Lactate, P-HBP and P-suPAR.

P-Glucose was analyzed in the ambulance, in accordance to current EMS guidelines[128] , using Contour® Blood Glucose Meter; Bayer, Basel, Switzerland.

The ED nurse receiving the ambulance collected the remaining blood tests. The samples were centrifuged and frozen at −70 °C until analysis. P-Lactate and P-SuPAR were analyzed at Karolinska University Hospital study laboratory, Solna. *P-Lactate* was analyzed in accordance to standard procedures.

P-suPAR levels were determined in duplicate samples using a commercial enzyme-linked immunosorbent assay (ELISA) (suPARnostic® Standard kit; ViroGates A/S, Birkerød, Denmark) according to the manufacturer’s instructions. The linearity of this assay is comprised between 2.0 and 15.6 ng/mL, and the total imprecision, expressed as the coefficient of variation (CV %), ranges from 2.3 to 6.0 %. Values below 1.2 ng/mL or above 20.8 ng/mL were registered as 1.2 and 20.8 ng/mL respectively.

P-HBP-samples were stored at Örebro Medicinska Biobank until analyses by the Inflammatory Response and Infection Susceptibility Centre (iRISC)[144] laboratory in Örebro. Levels of P-HBP were determined using a commercial ELISA assay (Axis-Shield Diagnostics Ltd, Scotland) according to the manufacturer’s instructions. HBP was quantified based on a standard curve of known concentrations ranging from 0-200 ng/mL, where the lowest detection limit of the assay was 5.9 ng/mL. Samples were run in duplicates; the mean CV was 7.2%. Values below 5,9 or above 200 ng/mL were registered as 5,9 and 200 ng/mL respectively.

4. Demographic variables

Three demographic variables were extracted from hospital records; age, gender and Charlson comorbidity score.

Outcomes

1. Sepsis

Sepsis was defined as sepsis within 36 hours from ED arrival, in accordance with the Sepsis-3 criteria[1].

2. Infection

Outcome infection was defined in accordance with the previous definition, see Appendix 5.

3. No infection

Patients that had neither sepsis nor infection according to above criteria were classified as no infection.

4.3 DATA ANALYSIS

The statistical analyses were performed using SPSS software (statistical package for the social sciences, version 21-25, IBM Company, Chicago, IL, USA) in all four studies.

Study I

Data analysis

EMS records were screened for the identification of sepsis according to two screening tools and clinical judgment as documented by EMS providers. McNemars two related samples test was used to compare the sensitivity of the two screening tools with the sensitivity of clinical judgment.

Study II

Data analysis

Time to antibiotics (Mann Whitney and Kaplan-Meier tests), and mortality (logistic regression) was compared between septic patients presenting to the ED with decreased general condition and septic patients presenting to the ED with other chief complaints, adjusting for sex, age, priority, comorbidity and fulfilment of the Robson score. The sensitivity and specificity of the Robson sepsis screening tool was compared to that of ED doctor clinical judgment (McNemars two related samples test) among patients presenting to the ED with decreased general condition, of which half were discharged with ICD code sepsis.

Study III

Data analysis

The mixed methods analysis[139,140] followed a sequential exploratory design[139], comprised of both a qualitative (content analysis) and a quantitative part (quantification of identified keywords).

Content analysis

The content analysis was a retrospective EMS medical record review using inductive manifest content analysis inspired by Krippendorff[145], using the terminology of the analysis process from Graneheim and Lundman[146]. The study focused on the, by EMS personnel documented, content of the narrative part of the EMS records, which described presentations of septic patients in the prehospital setting. The content analysis of the text was performed in several steps i.e.; 1) selection of meaning units (words or short phrases which reflect the aim of the study, symbolizing an expression, sentence or other meaning bearing text section), 2) condensing meaning units into shorter, condensed meaning units, 3) coding of units, 4) abstraction of the codes into subcategories until all meaning units were included in mutually exclusive subcategories and, 5) reduction and grouping of the subcategories into categories. Both condensing and coding involves shortening of the text, while preserving the core message.

Quantification of keywords

Quantitative methods were used to measure the prevalence of specific codes and subcategories related to presentations identified in the qualitative part. To describe and quantify clinically relevant keywords, the expressions “primary” and “combined” keywords were introduced. Primary keywords were codes and subcategories derived from the content analysis while combined keywords consist of several primary or combined keywords. Combined keywords were created in order to condense primary keywords. Keywords related to septic patients´ symptom presentation were presented separately and defined as keywords that describe the patient´s or bystanders´ experience of the disease i.e symptom.

In-hospital mortality within subgroups of various keywords related to symptom presentation was analyzed. The prevalence of keywords related to septic patients´ symptom presentation was compared between age categories, survivors and deceased, and between patients with severe and non-severe sepsis, using Fischer´s exact test. Differences in categorical variables between patients from 2012 and 2013 were analyzed using Fischer´s exact test and Mann Whitney U test was used to analyze differences in numeric variables (age).

Study IV

Data analysis

1. Characteristics

Normality distribution was assessed by the Kolmogorov–Smirnov and the Shapiro–Wilk tests, and visually by histograms. Median and interquartile range (IQR) were used to describe age, vital signs and POC-tests, since these variables were not normally distributed. Differences in numerical data were assessed by Mann-Whitney test for the two ambulance groups and by Kruskall Wallis test (including post hoc tests with Bonferroni correction for multiple comparisons) for the three outcome groups. Differences in categorical data were assessed by Fisher's exact test.

2. Classification of variables in the regression analysis

2a. Keywords related to medical history

Keywords were classified as present (yes)/ not present (no). Patients not able to answer yes or no, were included in the yes-category since they were few (11-30 patients per keyword) and the prevalence of sepsis was similar.

2b. Cut-off values for vital signs and POC-tests

Cut-off values for numerical variables were identified following a stepwise approach 1) 8-10 categories were created for each variable, including previously defined cut-off-levels according to NEWS[147], SIRS[19], Robson[103] as far as possible and with the additional categories created with as equal steps as possible. 2) These 8-10 categories were merged into 3-4 categories for each variable, based on similarities with respect to sepsis prevalence within the categories, odds ratios (ORs) and confidence intervals (CIs) for each category. 3) The 3-4 categories from step 2 were merged into final 2-3 categories as above.

Comparisons of receiver operating characteristics (ROC) curves and values of area under the receiver operator curve (AUC) for the continuous variable and its three categorized versions were performed for each step, in order to analyze whether the categorization caused an unacceptable loss of information.

3. Determination of predictors for sepsis among patients with suspected infection in the ambulance

3a. Logistic regression

To identify predictors for sepsis we used the following strategy; first an unadjusted univariable (crude) analysis was performed for each of the 21 variables. The AUC was calculated for all variables that showed a significant association ($p<0.05$) with sepsis. Second, a multivariable adjusted logistic regression was performed including variables which were significantly associated with outcome sepsis in the univariable analysis.

3b. Classification trees

Classification trees were used to identify factors associated with sepsis and to stratify groups of patients according to risk of sepsis. The CHi-squared Automatic Interaction Detection (CHAID) algorithm was used to build the tree[148]. Classification trees constitute a complementary method to logistic regression to visualize complex relationships between categorical variables. The analysis starts with all data in one group. Each possible split for each variable is considered to find the split that leads to the strongest association with the outcome: sepsis (yes/no). The analysis was based on the 21 variables described above with the outcome sepsis. The resulting groups were split until one of the following stop criteria was reached: tree depth was limited to five levels, no groups with less than 25 patients was formed and no split with a Bonferroni adjustment of less than 0.05 was executed.

4. Model design

Models were designed based on significant association with sepsis in univariable and multivariable regression analyses, in addition to significant association in univariable analysis in combination with significant p-values for the AUC of the variable.

There was a trade-off between the number of variables included in the model (the fewer variables included in a screening tool, the easier to use) and the contribution to prediction of outcome sepsis. This was evaluated using ROC curves.

Weights (based on association to sepsis in regression analyses and classification trees) were compared for each variable included in a new predictive model and evaluated with respect to sensitivity and specificity for sepsis through ROC curves.

The cut-off score of the model, classified as positive for suspected sepsis, was identified as follows: the ROC curve was calculated for the sum of the individual weights of the model, and the score associated with the best combination of sensitivity and specificity was sought.

The AUC, sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and likelihood ratios (LRs) were calculated for the final model; the Predict Sepsis screening tool, and for a model based on solely vital signs.

5. Comparison of screening tools

AUC, sensitivity, specificity, PPV, NPV and LR of the final models were compared with those of two earlier proposed sepsis screening tools for the prehospital setting; PRESEP and Robson scores[103,105].

4.4 ETHICAL CONSIDERATIONS

The retrospective parts of the study project (Study I-III) are based on analyses of EMS and ED records. Study I-III did not include any intervention and did not affect the treatment of the participating patients who received regular care. A review of patients´medical records can be considered as a type of personal intrusion, often revealing very personal information. However, only the research group had access to the data which was treated confidentially and stored locked in at the research center. All data was analyzed on group level and individuals could not be identified. The benefits of the studies were expected to exceed the possible harm associated with the review of patients´ medical records. Ethical permission was obtained from the Stockholm Regional Ethical Review Board (Reg.no 2012/1288-31/3 and 2015/1019-32).

In Study IV, the participants were asked eight questions covering medical history. The questions were of the same nature as questions routinely used by emergency care providers to acquire information of symptoms and underlying conditions. Blood tests were drawn. All invasive procedures, even drawing blood, are associated with a risk of complications such as infections. However, the risk of complications is low, and the EMS use point-of-care testing routinely (P-Glucose). Neither the questions nor the blood tests are expected to have delayed the transport or affected the care of the patients. The possible benefits for future emergency care patients were considered to exceed the possible risks of the study procedure.

Also, patients with a decreased level of consciousness were included in study IV. Patients with decreased level of consciousness are the most critically ill and to include them was of utter importance to enable the identification of predictors of sepsis among EMS patients. For these cases, as well as for patients who were not able to sign a consent document during EMS transport (but gave oral consent to participate), a written consent by the patient (or on behalf of the patient and signed by a relative) was required in retrospect. Relatives could sign the consent document if the patient deceased/ was unable to sign but was considered to have been positive to participate. If there was any uncertainty to whether the patient wanted to participate, the patient was excluded. The data was treated confidentially and was stored locked in at the research center. All data was analyzed on group level and individuals could not be identified. Ethical permission was obtained from the Stockholm Regional Ethical Review Board (Reg.no 2016/2001-31/2 and 2018/2202).

5 RESULTS

5.1 STUDY I

A total of 353 patients were included in the study; of these, 145 (41%) were women and 208 (59%) were men. The mean age of the patients was 74.8±14 years. 44.4% of the patients with the necessary documentation fulfilled the criteria for severe sepsis during the EMS transport. The in-hospital mortality in the total sample was 19.5%.

The modified Robson screening tool had a sensitivity of 75% among all septic patients. The sensitivity increased to 93% among patients presenting with severe sepsis. BAS 90-30-90 demonstrated a sensitivity of 43% in the entire population, and the sensitivity of the model increased to 70% among patients presenting with severe sepsis. EMS personnel documented suspected sepsis in 12% of the 353 patients and in 17% of the patients with severe sepsis.

5.2 STUDY II

61 patients were included in the group of septic patients presenting with ED chief complaint DGC, 516 patients in the sepsis reference group and 61 patients in the DGC reference group. The median age of septic patients in the DGC group was 78 years, and in the sepsis reference group 73 years.

Septic patients presenting to the ED with decreased general condition had a longer median time to antibiotics (05:26 hours:minutes; IQR 4:00-10:40, vs. 03:56 hours:minutes; IQR 2:21-7:32) and an increased in-hospital mortality (crude OR=4.01; 95% CI, 2.19-7.32), compared to other septic patients. This association remained significant when adjusting for sex, age, priority, comorbidity and fulfilment of the Robson score (OR 4.31; 95% CI, 2.12-8.77). The Robson sepsis screening tool had a higher sensitivity (63.0% vs. 24.6%, $p<0.001$), but a lower specificity (68.3% vs. 100.0%, $p<0.001$), as compared to clinical judgment.

5.3 STUDY III

Content analysis

We obtained no additional information after approximately 50 EMS records had been analyzed, but continued to analyze a total of 80 records in accordance with previously published content analyzes of medical records[149,150], so as not to risk including insufficient information. Hence, 80 patients were included in the content analysis and the median age was 73 years.

22 subcategories were identified from a total of 99 codes. Examples of these subcategories were: loss of energy, malaise, nausea, pain, gastrointestinal function, ability to stand/walk,

fallen/ found on the floor. The subcategories were grouped into five main categories: physical examination, sensations, mobility, elimination and additional information.

Quantification of keywords

All 403 EMS patients admitted through the ED and discharged with ICD-code sepsis during 2013 were screened, and 359 included. The median age was 78 years.

Primary outcomes

Eight keywords related to symptom presentation or medical history demonstrated a prevalence exceeding 20% of the septic patients: abnormal/ suspected abnormal temperature (64.1.%), pain (38.4%), acute altered mental status (38.2%), weakness of the legs (35.1%), risk factors for sepsis (30.6%), breathing difficulties (30.4%), loss of energy (26.2%) and gastrointestinal symptoms (24.0%).

Secondary outcomes

The highest in-hospital mortality was observed among patients with documented hypothermia (80.0%), decreased urinary volumes (58.3%), reduced intake of food, fluid or oral medicines (38.3%), history of acute altered mental status (37.2%) and breathing difficulties (35.8%).

New-onset weakness of the legs was significantly more frequent in the oldest age category (43.8 vs 26.1%, p-value 0.02) as compared with patients below 65 years of age.

Survivors had a higher prevalence of EMS documented abnormal, or suspected abnormal temperature (68.7 vs 51.1%, p-value 0.003) and shivering (19.6 vs 6.4%, p-value 0.002) as compared with deceased. Deceased had a higher prevalence of EMS documented hypothermia (8.5 vs 0.8%, p-value <0.001), acute altered mental status (54.3 vs 32.5%, p-value <0.001), breathing difficulties (41.5 vs 26.4%, p-value 0.009) and decreased urinary volumes (7.4 vs 1.9%, p-value 0.02), as compared with survivors.

EMS documentation of hypothermia (4.9 vs 0.0%, p-value 0.006), acute altered mental status (67.5 vs 0%, p-value <0.001) and reduced intake of food, fluid or oral medicines (16.7 vs 8.7%, p-value 0.04) was significantly more frequent among patients with severe sepsis compared to those with non-severe sepsis.

Documented pain (49.7 vs 29.6%, p-value <0.001) and nausea (14.1 vs 6.9%, p-value 0.03) were significantly more frequent among patients with non-severe sepsis compared to those with severe sepsis.

5.4 STUDY IV

Characteristics and comparison of variable prevalence between outcome groups

878 patients were included, of which 553 had an infection according to clinical judgment in the ambulance and 318 were considered to have no infection. Seven patients lacked documentation whether the EMS personnel suspected infection or not.

246 patients had outcome sepsis, 156 of them (63.4%) were men, 230 (95%) were identified by EMS as suffering from an infection, 47 (19.3%) were discharged with an ICD-10-code compatible with sepsis and 25 (10,2%) died during the hospital stay.

Patients with outcome sepsis had a higher prevalence of all keywords related to medical history except for pain, a higher respiratory rate/ heart rate/ temperature and a lower systolic blood pressure/ oxygen saturation/ GCS score compared to patients with outcome infection/no infection.

Predictors of sepsis

Among the 553 patients with suspected infection in the ambulance, 551 had sufficient documentation to determine whether the patient had sepsis or not, and these 551 patients were included in the logistic regression and classification tree analyses.

1. Logistic regression analysis

The keywords with the strongest crude association to outcome sepsis among patients with suspected infection in the ambulance were acute altered mental status and gastrointestinal symptoms.

The vital signs with the strongest association to outcome sepsis among patients with suspected infection in the ambulance were: GCS <15, systolic blood pressure ≤100 and temperature >38.5. Heart rate demonstrated the weakest association to sepsis.

All POC-tests except for P-Glucose had a significant association to outcome sepsis in the univariable logistic regression, among patients with suspected infection in the ambulance. The POC-test with the strongest association to outcome sepsis was P-Lactate >4.

No demographic variables were significantly associated with sepsis in the multivariable analysis.

2. Classification trees

Classification trees demonstrated that the vital signs GCS and temperature were most strongly associated with sepsis.

The Predict Sepsis screening tool and comparison of screening tools

The following variables were the strongest associated with sepsis according to logistic regression and classification trees and included in the final Predict Sepsis screening tool: acute altered mental status, gastrointestinal symptoms, systolic blood pressure, GCS, temperature and P-Lactate. Simplified weights for individual variables were chosen as follows: acute altered mental status=1, gastrointestinal symptoms=1, systolic blood pressure <=100 mmHg=2, GCS <15=2, temperature 38.1-38.5°C=1, temperature >38.5°C=2, P-Lactate>4=2. A score of two or more was considered positive for suspected sepsis

The AUC of the Predict Sepsis screening tool (0.77; 95%CI 0.73-0.81) exceeded that of both PRESEP and Robson scores (0.67 and 0.65) in the current study population, see Table 1 and Figure 3. When the Predict Sepsis screening tool was compared to a model including vital signs alone the AUCs did not differ significantly.

Table 1. Comparison of screening tools*.

	Predict Sepsis screening tool **≥2 points**	Vital sign model utilizing the current cut-offs of individual vital signs ≥2points	PRESEP score** ≥4 points	Robson score*** ≥2 points
Sensitivity (95%CI)	**0.90(0.85-0.93)**	0.89(0.84-0.93)	0.77(0.71-0.82)	0.93(0.89-0.96)
Specificity (95%CI)	**0.40(0.34-0.45)**	0.37(0.32-0.43)	0.46(0.41-0.52)	0.20(0.16-0.25)
PPV (95%CI)	**0.52(0.46-0.56)**	0.50(0.45-0.55)	0.51(0.45-0.56)	0.46(0.41-0.50)
NPV (95%CI)	**0.84(0.77-0.89)**	0.83(0.75-0.88)	0.74(0.67-0.80)	0.81(0.71-0.89)
Pos LR (95%CI)	**1.48(1.34-1.64)**	1.42(1.29-1.56)	1.44(1.27-1.62)	1.17(1.10-1.25)
Neg LR (95%CI)	**0.26(0.18-0.39)**	0.29(0.20-0.43)	0.49(0.38-0.63)	0.32(0.19-0.54)
AUC for sum of scores for the model (95%CI)	**0.77(0.73-0.81)**	0.75(0.71-0.79)	0.67(0.62-0.71)	0.65(0.61-0.70)

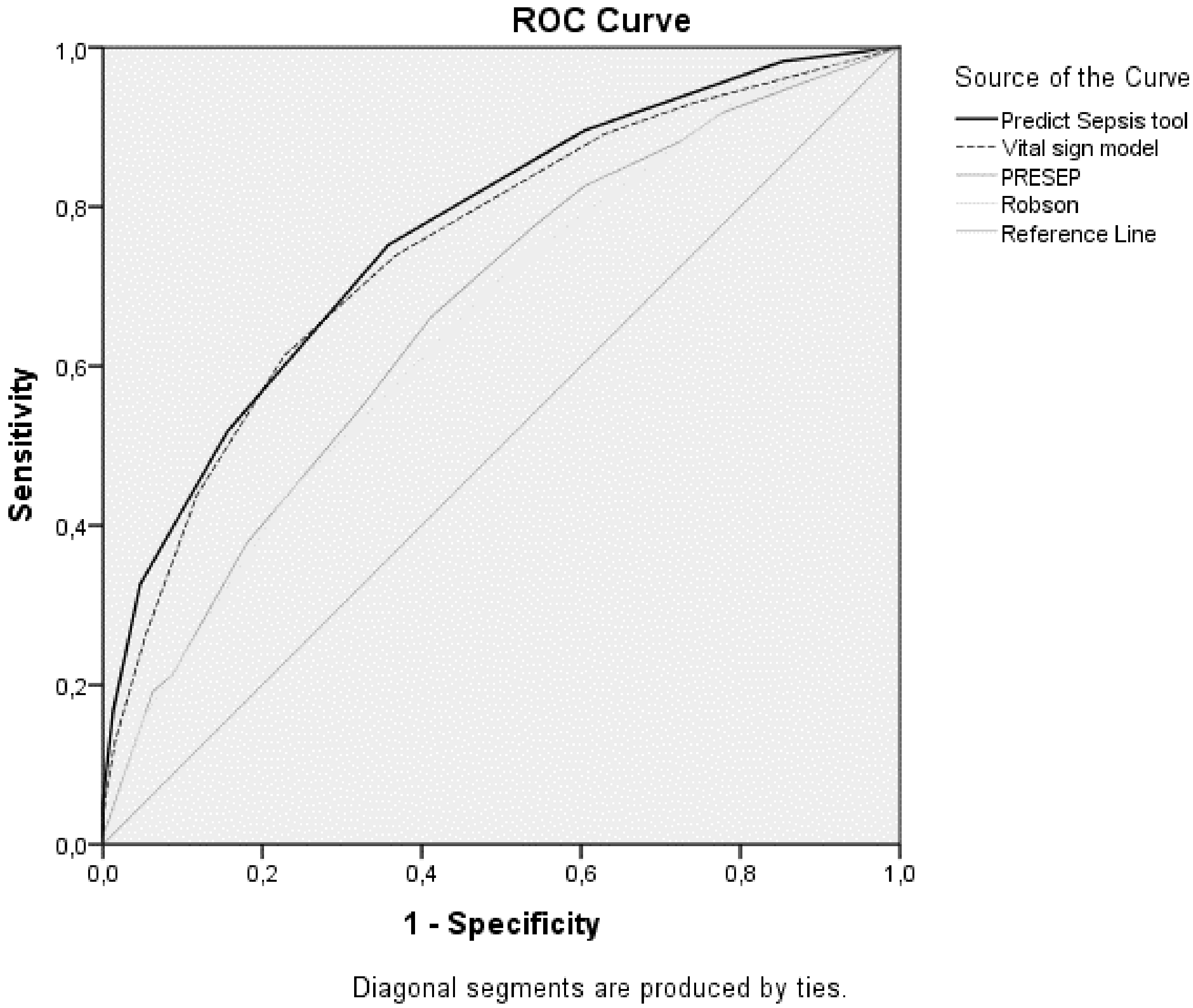
PPV= positive predictive value, NPV= positive predictive value, LR=likelihood ratio, AUC=area under the curve, PRESEP=PREhospital SEPsis, screening tool, CI=confidence interval, Temp= temperature, SpO2= saturation of peripheral oxygen, HR=heart rate, SBP=systolic blood pressure, RR=respiratory rate.

*Sensitivity, specificity, PPV, NPV, LRs and 95% confidence intervals for those were calculated by using www.vassarstats.net, calculator 1.

**PRESEP score includes the following variables with the following weights: Temp>38 =4, Temp<36=1, SpO2<92=2, HR>90=2, SBP<90=2, RR > 22=1. A score of ≥4 is considered positive for sepsis.

***Robson score includes the following variables with the following weights: Temp>38.3 /<36.0=1, HR>90=1, RR > 20=1, Acute altered mental status= 1, P-Glucose >6.6=1. A score of ≥2 is considered positive for sepsis.

Figure 3. Comparisons of the final models in addition to PRESEP and Robson scores.



6 METHODOLOGICAL CONSIDERATIONS

6.1 DEFINITION OF SUSPECTED INFECTION

The definition of suspected infection applied in all four studies of the current thesis can be questioned. To our knowledge, there is no previously published detailed definition of symptoms/ presentations that should prompt healthcare personnel to suspect a new-onset infection. Neither Sepsis-1, -2 nor -3 include a detailed definition of infection. The Sepsis-1 and 2 consensus documents[19,20] defined infection as “a pathological process caused by invasion of normally sterile tissue/fluid or body cavity by pathogenic or potentially pathogenic micro-organisms”. This definition is poorly adapted to emergency care where results of radiology and cultures are frequently unavailable. Consequently, there was a need for a definition of suspected new-onset infection. We based our definition on clinical experience from emergency care and signs and symptoms frequently reported by patients suffering from infection in our studies. However, we are aware that some of these combinations of symptoms are non-specific to their nature. Nevertheless, there was a high degree of overlap between the current definition and EMS clinical judgment of suspected infection in Study IV, which indicates a high degree of conformity regarding signs and symptoms indicating a suspected infection. The validity of the current definition of infection should be evaluated in future studies.

6.2 PATIENT INCLUSION

In Study I the lack of a non-septic control group and the associated inability to determine the specificity of the tools constituted a major limitation. A non-septic EMS control group should ultimately have been included for this reason.

In Study I-III study samples were included on the basis of hospital discharge ICD-codes. Inclusion based on ICD-codes has been used in several previous studies[29,48], and is the only reasonable way for database searches. However, this approach can be questioned as it is well known that diagnostic coding is a problem[33], and consistently underestimates the incidence[35]. Inclusion based on ICD-code could potentially entail a selection of more sick patients, as well as patients with symptoms more typical of the common picture of sepsis, e.g., fever and hemodynamic instability, since these patients may be more readily identified in the clinical setting. Hence, the inclusion based on ICD-codes may limit the generalizability of the results.

In study IV, patients were enrolled prospectively, and the diagnosis of sepsis was based on infection in addition to fulfillment of SOFA criteria. A five times higher prevalence of sepsis was observed when this approach was used, as compared to the prevalence based on ICD-codes. This discrepancy underscores that basing sepsis on ICD-codes is inappropriate if inclusion of all septic patients is a concern.

6.3 MISSING DATA AND LIMITATIONS OF RELYING ON DOCUMENTATION BY EMERGENCY CARE PROVIDERS

In study I-III missing data was a major limitation. Particularly in the first study, the patients with complete documentation were few, which may have affected the results. Both EMS and ED records can be brief which may have its advantages. However, in a retrospective study design it is a well-known obstacle, leading to an increased amount of missing data. Also, the lack of regulation with respect to documentation in both EMS and ED records likely contributed to missing data. It is possible that the actual rate of suspected sepsis is higher in prehospital care than that which is documented, as in Study I. During data collection in Study II, it was often apparent in the medical record that ED doctors suspected sepsis more frequently than was explicitly expressed. E.g., the ED doctors could order antibiotics recommended for severe sepsis without literally stating the suspicion thereof. Hence, lack of documentation of suspected sepsis in EMS and ED records may have contributed to the low sensitivity of clinical judgment in Study I and II.

In Study III, the analysis of sepsis presentation was based on EMS documentation which is associated with inherent restrictions. Documentation can be affected by many factors e.g., what EMS ask the patient, the patient's ability to explain his/her experience and the presence of relatives who may or may not be able to describe the situation at hand. It is, as described above, not always possible to discern the origin of the documented information. The EMS records present the symptoms as documented by EMS personnel. To perform open interviews with septic patients would be an alternative approach to explore sepsis symptom presentation. However, detailed interviews in the ambulance are difficult to perform for logistical reasons. In addition, there is a risk of bias towards less sick patients as the most sick septic patients may be unable to participate in an interview. If interviews are performed retrospectively, there is a risk of recall bias due to a high extent of altered mental status among the patients during the septic episode.

In study IV the prospective study nature reduced the amount of missing data. But still, documentation was sometimes missing which may reflect both the human nature and the often-stressful environment of emergency care.

6.4 SINGLE CENTER STUDIES

Study I-III were single centre studies in an urban setting, including only patients admitted to Södersjukhuset, which may limit the generalizability of our results. However, the hospital is one of the largest EDs of northern Europe, admitting patients both from the city centre of Stockholm as well as from rural areas, making the results most likely generalizable to other emergency care populations. In study IV patients admitted to all seven hospitals of Stockholm were included but there was only one ambulance provider involved. However, this is not expected to have affected our major results.

6.5 INFLUENCE BY PRECONCEPTIONS OF THE RESEARCHER

Personal experience of the researcher may influence the interpretation of data. This is always a risk when data analysis involves any kind of subjective interpretation. Within qualitative research this is particularly important, and measures need to be accounted for to ensure trustworthiness. Trustworthiness is a concept within qualitative research that corresponds to validity/reliability/generalizability within quantitative research. To ensure trustworthiness in Study III the three authors, all with different backgrounds, met regularly to ensure a consistent approach to the analysis of data.

6.6 SPECIAL CONSIDERATIONS CONCERNING STUDY IV

The strengths of Study IV were the prospective study design, the novel concept to include keywords relating to medical history in the study and that patients with an impaired level of consciousness were included.

The inclusion of solely EMS patients with suspected infection in the analysis of association to sepsis was a major limitation and limits the generalizability of the results to all patients presenting to the EMS. Septic patients with non-specific presentations have been shown to have a worse prognosis as compared with those who present with more obvious signs of an ongoing infection[14]. Furthermore, patients with non-specific presentations are most likely at higher risk of not being identified. The value of keywords related to medical history and POC tests should ultimately be analyzed prospectively in an unselected EMS population. However, this approach is costly since the overall sepsis incidence of all EMS assignments is approximately 3.3%[151]. This incidence may appear low, but can be compared with that of acute myocardial infarction (2.3% of all EMS encounters), and stroke (2.2% of EMS encounters)[151]. To achieve the needed 210 patients with outcome sepsis in Study IV, prospective inclusion of approximately 6.400 patients would have been required.

There is an inherent risk that the Predict Sepsis screening tool is over-adapted since it has been developed in the current population. The accuracy of a tool may deteriorate considerably during external validation, as in the case of the PRESEP score[105]. Hence, the Predict Sepsis screening tool needs to be externally validated within a new population.

7 DISCUSSION

7.1 STUDY I

We compared two prehospital sepsis screening tools with regular care, that is, clinical judgment by EMS, and found the sensitivity of the two screening tools to be superior. This is, to the best of our knowledge, the first study comparing prehospital sepsis screening tools with clinical judgment for identification of sepsis in the prehospital setting. The sensitivity of the Robson screening tool was superior to both the BAS 90-30-90 model and clinical judgment by EMS, and the sensitivity was higher among patients with severe sepsis. The BAS model focuses exclusively on hypotension, low oxygen saturation, and elevated respiratory rate as signs of organ failure. However, we suggest that other measures of organ failure need to be included in the patient evaluation. The identification of septic patients by clinical judgment during EMS transport was low, 12%, in the current study. A previous study by Studnek et al.[16] reported a sensitivity of EMS sepsis identification of 20.6%. The latter study, however, included patients presenting with septic shock/severe sepsis[16], that is, more overtly sick patients. The corresponding sensitivity for identification by clinical judgment among patients presenting with severe sepsis was 17% in the current study. The results of Study I demonstrate that clinical judgment is inadequate with respect to sepsis identification and supports proof of principle that a screening tool increases the identification of the septic patient in the prehospital setting.

7.2 STUDY II

This is, to the best of our knowledge, the first study comparing the outcome of septic patients according to ED presentation as described by chief complaint. Second, a screening tool was compared with ED doctor clinical judgment, with respect to sepsis identification among patients presenting with ED chief complaint DGC.

Time to antibiotics and mortality

The results indicate that septic patients presenting with ED chief complaint DGC have a longer time to antibiotics and an increased odds to die during hospital care, as compared to septic patients with other ED chief complaints.

The longer time to antibiotics among septic patients presenting with DGC may be explained by a tendency towards lower ED triage and by the fact that the identification to a higher extent is dependent on laboratory results among these patients, which may in turn delay the identification.

The four-fold increased odds of in-hospital mortality among septic patients presenting with ED chief complaint DGC may have several reasons. First, time to antibiotics differed between the groups, and timely antibiotic treatment has previously been shown to improve outcome for septic patients[74]. Second, less deviation of vital signs was observed among septic patients presenting with ED chief complaint DGC, which may in turn lead to a lower level of monitoring during hospital care and an increased risk of unnoticed deterioration. However, it has been previously described that sepsis can occur without deranged vital signs[39]. Hence, an optimal level of monitoring should be considered for all septic patients.

The accuracy of the Robson screening tool and clinical judgment

The sensitivity of the screening tool was superior, but the specificity inferior, to that of ED doctor clinical judgment.

The higher sensitivity of the Robson screening tool is in accordance with the results of Study I. However, the sensitivity of the tool was lower in Study II (63.0 vs. 75.0 %), which may be explained by the different study populations; in Study II the screening tool was applied solely to the patients presenting with ED chief complaint DGC, showing less deviation of heart rate and temperature, both included in the Robson screening tool[103]. The high proportion of patients in the DGC reference group suffering from infections and sepsis, but not discharged with ICD-codes consistent with sepsis, could decrease the specificity of the tool in our study. It was apparent on manual chart review that patients in the DCG reference group sometimes fulfilled sepsis criteria. However, we adjusted for this by performing a separate sub analysis excluding patients with discharge ICD-codes consistent with infection from the DGC reference group. This led to an increased specificity of the tool.

The sensitivity of ED doctor clinical judgment in the current study exceeded that of EMS providers in Study I (25 vs. 12 %). The latter could reflect a better knowledge of sepsis presentation among ED doctors but also an increased access to laboratory results. However, the results indicate that only one fourth of the septic patients presenting to the ED with the chief complaint DGC were identified as septic by ED doctors, according to chart review.

The specificity of ED doctor clinical judgment was 100 % which may reflect that the ED doctor clinical judgment strongly affects what diagnosis the patient receives upon discharge from hospital.

7.3 STUDY III

This is, to the best of our knowledge, the first study exploring the symptom presentation as documented by EMS, of septic patients in the prehospital setting. Keywords related to patients´ symptom presentation recurred in the EMS records of septic patients, so that a pattern was discernible. In addition, certain symptom presentations were associated with increased in-hospital mortality and the symptom presentation varied between age categories, survivors/ deceased and severe/ non-severe sepsis.

Symptom presentations

The most frequently documented keywords related to patients' symptom presentation were: abnormal, or suspected abnormal temperature, pain, acute altered mental status, weakness of the legs, breathing difficulties, loss of energy and gastrointestinal symptoms such as vomiting and diarrhea.

Almost all patients that presented with abnormal or suspected abnormal temperature had fever, while hypothermia was in general rare. Despite fever being frequently documented as a symptom in the EMS records; approximately one third of the patients lacked this finding. This observation is consistent with a previous study of bacteraemic ED patients by Lindvig et al.[102], showing that 34% of bacteraemic patients had a normal temperature recorded at ED arrival. Pain was frequently documented. The location often reflected the site of the original infection but general flu-like muscular pain was also common, in accordance to previous literature describing diffuse pain as frequent[118]. The frequent keyword acute altered mental status represents primary keywords ranging from altered behavior to the deepest level of non-responsiveness and may reflect the sepsis-associated encephalopathy described in section 2.5. Weakness of the legs was another common symptom presentation and has not previously been described for septic patients in the prehospital setting. This finding is interpreted as an expression of the sepsis-induced polyneuropathy and myopathy described in section 2.5. Breathing difficulties were frequent and only 39% of the patients with this symptom had a pulmonary origin of the underlying infection. This indicates that breathing difficulties may be caused by a systemic response to an infection rather than by focal effects of the underlying infection.

Mortality rate based on symptom-presentation

The highest mortality rates were observed among patients with documentation of hypothermia, reduced urinary volumes and reduced intake of food or fluid. Interestingly, the mortality rate among patients with these presentations exceeded that of patients presenting with keywords included in the former definition of severe sepsis such as acute altered mental status. However, these findings need to be replicated in larger cohorts.

Variations with respect to symptom-presentation within subgroups of septic patients

The documented presentations varied between age categories which may reflect a variation in the physiological response to an infection relating to age. However, it may also reflect that health care personnel direct their questions differently when encountering elderly patients, focusing on more basic functions e.g., food/fluid intake and whether they can stand and walk. Furthermore, presentations differed between survivors and deceased. Fever and shivering were more frequently documented among survivors which may indicate that these patterns reflect an appropriate immunological response or possibly a protective effect per se. This is consistent with previous studies demonstrating a decreased mortality in septic patients with fever[152,153].

7.4 STUDY IV

This is, to the best of our knowledge, the first prospective study in the prehospital setting to study the association between variables measurable in the ambulance, including symptom-variables, and outcome sepsis. Vital signs were, as a group, the strongest predictors of sepsis, but two symptom-variables and one POC test were significantly associated with sepsis in the multivariable analysis. The Predict Sepsis screening tool is the first screening tool including symptom-variables and the tool demonstrated an AUC superior to earlier proposed prehospital sepsis screening tools[103,105]. However, the predictive accuracy of the tool was similar to that of a model based on vital signs alone, utilizing the current cut-offs for individual vital signs.

Predictors of sepsis

Keywords reflecting gastrointestinal symptoms and acute altered mental status surpassed "classic" symptoms of sepsis such as a history of fever with respect to sepsis association. This finding is novel and indicates that these symptoms may require more attention.

Vital signs were, as a group, the strongest predictors of sepsis and GCS, systolic blood pressure and temperature demonstrated the strongest association with sepsis. However, two thirds of septic patients presented with normal GCS, one third had a normal systolic blood pressure and one third lacked fever. This is consistent with a previous study by Suffoletto et al[116], demonstrating that 39% of patients with severe infections present with normal prehospital vital signs.

Among *POCs*, P-Lactate demonstrated the strongest association to sepsis and was included in the final Predict Sepsis tool. A previous study by Singer et al that demonstrated a moderate to good specificity but low sensitivity for POC Lactate in adult ED patients with suspected sepsis[110].

No *demographic variables* were significantly associated to sepsis in our multivariable analysis. Age has in previous studies been shown to be a predictor of sepsis among EMS patients[106]. Our findings likely reflect that most patients were old and that the median age was similar among patients with outcome sepsis/infection/no infection. Neither gender differed significantly between the outcome groups.

Models and comparison of screening tools

Several models were developed and compared with respect to discriminative ability for sepsis and all developed models demonstrated good AUC values. Inclusion of fewer variables in the models did not significantly affect the AUCs. This is valuable information since the prehospital setting constitutes an environment where every minute counts, and less variables saves time.

The major challenge was to develop a model combining a high sensitivity with a high specificity. The low specificity of the developed models and prior screening tools[103,105] is troublesome, since it may cause false sepsis alerts. However, we believe that a high sensitivity is the major objective, since the prognosis is poor for septic patients when treatment is delayed[74].

The variables with the strongest association to sepsis according to multivariable logistic regression and classification trees were combined into a final model; the Predict Sepsis screening tool, and this tool demonstrated an AUC superior to previous prehospital sepsis screening tools[103,105]. However, there is always a risk of over-adapting a new model to the data material from where analyzes are performed. Hence, there is a high risk that the predictive properties of the Predict Sepsis screening tool would deteriorate if the tool is externally validated. Furthermore, both PRESEP and Robson has previously been proposed to usage among unselected EMS patients, i.e. not only applied on EMS patients with suspected infection. It is possible that the predictive properties of the tools would have been different if tested in an unselected EMS population.

Interestingly, the predictive accuracy of the Predict Sepsis tool was similar to that of a model based on the six vital signs routinely measured in the ambulance, utilizing the current cut-offs for individual vital sign. This suggests that a structured usage of vital signs, with well-chosen cut-offs, may be as good as the Predict Sepsis screening tool which includes two symptoms and an invasive part in the form of P-Lactate. Further prospective studies will be needed to evaluate the Predict Sepsis screening tool and the vital sign model among unselected EMS patients and not only among those with suspected infection, as the latter group may exhibit a greater extent of deviated vital signs and a lower benefit of adding variables others than vitals.

Comparison of variables in relation to in-hospital mortality

Fever and pain were associated with a lower mortality rate, compared with absence of these findings. An improved prognosis for septic patients presenting with fever has previously been demonstrated by Sunden-Cullberg et al[153], who also demonstrated that patients with fever received a more timely treatment[153]. However, the lower mortality was not attributable to improved care in the latter study[153], which raises the question whether fever may be protective from a physiological perspective.

7.5 GENERAL DISCUSSION

The overall aim of the current thesis was to evaluate the presentation of sepsis among adult patients within emergency care and to find a strategy to increase identification of these patients.

Sepsis presentation

Screening of medical records during data collection and analysis in Study I-III underscored that sepsis presentation within emergency care is extremely varied, emphasizing that sepsis may mimic a wide range of other conditions encountered within emergency care, which is consistent to previous knowledge[2,3]. The varied presentation is thought to reflect the heterogenicity of both microbes causing the underlying infection, the focus of the infection and the heterogenicity of host factors, e.g. variations in immunological response.

The presentation of sepsis may cover a spectrum from a rapid onset of high fever with obvious concurrent signs of focal infection to a non-specific picture such as in an older person who slowly deteriorates over a period of weeks. However, some features recurred in the current thesis.

Symptoms: Some symptoms were particularly common among septic patients, as demonstrated in Study III and IV. The pattern of described symptoms identified in Study III is to a great degree consistent with that described by Edman-Wallér 2016[126], and reflected a new-onset loss of energy, weakness of the legs including difficulties to walk/stand or a history of falling/being found on the floor, gastrointestinal symptoms such as vomiting and diarrhea (that often made health care personnel suspect gastroenteritis), an acute altered mental status that could present as changes in personality, somnolence, confusion or in its severest forms as unconsciousness. The latter presentation frequently induced stroke-alerts and CT scans. Fever, often considered as the "classical sign of sepsis", was common but it should be kept in mind that one third of the patients in both Study III and IV lacked this finding. This is consistent with the results presented by Gille-Johnson et al 2013[154], and patients lacking fever are expected to be of particular risk of not being identified as septic. Other common features of sepsis among EMS patients were pain and breathing difficulties.

Vital signs: In Study IV, we demonstrated that septic patients presented with a significantly lower systolic blood pressure, lower level of consciousness and a lower oxygen saturation as compared with other EMS patients. Furthermore, septic patients had a higher respiratory and heart rate and a higher temperature. These findings are consistent with former and current sepsis definitions[1,19,20]. Yet not all septic patients presented with deviations of vital signs, emphasized in Study II.

Other common features of sepsis, demonstrated in Study III, covering neither symptoms nor vital signs, included paleness of the skin and stated risk factors for sepsis such as ongoing or recent infection, recent invasive procedures and a compromised immune system.

Identification of sepsis within emergency care

A low sensitivity of clinical judgment with respect to sepsis identification was demonstrated in Study I-II. These findings are consistent with previous and recent research[15,16]. According to our findings in Study IV only one fifth of the septic patients were discharged with an ICD-code compatible of sepsis which indicates that the rate of sepsis identification is low also in hospital wards. This finding is consistent with the results demonstrated by Henriksen et al 2015[35].

In Study I and II, we demonstrated that identification of sepsis increased when a screening tool was applied. However, one tenth of the patients were still not identified, and we suspect that this group consists mainly of patients with non-specific presentations and a less conspicuous underlying infection. The suspicion of an underlying infection can be challenged by the absence of fever and lack of local symptoms from the focus of the infection.

Our hypothesis was that variables other than vital signs added in the screening process could increase the identification rate of sepsis within both the prehospital and the ED setting. An appropriate prehospital screening tool for sepsis may be incorporated into the current prehospital triage system and may thus serve as support for clinical decision-making. A prehospital recognition of sepsis may lead to an upgraded priority, pre-alerts to the receiving hospital and hence more timely treatment. Furthermore, it may lead to initiation of treatment already during the EMS care.

Study III focused on identifying novel variables, usable in a screening tool for sepsis identification and the focus was set on symptoms. In Study IV the association between variables measurable in the ambulance including vital signs, symptom-variables and point-of-care blood tests and outcome sepsis was analysed, among patients with by EMS suspected infection. Deviated vital signs were, as a group, the strongest predictors of sepsis in the study population, and to our disappointment the addition of symptom-variables and POC-tests did not significantly increase the predictive accuracy of a screening tool.

Although not specifically studied; the high EMS detection rate of suspected infection in Study IV may indicate that the education of EMS personnel associated to the Predict Sepsis study led to an increased awareness of sepsis among EMS personnel, in turn improving the identification of infection.

8 CONCLUSIONS

8.1 STUDY I

The Robson screening tool demonstrated a sensitivity superior to both BAS 90-30-90 and clinical judgment, which supports proof of principle that a screening tool increases the identification of the septic patient in the prehospital setting.

8.2 STUDY II

Septic patients presenting to the ED with non-specific presentations such as decreased general condition received antibiotics later and had a higher mortality, as compared to septic patients with more specific presentations. In addition, a screening tool may increase the identification of septic patients with non-specific presentations.

8.3 STUDY III

Keywords related to patients´ symptom presentation recurred in the EMS records of septic patients, so that a pattern was discernible. In addition, certain symptom presentations were associated with increased in-hospital mortality and symptoms varied in different subgroups of septic patients.

8.4 STUDY IV

The predictive accuracy of the Predict Sepsis tool exceeded that of previous prehospital screening tools, but when compared to a model based on vital signs alone, the AUCs were similar. A prospective study on unselected EMS patients, also those without clinically suspected infection, is necessary.

8.5 GENERAL CONCLUSIONS

In general, our findings indicate a low sensitivity of emergency care providers´ clinical judgment and support the use of a screening tool for the identification of septic patients within the prehospital and emergency department setting. However, neither earlier proposed tools nor the Predict Sepsis screening tool identifies all septic patients. The addition of novel variables such as symptoms in the screening process were not as valuable as we had expected. Nevertheless, this approach may be of greater benefit if tested among unselected emergency care patients, to identify septic patients with non-specific presentations.

Sepsis identification remains a challenge within emergency care, mainly due to the diversity of presentations and lack of specific biomarkers. Increased education would most likely increase sepsis identification. However, an enhanced understanding of the underlying pathophysiology to explain the diversity in sepsis presentation is of major concern to improve identification. Future identification and management of sepsis may require consideration of delineated sub-populations of septic patients.

Meanwhile, the suggestion is to always consider the possibility of sepsis when a patient's status deteriorates without an obvious reason, especially if the patient presents with signs of organ dysfunction involving several organ systems. Sepsis is the chameleon within emergency care.

9 IMPLICATIONS AND FUTURE RESEARCH

Further research is required to study presentations among subgroups of septic patients, with respect to a) host factors such as age/underlying comorbidity/gender/race/pathophysiological response, b) focus of infection, c) microbe factors. Subgroups of septic patients may require specific considerations with respect to identification and management.

The value of variables other than vital signs (i.e. symptoms and point-of-care blood tests) needs to be evaluated among unselected emergency care patients, not only among those with obvious signs of an ongoing infection. Suspecting infection is one of the major barriers to sepsis identification, as patients may present without obvious focal signs of an underlying infection and fever.

Intensified education of emergency care providers, underscoring the often-non-specific presentations of sepsis may most likely increase sepsis identification within emergency care.

There is a need of clearer guidelines defining suspected infection. The predictive value of the current definition of infection should be validated in future studies, as many of the signs and symptoms are believed to be non-specific. Furthermore, new bed-side biomarkers specific for infection could aid the troublesome differentiation between infectious and non-infectious critical illness.

Finally, extensive research with respect to the underlying mechanisms of sepsis is needed. As long as we do not fully understand what sepsis is, attempts to identify it and treat it successively will be inadequate. It is possible that sepsis consists of several different syndromes based on disparity of underlying pathophysiological mechanisms and responses rather than one homogenous syndrome. If sepsis covers a range of different syndromes no single screening tool will identify all septic patients just like no single treatment strategy will be suitable for all of them.

10 SVENSK SAMMANFATTNING (SWEDISH SUMMARY)

Sepsis är ett av de mest akuta tillstånden inom akutsjukvården, men är ofta svårt att känna igen på grund av en ospecifik presentation. Identifiering av sepsis baseras idag huvudsakligen på sjukvårdspersonalens kliniska bedömning, och vi vet att många patienter missas. Tidig identifiering och behandling är avgörande för patientens prognos.

Vi tror att screeningsverktyg kan öka identifieringen av septiska patienter, vilket i sin tur kan förbättra prognosen. Syftet med denna avhandling var att studera presentationen hos vuxna septiska patienter inom akutsjukvården och att hitta ett sätt att förbättra identifieringen. Avhandlingen bygger på fyra studier;

Studie I var en retrospektiv tvärsnittsstudie av 353 septiska ambulanspatienter. Två tidigare ej utvärderade screeningsverktyg jämfördes med ambulanspersonalens kliniska bedömning med avseende på sepsisidentifiering. Robsons screeningsverktyg (som inkluderar temperatur, puls, andningsfrekvens, förändrad medvetandegrad, blodsocker och en sjukhistoria tydande på en ny infektion) överträffade både BAS 90-30-90 (inkluderar systoliskt blodtryck, andningsfrekvens och syrgasmättnad) och klinisk bedömning med avseende sepsisidentifiering.

Studie II var också en retrospektiv tvärsnittsstudie där tid till behandling och dödlighet jämfördes mellan 61 septiska akutmottagningspatienter med ospecifik presentation (sökorsak "nedsatt allmäntillstånd" på akutmottagningen) och 516 septiska akutmottagningspatienter med andra presentationer. Vidare jämfördes sensitivitet och specificitet för Robson-screeningsverktyget med sensitivitet och specificitet för akutläkares kliniska bedömning. Septiska patienter med ospecifik presentation hade längre tid till behandling och högre dödlighet än patienter med andra sökorsaker. En högre andel av patienterna med ospecifik presentation identifierades som septiska då Robson-screeningsverktyget tillämpades. Dock överträffade akutläkares kliniska bedömning screeningverktyget avseende specificitet; dvs läkarna felbedömde mer sällan icke septiska patienter som septiska.

I studie III studerade vi presentation av septiska ambulanspatienter och identifierade nyckelord relaterade till symtombild och övrig sjukhistoria. Den retrospektiva studien involverade en blandteknik av kvalitativa metoder och kvantitativa metoder. Först utförde vi en innehållsanalys av 80 septiska patienters ambulansjournaler, för att hitta nyckelord som illustrerade olika symptom. Som ett andra steg kvantifierades de identifierade nyckelorden bland 359 andra septiska ambulanspatienter. Följande åtta nyckelord uppvisade en prevalens överstigande 20% av alla septiska patienter: "onormal temperatur" (oftast feber men ibland undertemperatur), "smärta", "akut förändrad medvetandegrad", "bensvaghet", "energilöshet", "andningssvårigheter", "gastrointestinala symptom" (kräkningar och diarre) och "riskfaktorer för sepsis".

Studie IV var en prospektiv studie av 878 ambulanspatienter där vi identifierade variabler associerade med utfall sepsis bland 551 patienter med misstänkt infektion i ambulansen, och skapade ett screeningsverktyg baserat på dessa variabler; Predict Sepsis-verktyget. Den prediktiva förmågan hos detta verktyg översteg den hos tidigare utvecklade screening-verktyg för ambulanssjukvården. Dock sågs ingen större vinst av att addera symptomvariabler och blodprov då Predict Sepsis-verktyget jämfördes med ett verktyg baserat på enbart vitalparametrar, där våra identifierade gränser för enskilda vitalparameterar användes. Vidare såg vi att vissa variabler var associerade med en hög dödlighet.

Slutsatser: Våra resultat indikerar en låg identifiering av septiska patienter då identifieringen baseras på klinisk bedömning hos ambulanspersonal och akutmottagningsläkare. Resultaten stödjer användning av ett screeningsverktyg för sepsisidentifiering inom akutsjukvården. Dock identifierar vare sig tidigare screeningverktyg eller Predict Sepsis-verktyget alla septiska patienter. Tillägg av nya variabler såsom symtomvariabler och blodprov i ett screeningverktyg var inte så värdefullt som vi trott och verktygets prediktiva förmåga ökade endast marginellt hos patienter med misstänkt infektion i ambulansen. Däremot kan tillägg av symptomvariabler ha en större betydelse hos oselekterade patienter inom akutsjukvården (dvs inte bara hos dem med tydlig infektionsmisstanke), för att identifiera septiska patienter med en ospecifik presentation. Sepsisidentifiering förblir en utmaning inom akutsjukvården, främst pga en stor variation av den kliniska presentationen och avsaknad av specifika biomarkörer för sepsis. Ökad utbildning skulle troligen bidra till ökad identifiering av septiska patienter. Dock är en förbättrad förståelse av den underliggande patofysiologin av stor betydelse för att förklara variationen i symptombild och presentation hos septiska patienter. Identifiering och behandling av septiska patienter kan i framtiden kräva hänsynstagande till olika subpopulationer av septiska patienter, baserat på tex heterogenitet i det immunologiska svaret på en infektion.

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