The epidemiology and characteristics of sepsis in Norwegian hospitals

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Thesis for the Degree of Philosophiae Doctor (PhD)
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SCIENTIFIC ENVIRONMENT

This work has been an interdisciplinary collaboration between the Department of Medicine and the Department of Anaesthesia and Intensive care at Haukeland University Hospital. The research group involves main supervisor and professor II Steinar Skrede (Head of the Division of Infectious Diseases), co-supervisor professor Hans Kristian Flaatten (former Head of the Department of Anaesthesia and Intensive care), and co-supervisor professor Nina Langeland (former Head of the Division of Infectious Diseases).

ACKNOWLEDGEMENTS

This work started a decade ago when I was an unexperienced student just a few weeks into the third year of medical school at the University of Bergen. I was assigned a patient with sepsis to present in front of my class, and was blown away when I learned about her dramatic disease course. Immediately, I wanted to know more about this condition and went to see Nina Langeland, Head of the Division of Infectious Diseases at that time. Soon, a research group consisting of my main supervisor Steinar Skrede, co-supervisor Hans K. Flaatten, Nina and myself was established. After a few years, I was admitted into the Medical Student Research Programme aiming for a PhD. This work would not have been possible without the Programme, hence, at first I want to acknowledge the great opportunity it gives to young students like me.

My greatest thank you goes to my main supervisor, Steinar Skrede. His impressive knowledge in the field of Infectious Diseases combined with a one of a kind enthusiasm makes him a unique role model, and he is most popular among both colleagues and students. Steinar, not only have you been a great academic tutor, but also a much appreciated advisor in more private and career related matters relevant for the aspiring clinician that I am. Even though you have a busy day, which is your rule rather than exception, you have always found time for me. I want to thank you for your continuous encouragement and believe in me despite some downturns of the project. Without you, there would not have been any thesis.

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ABBREVIATIONS

ACCP	American College of Chest Physicians
AIDS	Acquired Immune Deficiency Syndrome
AIE	Acute Infectious Endocarditis
ARDS	Adult Respiratory Distress Syndrome
BSI	Blood Stream Infection
CFR	Case Fatality Rate
CI	Confidence Interval
CNS	Central Nervous System
COPD	Chronic Obstructive Pulmonary Disease
DAMPs	Danger Associated Molecular Patterns
DIC	Disseminated Intravascular Coagulation
DNR	Do-not-resuscitate
ED	Emergency Department
ESBL	Extended-Spectrum Beta-Lactamase
ESICM	European Society of Intensive Care Medicine
GCS	Glasgow Coma Scale
GUI	Genitourinary Infection
HIV	Human Immunodeficiency Virus
HR	Hazard Ratio
ICD	International Classification of Diseases
ICIP	IntelliVue Clinical Information Portfolio
ICU	Intensive Care Unit
IQR	Interquartile Range
IRR	Incidence Rate Ratio
LOS	Length Of Stay
LR	Likelihood Ratio
MAP	Mean Arterial Pressure
MODS	Multiple Organ Dysfunction Syndrome
MRSA	Methicillin Resistant *Staphylococcus aureus*

NORM	Norsk overvåkingssystem for antibiotikaresistens hos mikrober / surveillance of usage of antimicrobial agents and occurrence of antimicrobial resistance in Norway
NPR	Norwegian Patient Registry
OR	Odds Ratio
PAMPs	Pathogen Associated Molecular Patterns
PRRs	Pattern Recognition Receptors
RTI	Respiratory Tract Infection
SAPS II	Simplified Acute Physiology Score II
SCCM	Society of Critical Care Medicine
SD	Standard deviation
SIRS	Systemic Inflammatory Response Syndrome
SOFA	Sequential Organ Failure Assessment
SSC	Surviving Sepsis Campaign
STI	Soft Tissue Infection
TLR	Toll-Like Receptor

LIST OF PUBLICATIONS

Paper I

Siri Tandberg Nygård, Nina Langeland, Hans K. Flaatten, Rune Fanebust, Oddbjørn Haugen and Steinar Skrede. Aetiology, antimicrobial therapy and outcome of patients with community acquired severe sepsis: a prospective study in a Norwegian university hospital. BMC Infect Dis. 2014 Mar;14:121 doi: 10.1186/1471-2334-14-121. PMID: 24588984

Paper II

Siri Tandberg Nygård, Steinar Skrede, Nina Langeland and Hans K. Flaatten. An observational study of community-acquired severe sepsis comparing intensive care and non-intensive care patients. Acta Anaesthesiol Scand. 2017 Feb;61:194-204 doi: 10.1111/aas.12848. PMID: 28058720

Paper III

Siri Tandberg Knoop, Steinar Skrede, Nina Langeland and Hans K. Flaatten. Epidemiology and impact on all-cause mortality of sepsis in Norwegian hospitals: A national retrospective study. PLoS ONE. 2017 Nov;12(11):e0187990 doi: 10.1371/journal.pone.0187990. PMID: 29149187

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SUMMARY

Background: Sepsis develops when the host's immune response to infection becomes dysregulated to such an extent that life-threatening organ dysfunction evolves. Sepsis epidemiology is influenced by population characteristics, environmental factors, and the occurrence and seasonal spread of pathogens. Thus, local knowledge in this field is highly desirable. With this thesis, we aimed to investigate the epidemiology and characteristics of sepsis in Norwegian hospitals from both a local and a national perspective.

Methods: **Paper I and II** are based on an observational survey of prospectively enrolled patients with community acquired sepsis at Haukeland University hospital in Bergen, Norway during the year 2008. **Paper III** is a retrospective, register based, nationwide study on patients hospitalized with sepsis throughout the years 2011 and 2012. It was performed by use of two databases containing hospitalization and general population data respectively; the Norwegian Patient Registry and Statistics Norway.
Main results: **In paper I,** the incidence of community acquired sepsis was estimated, the underlying infectious sources and microbial etiologies were presented, and the precision of clinical diagnostics as well as the compliance with local therapy recommendations were evaluated. **In paper II,** community acquired sepsis patients treated in an intensive care unit were compared with a cohort receiving treatment at a lower care level. Independent predictors for long-term survival up to five years after hospitalization were investigated. **In paper III,** the demographics of Norwegian sepsis patients were explored, the annual population incidence of sepsis was calculated, and the fraction of sepsis hospitalizations among all somatic hospital admissions was estimated. Finally, the impact of sepsis on all-cause mortality in Norwegian hospitals was assessed.
Conclusion: This thesis demonstrates that sepsis is frequent in Norway, most prevalent among the elderly, and significantly more common among men than women. A large proportion of sepsis patients never receive intensive care treatment. Areas that need improvement are especially the identification and initial handling of less frequent infections. Further, the choice of empirical antimicrobial treatment regimens should be in greater concordance with local sepsis guidelines, in particular for the oldest patients. Sepsis is either the cause of or a contributing factor to a large number of Norwegian hospital deaths. Consequently, improvements in treatment could significantly influence population mortality in the future.

CONTENTS

1. INTRODUCTION

1.1. The history of sepsis

Of Greek origin, the word sepsis [σηψις] translates to "decomposition of animal or vegetable organic matter in the presence of bacteria". It has been traced back over 2700 years to the poems of Homer, as a form of the Greek verb sepo ("*to rot"*), and was also used by Hippocrates and Aristoteles in the context of putrefaction [1]. Celsus in the 1st century described the clinical signs of inflammation: *rubor* (peripheral vasodilatation), *calor* (heat), *dolor* (pain) and *tumor* (capillary fluid leakage) [2], and Avicenna noted a concurrence of fever and putrefaction of blood (septicaemia) a millennium later [3]. However, it was not until the 19th century that the pathway of discoveries that eventually resulted in today's comprehension of sepsis truly started [4].

Before the importance of medical hygiene was recognized, operative procedures commonly led to severe infections called sepsis thought to be secondary to wound putrefaction. First, Semmelweis showed the effect of routine handwashing by decreasing mortality from puerperal fever. Around the same time Pasteur discovered that putrefaction was caused by bacteria. Lister then introduced the concept of antiseptics. In parallel, the term sepsis increasingly appeared in medical academic literature [5]. Nevertheless, the perception of the condition was not consistent, and it was soon evident that there was a need for a general sepsis definition [6].

In 1904 Osler was probably first to note the impact of the host's response in the fatal course of severe infection [7]. However, the first linkage of a systemic response to the word sepsis came in 1914 by Schottmüller: "*Sepsis is present if a focus has developed from which pathogenic bacteria, constantly or periodically, invade the blood stream in such a way that this causes subjective and objective symptoms. A therapy should not be directed against bacteria in the blood but against the released bacterial toxins*" [3].

Antiseptic procedures had tremendous impact on the occurrence of infections in relation to medical procedures, but still there was no treatment for sepsis. The invention of antibiotics was a milestone, initiated with the discovering of penicillin by Fleming and its further development as a therapeutic agent by Chain and Florey in the era of World War II [4]. Intensive care medicine evolved in the following decades,

with sepsis patients as a large patient population. Lewis was next to further develop the understanding of sepsis by marking out that "*it is the [host] response … that makes the disease*" [8]. Some years earlier, Ashbaugh and coworkers had described the Adult Respiratory Distress Syndrome (ARDS) [9]. ARDS was thought to be caused by an inflammatory reaction, and frequently seen together with sepsis. The 1980s brought evidence that this inflammatory reaction was present in the entire body. This led to the postulation of a sepsis definition by Roger C. Bone and colleagues that, with some modifications, has been valid ever since: "*Sepsis can be defined as the systemic response to infection"* [10, 11].

1.2. Definitions of sepsis

1.2.1. Past definitions

Although the cause of sepsis had been increasingly elucidated and accepted, there was no uniform definition that could be applied to identify the affected patients. Research on sepsis therefore had poor generalizability. Then, a consensus conference of the American College of Chest Physicians (ACCP) and the Society of Critical Care Medicine (SCCM) was established, and the first diagnostic sepsis definition was published in 1992. Sepsis was presented as infection accompanied by the "systemic inflammatory response syndrome" (SIRS) (Textbox 1) [12]. SIRS describes a physiologic reaction to harmful stimuli that can also develop in non-infectious conditions. "Severe sepsis" was defined as sepsis associated with organ dysfunction, hypoperfusion or hypotension, and "septic shock" as severe sepsis with hypotension refractory to fluid resuscitation. The use of terms such as "septicaemia" and "septic syndrome" were recommended to be abandoned to further promote uniformity. Sepsis, severe sepsis and septic shock defined progressive stages of increasing severity, as it was proposed that SIRS could evolve into "multiple organ dysfunction syndrome" (MODS).

The new definition was welcomed, and gradually its use as a standard template for inclusion in studies increased [13]. However, critics were not far away [14-17]. Some appointed the SIRS criteria as too inclusive because they were not restricted to infections, while others concluded that they were too restrictive as they were not

necessarily fulfilled in cases with infection and organ dysfunction. Consequently, a second ACCP/SCCM consensus conference in 2001 (Sepsis-2) was held, resulting in a revision of the sepsis criteria [18]. The terms sepsis, severe sepsis, and septic shock and their respective definitions were maintained. However, the criteria were considerably expanded with both clinical and laboratory parameters (Textbox 2). Overall, the revised sepsis criteria offered a more complete description of the condition. Nonetheless, the definition became less distinct and importantly, even more dependent on interpretation. Criteria for severe sepsis (hypoperfusion, hypotension and organ dysfunction) were at the same time included within the basic sepsis definition, and all together the new definition provided just as much confusion as utility. Hence, one continued to use the original definition dependent on the SIRS criteria [19-21], which in the lack of more specific tests were considered to have many advantages [22]. Definitions of organ dysfunction were on the other hand more standardized in the new definition, and were thus often applied. After some years, consensus definitions for the most frequent infections in septic patients were also developed [23].

Textbox 1. Sepsis criteria from 1992 [12]

Sepsis: infection accompanied by two or more signs of the following SIRS criteria:
- Temperature $< 36°C$ or $> 38°C$
- Heart rate > 90 per minute
- Respiratory rate > 20 per minute or $PaCO_2 < 4.3$ kPa in arterial blood gas analysis
- White blood cell count $> 12 \times 10^9$ or $<4 \times 10^9$/l or >10% immature forms in peripheral blood

Textbox 2. Sepsis criteria from 2001 [18]

Sepsis: documented or suspected infection and some of the following:

- *General parameters*
  - Fever (core temperature >38.3°C)
  - Hypothermia (core temperature <36°C)
  - Heart rate >90 per minute or >2 standard deviations (SD) above the normal value for age
  - Tachypnea
  - Altered mental status
  - Significant edema or positive fluid balance (>20 ml/kg over 24 h)
  - Hyperglycemia (plasma glucose >120 mg/dl or 7.7 mmol/l) in the absence of diabetes
- *Inflammatory parameters*
  - Leukocytosis (white blood cell count >12x10^9/l)
  - Leukopenia (white blood cell count <4x10^9/l)
  - Normal white blood cell count with >10% immature forms
  - Plasma C reactive protein>2 SD above the normal value
  - Plasma procalcitonin >2 SD above the normal value
- *Hemodynamic parameters*
  - Arterial hypotension (systolic blood pressure <90 mmHg, mean arterial pressure (MAP) <70, or a systolic blood pressure decrease >40 mmHg in adults or <2 SD below normal for age)
  - Mixed venous oxygen saturation >70%
  - Cardiac index >3.5 l/min/m^2
- *Organ dysfunction parameters*
  - Arterial hypoxemia (PaO_2/FiO_2 <300 mmHg or <40 kPa)
  - Acute oliguria (urine output <0.5 ml/kg/h for at least 2 h)
  - Creatinine increase ≥0.5 mg/dl or ≥45 μmol/l
  - Coagulation abnormalities (international normalized ratio >1.5 or activated partial thromboplastin time >60 s)
  - Ileus (absent bowel sounds)
  - Thrombocytopenia (platelet count <100,000/μl)
  - Hyperbilirubinemia (plasma total bilirubin >4 mg/dl or 70 μmol/l)
- *Tissue perfusion parameters*
  - Hyperlactatemia (>3 mmol/l)
  - Decreased capillary refill or mottling

1.2.2. The present definition: Sepsis-3

The formal sepsis definition was left unaltered for many years, although SIRS criteria were still subject to criticism from clinicians [24, 25]. As extensive progress in the understanding of sepsis' pathophysiology was made, there was an increasing demand for the term sepsis to encompass a distinct entity from infection, both of which commonly influence the clinical signs of inflammation [26]. A Task Force of 19 critical care, infectious disease, surgical and pulmonary specialists from the European Society of Intensive Care Medicine (ESICM) and the Society of Critical Care Medicine (SCCM) was established, and the novel Sepsis-3 definition was published in February 2016 [27]. Sepsis was defined as "*life-threatening organ dysfunction caused by a dysregulated host response to infection*" and the term "severe sepsis" was found superfluous. It was recommended that organ dysfunction should be defined according

to the previously established scoring system Sequential Organ Failure Assessment (SOFA) score, used in the critical care setting (Table 1) [28]. An acute change in total SOFA score ≥ 2 points is to be understood as organ dysfunction. Acknowledging the comprehensiveness of the SOFA score, the Task Force also suggested a new screening tool suitable for use outside the intensive care unit (ICU), called the quick SOFA (qSOFA), in order to identify patients at high risk of death or need for intensive care treatment. It consists of alteration in mental status, systolic blood pressure ≤100mmHg, and/or respiratory rate ≥22/min and is independent on laboratory tests. Fulfillment of qSOFA score parameters should stress clinicians to further investigate for organ dysfunction and initiate appropriate measures. Finally, the definition of septic shock was also updated in the Sepsis-3 definition. This condition is now recognized as vasopressor requirement to maintain MAP ≥65mmHg despite adequate volume resuscitation, accompanied by a serum lactate level >2 mmol/l.

Table 1. The Sequential Organ Failure Assessment (SOFA) score

SOFA score	0	1	2	3	4
Respiration: PaO_2/FiO_2 ratio, kPa	>53	53	40	27 (with resp. support)	13 (with resp. support)
Coagulation: Platelets, $\times 10^9$/l	≥150	<150	<100	<50	<20
Liver: Bilirubin, µmol/l	<20	20-32	33-101	102-204	>204
Cardiovascular: Hypotension, mmHg or otherwise specified	MAP ≥70	MAP <70	Dopamine <5 or dobutamine (any dose)[a]	Dopamine 5.1-15 or epinephrine ≤0.1 or norepinephrine ≤0.1[a]	Dopamine >15 or epinephrine >0.1 or norepinephrine >0.1[a]
CNS: GCS score	15	13-14	10-12	6-9	<6
Renal: Creatinine, µmol/l or urine output, mL/d	<110 -	110-170 -	171-299 -	300-440 <500	440 <200

Abbreviations: FiO_2, fraction of inspired oxygen; PaO_2, partial pressure of oxygen; resp., respiratory; MAP, mean arterial pressure; CNS, central nervous system; GCS, Glasgow Coma Scale.
[a]Catecholamine doses are given as µg/kg/min for at least 1 hour.

1.3. An overview of sepsis pathophysiology

Usually, a localized infection initiates a limited, protective inflammatory host reaction which serves to control pathogen invasion and initiate tissue repair. In sepsis, this reaction has become generalized, affecting organ systems remote from the infectious focus [29]. Exhaustion of inflammatory responses, characterized by apoptosis and hyporesponsiveness of immune cells, eventually results in immune suppression. The pro- and anti-inflammatory reactions occur simultaneously and their magnitude are modified by both host and pathogen factors. Importantly, sepsis patients may follow disease courses where either a pro- or anti-inflammatory state interchangeably dominates. To add even more complexity, different reactions occur at local, regional and systemic levels.

The inflammatory response is initiated by receptors known as pattern recognition receptors (PRRs). These are e.g. members of the Toll-like receptor (TLR) family, and are activated upon recognition of conserved pathogen associated molecular patterns (PAMPs) expressed by the causal microbes. When host tissue is damaged, PRRs can additionally react via endogenous structures released from dying cells, called danger associated molecular patterns (DAMPs). DAMPs are mimics of microbial PAMPs, and both PAMPs and DAMPs promote the inflammatory reaction in sepsis (Figure 1) [30]. Immune suppression results from defect functions of immune cells, inhibited pro-inflammatory gene transcription, and neuroendocrine regulation. There is also an imbalanced activity of coagulation and anticoagulant mechanisms that may result in concomitant microvascular thrombosis and bleeding. Furthermore, damage to the vascular endothelium and its barrier function, caused by a loss of function of cell-to-cell tight junctions, leads to capillary leak and loss of intravascular volume to interstitial fluid. Following is tissue hypoperfusion and edema which may result in a decrease in cardiac output. This may be aggravated by suppression of myocardial contractility and loss of vascular tone due to high levels of inflammatory mediators including nitric oxide, critically affecting organ perfusion. Cardiovascular compromise due to sepsis is therefore multifactorial, but recognized primarily as hypotension [31]. Damage to the alveolar-capillary membrane causes impaired lung function through altered vascular permeability causing excess fluid in both alveoli and the interstitium

(pulmonary edema) [32]. Consequences are impaired gas exchange, increased pulmonary arterial pressure and decreased compliance. Respiratory dysfunction in sepsis is classically manifested as ARDS, defined as acute onset hypoxemia with chest imaging showing evidence of bilateral opacities of noncardiac origin [33]. Besides, in sepsis oxygen delivery may be further lowered due to reduced red-cell deformability and metabolic events. Renal dysfunction demonstrates as increasing s-creatinine level and decreased urine output that may require renal-replacement therapy [29]. Dysfunction of the CNS is typically evident as delirium or obtundation without focal lesions on imaging studies. The aforementioned four organ systems: cardiovascular, respiratory, renal, and CNS, most commonly show evidence of dysfunction in sepsis patients. However, all parts of the body can be affected, and sepsis may present with paralytic ileus, disseminated intravascular coagulation (DIC), elevated liver enzymes, altered glycemic control, the euthyroid sick syndrome, adrenal dysfunction, myopathy as well as critical illness polyneuropathy [29].

Historically, organ dysfunction in severe sepsis and septic shock was thought in simple terms as synonymous with increasing tissue hypoperfusion and the following impairment in tissue oxygenation. Still, organ dysfunction can occur in the absence of apparent macrovascular abnormality (hypotension) [32]. Pursuing the theory of deficient oxygenation, this has been explained by impairment in regional perfusion second to redistribution of intraorgan blood flow with shunting away from nutrient capillaries as well as a constricted/obstructed microcirculation. However, the process behind the development of organ dysfunction in sepsis is increasingly understood as far more complex, and probably only partially elucidated at this point. Histopathological examinations that have shown low levels of cell injury (necrosis and apoptosis) [34, 35], as well as observations of dysfunctional or even failing organs that recover relatively fast in survivors of sepsis, have been interpreted as evidence for co-existence of other mechanisms [32]. In fact, both animal models and clinical studies of sepsis have been performed without observation of cellular hypoxia [36-38]. The mitochondria are by many authorities considered as a key element in this matter [39]. Oxidative stress caused by inflammation leads to inhibition of mitochondrial complex activities with resulting failure of energy production in exposed cells and structural

damage to e.g. mitochondrial DNA. Injured structures serve as alarmins in the extracellular environment that can activate immune cells and cause further injury. Theories of a cellular adaptive response to such events, i.e. only processes necessary for cell survival are maintained on behalf of specialized, organ specific functions, DNA replication, and cell cycling, have long been circulating [40]. Further details are however beyond the scope of this thesis.

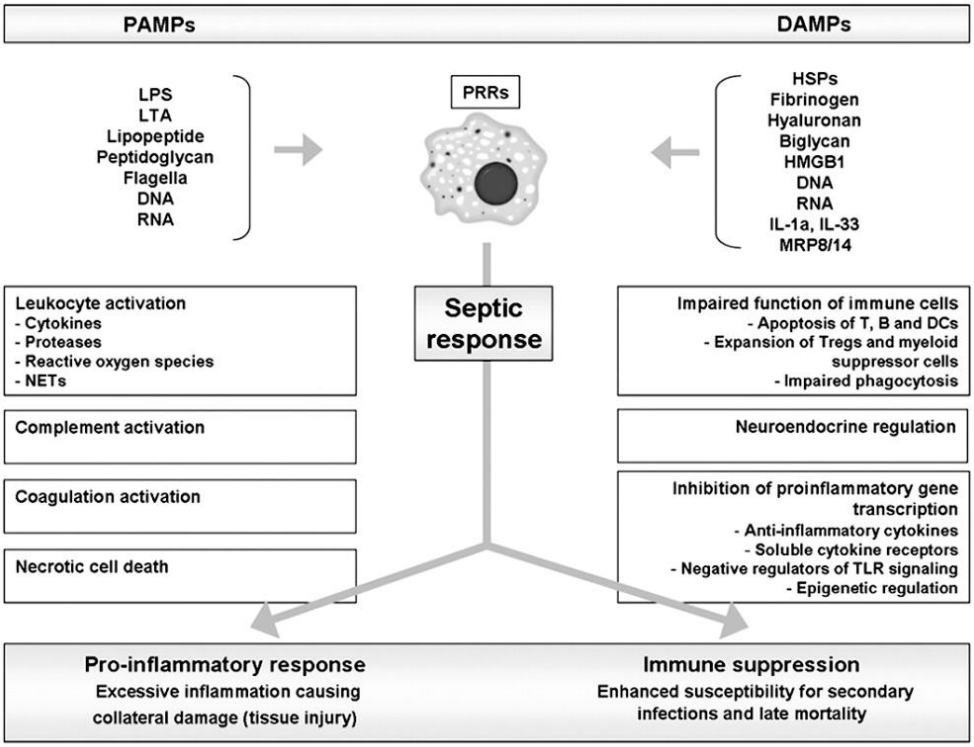

Figure 1. The host response to sepsis. Importantly, direction, extent, and duration of the septic response is determined by both host factors, such as genetic composition, age, comorbidity, and medication, and pathogen factors, including microbial load and virulence. Abbreviations: PRR, pattern recognition receptors; LPS, lipopolysaccharide; LTA, lipoteichoic acid; HSP, heat shock protein; HMGB-1, high mobility group box-1 protein; IL, interleukin; MRP8/14, migration inhibitory factor-related protein-8/14; NETs, neutrophils extracellular traps; T, T lymphocytes; B, B lymphocytes; DC, dendritic cells; Tregs, regulatory T lymphocytes.

1.4. Treatment of sepsis

Sepsis is a medical emergency requiring effective and prompt treatment once identified. Because of the heterogeneity of the affected patients, the underlying infections and the clinical presentation, it may seem inconvenient to have a standard way of care. However, several investigations have shown that time to antibiotic treatment and resolution of shock is of particular importance for hospital survival [41-43]. Therefore, successful management of affected patients mainly relies on early recognition, and there is broad consensus that therapy recommendations should be founded in clinical practice guidelines [44]. The Surviving Sepsis Campaign's (SSC) international guideline for management of (severe) sepsis and septic shock has been a valuable template since they were first published in 2004 [45]. The 4th revision appeared in 2016, and has influenced many local guidelines [46]. The current recommendations for sepsis therapy at Haukeland University Hospital, apart from anti-infective measures, are presented in Textbox 3.

Treatment of sepsis can be divided into two categories based on the following goals: 1. Eradication of the underlying infection, and 2. Supportive care to treat and prevent further development of organ dysfunction(s). In many cases the latter requires admission to an ICU. The first goal includes optimal sampling to identify causal pathogens and administration of appropriate antimicrobial therapy, as well as operative procedures in order to achieve control of the infectious source when appropriate. The new SSC international guideline recommends initiation of intravenous antibiotic therapy within one hour after sepsis has been diagnosed [46]. Initial antimicrobial therapy is most often empirical, and recommendations should be customized based on microbiological surveillance data at local level [47]. The recommended treatment regimens for sepsis in Norway are outlined in the national guideline for antimicrobial therapy issued by The Norwegian Directorate of Health [48]. Indiscriminate use of broad-spectrum antibiotics is undesirable [49], and identification of a plausible pathogen should result in adjustment to narrow-spectrum antibiotics when applicable [50]. Regarding goal number two, actions to be taken depend on both the pre-existing and the current condition of the patient. Hemodynamic resuscitation with intravenous fluids, and supply of vasoactive drugs when necessitated, is of immediate priority.

However, there are important exceptions in fluid challenge therapy, such as end-stage renal disease or congestive heart failure.

During the past few decades there has been an extensive search for new sepsis therapies, in particular in the field of immune-modulating drugs. Recombinant human activated protein C was available for approximately a decade, but eventually withdrawn in 2011 as it failed to prove beneficial effect on survival in a control study [19]. Despite the advancement in the understanding of sepsis' pathogenesis, virtually all approaches have thus failed, and to date no specific anti-sepsis treatment exists.

Textbox 3. Overview of the current recommendations for sepsis therapy at Haukeland University Hospital apart from anti-infective measures

Fluid therapy

- intravenous crystalloids (e.g. Ringer's Acetate), usually 20-30 ml/kg within the first four hours

Vasoactive medications

- norepinephrine is the first-choice vasopressor, and should be administered through a central venous catheter.
- an arterial catheter should be placed as soon as practical in all patients requiring vasopressors; target systolic blood pressure > 100 mmHg (or MAP > 65 mmHg).
- assessment of the hemodynamic response also includes monitoring of hourly urine output and lactate levels (which should be normalized to < 2 mmol/l as soon as possible); these are markers of tissue hypoperfusion

Ventilation

- in the case of mild respiratory dysfunction: nasal or facial mask supply of oxygen 2-10 l/minute.
- in more severe cases of respiratory failure: use of non-invasive or invasive ventilation support

Treatment of renal failure

- urinary catheter insertion, thoroughly monitoring of diuresis (hourly urine output)
- discontinue and/or restrict use of medications with negative influence on renal function
- monitor levels of potassium, and examine for metabolic acidosis and fluid overload
- if renal replacement therapy is required in patients with septic shock, continuous therapy is preferable to facilitate the management of fluid balance

Blood products

- red blood cell transfusion: when hemoglobin decreases < 7.0 g/dl
- platelet transfusion: when platelet counts are $< 10 \times 10^9$/l in the absence of bleeding; $< 20 \times 10^9$/l if significant risk of bleeding. Higher platelet counts ($< 50 \times 10^9$/l) in case of active bleeding, surgery, or invasive procedures
- fresh frozen plasma: should be considered in cases with disseminated intravascular coagulation, active bleeding and need of large amounts of intravenous fluids

Other

- insulin infusions: when blood glucose levels are > 10.0 mmol/l, with a target level of 6.6 to 10.0 mmol/l. Blood glucose levels should be monitored frequently
- corticosteroids: intravenous hydrocortisone at a dose of 50 mg x 4 per day in cases with unstable septic shock despite adequate fluid resuscitation and vasopressor administration
- stress ulcer prophylaxis: only administered in cases with risk for gastrointestinal bleeding
- venous thromboembolism prophylaxis: low-molecular-weight heparin if no contraindications exist

1.5. Epidemiology of sepsis: current findings and limitations

1.5.1. Reviewing studies on sepsis epidemiology

Before the first publishing of international consensus definitions of sepsis, research was encumbered by poor generalizability of study results. Today, most old data are of limited relevance and results published earlier than 1992 are therefore excluded from this work. Because the focus of the original papers in this thesis is sepsis with organ dysfunction (formerly designated severe sepsis, now sepsis), the following section is limited to studies providing data on this condition. We adhere to the term sepsis cf. the most recent definition. To facilitate the review of existing sepsis literature, important aspects to be aware of in the interpretation of previous results is presented in the following.

1.5.1.1. Definition

The formulation of a consensus definition laid a foundation for the use of standard inclusion criteria in studies of sepsis. However, the standardization was only valid to a limited extent, as there was still need for subjective interpretation. Questions such as what is the definition of a clinical suspected infection and which microbes qualify as a causative etiology, or what should be cut-off levels for presence of organ dysfunctions, were problems left to overcome for each study.

1.5.1.2. Methodology

Studies providing epidemiological data on sepsis can in general be divided into three categories on the basis of methodology (A-C).

A. Retrospective code-based studies

Based on national or regional databases, these studies aim to provide population-level epidemiological data. To identify sepsis, various sets of diagnostic codes according to International Classification of Diseases 9th or 10th revision (ICD-9 or -10) diagnostic codes for infection, sepsis or septic shock, and organ dysfunctions are extracted from registries. Hence, the quality of medical diagnostic coding, as well as the general

ability of physicians to identify sepsis in their work are determining factors for the quality and reproducibility of results. For a long time, specific codes for SIRS and sepsis with organ dysfunction (except for septic shock) did not exist. Data abstraction was then based on the combination of codes for clinical infection category and/or sepsis categorized by use of microbial etiology, plus codes for organ dysfunction(s) or procedures indicative of the latter. A major limitation is that codes for organ dysfunctions cannot be verified to have been caused by sepsis rather than another co-occurring condition. The introduction of the codes for SIRS without and with organ dysfunction (the year 2003 in the U.S., the year 2009 in Norway) did not fully solve this problem, as they are inconsistently used [51].

B. ICU-based studies

These studies are confined to intensive care units and are performed primarily to estimate the occurrence of sepsis, either in terms of prevalence or incidence, or both. In general, results are impaired because of a limited patient selection. Many patients with sepsis have a disease course that does not require intensive care therapy, while others are omitted from such facilities due to pre-defined restrictions in care (e.g. do-not-resuscitate (DNR) orders). Some of the studies are retrospective studies based on large ICU-registries. The majority are however based on prospective enrollment, enabling a systematic process of clinical case inclusion with the opportunity to identify all patients with sepsis admitted during a given study period. A number are very short lasting cross sectional surveys, down to point prevalence studies determined in the span of one day [52, 53]. This makes it possible to perform large multicenter studies. Generalization of the results has important limitations however, given variations in seasonal occurrence of infections, focus of infection, microbiological etiology and outcome of sepsis [54-56]. Besides, organ failures may develop later in the disease course than studied.

C. Observational studies with inclusion of non-ICU patients

To overcome many of the abovementioned problems, these studies focus on the group of sepsis patients not receiving intensive care, either by exclusive descriptions of this cohort or with intention to cover all sepsis cases in one study. As this task is very comprehensive, their main limitation is related to site of enrollment. They are mostly confined to single hospitals. Frequently substitutes for hospital-wide inclusion are used, either by selecting a few floor units to survey, or by restricting study enrollment to an Emergency Department (ED). The latter is troublesome if there is no follow-up beyond the ED, as suspected sepsis may not be verified later on during the hospital stay.

Two epidemiological studies have recently been published that do not fit in any of the aforementioned categories. The first is a retrospective survey based on a registry covering the use of intravenous antibiotics in a Swedish hospital [57]. The second is a large Chinese investigation in which all admission records in a subdistrict of Beijing were manually reviewed [58]. Furthermore, clinical intervention trials could have been included as a fourth category. They provide characterizations of the enrolled patients with sepsis and have to some degree influenced epidemiological viewpoints of the condition. However, as they were not designed as epidemiological research, their results are not presented herein.

1.5.1.3. Societal impact on study results

Several differences in the underlying general population and the society influence the risk of developing sepsis, as well as its outcome. Some examples are age, sex, race, socioeconomic conditions, health-care systems including ICU capacity and threshold for admittance, types of infections, occurrence of drug-resistant microbes, and prevalence of comorbidities. Expectedly, the largest discrepancies are seen between high-income countries versus low-income and middle-income countries [59]. There are however also significant differences among high-income societies [60-63], even within single countries, that limit the transferability of study results. Perhaps most relevant is institutional characteristics [52, 64, 65]. There are differences in both the

occurrence and severity of sepsis between local versus referral hospitals, especially in terms of ICU facilities. Consequently, one should evaluate not only whether a study is of single or multicenter origin, but also the type of participating centers. This leads to a fundamental issue of all sepsis studies, namely that they only include the hospital-treated cases. Because most studies of sepsis are from high-income countries, this is primarily an aspect in the group of multimorbid, older persons living in nursing homes or similar facilities. They often have a predetermined decision not to be hospitalized in case of acute illness. It is therefore evident that all aspects of sepsis, including its true burden on society, cannot be determined through existing hospital-oriented epidemiological studies only.

1.5.1.4. Follow-up

Most studies use outcome at the end of hospitalization or 28 days after inclusion as their primary endpoint. Long-term mortality is however significantly higher in patients with sepsis compared to the rest of the population [66]. This is another crucial point to be aware of in the evaluation of sepsis epidemiology.

To sum up, studies of sepsis epidemiology have several problems to overcome: a) study design, b) sepsis definition, c) exclusion criteria, d) duration, e) targeted population (national, regional, multi-, or single-center study), f) level of treatment (only ICU and/or non-ICU treated patients), g) seasonal variation, h) hospital admitted or ICU-treated incidence (and not population-wide), and i) length of follow-up. With this in mind, a summary of previous studies of the epidemiology of sepsis is presented in Table 1. There is a great variance in the results obtained in terms of occurrence and outcome. This underscores that sepsis is a condition with particular need for local data. Nevertheless, some general conclusions can be made.

Table 1. Investigations of sepsis epidemiology, according to study methodology

Category A. Retrospective code-based studies

Country	Study year(s)	Setting	Age range	Sepsis patients	ICUs (%)	Population incidence /100 000	Age	Men (%)	Hospital mortality (%)	Ref.
Norway	1999	National ICD-10	> neonatal	2 121	-	48	58[a, b]	52[a]	27	[67]
Denmark	2004-2007	Regional ICD-10, community acquired	≥15 years	212	41	-	71[b]	50	33	[68]
Sweden	1987- 2005	National ICD-9/-10, comparing 3 methods	All	37 990	-	10 vs 35[c]	-	54	22	[69]
				27 655	-	25 vs 43[c]	-	57	22	
				12 512	-	3 vs 13[c]	-	60	29	
Germany	2007-2013	National ICD-10	All	592 820	-	69 vs 138[c]	-	-	46	[70]
	2011	National ICD-10	All	87 901	56	107	69[b]	58	47	[71]
Spain	1995-2004	Regional ICD-9	All	17 834	21	24 vs 52[c]	57[a, b]	58[a]	60	[72]
	2001	Regional ICD-9	All	6 968	-	141	63[b]	60	33	[73]
	2006-2011	National ICD-9	All	240 939	-	64 vs 106[c]	65[b]	58	43	[74]
	2008-2012	Regional ICD-9	All	82 300	28	167 vs 262[c]	71[b]	57	22	[75]
U.S.	1979-2000	National ICD-9[d]	All	2 724 695	-	14 vs 91[c]	60[a, b]	48[a]	-	[76]
	1979-2003	National ICD-9[d]	All	3 831 394	-	14	-	-	37	[54]
	1995	National ICD-9[d]	All	192 980	51	300	64[b]	50	29	[77]
	1992-2001	National ICD-9[d], ED database	>18 years	59	23	10	-	43[a]	-	[78]
	1993-2003	National ICD-9[d]	All	2 857 476	-	67 vs 132	-	51[a]	46 vs 38[c]	[79]
	2001	National ICD-9[d]	All	282 292	54	397	-	-	25	[80]
	2000-2007	National ICD-9[d]	≥18 years	300 270 vs 781 725[c]	-	143 vs 343[c]	-	51	40 vs 27[c]	[81]
	2003-2007	National ICD-9[d]	≥18 years	2 899 917	-	200 vs 300[c]	-	50	37 vs 29[c]	[82]
	2004-2009	National ICD-9[d], comparing 4 methods	>18 years	12 267 065	-	905	-	52	-	[83]
				13 980 089	-	1 031	-	53	-	
				4 067 836	-	300	-	50	15	
				5 001 750	-	369	-	49	30	
	2007	National ICD-9[d], comparing 2 methods	≥18 years	2 544 857	-	303	71[e]	51	29	[84]
						1074	71[e]	47	14	
	2008-2012	National ICD-9[d]	>18 years	6 067 789		346 vs 436[c]	68[e]	51	22 vs 17[c]	[85]
Australia, New Zealand	1999-2003	Regional ICD-10	All	13 297	50	65 vs 76[c]	-	55[a]	31	[86]
Taiwan	1997-2006	National ICD-9[d]	All	5 258	47	135 vs 217[c]	72[e]	58	31	[87]

Category B. ICU-based studies

Country	Study year(s)	Setting	Age range	Sepsis patients	ICUs (N =)	Population incidence /100 000	Age	Men (%)	Hospital mortality (%)	Ref.
Sweden	2003-2005	Prospective, 3 years, sepsis within 24 h	≥18 years	127	1	-	63[b]	60	28	[88]
	2005-2009	Prospective, almost 4 years, sepsis within 24 h	Adults	101	1	-	64[e]	55	29	[89]
Finland	2004-2005	Prospective, 4 months	>18 years	470	24	38	60[b]	67	28	[90, 91]
Iceland	2008-2009	Prospective, 1 year, national	≥18 years	115	3	48	65[b]	53	30	[92]
United Kingdom	1996-2004	Retrospective, ICU database, sepsis within 24 h	≥16 years	92 672	172	46 vs 66[c]	61[b]	54	45	[93]
	1995-2000	Retrospective, ICU database, sepsis within 24 h	≥16 years	15 362	91	51	65[e]	54	47	[56]
	2000-2012	Retrospective, national ICU database	Adults	248 864	181	-	63[b]	54	46 vs 32[c]	[94]
Germany	2003	Prospective, one day, point prevalence	Adults	415	454	76	67[b]	58	55	[52]
	2013	Prospective, 4 weeks, point prevalence	Adults	1 503	133	-	71[e]	62	40	[95]
France	2001	Prospective, 2 weeks	≥16 years	546	206	95	65[b]	67	35	[96]
	2009-2011	Prospective, 2 years, septic shock only	Adults	1 495	14	-	68[e]	64	42	[97]
Netherlands	2001	Prospective, one day, point prevalence	-	134	47	54	64[b]	63	-	[98]
Spain	2002	Prospective, 6 months	≥18 years	311	14	25	68[e]	67	54	[99]
Italy	1993-1994	Prospective, first 3 cases each month	-	56	99	-	-	-	70	[100]
Poland	2003-2009	Prospective voluntary registration open to all ICUs nationwide	Adults	4 999	130	-	57[b]	58	49	[101]
	2012-2013	Prospective, one day times two, point prevalence	-	555	320	65	-	-	-	[53]
Slovak Republic	2002	Prospective, 6 months	≥18 years	121	12	-	-	60	51	[102]
Croatia	2000-2005	Partly prospective, 6 years	-	244	1	-	71[a, e]	52[a]	34 vs 72[f]	[103]
China	2009	Prospective, 2 months	≥15 years	484	22	-	66[e]	69	34	[104]

Japan	2010-2011	Prospective, 1 year	-	624	15	-	69[b]	63	30	[105]
	2011-2013	Prospective, 2 years	Adults	3 195	42	-		60	26	[106]
Pakistan	2014-2015	Prospective, 14 months	≥18 years	268	1	-	55[b]	55	41	[107]
Australia,	1999	Prospective, 3 months	≥15 years	691	23	77	61[b]	57	38	[108]
New Zealand	1997-2005	Retrospective, national ICU database, sepsis present in the ED	Adults	7 649	100	-	60[b]	54	28	[109]
	2000-2012	Retrospective, national ICU database	Adults	101 064	100	13 vs 45[c, g]	64[b]	54	35 vs 18[c]	[110]
Brazil	2001-2002	Prospective, 8 months	≥18 years	241	5	-	66[a, b]	-	47	[111]
	2004-2005	Prospective, 2 years	≥18 years	524	1	-	60[a, b]	58[a]	61	[112]
Multiple countries	1997-1998	Prospective, 1 year, Canada, Israel & 6 European countries	≥18 years	2 124	28	-	63[a, e]	64[a]	26-67[f]	[113]
	2002	Prospective, 2 weeks, 24 European countries	≥16 years	1 177	198	-	65[e]	63	36	[114]

Category C. Observational studies with inclusion of non-ICU patients

Country	Study year(s)	Setting	Age range	Sepsis patients	ICUs (%)	Population incidence /100 000	Age	Men (%)	Hospital mortality (%)	Ref.
Denmark	2010-2011	Prospective, 1 year, ED	≥15 years	1 071	7	457	72[e]	46	19	[55, 115]
Scotland	2009	Partly prospective, 3 months, EDs in 20 hospitals	>16 years	626	32	-	73[e]	-	28	[116]
Spain	2003	Prospective, 4 months,3 hospitals	>18 years	199	32	104	69[b]	43	28	[117]
Italy	2012	Prospective, 10 months, 31 medical wards, positive blood culture	Adults	316	0	-	73[a, b]	49[a]	20	[118]
U.S.	1992-1993	Prospective, 9 months, 3 ICUs 3 wards	≥16 years	577	-	-	55[a, b]	60[a]	25	[119]
	1993-1994	Prospective, 15 months, 8 tertiary care centers	Adults	1 063	59	-	59[b]	56	34	[120]
	2000-2001	Prospective, 1 year, ED	≥18 years	1 273	-	-	60[a, b]	55[a]	10	[121]
	2005-2009	Retrospective, 5 years, ED	Adults	1 853	59	-	53 vs 59[b,f]	53 vs 55[f]	5 vs 23[f]	[122]
Australia	2007-2008	Prospective, 1 year, community acquired	≥15 years	272	55	188	47[b]	52	17	[123, 124]
India	2012-2013	Prospective, 1 year, random patient selection	>18 years	172	43	-	58[a, b]	59[a]	49	[125]

Other epidemiological sepsis studies

Country	Study year(s)	Setting	Age range	Sepsis patients	ICUs (%)	Population incidence /100 000	Age	Men (%)	Hospital mortality (%)	Ref.
Sweden	2015	Retrospective, 4 independent days, patients on iv antibiotics	≥18 years	96 vs 109[h]	- -	687 vs 780[h]	78 vs 80[e, h]	47 vs 46[h]	20 vs 17[h]	[57]
China	2012-2014	Retrospective, 2 years, review of medical records from 111 hospitals	≥18 years	498	38	193	80[e]	58	26 vs 85[f]	[58]

Abbreviations: ICU, intensive care unit; ref., reference; ICD-10, International Classification of Diseases 10th revision; ICD-9, International Classification of Diseases 9th revision; vs, versus; ED, emergency department; h, hours; iv, intravenous

[a] Parameter including patients with no organ dysfunction (previous definition of sepsis) [b] Mean [c] Data from first versus last year of study period [d] National representative samples [e] Median [f] Sepsis vs. septic shock respectively, in Alberti et al. [113] further subspecified according to method of acquisition of infection (community / hospital /ICU acquired) [g] Calculated from eFigure 2 in the respective study [h] Results obtained by use of the Sepsis-2 versus the Sepsis-3 definition respectively

1.5.2. Occurrence

Sepsis is indisputably a frequent condition. Recent calculations indicate a population-incidence in the range of 100 to 350 per 100 000 inhabitants in high income countries (Table 1). In 2013, sepsis was ranked as the most expensive medical condition in a national investigation of inpatient hospital costs in the U.S. [126]. Eligible studies only include the hospital admitted fraction of patients and there are no explicit studies on sepsis outside the acute health care system. However, sepsis was the most common reason for hospitalization of nursing home residents in the U.S. in the year 2011, indicating a considerable occurrence in such facilities that contributes to the societal burden of sepsis [127]. When hospitalized, sepsis patients account for 1 to 2 % of all somatic admissions [58, 70, 74, 75, 77, 82, 117, 123]. The fraction of patients with sepsis that are not treated in an ICU is around 50% (Table 1). In ICUs, patients with sepsis constitute around 10 to 25 % of cases at any given time [77, 91, 94, 108, 111, 113, 123].

Traditionally, results from Scandinavia have indicated a lower occurrence than in most of Europe and the U.S. However, as there is a scarcity of previous results and the methods applied in these studies differ, firm conclusions cannot be made at this point. Adding to this uncertainty, a Danish prospective study from 2011 has recorded one of the highest previous estimates globally (Table 1), even though it was confined to community acquired sepsis [55]. There is only one previous epidemiological investigation of sepsis in Norway, a retrospective study from the year 1999 [67]. Table 1 demonstrates that the reported occurrence of sepsis has increased during the past decades. This observation is confirmed by studies on time-related trends in sepsis epidemiology [74, 76, 77, 79, 85, 93, 110]. The reason for this is probably multifactorial. In addition to changes in health care and aging of the population in general [128], diagnostic coding patterns and physicians' awareness as well as subjective perception of sepsis seem to have a substantial impact [129, 130], illustrated by Figures 2 and 3.

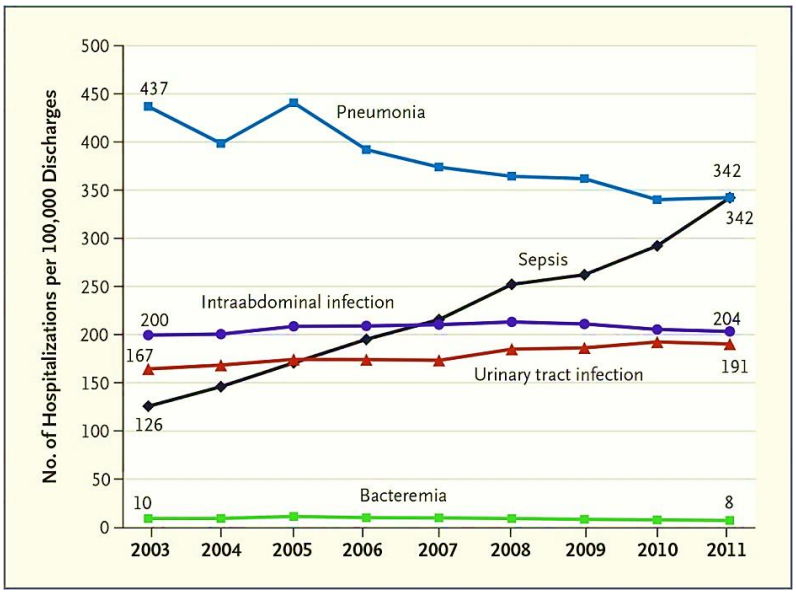

Figure 2. Hospitalizations for which certain infection codes were listed as a primary diagnosis, 2003–2011.

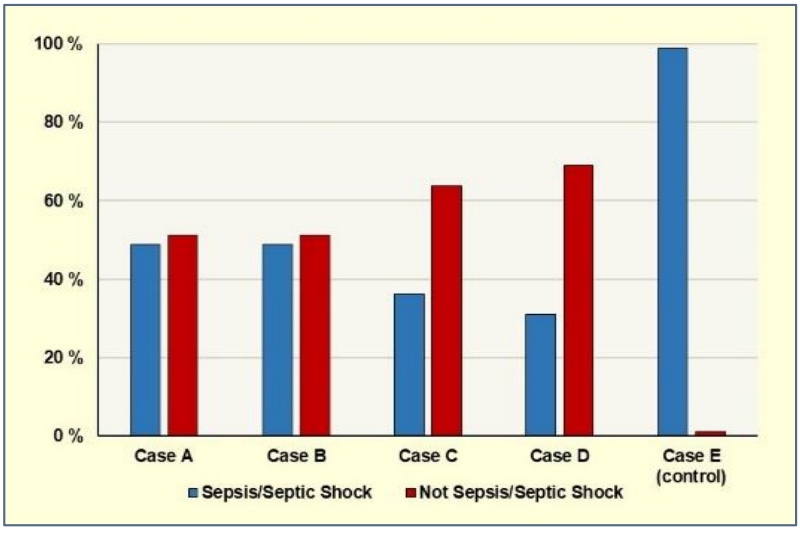

Figure 3. Distribution of classification of five case vignettes of patients with suspected or confirmed infection and organ dysfunction, done by 94 practicing intensivists.

1.5.3. Demographics

Sepsis is most common among the elderly. Reasons for this are immunosenescence, predisposing chronic diseases, repeated hospitalizations and/or residence in long-term care facilities, malnutrition, age-related physical loss including sarcopenia and cognitive impairment [131]. Mean age of affected patients have increased during the past decades [74, 93], and has passed 70 years in the most recent reports in Table 1. It has been shown that sepsis occurs more often in men than women in studies reporting age-specific incidences [70, 75, 77]. Many researchers have also found racial disparities in sepsis, the majority reporting a higher occurrence and a lower mean age among African-Americans compared to whites in the U.S. [80, 123, 132, 133]. However, the debate is still ongoing as these results are from retrospective surveys, whereas a recent longitudinal cohort study investigating community acquired infection could not confirm previous findings [134]. It has been postulated that the observed gender and racial disparities are influenced by cultural and socioeconomic differences that affect health behavior, risk for comorbidities, and access to or quality of medical care. Furthermore, a role for biological factors such as genetics, immune response and sex hormones has been suggested [59, 131, 132].

1.5.4. Comorbidities

Most patients with sepsis carry risk for contracting severe infection because of preexisting and significant comorbidity. Many categories of comorbidities render the host more susceptible to a given pathogen or type of infection, and influence outcome [131]. Most studies that offer crude data on the overall frequency of patients with comorbidities report that it affects around 50% of sepsis cases [74, 77, 88, 96, 99, 110, 133]. However, presence of comorbidities is highly dependent on the definitions used and patient population features. Accordingly, both much lower figures as well as frequencies up to 90% have been reported [58, 89, 93, 94, 135]. Although the estimates vary widely, it is possible to outline some general trends. Overall, cardiovascular disease is the most frequent preexisting condition in patients with sepsis. Prevalence of hypertension is substantial if this category is specified; 35-57%

[58, 85, 91, 117, 122]. Furthermore, coronary artery disease and congestive heart failure is prevalent [58, 74, 75, 81, 85, 92, 122]. The presence of diabetes mellitus is considerable (16-27%) [58, 81, 85, 91, 98, 117, 133]. Occurrence of malignancies is in the range of 10-30%, and studies that specify the proportion of patients with metastatic cancer are uniformly between 4-8% [58, 74, 75, 77, 88, 96, 122, 133]. From less than 10% to 25% of patients with sepsis have been found to have chronic respiratory disease, yet the respiratory tract is the most common focus of infection in sepsis [58, 75, 77, 81, 85, 88, 91, 117, 122, 133]. Chronic renal disease is less frequent, while chronic liver disease is rare [74, 77, 81, 91, 92, 117, 122, 133]. The criteria for categorizing patients as immunosuppressed vary between studies. Consequently, substantial variation is found in the results (6-39%) [88, 91, 92, 96, 99, 117, 136]. HIV positive, limited to patients with AIDS or not, constitute between 1-6% of patients in Southern Europe and the U.S [74, 75, 77, 81, 96, 99, 122]. Abuse of alcohol is not often specified, but was frequent in a Finnish ICU cohort (26%), while reports from other Nordic countries, Wales and Spain indicate lower numbers (5-11%) [55, 89, 91, 99, 117, 137]. Cognitive impairment (dementia) is specified in two studies only, both at 6% [66, 117].

1.5.5. Focus of infection

Pneumonia is the most prevalent infection in hospitals in high income countries (Figure 2). Expectedly, the most common focus of infection in sepsis is the lower respiratory tract (Table 2). Second are genitourinary infections (in retrospective studies) and abdominal infections (in ICU settings), followed by soft tissue infections (STIs). Infections in the central nervous system and acute infectious endocarditis (AIE) are rare causes. The fraction of cases with primary blood stream infections (BSIs) is variable (2-20%). Most reports of the proportion of patients with community acquired compared to nosocomial contracted infections are close to 50%, within the range of 33 to 73% [88, 89, 91, 95, 96, 99, 101, 113].

Table 2. Identified foci of infection (%) in selected studies of sepsis

Studies including both ICU and non-ICU patients

Cate-gory[a]	Country	N =	RTI	Abd	GUI	STI[b]	BSI[c]	CNS	AIE	Device	Other[d]	Ref.
A	Denmark	212	25	9	36	11[e]	5	3	1	-	10	[68]
A	Spain	82 300	33	11	37	4	-	<1	2	1	38	[75]
A	U.S.	381 878	39	8	15	8	20	<1	<1	1	7	[133]
A	U.S.	192 980	44	9	9	7	17	<1	<1	2	11	[77]
C	Denmark	1 071	68	10	25	4[e]	2	<1	<1	-	8	[55]
C	U.S.	1 853	28	13	23	10	13	-	-	-	-	[122]
Other	Sweden	96[f] 109[f]	42[f] 51[f]	15[f] 11[f]	18[f] 17[f]	7[f] 5[f]	-	-	-	-	19[f] 17[f]	[57]
Other	U.S.	49 331	40	9	27	-	-	-	-	-	23	[138]
Other	China	1 716	73	8	12	2	5	-	-	-	4	[58]

Studies including ICU patients only

Cate-gory[a]	Country	N =	RTI	Abd	GUI	STI[b]	BSI[c]	CNS	AIE	Device	Other[d]	Ref.
A	England	248 864	45	31	5	5	-	2	3	-	9	[94]
B	Sweden	127	21	20	13	7	-	-	-	6[g]	33	[88]
B	Finland	470	43	32	5	10	-	2	2	1	10	[91]
B	Iceland	115	37	28	11	8[e]	-	3	6	-	6	[92]
B	Nether-lands	134	47	34	2	7	2	1	-	-	7	[98]
B	Germany	1 503	52	29	13	10	2	2	2	3	6	[95]
B	Germany	415	63	34	7	9	-	-	-	-	-	[52]
B	Poland	4 999	28	49	6	6	8	3	-	3[g]	5	[101]
B	France	546	49	24	5	7[e]	5	1	2	3	6	[96]
B	Spain	311	45	32	6	6	-	-	-	5[g]	-	[99]
B	Canada Israel Europe	2 124	59	16	11	-	15	-	-	-	-	[113]
B	U.S. vs Europe	18 766 6 609	46 45	19 32	31 9	15[e] 8[e]	-	1 2	1 1	6[g] 4[g]	13	[60]
B	Japan	624	42	21	13	16[e]	-	2	<1	2[g]	4	[105]
B	Australia New Zealand	691	52	19	6	10	10	3	1	3[c]	2	[108]

Abbreviations: RTI, respiratory tract infection; Abd, abdominal infection; GUI, genitourinary infection; STI, soft tissue infection; BSI, blood stream infection; CNS, central nervous system infection; AIE, acute infectious endocarditis, Ref., reference; vs, versus

[a] Study category A, B, C or other cf. section 1.5.1.2. [b] Including surgical wounds if specified [c] Proportion of patients with presumed primary bacteriemia [d] Including unknown focus of infection [e] Including bones and joints [f] Patients identified using the Sepsis-2 versus Sepsis-3 definition respectively [g] Including central venous catheters

1.5.6. Microbial etiology and antimicrobial resistance

Even in prospective investigations, the microbial etiology of sepsis is detected in only 2 out of 3 patients [88, 89, 95, 96, 99, 108, 113, 114, 136, 139]. Equivalent detection rates are however the norm for hospitalized patients with severe infections in general [140]. The proportion of patients with detected bacteriemia is with few exceptions between 25-40% [88, 91, 95, 101, 113, 141]. Sepsis is first and foremost associated with bacterial infections, but fungi, viruses and parasites are all eligible pathogens. Viruses, especially influenza strains, may have additional impact as they are associated with secondary bacterial infections [142]. The detection of various pathogens in sepsis patients is dependent on geographical location, the level of care, the distribution of infections, seasonal variation and the quality of microbiological diagnostic services [47]. During the 1990s and first years after the millennium, Gram-positive bacteria were somewhat more frequently encountered than Gram-negative bacteria in sepsis patients [47, 91, 96, 108, 114]. In more recent years, the presence of Gram-negative bacteria has increased, together with the proportion of patients with fungal infections [74, 89, 99, 101, 133, 136, 140, 143]. This is possibly a reflection of advances in health care that inevitably leads to increasing numbers of frail patients more prone to these etiologies. Enterobacteriaceae, mainly *Escherichia coli* but also *Klebsiella* species, are the most important Gram-negative causes of sepsis. The most frequently observed Gram-positive microbes are *Staphylococcus aureus, Streptococcus pneumoniae* and *Enterococcus* species [99, 101, 108, 140, 144]. The presence of anaerobic bacteria is generally found to be low [74, 113, 140]. The occurrence of pathogens with relevant antimicrobial resistance is substantially different in various parts of the world. In a global perspective, the prevalence of resistant bacteria is low in the Nordic countries [47, 140, 145-147]. It is not well documented whether these pathogens are seen more frequently in sepsis compared to infection in general. Nevertheless, it is important to notice that the official Norwegian surveillance program for antimicrobial resistance (NORM) has recorded a substantial increase in the relative proportion of such microbes during the last decade [147]. In their last report (the year 2016), nearly 6% of *Escherichia coli* and 5% of *Klebsiella* species in investigated blood cultures were extended-spectrum beta-lactamase (ESBL)-producing, 17% of

Escherichia coli were non-susceptible to ciprofloxacin, and nearly 7% to gentamicin [10]. Furthermore, 1% of *Staphylococcus aureus* were methicillin resistant, 0.5% of *Enterococcus* species were vancomycin resistant (Van A or Van B positive), and 0.3% of *Streptococcus pneumoniae* penicillin resistant, while nearly 6% of the latter showed non-susceptibility to penicillin. *Candida albicans* isolates were all susceptible to fluconazol. However, the occurrence of bacteria with troublesome resistance is still low in Norway compared to most similar settings. This is reflected in the recommended empirical treatment regimens for sepsis in the national guideline for antimicrobial therapy; for instance the recommended choice of treatment when the infectious focus is considered unknown is benzylpenicillin and gentamicin [46].

1.5.7. Organ dysfunction

Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection. In ICUs, as many as 80-90% of patients have cardiovascular dysfunction [56, 60, 91, 92, 94], but figures closer to 50% are also reported [52, 95, 99, 110]. The proportion with respiratory failure is commonly found to be around 70% among ICU-treated sepsis patients in Europe [91, 94, 95, 99], while results from the U.S. usually are lower [60]. In the majority of studies targeting ICU cohorts, renal failure is seen in 40-50%, followed in occurrence by metabolic (usually around 40%), CNS (12-44%), and hematologic dysfunction (around 20-30%), while hepatic dysfunction is more rare (2-14%) [52, 60, 91, 92, 94, 95, 99]. Studies including patients outside ICUs have in general lower occurrences of most organ dysfunctions. Besides, a smaller fraction of patients with multiple organ dysfunctions is reported (14-55%) [55, 57, 74, 75, 79, 81, 82, 86, 141] than in studies restricted to ICU patients (70-90%) [56, 68, 86, 92-94, 99, 101]. Different from explicit ICU-studies is that renal failure is often most prevalent [75, 81, 82, 85]. Besides, a more equal occurrence of renal, respiratory and cardiovascular dysfunction is seen, often affecting approximately 50% of patients each [68, 74, 81, 82, 85, 136, 141]. However, there are exceptions. Most noticeable is perhaps the low number of cases with cardiovascular dysfunction reported from a prospective study of community acquired sepsis in a Danish ED and from a recent, large retrospective study from Spain (5-9%) [55, 75].

1.5.8. Outcome

Despite a notable decrease in recent years, hospital mortality from sepsis is still high [74, 81, 82, 85, 94, 110]. The most recent SSC guideline states that sepsis kills one in four patients [46]. Since outcome is dependent on a variety of factors, there are however large deviations in the results presented in Table 1. For instance, several of the more recent retrospective studies have estimated a mortality rate close to 15% [75, 82, 85, 136, 148], whereas other similar studies have found that one in every two or three sepsis patients died [68, 70, 71, 74, 81, 82]. The mortality rate in prospectively registered ICU cohorts is usually found to be higher than in prospective studies originating in part or completely from outside the ICU environment [115, 117, 123, 149]. Sepsis is also associated with negative long-term effects. Hospital survivors have been found to have increased mortality for up to ten years after hospitalization, suffer from cognitive impairment and functional disability, and many have decreased quality of life [66, 150-152].

2. AIMS OF THE THESIS

While the number of international studies on sepsis was rapidly increasing at the starting point of our current work, there was only a single study on sepsis epidemiology in Norway from 1999 available. Given the lack of contemporary local and national data, we decided to investigate different aspects of sepsis by use of two different, complementary approaches. The principal aim of the thesis has been to assess the epidemiology of sepsis, to characterize the patient cohort and to describe care and outcome of patients with sepsis treated in Norwegian hospitals. Furthermore, international studies were mainly focused towards the ICU-treated cohort of sepsis patients. At the same time, many patients in our institution with sepsis were treated outside the general ICU. Therefore we identified a need for characterizing and evaluating the entire hospital-treated sepsis population locally.

2.1. Main objective

- to provide epidemiological data for sepsis in Norway
- to investigate population incidence and hospital occurrence, etiology, patient features, location of care, treatment and outcomes

2.2. Secondary objectives

- to evaluate time-related trends in occurrence and outcomes of sepsis in Norway
- to evaluate the diagnostic precision and quality of care for patients with sepsis in a Norwegian setting
- to study the features of the population of sepsis patients treated outside intensive care in our hospital
- to compare characteristics, treatment intensity and outcomes in the ICU-treated sepsis cohort compared to the non-ICU treated cohort
- to evaluate the use of recommended empirical antimicrobial therapy
- to explore prognostic risk factors for in hospital and long-term mortality among sepsis patients
- to assess the impact sepsis has on all-cause mortality in Norway

3. MATERIALS AND METHODS

3.1. Summary of Methods Paper I and II

Paper I and II are based on a one year prospective, case defined observational study of patients hospitalized with community acquired sepsis at Haukeland University Hospital in the period from January 1st through December 2008. Enrollment took place in the following units: (1) a 10-bed general ICU at the Department of Anaesthesia and Intensive care; (2) a 12-bed combined ICU/non-ICU ward at the Department of Cardiology, composed of four fully equipped ICU beds and eight surveillance beds; and (3) a 13-bed ward at the Division of Infectious Diseases, Department of Medicine. All subjects transferred from the emergency department (ED) to any of the three units were screened to see if they fulfilled the consensus criteria for sepsis used at that time, with some minor modifications of the diagnostic criteria for organ dysfunctions which are specified in section 5.1.5. Patients older than 15 years of age hospitalized due to community acquired infection, including patients transferred from affiliated hospitals, were included if they developed sepsis within 24 hours of admission to the primary institution. We excluded patients if they had been hospitalized within the preceding 30 days to avoid inclusion of nosocomial infections. In patients with multiple sepsis admissions during the study year, only the first sepsis episode was included. Patients were evaluated for eligibility by use of admission records, patient charts and inquiries with senior physicians at the respective wards. Clinical data were registered prospectively until hospital discharge or in-hospital death, using predefined case report forms. Data from the ED and from affiliated hospitals before transfer were registered retrospectively. Information was collected from medical records, patient charts, and the intensive care electronic monitoring system IntelliVue Clinical Information Portfolio (ICIP, Philips Medical Systems, Eindhoven, the Netherlands). The following parameters were recorded at admission; time and date, department affiliation, demographics, comorbidities, vital parameters, suspected focus of infection and GCS. During surveillance of patients, variations in vital parameters, urine output and biochemical analyses were followed. Timing and adequacy of antimicrobial agents was evaluated together with their appropriateness according to local recommendations (presented in Paper I). Use of non-invasive or

invasive ventilation support and administration of intravenous fluids, vasoactive drugs, glucose-insulin and corticosteroids was registered. Simplified Acute Physiology Score II (SAPS II) was calculated in patients treated in an ICU bed. Surgical treatment in relation to severe infection was documented. Results from blood cultures and microbiological analyses of urine, abscesses, sputum, feces, deep tissue samples and cerebrospinal fluid were collected. Probable contaminants and commensals were excluded from analysis. Antimicrobial susceptibility patterns of cultured pathogens were registered when available. Finally, total hospital and ICU length of stay (LOS) as well as hospital and 28-day mortality rates were recorded. At discharge a final diagnosis was established by one consultant (S. Skrede), based on retrospective evaluation of all available records, clinical, microbiological, laboratory and diagnostic imaging data. Data from medical records and patient charts was verified before it was entered into a local database. The main outcome measure in both paper I and II was hospital mortality. Hospital survivors were followed up for 5 years after discharge.

3.2. Summary of Methods Paper III

Paper III describes a two year retrospective study from the years 2011 and 2012 conducted with data from the Norwegian Patient Registry (NPR) and Statistics Norway [153, 154]. The NPR is run by the Norwegian Directorate of Health and all Norwegian hospitals are obliged to report data from all of their admissions, including demographics, dates of hospitalization, characteristics of hospital and department, outcome, ICD-10 diagnostic codes as well as codes for surgical and medical procedures. First, we performed a primary search for selected discharge codes for infection, SIRS and sepsis (Textbox 4). For the eligible cases, up to eight additional codes for acute organ dysfunction were then registered. Information about hospital stay (days), hospital mortality and demographics for each patient, as well as the total number and duration of hospital stays in Norway during the study years was also collected from the NPR. Statistics Norway was used to find national population data and the national number of hospital deaths. The extracted information was processed and made into a local database in the program FileMaker, Inc, Pro (version 14.0; Santa Clara, CA, U.S.).

Textbox 4. ICD-10 discharge codes applied in paper III

Infection, sepsis or SIRS

ICD-10 code	Diagnosis
A02.1	Salmonella sepsis
A20.7	Septicaemic plague
A21.7	Sepsis (generalized) tularemic
A22.7	Anthrax sepsis
A24.1	Acute and fulminating melioidosis
A26.7	Erysipelothrix sepsis
A32.7	Listerial sepsis
A39.2	Acute meningococcaemia
A40 (.0, 1, 2, 3, 8, 9)	Streptococcal sepsis
A41 (.0, 1, 2, 3, 4, 5, 8, 9)	Other sepsis
A42.7	Actinomycotic sepsis
A46	Erysipelas
A48.3	Toxic shock syndrome
A54.8	Other gonococcal infections
B37.7	Candidal sepsis
J09	Influenza due to identified zoonotic or pandemic influenza virus
J10	Influenza due to identified seasonal influenza virus
J13	Pneumonia due to Streptococcus pneumoniae
J14	Pneumonia due to Haemophilus influenzae
J15	Bacterial pneumonia, not elsewhere classified
J18 (.0, 1, 2, 8, 9)	Pneumonia, unspecified microbiology
J36	Peritonsillar abscess
J39	Other diseases of upper respiratory tract
J85	Abscess of lung and mediastinum
J86	Pyothorax
K65	Peritonitis
K81	Cholecystitis
M72.6	Necrotizing fasciitis
N10	Acute tubulo-interstitial nephritis
O85	Puerperal sepsis
P36	Bacterial sepsis of newborn
R57.2	Septic shock
R65 (.0, 1, 9)	Systemic Inflammatory Response Syndrome [SIRS] of infectious origin without (.0) or with organ dysfunction (.1), or not further specified (.9)
T81.4	Infection following a procedure

Organ dysfunctions

ICD-10 code	Diagnosis
D65	Disseminated intravascular coagulation [defibrination syndrome]
D69	Purpura and other haemorrhagic conditions
E87.2	Acidosis
I50.9	Heart failure, unspecified
J80	Adult respiratory distress syndrome
J95	Postprocedural respiratory disorders
J96.0	Acute respiratory failure
K72	Hepatic failure
N17	Acute renal failure
N99.0	Postprocedural renal failure
R57	Shock

3.3. Statistical Methods

Descriptive statistics for continuous variables are presented as mean ± standard deviation (SD) or median and interquartile range (IQR), and compared between groups with Student's unpaired t-test when normally distributed and the exact Mann–Whitney U test when not normally distributed. Categorical variables are presented as frequencies and percentages, and compared between groups with the exact Pearson's chi-squared test ($\chi 2$) with odds ratios (ORs) and 95% confidence intervals (CIs).
Binomial logistic regression analysis was performed to identify predictors of outcome in paper I and predictors for ICU-admission in paper II. A multivariable stepwise backward model was used to adjust for confounding variables, and identify a final simplified model including only predictors significant at the 0.05 level. Results are reported as ORs with 95% CIs and p-values from the likelihood ratio (LR) test. Variations in effects (ORs) were evaluated to control for influence of collinearity among the explanatory variables. Hosmer–Lemeshow's goodness-of-fit test is reported for the fully adjusted and the final models.
Survival is illustrated with Kaplan-Meier plots, and the log-rank procedure was used to test for survival differences within categorical variables. Multivariable survival analysis was performed using Cox's regression model to determine prognostic components for long-term mortality in paper II, and results are presented as hazard ratios (HRs) with 95% CIs and p-value from the LR test.
The statistical analyses were performed using IBM SPSS Statistics (Aramonk, NY, U.S.). All tests were two-tailed, and a p-value < 0.05 was considered statistically significant.

3.4. Calculation of population incidence and all-cause mortality rate

In paper I, annual population incidence and the 28-day all-cause mortality rate was calculated with exclusion of patients transferred from affiliated hospitals, with the number of inhabitants > 15 years in the local catchment area in the study year as denominator.
In paper III, annual population incidence was calculated as the total number of included patients, with the sum of the total number of inhabitants in Norway during

the study period as denominator. In this paper, population incidence by age and gender was compared by incidence rate ratios (IRRs) with 95% confidence intervals (CIs). The IRRs were computed with MedCalc for Windows (Ostend, Belgium).

3.5. Ethics

All three studies were approved by the local Regional Ethics Committee (REC West) and conducted in accordance with the principles of the Declaration of Helsinki, with a waiver of informed consent (case number 2010/165 for paper I and II, and case number 2014/1922 for paper III). The prospective study (paper I and II) was initially approved as a quality study by the local privacy ombudsman in 2007. An extended ethical application was submitted in 2010 and approved.

4. SUMMARY OF MAIN RESULTS

4.1 Summary of results - Paper I

In total 220 patients with community acquired severe sepsis were enrolled prospectively, yielding an annual incidence of 50 per 100 000 inhabitants. They represented 0.34% of the total somatic admissions at Haukeland University Hospital during the year 2008. Median age was 67 years, 53% were male and 90% had significant comorbidity. The infectious source was correctly established at admission in 69% of patients, but the level of precision was highly dependent on the infection type and was low in e.g. abdominal infections (50% correctly identified at admission) and AIE (33% correct). Overall, 11% had an incorrectly proposed and 16% had an unidentified focus, while in the remaining 4% of patients infectious diagnoses were not suspected. The most frequent focus of infection, representing 52% of verified cases, was the respiratory tract. Genitourinary, abdominal and soft tissue infections were each found in 12-14%. The microbiological etiology could be identified in 61% and 37% of blood cultures were positive. The microbiological verified infections were monomicrobial in 81%. Overall, Gram-positive microbes represented 57% of pathogens. *Streptococcus pneumoniae, Escherichia coli* and *Staphylococcus aureus* were most prevalent. Troublesome antimicrobial resistance was observed in only two isolates containing ESBL-producing *Escherichia coli*. Median delay before administration of the initial dose of antimicrobial therapy was 2.8 hours after hospital admission. The delay was highest in abdominal infections (6.9 hours) and in patients ≥ 75 years when compared to the rest of the cohort. Empirical treatment was also less in compliance with current recommendations in the oldest cohort. Further, compliance with the recommendations proved to have been better when adequate therapy was given, in comparison to when inadequate therapy was given (83% vs. 44%, $\chi 2$ P< 0.001). The hospital case fatality rate (CFR) was 25%. Independent predictors of hospital death were abdominal infections, endocarditis, underlying malignancy, cardiovascular disease, undefined microbiological aetiology, delayed administration of antimicrobial agents ≥ 6 hours and use of inadequate antimicrobial regimens. A tendency towards higher hospital mortality with increasing age was observed, but it

was not statistically significant. Overall, one-year all-cause mortality was 34.5% and four-year mortality was 55.5%.

4.2 Summary of results – Paper II

In this paper, the patients with community acquired sepsis from the prospective study were separated according to their highest level of care during hospitalization (ICU versus non-ICU level). One hundred and seven patients were included in the ICU cohort and 113 in the non-ICU cohort. There were no significant demographic differences. Except for dementia, underlying comorbidities were also similarly distributed, while do-not-resuscitate orders were more common at ICU-level. Respiratory tract infections (RTIs) were the most frequent infection category at both care levels. Further, abdominal infections were more often encountered in ICU patients (77%, $\chi 2$ OR 4.10 (1.58, 10.66), P = 0.003), while most genitourinary infections were treated at non-ICU level (81%, $\chi 2$ OR 0.21 (0.08, 0.53), P < 0.001). Initially, soft tissue infections were also unequally distributed as 24 out of 27 patients were referred to non-ICU level. However, subsequent transfer of nine cases to an ICU evened this category. ICU patients had a greater burden of multiple organ dysfunctions, as 81% had three or more dysfunctional organs compared to 47% of the non-ICU cohort. Treatment intensity was consistently higher at ICU level. Supportive therapy with vasoactive drugs and non-invasive ventilation was also documented in 22% and 27% at non-ICU level, however only four patients received both. Administration of the initial dose of antimicrobial therapy occurred later at ICU level (median 3.5 versus 2.0 hours in non-ICU patients, p = 0.011). Median hospital LOS was 15 versus 9 days (P = 0.001), and hospital and 5-year mortality 35% versus 16% (P = 0.002) and 57% versus 58% (P = 0.892) in the ICU and non-ICU cohorts, respectively. Independent impact on long-term survival was found for increasing age (HR 1.06 (1.04, 1.07) per year, P < 0.001), and not care level during hospitalization (HR 1.19 (0.70, 2.02), P = 0.514), by multiple Cox regression.

4.3 Summary of results – Paper III

A total of 13 582 patients with 18 460 sepsis admissions were identified, of whom 53.9% were men and mean and median age was 73 and 78 years, respectively. The overall annual population incidence was 140 per 100 000 inhabitants, but differed with age from 10 to 2 270 patients per 100 000 inhabitants and was significantly higher among men in all adult age categories (Figure 4). Sepsis hospitalizations represented 1.0% of somatic hospital admissions and 3.5% of the total admission days during the years 2011 and 2012. Infections of the respiratory tract were most common, occurring in 64.2% of cases, and 14.7% had two or more acute organ dysfunctions. Median length of stay was 9 days. Hospital mortality for sepsis admissions was 19.4% and increased with age and number of organ dysfunctions. During the study period, 26.4% of the included patients died while hospitalized for sepsis. Sepsis related deaths represented 12.9% of the total hospital fatalities in Norwegian hospitals.

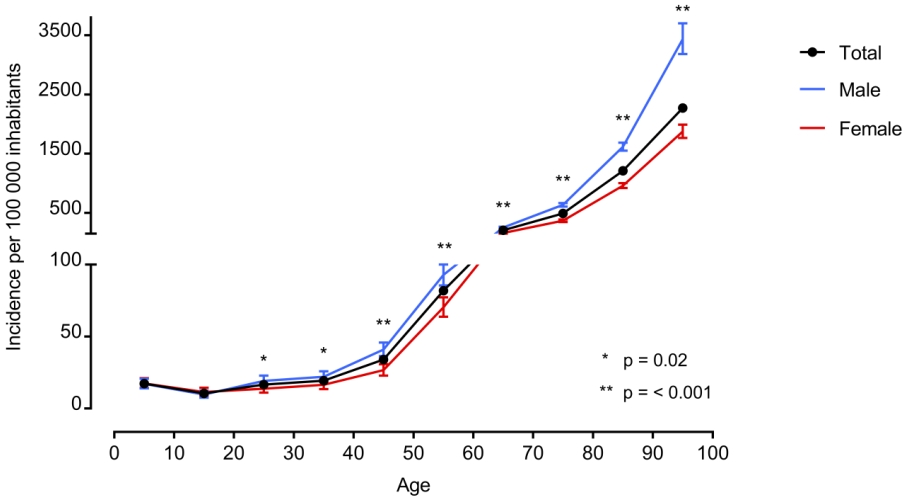

Figure 4. Age-specific annual incidence of sepsis hospitalizations by gender

5. DISCUSSION

5.1 Methodological considerations

5.1.1. Study designs, patient populations and data collection

The aim of this thesis was to describe sepsis in Norwegian hospitals from both a quantitative and qualitative perspective. To accomplish this, a prospective design was chosen in the first study (paper I and II), whereas a retrospective, code-based approach was used in paper III.

5.1.1.1. Prospective, single-center study of community acquired sepsis

By this method adult, case-defined patients were enrolled for one year in a single hospital. The study design secured that all patients within the defined population at risk were screened for eligibility by a quality-controlled inclusion process. Data were collected from all available sources of patient information, with high level of detail, by a limited number of study investigators. In this way, the number of missing data was minimized. To secure that the results were not influenced by seasonal changes in infectious diseases, inclusion lasted an entire year. It has been shown that even case-defined identification of sepsis may be subject to high variability [130]. However, in this study all eligible cases were discussed in consensus meetings within the study group before a final decision of inclusion was made. Furthermore, one experienced consultant (S. Skrede) reviewed all of the included patients retrospectively after discharge to secure diagnosis category, interpretation of microbiological tests, and appropriateness of antimicrobial therapy. Screening was in principle performed on daily basis. There were more than 100 different case report form variables registered. Yet, from a statistical viewpoint, a relatively small sample size was obtained. We chose to exclude patients with nosocomial infections, as these constitute a separate entity and hospital-wide inclusion of cases was not feasible within the study resources. We would like to have categorized patients with healthcare-associated infections separately, e.g. in residents from nursing homes, enabling us to explore unique features of this cohort [155]. Although we aimed to investigate community acquired sepsis in a hospital-wide setting, we limited inclusion to three departments. This may have led to

some missing cases. However, the selection of departments was based on a previous unpublished pilot-survey of community acquired sepsis, where we found that a small fraction of sepsis patients were treated in other locations at our hospital. The restriction of our current study to a single University hospital that holds a referral center function, with inclusion of patients from a combined ICU/ non-ICU ward in the non-ICU cohort, means that the results not necessarily have external validity in other Norwegian hospital settings. Still, we chose to include patients transferred from affiliated hospitals to best describe the clinical characteristics of patients with sepsis in a tertiary care environment. When calculating population incidence, transferred cases were however excluded from analysis. Unfortunately, we were unable to stratify the non-ICU patients by severity scoring. This would have been valuable for comparison with later sepsis studies.

5.1.1.2. Retrospective, code-based national sepsis study

Study III aimed to provide nationwide, quantitative data on sepsis in Norwegian hospitals, the former being its main strength. A national prospective multicenter survey of such nature, including both community and hospital acquired sepsis cases, seemed unfeasible. Thus, a retrospective method was applied. As a national register, the NPR holds excellent standard. Every hospital in Norway is obliged to provide data from all of their admissions. As NPR does not give access to patient's health care records, the study data are limited to the information specified in the register. To increase its robustness, the study period comprised all discharges registered within two full calendar years. When the study was conceived, the years 2011 and 2012 were the most recent years from which complete NPR data were available, and thus these two years were chosen. Identification of sepsis by use of ICD-codes relies not only on physicians' ability to recognize sepsis in their work. It is also dependent on the use and quality of diagnostic codes in the patient's discharge reports. There are no specific codes for organ dysfunction caused by infection. Furthermore, fatalities could in a similar manner primarily be the outcome of another co-occurring condition. Overall, we have therefore inevitably missed some cases, while others may be false positive.

Since one of our aims was to compare data from this study with previous data from 1999, we selected a spectrum of diagnostic codes as similar as possible to the codes applied in the previous Norwegian investigation [67]. However, since specific codes for SIRS and sepsis with organ dysfunction now had been introduced, we added these together with the code for neonatal sepsis to our primary search.

Importantly, the reuse of the method from 1999 was also founded in a review of the previous literature. Several authors have advised against limiting codes in retrospective studies to diagnoses specific for sepsis and septic shock only. Such an approach has been found to yield more severely ill patient populations than prospective settings, and underestimate sepsis incidence [51, 83, 156]. One study from the U.S. came to the opposite conclusion, but that study referred to cohorts with very high mortality rates up to 50% [84], indicating too narrow inclusion of cases. Also, their selection of infection codes included far more diagnoses than our current study. The latter was based on one of the most early and widely cited surveys on sepsis epidemiology, performed by Angus and coworkers [77]. Indeed, Angus' selection of codes has been copied by many authors up to date, although this method has not been further evaluated since the introduction of sepsis specific codes in 2003. It is thus primarily based on codes for various infections (n = 642); including both infections that in most circumstances are not severe, and conditions that are rarely the cause of sepsis. In comparison, our current study included a total number of 63 ICD-10 codes.

A comment concerning our selection of codes is that AIE was not included. Three factors reduce the influence this might have had on the current results. Firstly, AIE is rare, with an estimated population incidence of 3 to 15 cases per 100 000 inhabitants per year [157-159]. Many cases do not present with organ dysfunction, e.g. the cases with AIE in our prospective study constituted 1 in 3 of all AIE cases admitted to Haukeland University Hospital that year (S. Skrede, personal communication). Finally, most AIE cases are blood culture positive (≥90%) [159, 160]. A diagnostic code for microbial etiology is thus presumably frequently registered in this disease, and consequently included in registry data.

All studies that have evaluated a prospectively registered cohort against cases identified retrospectively by coding conclude that the retrospective approach leaves a

considerable number of undetected patients [55, 161, 162]. Noticeable, subanalyses in a Swedish survey showed that only community acquired sepsis was underestimated; nosocomial sepsis was on the contrary overestimated [161]. Nevertheless, an investigation that evaluated the Norwegian method from 1999 found that it identified only 39% of the sepsis cases in a Swedish prospective ICU-registry [162]. However, unlike in our current study, the new sepsis specific codes were not applied in that evaluation. There is also a possibility that the Norwegian method was erroneously interpreted due to an erratum in the original paper, where diagnoses for pneumonia are listed among codes for organ dysfunction instead of among infections. Last, the magnitude of the Swedish results is further indefinite as less than half of sepsis patients in eligible randomized controlled trials have actually been identified in the current ICU-registry [161]. In any case, the Norwegian method was definitely superior to two other simultaneously investigated retrospective methods, and overall we found it most suitable [76, 77].

5.1.4. End-points, follow-up periods and estimation of occurrences

The primary end-point in all of the three articles in this thesis is hospital mortality. In paper I and II, this was presented with CFRs as all hospital deaths were reviewed and the primary cause verified to be sepsis. We additionally provided 28-day mortality for the prospective study, as this parameter often is given in international sepsis literature. In the retrospective study only all-cause hospital mortality could be estimated, as this is the outcome registered in the NPR.

The prospective study (paper I and II) also presents long-term mortality for up to five years after sepsis hospitalization. Not only was information about mortality beyond hospital deaths non-existent in Norway previous to this study, also international data were scarce [163-166]. One large study from the United States had surveyed sepsis patients for five years after hospitalization, but that was a retrospective survey [166]. Assessment of long-term mortality in a prospective cohort was thus an important aim of this work. A limitation of our data is that we could not determine the cause of death in fatalities occurring after hospital discharge. Neither did we provide comparative data from the background population, both of which would be of interest.

Annual population incidence of community acquired sepsis as well as total sepsis patients in Norwegian hospitals were estimated in this thesis. The denominator in both estimates was the total number of inhabitants in the respective background populations for the calendar years studied, given by Statistics Norway. To calculate incidence, theoretically one should consecutively subtract the number of days left in the observation period for patients developing the disease of interest when measuring the size of the population at risk, or in the case of community acquired sepsis, even the sum of hospitalized days for patients admitted due to other conditions. Because the number of cases in our study was so small this would very unlikely have influenced our results [55]. Since we also considered nosocomial sepsis in the retrospective cohort, the latter was not an issue in that study.

When estimating the percentage of sepsis hospitalizations among the total number of hospitalizations in Norway in paper III, we excluded psychiatric admissions. Other researchers have excluded patients of minor age (< 18 years), and some have excluded hospitalizations related to childbirth. Since nosocomial sepsis was part of our investigation, we found rationale for inclusion of all patients in somatic hospitals. We age-stratified annual population incidence, but did not sub-specify the total number of hospitalizations according to age categories.

In the prospective study, we excluded any hospital admission later than the first community acquired sepsis episode. However, later we realized that re-hospitalization due to new episodes with infection in sepsis survivors is common [167]. By excluding these hospitalizations, valuable information about the true impact of sepsis on health care is lost. In the retrospective study, we therefore chose to include multiple admissions. However, we excluded any admission representing more than a fifth sepsis episode in the same individual during the two study years, after a manual review of our data had showed some cases with unreasonably many episodes. We suspect that these were e.g. patients in permanent renal replacement therapy subject to incorrect use of diagnostic coding.

5.1.5. Definitions of sepsis

In the prospective study, sepsis was defined according to the contemporary definition as infection with fulfillment of two or more SIRS criteria and presence of acute organ dysfunction(s). For identification of organ dysfunction, we used the local sepsis guideline at Haukeland University Hospital which contains the following minor modifications of the second sepsis definition:

- Hypoxemia (SpO2 <90% while breathing air)
- Acute oliguria (urine output <0.5 ml/kg/h for at least 4 hours)
- Lactic acidosis (pH <7.30 and s-lactate >4.0 mmol/l)
- Thrombocytopenia (platelet count <100 x 10^9/ l or a 50% reduction ≤3 days)

Definition of hypoxemia according to SpO_2-values instead of PaO_2/FiO_2 ratio was done in order to facilitate diagnosing in a non-ICU environment. In most cases SaO_2-values from blood gas analysis were considered, as SpO_2-measurement can be inaccurate. The other modifications are stricter than the original criteria presented by Levy and coworkers, which gives the possibility that our prospective sepsis cohort was slightly biased towards a more severely ill patient population. This is especially true for the parameters oliguria, where we doubled the minimum hours of low urine output, to minimize the risk that the cause was simply dehydration, and hyperlactatemia where we chose a cut-off of 4.0 instead of the 3.0 mmol/l recommended by the definition at that time. We attempted to calculate SOFA scores retrospectively in this cohort, but were unable to determine accurate scores for the majority of cases. We could however demonstrate that all of our included patients fulfilled the Sepsis-3 definitions in terms of having an increase in SOFA score ≥ two points. This ascertains the present validity of our data.

We chose to refer to the current definition for sepsis (Sepsis-3) at the time of publishing paper III. Since the patients included were hospitalized in the years 2011 and 2012, their diagnoses were not given according to SOFA scores. However, the Sepsis-3 definition only recommends, and not requires, that organ dysfunction is based on SOFA scoring. Thus we considered the obligate part of the definition, i.e. life-threatening organ dysfunction caused by a dysregulated host response to infection,

adequately covered by use of diagnostic codes. However, the definition of septic shock given in Sepsis-3 differ to such an extent that we are not providing estimates of septic shock, only cardiovascular organ dysfunction, in paper III.

5.1.6. Statistical considerations

To explore if there were independent predictors of hospital mortality and care level affiliation in paper I and II, we used a multivariable stepwise backward model to adjust for confounding variables. The Hosmer-Lemeshow's test of goodness-of-fit was used to verify the regression models for calibration. Further, the models were checked for collinearity by evaluating how the effect (OR) of each variable varied between different settings (i.e. between the unadjusted, fully adjusted (multivariable), and the final simplified model). In paper I, the variables in the multivariable analyses were screened to avoid collinearity by including only those with $p < 0.10$ in the unadjusted analyses (empirical antimicrobial therapy in cases with positive microbiological samples were excluded in the reported model due to sample size). In paper II, we had pre-specified the explanatory variables based on plausible relationships with the dependent variable. These were included without regards to statistical significance in the univariate analyses. Collinearity is especially a problem with regards to the many comorbidity variables in both papers. Another possible problem with the many comorbidity variables is that we ended up with inclusion of a higher number of explanatory variables than recommended to avoid over-fitting in the final model in paper I (it is recommended to have at least 10 end-points (e.g. fatalities) per explanatory variable, and in this study there were $n = 55$ deaths). Since no formal adjustment for multiple testing was performed, more emphasize should be given to the most significant predictors in the final model in paper I (i.e. with $p < 0.01$). In the logistic regression analyses shown in table format in paper I and II, all explanatory variables are categorical. In paper I we additionally tested for linear trend in age and timing of antimicrobial therapy to best explore the relationship of these categories with outcome. As there were two extreme outliers in timing of antimicrobials, we performed logarithmic transformation before inclusion of this variable to achieve linearity without excluding any cases.

Survival analysis was performed by two methods in this thesis: Kaplan-Meier and Cox' regression statistics. The Kaplan-Meier method is a non-parametric test where the number of patients at risk influences the accuracy of the survival estimates. Hence these are more precise at the start versus towards the end of a study, especially if there are a relatively small number of cases, as in our prospective study. An extenuating feature of our model is that follow-up was complete for all patients, which means that there were no censored cases in the analyses. Kaplan-Meier does not permit incorporating continuous explanation variables, and cannot adjust for covariates by stepwise addition of several variables. To investigate if there were variables with independent effect on long-term survival, a Cox regression analysis was thus applied in paper II.

Several of the significant results from the statistical analyses in the prospective study (paper I and II) have relatively wide 95% CIs, as an expression of the small sample size in some categories. The magnitude of the effect on the outcome of interest is therefore difficult to ascertain. The most extreme example is the category Endocarditis in the multivariable analysis in paper I, which has an OR of 18.94 with a 95% CI ranging from 3.45 to 104.06 in the final model. Relatedly, in retrospect we see that some of the $\chi 2$ p-values in the results section in Paper I lack ORs and 95% CIs. Besides, the IQRs for the medians in this paper are not specified.

5.2 Discussion of the Results

5.2.1. Incidence of sepsis in Norway

In this thesis, the annual population incidence of hospitalized sepsis in Norway was estimated to 50 per 100 000 inhabitants when restricted to patients > 15 years of age with community acquired infections in the year 2008, and to 140 per 100 000 inhabitants for all cases in the years 2011 and 2012. The previous estimated overall annual population incidence of sepsis in Norway was 50 per 100 000 inhabitants [67]. Since we used a similar method as that study from 1999, we find it plausible that the observations in paper III reflect that sepsis occurrence is increasing. This is in accordance with recent studies and may be attributable to a growing population at

elevated risk for infection [74, 76, 77, 79, 85, 93, 110]. Retrospective observations can additionally be biased by changes in discharge coding patterns (Figure 2) [129]. By including both codes for severe infections, SIRS, sepsis by causative pathogens, and septic shock in the primary search, we tried to minimize this problem. Nosocomial infections constitute a considerable amount of sepsis cases (33 - 73%) [88, 89, 91, 95, 96, 99, 101, 113]. The detected incidence in our prospective study is therefore well in line with the retrospectively obtained observations.

Although there are numerous international reports on sepsis epidemiology, population-level incidences have only been provided in eight countries and solely four previous European studies have provided nationwide data [58, 67, 69, 70, 74, 124]. There are substantial differences in the previous estimates, which partly can be attributed to different study designs (Table 1) [59, 124, 128, 168]. Overall, our current nationwide estimate is similar to recent results from two nationwide retrospective European surveys (140 and 110 per 100 000 inhabitants per year) as well as a population-based investigation from China (190 per 100 000), while the most recent studies from the U.S. report higher figures (mostly of the order 300 to 400 per 100 000) [58, 70, 74, 81-83, 85]. This may be a reflection of different health care systems, but also different ICD-coding practices [59]. Medical care in Norway and most of Europe and China is government funded, in contrast to the U.S. where it to a greater degree has been funded by private insurances. It may therefore be speculated that a large cohort of predisposed persons will seek and receive medical care at an earlier stage of an infectious episode in Europe and China, before the development of sepsis. The low percentage of patients with sepsis (16.0%) in the primary cohort of patients with infection in our retrospective report supports this assertion. Moreover, studies from the U.S. report incidence as the number of sepsis *admissions* per unit of population older than18 years of age. If we use the same criteria, our corresponding rate is 290 per 100 000 population in the year 2012 (data not shown). This highlights that awareness of methods and criteria for inclusion is crucial in epidemiological sepsis studies.

Previous population-level prospective investigations with calculations of sepsis occurrence are scarce and mostly confined to community acquired cases [55, 117, 121, 123]. A Spanish study from the year 2003 estimated the annual incidence of

hospitalized sepsis to 100 per 100 000 inhabitants >18 years of age, from a cohort where 83% of infections were community acquired [117]. Higher figures were reported in a one-year prospective survey from the medical ED of a Danish University Hospital [55]. They estimated an annual incidence of 457 per 100 000 inhabitants ≥ 15 years of age during the years 2010 – 2011, corresponding to 13% of all patients admitted to the respective ED. Similar high occurrence rates were estimated in a recent Swedish study that retrospectively reviewed patients with a new administration of intravenous antibiotics during four different days in 2015 [57]. They calculated an annual incidence of 687 and 780 per 100 000 inhabitants with the Sepsis-2 and Sepsis-3 definition respectively. Both our prospective and retrospective survey identified a considerably lower incidence than these recent Scandinavian reports. Regarding our prospective study we may have missed some patients by not screening all ED admissions, but we believe the difference is also explained by dissimilar inclusion criteria. Whereas we used strict definitions for organ dysfunction, the Danish study defined respiratory dysfunction as oxygen saturation by pulse oximetry < 92% at arrival or arterial oxygen tension < 9.75 kPa, in a cohort where 68% of cases presented with RTI. Respiratory organ dysfunction was present in 65% of their subjects, while cardiovascular and renal dysfunction was present in only 7% and 9% respectively. When we evaluated patients with RTI for eligibility in our prospective study, strict clinical judgement was used for patients with e.g. pre-existing COPD. In the retrospective study such evaluation was not possible, but we tried to overcome this problem by excluding codes for infectious exacerbation of COPD. Indeed, the focus of the studies in this thesis has been to identify patients that to the most certain degree have organ dysfunction caused by a dysregulated inflammatory response to infection. We speculate that some studies have mainly focused on identifying patients with infection fulfilling the criteria for organ dysfunction, without further regard to the mechanism eliciting this dysfunction. In our retrospective survey we found that sepsis cases constituted 16% of patients with confirmed infection. This is comparable to recent results from China, but only half of what was found in the respective Scandinavian studies. Interestingly, the estimated annual incidence of sepsis in the

Chinese study (190 per 100 000 population ≥ 18 years) is also comparable to our results.

The two other Scandinavian studies have investigated how many of their sepsis patients that were retrieved by use of ICD discharge codes. Both found a low detection rate, close to 15%. It would have been interesting to know how many of the patients in these studies that were assigned a code for related conditions, such as exacerbation of COPD or pyelonephritis with prerenal and shortly resolving oliguria. In the end, as long as sepsis is case-defined, comparisons between studies will not only be influenced by the choice of methodology, but also hampered by the subjective component in the perception of the syndrome [130].

5.2.2. Utilization of Norwegian hospital capacity and ICU resources

In the year 2008, we estimated that community acquired sepsis in adults caused 0.34% of the total somatic admissions (n = 64 405) at Haukeland University Hospital (P. O. Vadset, hospital data management unit, personal communication). During 2011 and 2012 the corresponding admission rate was 1.0% for all patients hospitalized with sepsis, a considerable increase from the previous Norwegian estimate of 0.3% from 1999. Other international studies present admission rates in the range of 0.9 – 2.3% [58, 70, 74, 75, 77, 82, 117, 123]. The highest rate was found in the retrospective U.S. investigation which included a great number of codes for infection [77], while studies that included all age categories in their analyses are on the opposite end of the scale [70, 74]. There are little data on which fraction patients with community acquired sepsis constitute of total hospitalizations, and most studies are restricted to ED admissions [55, 78, 116, 169]. Only two prospective studies, from Spain and Northern Australia respectively, have calculated rates from all hospitalized patients. Both estimates are considerably higher than our 0.34%, around 1.5% each [117, 123]. It is however unclear how comprehensive the account of total somatic admissions was in these studies. In addition to including e.g. the Department of obstetrics and gynecology as a somatic unit in their hospital management statistics, Haukeland University Hospital serves as a referral center and has comprehensive activity on a regional and national basis in several fields, possibly influencing our results.

The total utilization of hospital days for sepsis patients during 2011 and 2012 equaled 3.5% of all somatic overnight stays in Norwegian hospitals. The mean and median LOS was fourteen and nine days, which is comparable to several contemporary results [75, 81, 85], yet lower than other findings [58, 74]. In 2008, the median LOS for community acquired sepsis at Haukeland University Hospital was eleven days. This is higher than the eight days reported by the simultaneously performed study from Northern Australia and definitely higher than the six days found in a U.S. retrospective study comparing the characteristics between community acquired and nosocomial sepsis [123, 170]. This supports an assumption that patients in our prospective study were more severely ill than those of other cohorts with inclusion of non-ICU treated patients. The median ICU LOS was also shorter in the two before mentioned studies, four and three days respectively, versus six days in our patients. However, other observations include both shorter and longer median ICU stays, leaving our findings well within the range of previous results [44, 91, 95, 117]. Besides, several factors such as the threshold for ICU admissions, ICU capacity, and characteristics of the underlying infections may bias ICU LOS. Relatedly, sepsis patients have been found to account for 10 to 25% of all ICU admissions in various settings [77, 91, 94, 108, 111, 113, 123]. In 2008, community acquired sepsis constituted 11% of all admissions to the general ICU at Haukeland University Hospital (n=423 admissions in 390 patients).

The proportion of patients with sepsis treated inside an ICU in our prospective study was 49%. Similar ICU treatment rates (32-55%) have been estimated in both prospective and retrospective settings [58, 68, 77, 86, 91, 116, 117, 123, 149, 171]. Oppositely, in the Danish investigation of community acquired sepsis, only 7% of patients were admitted to an ICU [115]. Although the Danish registration was restricted to the first 24 hours after hospitalization, it has been shown that most ICU admissions for sepsis take place early in the disease course, indicating that their total ICU treatment rate would not have changed noteworthy with a longer follow-up period [44]. Relatedly, in our study 17% of patients initially admitted to a medical ward were later transferred to an ICU, not different from other investigations (10-14%) [116, 122].

5.2.3. Characteristics of Norwegian sepsis patients

The demographic characteristics of the two sepsis cohorts in this thesis are comparable with most cohorts from contemporary sepsis studies (Table 1). Several studies have shown that the mean age of sepsis patients has increased significantly over the past decades [74, 76, 93]. Mean age was 58 years in the Norwegian sepsis report from 1999, in our prospective study it was 64, whereas in the most recent retrospective study it was 72 years [67]. This is likely a reflection of the steadily growing population of elderly in our society, and gives reason to assume that the observed increase in sepsis incidence will maintain in the forthcoming years.

A gender related age-specific difference in sepsis incidence similar to that found in our retrospective study has been shown previously [58, 70, 75-77]. It has been discussed whether observed gender disparities in sepsis occurrence reflect true conditions or rather is a bias from different care providing among the sexes [172]. Since we have estimated the incidence of sepsis with both hospital and nationwide data, we find reason to discard the last objection. The higher occurrence of sepsis among men is multifactorial, where chronic health and behavioral factors, gender specific susceptibility to microbes, hormones, and genetic factors interacting with immunity all may play a part [59, 173]. This topic is however beyond the scope of this thesis.

Unfortunately, we were unable to adjust for comorbidity when analyzing data in the retrospective study. In the prospective study, 90% of the included patients had at least one coexisting chronic disease, which is a high percentage compared to previous estimates [58, 74, 77, 88, 89, 93, 94, 96, 99, 110, 133, 135]. This may in part be explained by our inclusion of hypertension and psychiatric disease categories, common conditions that are often not accounted for. Further, cardiovascular diseases were the most prevalent category among our patients (49%). Most studies have only included coronary artery disease, in some instances restricted to confirmed heart attacks [74, 75]. Last, prospective inclusion is the most suitable way of registering comorbidity, which means that comparison with retrospective code-based studies in terms of absolute proportions is difficult. Nevertheless, our distribution of diagnoses from the more to the less prevalent conditions resembles previous studies in general.

Studies investigating differences in burden of underlying disease among sepsis patients hospitalized inside versus outside ICUs have divergent findings. One prospective study found patients on the wards to have more severe comorbidities in terms of a worse McCabe score [117], while a retrospective U.S. study found slightly fewer comorbidities in this subgroup [122]. Among our prospective cohort, we found that dementia was the single unevenly distributed condition with a significantly higher occurrence in the non-ICU cohort. Further, a do-not-resuscitate (DNR) order was given more frequently in our non-ICU patients (9% versus 5% of ICU patients), but the significance disappeared in multivariable analyses. Relatedly, among non-survivors of the Spanish study, it was a higher proportion of DNR orders in non-ICU patients (46% versus 8% in the ICU-patients), but overall, withholding or withdrawal of treatment was equally frequent among the different care levels [117]. Differently, the retrospective U.S. study found that ICU admitted patients were given slightly more DNR orders after examination in the ED (5% vs 4%) [122]. Again, we speculate that differences in health care organization may influence the characteristics of patients admitted to the different levels of care among different countries. Based on clinical experience, we find the results from our prospective study consistent with Scandinavian conditions, in line with a retrospective Danish study of community acquired sepsis that found that 17% of their patients were not ICU eligible on the basis of pre-existing conditions [68].

5.2.4. Infectious foci and diagnostic precision

The most common focus of infection in both of the studies in this thesis was found to be the respiratory tract, consistent with previous literature (Table 2). In our prospective study, the various community acquired infections was differently distributed between the care levels (paper II). More specifically, genitourinary infections and abdominal infections was the second most frequent focus in the non-ICU and ICU cohort respectively. Overall, the total proportion of cases with abdominal infections was in the lower range of previous results. Genitourinary infections have indeed been reported as more prevalent in studies covering non-ICU patients while abdominal infections are more common in explicit ICU settings (Table 2). A distinct finding of

our study is that AIE was more prevalent compared to other investigations. Together with an increasing occurrence of patients hospitalized due to AIE in general (S. Jordal, M.D., personal communication), the tertiary care and referral center status of Haukeland University Hospital have influenced this result as 8 out of 12 of our cases with AIE were transfers from affiliated hospitals.

Identifying the source of infection in sepsis by use of discharge codes has important limitations, as previously explained. Nevertheless, we chose to specify the proportion with the most common infections in paper III and found that RTI was identified very often (64%), whereas the three second most prevalent foci showed low frequencies (from 4.3 to 4.9% of the cases). In the prospective study, the proportion of cases with identified microbiological etiology was lower in RTI compared with other infection categories, in line with other prospective investigations of community acquired pneumonia [174]. Thus, it is likely a higher probability of receiving one of the microbiological founded sepsis codes in other infection categories than RTI. This difference may decline if more comprehensive molecular methods become a part of routine testing [175, 176].

An important secondary objective of our prospective study was to evaluate the precision of diagnostic practice in sepsis. To accomplish this, we compared the confirmed focus of infection at hospital discharge with the suspected focus at admission (paper I). We have not found other similar investigations, but it has in a related manner been reported that a significant proportion of patients with suspected sepsis in fact have noninfectious, mimicking diagnoses [169]. In some infection categories our results were worrisome, considering that empirical treatment is tailored on the basis of a suspected infectious source. As long as diagnostic algorithms for sepsis focus on the identification of an infection's complications rather than its origin, our results justify increased focus on this aspect in everyday clinical practice and education.

5.2.5. Microbiological etiology of sepsis in Norway

In our investigation of community acquired sepsis we identified a plausible pathogen in 61% of the microbiological tested patients, and 37% of blood cultures were positive

(paper I). These results resemble prospective studies of sepsis from ICU settings [88, 91, 95, 96, 99, 101, 108, 113, 114, 139, 171]. Other prospective studies with inclusion of non-ICU patients present lower detection rates than we found. The Spanish and Northern Australian studies included patients with no organ dysfunction and found overall rates of 42-45% [117, 123]. Unlike the Spanish results, we did not find a difference in the microbiological detection rate between the levels of care (paper II) [117]. However, in addition to include patients without organ dysfunction that study also comprised nosocomial sepsis, both of which exert influence on the detection rate [55, 113, 114, 119, 141]. The studies from Denmark and Sweden that calculated very high incidences of sepsis, found growth in blood cultures in solely 13% and 19-24% respectively [55, 57]. Overall detection rates are not offered. In retrospective surveys, the overall detection rate has been specified at 10% and 26% in two studies [74, 133]. Surprisingly, older investigations that included cases without organ dysfunction found higher rates, 30 and 51% of patients [67, 76]. All of these rates are however naturally dependent on the selection of codes used. We chose not to explore this subject in our retrospective study (paper III).

Gram-positive bacteria were the most common cause of community acquired sepsis in our prospective study, representing 57% of all identified pathogens, while Gram-negative microbes constituted 38% (paper I). A similar distribution was also found among positive blood cultures. The overweight of Gram-positive bacteria in our environment is different from results seen in many other Western countries at the same time. For example, a very large point-prevalence survey of infections in ICUs with 75 participating countries found Gram-negative bacteria in 62% of patients, Gram-positive in 47%, and fungi in 19% [140]. In a more recent Norwegian investigation of bloodstream infections, Gram-negative microbes similarly constituted 56%, Gram-positive 38%, whereas 7% of infections were mixed [144]. Compared to a previous Norwegian study of BSIs which found Gram-positive aerobic bacteria in 50% and Gram-negative aerobic bacteria in 43% of cases during the late 1980s [177], the recent Norwegian study shows a change towards Gram-negative bacteria that is more in line with international studies than our data. Our study may have been influenced by the fact that Gram-negative bacteria have been found more frequently in nosocomial than

community acquired infections [113]. Furthermore, an outstanding feature of our study is that *Streptococcus pneumoniae*, which is very uncommon in hospital-acquired infections, was the most prevalent microbial etiology [178, 179]. A conjugated vaccine was included in the official program for vaccination of children in 2006. From that point, a marked decline in cases with invasive *Streptococcus pneumoniae* has been seen, in particular among the elderly [147, 179, 180].

There are very few studies that specify the whole spectrum of encountered microbes in sepsis, and none from settings comparable to our investigation. On the other hand, several other Scandinavian studies present results from blood cultures. With exception of *Staphylococcus aureus* being more common than *Streptococcus pneumoniae*, their findings resemble ours [55, 57, 68, 89].

More than one pathogen was present in 19% of our test-positive patients (paper I). In other studies the exact amount of polymicrobial infections is most often not stated, but it has been specified between 18 and 36% in explicit ICU sepsis studies during the preceding years of our study [101, 108, 114]. Fungal infections were among the polymicrobial cases, and altogether eight fungi were detected from a total of four patients, indicating that this type of pathogen was more seldom in our hospital than other settings at that time [74, 101, 113, 114, 133, 140]. Furthermore, we did not see acquired drug-resistance among other microbes than *Escherichia coli*, of which two out of 27 isolates (7%) were ESBL producing. Only one other Scandinavian sepsis study, a Swedish survey of 101 patients in a single ICU, have stated that they encountered drug-resistant bacteria [89]. Among their blood cultures, two out of 18 *Escherichia coli* were ESBL producing (11%). These sample sizes are small, but theoretically troublesome resistance could be more prevalent in sepsis than in general infections. This could be due to a higher prevalence of these microbes in subjects with increased risk of sepsis. In comparison, the Norwegian study of BSIs in a local hospital performed during the years 2002 to 2013 found ESBL production in 2% of *Escherichia coli* [179]. The official Norwegian surveillance program for antimicrobial resistance (NORM) similarly calculated that 1.5% of *Escherichia coli* in investigated blood cultures were ESBL producing in the year 2008 [181]. Furthermore, this proportion increased to 6.5% in 2015, while aminoglycoside resistance simultaneously

increased from 2.7 to 6.4% [182]. Thus, the occurrence of multi-drug resistant *Enterobacteriaceae* in Norwegian sepsis cases has increased significantly since our study was conducted. Regarding other mechanisms for acquired drug-resistance, the Norwegian study of BSIs until the year 2014 encountered only one Methicillin Resistant *Staphylococcus aureus* (MRSA), and 1% of *Streptococcus pneumoniae* were resistant to penicillin [179]. Surveillance of resistance in sepsis patients should be a prioritized field to investigate in the future to continuously guide evidence based selection of empirical antimicrobial treatment regimens.

5.2.6. Organ dysfunction

In our prospective study, 88% of patients had more than one dysfunctional organ system. This is a higher fraction than in comparable prospective studies. We collected data throughout the entire hospital stay for all patients, to ensure an inclusion of all cases with organ dysfunction. In fact, two retrospective studies that also performed manual reviews of their patient's medical records found similar figures (77-82%) [68, 136]. The presence of multiple organ dysfunctions was high also among our non-ICU patients, affecting 81% of cases versus 94% of the ICU patients. Nevertheless, the ICU cohort had a significantly greater burden with more cases in the range above two dysfunctions, similar to other comparable settings [86, 117]. A limitation of the comparison between the two levels of care in our study is that we were unable to perform severity scoring of all patients. This would have given a more detailed picture of the degree of organ dysfunctions. E.g. cardiovascular dysfunction was present in 68% and 79% of the non-ICU and ICU cohort respectively; however, vasoactive drugs were administered in 32% and 94% of the respective patients, indicating that ICU patients were more severely affected. Similar to a retrospective Australian sepsis investigation, we noticed that cardiovascular, renal, hematological and hepatic dysfunction were treated in an ICU in just above half of the cases, while metabolic acidosis was most often ICU-admitted (73%) in contrast to neurologic impairment that was less often allocated to an ICU (37%) [86]. The Australian distribution of respiratory dysfunction (ICU-treated in 89%) is however considerably different from our corresponding proportion (56%). The Australian study was performed around the

millennium, when treatment facilities outside ICUs probably were less comprehensive than at the time of our study some years later. If we transfer non-ICU cases receiving ventilation support to the ICU group for comparison, our corresponding estimate is 80%. Metabolic acidosis was the organ dysfunction with the second highest ICU-admission rate in both the Australian and our study (73% and 75% of patients). Thus, it seems that respiratory and metabolic dysfunctions are especially associated with high demands for critical care. Overall, our findings are likely affected by the expanded facilities for patient surveillance and treatment that are available outside the ICUs in our hospital. This is in particular relevant for the burden of respiratory and cardiovascular dysfunctions. In other settings, some of our non-ICU patients may therefore have been admitted to an ICU. Apart from hematologic dysfunction, our overall distribution of organ dysfunctions is comparable to previous results, with two important exceptions that have already been addressed in this thesis [55, 75]. When we classified organ dysfunctions, only patients with a diagnosis of DIC and/or purpura were included in the hematologic category. This should have been noted in our manuscript. If we, like others, had used a definition identical to our inclusion criteria (i.e. platelet count $<100 \times 10^9/l$), this rate would be comparable (17%, data not shown).

In our retrospective study (paper III), the estimated occurrence of organ dysfunctions was much lower than in our prospective study, with multiple dysfunctions present in 15% of cases. Since the prospective study was performed at a single university hospital which serves as a referral center, it is plausible that the overall severity of sepsis in that study is above the national average. Also, the retrospective study did not include dysfunction of the central nervous system, present in 34% of the prospective cases, as we could not find a distinct ICD-10 code to substitute this condition. However, these matters probably contributed to a smaller part of the discrepancy, while insufficiencies in ICD-coding practice likely caused the greater part. This is illustrated by the fact that solely 96 cases (0.5%) in the retrospective study were found to have four or more organ dysfunctions during the two study years all together, while the corresponding number for community acquired cases in the prospective, single center study with one-year duration was 69 (31%) (paper II).

5.2.7. Treatment and compliance with guidelines for sepsis management

Protocolized identification and care for sepsis patients have been the recommended norm for one and a half decade, and favorable evidence continues to emerge [46, 138, 144, 149, 183-185]. Haukeland University Hospital was the first Norwegian hospital to establish a hospital wide sepsis guideline in the year 2002, and this guideline has later served as a template for many other hospitals. A secondary objective of the prospective study was to investigate the nature of sepsis treatment at our hospital and to evaluate if this was in accordance with the local guidelines. We chose to focus on the use of antimicrobials alone in the evaluation because this is the only parameter that is standard for all sepsis patients (paper I). Other therapies were solely compared between the two levels of care (paper II). We have not found other studies providing details on the treatment of sepsis outside of ICUs. In fact, in a review of evidence supporting the use of the 2012 SSC recommendations in patients on hospital wards, the authors found that quick administration of empirical antimicrobial therapy was the only one of 25 relevant recommendations actually supported by studies that included non-ICU patients [186].

Considering the use of antimicrobial therapy in our study, the local guidelines were not followed in approximately one in five patients and the compliance was poorest among patients ≥ 75 years of age (paper I). Importantly, when microbe identity and/or susceptibility tests revealed that adequate therapy had been provided, compliance with routines had been better than when inadequate regimens had been given. This adds evidence based rationale for the use of guidelines.

Overall, the median time from the moment of hospital admittance to administration of the first dose of antimicrobial treatment was 2.8 hours in our cohort. Compared to the SSC guideline, which since the year 2008 has recommended antimicrobial administration to take place within one hour, our result stands out as unsatisfactory. Nevertheless, similar results were encountered around the time of our study conduction [116, 187], and our results were superior from a previous North-American investigation [43]. A further extenuating circumstance is that the last mentioned retrospective study of patients with septic shock was the only study accentuating

timing of antibiotics available to the SSC guideline from 2008. Last, the SSC uses the moment of sepsis *recognition* while we used admission to hospital as index time [188]. Of concern is however the range in our results, with extended delay in abdominal infections, elderly patients, and in the ICU cohort compared to the non-ICU cohort. Indeed, the majority of abdominal infections did require intensive care, so a higher occurrence of abdominal infections may account for some of the delay in the latter group or vice versa. In addition, there was a trend towards more preliminary diagnoses with an incorrect focus of infection (p=0.123) and also more cases where infection was not suspected at all (p=0.094) in the ICU cohort. Altogether, this indicates that a more severe and complex spectrum of symptoms necessitated immediate efforts on investigative modalities and organ supportive therapeutic measures. Similar considerations could be done among the elderly, where more comorbidities including higher occurrence of cognitive impairment, as well as greater impairment of renal function, was present.

5.2.8. Outcome of hospitalized sepsis patients in Norway

5.2.8.1. Hospital mortality

We found that CFR from sepsis was 25% for community acquired cases at a tertiary care level in the year 2008, and 19% for all cases nationally during 2011 and 2012. These results are well in line with previous international figures [75, 85]. The hospital CFR among our retrospective cohort represents a considerable decrease compared to the previous Norwegian estimate from 1999 (27%) [67]. Furthermore, during these years (1999 to 2011-2012) the mean number of admission days fell and the mean age of the patients rose. Similar observations have been made in other international nationwide settings [74, 81, 82, 85]. It has been speculated that the recent decrease in hospital mortality from sepsis originate from changing coding practices [84, 129]. A retrospective study reported that the average number of organ dysfunctions among their sepsis cases increased, whereas hospital mortality and mean hospital cost in parallel declined [82]. Nevertheless, general improvement in care may still be a major underlying cause of favorable trends regarding outcome. In support of the latter is a

meta-analysis from the U.S. which concluded that mortality among patients enrolled in the control groups of 36 multicenter clinical trials have decreased in a corresponding manner as data derived from administrative coding [148]. Further, two major nationwide ICU studies have come to the same conclusion [94, 110]. Ideally, future code-based epidemiological studies of sepsis should in their search for time-related changes specify sepsis mortality at the level of different ICD-diagnoses, and also investigate the frequency and mortality of the corresponding cases without organ dysfunction(s).

An additional possible confounder in the measurement of hospital mortality is the time to hospital discharge. A shift towards an earlier discharge practice, in our setting presumably to a facility in the primary health care services, may transfer late occurring deaths from before to after hospital discharge. Interestingly, a national reform issued by the Ministry of Health and Care Services in Norway called *Samhandlingsreformen* (English: the Coordination reform), aiming to promote the use of primary health care services in order for care providing to occur closer to the patient's home, was implemented January the 1st 2012. In parallel hospital mortality from sepsis decreased from 22% in 2011 to 17% in 2012 (paper III). Similarly, hospital LOS for patients discharged to a primary care facility (e.g. nursing home) in general decreased with two days during the following years [189].

Results in our prospective investigation are likely affected by the study center being a tertiary care referral center. This makes it difficult to compare mortality among this cohort with the previous Norwegian study. Other prospective studies of community acquired sepsis have described that 19%, 17% and 28% of their sepsis patients from Denmark, Northern Australia and Spain were hospital non-survivors during the years 2010-2011, 2007-2008 and 2003 respectively [115, 117, 123]. None of these estimates are far from our result, even though there are notable variations in study settings.

Dichotomization of our cohort dependent on the level of care showed that ICU-patients had more than twofold the mortality as non-ICU treated subjects (35% versus 16%, paper II). While our hospital mortality at ICU level is similar to many other ICU settings (Table 1), mortality in sepsis patients not admitted to an ICU bed was lower than in other publications (23-30%) [77, 116, 117, 190]. This discrepancy may be

explained by our exclusion of nosocomial infections [191], the year of study conduction, as well as our study setting, which may favorably have influenced outcome due to qualifications and relative number of the personnel.

In paper I, we explored predictors for hospital death in community acquired sepsis. Increased risk of mortality was found for abdominal infections and AIE using RTI as a reference. Abdominal infections are often polymicrobial and anaerobic bacteria are not uncommon in this category, meaning there is a significant risk for empirical antibiotics to be inadequate in this category when the diagnosis is not suspected at admission [192]. All twelve cases with AIE in our study were on the other hand monobacillary. Our findings are nevertheless supported by a large-scale national ICU study from England, that found AIE to be the infection category with the highest hospital mortality in sepsis [94]. We have not found similar adjusted calculations of focus-dependent risk of mortality from sepsis in other prospective studies with inclusion of non-ICU treated patients. ICU-based studies are not consistent in this matter [192], with the exception that GUIs are almost invariably reported to have a higher survival rate than other infections [77, 94, 95, 110, 193, 194]. A large French ICU study has elucidated a possible explanation for the divergent results among previous ICU studies [191]. They found no association between site of infection and mortality in a large series of sepsis in a 10 year prospective observational cohort. Similar conclusions were also drawn for detection of microbiological etiology and mortality. The researchers adjusted for both severity of illness and organ dysfunctions (SAPS II and SOFA score), in addition to appropriateness of initial antimicrobials which was confirmed to be the only independent predictor of outcome. The remaining question is whether or not it is correct to consider severity stratification in this matter. The French study indicates that there is no explicit impact on survival when the various infections and/or pathogens reach the same level of severity. However, overlooking the fact that there are dissimilar risks of both sepsis development and sepsis severity among different infections seems in our opinion to be of limited clinical value.

A more uniform finding in sepsis studies is that the timing of initial antimicrobial therapy matters [46]. We found that a delay of ≥ 6 hours was associated with an increased mortality rate. A high-publicity North-American study have described that

each hour of delayed administration of antibiotics from the first hour after septic shock recognition was associated with a continuous decrease in survival [43]. Like us, several subsequent studies failed to produce similar conclusions [42, 195, 196], but corresponding findings have now been produced in three large retrospective analyses and thus strengthened the recommended urgency in antimicrobial administration substantially [41, 138, 197]. Further restricted analyses presented in our original publication (paper I) produced a small but significant impact in multivariable statistics of hourly delays on hospital mortality also with our data. In brief, variables such as a small sample size, the heterogeneity of the population studied, accounting for antimicrobial susceptibility or not, and different definition of index time points are likely biases in this question [46].

We also found that use of antibiotics prior to hospitalization had a negative relation to survival. Two other studies have concluded that antibiotic therapy within the last 30 days before sepsis admission was independently associated with administration of inadequate agents [198, 199]. One of these studies also calculated that to prevent a single fatality from sepsis, the number needed to treat with adequate antimicrobial therapy was solely four cases [199]. Further, inadequate regimens were associated not only with excess mortality but also increased ICU and hospital LOS in survivors in another study [200]. Thus, although the sample size in our study was small, our result is probably credible.

Two final independent predictors for hospital mortality in our prospective study were severe underlying illness in the form of malignancy and cardiovascular disease. Most cancer types have both a higher risk of and increased mortality from sepsis compared to non-cancer patients [201]. We have not found specific investigations on sepsis patients with pre-existing cardiovascular disease. However, there are currently focus on cardiovascular events in sepsis survivors, which comes up as one of the major reasons for their increased long-term risk of death [202-204].

In the prospective study, we observed that an increase in age had a tendency towards a parallel increase in hospital mortality in univariable analysis (paper I), but it was not statistically significant like in other settings [205]. This could be due to a relatively small sample size. Patients ≥ 75 years of age had a significant higher burden of

cognitive impairment, on average one extra comorbidity and their creatinine level was significantly higher at admission than in younger patients (data not shown). It should however be kept in mind that administration of antimicrobial therapy was significantly more delayed in this subgroup. Thus, we find reason to question whether previous results are explained by host factors alone. Like in other similar settings, hospital mortality increased with age in the retrospective study (paper III) without controlling for confounding factors [58, 70, 77]. Furthermore, we did not find any significant gender disparities in this thesis, neither in hospital (paper I and III) nor long-term survival (paper II). Previous large epidemiologic studies have been disparate in this matter, making it difficult to draw any conclusions based on our results alone [132, 206-208].

To estimate the impact sepsis has on all-cause mortality, several studies have analyzed data from multiple causes of death registries [209-212].This approach is well-known to underestimate sepsis-related mortality in comparison to administrative datasets [213]. In the retrospective study (paper III) we calculated that sepsis contributed to 1 in every 8 hospital deaths during 2011 and 2012. In contrast, The Norwegian Cause of Death Registry only superficially describes sepsis as a cause of death in their annual report [214]. Likewise, a corresponding report from the U.S. specifies that sepsis caused 1.5% of total deaths in 2014, while two U.S. retrospective code-based investigations of hospital mortality have reported that sepsis contributed to 1 in every 2 to 3 deaths and 18.5% of national hospital deaths respectively, the latter restricted to first-listed diagnoses [215-217]. All of the U.S. estimates adhered to the previous definition of sepsis and included cases with no evidence of organ dysfunction. However, the proportion of fatalities among our primary search (i.e. selection of sepsis, infection, or SIRS codes), 29.5% (data not shown), is comparable to the similarly conducted U.S. study [216]. Unfortunately we were only able to estimate sepsis' influence on total hospital deaths and not its contribution to population-level mortality in Norway, because identification of non-hospitalized afflicted subjects are not possible.

5.2.8.2. Long-term survival after hospitalization for sepsis in Norway

Long-term survival was described in our prospective cohort only and therefore limited to community-acquired sepsis (paper I and II). All-cause mortality was 34.5% after one and 58% after five years. Out of hospital survival was independently affected by age but not by care level during index hospitalization, yet the non-ICU treated hospital survivors experienced two-fold the mortality as ICU treated subjects after hospital discharge. Our results are limited due to a small sample size, however, numerous studies have encountered resembling patterns of outcome in sepsis survivors [151]. It has long been known that these survivors have a long-lasting increased risk of mortality compared to the general population or cohorts of patients hospitalized for other conditions [152, 164]. This has also been studied explicitly for community acquired sepsis [68, 115, 218], but the most comprehensive investigation were performed with inclusion of cases without organ failure [218]. Nevertheless, it has only recently been established that these observed poor outcomes are truly influenced by the sepsis episode, rather than pre-existing factors such as comorbidities or hospital admittance in general (i.e. similar events would have occurred if the patients were hospitalized for another reason) [219]. Such knowledge is of importance should targeted interventions to reduce the excess mortality be invented. Two studies, one based on a longitudinal prospective cohort in the U.S. and one retrospective nationwide survey from Taiwan, have strengthened the evidence for a causal linkage to sepsis itself by use of propensity score matching to adjust for possible confounding variables [66, 203]. Both studies performed comparison with matched controls from the general population as well as patients hospitalized without sepsis, and their findings were confirmed up to five years after hospital discharge. A prospective Canadian study that focused on previously healthy subjects with ICU admittance for sepsis also came to similar conclusions with an average follow-up of ten years [152]. Further extenuating the severity of the latter observations is that the excess mortality in sepsis survivors was greatest in the youngest subgroup (patients < 60 years of age). Analogue to their high long-term mortality, sepsis survivors are invariably found to carry more comorbidity than controls. They have a higher occurrence of cardiovascular events [202-204], cognitive impairment and functional disability [150],

and approximately 60% experience a new hospitalization during the first year after sepsis discharge, most often due to infection [167]. The underlying biological mechanisms for the increased morbidity and accelerated mortality are currently not established. Studies imply that epigenetic regulation is a mechanism of immunosuppression in sepsis survivors [220, 221]. Epigenetic alterations could be a part of accelerated aging, postulated as a potential mechanism for impaired immune function, development of chronic illness and general frailty in these patients. Also, exposure to antimicrobials and critical illness may damage the gastrointestinal microbial flora and constitute a pathway for secondary infections and rehospitalization in addition to immunosuppression [222]. Last, cognitive impairment has been suggested to be second to persistent neuronal inflammation affecting the central nervous system, or simply originate from degeneration of neurons induced by sepsis-associated encephalopathy and brain hypoperfusion [223].

6. CONCLUSIONS AND FUTURE PERSPECTIVES

This thesis confirms that sepsis is frequent in Norway, with afflicted cases occupying as many as 3.5% of total somatic inpatient days during the years 2011 and 2012. The incidence is considerably higher than the previous Norwegian estimate from 1999, most prevailing among the elderly, and significantly higher among men than women. Based on official population projections from Statistics Norway (Figure 5) there is reason to believe that this trend will continue throughout the coming years. Further, we have shown that sepsis is contributing to a high number of hospital deaths, implying that improvements in treatment and survival could influence population mortality in the future. It is thus desirable that sepsis receives greater attention in official Norwegian death statistics.

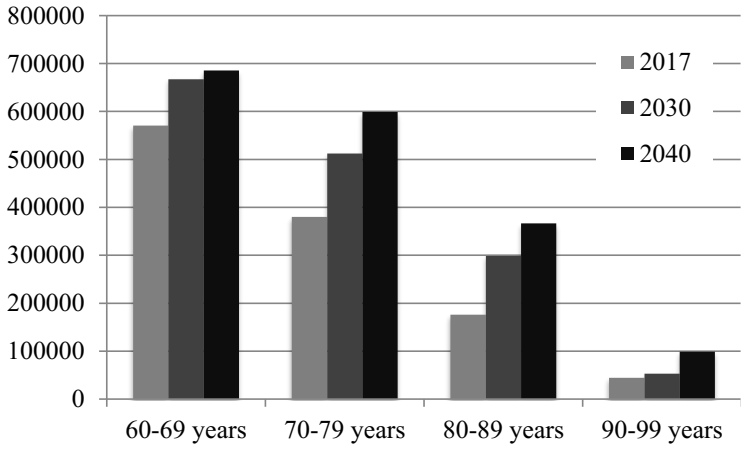

Figure 5: Norwegian population projections for inhabitants 60 to 99 years of age in the calendar years 2017, 2030 and 2040. Data from [154].

Sepsis is a medical emergency and has traditionally been associated with critical care settings. We have shown that a large proportion of sepsis patients never receive intensive care treatment and we have described this cohort and their ICU-treated counterpart. Although we were not able to severity stratify the respective cohorts to present an unbiased comparison, our description may still be useful for future health

care priorities. Considering the different mortality rates in favor of the non-ICU group, we find reason to encourage the allocation of selected sepsis patients to high dependency units; yet there is still need for future studies accounting for illness severity. On the other hand, we found several points that need improvement when evaluating the handling of sepsis patients at admission to our emergency department. Areas that should receive thorough attention are identification and handling of less frequent infection categories (i.e. not respiratory and urinary tract infections), including proper microbiological sampling and choice of empirical treatment, as well as the effort put into the oldest sepsis patients.

Throughout the current work we have highlighted several important limitations of existing research in the field of sepsis epidemiology. However, irrespective of these weaknesses there is no doubt that sepsis is one of the most common forms of severe illness today. Its clinical presentation and disease course is variable, influenced by multiple qualities such as the causative pathogen, host factors, preexisting medication and the timing and nature of provided care. The common denominator is a dysregulated host response to infection, where increasing insight into its underlying processes now points towards an area of personalized medicine for sepsis patients [59]. Already a decade ago, prominent researchers called for a rethinking in this direction [224]. Interesting concepts include endothelial and epithelial barrier recovery, mitochondrial sparing agents, immune-stimulating agents to resolve immunosuppression, extracorporeal blood purification techniques to control hyperinflammation, and other strategies to clear extracellular histones that are important parts of the DAMP response (Figure 6) [39, 221, 225, 226]. Hopefully this approach will have greater success than the preceding years' trials.

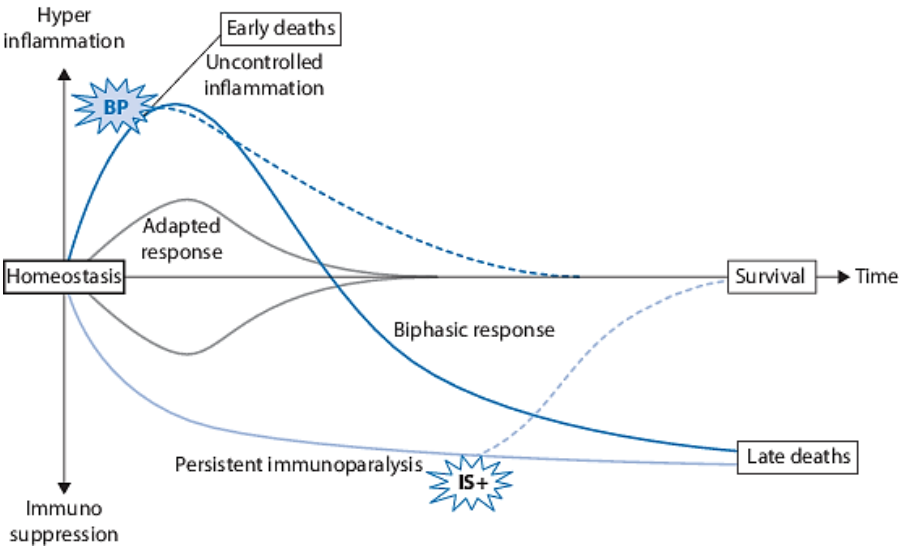

Figure 6: Host immune response to sepsis and impact of immunomodulation therapies. *Continuous lines*: possible patient immune status; *dotted lines*: potential effects of therapies; BP: blood purification techniques; IS+: immunostimulant drugs.

Nevertheless, sepsis is indisputably an infectious disease, where antimicrobial treatment will always be of paramount importance. Efforts to reduce the development of resistant microbes are now more important than ever before. In the end, the greatest challenge in sepsis will not only remain, its relevance will increase in parallel with the forthcoming expansion of the elderly population (Figure 5). That is to know when to keep hands-off and remember a famous statement by John C. Marshall:

"*What was the old name for severe sepsis? Natural causes*" [61].

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ERRATA

Paper I:

- The word multivariate is used instead of multivariable.
- There is an error in the estimated rate of sepsis patients per 1000 hospital admissions, which is corrected in the summary of the results herein. The reason for this was an incorrect denominator which included day patient stays in addition to overnight admissions. In this relation, we acknowledge that "hospital incidence" is no formal term, and have therefore now presented the percentage of sepsis admissions among total somatic hospitalizations in patients >15 years.
- The interpretation of ORs is incorrect in the section Antimicrobial agents, where the wording "risk" should be replaced by "odds".

PAPERS I - III

I

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RESEARCH ARTICLE Open Access

Aetiology, antimicrobial therapy and outcome of patients with community acquired severe sepsis: a prospective study in a Norwegian university hospital

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Abstract

Background: Severe sepsis is recognized as an inflammatory response causing organ dysfunction in patients with infection. Antimicrobial therapy is the mainstay of treatment. There is an ongoing demand for local surveillance of sepsis aetiology and monitoring of empirical treatment recommendations. The present study was established to describe the characteristics, quality of handling and outcome of patients with severe sepsis admitted to a Norwegian university hospital.

Methods: A one year prospective, observational study of adult community acquired case-defined severe sepsis was undertaken. Demographics, focus of infection, microbiological findings, timing and adequacy of empirical antimicrobial agents were recorded. Clinical diagnostic practice was evaluated. Differences between categorical groups were analysed with Pearson's chi-squared test. Predictors of in-hospital mortality were identified in a multivariate stepwise backward logistic regression model.

Results: In total 220 patients were identified, yielding an estimated annual incidence of 0.5/1000 inhabitants. The focus of infection was established at admission in 69%. Respiratory tract infection was present in 52%, while genitourinary, soft tissue and abdominal infections each were found in 12-14%. Microbiological aetiology was identified in 61%; most prevalent were *Streptococcus pneumoniae*, *Escherichia coli* and *Staphylococcus aureus*. Independent predictors of in-hospital mortality were malignancy, cardiovascular disease, endocarditis, abdominal infections, undefined microbiological aetiology, delay in administration of empirical antimicrobial agents ≥ 6 hours and use of inadequate antimicrobial agents. In patients ≥ 75 years, antimicrobial therapy was less in compliance with current recommendations and more delayed.

Conclusions: Community acquired severe sepsis is common. Initial clinical aetiology is often revised. Compliance with recommendations for empirical antimicrobial treatment is lowest in elderly patients. Our results emphasizes that quick identification of correct source of infection, proper sampling for microbiological analyses, and fast administration of adequate antimicrobial agents are crucial points in the management of severe sepsis.

Keywords: Severe sepsis, Epidemiology, Aetiology, Antimicrobial therapy, Compliance, Outcome

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Background

Sepsis is recognized as a dysregulation of the inflammatory response in patients with infection. Progression to severe forms with organ dysfunction develops in one out of three patients, commonly resulting in long-term hospitalization and death [1,2]. Algorithms for identification and management of severe infection hence emphasize recordings of vital signs and laboratory data, aiming at discovering circulatory failure and other organ dysfunctions at an early stage [3,4]. In recent years, one of the main focuses in sepsis related research has been on candidate biomarkers in the host and their possible role in targeted therapy. However, definite novel therapeutic approaches have not been established and optimized anti-infective therapy is still the mainstay of treatment in severe sepsis. Delayed administration of the initial dose of antimicrobial agents, the adequacy of antimicrobial therapy and, where applicable, delayed surgical source control, are all independent prognostic factors [5-8]. Care bundles with guidance on how to diagnose and handle affected patients, including up-to-date recommendations on empirical treatment, therefore emerges as one of the most important measures to improve outcomes in sepsis. In 2007, Llewelyn and Cohen addressed the relevance of monitoring the microbial epidemiology of sepsis on a local basis [9]. Based on such knowledge, empirical recommendations may be customized. Accordingly, we established the present study of adult community acquired severe sepsis to describe the occurrence, characteristics and handling of affected patients admitted to our hospital. Secondary objectives were to evaluate our physicians' compliance with local guidelines and to identify potential predictors of in-hospital mortality in severe sepsis.

Methods

Study setting

Haukeland University Hospital is serving as a local hospital with approximately 350.000 inhabitants in the catchment area. It is also a tertiary care referral center in western Norway, with a population of 1.1 million inhabitants. The current investigation was a one year prospective, case defined observational study of patients hospitalized in the period from January 1st through December 2008. Enrollment of patients took place in the high dependency unit at the Division for infectious diseases, Department of Medicine, in the general intensive care unit (ICU) at the Department of Anesthesia and Intensive care, and in the combined intensive care and high dependency unit at the Department of Cardiology.

Patient selection

All subjects transferred from the emergency department (ED) to any of the three units were screened for severe sepsis according to consensus criteria [3,4]. Patients older than 15 years of age hospitalized due to community acquired infection, including patients transferred from affiliated hospitals, were included if they developed severe sepsis within 24 hours of admission to the primary institution. Five patients were not recognized within 24 hours, but suspected to have non-infectious conditions. However, they were identified with delay and included, as their fulfillment of inclusion criteria within the first 24 hours of hospitalization was documented. Daily screening in the three units involved were performed. Patients were evaluated for eligibility by use of admission records, patient charts and inquiries with senior physicians at the respective wards. All of the eligible subjects were discussed in consensus meetings within the group of co-authors before a final decision of inclusion was made.

Data collection and follow-up

Clinical data were registered prospectively until hospital discharge or in-hospital death, using predefined case report forms. Information was collected from medical records, patient charts, and the intensive care electronic monitoring system IntelliVue Clinical Information Portfolio (ICIP, Philips Medical Systems, Eindhoven, the Netherlands). The following parameters were recorded at admission; time and date, department affiliation, demographics, comorbidities, suspected focus of infection, heart rate, respiratory rate, blood pressure, body temperature and Glasgow coma scale (GCS). Laboratory results were registered continuously. During the follow-up, data on organ dysfunction and adjunctive sepsis therapies was recorded. Timing and adequacy of antimicrobial agents was evaluated together with their appropriateness according to local recommendations. Results from blood cultures and microbiological analyses of urine, abscess drainage, sputum, feces and cerebrospinal fluid were collected. Possible contaminants of samples were excluded from analysis. Antimicrobial susceptibility patterns of cultured pathogens were registered when available. At discharge a final diagnosis was established by one consultant (SS), based on retrospective evaluation of all available records, clinical, microbiological, laboratory and medical imaging data. Data from medical records and patient charts was verified before it was entered in a local database. The main outcome measure was the in-hospital case fatality rate (CFR). We also calculated the 28-day all-cause mortality rate. Long-term survival was assessed after four years.

Calculation of incidence and mortality rate

The population incidence and the 28-day all-cause mortality rate was calculated based on the number of inhabitants > 15 years in the local catchment area in the year 2008. Patients transferred from affiliated hospitals were

excluded from this estimation. Incidence per hospital admissions was calculated from total cases in the study.

Statistical analyses

Data were analyzed using PASW Statistics 18 software (SPSS Inc., Chicago, Ill. USA). Differences between categorical groups were analyzed with Pearson's chi-squared test (χ^2). To identify predictors of outcome, univariate logistic regression analyses of factors previously reported to be associated with mortality was performed. Variables with P values < .10 were entered into a multivariate stepwise backward model. Results from the logistic regression analyses are reported as odds ratios (ORs) with 95% confidence intervals (CIs) from the unadjusted (univariate) models, the fully adjusted model (step 1 in backward stepwise regression), and final model (4th and last step in backward stepwise regression) with p-values from the likelihood ratio test. For the latter two models the results of Hosmer-Lemeshow's goodness-of-fit-test are reported. All variables in the logistic regression analyses presented in table form are categorical. We additionally tested for linear trend across age groups with 15 years intervals, with time to administration of the initial antimicrobial agents assessed as a continuous variable measured in hours (with exclusion of two extreme outlying values > 100 hours) and with time assessed as a continuous variable after logarithmic transformation. Long-term survival was compared across age groups by a Kaplan-Meier plot with log rank computation results. Overall, two sided P values < 0.05 were considered significant.

Ethical considerations

The study was approved by the Regional Committee for Medical and Health Research Ethics, Health Region West (REK-Vest, case number 2010/165).

Results

Base-line characteristics

A total of 220 patients with community acquired severe sepsis were identified, corresponding to an annual incidence of 2.2/1000 hospital admissions and 0.5/1000 inhabitants. Median age was 67 years and there was a small predominance of male patients (53%). Significant comorbidity was present in 90%.

Focus of infection

A final clinical diagnosis was established in all patients at discharge (Table 1). At admission, the correct primary focus of infection was identified in 69%. The focus was considered unidentified in 16%, an incorrect focus was suggested in 11%, whereas the remaining 4% were not suspected to have infection at admission.

The level of diagnostic precision differed depending on the nature of the infection. Respiratory tract infection (RTI) was e.g. suspected in 101 subjects at admission, of whom 93 were later confirmed while 8 turned out to have another focus. Overall, RTI was verified in 115 patients and among these, 22 cases were missed at admission. As follows, 81% of actual RTIs were assigned with a correct diagnosis in the ED. In the less frequent causes of sepsis the level of precision was lower (Table 1).

Microbiology

Microbiological tests were performed in 212 of 220 patients. A plausible pathogen was identified in 61% of tested subjects, with a total of 171 positive tests all together (Table 2). Gram-positive microbes constituted 57%. Overall, *Streptococcus pneumoniae* was most prevalent, closely followed by *Escherichia coli*, *Staphylococcus aureus* and alpha hemolytic streptococci. Blood cultures were obtained in 198 cases. Of these, 37% were positive, most often with *E. coli*, *S. pneumoniae* or *S. aureus* respectively.

Table 1 Suspected, confirmed and proportion of correct identified focus of infection in community acquired severe sepsis (n (%))

Infection	Suspected at admission[a]	Confirmed at discharge[a]	Correct at admission[b]
Respiratory	101 (45.9)	115 (52.3)	93 (80.9)
Genitourinary	25 (11.4)	31 (14.1)	20 (64.5)
Soft tissue	23 (10.5)	27 (12.3)	18 (66.7)
Abdominal	16 (7.3)	26 (11.8)	13 (50)
Endocarditis	4 (1.8)	12 (5.5)	4 (33.3)
Bacteremia	2 (0.9)	5 (2.3)	1 [20]
CNS	4 (1.8)	4 (1.8)	2 (50)
Unknown	36 (16.4)	0 (0.0)	n.a.
Not suspected	9 (4.1)	n.a.	n.a.
Total	220 (100)	220 (100)	151 (68.6)

Abbreviations: CNS, central nervous system; n.a., not applicable.
[a]Percent calculated column-wise, from total cases.
[b]Percent calculated row-wise, from each infection category's total number of confirmed cases.

Table 2 Microbiological aetiology in community acquired severe sepsis (n)

	Total	Blood	Urine	Abscess drainage	Other
Gram-positive[a]	90	44	27	25	18
Streptococcus pneumonia	29	14	20[b]	0	5
Alpha hemolytic streptococci	18	7	0	6	7
Group A/C/G streptococci	13	6	0	9	1
Group B streptococci	2	1	0	1	0
Enterococci	6	3	2	0	2
Staphylococcus aureus	20	11	4	9	3
Staphylococcus caprae	1	1	0	0	0
Aerococcus viridans	1	1	1	0	0
Gram-negative[a]	55	32	21	8	9
Escherichia coli	27	19	13	3	3
Klebsiella	10	6	5	0	1
Enterobacter	1	1	0	0	0
Proteus	2	0	0	1	1
Other Enterobacteriaceae	5	2	3	1	0
Pseudomonas aeruginosa	2	1	0	1	1
Stenotrophomonas maltophilia	1	0	0	1	0
Neisseriae meningitides	2	2	0	0	0
Haemophilus influenzae	2	1	0	0	1
Haemophilus parainfluenzae	2	0	0	0	2
Unspecified gram negative rods	1	0	0	1	0
Anaerobic bacteria	17	6	0	3	9
Clostridium species	5	2	0	0	3[c]
Bacteroides species	5	3	0	1	2
Prevotella	4	0	0	2	2
Slackia exigua	1	1	0	0	0
Fusobacterium	1	0	0	0	1
Unspecified gram positive rods	1	0	0	0	1
Other	9	0	0	3	6
Candida species	7	0	0	3	4
Aspergillus species	1	0	0	0	1
Influenzavirus A	1	0	0	0	1
Patients with ≥1 positive test	129	74	40	23	29

Unless otherwise specified, numbers shown are all isolated microorganisms in category.
[a]Anaerobic species not included.
[b]Positive antigen tests in all 20 cases (14 cases were detected in antigen tests only).
[c]Detection of *Clostridium difficile* toxin A in all cases.

Among the most prevalent bacteria, resistance towards empirical antimicrobial regimens was observed in two isolates only. Both were ESBL-producing *E. coli*. Polymicrobial infections were found in 19% of test-positive patients, namely in eight soft tissue infections (STIs), six abdominal infections, six RTIs (aspiration in all cases) and four genitourinary infections (GUIs). Figure 1 shows the relationship between the focus of infection and the proportion of patients with confirmed microbiological aetiology. Fifteen subjects received antimicrobial treatment prior to hospitalization. Microbiological samples were obtained from all of them, yet a plausible pathogen was identified in only five cases.

Antimicrobial agents

Table 3 outlines the initial choice of empirical antimicrobial agents and the physicians' compliance with the recommendations for empirical treatment of severe sepsis

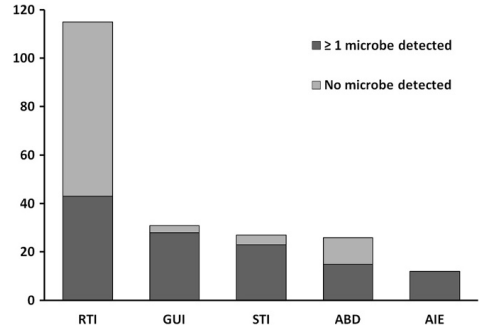

Figure 1 Microbiological identification rates in different infection categories (n). Relationship between focus of infection and the proportion of patients with confirmed microbiological aetiology. The most prevalent microbe was in RTI (respiratory tract infection); *Streptococcus pneumoniae* (28/43), GUI (genitourinary infection); *Escherichia coli* (16/28), STI (soft tissue infection); Group A/C/G streptococci (10/23), ABD (abdominal infection); *Escherichia coli* (8/15), and AIE (acute infectious endocarditis); *Staphylococcus aureus* (5/12).

at our hospital in 2008. Considering the suspected focus of infection at admission, the empirical choice of antimicrobial therapy was correct in 81% of the cases. Compliance with the recommendations was lower when patients were ≥ 75 years of age (χ^2 P = 0.029). When comparing the initial given agent with the confirmed focus at discharge, 76% had received empirical treatment appropriate for their final diagnosis. Susceptibility tests revealed that in the group with defined microbiological aetiology (n = 129), 82% had been treated with adequate antimicrobial therapy from the first dose. Compliance with the recommendations proved to have been better when adequate therapy was given, in comparison to when inadequate therapy was given (83% vs. 44%, χ^2 P < 0.001).

Median delay before administration of the initial dose of antimicrobial therapy was 2.8 hours after hospital admission. Compared to subjects with RTI, the delay was highest in abdominal infections (2.5 hours vs. 6.9 hours). Patients in the latter category had a 4.5 times greater risk of receiving their initial dose after more than six

Table 3 Choice of empirical antimicrobial regimen according to suspected and confirmed focus of infection and compliance with recommendations (n/n (%))

Focus of infection with recommended regimen	Suspected focus at admission Total cases/Cases with correct regimen[a]	Confirmed focus at discharge Total cases/Cases with appropriate regimen[a]
Respiratory[b,c]	100[d]/82 (82.0)	115[d]/96 (83.5)
penicillin G and *ciprofloxacin* or		
penicillin G and *gentamicin*[e,f]		
Genitourinary	25[d]/20 (80.0)	30[d]/24 (80.0)
ampicillin and *gentamicin*[f]		
Soft tissue	23/18 (78.3)	27[d]/18 (66.7)
penicillin G and *clindamycin* (+/− *gentamicin*)		
Abdominal	16[d]/11 (68.8)	26[d]/13 (50.0)
ampicillin and *gentamicin* and *metronidazol* or		
3rd generation cephalosporin and *metronidazol* or		
piperacillin-tazobactam or		
meropenem		
Endocarditis	4/3 (75.0)	12/7 (58.3)
penicillin G and *gentamicin* or		
3rd generation cephalosporin		
CNS	4/3 (75.0)	4/4 (100)
penicillin G and *3rd generation cephalosporin*		
Unknown/bacteremia	38[d]/34 (89.5)	5/5 (100)
penicillin G and *gentamicin* (+/− *metronidazol*)[e,f]		
Total	210/171 (81.4)	219/167 (76.3)

[a]Correct and appropriate regimen according to recommendations for empirical antimicrobial therapy in Haukeland University Hospital in 2008.
[b]One patient with a suspected and later verified respiratory tract infection died before antimicrobial therapy was implemented.
[c]Suspected atypical pneumonia: macrolide or doxycycline is added.
[d]Number of correct cases including one patient given meropenem as initial agent (n = 4 in total).
[e]If allergic to penicillin: clindamycin.
[f]If gentamicin is contraindicated: 3rd generation cephalosporin monotherapy.

hours of hospitalization (95% CI 1.8-11.0, χ^2 P = 0.005). Moreover, patients ≥ 75 years of age had a 2.3 times greater risk of receiving antimicrobial therapy beyond six hours compared to younger patients (95% CI 1.2-4.4, χ^2 P = 0.008). Among cases with no suspicion of infection at admission, the delay was 13 – 75 hours.

Outcome

Table 4 shows case fatality rates (CFRs) for subgroups of patients and predictors of outcome in uni- and multivariate logistic regression analyses. High CFRs were seen in patients with malignancy or cardiovascular disease. In the multivariate analysis, patients with confirmed endocarditis and abdominal infections had a significantly greater risk of death compared to RTI. Detection of microbiological aetiology and adequate antimicrobial treatment increased survival. Mortality was increased when antimicrobial agents had been given before hospital admission and when time to administration of the initial in-hospital dose of antimicrobial agents was more than six hours. There were not significant results in multivariate analyses with cut-offs below six hours or when testing for linear trend in mortality according to hourly increasing delays of antimicrobial agents. When limiting the latter analysis to patients receiving appropriate empirical therapy (adequate antimicrobial agents in cases with detection of a plausible pathogen, and correct empirical antimicrobial agents according to Hospital guidelines in patients with no detection of a pathogen, n = 178) there was a small significant impact also in multivariate analysis (p = 0.001, OR 1.06, 95% CI: 1.02 to 1.09). In univariate analyses, patients with a correctly identified source of infection at admission and patients receiving appropriate empirical antimicrobial agents according to Hospital guidelines had a higher chance of survival. However, these findings could not be validated by multivariate analysis. A tendency towards greater mortality with increasing age was observed, but was not statistically significant. Replacing age categories in Table 4 with trend across age groups provided a similar non-significant result in multivariate analysis, as did categorization of patients into two groups on the basis of age below versus ≥75 years. Total in-hospital CFR in this study was 25%. The 28-day CFR was 24.5% and the 28-day all-cause mortality rate was 13/100 000 inhabitants per year. One-year mortality was 34.5%. A Kaplan-Meier curve on survival is presented in Figure 2.

Discussion

We estimated the annual incidence of community acquired severe sepsis in our hospital to be 2.2/1000 admissions and 0.5/1000 inhabitants. In-hospital mortality was 25% and the 28-day all-cause mortality rate was 13/100 000 inhabitants per year.

Previous data on the occurrence of sepsis in Norway is limited to a retrospective study using data from the Norwegian Patient Registry, in which the total incidence of severe sepsis was calculated to 3.0/1000 admissions and 0.47/1000 inhabitants [10]. In contrast to this study, we did not include nosocomial sepsis which constitutes approximately 50% of all cases [5,6,11-14]. During three months prior to the present study we performed a prospective pilot survey of case-defined sepsis in our ED. Subsequent comparison with cases identified retrospectively by discharge ICD-10 codes revealed that 50% of all sepsis-cases were missed when using the retrospective method alone (Nygård, unpublished results). Thus, the calculation in our current prospective study probably represents a more accurate estimation of the Norwegian incidence of community acquired severe sepsis than previous results. Previous prospective studies with systematic inclusion from both ICUs and non-ICUs, reporting details on the occurrence of severe sepsis, are to our knowledge limited to a single survey from Spain [15]. They calculated an annual incidence of 1.0/1000 inhabitants, including nosocomial cases. Other studies of community acquired severe sepsis have used different methods for patient inclusion, and many do not offer data on incidence or are not applicable for such purpose [16-22].

The respiratory tract was the most frequent origin of infection in our patients. This is consistent with results from other studies [5,11-14,23-25]. We diagnosed abdominal infections less frequently, while GUI and STI were found more often than in many previous reports [6,11-13,25-27]. However, studies with inclusion of patients treated outside ICUs have found a distribution of diagnoses more similar to ours [15,16,23,28,29]. Patients with abdominal infections have been shown to have a high demand for intensive care treatment [11]. There are in addition more abdominal infections in nosocomial compared to community acquired sepsis [15,30]. In our study most patients with this diagnosis were treated in an ICU, whereas patients with GUI on the contrary mainly were treated outside ICUs. Moreover, patients with abdominal infection had a prolonged length of stay (data not shown). In many studies on sepsis epidemiology, frequencies are estimated on the basis of prevalence data from ICUs only. Together, these observations suggest that distribution of various infections is influenced by study design, e.g. our low occurrence of abdominal infections is likely conditional to inclusion of patients from outside ICUs.

A likely pathogen has been found in 60-75% of eligible subjects in other studies on sepsis [5,6,13,19,24,31], comprising positive blood cultures within the range of 22-37% [5,6,12,19,30-33]. This is comparable to our data. In line with related observations, we identified more Gram-positive than Gram-negative bacteria [1,12,24].

Table 4 In-hospital mortality in patients with community acquired severe sepsis at Haukeland University Hospital in 2008

	All[a]	Non-survivors		Unadjusted models			Fully adjusted model[b]			Final model[c]		
Characteristic	**n**	**n**	**(%)**	**OR**	**95% CI**	**P value**	**OR**	**95% CI**	**P value**	**OR**	**95% CI**	**P value**
Gender						0.240						
Male	117	33	(28.2)	1.00	Reference							
Female	103	22	(21.4)	0.69	(0.37, 1.29)							
Age (years)						0.065			0.619			
16-30	18	1	(5.6)	1.00	Reference		1.00	Reference				
30-45	22	4	(18.2)	3.78	(0.38, 37.28)		0.99	(0.07, 14.18)				
45-60	36	8	(22.2)	4.86	(0.56, 42.30)		2.27	(0.19, 26.64)				
60-75	68	16	(23.5)	5.23	(0.65, 42.43)		2.88	(0.28, 29.54)				
≥75	76	26	(34.2)	8.84	(1.11, 70.18)		3.09	(0.28, 33.54)				
Comorbidity												
None	23	1	(4.3)	0.12	(0.02, 0.92)	0.005						
Hypertension	91	18	(19.8)	0.61	(0.32, 1.17)	0.130						
Cardiovascular	107	35	(32.7)	2.26	(1.20, 4.24)	0.010	2.18	(0.85, 5.61)	0.101	3.29	(1.45, 7.48)	0.003
Pulmonary	61	14	(23.0)	0.86	(0.43, 1.72)	0.662						
Diabetes	38	9	(23.7)	0.92	(0.40, 2.08)	0.836						
Malignancy	31	13	(41.9)	2.53	(1.15, 5.58)	0.025	5.97	(1.96, 18.19)	0.001	5.50	(1.92, 15.78)	0.001
Dementia	17	6	(35.3)	1.71	(0.60, 4.88)	0.324						
Psychiatric	51	9	(17.6)	0.57	(0.26, 1.27)	0.155						
Substance abuse	31	6	(19.4)	0.69	(0.27, 1.77)	0.423						
Other[d]	74	27	(36.5)	2.42	(1.29, 4.53)	0.006	2.52	(1.11, 5.70)	0.025	2.43	(1.10, 5.35)	0.026
Correct suspected focus of infection						0.020			0.606			
Yes	152	31	(20.4)	1.00	Reference		1.00	Reference				
No	68	24	(35.3)	2.13	(1.13, 4.02)		0.79	(0.33, 1.91)				
Confirmed focus of infection						0.007			0.003			0.001
Respiratory	115	25	(21.7)	1.00	Reference		1.00	Reference				
Genitourinary	31	4	(12.9)	0.53	(0.17, 1.67)		0.41	(0.08, 2.21)		0.47	(0.09, 2.39)	
Soft tissue	27	6	(22.2)	1.03	(0.38, 2.82)		2.04	(0.55, 7.60)		2.42	(0.68, 8.68)	
Abdominal	26	12	(46.2)	3.09	(1.27, 7.51)		2.95	(0.87, 10.03)		3.54	(1.09, 11.43)	
Endocarditis	12	7	(58.3)	5.04	(1.47, 17.25)		17.43	(2.74, 111.06)		18.94	(3.45, 104.06)	
Bacteremia	5	0	(0.0)	0.00	(0.00,)		0.00	(0.00,)		0.00	(0.00,)	
CNS	4	1	(25.0)	1.20	(0.12, 12.04)		9.22	(0.71, 118.97)		7.66	(0.63, 93.73)	
Microbiological samples						0.008			0.028			0.025
Positive	129	24	(18.6)	1.00	Reference		1.00	Reference		1.00	Reference	
Negative	83	26	(31.3)	2.00	(1.05, 3.79)		3.58	(1.34, 9.55)		3.34	(1.29, 8.63)	
Not obtained	8	5	(62.5)	7.29	(1.63, 32.63)		2.91	(0.35, 24.09)		4.44	(0.60, 32.95)	
Empirical antimicrobial agents												
Suspected focus of infection						0.433						
Appropriate compliance	171	38	(22.2)	1.00	Reference							
Inappropriate compliance	39	11	(28.2)	1.38	(0.63, 3.02)							
Confirmed focus of infection						0.027			0.241			
Appropriate	168	35	(21.0)	1.00	Reference		1.00	Reference				

Table 4 In-hospital mortality in patients with community acquired severe sepsis at Haukeland University Hospital in 2008 *(Continued)*

Inappropriate	52	19	(36.5)	2.17	(1.10, 4.27)		0.79	(0.33, 1.91)				
Microbiological aetiology[e]						< 0.001						
Adequate	106	12	(11.3)	1.00	Reference							
Inadequate	23	12	(52.2)	8.55	(3.10, 23.58)							
In-hospital initial dose administered						0.002			0.051			0.046
<6 hours after admission	157	30	(19.1)	1.00	Reference		1.00	Reference		1.00	Reference	
≥6 hours after admission	54	22	(40.7)	2.91	(1.49, 5.71)		2.52	(1.00, 6.38)		2.48	(1.02, 6.02)	
Pre-hospital administration						0.059			0.055			0.041
No	205	48	(23.4)	1.00	Reference		1.00	Reference		1.00	Reference	
Yes	15	7	(46.7)	2.86	(0.99, 8.30)		4.13	(0.99, 17.21)		4.20	(1.08, 16.39)	

Abbreviations: OR: odds ratio; CI: confidence interval.
[a]n = 220.
[b]Includes all categories with P < 0.10 in the unadjusted analyses; n = 211; Hosmer-Lemeshow's chi-square = 12.38, df = 8, P = 0.135.
[c]From backward stepwise selection at significance level 0.05; n = 211; Hosmer-Lemeshow's chi-square = 3.18, df = 8, P = 0.923.
[d]Including chronic kidney, liver and rheumatic diseases.
[e]Not included in multivariate analysis due to a substantial number of not applicable cases (if included, significant in multivariate analysis).

Antigen- and toxin tests were included in our analysis of microbiological aetiology. A positive urinary antigen assay was the only laboratory documentation in 48% of subjects with *S. pneumoniae.* This is in accordance with a prospective report on community acquired pneumonia, where 44% of 171 cases with *S. pneumoniae* were diagnosed by urinary antigen detection alone [34]. In Norway, guidelines for pneumococcal vaccination of adults ≥ 65 years and pre-defined younger persons at risk have been established since 1996, but vaccine coverage has not been satisfactory. However, a pneumococcal conjugated vaccine has been a part of the routine vaccination program for children with nearly completely coverage since 2006. From this point there has been a marked decline in the number of cases with invasive *S. pneumoniae*, also among adults. Thus, the proportion of patients with severe sepsis originating from this microbe is probably decreasing.

The proportion of patients with detection of a plausible pathogen differed among the various origins of infection in our study. The detection rate was low in RTI and abdominal infection in particular. This is also previously

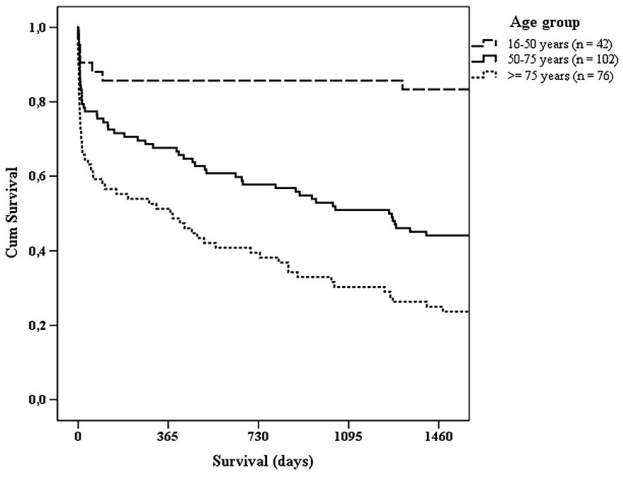

Figure 2 Long-term survival after community acquired severe sepsis. Kaplan-Meier curve on survival after community acquired severe sepsis in different age groups. Follow-up was four years after hospital admission for all 220 patients. Survival in all three groups were significant different according to Log rank test results (P = 0.000 in analysis of age group 16–50 vs. 50–75 and P = 0.001 in analysis of age group 50–75 vs. ≥75). Overall, four-year mortality was 55.5%.

documented [20,31]. Patients with negative microbiological samples had a significant greater risk of death than patients with positive samples. Although not significant in all categories, this result is consistent when stratification of infection categories is performed, supporting that the increased risk of death in cases with negative samples was retained throughout our multivariate model. Detection of a plausible pathogen gives the opportunity to administer validated adequate antimicrobial treatment. In subjects with negative microbiological samples, correct antimicrobial therapy can be delayed or not provided. An increased risk of death has been demonstrated in patients with severe infection receiving inadequate antimicrobial therapy [6,7,35-37]. In many of these studies multiresistant isolates were often encountered. We identified no isolates of MRSA, MRSE or VRE, and only two cases of ESBL-producing Gram-negative bacilli (of which one was even suspected, and treated accordingly, at admission). On the contrary, *S. pneumoniae* and *E. coli* were frequently identified. The CFRs in these two categories were low; 7 and 18.5% respectively (data not shown). Hence, a possible contributor to the different risk of death among patients with positive versus negative microbiological samples might be our high frequency of microbes with unproblematic resistance properties. Inability to tailor treatment with effective antimicrobial agents might also have influenced outcomes of the patients which received pre-hospital antimicrobial agents. In a study by Garnacho-Montero et al., previous antibiotic therapy within the last month was independently related to administration of inadequate antimicrobial therapy [6].

We were able to demonstrate a correlation between correct use of empirical antimicrobial agents and susceptibility in detected pathogens. It is therefore of concern that one in five patients did not receive the recommended regimen. One possible explanation for this is that sepsis is diagnosed on the basis of unspecific criteria, independent of primary focus, microbiological aetiology and host factors. Current diagnostic algorithms focus on identifying complications of an infection rather than its aetiology. The level of precision in establishing the focus of infection was variable and often low in our study. Only 17 of 38 patients with confirmed abdominal infection or endocarditis were assigned with the correct focus, and half of them received initial treatment as recommended. The longest delays before initiation of antimicrobial therapy were found in these two groups, and their hospital mortality was high. An evaluation of the quality of clinical diagnostic practice in severe sepsis, comparing the suspected focus at admission with a confirmed diagnosis at discharge, has to our knowledge not been published previously. We identified severe sepsis in nine subjects not suspected with infection at admission. Opposite, a study of the aetiology of illness in suspected severe sepsis found that 18% of the patients had noninfectious diagnoses mimicking sepsis [20]. Seen together these observations suggest a two-sided limitation in commonly used sepsis algorithms.

We found that a six hour delay or more in administration of the initial dose of antimicrobial treatment was associated with an increased risk of death, but could not demonstrate independent impact on mortality during the preceding hours, as reported by Kumar et al. in a study of patients with septic shock [5]. Other studies investigating the impact of early administration of antimicrobial therapy have also failed to demonstrate an hourly decrease in survival [36,38]. Some have demonstrated beneficial effects on survival with administration of antimicrobial therapy within the first hour [36,39]. Kumar et al. limited their inclusion to cases given effective antimicrobial therapy. Likewise, the beneficial effect found by Gaieski et al. was significant only when antimicrobial therapy was considered appropriate [36]. Analyses of our data with the same limitations as Kumar and Gaieski resulted in significant impact of hourly increasing time to administration of antimicrobial agents on mortality in multivariate analysis. However, the hourly effect was low. Since we have included a broad selection of the population with severe sepsis, ranging from septic shock to cases with other and less severe organ dysfunctions, our results concerning timing is inevitably influenced by the different levels of severity in our population. We were not able to severity stratify our patients and cannot investigate this matter any further.

In patients ≥ 75 years, antimicrobial therapy was less in compliance with current recommendations and more delayed. An age dependent risk of in-hospital mortality has been demonstrated in severe infection [40]. Following the results in our study, we question whether this is solely caused by host factors. Increasing age did not emerge as an independent risk factor. Subjects ≥ 75 years had on average one additional comorbidity, a significant higher presence of cognitive impairment and a significant higher creatinine level at admission than younger patients (data not shown). These data indicates that there were more potentially complicating factors among elderly patients. However, our Hospital guidelines are clear in terms of instructions on adjusting the doses of antimicrobial agents when needed, as well as recommending alternative treatment if the primary choice of drug is contraindicated. This was taken into account when we evaluated the level of compliance. Hence, we consider that there is room for improvements in the handling of our elderly patients, especially given the small difference in mortality after hospital discharge between patients aged 50–75 versus ≥75 years during the long-term follow-up (Figure 2).

Strengths and limitations

Major strengths of this study are the prospective design, inclusion throughout an entire year, a small group of dedicated investigators and recruitment of patients from both ICUs and non-ICUs. Major limitations are the sample size and a lack of severity stratification of the included patients. Consequently, statistical results are encumbered with uncertainties. Due to the high number of explanatory variables included in the logistic regression analysis and the screening and stepwise selection of variables in the reported results, over fitting is most likely present in the final model reported. As no formal adjustment for multiple testing has been performed, most emphasize should thus be given to the most significant predictors (i.e. with $P < 0.01$).

Conclusion

We have found a high incidence of community acquired severe sepsis in a Norwegian university hospital. Initial clinical aetiology was often revised and the diagnosis sometimes overlooked in the emergency department. Adequate antimicrobial therapy improved outcome, while undefined microbiological aetiology, endocarditis, abdominal infections and delayed administration of antimicrobial agents increased the risk of death. A need for improved handling of elderly patients was identified. Our results emphasizes that quick identification of correct source of infection, proper sampling for microbiological analyses, and fast administration of adequate antimicrobial agents are crucial points in the management of severe sepsis.

Abbreviations

ABD: Abdominal infection; AIE: Acute infectious endocarditis; CI: Confidence interval; CFR: Case fatality rate; ED: Emergency department; ESBL: Extended-spectrum beta-lactamase; GCS: Glasgow coma scale; GUI: Genitourinary infection; ICU: Intensive care unit; OR: Odds ratio; RTI: Respiratory tract infection; STI: Soft tissue infection.

Competing interests

The study has been financed by the Department of Medicine, Haukeland University Hospital. All the authors report no competing interests.

Authors' contributions

STN participated in the design of the study, inclusion of cases, data collection, statistical analyses and drafted the manuscript. NL participated in the design of the study, inclusion of cases, statistical analyses and helped to draft the manuscript. HF participated in inclusion of cases, statistical analyses and drafting of the manuscript. RF and OH participated in inclusion of cases and drafting of the manuscript. SS participated in all parts of the present work. All the authors contributed to and approved the final manuscript.

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II

An observational study of community-acquired severe sepsis comparing intensive care and non-intensive care patients

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Conflicts of interest
All authors declare that they have no competing interests.

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Background: Most studies of sepsis are from intensive care units (ICUs). We aimed to investigate community-acquired severe sepsis in a broader population, in order to compare patients treated in or outside an ICU .

Methods: We performed a 1-year prospective observational study with enrollment of patients from three units; a general ICU, a combined ICU/non-ICU and a medical ward with limited surveillance facilities. Hospital survivors were followed up for 5 years.

Results: Overall, 220 patients were included, of which 107 received ICU treatment. The majority of abdominal (77%, $P = 0.003$) and genitourinary (81%, $P < 0.001$) infections were found in ICU and non-ICU patients, respectively. Time to first antibiotic administration was longer in ICU-patients (median 3.5 vs. 2.0 h in non-ICU patients, $P = 0.011$). ICU developed more organ dysfunctions than non-ICU patients ($P < 0.001$), nevertheless supportive therapy with vasoactive drugs and non-invasive ventilation was documented in 22% and 27% of the latter. Median hospital length of stay was 15 vs. 9 days ($P = 0.001$), and hospital and 5-year mortality rates 35% vs. 16% ($P = 0.002$) and 57% vs. 58% ($P = 0.892$) among ICU and non-ICU patients, respectively. Increasing age (HR 1.06 (1.04, 1.07) per year, $P < 0.001$), not care level during hospitalization (HR 1.19 (0.70, 2.02), $P = 0.514$), influenced long-term survival.

Conclusion: Half of the subjects with community-acquired severe sepsis never received ICU treatment. Still, use of organ supportive therapy outside the ICU was considerable. Hospital mortality was higher, whereas 5-year survival was similar when comparing ICU with non-ICU patients.

Editorial Comment:
This study examined the course of patients with sepsis who did not receive treatment in the ICU. Approximately half of sampled patients meeting these (sepsis) diagnosis criteria received their care outside of the ICU. When compared to a simultaneous ICU-treated sepsis cohort, the long-term survival was similar.

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Severe sepsis is a major cause of long-term hospitalization and morbidity, recently estimated to contribute to one in every two to three hospital deaths in the United States.[1] Most of the studies regarding this condition have been performed from an intensive care unit (ICU) perspective. However, a substantial number of affected subjects are never admitted to an ICU, making our understanding of this patient group incomplete.[2–11] In order to describe the characteristics, ICU treatment rate, treatment intensity and outcome of patients with community-acquired severe sepsis in Haukeland University Hospital, we undertook an observational study with enrollment from different units. Our hypothesis was that a considerable number of these patients also in our hospital are handled outside an ICU. We have in this way, to the best of our knowledge, for the first time compared treatments administered to ICU vs. non-ICU-treated individuals with severe sepsis.

Methods

Definitions

Severe sepsis was defined by the presence of sepsis in conjunction with organ dysfunction.[12] We used a modified selection of the expanded diagnostic criteria presented by Levy et al. as criteria for organ dysfunctions:[13]

- Arterial hypotension (systolic blood pressure <90 mmHg or a mean arterial pressure decrease >40 mmHg)
- Hypoxemia (SpO_2 <90% while breathing air)
- Acute oliguria (urine output <0.5 ml/kg/h for at least 4 h)
- Increase in s-creatinine >50 μmol/l
- Lactic acidosis (pH <7.30 and s-lactate >4.0 mmol/l)
- Thrombocytopenia (platelet count $<100 \times 10^9$/l or a 50% reduction ≤3 days)
- Hyperbilirubinemia (s-bilirubin >70 μmol/l)
- Altered mental status (Glasgow Coma Scale <15 or if known cognitive impairment; clinical judgment)

Setting

This was a 1-year prospective, case-defined observational study of patients with community-acquired severe sepsis in a tertiary care referral center and teaching hospital in western Norway. Since 2003, the hospital has had common guidelines for initial handling of sepsis and severe sepsis. Full details of the study setting, inclusion criteria and data collection have been provided elsewhere.[14] Patients were included consecutively from 1 January through 31 December 2008. Enrollment took place in the following units: (1) a 10-bed general ICU at the Department of Anaesthesia and Intensive care; (2) a 12-bed combined ICU/non-ICU ward at the Department of Cardiology, composed of four fully equipped ICU beds and eight surveillance beds; and (3) a 13-bed ward at the Division for infectious diseases, Department of Medicine. Two of the 13 beds at the medical ward had surveillance facilities offering intra-arterial blood pressure monitoring and treatment with vasoactive drugs as well as non-invasive ventilation support. The non-ICU beds at the Department of Cardiology had the same facilities.

The three units are run by different clinical departments in separate units. They also differ with regard to nurse to patient ratio which was 0.43 in the Medical Ward, 0.71 in the combined unit and 1.0 in the general ICU. The latter had a dedicated on-call by intensivists, different from the other two units with on-calls from their respective departments. Only the general ICU had the possibility of giving continuous renal replacement therapy. In the current investigation, patients were separated into two cohorts according to their highest level of care, that is, if they were receiving treatment in an ICU bed at any time during their hospital stay or not (ICU vs. non-ICU level, Fig. 1).

Patient selection

All subjects transferred from the emergency department (ED) to any of the three units were screened for eligibility. Patients ≥16 years of age hospitalized due to community-acquired infection, including patients transferred from affiliated hospitals, were included if they developed severe sepsis within 24 h of admission to the primary institution. Unit affiliation was decided in the ED upon the attending physicians' discretion, based on clinical risk stratification and

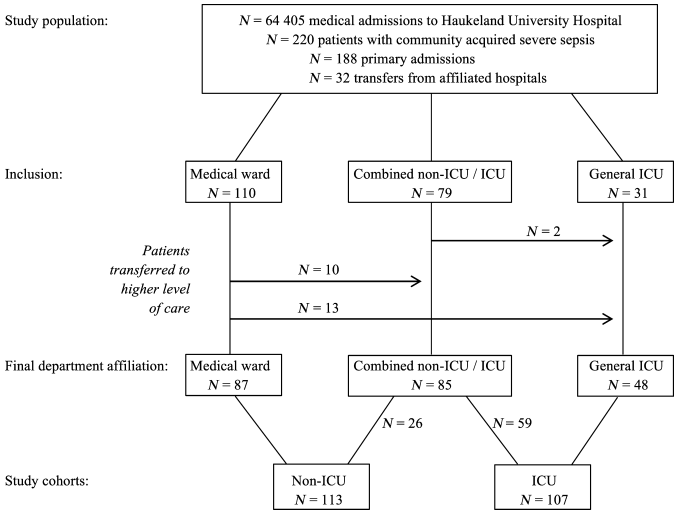

Fig. 1. Flowchart of the inclusion process and separation into study cohorts.

need for advanced organ support aided by the hospital's sepsis guidelines.

Data collection

Data were collected prospectively on a daily basis in the three participating units. Data from the ED and from affiliated hospitals before transfer were registered retrospectively. During surveillance of patients, variations in vital parameters, urine output and biochemical analyses were followed. Use of non-invasive or invasive ventilation support and administration of antimicrobial therapy, intravenous fluids, glucose-insulin, vasoactive drugs and corticosteroids was registered. Surgical treatment in relation to severe infection was documented. Simplified Acute Physiology Score II (SAPS II) was calculated in patients treated in an ICU-bed. Finally, total hospital and ICU length of stay (LOS) as well as hospital outcome were recorded. Hospital survivors were followed up for 5 years after discharge.

Statistical methods

Descriptive statistics for continuous variables are presented as mean ± standard deviation (SD) or median and interquartile range (IQR) and compared between groups with Student's unpaired *t*-test or the exact Mann–Whitney *U*-test when appropriate. Descriptive statistics for categorical variables are compared between groups with the exact Pearson's chi-squared test (χ^2) with odds ratios (ORs) and 95% confidence intervals (CIs). Binominal logistic regression analysis was performed, both simple (unadjusted) and multiple, to adjust for confounding variables. Variations in effects (ORs) were evaluated to control for influence of collinearity among the explanatory variables. All variables with a pre-specified plausible relationship with the dependent variable were included; both variables with a relationship in univariate analysis ($P \leq 0.05$) and those which did not reach statistical significance. Backward stepwise selection was used to identify a final simplified model including only predictors significant at the 0.05 level. Results are reported as ORs with 95% CIs and *P*-value from the likelihood ratio (LR) test. Hosmer–Lemeshow's goodness-of-fit test is reported for the final model. Survival is illustrated by Kaplan–Meier plots and compared between groups with log rank tests. Multivariable survival analysis was performed using Cox's regression model, and results are

presented as hazard ratios (HRs) with 95% CIs and *P*-value from the LR test. All tests were two-tailed and a *P*-value ≤0.05 was considered statistically significant. The statistical analyses were performed using SPSS software (IBM SPSS Statistics, version 22.0; Chicago, IL, USA).

Ethical approval

This study was initially approved by the privacy ombudsman at Haukeland University Hospital as a quality study in 2007. Later, an extended ethical application was sent to The Regional Committee for Medical and Health Research Ethics in Western Norway, which was approved (case number REK-West 2010/165).

Results

Baseline characteristics

In total, 220 cases with community-acquired severe sepsis were identified, of which 107 were included in the ICU cohort and 113 in the non-ICU cohort (Fig. 1). Baseline characteristics and clinical presentation according to care level is outlined in Table 1. There were no significant differences in gender or age distribution, but there was a tendency toward older age among non-ICU patients. Presence of underlying comorbidities was similarly distributed with the exception of dementia. Limitations of care were less frequent in the ICU cohort, where five patients were given a do-not-resuscitate order compared with 15 in the non-ICU cohort (χ^2 OR 0.32 (0.11, 0.92), $P = 0.034$). The number of fulfilled systemic inflammatory response syndrome (SIRS) criteria at admission did not differ.

Infection

The respiratory tract was the most frequent focus of infection at both care levels (Table 1). The majority of abdominal infections were found in ICU patients (77%, χ^2 OR 4.10 (1.58, 10.66), $P = 0.003$), whereas genitourinary infections most often were found in non-ICU patients (81%, χ^2 OR 0.21 (0.08, 0.53), $P < 0.001$). The different occurrence of these two infections was significant also in multivariable analysis. Twenty-four out of 27 patients with soft tissue infections were initially referred to non-ICU level; however, nine cases were subsequently transferred to an ICU. A confirmed pathogen was detected in 60 vs. 69 patients in the ICU vs. non-ICU cohort, respectively (χ^2 OR 0.81 (0.48, 1.39), $P = 0.50$).

Organ dysfunction

The median number of acute organ dysfunctions was 3 and 2 in ICU and non-ICU patients, respectively (IQR = 1 for both groups, $P < 0.001$). Patients receiving intensive care had a higher median s-creatinine and a lower urine output level (Table 2). They also developed more hypoxia, hypercapnia, hyperlactatemia and severe acidosis. In addition, their mean arterial blood pressure was lower. Average SAPS II score among ICU-treated patients was 52 ± 20 (95% CI (48, 56)). The distribution of acute organ dysfunctions is shown in Table 3.

Treatment

Treatment is specified in Table 3. Consistently, the intensity of treatment was significantly higher at ICU level. Organ supportive therapy was also documented at non-ICU level, however, only four non-ICU patients received both vasoactive drugs and non-invasive ventilation. Time from hospital admission to administration of the initial dose of antimicrobial therapy was longer at ICU level.

Resources and outcome

Median hospital LOS was 15 days at ICU and 9 days at non-ICU level ($P = 0.001$) (Table 4). Median ICU LOS was 6 days for eligible patients. The hospital case-fatality rate (CFR) was higher in ICU compared with non-ICU patients (35% vs. 16%, $P = 0.002$). ICU patients also had a higher mortality rate after 1 year (42% vs. 27%, $P = 0.024$), whereas 5-year mortality rates were similar in the two cohorts (57% vs. 58%, $P = 0.892$). Among patients admitted to the medical ward but subsequently transferred to an ICU, the hospital CFR was 44%, while it was 23% among non-ICU patients receiving organ supportive therapy. Kaplan–

Table 1 Baseline characteristics of ICU and non-ICU-treated patients compared by logistic regression analysis.

Characteristics	All *n* = 220	ICU *n* = 107	non-ICU *n* = 113	Unadjusted models OR	95% CI	*P*	Fully adjusted model* OR	95% CI	*P*	Final model† OR	95% CI	*P*
Gender												
Male	117	59	58	1.00	Reference	0.571			0.271			
Female	103	48	55	0.86	(0.51, 1.46)							
Age, years												
16–30	18	9	9	1.00	Reference	0.296	1.00	Reference	0.677			
30–45	22	13	9	1.44	(0.41, 5.07)		1.20	(0.29, 4.93)				
45–60	36	21	15	1.40	(0.45, 4.36)		0.85	(0.22, 3.21)				
60–75	68	34	34	1.00	(0.35, 2.83)		0.70	(0.20, 2.44)				
75	76	30	46	0.65	(0.23, 1.83)		0.51	(0.13, 1.95)				
Median (IQR)	67	64 (25)	69 (23)			0.056‡						
Mean ± SD	64	62 ± 19.2	66 ± 19.6									
Comorbidity												
Hypertension	91	48	43	1.32	(0.77, 2.27)	0.305	1.60	(0.82, 3.13)	0.168			
Cardiovascular	107	48	59	0.75	(0.44, 1.27)	0.275	0.90	(0.43, 1.89)	0.785			
Pulmonary	61	33	28	1.35	(0.75, 2.45)	0.315	1.32	(0.67, 2.60)	0.417			
Diabetes	38	17	21	0.83	(0.41, 1.67)	0.597	1.05	(0.45, 2.44)	0.914			
Malignancy	31	18	13	1.56	(0.72, 3.36)	0.257	1.31	(0.54, 3.20)	0.554			
Dementia	17	2	15	0.12	(0.03, 0.56)	0.001	0.16	(0.03, 0.89)	0.014	0.15	(0.03, 0.73)	0.005
Psychiatric	51	23	28	0.83	(0.44, 1.56)	0.564	0.67	(0.32, 1.41)	0.290			
Substance abuse	31	17	14	1.34	(0.62, 2.86)	0.456	0.91	(0.38, 2.22)	0.843			
Other	74	34	40	0.85	(0.49, 1.49)	0.570	0.87	(0.45, 1.68)	0.676			
SIRS criteria §												
0	7	3	4	0.86	(0.18, 4.07)	0.549	0.93	(0.13, 6.48)	0.800			
1	20	12	8	1.72	(0.64, 4.62)		1.54	(0.50, 4.76)				
2	57	31	26	1.37	(0.70, 2.67)		1.26	(0.58, 2.74)				
3	88	41	47	1.00	Reference		1.00	Reference				
4	44	18	26	0.79	(0.38, 1.65)		0.68	(0.29, 1.58)				
Missing	4	2	2	1.15	(0.15, 8.51)		0.74	(0.09, 6.33)				
Infection												
Respiratory	115	54	61	1.00	Reference	0.001	1.00	Reference	0.011	1.00	Reference	0.004
Genitourinary	31	6	25	0.27	(0.10, 0.71)		0.32	(0.11, 0.89)		0.30	(0.11, 0.81)	
Soft tissue	27	15	12	1.41	(0.61, 3.28)		1.20	(0.48, 2.99)		1.35	(0.58, 3.18)	
Abdominal	26	20	6	3.77	(1.41, 10.06)		3.50	(1.16, 10.58)		3.40	(1.27, 9.11)	
Endocarditis	12	6	6	1.13	(0.34, 3.71)		1.30	(0.35, 4.77)		1.61	(0.34, 3.92)	
Bacteremia	5	3	2	1.69	(0.27, 10.52)		1.79	(0.25, 12.59)		1.53	(0.25, 9.51)	
CNS	4	3	1	3.39	(0.34, 33.55)		6.19	(0.51, 75.38)		5.76	(0.44, 74.82)	

Data presented are number of patients compared by logistic regression analysis, unless otherwise specified. *ICU* intensive care unit, *OR* odds ratio, *CI* confidence interval, *p P*-value, *SD* standard deviation, *IQR* interquartile range, *SIRS* systemic inflammatory response syndrome, *CNS* central nervous system, *DNR* do-not-resuscitate. *Hosmer and Lemeshow's chi-square test of fit = 8.02, df = 8, *P* = 0.431. †Hosmer and Lemeshow's chi-square test of fit = 1.51, df = 5, *P* = 0.912. ‡Mann–Whitney *U*-test. §At hospital admission. All patients fulfilled criteria for severe sepsis with 2 SIRS criteria within 24 h of hospitalization.

Meier curves on hospital and long-term survival after community-acquired severe sepsis, according to the level of care during hospitalization, are presented in Fig. 2A and B. By multiple Cox regression, effect (HR; 95% CI; *P*-value) on mortality after discharge in 165 hospital survivors was found for increasing age (1.06 per year; (1.04, 1.07); <0.001) and soft tissue infection (0.15; (0.04, 0.60); 0.008), whereas not for gender (1.31; (0.80, 2.14); 0.288), care level during hospitalization (1.19; (0.70, 2.02); 0.514) or other foci of infection (data not shown).

Table 2 Vital signs and biochemical values in ICU and non-ICU-treated patients.

	All		ICU		non-ICU		
Characteristics	*n*	Value	*n*	Value	*n*	Value	*P*
Vital signs							
Temperature, Celsius *	213	38.1 ± 1.5	103	37.7 ± 1.5	110	38.4 ± 1.3	0.001
Pulse, *n* per minute *	214	105 ± 23.9	104	107 ± 24.7	110	104 ± 23.0	0.356
Respiratory rate, *n* per minute *	153	29 ± 8.6	70	30 ± 8.6	83	29 ± 8.5	0.369
Mean arterial pressure, mmHg†	220	53 ± 12.0	107	51 ± 10.8	113	56 ± 12.6	0.001
Diuresis, ml/h†	210	25 (38.3)	107	17 (35)	103	40 (46)	<0.001
Biochemical values							
White blood cell count, 10^9/l*	219	13.7 (9.8)	107	13.7 (9.3)	112	13.7 (11.1)	0.618
CRP, mg/l*	217	122 (225)	105	82 (235)	112	149 (221)	0.075
Platelet count, 10^9/l†	220	192 (132)	107	175 (133)	113	206 (121)	<0.001
Lactate, mmol/l†	203	2.4 (2.6)	107	3.4 (4.3)	96	1.8 (1.5)	<0.001
Creatinine, µmol/l†	220	140 (157)	107	182 (215)	113	117 (93)	<0.001
Bilirubin, µmol/l†	173	13 (17)	99	14 (17)	74	12 (16)	0.204
Glucose, mmol/l†	217	4.9 (1.9)	107	4.5 (1.7)	110	5.4 (2.0)	<0.001
pH†	212	7.33 (0.23)	107	7.19 (0.19)	105	7.41 (0.11)	<0.001
pO2, kPa†	213	7.1 (2.1)	107	6.9 (2.3)	106	7.7 (2.4)	0.005
pCO2, kPa†	213	6.0 (3.0)	107	7.5 (3.9)	106	5.1 (1.6)	<0.001

Data presented are means ± standard deviation or medians with interquartile range, respectively, compared with Student's unpaired *t*-test or the exact Mann–Whitney *U*-test as appropriate. *ICU* intensive care unit, *p P*-value. *Value at admission. †Outermost value (highest/lowest of registered values during surveillance of organ dysfunction).

Discussion

In this prospective observational study, half of the subjects with community-acquired severe sepsis never received treatment in an ICU. They developed less organ dysfunctions, and hence used less hospital resources than ICU-treated patients. While their hospital mortality was low, overall 5-year mortality rates were similar in the non-ICU and ICU cohorts. Increasing age, not care level during hospitalization, had independent impact on long-term survival in multivariable analysis.

An objective of our study was to describe the ICU treatment rate of patients with community-acquired severe sepsis in our hospital. However, inclusion was restricted to three units. In a previous hospital survey, we had found that only 5% of patients with community-acquired severe sepsis were treated outside these units (unpublished results). Hence, we consider our current inclusion process to be an acceptable modification of hospital-wide screening.

All of the investigated units in our study had some sort of surveillance facility and offered treatment with vasoactive drugs and ventilation support, although at different levels. One may suspect that patients receiving organ supportive therapy in our non-ICU cohort would have been admitted to an ICU in a hospital with different organization. However, opposing our ICU treatment rate correlates to the upper fraction of previous results.[2–6] To the best of our knowledge, other descriptions of treatment of severe sepsis outside ICUs do not exist. This makes it difficult to judge the external validity of our data.

Previous retrospective studies from the United States and Australia have estimated ICU treatment rates similar to our result.[2–4] Another retrospective US study found that only 23% of their patients were admitted to an ICU, but this was solely based on ED reports.[5] In our study, 17% of patients initially admitted to a medical ward were later transferred to an ICU. Previous prospective sepsis investigations include a Spanish multicenter observational study where the majority of infections were community acquired.[6] Severe sepsis was identified in an ICU in 32% of their subjects. Other prospective studies that specify their proportion of ICU-treated sepsis have inclusion criteria that make comparison with our study difficult.[7–10]

The characteristics of patients with severe sepsis treated outside ICUs have been described

Table 3 Organ dysfunction and treatment in ICU and non-ICU-treated patients

Category	All *n* = 220	ICU *n* = 107	non-ICU *n* = 113	*P*	OR	95% CI
Acute organ dysfunction						
Number of organ systems						
1	27	6	21	<0.001	1.00	Reference
2	53	14	39		1.26	(0.42, 3.75)
3	71	35	36		3.40	(1.23, 9.43)
4	48	37	11		11.77	(3.80, 36.43)
≥5	21	15	6		8.75	(2.36, 32.47)
Organ system						
Respiratory	173	97	76	<0.001	4.72	(2.21, 10.10)
Circulatory	162	85	77	0.067	1.81	(0.98, 3.34)
Renal	145	84	61	<0.001	3.11	(1.72, 5.62)
Metabolic acidosis	73	55	18	<0.001	5.58	(2.97, 10,49)
CNS	75	34	41	0.569	0.82	(0.47, 1.43)
Hematologic	11	6	5	0.763	1.28	(0.38, 4.34)
Hepatic	7	4	3	0.716	1.42	(0.31, 6.52)
Treatment						
Any ventilation support	129	98	31	<0.001	28.80	(12.97, 63.97)
Non-invasive ventilation*	59	28	31			
IPPV	70	70	0			
Vasoactive drugs	105	80	25	<0.001	10.43	(5.60, 19,44)
Corticosteroids	39	29	10	<0.001	3.83	(1.76, 8.33)
Glucose-Insulin	86	66	20	<0.001	7.49	(4.02, 13.93)
Surgery	38	25	13	0.021	2.35	(1.13, 4.87)
Fluids, ml†	5200 (3500)	6000 (4675)	4625 (3500)	0.002		
Antibiotics, hours‡	2.7 (5.2)	3.5 (7.8)	2.0 (3.7)	0.011		

Data presented are number of patients compared with chi-square test unless otherwise specified. *ICU* intensive care unit, *p P*-value, *OR* odds ratio, *CI* confidence interval, *IPPV* intermittent positive pressure ventilation. *Non-invasive ventilation as highest level of ventilation support. †Fluid resuscitation (median with IQR) during the first 24 h after hospital admission, compared with the Mann–Whitney *U*-test. *N* = 187 patients included in analysis, 85 in ICU group and 102 in non-ICU group. ‡Time to administration of first antibiotics (median with IQR), compared with the Mann–Whitney *U*-test. *N* = 209 patients included in analysis; two patients died before antibiotics was administered, six patients from affiliated hospitals had no information about timing, and in one patient, the time of administration was not documented. In addition, two outliers in non-ICU group with administration of the initial dose >100 h after hospital admission was excluded from analysis.

elsewhere.[4,6,7,11] Patients at the wards have been found to have higher age, more severe comorbidities and less acute organ dysfunctions than ICU patients. Similar to our results, the Spanish observational study documented a lower overall occurrence of abdominal infections than many previous reports.[6] Furthermore, we showed that the majority of abdominal infections were found in ICU patients. These observations are in line with studies that have noticed a high demand for intensive care and a higher occurrence of nosocomial than community-acquired sepsis in this infection category.[6,15,16]

Noticeably, time to initial administration of antibiotics was longer in our ICU cohort, but further analyses did not point out an underlying explanation (data not shown). However, at hospital admission, there was a tendency toward a higher proportion of incorrect suspected infectious focus ($P = 0.123$), and similarly more cases with no suspicion of infection at all ($P = 0.094$) in this group. Altogether, we speculate that a more complex and severe spectrum of symptoms have necessitated immediate focus on other therapeutic measures and investigative modalities.

We found that ICU-treated patients with severe sepsis stayed a median of 6 days longer in the hospital than non-ICU-treated patients. Similarly, a retrospective study from the United States found a difference of almost 8 days in mean hospital LOS for ICU vs. non-ICU patients.[2] A retrospective Australian study

Table 4 Length of stay and outcome in ICU and non-ICU-treated patients

	All		ICU		non-ICU				
Category	*n*	value	*n*	Value	*n*	Value	*P*	OR	95% CI
Length of stay, median days									
Hospital, total	220	11 (17)	107	15 (24)	113	9 (12)	0.001		
ICU			107	6 (9)					
Respiratory tract infection *	115	12 (14)	54	15 (15)	61	8 (11)	0.009		
Genitourinary infection	31	8 (7)	6	20 (15)	25	7 (6)	0.004		
Abdominal infection	26	14 (40)	20	17 (54)	6	12 (14)	0.700		
Soft tissue infection	27	24 (33)	15	34 (38)	12	21 (24)	0.323		
Case-fatality rates†									
In-hospital	220	55 (25)	107	37 (35)	113	18 (16)	0.002	2.79	(1.47, 5,30)
28-days	220	54 (25)	107	36 (34)	113	18 (16)	0.003	2.67	(1.41, 5.10)
1-year	220	76 (35)	107	45 (42)	113	31 (27)	0.024	1.92	(1.10, 3.38)
5-year	220	127 (58)	107	61 (57)	113	66 (58)	0.892	0.94	(0.55, 1.61)

Data presented are medians with interquartile range and numbers with percentages in parentheses, compared with the Mann–Whitney *U*-test or the chi-square test as appropriate. *ICU* intensive care unit, *p P*-value, *OR* odds ratio, *CI* confidence interval. *Endocarditis, bacteremia and central nervous system infection not shown due to a low number of cases in these categories. †Registration from hospital admission, including hospital deaths.

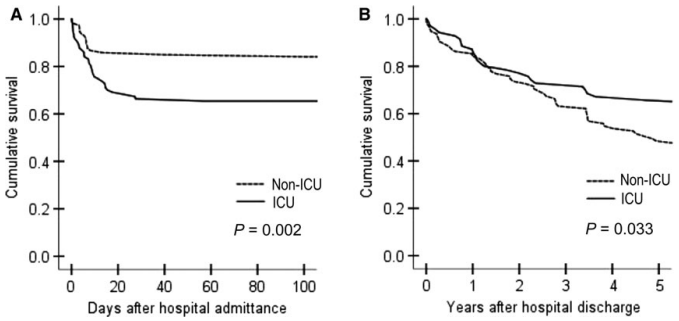

Fig. 2. Hospital and long-term survival after community-acquired severe sepsis. Kaplan–Meier curves illustrating (A) hospital survival in 220 patients and (B) 5-year survival after hospital discharge in 165 hospital survivors, compared across different levels of care (non-ICU vs. ICU) during hospitalization. *ICU* intensive care unit.

calculated a larger difference, but their population included subjects without organ dysfunction.[4] Our 6 days median ICU LOS is in the lower range of previous observations, probably due to our exclusion of nosocomial severe sepsis.[2,15,17–19] A recent prospective study of community-acquired early septic shock reports a comparable mean ICU LOS of approximately 5 days.[10]

The crude hospital mortality rate for severe sepsis was 27% in the single previous Norwegian sepsis report, a retrospective nationwide study from the year 1999.[20] Mortality from sepsis has been decreasing over time in several investigations, so our status as a tertiary care referral center may have influenced our present 25% hospital mortality rate to be in the upper fraction of nationwide data.[21–25] Relatedly, the corresponding rate in the year 2008 was also close to 25% in a retrospective study from an Australian and New Zealand ICU database including some *high dependency units*.[26] Hospital mortality was 16% in our non-ICU-treated patients. This is lower than the 30%, 26% and 23% documented in non-ICU-treated severe sepsis cohorts from Australia, Spain and the United

States[2,4,6] We did not include patients with nosocomial infection from units associated with severe comorbidity like, for example, the department of oncology. Furthermore, these studies originate from the years 1995–2003 and a time-related decline in mortality could have occurred. Finally, our inclusion from a combined ICU/non-ICU ward may have exerted favorable influence on mortality because of a better staffing ratio and more skilled personnel serving the non-ICU beds. On the contrary, our 35% hospital mortality at ICU level is similar to results from both the current three studies as well as other preceding observational studies of severe sepsis.[2,4,6,17,18,27] Part of the discrepancy in survival between our ICU and non-ICU cohort when comparing with the previous literature could be due to a different ICU admission threshold in our hospital. However, prospective studies on severe sepsis in ICU settings have presented median or mean SAPS II values that range from 45 to 56, corresponding to our ICU cohort's mean value of 52.[15,17,27–30] A final noticeable result concerning hospital outcome in our study is the high CFR among patients who were transferred to an ICU from the medical ward. This could be explained by unexpected deterioration of detected infections, or also be a consequence of delayed recognition of severe sepsis and secondary postponed admittance to the appropriate level of care. Unfortunately, we did not register the time to diagnosis of severe sepsis and cannot comment any further on this matter.

A recent publication has confirmed that community-acquired sepsis is independently associated with an increased risk of death for a long period after hospitalization.[31] It describes a national population-based longitudinal cohort of adults ≥45 years of age, where the 1-year, 2-year and 5-year all-cause mortality rates among individuals with sepsis were 23%, 29% and 44%. Similarly, in our study, the 1-year mortality rate after severe sepsis was 27% and 42%, and the 5-year mortality rate 58% and 57% in patients treated at non-ICU and ICU level, respectively. Our 1-year mortality rate in ICU patients is comparable with other results.[10,17,32] In the United States, further long-term survival after severe sepsis has been surveyed in patients ≥65 years of age.[24] Around 80% of the patients in that study died within 5 years after a severe sepsis episode. When we split our data at the same age level, the resulting 5-year mortality rate among patients ≥65 years was 77% in contrast to 35% in subjects <65 years (data not shown). Out–of-hospital survival was significantly different in our ICU and non-ICU cohorts by log rank test, but care level during hospitalization did not have independent impact in our multiple Cox regression model. Comparably, long-term mortality was unrelated to sepsis severity in a recently published Danish investigation of community-acquired sepsis.[33] Increasing age was, on the contrary, associated with long-term mortality in our study. Overall, there was only a tendency toward a difference in median age between our ICU and non-ICU-treated patients, however, the lack of significance could be a matter of sample size. Regardless of this, we believe the difference in long-term survival among the two cohorts is an indicator of appropriate allocation of our ICU resources. After discharge, the ICU-treated hospital survivors exhibited one half the mortality rate when compared with non-ICU-treated subjects, and were therefore probably less morbid at baseline. Yet, the non-ICU cohort had significantly lower hospital mortality, justifying their level of treatment during hospitalization.

Major strengths of this study are the prospective design, inclusion throughout an entire year to detect seasonal changes in infectious diseases, and a long follow-up. Major limitations are the sample size and that the inclusion of patients was not performed hospital-wide. Although rare in our hospital, some patients with community-acquired severe sepsis may have been treated outside the surveyed three units, leading to an overestimated ICU rate. Finally, the acute organ dysfunctions are insufficiently described as no severity of disease classification system was used at non-ICU level. This makes it difficult to compare the quality of treatment across the two care levels. Ideally, we should have obtained SOFA scores prospectively for all patients.

In conclusion, half of the subjects with community-acquired severe sepsis in our hospital never received ICU treatment. Still, use of low-level organ supportive therapy outside the ICU was considerable. Hospital mortality was higher, whereas 5-year survival was similar when comparing ICU with non-ICU patients.

There is a need for additional studies of sepsis with inclusion of patients from both inside and outside the ICU. Future studies should use disease severity scoring systems in order to compare the quality of treatment offered at different levels of care.

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III

PLOS ONE

RESEARCH ARTICLE

Epidemiology and impact on all-cause mortality of sepsis in Norwegian hospitals: A national retrospective study

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Abstract

Background

Although sepsis is the leading cause of death from infection, there are few population-level epidemiological sepsis reports. The impact of sepsis-related deaths on all-cause hospital mortality is insufficiently described, in particular in Europe where data are non-existent. The objective of this study was to provide nationwide epidemiological results on sepsis hospitalizations in Norway and to estimate sepsis' contribution to overall hospital mortality in a European setting.

Methods

We performed a retrospective study using data from the Norwegian Patient Registry and Statistics Norway. The occurrence, patient characteristics and outcomes of sepsis hospitalizations during the years 2011 and 2012 were estimated and compared with Norwegian population data. Sepsis was defined as organ dysfunction caused by a dysregulated host response to infection and identified with International Classification of Diseases 10th revision codes.

Results

We identified 18 460 sepsis admissions occurring in 13 582 individuals. The annual population incidence of hospitalized sepsis was 140 patients per 100 000 inhabitants; ranging from 10 to 2270 per 100 000 in different age groups and with statistically significant male predominance in all adult cohorts. Hospital mortality for sepsis admissions was 19.4% and overall, 26.4% of the included patients died while hospitalized for sepsis. Sepsis related deaths constituted 12.9% of all hospital fatalities, while hospitalizations with sepsis accounted for 1.0% of the total number of admissions and 3.5% of the total admission days during 2011 and 2012.

Competing interests: The authors have declared that no competing interests exist.

Abbreviations: NPR, Norwegian Patient Registry; ICD-10, International Classification of Diseases 10th revision; U.S., United States; SD, standard deviation; IQR, interquartile range; IRR, incidence rate ratio; CI, confidence interval; SIRS, systemic inflammatory response syndrome.

Conclusions

This study confirms that hospitalized sepsis is frequent in Norway and a major contributor to hospital fatalities in a European setting. The incidence is higher among men than women. Sepsis is in particular a disease of the elderly, and its impact on health-care will assumingly continue to increase in parallel with an aging population. Improvements in treatment and survival of sepsis could influence population mortality, and sepsis should receive greater attention in official death statistics in the future.

Introduction

Sepsis is the leading cause of death from infection and a major public health concern in most countries. Still, the epidemiology of this condition is insufficiently described. Population-level results on the incidence of hospital-treated sepsis exist for only eight countries around the world, including Norway as one of four European sites [1, 2]. The currently available Norwegian study is however from the year 1999, and thus of uncertain validity as the occurrence and outcome of sepsis has changed during the last decades [1, 3]. Hence, this study was conducted to gain updated results on the epidemiology of sepsis hospitalizations in Norway. Furthermore, a secondary objective was to investigate sepsis' contribution to hospital fatalities, which previously has been surveyed in the United States (U.S.) only [4]. Since we were able to extract information from all Norwegian hospitals, we present the first estimate of sepsis' impact on overall hospital mortality from complete nationwide data.

Materials and methods

This was a retrospective study combining hospitalization data from the Norwegian Patient Registry (NPR) and population data from Statistics Norway [5, 6]. The years 2011 and 2012 were chosen because these were the most recent years from which complete data were available when the study was conceived. The NPR is a national database run by the Norwegian Directorate of Health, containing information about all hospital admissions in Norway (patient data, dates of hospitalization, type of hospital and department, vital status at discharge and International Classification of Diseases 10th revision (ICD-10) discharge codes). Reporting to the NPR is mandatory. In the current study, a primary search throughout the years 2011 and 2012 was performed by use of selected ICD-10 discharge codes for infections, systemic inflammatory response syndrome (SIRS), sepsis by causative microbes, and septic shock (Table 1). In this primary cohort, we then searched for the presence of up to eight additional ICD-10 discharge codes indicating acute organ dysfunction. Sepsis was defined as life-threatening organ dysfunction caused by a dysregulated host response to infection, inspired by the Third International Consensus Definitions for Sepsis and Septic Shock [7]. Accordingly, the final study cohort consisted of cases fulfilling one or several infection or sepsis related ICD-10 codes as well as one or several codes for acute organ dysfunction (Fig 1).

The NPR database was used to obtain data regarding hospital stay (days), outcome (hospital mortality), age and gender. Information about the total number and total duration of somatic hospital stays in Norway during the years 2011 and 2012 was also collected from the NPR, while national population data including total number of hospital deaths were retrieved from Statistics Norway. The extracted patient data were transferred to a local database (FileMaker, Inc, Pro 14.0; Santa Clara, CA, U.S.). In patients with more than five admissions during the

Table 1. ICD-10 codes used in this study.

ICD-10 code [a]	Diagnosis
Infection, sepsis or SIRS	
A02.1	Salmonella sepsis
A20.7	Septicaemic plague
A21.7	Sepsis (generalized) tularemic
A22.7	Anthrax sepsis
A24.1	Acute and fulminating melioidosis
A26.7	Erysipelothrix sepsis
A32.7	Listerial sepsis
A39.2	Acute meningococcaemia
A40 (.0, 1, 2, 3, 8, 9)	Streptococcal sepsis
A41 (.0, 1, 2, 3, 4, 5, 8, 9)	Other sepsis
A42.7	Actinomycotic sepsis
A46	Erysipelas
A48.3	Toxic shock syndrome
A54.8	Other gonococcal infections
B37.7	Candidal sepsis
J09	Influenza due to identified zoonotic or pandemic influenza virus
J10	Influenza due to identified seasonal influenza virus
J13	Pneumonia due to Streptococcus pneumoniae
J14	Pneumonia due to Haemophilus influenzae
J15	Bacterial pneumonia, not elsewhere classified
J18 (.0, 1, 2, 8, 9)	Pneumonia, unspecified microbiology
J36	Peritonsillar abscess
J39	Other diseases of upper respiratory tract
J85	Abscess of lung and mediastinum
J86	Pyothorax
K65	Peritonitis
K81	Cholecystitis
M72.6	Necrotizing fasciitis
N10	Acute tubulo-interstitial nephritis
O85	Puerperal sepsis
P36	Bacterial sepsis of newborn
R57.2	Septic shock
R65 (.0, 1, 9)	Systemic Inflammatory Response Syndrome [SIRS] of infectious origin without (.0) or with organ dysfunction (.1), or not further specified (.9)
T81.4	Infection following a procedure
Organ dysfunctions	
R57	Shock
I50.9	Heart failure, unspecified
J80	Adult respiratory distress syndrome
J95	Postprocedural respiratory disorders
J96.0	Acute respiratory failure
N17	Acute renal failure
N99.0	Postprocedural renal failure
D65	Disseminated intravascular coagulation [defibrination syndrome]
D69	Purpura and other haemorrhagic conditions

(*Continued*)

Table 1. (*Continued*)

ICD-10 code [a]	Diagnosis
K72	Hepatic failure
E87.2	Acidosis

[a] Norwegian version, URL https://finnkode.ehelse.no/#icd10/0/0/0/-1

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study period, the ≥ 6.th admission(s) were excluded from analyses. In the presentation of the results, descriptive statistics for continuous variables are given as mean ± standard deviation (SD) or median and interquartile range (IQR). Annual population incidence of hospitalized sepsis was calculated as the number of patients experiencing one or more sepsis episode(s) during 2011 and 2012, divided by the sum of the total number of inhabitants in Norway during the same years. Population incidence by age and gender was compared by incidence rate ratios (IRRs) with 95% confidence intervals (CIs). Survival is illustrated by Kaplan-Meier plots and was compared between groups with log rank tests. A p-value ≤ 0.05 was considered statistically significant. The statistical analyses were performed using IBM SPSS Statistics (version 23.0; Aramonk, NY, U.S.); with the exception of the IRRs which were computed with MedCalc for Windows (version 12.7; Ostend, Belgium).

Ethics approval

The study was approved by the Regional Committee for Medical and Health Research Ethics in Western Norway, with a waiver of informed consent (case number 2014/1922).

Results

During the years 2011 and 2012, we identified 18 460 sepsis admissions occurring in 13 582 individuals in Norway. Hospitalizations with sepsis constituted 1.0% of the total number of somatic hospital admissions (n = 1 767 535, Fig 1), and the annual population incidence of hospitalized sepsis was 140 per 100 000 inhabitants. The incidence showed a great age dependent increase; from 10 to 2270 patients per 100 000 inhabitants per year in different age groups (Fig 2). The increase was more pronounced among men, who reached a maximum age-specific annual incidence of 3430 per 100 000 inhabitants, while the corresponding rate for women was 1880 per 100 000. However, significant gender disparities in incidence rates were found across all adult age categories, starting from 20–29 years and upwards (S1 Table).

Characteristics of the study cohort are presented in Table 2. In total 82.8% of patients were ≥ 60 years and the respiratory tract was the most common site of infection. Two or more acute organ dysfunctions were documented in 14.7% of cases. The hospital mortality for sepsis admissions was 19.4%, and overall during the study period 26.4% of the included patients died while hospitalized for sepsis. Hospital mortality increased with age (Fig 3A, log rank $p < 0.001$) and number of organ dysfunctions (Fig 3B, log rank $p < 0.001$).

The total number of hospital deaths in Norway during 2011 and 2012 was 27 705, and deaths during hospital stays for sepsis constituted 12.9% of all hospital fatalities (Table 3). Furthermore, hospitalizations with sepsis accounted for 3.5% of the total admission days during the same period.

Discussion

This nationwide retrospective register-based study from 2011 and 2012 confirms that sepsis is frequent and often fatal in Norwegian hospitals. The overall annual population incidence was

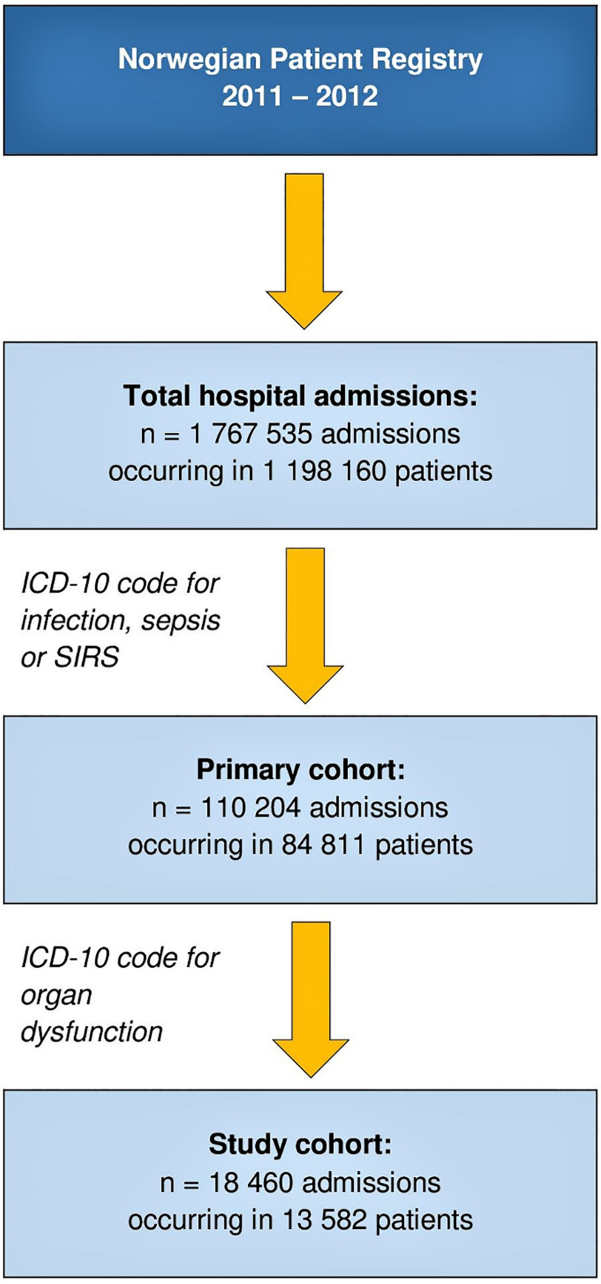

Fig 1. Diagram of the inclusion process.

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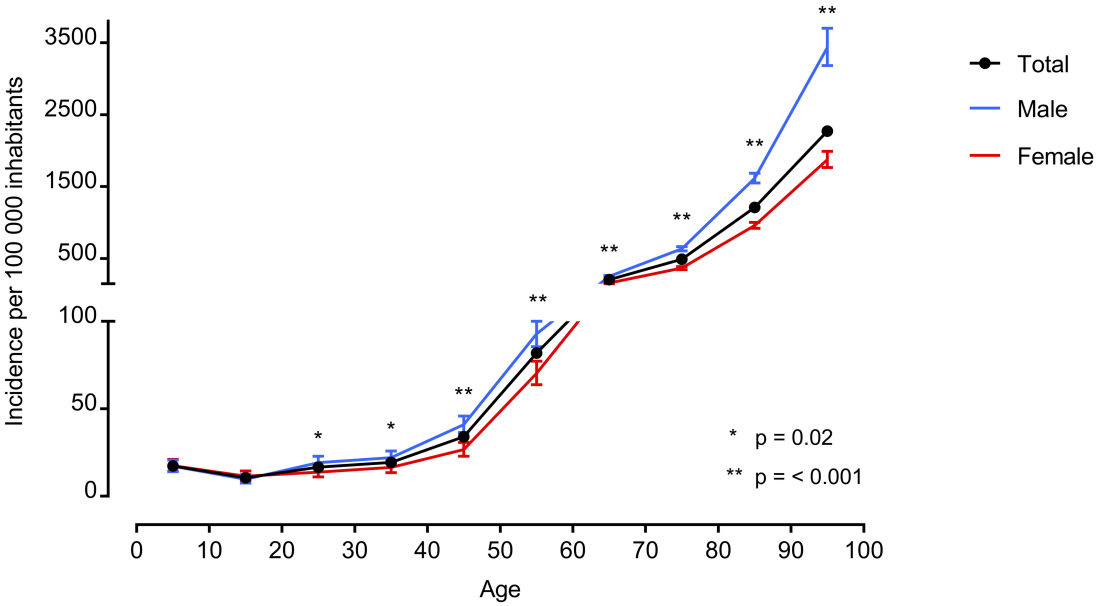

Fig 2. Age-specific annual incidence of sepsis hospitalizations by gender in Norway 2011–2012. Significant gender differences in incidence rate ratios were found starting from category 20–29 years and upwards, as shown in S1 Table.

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140 per 100 000 inhabitants, showed a considerable age dependent increase, and was highest among males. Sepsis admissions occupied 3.5% of the total admission days and had a mortality rate of 19.4%. The observed number of deaths corresponded to 12.9% of the total number of hospital fatalities during the study period, which to our knowledge is the first estimate of sepsis' impact on overall hospital mortality from complete nationwide data.

The definition of sepsis was recently changed, and the term severe sepsis abandoned [7]. To facilitate the interpretation of our results, we use the word sepsis as synonymous with the new definition throughout the following discussion (i.e. life-threatening organ dysfunction caused by a dysregulated host response to infection).

This is the second nationwide retrospective study of sepsis in Norway. Compared with previous data, the most notable difference is an almost threefold increase in the annual population incidence which was estimated to 50 per 100 000 inhabitants in the year 1999 [3]. Other epidemiological studies of sepsis in Norway is restricted to a single-center, prospective study performed by the current authors in 2008 [8, 9]. Then, we detected an incidence of community acquired sepsis of 50 per 100 000 inhabitants per year. It is plausible that these observations reflect an ongoing trend of increasing sepsis occurrence, attributed to a growing number of individuals at risk for severe infection [10–13]. Register-based studies are additionally likely influenced by changes in coding patterns [14]. However, we included both codes for severe infections, SIRS, sepsis by causative microbes, and septic shock in our primary search. Thus influence of a potential shift in coding towards more frequent use of sepsis specific codes was limited.

Throughout the last two decades there have been numerous international publications on the epidemiology of sepsis. Yet, only eight countries have reported population-level incidences

Table 2. Characteristics of patients with sepsis in Norwegian hospitals 2011–2012.

Characteristic	N (% of total) [a]
Gender [b]	
Male	7 327 (53.9%)
Female	6 255 (46.1%)
Age [b]	
Median (IQR)	78 (21)
Mean ± SD	73 ± 18
ICD-10 codes found in the primary search [c, d]	
Respiratory infections	12 932 (70.1%)
Soft tissue infections	899 (4.9%)
Genitourinary infections	822 (4.5%)
Abdominal infections	798 (4.3%)
Infection following a procedure	641 (3.5%)
Streptococcal sepsis	557 (3.0%)
Other sepsis (A41)	5 092 (27.6%)
SIRS (R65.0,1 or 9)	1 087 (5.9%)
Septic shock	735 (4.0%)
Other	159 (0.9%)
Organ dysfunctions [c]	
Cardiovascular	8 944 (48.5%)
Respiratory	5 907 (32.0%)
Renal	4 597 (24.8%)
Hematologic	1 659 (9.0%)
Hepatic	436 (2.4%)
Metabolic	259 (1.4%)
Number of organ dysfunctions [c]	
1	15 750 (85.3%)
2	2 198 (11.9%)
3	416 (2.3%)
≥ 4	96 (0.5%)
Length of stay, days [c]	
Median (IQR)	9 (12)
Mean ± SD	14 ± 19
Hospital mortality [b]	
Total	3 620 (26.4%)
Male	2 021 (27.6%)
Female	1 565 (25.0%)

[a] if not otherwise specified.

[b] calculated from total number of patients hospitalized with one or more sepsis episode(s) (n = 13 582).

[c] calculated from total number of sepsis admissions (n = 18 460).

[d] in total 23 722 primary diagnostic codes were identified; patients could have more than one code.

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and only four previous studies from Europe are performed with nationwide data [1–3, 11, 15, 16]. It is well known that there are large differences in previous reports of sepsis occurrence, which partly may be explained by different study designs [1, 10, 17, 18]. Overall, our current results are in line with two recent nationwide European studies as well as a population-based study from China, while the most recent studies from the U.S. tend to report higher estimates

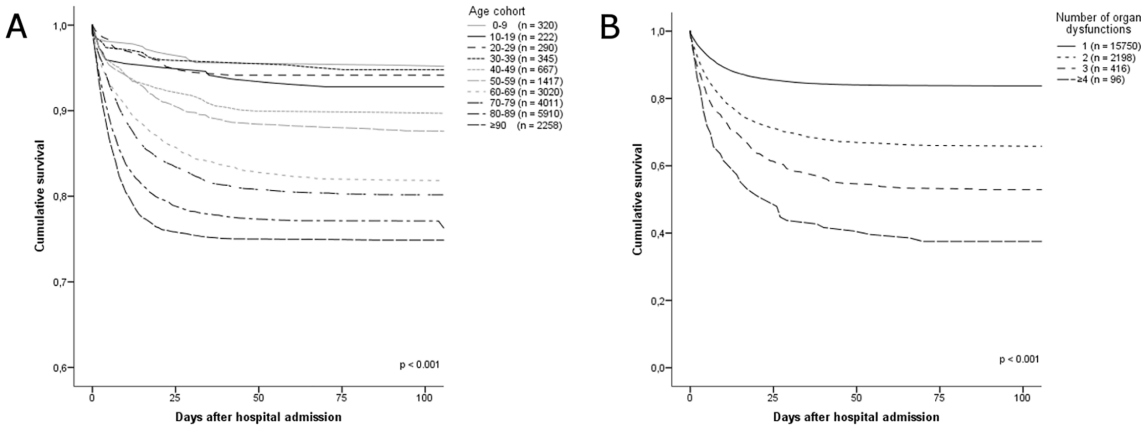

Fig 3. Hospital mortality for sepsis admissions in Norway 2011–2012. Kaplan-Meier plots illustrating hospital mortality for sepsis admissions in Norway during 2011 and 2012, according to A. different age cohorts and B. number of affected organ systems.

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[2, 11, 13, 15, 19–21]. This may reflect differences in health care systems as well as ICD-coding practices [17]. Also, studies from the U.S. tend report incidence as the number of sepsis *admissions* per unit of population older than18 years of age. If we use the same criteria, our corresponding rate was e.g. 270 per 100 000 population in the year 2012.

We found a slight predominance of males in our study. There was in particular a higher age-specific incidence of sepsis in males compared to females among the elderly, but significant differences in incidence rate ratios were present in all adult cohorts. Possible explanations for gender disparities in sepsis have been reviewed elsewhere [17], as similar age and gender differences in sepsis occurrence have been observed [2, 15, 22–24]. In line with studies of trends in sepsis epidemiology, our mean age of 72 years is higher than the equivalent of 58 years found in the previous nationwide report from Norway [3, 11, 23, 25]. The high average age among our patient population furthermore corresponds to recent results [11, 13, 24]. The elderly is especially predisposed to sepsis due to their high prevalence of chronic diseases, polypharmacy, repeated hospitalizations, functional loss, malnutrition, common residencies in long-term care facilities and, of course, due to age-related immunosenescence itself. Yet there is no doubt that the registered hospitalizations among the oldest patients represent cases of severe and resource demanding illness, these circumstances indicate that the elderly on average will have a greater number of diagnostic codes per hospital stay. This probably leads to a greater chance of false positive sepsis cases by use of a code-based identification strategy, and

Table 3. Summary of total and sepsis related hospitalizations in Norway 2011–2012.

Study year	Population in Norway	Total hospital admissions	Sepsis admissions	Total patients	Sepsis patients	Sum total hospital admission days	Sum sepsis admission days	Total hospital deaths	Sepsis related deaths
2011	4 920 305	878 368	8 069	596 704	6 574	3 806 900	124 792	14 088	1 795
2012	4 985 870	889 167	10 391	601 456	7 008	3 667 016	139 679	13 617	1 791
Sum	9 906 175	1 767 535	18 460	1 198 160	13 582	7 473 916	264 471	27 705	3 586

If not otherwise specified, data represents number of cases (n =)

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estimation of sepsis incidence is therefore especially prone to uncertainty in this subgroup of patients.

Respiratory tract infections dominated among the infectious sources of sepsis in our patients. Most of the previous register-based studies do not specify the distribution of infection codes. However, similar results were found in the U.S. in 1995, and respiratory tract infection was the most frequent infection category in recent prospective studies from both emergency department and intensive care unit settings, as well as in our previous prospective study from Norway [8, 22, 26, 27].

The number of organ dysfunctions among our patients is in the lower range compared to previous nationwide figures from Spain and the U.S. [11, 13, 20, 21]. Case inclusion in these retrospective studies was performed with fewer ICD-codes for infection and additional codes for organ dysfunction. This may have resulted in selection of more severely ill patient populations [19, 28–30]. Of interest is a Swedish study that evaluated previously used approaches for database extraction and found a lower presence of multiple organ dysfunctions among their Swedish cohort than in two reference publications from the U.S. [16, 22, 23]. Nevertheless, these findings do not reveal whether the apparent lower disease burden of sepsis in Scandinavia actually is a true reflection of the disease, or a bias from a pattern of under-coding. Previous prospective reports from Scandinavia have found a higher occurrence of multiple organ dysfunctions, but they are single-center studies from large University Hospitals [9, 26]. Prospective registration is inevitably superior in this setting, as it does not rely on compliance during discharge coding. In addition, we excluded dysfunction of the central nervous system which was present in 30–34% of the prospectively identified Scandinavian cases, due to lack of a distinct ICD-10 code.

Hospital mortality for sepsis admissions was 19.4% in our study, and 26.4% of the cohort died while hospitalized for sepsis. This is consistent with other similar recent international studies [13, 24]. Further, hospital mortality from sepsis in Norway has decreased from the previous estimation of 27.1%; despite an increase in mean age and a co-occurring decrease in the mean number of admission days [3]. The latter has also been noted elsewhere [11, 13, 20].

We found that sepsis contributed to 12.9% of the total number of hospital deaths during the study period. This is in contrast to the official cause of death statistics in Norway, where sepsis is only superficially described in the annual report based on death certificates [31]. Similarly, the corresponding report in the U.S. specifies sepsis to have caused 1.5% of all deaths in the year 2014, while a retrospective investigation of hospital mortality showed that sepsis contributed to 1 in every 2 to 3 deaths [4, 32]. Both of these U.S. estimates include patients without organ dysfunction. If we use the number of deaths found in our primary cohort (i.e. hospital fatalities among the patients with selected codes for infection, sepsis or SIRS, n = 8186), our corresponding number is 29.5%. With the exception of the mentioned retrospective report, we found no previous literature on sepsis' influence on total hospital mortality [4]. Other researchers have used multiple causes of death data to assess the impact of sepsis on population-level all-cause mortality [33–36].This approach underestimates sepsis-related mortality compared with administrative datasets [37].

The aforementioned findings illustrate important difficulties in sepsis surveillance and reporting. Several authors have reviewed approaches for code-based identification of sepsis. Many have advised against limitation of discharge codes to diagnoses specific for sepsis and septic shock. This has been found to yield more severely ill patient populations than prospective settings, and underestimate sepsis incidence [19, 28, 30]. Furthermore, a prospective survey of sepsis in the medical emergency department at a Danish University Hospital re-identified only one in seven cases with a subsequent search based on ICD-codes [26]. The latter results are undoubtedly notable, yet the prospective inclusion is subject to some limitations

such as lack of verification of sepsis beyond the ED, and an unusual distribution of organ failure (65.1% had respiratory failure, denoted as SpO2 < 92% at admission, versus only 7.4–9.2% with cardiovascular and renal failure). Just recently, a Swedish study evaluated three retrospective strategies including the previously used Norwegian method, against an intensive care unit registry [38]. In this context, one should note that all of the evaluated methods were designed prior to the introduction of specific codes for SIRS and sepsis with organ dysfunction. Although an incomplete amount of patients was identified by the Norwegian approach, it was found to be the superior strategy [3, 22, 23].

Limitations

The main limitation of this study is its retrospective, code-based design [16, 17, 19]. In short, it encumbers our results with uncertainties due to 1) its reliance on physicians' ability to recognize sepsis, 2) its susceptibility to under-documentation of sepsis *per se* and/or of accompanying clinical findings, and, oppositely, 3) its susceptibility to identify false positive cases because codes for organ dysfunction not necessarily originate from infection. Likewise, fatalities could be caused by another co-occurring condition. Nevertheless, our results are similar to contemporary results from a comprehensive manual review of all medical records of a Chinese population [2]. Ideally we should have used a prospective design. This is unfortunately not feasible on a national level, besides, recent data highlights that even case-based identification of sepsis may be subject to high variability [39]. We confined our search to infections of a certain severity in addition to the sepsis specific codes, and used a modest selection of acute organ dysfunctions based on the previously applied method in Norway. In light of the above discussion, we therefore consider our current criteria for inclusion reasonable.

Conclusions

This nationwide study of sepsis in Norwegian hospitals shows an increasing occurrence compared with previous data from 1999, while hospital mortality still is considerably high. Sepsis should be recognized as an important contributor to hospital deaths, and receive attention in official reports in the future. Improvements in treatment and survival could influence population mortality. This is highly relevant, as there is reason to assume that the annual number of hospitalizations and deaths from sepsis will continue to increase due to an aging population.

Supporting information

S1 Table. Age-specific incidence rates for sepsis per 100 000 person-years at risk in Norway 2011–2012, according to gender.
(DOCX)

S1 Dataset. Hospitalization data obtained from the Norwegian Patient Registry (published with permission).
(XLSX)

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