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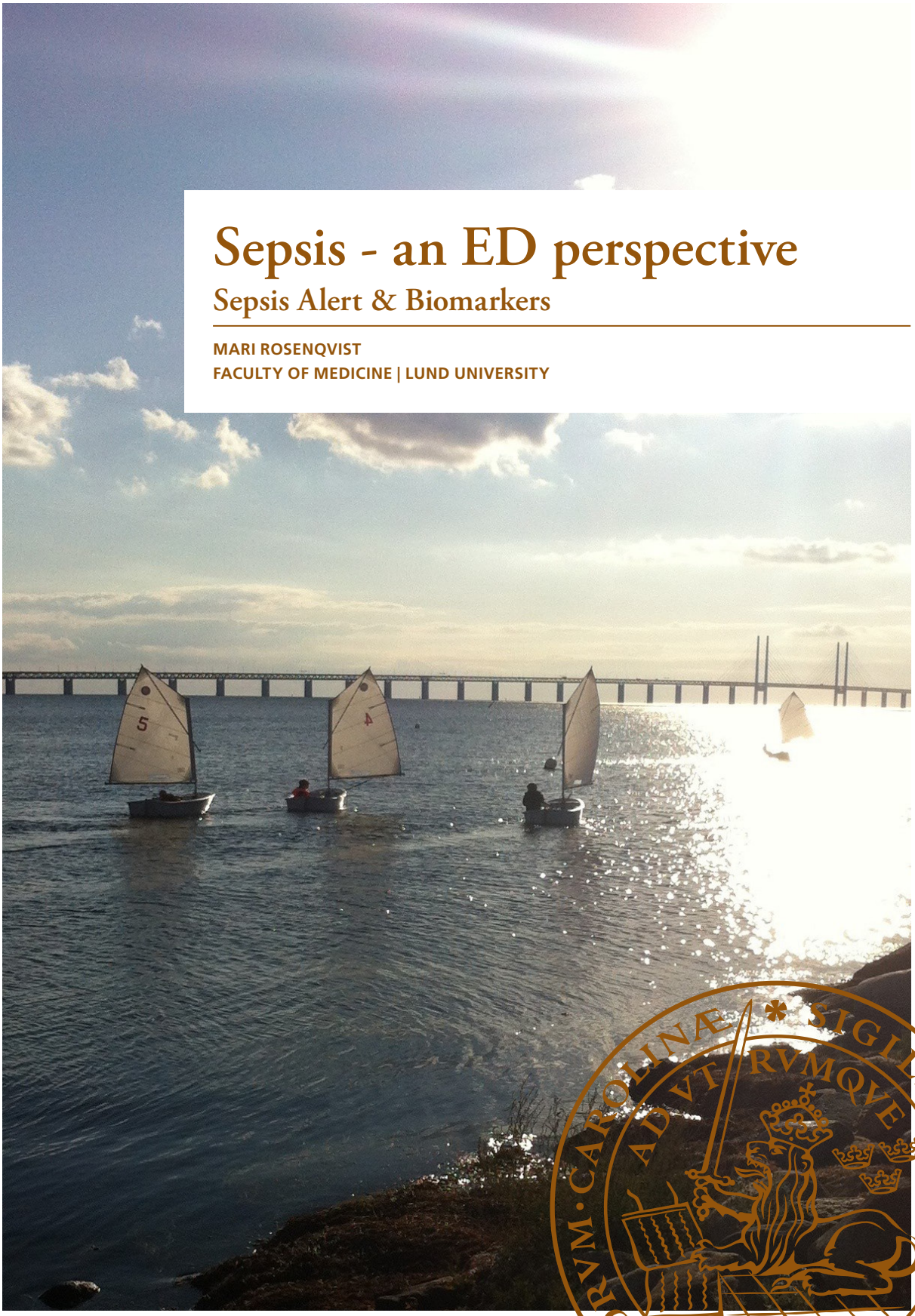

Sepsis - an ED perspective

Sepsis Alert & Biomarkers

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FACULTY OF MEDICINE | LUND UNIVERSITY

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Sepsis - an ED perspective

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LUND
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by
Mari Rosenqvist

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Abstract

Background

Sepsis, the life-threatening organ dysfunction due to dysregulated host response to an infection, is a medical emergency. Early diagnosis and treatment are important factors to prevent mortality and morbidity. However, sepsis can be diffuse and difficult to interpret. Therefore, it is important to define models for early identification applicable in the Emergency Department (ED), in order to meet the therapeutic goals of the Surviving Sepsis Campaign (SSC).

Aim

To improve initial sepsis care at the ED by identifying biomarkers for risk stratification and by a region-wide implementation of the novel triage model Sepsis Alert.

Methods

In the first study we retrospectively evaluated the implementation of the Sepsis Alert at the ED, SUS Malmö. The second study was a post-hoc analysis of the biomarker mid-regional proadrenomedullin (MR-proADM)´s ability to guide antibiotic administration at the ED. In the third study, a prospective observational study, we investigated the biomarker proenkephalin A 119-159 (penKid) as a predictor of acute kidney injury, multi-organ failure (MOF) and mortality in unselected sepsis patients at the ED. The fourth study was a before-and-after multicenter study to assess whether the Sepsis Alert resulted in improved initial care of patients with severe infections at the ED.

Results

We found that the implementation of Sepsis Alert led to shorter time to (appropriate) antibiotics, improvement of quality markers of sepsis care in accordance with SSC, and decreased length of hospital stay. Also, in a subgroup of 5/8 EDs, ICU care decreased after the intervention (Studies I & IV). In Study II, MR-proADM on arrival at the ED had the strongest association with the requirement for antibiotic administration, compared to other biomarkers. Also, ICU care and 28-day mortality was zero in patients with low concentrations of MR-proADM. In study III, penKid in unselected sepsis patients at the ED significantly predicted progression from renal-SOFA ≤ 1 to higher renal-SOFA scores, MOF and mortality.

Conclusions

The triage model Sepsis Alert improves sepsis care and is today an integrated part of the daily routine at the EDs in Skåne Region, and the experiences from this work are applied in the national mandatory guidelines "Personcentrerat och sammanhållet vårdförlopp för sepsis". Moreover, the biomarker studied in this thesis may identify sepsis patients with good (low MR-proADM), and poor (high penKid) prognosis.

Key word

Sepsis, Emergency Department, biomarkers, MR-proADM, penKid, triage, Sepsis Alert, implementation

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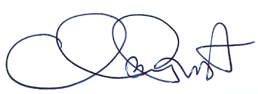
Signature  Date 2021-07-28

Sepsis - an ED perspective

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List of papers

This thesis is based on the following papers, referred to in the text by their Roman numerals:

I. Rosenqvist M, Fagerstrand E, Lanbeck P, Melander O, Åkesson P. Sepsis Alert - a triage model that reduces time to antibiotics and length of hospital stay. Infect Dis (London) 2017; 49(7):507-13.

II. Rosenqvist M, Wilson DC, Tegnér L, Bengtsson-Toni M, Peyman M, de Castillo JD, Saeed K, Melander O. Biomarkers to guide antibiotic timing and administration in infected patients presenting to the emergency department. Critical Care 2019; 23(1):141.

III. Rosenqvist M, Bronton K, Hartmann O, Bergmann A, Struck J, Melander O. Proenkephalin a 119-159 (penKid) - a novel biomarker for acute kidney injury in sepsis: an observational study. BMC Emerg Med 2019;19(1):75.

IV. Rosenqvist, M, Bengtsson-Toni, M, Tham, J, Lanbeck, P, Melander, O, Åkesson, P. Improved outcomes after regional implementation of Sepsis Alert: a novel triage model. Crit Care Med 2020; 48(4):484-90.

Related papers not included in this thesis:

I. Saeed K, Wilson DS, Bloos F, Scheutz P, van der Doos Y, Melander O, Hausfater P, Legramante JM, Claessens Y-E, Amin D, Rosenqvist M et al. The early identification of disease progression in patients with suspected infection presenting to the emergency department: a multi-centre derivation and validation study. Crit Care 2019;23(1):40.

II. Lundberg OHM, Bergenzaun L, Rydén J, Rosenqvist M, Melander O, Chew MS. Adrenomedullin and endothelin-1 are associated with myocardial injury and death in septic shock patients. Crit Care 2016;20(1):178.

Populärvetenskaplig sammanfattning

Avhandlingens fyra delarbeten berör två olika sätt att identifiera och prognostisera patienter med allvarliga infektioner tidigt i sjukdomsförloppet, dels genom sepsislarm (Sepsis Alert) och dels genom analys av ämnen i blodet s.k. biomarkörer.

Sepsis (tidigare kallat blodförgiftning) är ett potentiellt livshotande tillstånd som uppstår till följd av kroppens immunologiska svar på en infektion. Man kan förenklat beskriva sepsis som en infektion som blivit livshotande. Sepsis drabbar runt 49 miljoner människor årligen världen över. Uppskattningsvis sker 85% av sepsisfallen i låg- och medelinkomstländer och i Sverige drabbas cirka 40 000 personer varje år av sepsis.

I princip alla infektioner kan leda till sepsis, men de vanligaste infektionerna är lunginflammation, urinvägsinfektion, bukinfektioner och hud- och mjukdelsinfektioner. Alla kan drabbas av sepsis, men spädbarn, äldre och personer med kroniska sjukdomar eller nedsatt immunförsvar löper ökad risk. Sjukdomsspektrumet vid sepsis sträcker sig från relativt mild sjukdom till allvarlig organskada och dödligheten vid sepsis är cirka 20%. En betydande andel av patienterna som drabbas av sepsis är äldre och/eller har annan svår sjukdom vilket påverkar prognosen. Då en patient med sepsis kan uppvisa en mångfacetterad sjukdomsbild med många olika symtom kan det vara svårt både för patienter, anhöriga och ibland även för sjukvårdspersonalen att tolka dess initiala tecken.

När vi inledde arbetet med att förbättra sepsisomhändertagandet i Skåne för tio år sedan, visade vår första studie, **Studie I**, att de allra svårast sjuka sepsispatienterna erhöll behandling i enlighet med nationella riktlinjer, om antibiotika inom en timme, i endast 22% av fallen. Resultaten vittnade om en betydande förbättringspotential och blev en stark drivkraft för att försöka förbättra den inledande sepsisvården i Skåne genom fokus på tidig identifiering av patienter med sepsis.

Inspirerade av kardiologer och neurologers arbete med snabbspår för patienter med hjärtinfarkt och stroke, ville vi försöka skapa ett liknande snabbspår för patienter med allvarliga infektioner/sepsis. En Sepsiskedja inkluderande sepsislarm (Sepsis Alert), baserat på det sorterings- och prioriteringsverktyg som används på akutmottagningarna i Sverige (RETTS), togs fram för att möjliggöra tidig identifiering av sepsispatienter. Vid sepsislarm engagerades infektionsläkare systematiskt redan på akutmottagningen och bidrog med råd om utredning, behandling och fortsatt omhändertagande. Efter införandet av sepsislarm i

Malmö ökade andelen patienter som erhöll antibiotika inom en timme från 22% till 90% och vårdtiden kortades från 9 till 7 dygn i median, vilket redovisas i **Studie I**.

För att förbättra det initiala sepsisomhändertagandet i hela Skåne, fattades sedermera beslut i Hälso- och sjukvårdsnämnden att införa sepsislarm på alla Skånes akutmottagningar. Implementeringen genomfördes 2016 av tre regionala sepsiskoordinatorer i samarbete med de tio sepsisteamen på Skånes akutmottagningar. Den vetenskapliga utvärderingen av det regionala införandet av sepsislarm baserades på 200 000 akutsökande patienter och beskrivs i **Studie IV.** Det regionala införandet av sepsislarm ledde till tydligt förbättrade nationellt vedertagna kvalitetsmått, att högre andel patienter erhöll adekvat initial antibiotikabehandling i tid och i en före-efter-analys av införandet av sepsislarm på fem av åtta akutmottagningar utan tidigare sepsislarm, minskade behovet av intensivvård.

Med siktet inställt på att ta fram kliniskt applicerbara biomarkörer för tidig identifiering och prognostisering av allvarliga akuta tillstånd inleddes 2013 arbetet med att bygga upp en biobank på Akutmottagningen i Malmö. Nära 3000 akutsökande patienter med dyspné (andnöd), sepsis och diabetes har inkluderats i studiens tre olika delar, varav drygt 800 utgörs av patienter med sepsis. De två biomarkörerna som har studerats i detta avhandlingsarbete innefattar mid-regional proadrenomedullin (MR-proADM) och proenkephalin A 119–159 (penKid). I **Studie II** visar vi att MR-proADM taget vid ankomst till akutmottagningen var starkt associerat till behov av antibiotikabehandling jämfört med andra infektionsbiomarkörer såsom procalcitonin, CRP och laktat. En annan intressant observation i denna studie var att andelen sepsispatienter som behövde IVA-vård eller avled inom 28 dagar var noll hos patienter med låga nivåer av MR-proADM.

Ett organ som ofta påverkas vid sepsis är njurarna. Ett problem med den biomarkör som används idag (s-kreatin) är bland annat att det tar tid innan njurskadan återspeglas i blodproven och att upprepade värden krävs för att skapa sig en adekvat bild av skadans omfattning. Det är angeläget att upptäcka sepsisorsakad njurskada tidigt i förloppet för att kunna dosanpassa läkemedel och vidta andra njurskyddande åtgärder i syfte att minimera skadans omfattning. Biomarkören penKids förmåga att tidigt signalera risk för akut njurpåverkan, multipel organskada och risk för död vid sepsis beskrivs i **Studie III**.

Flera positiva initiativ bidrar för närvarande till att förbättra sepsisvården, inte minst Världshälsoorganisationens beslut att utnämna sepsis till en så kallad ”Global Health Priority” för att ge tillståndet vederbörligt fokus. På mer lokal nivå gläds vi åt att de skånska erfarenheterna kring sepsislarm tagits till vara i det nationella arbetet med ”Personcentrerat och Sammanhållet Vårdförlopp för Sepsis”, vilket bl.a. innefattar införandet av sepsislarm på nationell basis.

Abbreviations

ACCP	The American college of chest physicians
ADM	Adrenomedullin
aPTT	Activated partial thromboplastin time
AKI	Acute kidney injury
AUROC	Area under the receiver operating characteristic curve
CHIS	The centre for health economics, informatics, and healthcare research
CDC	The centres for disease control and prevention
CKD	Chronic kidney disease
COPD	Chronic obstructive pulmonary disease
CReDECI	Criteria for reporting the development and evaluation of complex interventions in healthcare
CRP	C-reactive protein
DAMPs	Damage associated molecular patterns
DIC	Disseminated intravascular coagulation
ED	Emergency department
EGDT	Early goal directed therapy
EHR	Electronic health records
eGFR	Estimated glomerular filtration rate
ESICM	The European society of intensive care
FiO2	Fraction of inspired oxygen
GFR	Glomerular filtration rate
ICD	International classification of disease
ICU	Intensive care unit
ID	Infectious disease(s)
IDSA	Infectious diseases society of America
INR	International normalised ratio

LOS	Length of hospital stay
MAP	Mean arterial pressure
mmol	Millimole
mM	Millimole
MOF	Multi-organ failure
MR-proADM	Mid-regional proadrenomedullin
NEWS	National early warning score
NEWS2	National early warning score 2
PAMPs	Pathogen associated molecules
PCT	Procalcitonin
PCR	Polymerase chain reaction techniques
penKid	Proenkephalin A 119-159
PIRO	Predisposition, insult, response, organ dysfunction
qSOFA	Quick sequential organ failure assessment
RETTS	Rapid emergency triage and treatment system
rSOFA	Renal sequential organ failure assessment
RCP	Royal college of physicians
SCCM	The society of critical care medicine
SCr	Serum creatinine
SIRS	Systemic inflammatory response syndrome
SOFA	Sequential organ failure assessment
SSC	Surviving sepsis campaign
WBC	White blood cell count
WHO	World health organisation

Background

An introduction to sepsis in the Emergency Department

Humanity has always faced challenging situations that demand collaboration to utilise existing resources. The ability to envision and make plans for the future is one of mankind's strengths. However, not all situations are preventable, and humans are still plagued by infectious disease. Since microbes will undoubtedly continue to share our world, causing severe infections, healthcare personnel must be well prepared and vigilant in handling a wide variety of present and emerging infections, to reduce human suffering and to save lives.

Sepsis, the life-threatening organ dysfunction due to dysregulated host response to an infection, is a medical emergency, and early recognition, appropriate, and timely interventions are important factors to prevent mortality and morbidity. In order to meet present therapeutic goals of the Surviving Sepsis Campaign (SSC), it is important to define models for early identification applicable in the Emergency Department (ED).

Triage based upon vital signs, symptoms, and/or biomarkers has become a viable means of early identification and risk stratification in patients with severe infections, to enable adequate care for individual patients and optimised healthcare. The early engagement of infectious diseases physician at the ED is essential, contributing with knowledge regarding severe infections and ensuring high-quality initial sepsis care and the responsible use of effective antimicrobials.

Despite considerable advancement in recent decades in sepsis care, we impatiently await development of novel therapeutic individualised strategies that may be guided by biomarkers or other risk-stratification tools. Concurrently, sepsis care models applicable in low- or middle-income countries needs to be developed, and here models based on vital signs may have an advantage.

In this thesis, early recognition and risk-stratification of sepsis based on the novel triage algorithm Sepsis Alert, and the biomarkers mid-regional proadrenomedullin (MR-proADM) and proenkephalin A 119-159 (penKid), are explored.

Sepsis definitions and its shortcomings in the ED setting

Sepsis is a syndrome rather than a disease, which includes the full spectrum from relatively mild infectious disease to multi-organ failure, circulatory shock, and death. The constellation of symptoms and organ dysfunction for diagnosis makes sepsis an entity of its own, not comparable to other life-threatening conditions present at the ED, such as acute myocardial infarction or stroke. Although applicable in an Intensive care unit (ICU) setting, the consequences of the convolute and volatile sepsis definitions may become most apparent at the ED.

Before exploring sepsis definitions further, definitions of infection and infectious diseases ought to be addressed. Interestingly, in the previous sepsis consensus documents Sepsis-1 and Sepsis-2 (1, 2), infection was defined as "a pathological process caused by invasion of normally sterile tissue/fluid or body cavity by pathogenic or potentially pathogenic micro-organisms". However, in the current Sepsis-3 guidelines, definition of infection is not included (3). This is disappointing, since the definition of infectious disease is essential in clinical and research work, and inaccuracies are subsequently reproduced throughout the care chain, influencing use of antibiotic treatment and other decisions on care and outcomes.

As defined in the *Handbook of Epidemiology*, infection and infectious disease are "the entry and development or multiplication of an infectious agent in the body of humans or animals". The Centres for Disease Control and Prevention (CDC)'s infectious disease criteria were initially developed for surveillance of nosocomial infections but were subsequently extended to include infections in general and in critically ill patients (4). However, infection is not synonymous with disease, since disease implies signs, symptoms, or some negative impact on the health status of the individual. Some of these may be minor, and at the end of the spectrum are individuals with no signs or symptoms who have asymptomatic or subclinical infections, as in the asymptomatic phase of HIV infection, or the Hepatitis B carrier state (5).

Although these definitions are distinct and valuable in theory, a more pragmatic perspective is needed in the ED. Most ED and pre-hospital personnel would readily and swiftly identify a patient with a typical infectious presentation, however, since sepsis may be diffuse and mimic other conditions, symptoms may be difficult to interpret even for more experienced health care personnel (6).

With previous infectious disease definitions in mind, let us return to the definitions of sepsis. One can ascertain that great effort has been put into developing and improving sepsis criteria over time. The first consensus statement with intention to uniformly define sepsis (Sepsis-1) was composed in 1991 by the American College of Chest Physicians

(ACCP) and the Society of Critical Care Medicine (SCCM) (1). These definitions emanated from sepsis being due to an exaggerated immune response, Systemic Inflammatory Response Syndrome (SIRS), and if two of the four SIRS criteria (heart rate >90/ minute, respiratory rate >20/minute, temperature >38°C, <36°C or leucocytes >12 or <4 x 10^9/L) plus infection were present, the condition was defined as sepsis, and with the simultaneous presence of organ dysfunction, the criteria for severe sepsis were fulfilled. Further, septic shock was defined as sepsis-induced hypotension despite adequate fluid resuscitation along with the presence of hypoperfusion (Table 1).

Table 1 – Sepsis-1 criteria in accordance with ACCP and SCCM (1).

Term	**Criteria/definitions**
Infection	Microbial phenomenon characterised by an inflammatory response to the presence of microorganisms or the invasion of normally sterile host tissue by those organisms.
Systemic inflammatory response syndrome (SIRS)	The systemic inflammatory response to a variety of severe clinical insults. Two or more of the following criteria: Temperature >38°C or <36°C; heart rate >90 beats per minute; respiratory rate >20 breaths per minute or PaC02 <32 mm Hg; and white blood cell count >12 or <4 x 10^9/L, or >10% immature (band) forms.
Sepsis	The systemic inflammatory response (SIRS) to infection. Two or more of the following conditions: Temperature >38°C or <36°C; heart rate >90 beats per minute; respiratory rate >20 breaths per minute or PaC02 <32 mm Hg; and white blood cell count >12 or <4 x 10^9/L or >10% immature (band) forms.
Severe sepsis	Sepsis with organ dysfunction, hypoperfusion, or hypotension. Hypoperfusion and perfusion abnormalities may include, but are not limited to lactic acidosis, oliguria, or an acute alteration in mental status.
Septic shock	Sepsis induced hypotension despite adequate fluid resuscitation along with the presence of perfusion abnormalities that may include, but are not limited to, lactic acidosis, oliguria, or an acute alteration in mental status.

In 2001, the slightly revised Sepsis-2 criteria were established by a collaboration of the SCCM, the ACCP, the European Society of Intensive Care Medicine (ESICM), the American Thoracic Society (ATS), and the Surgical Infection Society (SIS) (Table 2, 3).

Table 2 – Sepsis-2 criteria in accordance with ACCP, ATS, ESCIM, SCCM, SIS (2).

Term	**Definitions & clinical criteria**
Infection	Pathologic process caused by the invasion of normally sterile tissue or fluid or body cavity by pathogenic or potentially pathogenic microorganisms.
Sepsis	Suspected or established infection, plus some of the parameters in Table 3.
Severe sepsis	Suspected or established infection, plus hypotension, hypoperfusion or organ dysfunction (Marshall or SOFA).
Septic shock	Acute circulatory failure, persistent arterial hypotension (systolic arterial blood pressure <90 nn Hg or MAP <60 mm Hg or a reduction of 40 mm Hg compared to baseline.

Table 3 - Parameters & criteria for sepsis in accordance with Sepsis-2 (2).

Term	**Criteria**
General parameters	Fever >38.3°C Hypothermia <36°C Heart rate >90 bpm Tachypnea >30 bpm Altered mental status Significant edema or positive fluid balance (>20 ml/kg/24 h) Hyperglycemia (plasma glucose >110 mg/dL or 7.7 mM/L) in the absence of diabetes
Inflammatory parameters	WBC count >12,000/μl or <4,000/μl, or >10% or immature CRP >2 SD above the normal value PCT >2 SD above the normal value
Organ dysfunction parameters	Arterial hypoxemia (PaO_2/FiO_2 <300) Acute oliguria (urine output <0.5 ml/kg/h or 45 mM/L for 2 h) Creatinine increase ≥0.5 mg/dL Coagulation abnormalities (INR >1.5 or aPTT >60 s) Ileus (absent bowel sounds) Thrombocytopenia (platelet count <100,000/μl) Hyperbilirubinemia (plasma total bilirubin >4 mg/dl or 70 mmol/L)
Hemodynamic parameters	Arterial hypotension (systolic blood pressure <90 mmHg, MAP <70, or a systolic blood pressure decrease >40 mmHg) Mixed venous oxygen saturation >70% Elevated cardiac index
Tissue perfusion parameters	Hyperlactatemia (>3 mmol/L) Decreased capillary refill or mottling

To improve risk stratification among patients with a suspected infection, in 2016 new consensus definitions of sepsis and related clinical criteria, Sepsis-3, were established by the ESICM and the SCCM (3). The updated sepsis criteria were based on literature review and analysis of current research, rather than the consensus documents used in previous sepsis definitions. In Sepsis-3, sepsis is defined as a life-threatening dysregulated host response to infection. The SIRS categorisation is omitted, and emphasis is put on evaluating organ dysfunction according to the Sequential Organ Failure Assessment (SOFA) score that is based on six different components: respiratory, cardiovascular, hepatic, coagulation, renal, and neurological systems. An increase in baseline SOFA score ≥ 2 SOFA points defines organ dysfunction, where baseline SOFA score is assumed to be zero in patients with no known pre-existing organ dysfunction. An advantage of this classification is that organ dysfunction is evaluated along a continuum, rather than binary clinical entities. Septic shock is defined as hypotension despite "adequate" fluid resuscitation in need of vasopressor to reach mean arterial pressure (MAP) ≥ 65 mm Hg and elevated serum lactate concentration >2 mmol/L (Table 4, 5).

Table 4 – Sepsis-3 criteria in accordance with ACCP and ESCIM (3).

Term	**Definitions & clinical criteria**
Infection	A definition of infection was not included.
Sepsis	The life-threatening organ dysfunction caused by dysregulated host response to infection. An acute increase of ≥ 2 SOFA points as a consequence of infection, defines organ dysfunction, Table 5.
Severe sepsis	Considered redundant.
Septic shock	Septic shock, include a subset of sepsis in which the underlying circulatory and cellular/metabolic abnormalities are profound enough to substantially increase mortality. Persisting hypotension requiring vasopressor to maintain MAP 65 mm Hg and having a serum lactate level >2 mmol/L despite adequate volume resuscitation, defines septic shock.

Table 5 – The Sequential (sepsis-related) organ failure assessment score (SOFA score). Singer et al (3)

Organ system	SOFA score				
	0	**1**	2	**3**	**4**
Respiration PaO_2/FiO_2, mmHg	≥400	<400	<300	<200 with respiratory support	<100 with respiratory support
Coagulation Thrombocytes $x10^3/\mu L$	≥150	149-100	99-50	49-20	<20
Liver Bilirubin, umol/L	<20	20-32	33-101	102-204	>204
Cardiovascular MAP, mm Hg	≥70	<70	Dobutamine[a] (any dose) or Dopamine[a] <5	Epinephrine/ norepinephrine[a] ≤0.1 or Dopamine[a] 5.1-15	Epinephrine/ norepinephrine[a] >0.1 or Dopamine[a] >15
Central nervous system Glasgow coma scale (GCS)[b]	15	13-14	10-12	6-9	<6
Renal Creatinine, umol/L Urine output, mL/d	<110	110-170	171-299	300-440 <500	>440 <200

a Catecholamine doses are given as µg/kg/min for at least 1 hour
b Glasgow coma scale ranges from 3-15; higher scores indicate better neurological function.

Surprisingly, the Sepsis-3 guidelines were not prospectively validated before being launched. Per contra, the criteria were mainly based on retrospective analysis of large US and German hospital databases, with considerable predominance of the former country and ICU wards, and the majority of infections being respiratory or postoperative. Also, a non-validated definition of suspected infection, as collection of biological samples and prescription of antibiotics within a given time interval, was used. Not being representative for the wider clinical spectrum of sepsis patients that present at the ED, far-reaching conclusions applicable in the emergency setting were not conceivable (3, 7, 8). In an attempt to resolve this shortcoming, a new clinical sepsis screening tool, the quick Sequential Organ Failure Assessment (qSOFA), was constructed to be used to identify sepsis patients outside the ICU. Quite surprisingly, a similar retrospective approach was applied when developing this score, and the deficient sensitivity for the model in the ED was destined (9-13).

The Sepsis-3 criteria contain some challenges. For example, the former rationale for severe sepsis has been replaced by sepsis, and the two concepts are not fully compatible (2, 3, 14, 15). Patients who meet the sepsis criteria in accordance with Sepsis-3 have been shown to be less ill than patients with severe sepsis, according to the previous sepsis criteria, which may be explained by the more permissive saturation criteria <92 equivalent to 2 SOFA-points in Sepsis-3. Further limitations in the updated sepsis criteria are the omission of time span for organ dysfunction, and that PaO_2/FIO and MAP is used, which is not routine at the ED (15, 16). Also, despite being a sensitive marker for severity of sepsis, measurement of lactate is not part of the updated sepsis definitions other than in the definition of septic shock. Altogether, these alterations may reflect the lack of ED representation in the ESICM's and the SCCM's task force, and risk leading to huge unforeseen challenges when implementing Sepsis-3 at the ED.

In addition, in Sepsis-3, patient data were collected from adults in high-income countries, so the utility of the current sepsis definitions in other geographic regions, and particularly in low-income settings, is unknown. To be universally accepted, the sepsis guidelines should facilitate urgent sepsis care on a global level and must be applicable in settings with less resources (7).

Epidemiology

Due to the inconsistent approach to definitions and diagnosis in sepsis, evaluating the epidemiology of sepsis has been a demanding and sometimes unattainable assignment. To achieve high-quality epidemiological data, factors such as sex, age, socio-economic status, health care setting, educational level, and low- and middle-income countries need to be included in the analysis. To date, knowledge of global sepsis epidemiology has been hampered by the fact that regions with the highest sepsis burden have been the same areas where data have been lacking. The recent and gratifying data regarding sepsis incidence in low- and middle-income countries, by Rudd et al. (17), reduce knowledge gaps and contribute to a more complete depiction, rendering a global sepsis incidence of 623 per 100 000 inhabitants/year.

Interestingly, in addition to her accomplishments in the Crimean War, Florence Nightingale was the first to propose a model of systematic collection of hospital data in the mid eighteen-hundreds (18). Later, in 1948, the World Health Organisation (WHO) introduced the International Classification of Disease coding system (ICD-6) to facilitate national and international recording and reporting of mortality and morbidity statistics (19). Since then, the coding system has been revised to reflect the

ongoing advances and development in health care, and the eleventh version adapted to the digital era is currently being implemented (20).

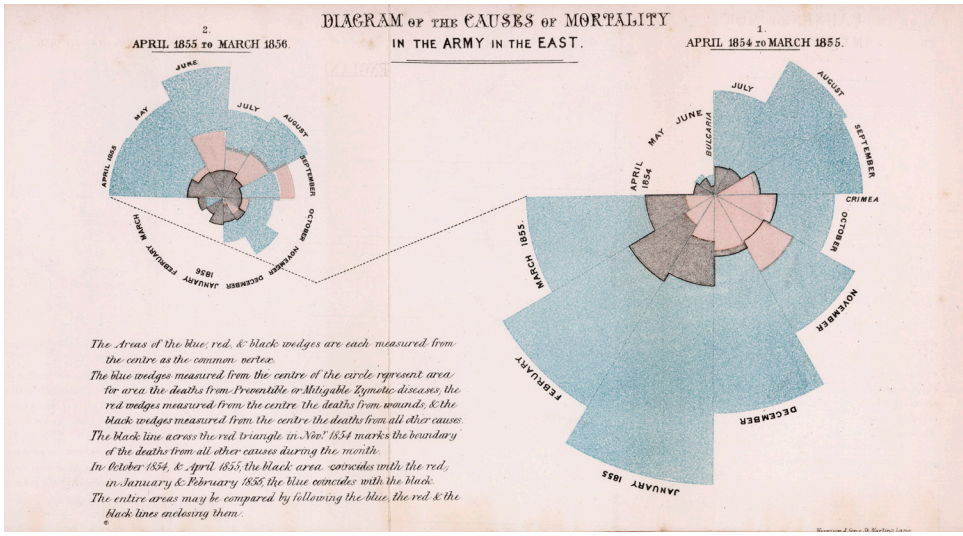


Figure 1. Florence Nightingale´s report on the situation in the Crimea from 1858 (18).

The reliability of ICD data is highly dependent on the accuracy of the coding, and biases are inevitable in the coding process. Consequently, the reliability has varied considerably, depending on awareness of sepsis, the coding system, the financial compensation schemes, or other financial incentives. Several studies suggest that only 10–50% of patients with sepsis are coded correctly using the ICD system (21-24). Thus, to enable an accurate sepsis incidence estimation in an ED setting, an extensive, labour-intensive, chart-based review is preferrable and is still considered golden standard, although electronic health records (EHR) are becoming more frequent (25).

An alternative approach to study sepsis epidemiology retrospectively, via electronic chart algorithms, was applied by Rhee and colleagues in 2017 (26). They used a pseudo-marker for sepsis, namely presence of organ dysfunction, blood cultures taken, plus antibiotic treatment for four days. This set-up may immensely simplify the evaluation, however not all sepsis patients have blood cultures taken. In addition, patients with virus-related sepsis, or misjudged sepsis patients, may also be omitted in this setting. However, when using this method, an annual incidence of 500/100 000 was found, but when validating the results by manual chart review it was shown that 30% of patients were missed, and that another 30% were misclassified. Despite these insufficiencies, the method is considered to be useful in the future (27).

In recent decades, some assessments have shown a trend of increasing sepsis incidence (21, 28), while other estimates point in the opposite direction (29, 30). However, the highest quality epidemiologic studies indicate that sepsis is becoming both more common and less deadly. Increased sepsis incidence may be due to more patients being detected, but also due to an ageing population and increased incidence of sepsis risk factors such as antibiotic resistance, enhanced use of immunosuppressive treatments, and foreign material in the body. An ageing population entails a significantly increased risk for sepsis, as patients ≥ 65 years account for 60–85% of sepsis episodes. But the increase may also be due to better coding and a heightened awareness of sepsis (14, 17, 31-36)

In addition to the study population, organ dysfunction criterion, definition of infection, and whether diagnosis is based on ICD code or manual chart evaluation, the applied sepsis definitions (Sepsis 1, 2 or 3) are also of major importance when handling epidemiological aspects of sepsis. Since a majority of epidemiological studies were conducted before 2016, most studies are based on Sepsis-2 guidelines and must be reproduced using current Sepsis-3 criteria. Also, most epidemiological sepsis studies have been conducted in hospitalized sepsis patients, a selection that might risk leading to bias since patients with milder forms of sepsis may be treated as out-patients. Further, patients from nursing homes who may be readmitted to institutions are consequently omitted, as are patients who die during ED stays. Despite these limitations, even fewer studies have evaluated the epidemiology of infectious diseases at the ED. Some studies have been conducted in a paediatric ED setting, but corresponding broad epidemiological research in adults at the ED are lacking (37-39).

With these limitations in mind, one can conclude quite illustratively that sepsis incidence has been reported to range between three and one thousand patients per 100 000 inhabitants and year (21). One of the first large studies on sepsis incidence, from 2001 by Angus and colleagues, included almost 200 000 sepsis patients by using ICD-9 codes, and showed a sepsis incidence of 300/100 000. In this study, 50% received ICU care and the in-hospital mortality rate was almost 30%, which reflects severely ill sepsis patients (35). Further, in a Danish chart-based ED study, the incidence of community onset sepsis, according to Sepsis-2, landed in the middle of this large range, at 457 per 100 000 inhabitants and year (23), and in a study from the Faroe Islands the incidence of community onset sepsis was 644 per 100 000 inhabitants and year (22).

In a Swedish point prevalence study, 482 hospitalized patients receiving intravenous antibiotic treatment were evaluated, with results indicating an incidence of severe sepsis of 687 per 100 000 inhabitants and year, when applying Sepsis-2 criteria, and an incidence of sepsis in 780 per 100 000 inhabitants and year, according to the updated

Sepsis-3 definitions (24). This finding is somewhat inconsistent with other studies that have shown greater discrepancies between the Sepsis-2 and Sepsis-3 definitions. Ljungström and colleagues evaluated 2 462 patients in-hospital who received antibiotics within 48 hours and found an annual incidence of community onset severe sepsis of 276/100 000 inhabitants, however, when applying the Sepsis-3 definitions, the incidence was three-fold higher, 838/100 000 inhabitants and year (14). Also, the incidence of septic shock varies greatly among studies, at 9/100 000 and 80/100 000, and current septic shock definitions will surely result in a smaller septic shock population (23, 35, 40).

Pathophysiology at the ED and after

The host response to infection witnessed at the ED is often multifaceted and varied, and the individual immunological response, the pathogen, site of infection, and the point when, in the course of sepsis, patients present at the ED, all complicate the initial evaluation and may impart different types of delays of recognition (41).

The cytokine activation manifested as fever and signs of infection increases the possibility to correctly identify the sepsis patient at the ED. However, the opposite is illustrated in patients with immunosuppression, where these symptoms may be lacking due to diminished cytokine effects, which may further complicate identification and evaluation. The early signs of infection relate to the innate (non-adaptable) immunity, including macrophages, monocytes, neutrophils, natural killer cells, and dentritic cells, which are rapidly activated to a common and broad range of microbes. The initial response consists of an intricate interplay of pro- and counteracting anti-inflammatory mechanisms, which achieves effective control of minor and localized infections and repair damaged tissue (42, 43). However, when certain thresholds are met, complex cytokine cascades are triggered by the local infection reliant on the pathogen and site of infection, but also on host response factors such as age, comorbidity, environmental factors, microbiome, genetic polymorphism, epigenetic modifications, and the ability to re-establish homeostasis (42, 44).

By detecting certain pathogen associated molecules (PAMPs) as endotoxins, and detecting damage associated molecular patterns (DAMPs) as molecules originating from the damaged cell, complex responses are activated. The PAMPs and DAMPs activate a wide range of pattern recognition receptors, rendering increased transcription of pro-inflammatory mediators such as interferons and tumour necrosis factor-alfa, interleukin-1, and interleukin-6 (42, 45, 46). In Gram-negative bacteria, lipopolysaccharide-binding protein, CD14, and toll-like receptor 5 are key molecules

in the defence. Further, in Gram-positive bacteria, components of the bacterial cell wall and exotoxins produced by bacteria may constitute super antigens that unselectively stimulate the T-lymphocytes by binding to major histocompatibility complex class II in antigen presenting cells, leading to massive cytokine production (41).

The vascular endothelium, composed of a single layer endothelial cell, separates the intravascular space from the interstitial and regulates diffusion of molecules. The endothelium is central in the pathogenic sepsis cascade serving as a link between local and systemic immune responses. The endothelium is engaged in initiating increased leucocyte adhesion, a shift to a procoagulant state, vasodilatation and loss of barrier function resulting in widespread oedema in the interstitial spaces, body cavities, and subcutaneous tissue (47). The endothelium also regulates vasomotor tone, the migration of cells and nutrients in and out of tissue, and the coagulation system. Endothelial barrier leak is part of the host response to infection, since it is needed to combat pathogens in the tissues. However, as previously mentioned this may result in huge amounts of fluid in the tissues, leading to interstitial oedema and subsequent septic shock.

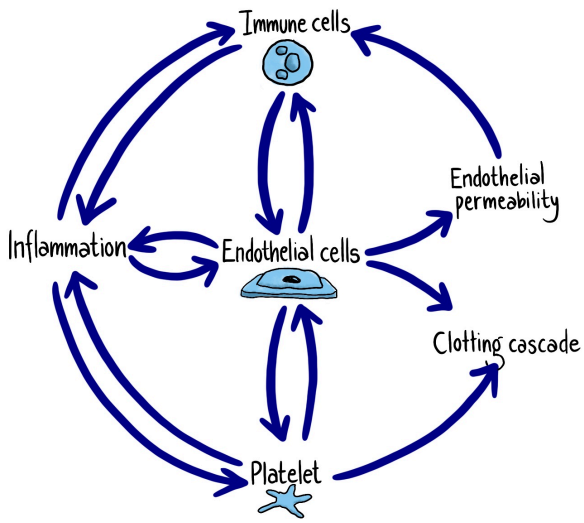


Figure 2. The role of the endothelium in sepsis. Adapted from Dolmatova et al.

Further, the bacterial and microbial toxins activate other parts of the innate immunity, viz the coagulation and complement systems, in an attempt to further defend the host. The activation of the coagulation system may cause a continuum from mild thrombocytopenia to fulminant disseminated intravascular coagulation (DIC), probably driven by tissue factor from endothelial cells and leukocytes. In addition to the procoagulant state, diminished anticoagulant effects are observed, as is a concurrent depression of the fibrinolytic system. Subsequent formation of microthrombi may lead to local perfusion defects, resulting in tissue hypoxia and organ dysfunction and depletion of clotting factors.

The complement system is another vital part of the innate host response, involved in several steps of the battle against pathogens; enhancing the phagocytic cell's ability to clear microbes by attacking the pathogens cell membrane, creating barriers that inhibit microorganism spread, and subsequently contributing to their clearance. The complement system is amplified by the coagulation system, which further fortifies this intricate interplay. Finally, the neutrophile contribute to innate immunity by releasing extracellular traps (NETs) containing proteolytic activity that traps and kills microbes, which further enhances vascular inflammation and the effects on the coagulation (48).

The host has several ways to protect itself against invasive pathogens, one being the described innate (non-adaptable) immunity. Another is adapted immunity. In contrast to innate immunity, adapted immunity is a highly specific immunological response to each particular microbe the host has encountered. Adaptive immunity consists of B and T-lymphocytes that together create an immunological memory and generate specific antibodies to pathogens in a sophisticated interplay.

Later on, in the course of sepsis, the sepsis-related immunological dysfunction in combination with a catabolic state may render the patient highly susceptible to opportunistic infections and infections with antibiotic resistant bacteria. This later phase is dominated by anti-inflammatory cytokines, apoptosis of T and B-cells and dentritic cells, exhaustion of T-lymphocytes, and expansion of anti-inflammatory immune cells (49, 50). Clinically illustrative, lymphopenia four days after sepsis diagnosis has been postulated as a biomarker for immunosuppression since it has been found to be associated with secondary bacterial infection and predicts mortality at 28 days and 1 year (51). Harmful effects of broad-spectrum antibiotics on the microbiota, the presence of endotracheal tubes, and several indwelling catheters add further risk to the patients. Also, viruses as cytomegalovirus, Epstein-Barr virus, herpes simplex virus, and human herpesvirus 6 are often reactivated during the course of the critical illness (52). However, interestingly, even in severe, lethal septic shock and multiorgan failure, limited cell death is found outside the lymph tissue at autopsy (53).

Morbidity, mortality, & long-term effects

Sepsis is one of the most common causes of hospitalization and premature death in hospital, and for survivors, sepsis may cause severe short- and/or long-term morbidity and sequelae. Mortality in sepsis ranges from 10 % to 60 %, depending on the severity of illness and what population is studied, with the lowest numbers reflecting care at general wards or ED, and the highest numbers illustrating mortality in ICU patients (22, 30, 35, 54-58). Mortality in sepsis has been reported to decline (29, 59), however whether this decrease is a true reflection of improvement in sepsis care, and subsequent patient outcomes or part of a Will Rogers Phenomenon ascertainment bias, need to be further investigated (60, 61).

When considering mortality in sepsis it is vital to include the patient's pre-morbid status and presence of limitation of care (62, 63). Hence, regardless of the excellence of current sepsis care, the mortality in sepsis may remain relatively high due to sepsis being the terminal diagnosis in patients with e.g., cancer, and in the multimorbid elderly patient. However, the opposite is also true, since patients with limitation of care at the ICU, often recover and are discharged back home (64, 65).

Approximately 50% of the patients who survive sepsis fully recover and about 30% die within a year. Of patients that die within a year, 50% die from direct complications of the sepsis episode (66, 67). Further, 40% of patients are estimated to be readmitted within 90 days (68). A causal relationship between sepsis and long-term complications has been suggested. However, due to insufficiencies in available studies, a substantial knowledge gap remains. Lack of information on pre-septic morbidity; use of research data retrieved from registers intended for other medical conditions, such as stroke or cardiovascular disease; patient materials selected by age or otherwise; and self-reported sepsis diagnosis in some studies, all are examples of current insufficiencies. These uncertainty factors in present long-term studies make the outcome precarious and generalizability limited.

Despite the existing knowledge gap regarding sepsis' long-term effects, the patient may be in need of medical support. The various types of problems that have been reported in sepsis survivors include decreased level of function, psychological problems, and cognitive dysfunction. Sepsis patients also have a greater need for care in the year after sepsis, compared to the year prior to the sepsis episode (35, 69-71).

The morbidity seen in sepsis may to some extent be preventable. One important improvement aspect may be to avoid delay in the sepsis care chain, which starts as soon as the patient contacts health care, in practice often at the ED. Another way to prevent deterioration and subsequent hospital care may be through early evaluation of the sepsis

patient after hospital discharge. Since 22 % of readmissions have been shown to be due to conditions that often can be treated in outpatient care, such as heart failure, urinary tract infections, and exacerbation of chronic obstructive pulmonary disease (COPD), by identifying and treating these patients timely, in the best case, patients may be more stable and further hospital care may be prevented (72). Also, applying other preventive measures, further described in the next chapter, may improve long-term outcome for sepsis patients.

Preventive measures

In his oath, "*primum non nocere*", Hippocrates stated more than 2 500 years ago that, "I will use treatments for the benefit of the ill in accordance with my ability and my judgment, but from what is to their harm and injustice I will keep them." (73). This oath is still essential in health care prevention of infections, and a basic responsibility towards our patients.

CDC estimates that 1,7 million hospitalised patients in the USA acquire health care-associated infections annually, while being treated for other health issues, and that one in 17 patients die due to these infections (74). Since preventing infections is the best and most efficient way to prevent sepsis, this area deserves appropriate attention. Although most community-onset sepsis episodes may be difficult to prevent despite advice on vaccination, preventive measures in the form of providing sepsis information to risk groups, and increased public awareness, efforts to try to prevent infections are still important (75, 76).

At the hospital and throughout the sepsis care chain, whether starting prehospitally or at the ED, the beneficial effects of applying early appropriate basic care hygiene routines and, more specifically, to prevent occurrence of some important infections, propagates throughout hospital stay (77). This fact has been illustrated by the ongoing COVID-19 pandemic situation, during which ED personnel in collaboration with hygiene and infectious diseases (ID) physicians applied life-saving hygiene measures, assuring that patients are cared for appropriately to prevent spread of infection. To enable adequate handling of the patient, it is vital to ensure easily available hygiene and ID expertise at the ED.

In addition to such countermeasures for infection spread as basic care hygiene routines, patient isolation, and use of appropriate personal protective equipment (PPE), other adequate measures to prevent infections that must be applied within the health care continuum are often initiated early in the care chain at the ED. These measures include

decubital prophylaxis, adequate nutrition, carefully considered urinary catheterization (78), and care of wounds. Also, venous catheters, inserted under non-sterile conditions prehospitally or at the ED, must be replaced as soon as the patient is stable (79).

However, huge barriers to achieving these preventive measures exist at the ED, due to crowding, high patient volume, delays in hospital admission, frequent interruptions, simultaneous care of multiple patients, use of areas such as hallways, and proximity of patients who often are only separated by curtains (80, 81). Further, personnel and patients encounter a large number of contacts that increase risk of transmission of infectious diseases, and the rapid room turnovers place high demands on the appropriate cleaning and disinfection of health care surfaces (77). Also, several types of patients presenting at the ED have an increased risk of incurring sepsis, since natural defence barriers often are diminished due to medication, recent surgery, age, and comorbidity. Patients with immunosuppressive conditions or treatment are a vulnerable group that often present diffuse and nonspecific symptoms despite severe infections. This patient group needs thorough information regarding how and when to contact health care, and often need acute assessment by a physician with special knowledge of infections. Close collaboration between ED and ID physician/staff is a prerequisite to enable everyday clinical practice to be as safe and beneficial as possible to the patient and health care personnel.

In addition to the customary preventive measures, special attention should be paid to the frail patients at the ED. Preventive measures in this patient group include preventing decubitus, malnutrition, dehydration, and fall injuries, and to enable this, frail patients are for example cared for in a real bed, instead of a cot, and have access to nutritional drinks and extra supervision during the ED stay.

WHO sepsis resolution

The World Health Organization (WHO) consists of 194 member states and was founded by United Nations in 1948 with the objective to enable people to attain the highest possible level of health (82*).* WHO applies prioritised health areas, and in the 70th World Health Assembly, in May 2017, sepsis was appointed a WHO "Global health priority" due to its high mortality and morbidity (83, 84).

Although difficult to ascertain, globally about 49 million sepsis cases account for 20% of all-cause deaths. Approximately 85% of sepsis cases and sepsis-related mortality occurred in low- or middle-income countries, and almost half of sepsis cases each year affected children, resulting in 2.9 million deaths. A majority of these deaths were

reported to be related to gastrointestinal or lower respiratory infections, and to a large extent preventable. Hence, efforts need to be adapted and focused on the most beneficial areas, such as prevention and early diagnosis and treatment of sepsis, for the best possible outcome (17).

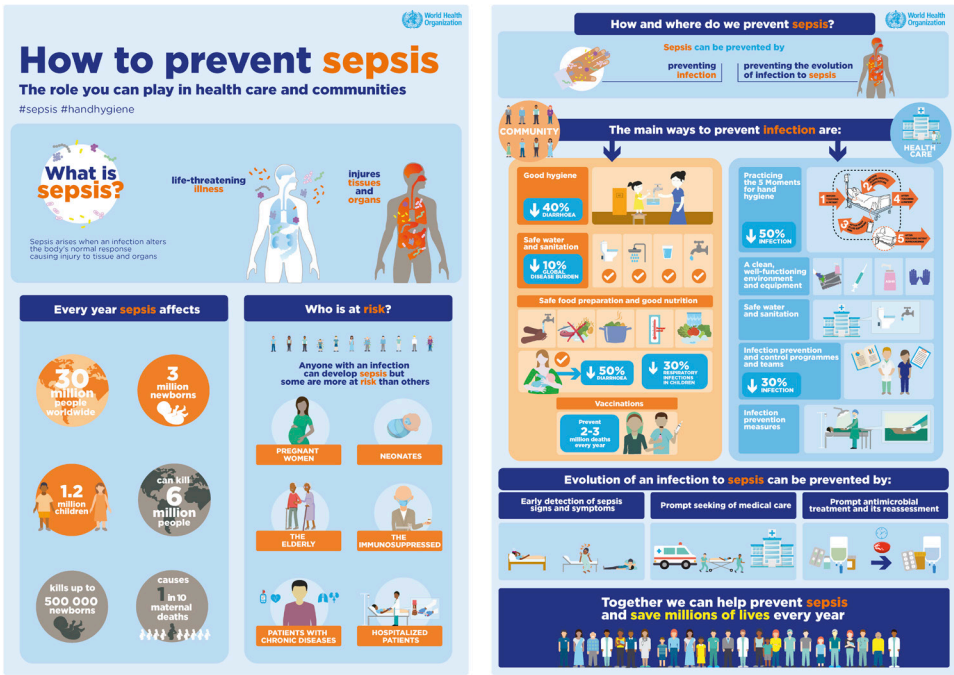


Figure 3. How to prevent sepsis, WHO.

To date, sepsis research has been limited in regions where sepsis effects are most deleterious, which highlights the importance of achieving standardised sepsis research to address these shortcomings. Further, sepsis mainly affects the susceptible population, leading to deleterious effects in, inter alia, neonates, pregnant women, or during puerperium in low-income countries. Consequently, efforts need to be adapted to particular situations in particular countries. Also, the sepsis resolution supports and reinforces former WHO programs for vaccination, access to clean water, sanitation, and hygiene.

The clinical picture

Aetiology & site of infection

Although all infections may eventually lead to sepsis, the most common infections comprise pneumonia, urinary tract and intra-abdominal infections, and skin and soft tissue infections (85). In patients that present to the ED with severe infections, 70%–80% have acquired the infection in the community, however, some patients have recently been treated in-hospital or in other health-care facilities, which needs to be properly addressed (41, 84).

The majority of studies that evaluate the role of the site of the infection exclude patients outside the ICU setting (86). Hence, evidence for the role of infection site in the early stages of sepsis, and in less severely ill patients, is insufficient. This is unfortunate, since different pathophysiological mechanisms may be of importance in different stages of sepsis, where the later stages may be dominated by immune dysfunction and related multiple organ failure, and less related to the site of infection (87).

In the ICU, a microbiologic agent is present in about 70% of the cases (85). In contrast to sepsis patients at the ICU, community onset sepsis patients encountered at the ED less often include microbial resistant pathogens, fungal, and opportunistic infections (85, 88, 89). Since the initial aetiology often is revised, in order to improve sepsis care and adjust empirical antibiotic treatment, the collection of specimens for cultures from, e.g., blood, urine, sputum, or wound at the ED is vital and needs to be emphasised in the ED situation (88, 90).

The importance of acknowledging international, regional, and local differences in the prevalence of infections, types of pathogens, presence of antimicrobial resistance, mortality rate, is crucial. The EPIC II trial, for example, demonstrated significant differences in Eastern Europe as compared to Western Europe (85). Hence updated knowledge of these epidemiologically different situations is vital.

Blood cultures at the ED - “Are they really necessary”?

As stated, about 70%–80% of sepsis episodes are community-onset, and the ED often represent patients’ first contact with health care systems. The importance of appropriate collection of (blood) cultures at the ED, before antibiotic administration, cannot be overestimated, since sepsis can be caused by virtually any infecting organism, including bacterial, viral, fungal, or parasitic organisms (84, 85, 91, 92). Also, collecting blood cultures early in the care chain reduces the risk of false-negative results due to previous antimicrobial exposure, and has also been shown to reduce antibiotic overuse and costs (93, 94).

Most guidelines recommend that at least two sets of blood cultures are taken to achieve relevant detection rates, each set comprising one aerobic and one anaerobic bottle rendering a total of 40 ml blood (95). However, strained circumstances at EDs sometimes risk leading to difficulties in achieving this task (96, 97). To facilitate collection of cultures at the ED, in contrast to previous recommendations, the same sting site including an extra vial for collection of a blood sample to be disposed of, may be advantageously used, since studies suggest a lower incidence of contamination with this approach (95).

The percentage of contaminants in blood cultures is often higher in the ED than in general wards because inter alia, higher personnel turnover demands continuous education in the technique of blood culture collection to improve the yield of this measure (98). Another important practical aspect in the ED, and prehospital setting, is the non-sterile situation that occurs at times due to urgent life-threatening situations and replacing peripheral venous catheters (PVC) when situation stability permits is of utmost importance. Also, placing blood culture incubators close to the ED may further improve the BC procedure at a relatively low cost (99).

Blood cultures have been shown to be negative in about 30%–70% of sepsis cases depending on the type and severity of sepsis. Ambiguous results regarding the prognostic value of positive blood cultures have been presented. Negative microbiological samples in sepsis patients have been associated with increased mortality, illustrating the value of a positive blood culture to enable adequate antimicrobial treatment. Conceivably, when blood cultures are negative or omitted, the culture-positive “red flag” indicating ongoing severe infection is not hoisted, which risks leading to decreased awareness of sepsis. However, when blood cultures are positive it may also reflect greater bacterial burden and, thus, poorer prognosis (88, 94, 98, 100).

The Sepsis Occurrence in Acutely III Patients (SOAP) study reports an almost equal prevalence of Gram-positive and Gram-negative bacterial infections in ICU sepsis, however discrepancy exists per specialty and when the blood cultures are taken (54). The predominating pathogens that cause community onset sepsis include the Gram-positive species *Staphylococcus aureus* and *Streptococcus pneumoniae*, and the Gram-negatives *Escherichia coli, Klebsiella* spp., and *Pseudomonas aeruginosa* (35, 85). Due to more patients being on immunosuppressive therapies, fungal sepsis has become more prevalent in recent decades. In the few studies available evaluating the heterogenous sepsis population at the ED, a similar pattern in aetiology was found (14, 23, 94). The role of the causative organism on mortality has shown divergent results. However, higher mortality rates for Gram-positive compared to Gram-negative organism have been found, a finding that may be explained by the higher prevalence attributed to the increased presence of methicillin-resistant *Staphylococcus aureus*. Also, increased mortality was demonstrated for severe sepsis secondary to infection by anaerobic organisms (101).

Although blood cultures are considered the gold standard for diagnosing bacteraemia, the shortcomings of blood cultures include the lengthy time required for growth, and risk of contamination leading to false positive results and subsequent redundant antimicrobial treatment, as well as the risk of exacerbating antimicrobial resistance (102). Also, the sensitivity of blood cultures in identifying a pathogen seems to be inferior to that of modern Polymerase Chain Reaction techniques (PCR), since 20% of culture negative sepsis patients were found to have positive whole-blood PCR (103). In addition, multiplex real-time whole-blood PCR may lead to a faster and more accurate diagnosis of bacteria and fungi, particularly in patients where antibiotic therapy has been started, resulting in a reduction of days on inadequate antimicrobial treatment (104, 105). On the downside, PCR analysis is costly, adequate DNA target sequences need to be identified, non-viable bacteria may lead to false positive results, and there are difficulties in identifying polymicrobial infections.

In conclusion, and to answer the question that began this section - Yes, blood cultures are necessary at the ED, and may even save lives.

Risk factors

An exact estimate of the prevalent risk factors for sepsis remains elusive, and although most are non-modifiable, risk factors add important information when evaluating patients at the ED.

Advancing age increases the risk for sepsis, which may be partly explained by the increased burden of comorbid conditions (34, 35, 106). Patients ≥65 years comprise 12% of the total population, but account for about 65% of sepsis cases (106). Further, women have been reported to have lower incidence of sepsis, although the cause of this gender difference remains uncertain. Hormonal effects on innate and/or adaptive immunity, cardiovascular responses, or differences in identification may explain some of the difference (14, 17, 34, 107, 108).

High risk features also include comorbidities that depress host defence such as cancer, renal and hepatic failure, diabetes type 2, obesity, asplenism and immunosuppressive and immunomodulating treatments. Moreover, presence of antimicrobial resistant bacteria, alcohol abuse, recent surgical interventions, indwelling catheters, or conditions associated with diminished skin integrity predispose patients to infections leading to sepsis (54, 109-112). Recent hospital stay and subsequent altered microbiome is another important risk factor associated with increased risk of sepsis. Prescott and colleagues reported a three-fold increased risk of sepsis within the first 90 days after hospital stay in this patient group (113).

Further, genetic factors including the innate and adaptable immune system have been associated with increased susceptibility to certain pathogens (114). The identification of subgroups of sepsis patients based on molecular endotypes has been suggested in order to add prognostic and pathophysiological value (115). On the upside, some risk factors are to some extent modifiable, such as alcohol abuse, cigarette smoking, and lack of exercise (116-118).

Symptoms & signs

Despite the development of numerous triage and supportive systems at the ED, the words of Sir William Osler, *"Listen to your patient, he is telling you the diagnosis,"* remain highly relevant, and in low- and middle-income countries this method may be the only available way to assess the patient (119).

Since sepsis may be caused by virtually any infecting agent and include several different foci, the clinical presentation, varies extensively (6, 54, 120, 121). The patient may present with non-specific sepsis symptoms as fever, chills, hypothermia, and malaise, which are hallmarks of the proinflammatory state rendered by the host response to infection, or by symptoms related to the infected organ such as cough, headache, dysuria, and skin changes. Common sepsis symptoms also include acute muscular weakness, confusion, dyspnoea, vomiting, diarrhoea, and acute severe pain in muscles,

abdomen, or elsewhere (41). Occasionally patients with severe forms of sepsis say, "It feels like dying". This is vital information, since encountering a life-threatening infection as sepsis for the first (and hopefully the last) time may be a new experience.

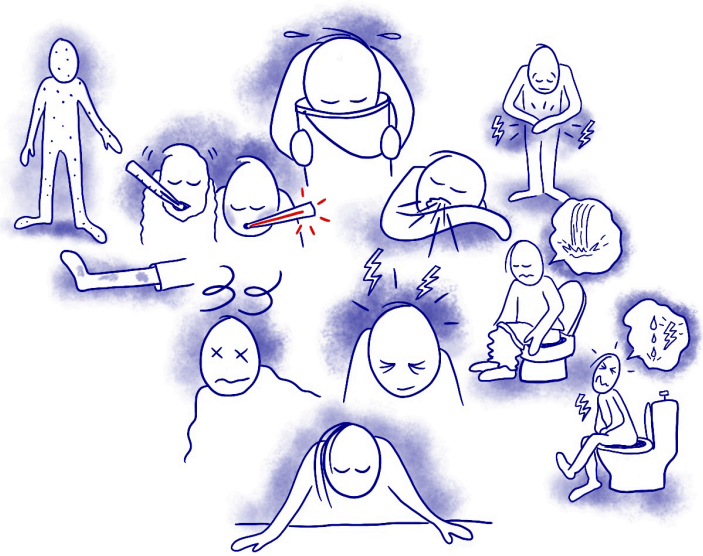


Figure 4. Sympthoms of sepsis

To identify patients prehospitally and at the ED, vital signs are measured. The presence of changes in body temperature, tachycardia, lowered oxygen saturation and blood pressure, tachypnoea, altered mental status, oliguria, and increased capillary refill time are evaluated (122-124). High body temperature signals risk of severe infection, and hereby facilitates early recognition, which may be one of the reasons for the association between low body temperature (<36 °C) at ED and higher 30-day in-hospital mortality risk in patients with suspected sepsis (125-127).

The sepsis patient usually presents after a relative short period of illness, from hours to days, and the presentation is often characterised by severe signs and symptoms of sepsis, although the opposite case, where symptoms are more diffuse and difficult to interpret, occurs frequently (128). When evaluating patients with severe infections at the ED, the risk of getting an insufficient medical history from patients with communication difficulties, an altered mental status, or language barriers, needs to be highlighted (91).

Organ dysfunction

Organ dysfunction is an important predictor of outcome in sepsis and is currently defined in accordance with Sequential Organ Failure Assessment (SOFA). The immune response in sepsis induces severe macro and microcirculatory dysfunction that leads to profound global hypoperfusion, injuring multiple organs as the kidneys, liver, lungs, heart, central nervous system, and hematologic system. Presence and extent of organ dysfunction constitutes the hallmark of sepsis and determines the prognosis in the sepsis patient (33, 41, 57, 111, 129). Given that sepsis is a continuum of processes occurring simultaneously throughout the body, the damage should not be considered as isolated events. To ensure accurate supportive treatment of sepsis-related organ dysfunction at the ED, early identification of organ dysfunction by measurement of vital signs is essential.

Central in sepsis-induced organ damage is a mismatch between the perfusion and the tissues metabolic requirements. This discrepancy is further exacerbated by the inflammation-induced dysfunction, the redistribution of systemic blood volume, and the impaired tissue oxygen utilization. A global hypoperfusion state exhibits in the patient as **hypotension**, decreased capillary refill time, cold extremities, and mottled skin (33, 129). Previously, septic shock in sepsis was considered solely a distributive shock with intact cardiac function. Today, we know that **systolic and diastolic dysfunction** may be present even in early stages of sepsis (130).

In the lungs, the altered barrier function due to endothelial changes leads to accumulation of protein-rich oedema fluid in the interstitial spaces and subsequent impaired gas exchange, hypoxemia, and hypercapnia. A similar process is present in the **gut epithelium,** leading to a vicious cycle of bacterial translocation and further gut injury by luminal contents (131). Although the intestinal system may not be considered in the SOFA evaluation, it represents an important body surface that contain high density of lymphatic tissue and immune cells and may be a target of therapeutic potential (132).

Sepsis related **acute kidney injury (AKI)** is common, and more than half of the patients with septic shock develop AKI leading to substantially increased risk of death (130, 133). Despite its high frequency, the mechanisms of sepsis-associated AKI are still not completely understood. Previously, septic AKI was thought to be attributed to impaired renal perfusion and tubular necrosis. However, AKI has recently been suggested to involve more complex mechanisms of cytokine and immune-mediated microvascular and tubular dysfunction (130, 134-135).

In the coagulation system, sepsis leads to a procoagulant up-regulation and a subsequent platelet consumption and coagulation factors depletion, leading to sepsis-associated thrombocytopenia and DIC associated with worse outcomes (130).

In the liver, hypoxic hepatitis due to reduced oxygen delivery and sepsis-induced cholestasis seem to explain the organ dysfunction in sepsis. Also, the profound hemodynamic alterations, microthrombi formation, sinusoidal obstruction, and endothelium dysfunction impairs liver perfusion leading to subsequent injury and hypoxic hepatitis (130).

Due to the impaired systemic perfusion compared to the metabolic requirement in the **central nervous system,** approximately 70 percent of critically ill patients with sepsis have some degree of sepsis-associated encephalopathy (130). In addition, cardiac arrhythmias and sepsis-induced coagulopathy may further increase the risk of ischemic and haemorrhagic stroke among patients with sepsis. Moreover, when areas like the brainstem are affected, the autonomic dysfunction is exacerbated, perpetuating the hemodynamic instability, and increasing the risk of death.

Diagnosis & prognosis

Considering the time-critical clinical course of sepsis, in which the early stages are highly amenable to treatment, early and correct sepsis diagnose at the ED is of huge importance. Yet, as previously described, diagnosing sepsis at the ED renders its own unique difficulties, since sepsis diagnosis requires an SOFA score of ≥ 2 SOFA points, and all SOFA parameters are not available at attendance (3).

In addition to the clinical evaluation by the ED or ID physician, laboratory testing including lactate levels, white blood cell count (WBC), C-reactive protein (CRP) or procalcitonin (PCT) concentrations, and the laboratory-demanded complete SOFA score assessment (thrombocytes, bilirubin, creatinine) are required, as are relevant cultures (e.g., blood, urine, sputum, wound). Further, diagnostic imaging may be useful to obtain correct diagnosis and subsequent effective sepsis treatment, including removal of the source of infection by surgery, or non-invasive interventional techniques, antimicrobials, and supportive measures.

In addition to inadequate antibiotics, source control, or supportive care, increased risk of mortality in sepsis has been associated with the extent of organ dysfunction, site of infection, aetiology, socioeconomics, and gender (41, 55, 101, 136). The outcome is also related to pre-septic morbidity, age, whether the infection is community acquired or health associated, and the presence of antimicrobial resistant bacteria (137, 138).

Also, the level of consciousness at presentation to the ED has been identified as a relatively strong predictor of mortality. Further, sepsis associated with health care-associated infections is often severe and has a high fatality rate. It can also be concluded that, the more that vital signs deviate from normal ranges, the greater the likelihood of mortality or admission to the ICU (139).

In an attempt to grade and classify the heterogenous group of sepsis patients, in a similar way oncologist have classified cancer patients with the Classification of Malignant Tumours (TNM), the PIRO (predisposition, insult, response, organ dysfunction) model, where four different aspects of sepsis are assessed, has been suggested. Predisposing factors as age, gender, and comorbid condition are considered, as well as site of infection, current pathogen, and if the infection is community or hospital acquired. Host response factors and the severity of the disease also render a way to describe sepsis in a standardized manner. Several of the four elements described are available at attendance at the ED, and the PIRO model may be applicable at the ED to assist personnel in identifying certain sub-phenotypes of sepsis with poorer prognosis as early as possible (140).

Another way to assess and stratify sepsis patients at presentation to the ED, based on routinely available clinical data, is suggested by Seymour et al. as part of the Sepsis Endotyping in Emergency Care (SENECA) project, which presents four distinct clinical phenotypes based on host-response patterns and clinical outcome (α, β, γ, δ) that may allow improved decisions on evaluation, treatment, and surveillance in sepsis (141).

Antibiotics, source control, and supportive measures

When considering the improvement in sepsis ED care in recent decades, it is notable that the situation used to be quite different, with huge delays in administration of antimicrobial treatment occurring after the initial encounter with the physician in severe infectious diseases such as meningitis (142). Antibiotic administration at the ward was the norm, and we have come a long way in this regard. Despite the failure of many novel therapeutics in clinical trials, sepsis care has improved considerably.

Source control, including drainage of abscesses, removal of foreign bodies, and debridement of devitalized tissue, was first described in cuneiform Mesopotamian and Egyptian hieroglyphs, circa 3 000–600 years B.C. Hippocrates also applied similar techniques, and drained empyema with a thin tube into the lower costal spaces. The phrase *"pus bonum et laudabile",* was associated with pus which flowed, in contrast to

the malodorous and stagnant pus related to poor prognosis. Nearly 500 years later, the Roman physician Cornelius Celsus coined the phrase *"rubor et tumor cum calore et dolore"*, i.e., the redness and swelling with heat and pain, describing the process of inflammation, and suggested further that pus should be allowed to exit from wounds by not suturing them too tight. Later, in the 19th century, microorganisms were discovered, and Virchow added the fifth sign of inflammation, *"functio laesa",* loss of function (143).

Source control includes all measures applied in order to control an infectious focus, and to restore optimal function in the area of infection. An experienced surgeon once explained source control in infectious diseases as "a clogged pipe, or a hose with a leak". Surely, surgery is a lot more complicated, and interventions range from percutaneous drainage with radiological guidance to open traditional surgery, like laparotomy and thoracotomy (144, 145).

Although the principles of source control have been known for centuries, sepsis research has mainly focused on other measures, such as early recognition and timely antibiotics. Surgical approaches have evolved through principle and tradition, and only a few randomised clinical trials are available, due to the need to tailor the intervention to the unique circumstances, making it hard to standardise surgical therapy. Nevertheless, the area is vital, since one-third of ICU-treated sepsis patients are reported to be in need of source control (145). The optimal timing for source control measures is unknown, since prospective randomised trials are lacking, but SSC guidelines suggest adequate measures within twelve hours after attendance to the ED. However, the general rule is that source control should be achieved as soon as possible (92).

At the beginning of the 20th century, Paul Ehrhlich coined the term 'chemotherapy'. Ehrhlich later developed the first treatments against Treponema Pallidum, Salvarsan and Neosalvarsan, transforming syphilis treatment completely, and for twenty years these were the only treatments available for bacterial infections.

The discovery of **antibiotics,** from an extract of agar plate mould, by Alexander Fleming in 1929, would change the course of medicine. Fleming determined the antibacterial effect of penicillin on *staphylococci* and other Gram-positive pathogens. However, difficulties in purifying the compound led to waning interest in 'chemotherapy', and a decade later, the German pathologist and bacteriologist Gerhard Domagk discovered sulfamidochrysoïdine (Prontosil), shown to be effective in treating bacterial infections caused by *streptococci* in the body, despite having no effect in a test tube. A French scientist later found that Prontosil needed to be metabolised into sulphanilamide to be active, and interest in bacteria chemotherapy returned. As the first broad-spectrum antibiotic available, years before penicillin, sulpha had a central role in preventing and

treating wound infections during World War II (146). Domagk received the Nobel Prize in Medicine and Physiology for this discovery in 1939.

The success of sulpha sparked new interest in attempts to purify penicillin. In 1939, a research group in Oxford, including Ernst Chain and Howard Florey, purified penicillin from a strain saved from Fleming, and injected eight mice with virulent *Streptococcus*. Half of the mice received penicillin and the other four constituted an untreated control group. The next morning all control mice were dead, and the treated mice were alive. These experimental findings, and a description of production and purification of penicillin, were published in *The Lancet* in 1940, and in 1941 the first person to receive penicillin was a policeman exhibiting a serious infection with multiple abscesses. The policeman improved significantly, but the supply of penicillin was unfortunately not sufficient for a full treatment course, so he died a few weeks later. Other patients received the drug with sustainable and successful effects. The revolutionary effect of penicillin resulted in Alexander Fleming, Ernest Chain, and Howard Florey receiving the Nobel Prize in Medicine and Physiology in 1945. The secondary effects of penicillin research were huge, leading to discovery of many other antibiotics in the coming years, including streptomycin, chloramphenicol, erythromycin, and vancomycin (146).

Antibiotic treatment is a cornerstone of sepsis care, and the empirical choice of antibiotics is based on the likely pathogens, site of infection, pharmacokinetics, and whether the infection is acquired in the community or health care. The decision is a delicate balancing act between ensuring adequate acute treatment for the life-threatening sepsis patient with subsequent high mortality, and at the same time hindering the inappropriate and excessive use of antimicrobials which enhances the risk of antimicrobial resistance (147). Despite perennial attention, adherence to sepsis guidelines remains sometimes poor, and initiatives to implement and evaluate sepsis interventions are still needed (92, 148, 149). In antibiotic treatment, focus also needs to involve decisions on subsequent dosing, since this is essential to achieve adequate antibiotic blood concentration, which is of great importance in critically ill patients (149, 150). By introducing antimicrobial stewardship as an adjuvant in sepsis management, these aspects of antibiotic treatment may be more effectively handled (96, 151).

Supportive measures in sepsis care are more recent. In 1964, a vascular surgeon in Boston, USA, Edward Frank, published a protocol for the management of septic shock, including continuous bedside attendance by a senior physician. In addition to cardiac and respiratory resuscitation, he recommended correction of hypovolemia, support for respiratory insufficiency, inotropic support with cautious use of pressors for hypotension, and the identification and prompt treatment of the causative infections.

Few hospitals were able to follow these recommendations in the 1960s, and while some of Frank's suggested interventions were irregular, others remain accepted practice fifty years later (152).

The evidence bases for supportive measures in sepsis care remain relatively weak, despite being part of current daily clinical practice for decades. There is still controversy regarding, for example, what fluid to use, and when and how to exert vasoactive therapy (92). The Early Goal Directed Therapy (EGDT), including several different interventions within 6 hours, administration of fluids, vasopressors, and transfusions of red blood cells, was suggested by Rivers et al. in 2001 (148). In this randomised study, 263 patients with severe sepsis and septic shock were randomised to EGDT or standard care, resulting in a 16% absolute risk reduction in mortality in the EGDT arm. However, since 2001, the EGDT has been re-evaluated in several studies, including the Protocolised Care for Early Septic Shock (ProCESS) trial, Protocolised Management In Sepsis (ProMISe), and the Australasian Resuscitation in Sepsis Evaluation Randomised Controlled (ARISE) trial (120, 153, 154). In these studies, no mortality benefits were found when applying EGDT compared to standard care. In summary, current research supports fluid administration in septic patients with hypotension, however the amount of fluid administrated will vary due to comorbidities and severity of sepsis. Further, other previously accepted 'truths' have been reconsidered when research has shown interventions to be less beneficial. An example, not limited to sepsis patients, is oxygen therapy, which was shown to be associated with inferior survival rates when targeting the interval 97–100%, compared to 94–98% (155).

In addition to fluid resuscitation, other essential parts of the ICU care include vasoactive treatments, ventilators, and renal replacement therapy (RRT). Also, corticosteroids, glucose control, deep vein thrombosis prophylaxis, stress ulcer prophylaxis in patients with risk factors of gastrointestinal bleeding, and nutritional support should also be considered and sometimes initiated at the ED in severely ill sepsis patients (92, 111).

Advances in sepsis care involve individualised approaches to treatment. The trend from a protocol-based care comprising a one-size-fits-all approach to a more personalised treatment of sepsis is appealing. Also, antibiotic stewardship may contribute with knowledge regarding tailored decisions in sepsis care. Several immunomodulatory agents are available. However, it remains unclear which patients will benefit from individualised approaches to treatment, and, in the future, treatments may be based on genetic profiles (114, 115). Also, to enable administration of these modern interventions, early recognition at the ED and adequate monitoring of the sepsis patients in order to identify deterioration at an early phase is vital throughout the sepsis care chain.

Sepsis at the ED vs. sepsis at the ward or ICU

A sepsis snapshot - the importance of vigilant ED staff

Sepsis studies are often conducted from an intensive care perspective, for several reasons: the most severely ill sepsis patients are cared for at ICU, patients there form a well-defined cohort where vital signs and laboratories are frequently monitored, and patients are systematically evaluated by ICU personnel. However, when applying an ICU perspective on sepsis, in addition to a considerable selection bias, important upstream aspects in sepsis care as early recognition are left out. Moreover, the research findings risk being non-generalisable and less beneficial for large patient groups, as the elderly, patients with limitations of care, and misjudged patients. Ineligibility for ICU care certainly does not mean that patients would not benefit from high acuity levels and subsequent adequate sepsis care (14, 65).

To optimise sepsis care, it is important to identify sepsis patients with a high risk of poorer prognosis at the earliest time point prehospitally or at the ED since proper initial interventions will reflect throughout the sepsis care chain. Although labour intensive, research in the ED setting is needed to minimise selection bias in sepsis research. However, an ED perspective to sepsis also offers unique challenges, e.g., strain and overcrowding in an ED with a high turnover of severely ill patients with a wide spectrum of life-threatening conditions.

The exceptional situation at the ED is demanding for patients, relatives, and personnel. For patients and relatives, ED visits are often characterised by the waiting time, anxiety and concern they entail. For ED personnel, high stress levels are inevitable, since they must handle high workloads under pressure without reduced quality and efficiency. On a daily basis, the ED staff witness how life can change dramatically in a moment, while myriad benign conditions are handled skilfully and swiftly. The ED personnel are remarkable in this respect, treating patients from the complete medical strata, as well as dealing with the consequences of language barriers, drug-addicted patients, and the most vulnerable members of society. Also, vigilance and great efforts are required of the

ED staff, who are first to encounter emerging infections, and who, during mass casualties and public health emergencies, must rapidly treat huge amounts of patients in need of urgent medical attention (156, 157).

Another important aspect at the ED is prevention of health care-associated infections, which have traditionally focused on in-patient care (158, 159). Since more than half of all health care-associated infections are estimated to be preventable, the ED, as a bridge between ambulatory and hospital care, offers an important opportunity to apply preventive measures early in the care chain (77).

Further, sepsis recognition and risk stratification at the ED place a great deal of responsibility on the individual ED physician, compared to other medical emergencies. For example, patients with ST-elevation acute myocardial infarction rapidly receive a relevant screening with ECG and troponin initiated by the ED physician, and thereafter the cardiologist decides on treatment, classifies the type of infarction, cardiovascular damage, etc. In contrast to the AMI situation, patients with sepsis need an extensive evaluation to address the sepsis severity and organ dysfunction at the earliest time point, without sufficient screening tools and without having access to adequate information to enable SOFA evaluation. Surely this aspect hampers improvement work and emphasises the importance of developing relevant sepsis triage tools applicable in the ED setting.

In sepsis patients, therefore, the principle of "treat first what kills first" can be supplemented with "judge first and calculate later."

Quinten et al. 2018

To enable successful implementation of the Sepsis-3 in health care, the criteria will need to be adapted to such various settings as the ED. Primarily, this concerns the evaluation and grading of respiratory failure and blood pressure. Since respiratory Sequential Organ Failure Assessment is based on analysis of arterial blood gas that is lacking in most sepsis cases at the ED, using pulse oximetry (Sp02), although less exact, will be needed. Another parameter that needs to be customised to care outside the ICU is the mean arterial pressure (MAP), which can be calculated if needed from systolic and diastolic blood pressure. Another complicating aspect of the Sepsis-3 definition is that specified time frames for the organ dysfunction are lacking, which further hampers the appropriate diagnosis of sepsis (3). Also, the fact that the criteria for shock in sepsis require vasopressor-sustained MAP *and* elevated lactate levels, somewhat inconsistent with shock due to other conditions, may also need to be addressed.

In addition to patient or health care delay, the delay in sepsis care at the ED may also be influenced by the ICU capacity that varies greatly between different countries and hospitals, a fact highlighted during the ongoing COVID-19 pandemic (160). Further, not all patients will benefit from ICU care, hence an important assignment for the ED and ID physicians is to identify which patients will benefit from intensive care and who can be adequately handled at the general ward, to add quality to the ICU consultations (161).

Last, but not least, a decisive part of the sepsis chain is prehospital care. Suspected infections are common in the prehospital setting, and up to 80% of patients with severe sepsis admitted to the ICU from the ED arrived at ED by ambulance (162, 163). It is of great importance to identify sepsis patients prehospitally, since time to treatment has been shown to be halved when the septic patient is identified prehospitally (164). However, sepsis recognition is highly variable in the prehospital setting, and about one third of patients with severe infections present with normal vital signs to the ambulance, hence the difficulties in applying Sepsis-3 in a prehospital setting render even more challenges (165-167).

Timely interventions - how early is prompt?

Timely antibiotic treatment reduces pathogen burden, modifies the host response, and reduces the extent of organ dysfunction. However, the exact temporal benefits of antimicrobial treatment may be unattainable since randomised trials would be unethical. However, studies evaluating the outcome in sepsis patients receiving inappropriate antibiotics, showed increased organ dysfunction and mortality (168, 169). In septic shock, the importance of the timeliness of sepsis treatment and the appropriateness of the first dose of antibiotics has been clarified (88, 92, 170-174). Further, in sepsis patients without shock, mortality benefits may also be conceivable in other rapidly progressive infectious diseases (170, 171).

An interesting and abundantly cited protocol-based ED study was conducted in New York State, USA. In this study, a protocol including blood cultures, lactate, and broad-spectrum antibiotics within 3 hours, and assessment for the need of vasopressor within 6 hours, was applied, rendering a decrease in risk-adjusted in-hospital mortality from 28.8% to 24.4% in the group receiving the protocol-based sepsis care, while it remained unchanged in the control group (175).

In another ED study, conducted by Seymour and colleagues, about 50 000 patients with severe sepsis and septic shock were included. In this study, mortality correlated with delay in bundle application, including measurement of lactate, collection of blood

cultures and antibiotic treatment. However, the correlation was strongest in a subgroup of patients receiving vasopressor treatment, i.e., patients with suspected septic shock (171). Another ED study of 35 000 patients with sepsis that received antibiotic treatment within 6 hours, showed that every hour of delay of antibiotics increased the absolute mortality in uncomplicated sepsis patients by 0.3%, in severe sepsis by 0,4%, and by 1.8% in patients with septic shock (170).

One of few randomised controlled trials was conducted in a prehospital setting, randomising about 2 700 patients to pre-hospital antibiotics or antibiotic treatment at the ED. In this study, time to antibiotic treatment decreased significantly but no differences in outcome were found, regardless of the severity of sepsis (176).

Interestingly, the two central consensus groups SSC and Infectious Diseases Society of America (IDSA) diverge in what level of urgency is needed in sepsis interventions. Currently, SSC recommends the use of bundles, including standardised broad-spectrum antibiotics to all patients with sepsis within one hour (92), whereas IDSA objects to this assessment, considering it being too rigid and standardised, and that the recommendations risk leading to antibiotic resistance and adverse effects for the patient (147). On the one hand, delays in antibiotic administration may lead to deleterious effects, while on the other hand focusing on speed in sepsis interventions may come at the expense of clinical accuracy.

Lactate – an accessible & beneficial biomarker at the ED?

Lactate acid was isolated in 1780 in sour milk by Carl Wilhelm Scheele (177), a Swedish chemist, however it was the German physician–chemist Johann Joseph Scherer who in 1843 first demonstrated lactate in human blood, during deterioration in puerperal fever (178). Several hundred years later, understanding and use of lactate in health care has developed considerably, and today it is an elemental tool in the management of severely ill patients at the ED.

Lactate acid is formed in cell metabolism from pyruvate, which cannot be disposed via the citric acid circle. Initially, lactate was considered solely a metabolic waste product, but we now better understand lactate's role in energy use and oxidation/reduction reactions, even under aerobic conditions (179). And in contrast to previous understanding, lactate may not be elevated as a consequence of diminished perfusion, but rather is accelerated glycolysis from adrenergic stress, thought to be an important cause of hyperlactemia in sepsis patients, and particularly in sepsis patients without overt shock symptoms (180).

Measurements of venous lactate correlates well to arterial lactate, and is preferable at the ED, since arterial measurements may be painful, time consuming, and challenging in certain patient groups (181). Venous lactate levels are easily taken and may be readily monitored for trends within minutes with "point of care models", with adequate correlation to traditional methods. In Sepsis-3, lactate is included in the septic shock definition, where a lactate level above 2 mmol/L, in combination with hypotension requiring vasopressor therapy to maintain a mean arterial blood pressure of 65 mmHg or greater, is a requisite for meeting the criteria. However, as a marker for organ dysfunction, lactate has been omitted from the updated guidelines (3).

The early measurement of lactate enriches the ED and prehospital risk stratification and is an important supplement to vital signs and other clinical findings to identify sepsis patients with poorer prognoses (182). Also, valuable clinical support from lactate in occult hypoperfusion is essential since elevated lactate may reflect a relatively high mortality rate despite normal blood pressure (183). While a value within normal range does not rule out sepsis, an elevated value may identify patients with non-specific ID presentation, a not-infrequent occurrence at the ED.

The inability to clear lactate is associated with poorer prognosis in several emergency conditions besides sepsis, including trauma and cardiac arrest (184, 185). Patients admitted with a lactate level greater than 4 mmol/L represent, in most cases, non-infectious conditions like seizures, mesenteric ischemia, trauma, burns, toxins, or thiamine deficiency (186). In patients with elevated levels of lactate with no evidence of circulatory shock or general hypoperfusion, the patients' medical history (e.g., hematologic malignancy), ongoing medication (e.g., biguanide therapy), and potential exposures must be thoroughly evaluated.

A prospective ED study of patients with infection and an initial lactate level ≥4 mmol/L showed that mortality rates increased with increasing levels of lactate, and mortality in patients with lactate level ≥4 mmol/L was associated with a 28% in-hospital mortality (187). In another study of patients with severe sepsis, the prognostic value of lactate was found to be independent of shock state (188). Thus, the prognostic value of lactate may best be viewed as a continuous variable rather than a dichotomous ditto. In SSC, evaluation of lactate is recommended within 2–4 hours after initiation of therapy, to assure the physician that initiated treatment is working well, but also to indicate the need of a higher level of surveillance (92). Although consensus regarding exact goals or time frames for the lactate clearance is missing, a normalisation of the lactate level as soon as possible appears to be a reasonable goal (189).

Not all sepsis is severe, and vice versa

As previously stated, due to inconsistency and inaccessibility, the diagnostic criteria for sepsis risk becoming less relevant in an ED setting. As clinicians, we aim at identifying patients with urgent severe infections with poor prognosis, regardless of classification, and, despite support from triage tools and biomarkers, a skilful clinical approach to the patient with severe infections is crucial (161).

"A good doctor takes care of the patient not the disease"

W. Osler

Several important urgent patient groups risk being omitted when applying the Sepsis-3 definitions at the ED, including patients with pneumonia without organ dysfunction, patients with (viral and) bacterial meningitis with predominating symptom being headache, patients in the early stages of necrotizing fasciitis without organ dysfunction, immunosuppressed patients with diffuse infectious presentation, and patients with inability to communicate their medical history (8, 128). Urgent infections are common in the elderly, and often have an atypical presentation in this patient group including altered mental status, lack of fever, lethargy, loss of appetite, and incontinence, which are all nonspecific markers of infection (190, 191). Importantly, these patients need to be properly addressed to achieve necessary interventions (128).

To date, it is uncertain whether Sepsis-2 or Sepsis-3 best identifies patients with severe infections in need of timely interventions. However, when considering sepsis in a dichotomous way, instead of a continuous spectrum from mild infectious disease to full-blown septic shock in patients without organ failure, this risk leading to delayed recognition and therapeutic intervention. Regardless of current definitions, the approach to the patient with suspected infection in the ED setting must be clinical and adapted to the ED situation.

Implementing sepsis guidelines in an ED setting

In contrast to the considerable effort in clinical research, surprisingly limited attention has been paid to ensuring that research findings are appropriately implemented in daily health care routines. The health care system is complex and involves several vital interacting components, including different professions, generalists, and intensely specialised participants, as well as different organisational levels, all collaborating to ensure best treatment of patients (192). The ability to coordinate medical interventions requires knowledge, communication skills, and humility, and may be challenging, but the unique situation when implementing interventions at the ED adds an extra dimension of complexity to the process.

Although available research is limited regarding the cost effectiveness of implementation of interventions in health care, knowledge is steadily increasing. Implementation of new healthcare guidelines often renders modest changes in performance, which may be explained by the fact that research-distribution methods applied in daily healthcare include the passive dissemination of information by mailing of educational materials, and publication of consensus conferences in professional journals. Unfortunately, regardless of importance, the impact of these methods has been shown to be insufficient. To achieve altered practices and ensure sustainable results, specific and intensive implementation strategies are necessary (193).

At best, implementation at the local and regional level are actively coordinated. Factors associated with successful implementations include educational outreach visits, recurrent reminders, and workshops. A multifaceted approach combining audits, feedback, reminders, and local consensus processes has proven to be more effective (194). The use of local opinion leaders, local consensus processes, and patient-mediated interventions has shown variable effectiveness, and guidelines, lectures, and distribution of educational material are unlikely to make substantial impact. To achieve a successful and sustainable implementation, a relevant long-term plan, including key tasks and job descriptions, roles, and responsibilities is vital, and economical resources must also be ensured. Also, when planning implementation of new guidelines, it is vital to fully recognise and adequately address the influence and importance of health care organisational factors (193, 195).

When implementing changes in an ED setting, special considerations must be addressed, including high personnel turnover, overcrowding, poor patient flow, and the preparedness of the healthcare personnel (196, 197). The base-line situation should also be evaluated to identify if and where practice diverges from guidelines, although such evaluations are labour intensive. To determine the impact of the implementation,

continuous monitoring of process outcomes must be assessed as compliance. The concurrent monitoring of patient-oriented outcomes ensures that the implementation strategy leads to the anticipated effect. Useful tools to evaluate and monitor the quality of sepsis care, such as real-time measurements of quality markers of sepsis care, are advantageous and a way to achieve quality in sepsis care at the ED.

Further, knowledge and behavioural gaps at each local ED need to be addressed accordingly, and since all relevant stakeholders should be involved in a team-based approach, strategies for communicating and facilitating the desired changes will be acquired simultaneously and at multiple levels (196). Also, interventions should target clinical problems where sufficient evidence is present, and where emergency care can be significantly improved. Although it may be enticing to apply general implementation strategies, a certain degree of tailoring is often advantageous when implementing at the ED, since local culture and circumstances play a significant role in the results of the intervention (198).

In the health care, skilful personnel are the most valuable resource, performing highly specialised sepsis care relentlessly. Hence, in improvement work, attention must also be paid to the individual human beings who bring their own values, attitudes, and opinions to daily practice. Professionalism in the ED, in addition to skills and experience, is also ensured by correct prioritisation that enables workflow. Due to the unique and often crowded ED environment, it is important that the ED staff are provided with adequate support to enable change, and that the ED workflow is not disrupted by new procedures, but that guideline changes rather facilitate daily routines and empower personnel (196).

It has proved difficult to implement SSC bundles at the ED. However, in a large Spanish prospective multicentre study, the SSC guidelines were implemented by applying a standardised protocol and special training of physicians and nursing staff, rendering improvement in sepsis management bundles and reduced mortality (172). Another important example of a multifaced intervention was conducted in an ICU setting to improve sepsis care in accordance with SSC (199). In this study, local interdisciplinary teams, education materials, audits, and feedback of bedside compliance were applied, leading to improved compliance with the resuscitation bundle, improved quality of sepsis care, and decline in mortality. Even though the study was not applied in an ED setting, it illustratively targets the important aspect of monitoring both process outcomes, as compliance, and patient related outcomes. Although not applying exclusively an ED perspective, a few studies have evaluated the implementation of improvement work for patients with sepsis by comparing costs and health effects before and after implementation (200-203).

To enable standardisation of reporting in evaluation of complex health care interventions, valuable guidelines adhering to the recommendations of the Equator NETWORK, such as the Criteria for Reporting the Development and Evaluation of Complex Interventions in healthcare (CReDECI), have been developed (204). The CReDECI consensus recommendations were developed in 2012 and include 13 guiding items for a comprehensive reporting of the development, feasibility and piloting, and evaluation of a complex intervention in health care (205).

Triage

An introduction to sepsis triage

To realise that our present knowledge of health care triage originates from casualties of war is disheartening. Although much of its history remains obscure, the documentation of triage dates back to at least the Napoleonic era, when the urgent need to prioritise casualties was evident. The early triage models were represented by two different segments, one focusing on returning soldiers to the front despite war injuries, the other with a more philanthropic focus. The philanthropic focus was represented by military surgeon-in-chief to Napoleon's Imperial Guard, D.-J. Larry, who performed hundreds of amputations in battle, and developed a system that categorised patients into three groups according to the severity of their illnesses or wounds and established that the most seriously wounded soldiers should receive priority attention, regardless of rank or distinction. Simultaneously, another of Napoleon's military surgeons, Pierre-François Percy, developed the ambulance system, in which a four-wheeled vehicle that conveyed surgeons and their equipment to the battlefield was developed, and which enabled wounded soldiers to return to battle more promptly (206, 207). These two systems continued to develop throughout the military conflicts of the nineteenth and twentieth centuries (208).

In addition to military current triage systems, medical triage includes prehospital and ED triage, inpatient triage, and mass casualty triage, where needs exceed the available resources. The first triage system, The Simple Triage and Rapid Treatment, was developed in the US in the 1980s (209). Over the years, algorithms to increase the benefits for each individual patient, and to prioritise patients with the most urgent need based on physiological data, have been developed. The algorithms applied, such as the Emergency Severity Index, in the US (210), the Manchester Triage Scale (MTS), used in the United Kingdom (211), the Canadian Triage and Acuity Scale (212) and the Australian Triage Score (213), often use a 3- or 5-level system. In Sweden the triage system most often used in the EDs and prehospitally is the Rapid Emergency Triage and Treatment System (RETTS), and, in surveillance, National Early Warning Score (NEWS/NEWS2) is applied (214, 215).

The burden on emergency care is increasing and patient expectations are rising, as are demand, financial pressure, and the ability to apply advanced medical interventions in patients that previously would have been non-survivors. It is vital to separate demand from need when handling patients prehospitally and in the ED, to enable appropriate focus in accordance with the philanthropic approach by D.J. Larry. However, developing a system that can span the full strata from critical illness and injury to minor illnesses and minor injury is a true challenge. Adding additional focus on certain patient groups further complicates the task.

Further, the differences between a screening tool and a risk-stratification tool need to be acknowledged, since a screening tool aims to identify patients with a particular disease from a larger pool of patients. Once these patients are identified, a risk-stratification tool can be applied to determine their likelihood of meeting a particular outcome. In addition to the initial triage prehospitally and at the ED, adequate surveillance of sepsis patients is necessary, since patients with less severe sepsis may progress to shock after attendance at the ED (58).

Early identification & risk-stratification - vital signs

Although no standardised system can replace the evaluation of an experienced and skilful physician or nurse, an easy and accessible way to assist in identifying, prioritising, and monitoring sepsis patients is to measure vital signs. The advantages of this established routine are several: vital signs can be promptly and repeatedly measured by all health care workers, and may be used objectively for clinical evaluation, triage, decisions on treatment and in monitoring and surveillance. Also, in patients with language barriers or other communication difficulties, vital signs can contribute information to the initial and critical evaluation, pending interpreter or information from relatives.

Patients with sepsis are identified in all areas of health care, and since a majority of sepsis cases are community-onset, patients are often diagnosed at the ED (84). In order to reach the therapeutic goals of SSC and IDSA, it is therefore important to focus on early recognition and triage of sepsis in the unselected patient material present at the ED. Ideally, patients with severe infections should be identified before organ dysfunction is established, therefore it is questionable to have a sepsis definition that recognises organ dysfunction once it has occurred (3).

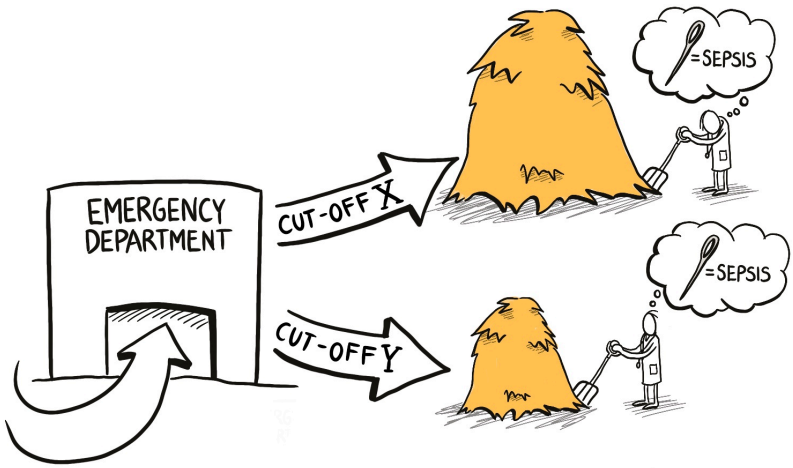
Despite being widely used at the ED, surprisingly limited knowledge about vital signs in relation to clinical outcomes is available (14, 216-218). Current screening scores lack

sensitivity or specificity, and, in some cases, both (219, 220). Another important limitation is that most available studies have evaluated need of ICU or mortality, rather than the identification of patients with the most urgent need (220). Since sepsis patients are often elderly, have comorbid conditions, and/or limitation of care, it is important to include the full spectrum of patients that present to the ED (14).

To identify, prioritise, and remedy sepsis patients adequately in the daily routine at the EDs, triage models with a common denominator of measuring vital signs to systematically divide emergency patients into categories based on medical degree of urgency, have evolved. The qSOFA was developed to replace SIRS in identifying sepsis patients outside the ICU. qSOFA includes values for circulation, respiration, and CNS, and concerns have been raised that a screening tool like this should not be limited to three organ parameters, but should rather include the whole spectrum, including respiratory rate, oxygen saturation, blood pressure (systolic and diastolic or MAP), heart rate, and conscious state (9, 15). Also, the qSOFA only evaluates whether mental status is abnormal, not whether it has changed from baseline sensorium (15).

Regrettably, both SIRS criteria and qSOFA have shown to be insufficient screening tools in sepsis, being too unspecific and/or insensitive (10-13, 221-223). The Modified Early Warning Score (MEWS) and the similar National Early Warning Score (NEWS) seem to perform somewhat better, compared to qSOFA (224-226). However, not much is needed to perform superior to the qSOFA in this aspect, thus the comparison adds little or no relevance to the clinician. In theory, an advantage of using NEWS throughout the care chain could be that evaluation over time would improve and applying an equivalent terminology may be beneficial. This may seem appealing, but one must be aware of the difference between triaging an unselected large group of patients and monitoring or risk-stratifying patients with an established or suspected diagnosis. Some triage models add information about presenting symptoms and medical history to the information provided by the vital signs, a fact that may increase valuable focus on, e.g., immunosuppressed patients, patients at increased risk of bacteria with antimicrobial resistance, or patients who have visited endemic risk areas (214).

NEWS (National Early Warning Score) developed in 2012 and updated 2017, is based on the measurement of six physiological parameters (respiratory rate, oxygen saturation, body temperature, systolic blood pressure, pulse rate, and level of consciousness). The color-coded risk scale is divided into four categories, low, low/medium, medium, and high, and each parameter is graded from 1–3 with a total value of 20 (215). The guidelines also contain advice on adequate urgent measures and follow-up evaluations.



NEWS' ability to predict cardiac arrest, death, or unplanned intensive care of critically ill patients on a ward has a certain scientific basis (227). However, the corresponding research in sepsis patients is limited, and NEWS guidelines in sepsis care are essentially based on clinical consensus rather than prediction models (215). The scientific basis for NEWS' ability as a triage tool is often studied in non-representative, small patient cohorts and it is sometimes combined with a triage system like the Manchester Triage Scale (MTS) (11, 228). In several studies, NEWS has shown good sensitivity at the cut-off of 3–5 points, however, the specificity is very low at this level, which inevitably risks leading to depleted triage function in both the ED and ward (11, 228-231). Hence, establishing an appropriate cut-off for NEWS has proved to be problematic. A recent Swedish study comparing the ability of NEWS2 and RETTS to identify sepsis patients has been conducted. Unfortunately, in this study severe sepsis within 72 hours is evaluated, thus reflecting NEWS2' ability in monitoring rather than its triage function, which renders the results from this study less relevant in terms of ED triage (232).

In Sweden the triage system **RETTS** (Rapid Emergency Triage and Treatment System), which combines vital parameters and acute symptoms in accordance with ***Emergency Symptoms and Signs*** (ESS) to categorise emergency patients of different acuity levels, is used at the majority of EDs (214). The combination of vital parameters and symptoms prehospitally, or at arrival to the ED, results in one of five priority levels (red, orange, yellow, green, and blue) which determines the urgency of medical assessment, the level of monitoring required, and recommended blood tests. The blue

acuity level is often omitted in research, since patients in this category are referred to treatment outside the ED. Patients classified in the highest priority level, red, have a potentially life-threatening condition, and should be evaluated immediately by a physician, while patients in the next priority level should be evaluated by a physician within 20 minutes, with a decreasing need for early assessment for each colour.

To date, a Norwegian study showed good sensitivity for red and orange RETTS in identifying seriously ill sepsis patients in the ED. However, the evidence bases for RETTS as a sepsis triage tool remains sparse (13).

BAS 90-30-90 is another Swedish model used to identify severe sepsis patients in healthcare. The model focuses on the occurrence of either systolic blood pressure <90 mm Hg, respiratory rate > 30 / min, or oxygen saturation <90%. The model has been evaluated in a couple of retrospective studies and has lower sensitivity than modern triage systems (124).

MEDS (Mortality in Emergency Department Sepsis score) is another validated scoring system at the ED. Here, the focus has been on patients with suspected sepsis in the ED, and independent risk factors for death have been identified in this population (233). In addition to vital signs and predictors of mortality, the model relies on lab values, which inevitably leads to delay in triage decisions.

Importantly, when implementing sepsis bundles in an ED setting, complicating factors may affect the initial diagnosing. In patients with suspected sepsis admitted to the ICU, only half had a diagnosis of probable or proven infection at the ICU (90). It is a delicate balancing act to identify as many sepsis patients as possible, but at the same time consider the risk for alert fatigue (234-236). Concurrently, the risk of under-triage in patients without fever, or in patients with a diffuse presentation, must be taken into consideration (123, 128, 167). Quite dispiriting is the fact that, despite the latest SSC guidelines endorsing re-evaluation of vital signs as parameters for response to treatment, the corresponding recommendation for the vital role of early recognition of sepsis at the ED is not as clear (92). To support emergency personnel further in early identification and adequate monitoring of patients with sepsis, various electronic support systems are becoming more frequent. Hopefully, these will simplify identification and monitoring and contribute to adequate focus on patients at risk of poor prognosis (237).

However, any sepsis tool or surveillance model used must be validated in the emergency setting. Also, to attain a global focus, models for early recognition need to be low-cost, and to utilise non-invasive and easily measurable physiological parameters with high sensitivity outside the hospital setting. Here, models based on vital signs may be

advantageous, however, large multicentre trials are needed to explore whether these models are applicable globally (7, 238).

The infectious diseases physician - a key feature at the ED

In addition to the dedicated work carried out around the clock by ED colleagues, the ID physicians may contribute special knowledge to ensure that serious and sometimes rare and complicated infectious diseases are adequately cared for, in a similar way that cardiologists and neurologists assist in the treatment of patients with acute myocardial infarction or stroke. Also, a well-established collaborative relationship between ED and ID colleagues is advantageous and increases preparedness for different kind of infectious disease scenarios (239).

There have been several interventional studies to improve sepsis care at the ED in accordance with SSC, involving early recognition, Rapid Response team (RRT), and automatised algorithm sepsis screening, leading to shortened ICU length of stay and overall hospital stay, reduced mechanical ventilation use, and lower mortality (199-201, 240-244). Recent sepsis studies have often focused on speed, but by adding routine bedside or virtual/on-line/telephone consultation with an ID physician to the therapeutic arsenal, a balanced focus between speed and accuracy may result. There is growing evidence supporting the association between early engagement of ID physician and improved outcomes, including reduced mortality, shortened length of hospital stay, fewer readmissions, and subsequent lower health care cost (96, 151, 203, 245, 246).

At the ED, the ID physician may contribute knowledge on appropriate antibiotic treatment. In the majority of sepsis cases, the empirical antibiotic therapy needs to be directed against a broad range of pathogens and spectrum, route, dose, and dosing intervals need to be addressed. Indeed, the empirical antibiotics initiated at the ED have major impact, since it is often continued in the first days after admission. The importance of avoiding otiose antibiotic treatment and applying appropriate and rapid de-escalation of antimicrobial therapy to reduce the risk of antibiotic resistance, negative effects on the microbiota, drug intolerances, toxicity, and other side-effects, also needs to be properly highlighted (247). Importantly, nearly a tenth of patients with infections that presented to the ED were shown to be misdiagnosed at the site of infection, a finding associated with a >10% increase in in-hospital mortality (91). Also, as previously stated, one-third of all sepsis patients in the ICU are in need of source control, consultation with other specialists, in addition to the ID physician, may also be indicated (145).

Although every day clinical practice cannot be rigged for a pandemic, more common ID events, such as outbreaks of antimicrobial resistant bacteria and influenza epidemics, may motivate the regular presence of ID physicians at the ED. Most countries in Europe have acknowledged infectious diseases as an independent specific specialty, often within general internal medicine. However, in absence of ID physicians, a physician with special interest in infections and antimicrobial treatment may also be of great value at the ED when evaluating patients with severe infections. Despite the fact that the necessary number of ID physicians in a population is not established, the ongoing COVID-19 pandemic quite clearly illustrates an unprecedented demand for ID physicians, and deficits in the ID-physician workforce in some countries have resulted in insufficient preparedness for the current situation (239, 248).

The increasing incidence of antibiotic resistance will probably further complicate the treatment of patients with severe infections, and ID physicians play a central role in ensuring sustainable use of antibiotics and preventing antibiotic resistance and health-associated infections. Also, the importance of minimising the inappropriate and inconsistent use of antibiotic applies to both humans and animals (249).

The triage nurse - another key feature at the ED

As previously stated, both ED and ID physicians are vital in the initial sepsis care at the ED, however, without appropriate triage to identify which patients to treat first in a strained and overcrowded ED, this task is difficult. As the first health-care professional to encounter patients at the ED, the triage nurse has a unique opportunity to initiate and facilitate a process that will lead to prompt evaluation of the sepsis patient (250-254). The triage nurse contributes clinical experience and being 24-hour availability, seven days per week, providing an important role in enabling correct and continuous generation of alerts. To enable this task, the triage nurse relies on symptoms and physiological indicators as vital parameters, and consciousness according to different scoring systems that reflect the need for time-sensitive interventions. Also, measurement of lactate may be advantageous in highlighting sepsis patients with poor prognosis and hence a helpful tool for the triage nurse and, when needed, to correctly alert the ED or ID physician (92, 182, 183, 187).

Triage decisions are complex, and the body of evidence in the role of the triage nurse in sepsis care is scarce and often linked to (electronic) tailored protocols that are used, in addition to current triage system, rather than the role of the individual triage nurse (255). However, in cardiology and other well-defined areas, the scientific yield is greater, and here decisions on triage have been shown to be influenced by several

factors, both patient-related and contextual. Although knowledge of the varying presentation related to age and sex is increasing, general appearance, communication barriers, physiological markers are factors that also may affect the triage decision (256-259). Contextual factors include overcrowding and when and how the patients arrive at the ED (260).

In sepsis triage, it is a strength that the triage nurse is used to apply methods for the rapid identification and management of other medical conditions, such as the golden hour in multi-trauma patients, and the need for timely percutaneous coronary intervention in acute myocardial infarction. Given that the most common reason for delay in sepsis interventions relates to insufficient recognition, the combination of education and easily applicable triage tools to identify sepsis patients with high acuity is probably the most efficient way of improving this time-critical aspect of the sepsis care chain (203, 219, 220, 261). Also, to continuously evaluate why some patients are misclassified (for example, patients with immunosuppressive treatment, and patients with hypothermia) by triage audits or follow-up with nurses, is of huge importance to promote further improvement in this area (262).

In the future, support from electronic systems in screening for sepsis at the ED may further decrease the time to evaluation and intervention, and by applying sepsis-response teams at the ED, sepsis bundle compliance may improve further (200, 263-265)

Biomarkers

An introduction to biomarkers

A biomarker is an objective, quantifiable, and reproducible indicator of biological state or condition, and these have a long history of use in clinical medicine, for example, the measurement of blood pressure as an established surrogate marker to determine adverse cardiovascular outcomes (266).

The concept of biomarkers was applied as early as the 1940s, by Mundkur et al. who first used the term biochemical markers (267). In rheumatology, the detection of certain autoantibodies as rheumatoid factor has been a reliable and important diagnostic marker for rheumatoid arthritis for over 50 years. Today, laboratory-measured biomarkers are important tools in most medical areas, are continuously being developed and refined, and form an essential part of the future of 'personalised' medicine.

In 2000, the National Institutes of Health (NIH) convened a Biomarkers Definitions Working Group that defined a biomarker as "a characteristic that is objectively measured and evaluated as an indication of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention" (268). A few years later, the WHO defined a biomarker as "any substance, structure, or process that can be measured in the body or its products and influence or predict the incidence of outcome or disease" (269). WHO further stated that a true definition of biomarkers includes "almost any measurement reflecting an interaction between a biological system and a potential hazard", including everything from pulse and blood pressure, through basic chemistries, to more complex laboratory tests of blood and other tissues (270).

A plethora of biomarkers for a variety of diseases has been discovered and evaluated last decades, and in several medical fields, the development of biomarkers has revolutionised care in, for example, diabetes, cancer, neurodegenerative and cardiovascular disease. However, due to the complex nature of disease pathogenesis and outcome, in-depth knowledge of the underlying abnormalities associated with the condition is a prerequisite. However, we rarely or never have the complete picture of a pathophysiological process, hence continuous evaluation of biomarkers as surrogate

markers is needed, and studies using biomarkers should preferably apply clinically meaningful outcomes (271, 272).

Early identification & risk-stratification - biomarkers

In addition to clinical scores, biomarkers constitute a helpful tool in risk-stratification of sepsis patients at the ED, assisting in detection, risk assessment, prognosis, diagnosis, and therapeutic guidance. Biomarkers may also identify patients at risk of deterioration and the need for early escalation of interventions and surveillance, and accurately differentiate the 'ill-looking well' from the 'well-looking ill', which sometimes may be difficult in vital parameter-based models or in patients with communication barriers. In sepsis, biomarkers may, in addition to risk stratification, assist in identifying specific types of infections and guide targeted antibiotic therapy, or identify septic patients at risk of certain organ dysfunction, and biomarkers may, in the future, enable physicians to develop individualised treatment plans (273-277)

The ideal biomarker in infectious diseases would rapidly identify and differentiate bacteria, virus, parasite, and fungi, including susceptibility and resistance patterns. It should also be highly sensitive and specific to enable tailored antimicrobial therapy leading to diminished risk of antibiotic overuse and antimicrobial resistance. To enable implementation in low-income countries, the methods also need to be simple to use and associated with relatively low cost. Also, in the ED, practicability is important when using biomarkers. Tests should optimally be non-invasive, and easy to execute, and the results should be rapidly available. Ideally, the test should be suitable for point-of-care testing (278).

Several potential biomarkers have been suggested in sepsis care. In a study from 2010, Pierrakos and colleagues evaluated 178 biomarkers, including WBC, PCT, lactate, interleukins and other cytokines, CRP, and procoagulant factors, and concluded that few had sufficient specificity or sensitivity to be routinely applied in clinical practice. Ten years later, the same authors conclude that progress in identifying biomarkers with clinical significance has been limited. Perhaps it is not unexpected that a heterogenous and dynamic condition such as sepsis would fail to be identified by one single biomarker, the large number of pathogens, sites of infection, host-related factors, and treatments altogether rendering a somewhat unique situation. Hence, measuring a set of biomarkers involved in different sepsis pathways may be an appealing future approach (279).

Pierrakos highlight the methodological insufficiency in current biomarker studies, where only few biomarkers had been assessed in studies of more than 300 patients, sepsis biomarkers rarely exceed Area Under the Receiver Operating Characteristic Curve (AUROC) above 70, and many of the biomarkers have been evaluated in a limited number of clinical studies and one third in just a single study. Further, biomarker studies need to have a more standardised methodology to accurately evaluate effects on relevant clinical outcomes, and to ensure random distribution of risk factors, a significant number of patients needs to be included (274, 275).

Current biomarkers used at the ED include, leukocytes, CRP, PCT, lactate, thrombocytes, creatinine (SCr), and bilirubin. CRP, lactate, and PCT are by far the most widely used biomarkers in an international spectrum (280). In Scandinavian countries, CRP is a natural part of daily clinical practice, however, in other parts of the world the situation is somewhat different, and PCT or other biomarkers are more common in the ED setting.

The currently available biomarkers have been used in clinical daily practice for decades, and thoughtful clinicians are aware of their clinical use and shortcomings. However, to establish the clinical value of novel biomarkers is quite challenging due to insufficient research. For example, PCT, the pre-hormone of calcitonin, which is elevated in various inflammatory and infectious situations, was initially suggested as useful in diagnosing and assessing prognosis in sepsis at the ED, since high levels were found in patients with sepsis and multiorgan failure (281). However, due to moderate diagnostic accuracy, and difficulties in establishing an appropriate cut-off for sepsis, PCT has shown to be less useful in the ED setting (282). On the other hand, in the ICU, a PCT-based algorithm has been shown to reduce antibiotic treatment without compromising outcomes, and SSC recommends PCT as guidance for the discontinuation of antibiotic therapy in the ICU (92).

Further, in a Cochrane analysis including 32 studies in 12 countries in primary care, ED, and ICU settings, when PCT was used to guide antibiotic treatment in acute respiratory infections participants compared to control participants, a reduction of total antibiotic exposure, and a reduction of side effects, with lower mortality, was shown. Since patients with immunosuppression and non-respiratory infections were not included, further research is needed to assess these patient groups (283).

Mid-regional proadrenomedullin (MR-proADM)

Adrenomedullin (ADM) is a 52 amino acid peptide hormone, and a member of the calcitonin peptide family, that was originally identified in 1993 in a patient with pheochromocytoma (284). ADM is produced throughout the body by cells as endothelial cells, monocytes and macrophages, and circulates at low picomolar concentrations in healthy persons. However, plasma concentrations are significantly elevated during pathological events, and the dynamic ADM concentrations reflect disease severity. Since measurement of ADM has been shown to be difficult due to its rapid blood clearance (T½ 22 minutes), the more stable and reliable precursor, mid-regional pro-adrenomedullin (MR-proADM), is used to estimate ADM in a 1:1 ratio (285-287).

ADM is a multifaceted regulatory peptide involved in several biological processes, including vasodilatation, inotropic, diuretic, natriuretic, and bronco dilating effect (288). ADM has also been shown to be a molecule capable of ameliorating endothelial dysfunction, seize anti-inflammatory effect, and to exert bactericidal effects through activation of complement. Potential clinical application of MR-proADM measurements in diagnosis and risk stratification has been suggested in acute myocardial infarction and congestive heart failure and, in sepsis, elevated MR-proADM levels has shown to reflect the early microvascular changes that subsequently lead to organ damage in sepsis (287, 289-291).

MR-proADM is emerging as a promising biomarker for early identification of organ failure and has been shown to be rapidly elevated in the initial sepsis stages following burns, in invasive fungal infections, and in patients with septic shock (292, 293). Albeit conflicting evidence, MR-proADM has been shown to have a more accurate disease severity and mortality risk stratification compared to clinically established biomarkers and scores in several studies (294-298). Also, changes in MR-proADM kinetics may be used to identify patients at risk of treatment failure, who are in need of alternative therapeutic interventions despite ongoing antibiotics (295). Hence, MR-proADM may be of clinical utility in the early risk stratification of sepsis patients, however, interventional studies are needed to confirm current hypotheses, and take further steps to enable incorporation of MR-proADM measurements in clinical daily practice.

Since ADM has shown several beneficial effects in sepsis, including stabilising the microcirculation in inflammation, protecting against endothelial permeability and deleterious effects in organs in response to bacterial induced shock, and restoring endothelial stability in infected organs, an interesting target for therapeutic intervention

has arisen. However, since ADM causes vascular smooth muscle cell vasodilation, increasing its concentration may be harmful in patients with septic shock. To avoid the hypotensive effects and increase the beneficial effects of ADM, different efforts have been made to counteract this effect. Adrecizumab, a non-neutralizing adrenomedullin-specific antibody that inhibits the production of pro-inflammatory cytokines, restoring endothelial integrity without leading to vasodilatation, has shown beneficial effects on hemodynamics and mortality in animal models of septic shock. Adrecizumab redistributes ADM from the extravascular to the intravascular space and hereby promotes the valuable effects of closing endothelial gaps, while preventing vasodilatation. An ongoing randomised, double blind, placebo-controlled, biomarker guided, phase II study, is currently evaluating Adrecizumab in patients with early septic shock and high concentrations of circulating biologically active plasma adrenomedullin (299-301).

Interestingly, in addition to its suggested role in sepsis, MR-proADM concentrations in patients with COVID-19 seems to be constantly elevated in non-surviving patients at the ICU and may predict mortality more accurately than other biomarkers (302).

Proenkephalin A 119-159 (penKid)

Proenkephalin A 119-159 (penKid) is a 5-kDa peptide first identified in 1980 in the adrenal gland (303). PenKid is part of the enkephalin family, derived from the same precursor as met- and leuenkephalins, and is stable for at least 48 hours, to be compared to the more unstable enkephalins, which have a half-life of less than 15 minutes. PenKid is considered a reliable surrogate marker for enkephalins (304).

Enkephalins are small endogenous opioid peptides that are involved in a wide range of biological processes by acting on delta opioid receptors (305). Second to the central nervous system, the highest density of delta opioid receptors is found in the kidneys (306). Despite knowledge gaps regarding the exact effect of enkephalins on the kidneys, studies suggest a possible regulatory role of diuresis, natriuresis, or by inhibiting antidiuretic hormone (307, 308). Since penKid is not influenced by age or sex and is protein-bound in plasma, and filtrated in the glomerulus, it is an interesting biomarker for kidney function in critically ill patients (309). PenKid has been associated with impaired outcomes in critical illness, sepsis, heart failure, and in CKD (309-313). Further, penKid has shown to be a specific biomarker for renal function and associated with AKI in septic patients at the ICU (309, 310, 313).

The gold standard method to determine GFR is through inulin or iohexol clearance, methods that are labour intensive and unfeasible in acute clinical settings. Assessment of kidney function at the ED has to date been based on urine output and creatinine-based methods to estimate glomerular filtration rate (GFR). Due to confounding factors as muscle mass, volume status, nutrition, and medication, creatinine-based methods tend to be unreliable. In addition to the confounding factors, latency in elevation of SCr inevitably leads to delays in recognition of AKI (314). Particularly, the shortcomings of SCr are most deleterious in critically ill patients where kidney function can change rapidly (315).

An accurate and rapid estimation of the non-steady state of kidney function in acute sepsis care is crucial. In patients at risk of AKI, early preventive and therapeutic strategies in accordance with "Kidney Disease: Improving Global Outcomes Bundles" are of huge importance. Unfortunately, the importance of early recognition of AKI, still seem to be insufficient. Current evidence suggests that penKid is a more accurate surrogate marker to estimate GFR or to detect AKI compared to SCr-based methods. In the future, measurements of penKid may be part of the daily handling of sepsis patients. However, as with the majority of sepsis biomarkers, the availability, price, and limited data on penKid-based management on clinical outcomes must be further addressed (316).

The present investigation

Aims

The overall aim in this thesis was to improve early recognition and initial sepsis care at the ED by a region-wide implementation of a novel triage algorithm, Sepsis Alert, and by identifying biomarkers for risk stratification in sepsis patients at the ED.

The specific aims of this thesis were:

I. To study whether a newly established triage model, Sepsis Alert, affected time to antibiotics, number of blood cultures and lactate measurements taken, length of hospital stay, and mortality at the Emergency Department at Skåne University Hospital, Malmö.

II. To investigate whether the triage model, Sepsis Alert, affected fulfilment of the current Surviving Sepsis Campaigns process measures of sepsis care, length of hospital stay (including ICU care), and mortality at the Emergency Departments in the Skåne Region.

III. To evaluate whether a single assessment of MR-proadrenomedullin taken at arrival at the ED may guide the need of antibiotic treatment in patients with sepsis.

IV. To investigate whether a single assessment of proenkephalin A 119-159 (penKid) taken at arrival at the ED predicts sepsis related acute kidney injury, multi-organ failure, and 28-day mortality.

Materials & methods

Study designs & settings

The patients in Studies I-III included in this thesis were recruited at the Emergency Department of Skåne University Hospital in Malmö, a tertiary academic centre that serves about 350 000 inhabitants, with approximately 85 000 visits per year. In Study IV, the patients were included from eight EDs in Skåne Region, a region with 1.3 million inhabitants and approximately 400 000 annual ED visits, including two tertiary academic care centres, three secondary care hospitals, and three community hospitals. At the tertiary academic centres, ID physicians were available all day and night. At the secondary care hospitals, ID physicians were available from about 8 am–10 pm, and otherwise available for phone consultation. At the community hospitals, the consultations were solely conducted by phone.

Study I was a retrospective, observational, interventional study, and Study IV was an interventional multicentre study that was prospectively planned and retrospectively evaluated. In Study IV, the development of new Regional Sepsis Care Guidelines, the ethical committee application, the formation of the regional and local sepsis care teams, the start-up meetings at each hospital engaging the ED head and management, the special education program, the presentation of base-line values for quality markers of sepsis care at each hospital, and, finally, the execution of the model, all constituted prospective efforts. However, since data were collected retrospectively, the setting did not fulfil the demands of a prospective study. Studies II & III were observationally and prospectively designed, and in addition Study II included a post-hoc analysis.

The most important purpose of the study designs chosen was to diminish selection bias and enable inclusion of patients often left out of sepsis studies, such as those with language barriers, impaired consciousness, and patients that died during ED stay. Randomised Clinical Trials (RCT) are often considered superior to other available study designs. This may withstand discussion when aiming at conducting studies in unselected patient cohorts, since the need of informed consent inevitably leads to selection. Also, when applying a randomised clinical trial setting to an implementation

process including educational efforts, the educational effects will inevitably be contagious and carry over to the control group.

Participants

Patients attending the EDs in the Skåne Region are registered in a database at presentation to the ED and categorised in accordance with urgency by the RETTS system as red, orange, yellow, or green (blue). The RETTS is based on vital parameters at presentation at the ED or prehospitally. Patients that present with one or more of the following criteria are categorised as red RETTS (highest priority group), i.e., SBP <90 mmHg, venous oxygen saturation <90% despite oxygen treatment, respiratory rate >30 breaths per minute, HR >130 beats per minute, seizures, or unconscious state. A more complete description of the different RETTS categories is provided in the Supplementary material in Study IV. Patients included in the final analysis were selected according to this initial RETTS registration by staff not engaged in the study, which should diminish the risk for selection bias.

We extracted the ED charts from 58 436 and 195 607 unselected patients ≥18 years presenting at the ED with red RETTS. In **Study I**, 1 837 patients, and in **Study IV**, 5 321 patients were identified as red RETTS from the electronic ED database register "Liggaren". A triage nurse then manually reviewed these charts to search for information regarding fever ≥38°C or history of fever/chills within the past 24 hours. In Study I, hypothermia, <35°C, was also evaluated. Of the 1 837 and 5 321 patients, 221 and 1 066, respectively, fulfilled the fever criteria. Medical records from three 3-month periods between 1 January and 31 March, prior to start-up 2010, at start-up 2012, and after implementation, in 2014, of the Sepsis Alert, were further analysed in Study I. And in Study IV, three-month periods were evaluated in a similar way before 2015, and after implementation in 2017. Patients with predominating surgical conditions or trauma were not included.

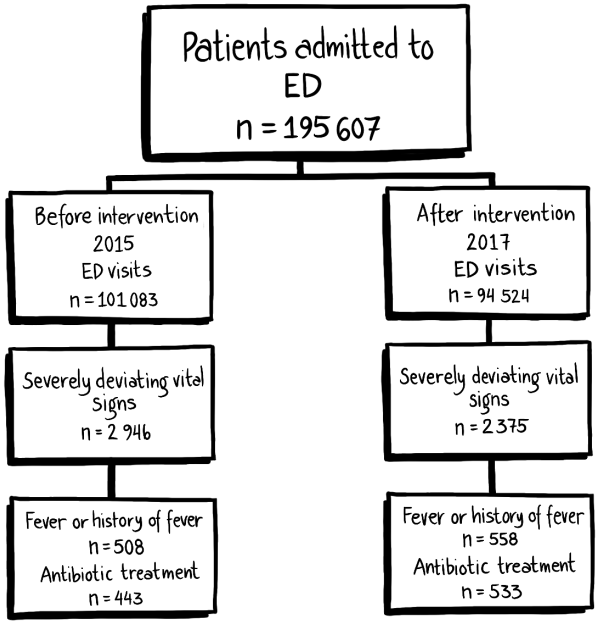


Figure 5. Flow chart participants 2015 and 2017, Study IV.

Inclusion criteria for **Studies II and III** were suspicion of infection as judged by the research nurses at the ED. In addition, the patient needed to fulfil two or more of the following SIRS criteria: body temperature >38°C, <36 °C or self-reported fever within 24 h, respiratory rate >20 breaths per minute or heart rate > 90 beats per minute, hence meeting the definition of sepsis in accordance with Sepsis-2. Leucocytosis and leucopoenia were not used due to unavailability during triage. The study patients were enrolled upon admission to the ED at Skåne University Hospital in Malmö, 6 am–6 pm. During the recruitment phase from 1 December 2013 to 1 February 2015, a total of 647 patients ≥ 18 years old were enrolled. Patients with predominating surgical condition or trauma were not included.

Data collection

In all four studies, research nurses manually reviewed the medical charts to collect data regarding comorbidities, concurrent medication, clinical parameters, vital signs, standard blood tests, culture results, limitation of care, and RETTS acuity level. Time to antibiotics, type of antibiotic treatment, and non-specific supportive therapy, such as oxygen, intravenous fluids, vasopressor treatment, mechanical ventilation, renal replacement therapy (RRT), length of hospital stay, level of care, in-hospital and 28-day all-cause mortality were also recorded. In addition, in Study IV, 90-day mortality was documented. Also, in Studies II and III, the research nurses interviewed patients about, i.a., social factors. All patients were followed for at least 28 days.

Laboratory results including haemoglobin, WBC, platelet count, CRP, SCr, serum bilirubin, serum lactate, activated partial thromboplastin time (aPTT), and International Normalized Ratio (INR), were recorded. Further, microbiological tests and radiological examinations were noted. For some of the criteria defining organ dysfunction, the data set was incomplete. Laboratory values for estimation of coagulation and liver function (bilirubin) were absent in 20% of the cases in Study IV, and in Study I the values for estimation of coagulation were absent in 35%, and for liver function (bilirubin) in 50%.

Missing values (i.e., data collected at the ED or blood samples for biomarker analysis) in studies II-III occurred mainly in the early phase of the patient collection. In study 2 (final n=213), fifty subjects were excluded due to missing data. The subjects with missing data vs those included in study II did not differ significantly in terms of 28-day mortality (9.8% vs 8.9%) or age 74 (62-82) vs 71 (60-84) years. In Study III, fifty-six patients were excluded due to incomplete data sets. The subjects with missing data vs those included in study III differed slightly but not significantly in terms of 28-day mortality (10.5% vs 8.5%) and age 72 (55-80) vs 73 (61-82) years.

In all four studies, the study physician examined the medical charts to evaluate clinical, microbiological, laboratory, and radiological findings to establish infectious diagnosis and organ dysfunction in accordance with consensus criteria and the current Surviving Sepsis Guidelines (111). In patients not clearly meeting criteria for the infectious diagnosis or organ dysfunction, two ID physicians reviewed the data independently and determined the final classification.

The biobank

Samples for analysis of biomarkers were collected within one hour after attendance to the ED, including 2 EDTA tubes, 1 serum tube and 1 citrate tube. After centrifugation, the plasma was pipetted aliquoted into 250 ul microliter to REMP-plates. The blood samples were centrifuged and stored at -80°C until analysis.

The routine laboratory analysis was conducted at the local certified laboratory at the Department of Clinical Chemistry of Skåne University Hospital. MR-proADM was analysed using a commercially available double sandwich immunoassay (KRYPTORT™ Thermo Fisher Scientific, Germany) at the Clinical Research Center, Lund University, Malmö. PenKid was measured in duplicates using chemiluminescence immunoassay (Sphingotec GmbH, Hennigsdorf, Germany) at ASKA Biotech, Hennigsdorf, Germany, in June 2018. Estimated glomerular filtration rate (eGFR) was determined by the formula derived from the Modification of Diet in Renal Disease (MDRD) Study.

Sepsis Alert – the triage model

When developing the Sepsis Alert, we emanated from the available RETTS system, that was used at all the EDs in the Skåne Region during the study periods. For proper focus on patients with severe infections, we added information regarding fever ≥38°C or history of fever/chills within the past 24 hours to existing RETTS categorisation. If both the red RETTS criteria (described at p. 72) and the fever criteria were fulfilled, the Sepsis Alert would be triggered, and the patient was triaged to a designated sepsis line for immediate evaluation by the attending physician supported by an infectious diseases (ID) specialist at the ED. When an ID physician was not available, consultation by phone was conducted. The ID physician advised on diagnostic procedures, antibiotic and supportive treatment, level of care, and surveillance.

Also, an interactive mandatory educational program consisting of one-hour case-based seminars for smaller groups of ED personnel (15–20 participants), was conducted by the local sepsis care team supported by the regional coordinators. These seminars covered the definitions, recognition, and treatment of sepsis patients, and briefing on the new triage algorithm. Having authentic and credible patient cases that represented each ED, was emphasised. In addition, all prehospital personnel received a one-hour lecture on sepsis and Sepsis Alert, which was conducted as part of their continuing education. Also, a physician or an ED nurse attended weekly meetings to remind the ED staff of the new triage line and to provide feed-back on quality markers of sepsis care.

Sepsis Alert - the implementation

When implementing the triage algorithm Sepsis Alert regionally, a coordinator (the study physician) was appointed to lead the process. The coordinator initiated the process by creating a small regional sepsis team consisting of an experienced ED nurse with research experience and an experienced ED medical secretary, to prepare for the upcoming implementation.

Thenceforth, at an early stage of the planning, the coordinator engaged all ED management levels in a considerable information campaign. Thereafter, sepsis teams consisting of one physician (either an ID or an ED physician, or a specialist in internal medicine), one ED nurse, one ED nursing assistant, and one ED medical secretary, was appointed by the ED management at each ED. The local sepsis care teams participated in a specialised educational program before the start-up of the intervention. Also, the regional coordinators hosted group-specific coaching when needed throughout the study period.

During the implementation process, the ED management and local sepsis care teams decided on "how" and "when" to implement the Regional Sepsis Care Guidelines, while the Regional Sepsis Care Guidelines provided “what” was to be implemented.

The implementation was then carried out at one ED at a time. This allowed for focus to shift to the current ED and also contributed to valuable experiences along the way. A combination of well-known strategies for implementation were applied, including specialised educational programs for the sepsis teams, group-specific coaching, mandatory interactive case-seminars, weekly reminders, recurrent feed-back on key performance indicators, e-learning, and use of leaflets and posters.

All personnel were included in the implementation process, a team-based approach that we believe facilitated the implementation process. Although the triage nurse and the ID physicians were essential features of this work, our experience has been that it is a great advantage to involve all personnel categories when implementing new ED processes. As an example, in Study I, the medical secretaries were not engaged in the local sepsis care team at start-up. However, the medical secretaries often participate actively in the emergency room, assisting in for example documentation and x-ray referrals. When the medical secretaries were included in the process, the team became more complete, and the handling of data more accurate, and subsequently compliance improved.

The group of ED heads in the region consisting of representatives from each emergency hospital, were involved early on in this work. The group was an important facilitator for the implementation. Also, broad anchoring, and close collaboration between the regional coordinators, the local sepsis care teams, and the different management levels at the ED and ID clinics, was vital throughout the process. A more detailed description of the implementation process in accordance with CReDECI, is provided in the Supplementary material in Study IV.

Outcomes and quality markers of sepsis care

In Study 1 the primary outcomes were the time from admission to the first dose of antibiotics, LOS (including ICU care), and 28-day mortality, and the primary outcomes in Study IV were the time from admission to the first dose of antibiotics, LOS (including ICU care), and 28-day and 90-day mortality. The secondary or process outcomes were measurement of lactate at admission, blood culture drawn before the start of antibiotics, administration of iv fluids prehospitally or at the ED, and appropriate initial antibiotic treatment based on blood culture results and resistance.

Study endpoints in Study II were need of and time to administration of antibiotics, 28-day mortality, and ICU care. Uncomplicated infections were defined as absence of ICU admission and survival by day 28.

In Study III, the primary outcomes were AKI development within either 48 hours or 7 days, as defined by SCr increase of > 44 µmol/L (> 0.5 mg/dL) between any two

measurements or need for acute RRT, or an increase in creatinine corresponding to 1.5-fold of baseline with an initial value of > 160 µmol/L (> 2.0 mg/dL). The secondary outcomes were multi-organ failure (MOF), defined as four or more failing organ systems, and 28-day all-cause mortality.

Statistics

In all studies, baseline characteristics were summarised using descriptive statistics. Data were reported as mean (standard deviation, SD) for symmetrically distributed variables, and for variables with a skewed distribution, median (interquartile range, IQR) was used. When comparing groups regarding normally distributed continuous variables, the Student T-test was used. For non-normally distributed variables, the Mann-Whitney u-test was applied. For differences in dichotomous variables, the Chi2-test was used. However, when the minimum expected number of a category was less than five, Fisher´s Exact test was applied.

For continuous outcomes, multivariate linear regression analysis with the dependent variable log-transformed was applied in Studies I and IV and study period as the main independent variable. Variables that were further adjusted for were age, gender and each of the variables that differed significantly between the study periods. All tests were two-sided, and p-values <0.05 were considered significant. Bonferroni corrected p-values were calculated for the primary outcome measures in Study IV. Bivariate correlations were analysed with Pearson´s or Spearman´s correlations, depending on distribution of residuals. Also, we calculated odds ratios and 95% confidence intervals for each of the binary EGDT outcomes and adjusted for all covariates differing between 2015 and 2017 using logistic regression.

Further, in Study II, Youden's criterion was used to establish optimal cut-off values (in terms of balance between sensitivity and specificity of MR-proADM vs outcome), and univariate and multivariate logistic regression was used to relate levels of MR-proADM with requirement for antibiotic administration, ICU care, and 28-day mortality.

In Study III, logistic regression analysis was used to correlate levels of penKid at presentation to AKI, multi-organ failure, 28-day mortality and progression of renal SOFA score. Odds ratios were expressed per number of SDs from the mean of log-transformed penKid (Z-score of ln-penKid). Moreover, quartiles of penKid were related to outcomes with the first quartile (lowest value) defined as reference. We also applied a dichotomised cut-off value of above vs below 100 pmol/L. Also, Kaplan-Meier plots were calculated with the lowest quartile as a reference.

Ethical considerations

All studies were approved by the Regional Ethical Review Board at Lund University in Lund, Sweden 2013/635 and 2016/546. The Ethical Review board did not recommend informed consent in 2016/546. The studies were otherwise conducted in accordance with the Helsinki Declaration. In 2013/635, an oral informed consent was requested from patients or next of kin. If patients were unable to consent, and no next of kin was available, the Ethic committee agreed on including patients if no evident opinion against participation was present.

Main results

The Sepsis Alert studies - Papers I & IV

The care bundles recommended by SSC were part of the local guidelines before the start of Sepsis Alert, but compliance was unsatisfactory. When reviewing patient records from the ED at Skåne University Hospital Malmö in 2010, it emerged that one of SSCs quality goals for sepsis care, antibiotics within one hour, were met in only 22% of patients in the highest RETTS priority with ≥38°C or history of fever/chills within the past 24 hours. The results reflected suboptimal acute sepsis care and formed the basis for the upcoming improvement work.

In Study I, a total of 58 436 patients visited the ED during the study periods, and of these 1 837 (3,1%) patients presented abnormal vital signs according to red RETTS. Of the 1 837 patients, 221 (12%) patients fulfilled the fever criteria. The 28-day mortality in the total cohort was 16.3%. Eighty-six percent of the patients were diagnosed with an infection; the most frequent being pneumonia, followed by upper respiratory infection, urinary tract infection, and skin and soft tissue infection. Blood cultures were positive in 25.1% of cases, and the most prevalent pathogens were *Escherichia coli*, followed by *Staphylococcus aureus*, and *Streptococcus pneumoniae*.

After implementation of the Sepsis Alert, the time from admittance to the first dose of antibiotics was significantly reduced, to 24.5 minutes from 190 minutes. The proportion of patients receiving antibiotics within 60 minutes was 22% before, 53% during the start-up period, and 90% after the implementation. The length of hospital stay (LOS) was significantly reduced following implementation, from 9 to 7 days in median. The proportion of patients treated in the ICU was unchanged between the studied periods. The compliance to apply the Sepsis Alert was low at the start-up, 22%, however, two years later, compliance had increased to 70%. Further, outcomes such as measurement of lactate and blood culture drawn before the start of antibiotics at admittance, were continuously improved even two years after the initiation of the project.

The results and experiences from Study I emanated in regional financing of a project to enable the implementation of the Sepsis Alert at all Skåne's EDs (Study IV).

However, at three of the study hospitals, a sepsis triage line was already present at start-up. Two of the hospitals used the Sepsis Alert, the pilot tertiary academic care centre (Hospital A) and a secondary care hospital (Hospital C). Hospital B, a tertiary academic care centre, had a triage model based on different infectious diseases, sepsis being one infectious diagnose out of several. These three hospitals showed the best base-line situation, probably due to previous focus on sepsis patients. Two of ten EDs in the region were not included in Study IV due to local circumstances, leading to delayed implementation at one ED, and the other ED was a private hospital which made data collection difficult.

In Study IV, a total of 195 607 patients visited the ED during the study periods, and of these 5 321 (2.7%) patients presented abnormal vital signs according to red RETTS. Of the 5 321 patients, 1 066 (20%) patients fulfilled the fever criteria. The 28-day mortality was 17.7% in 2015, and 15.2% in 2017, respectively. One-thousand and twenty-five (96%) of study patients were diagnosed with infection, the most frequent being pneumonia, followed by upper respiratory infection, urinary tract infection, and skin and soft-tissue infection. Blood cultures were positive in 26.3% of the cases, and the most prevalent pathogens were *Escherichia coli*, followed by *Staphylococcus aureus*, and *Streptococcus pneumoniae*.

The regional implementation of Sepsis Alert resulted in shorter time to antibiotics, 37 minutes before, and 26 minutes after the implementation, and the proportion of patients receiving antibiotics within 60 minutes were 68% before, and 89% after the implementation. Also, the proportion of patients receiving correct empirical antibiotics at the ED, when compared to subsequent blood culture results, increased significantly after the implementation, to 90.2% from 78.6%. The LOS was not significantly changed between the study periods, 7 to 6 days in median. However, several quality markers of sepsis care improved after the implementation (Table 6). The compliance to apply the Sepsis Alert was high at follow-up in 2017, 81.7%.

Table 6. Quality Markers of Sepsis Care before and after the implementation of Sepsis Alert.

Quality Markers of Sepsis Care	2015 (*n* = 508)	2017 (*n* = 558)	*p*
Lactate, *n* (%)	485 (95.5)	554 (99.3)	< 0.001
Fluid administrated IV, *n* (%)	382 (75.2)	491 (88.0)	< 0.001
Amount of fluid administrated IV[a]	1.01	1.27	< 0.001
Blood cultures, *n* (%)			
Obtained	448 (88.2)	546 (97.8)	< 0.001
Positive	114 (25.4)	147 (26.9)	NS
Significantly positive blood culture[b]	88 (19.6)	106 (19.4)	NS
Patients with sign positive blood culture[b]	84 (18.8)	102 (18.7)	NS
Appropriate antibiotics (patients)[c]	66 (78.6)	92 (90.2)	0.027
All items, *n* (%)[d]	237 (46.7)	422 (75.6)	< 0.001
In ward, ICU, *n* (%)	56 (11.0)	52 (9.3)	NS
Sepsis *International Classification of Diseases*: diagnose at discharge, *n* (%)	49 (9.6)	59 (10.6)	NS

NS = not significant.
[a]Ringer acetate, liters.
[b]Excluding positive cultures that were judged as being contaminated.
[c]Empirical antibiotic based on subsequent culture results.
[d]Including antibiotic treatment within 60 min, IV fluid administrated, lactate and blood cultures taken.

In Study IV, the number of patients with shock at presentation was low, about 10% presented with blood pressure ≤90 mmHg prehospitally or at the earliest time point at the ED, and of these 50% presented blood pressure below 90 mmHg. Limitation of care orders were present in 27.5% of the patients at attendance to the ED, and in 40.4% of the patients during hospital stay. The percentage of patients that reached the ICU was unchanged between the study periods, 11,0 and 9,3%, respectively. Interestingly, in a subgroup of 5/8 EDs without previous sepsis triage, the need for ICU care declined significantly after the implementation of Sepsis Alert, to 6.5% from 12.2% (p = 0.04) without affecting 28-day mortality. On demand, we complemented the analysis post-hoc and adjusted for all variables that differed in-between the study periods, after which the statistical significance remained (p=0.003).

Despite the improvements in processes of sepsis care, the 28-day and 90-day mortality rates were not significantly reduced after the implementation of Sepsis Alert (17.7% vs 15.2% and 24% vs 22.8%). Although caution should be applied when evaluating subgroups, interestingly, at one of the secondary care hospitals (Hospital D) the baseline situation differed from the other hospitals, with poorer values for sepsis quality markers and higher 28-day and 90-day mortality. In this hospital, median (IQR) time to antibiotics and the percentage of patients receiving antibiotic treatment within one hour after ED admittance at the ED were 49 (34-112) minutes and 59 percent, respectively. This start-up situation was significantly inferior to the situations at the other hospitals. Also, 28-day and 90-day mortality were significantly higher at this

hospital before start-up, 28.7% (p=0,005) and 36.3% (p=0,005) respectively. At this hospital 28-day mortality was significantly reduced after the intervention, to 16% versus 28,7% before the intervention (p=0,016). On demand, we adjusted for all variables that differed in-between the study periods, and the significance remained (p=0,001).

The proportion of patients that presented with severe sepsis *at arrival* at ED was 77.2% in 2015 and 75.3% in 2017, respectively. When evaluating patients not presenting with severe sepsis at triage, almost all patients had an infectious diagnosis, however forty-one of 1 066 (3.8%) patients were shown not to have an infectious diagnose at presentation. These 41 patients had acute internal medical diseases that may include fever or history of fever/chills such as pulmonary embolism, rheumatic diseases, stroke, COPD, and heart failure.

Sepsis Alert - sensitivity

In an attempt to evaluate sensitivity, a novel cohort was identified consisting of 850 consecutive patients with severely deviating vital signs (red RETTS) from study hospital A during the study period 1 January–31 March 2015. Thus, this cohort also contained patients without fever ≥38°C or history of fever/chills. First, an experienced ED nurse reviewed all 850 ED charts and excluded obvious non-infectious diagnoses. A detailed review was made by ID physician of the remaining 190 patients. 146 patients with severe sepsis within 48 hours, in accordance with the Sepsis-2 guidelines, were identified. Of these, 116 had ≥38°C or history of fever/chills within the past 24 hours and would have been identified by Sepsis Alert if properly applied.

The sensitivity for the Sepsis Alert to identify severe sepsis within 48 hours in this cohort was calculated at 79.5%. Hence, 30 patients with severe sepsis *within 48 hours* presented without fever or history of fever/chills at the ED. Interestingly, the 28-day mortality among these 30 severe sepsis patients was 30%, higher than the 28-day mortality in the Sepsis Alert triggered cohort. There were some explanations for this, such as higher age, rate of terminal illnesses, and percentage of limitation of care. However, all 30 were handled immediately upon presentation to the ED and were evaluated by ED physicians, and even if sepsis was one of the final diagnoses, it was not the primary diagnosis except in one case of necrotizing fasciitis.

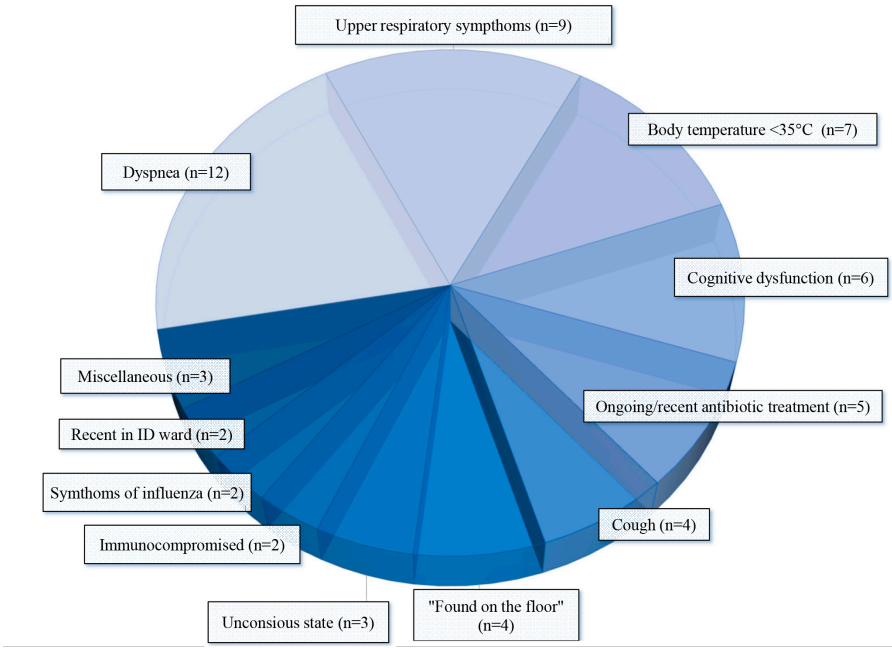


Figure 6. Symptoms or keywords found when reviewing the ED charts from patients not identified by current trigger of the Sepsis Alert n=30 (more than one keyword or symptom per patient).

Interestingly, seven of the thirty severe sepsis patients in this group presented with hypothermia (<35°C), a finding that highlights the complex presentation of severe sepsis and the need to consider including a hypothermia criterion in the Sepsis Alert algorithm in the future (Figure 6). Also, the inability to report history of fever/chills due to language barriers and/or unconscious state are important aspects to take into consideration when evaluating sepsis patients at the ED.

The Biomarker studies - Papers II & III

Due to challenges in diagnostic criteria for sepsis, identifying biomarkers that may assist in diagnosis, assessment of organ dysfunction, and prognosis in sepsis, would be desirable. In the following two studies, we evaluated the ability of the biomarker MR-proADM to guide antibiotic administration at the ED (Study II). We also investigated the biomarker Proenkephalin A 119-159 (penKid)'s ability to predict AKI, MOF, and mortality in unselected sepsis patients at the ED (Study III).

In Study II, presented as a letter, two-hundred and thirteen patients with sepsis in accordance with Sepsis-2, were included in the post-hoc analysis, of which 187 (87.8%) received antibiotics at the ED. The median time to administration was 93 min, and 43.8% of patients received antibiotics within 60 min. In this study, MR-proADM had the strongest association with the requirement for antibiotic administration at the ED, (OR 3,1, CI 1,9-4,9; p<0.001) (Table 7).

Table 7. Univariate and Multivariate analyses found that MR-proADM had the strongest correlation with the requirement for antibiotic administration during ED treatment.

Biomarker	Patient population (*N*)	Antibiotic administration (*N*)	*p* value	C index	Univariate OR [95% CI]	Multivariate OR [95% CI]
MR-proADM	213	164	< 0.001	0.76	3.1 [1.9–4.9]	3.3 [1.9–5.9]
PCT	213	164	< 0.001	0.74	2.7 [1.7–4.3]	2.7 [1.7–4.5]
CRP	207	159	< 0.001	0.68	1.8 [1.3–2.5]	1.9 [1.4–2.8]
Lactate	204	158	0.002	0.66	1.8 [1.2–2.6]	1.6 [1.1–2.5]

Age, cardiovascular, neurological, renal and malignancy comorbidities were used as adjusting variables within the multivariate regression analysis, as previously outlined [4]. Univariate and multivariate odds ratios were expressed per 1 SD increment of the log-transformed value for each respective biomarker. *CI* confidence interval, *CRP* C-reactive protein, *DF* degrees of freedom, *MR-proADM* mid-regional proadrenomedullin, *N* number, *OR* odds ratio, *PCT* procalcitonin

When an optimised MR-proADM cut-off for antibiotic administration (1.27 nmol/L) was applied, ICU care and 28-day mortality was zero in patients with low MR-proADM despite lower percentage of antibiotic administrations and significantly longer time to antibiotic administration. This observation was independent on PCT levels, and similar when the pre-established cut-off for mortality was applied (1.54 nmol/L).

In Study III, a total of 647 patients with sepsis were enrolled, of which 59 patients were excluded due to incomplete data, leaving 588 sepsis patients for the final analysis. The 28-day mortality in the total cohort was 8.5%. Five-hundred and twenty-three (88.9%) patients were diagnosed with an infection; the most frequent being pneumonia, followed by urinary tract infection, skin and soft tissue infection, and upper respiratory tract infections. The most prevalent pathogens were *Escherichia coli*, followed by

Staphylococcus aureus, and *Klebsiella pneumoniae*. Limitation of care was present in 15.3% of patients at admission. The percentage of patients receiving ICU care was 4.6%, and 0.3% received RRT during the study period. The cohort may be deemed rather healthy in comparison to patients receiving care in the ICU, presenting lower mortality rate and fewer interventions as RRT, reflecting the significant differences that exist in the heterogenous ED patient material compared to the ICU ditto.

Of patients included in the study, 13.4% developed AKI within 48 hours, and an additional 2.6% after 48 hours but within 7 days. In age and sex adjusted models, penKid strongly predicted AKI within 48 h and 7 days, however these associations were attenuated when adjusting for estimated creatinine-based glomerular filtration rate (eGFR). Also, penKid significantly predicted progression from rSOFA = 0 and ≤ 1 to higher rSOFA. When applying previously established cut-off for level penKid and poor outcome (100 pmol/L), the prediction of worsening renal function among patients with SOFA ≤1 remained significant, in non-eGFR adjusted analysis the OR was 10.1, (CI 3.2-31.7; p< 0.0001), and the OR when adjusted for eGFR was 3.7 (CI 1.0-13.1; p=0.045). Thirty-three patients (5.6%) developed severe MOF within 48 hours. In models adjusted for age, sex and eGFR, patients in the highest penKid quartile had an OR for developing MOF of almost 30, compared to the lowest penKid quartile (reference). In continuous analysis, each 1 SD increment of log-transformed penKid yielded an OR of about 3.6. Further, the OR for mortality within 28 days was 1.5 per 1 SD increment of log-transformed penKid quartile (Table 8).

Table 8. Proenkephalin A 119–159 (penKid) for prediction of MOF and 28-day all-cause mortality

	All patients (*n* = 588)	*P*-value	Quartile 1 (*n* = 147)	Quartile 2 (*n* = 147)	Quartile 3 (*n* = 147)	Quartile 4 (*n* = 147)	P for trend
[a]Severe Multi-Organ Failure							
[b]N events (% of total)	33 (5.6%)		1 (0.7%)	2 (1.4%)	6 (4.1%)	24 (16.3%)	
[c]OR (95% CI)	3.6 (2.5–5.3)	< 0.001	Reference	2.1 (0.2–23.0)	6.5 (0.8–55.2)	29.9 (3.8–235.3)	< 0.001
28-Day All-Cause Mortality							
N events (% of total)	50 (8.5%)		5 (3.4%)	10 (6.8%)	13 (8.8%)	22 (15.0%)	
OR (95% CI)	1.5 (1.1–2.0)	=0.009	Reference	1.3 (0.4–4.0)	1.5 (0.5–4.6)	2.2 (0.8–6.5)	=0.079

[a] Severe multi-organ failure defined as ≥4 organ systems failing. Organ failure constitutes seven categories: central nervous system, circulatory failure, respiratory failure, kidney failure, liver failure, coagulopathy, metabolic dysfunction. bN events (% of total) refers to the number of participants (proportion of total number participants) for each respective endpoint. cOR (95% CI) are expressed per one standard deviation (SD) increment of log-transformed penKid and in analyses of quartiles the lowest quartile (quartile 1) was defined as the reference category and the OR (95% CI) for each of quartiles 2, 3 and 4 were compared with the reference quartile. Analyses were adjusted for age, sex and eGFR calculated through the Modification of Diet in Renal Disease (MDRD) Study formula

Discussion

The Sepsis Alert studies - Papers I & IV

About ten years ago, several severe sepsis patients with a particularly aggressive disease course were treated in our hospital. These cases drew attention to severe infectious disease with organ failure. Did we treat these patients correctly? Were they treated quickly enough, and did we perform adequate processes of care? As at many centres around the world, the guidelines of the Severe Sepsis Campaign were introduced in our region in 2006. However, adherence to the guidelines had not been evaluated during the years after implementation.

In sepsis, the multifaceted presentation and volatile definitions complicate patient care and research, difficulties that probably become most apparent at the ED, where time constraints and overcrowding further complicates the assignment. To save lives, a screening tool that exhibits high sensitivity, even at the expenses of specificity, is preferred. Although the up-dated definitions may be of great help in an ICU setting, they may not be representative of the wider clinical community. Regrettably, the Sepsis-3 de-emphasizes interventions at earlier stages of sepsis when the syndrome is most efficiently treated (3). The qSOFA was designed to fulfil this task, however methodological shortcomings and lack of validation resulted in significant sensitivity limitations, which diminished its value at the ED (10-13, 15, 224, 225). Further, lactate, previously an important part of determining organ dysfunction, and in addition a valuable parameter in risk-stratification of sepsis patients at the ED, is missing in the updated guidelines (2, 3, 92, 182, 183, 187, 188).

In 2012, the novel triage model Sepsis Alert for early identification of patients with severe infections, was introduced at the ED at Skåne University Hospital Malmö. In this triage model, the most severely ill sepsis patients (categorised as red RETTS) are rapidly evaluated by ED physician supported by an ID physician, assuring that the processes of care in accordance with SSC are properly initiated; measurement of lactate at admission, blood culture drawn before the start of antibiotics, appropriate broad-spectrum antibiotics within one hour, and administration of intravenous fluids (111). The encouraging outcomes of the implementation at this single centre were presented

in Study I, and resulted, a few years later, in regional implementation of the triage model at all EDs in Skåne. The two Sepsis Alert studies presented in this thesis show that the implementation of the triage model Sepsis Alert led to improved compliance with the SSC bundles, including prompt and appropriate antibiotics, improved quality markers of sepsis care, shortened LOS and, in 5/8 EDs with no prior sepsis triage, the need for ICU care decreased significantly without affecting mortality. Interestingly, in Study IV, when matching empirical antibiotics administrated at the ED to subsequent blood culture results, the proportion of patients receiving appropriate antibiotics was significantly improved after the implementation of Sepsis Alert, 78,6% and 90,2%, respectively. It is possible that the input from ID physicians in the ED may explain this finding.

Several previous studies describe the effects of quality improvement work on sepsis as leading to reduced mortality (96, 151, 175, 201, 203), however, 28-day mortality was not significantly reduced after the implementation of Sepsis Alert, 17,7% and 15,2%, respectively. One may ask why, and insufficient power may be one aspect. Another aspect may be a rather good start-up situation, with 68% patients receiving antibiotics within one hour, a finding that may have been attributed to carry over effects from Study I. Also, two hospitals in Study IV applied the Sepsis Alert at study start-up, and a third had an infectious diseases triage, which may have influenced the results.

Interestingly, at one of the studied EDs with a significantly poorer goal completion of quality markers of sepsis care, compared to the other EDs at start up, the 28- and 90-day mortality was significantly higher. Opposed to the other EDs, the 28-day mortality declined significantly at this hospital after the start of Sepsis Alert, from 28.7% to 16%. Although basing assumptions on a subgroup requires caution, this may indicate that quality markers of sepsis care need to be below a certain threshold to enable positive impact on mortality.

Further, a significant amount of the patients included in the study had limitation of care, 27.5% of the patients at attendance to the ED, and 40.4% of the patients during hospital stay, which may diminish the possibility to affect mortality. Also, we evaluated sepsis patients from a cohort of unselected ED patients, reflecting real-life setting, which may have influenced the outcomes in comparison to studies targeting certain subgroups of patients. Since sepsis mainly affects patients with comorbidities and/or high age, the percentage of patients with limitation of care found in our studies may not be a surprise (13, 34, 35, 64, 106). Importantly, the multimorbid elderly patient seems to have a lot to gain on appropriate initial sepsis treatment. Studies report small differences in mortality after hospital discharge in patients aged 50–75 compared to patients ≥75, a fact that motivates focus on this patient group (65, 88).

As highlighted in the background of this thesis, sepsis treatment is complex and can hardly be reduced to a simple table, and to avoid a one-size-fits-all approach, the early evaluation of ID physician is paramount (96, 151, 201, 245-247). In addition to advice on diagnostic procedures, antibiotic and supportive treatment, level of care, and surveillance, the ID physician may contribute to secure and evaluate the need of care at an ID ward, whether isolation is necessary, and, when needed, contribute with decisions on limitation of care. Another decisive task for the ID physician is to contribute on a macro level to overall decisions on development of patient safety of ID, and fellow patients at the ED, for example to create isolation rooms with camera and surveillance of vital signs. By being regularly visible at the ED, a beneficial ID physician "side-effect" is lowering the bar for consultations from ED physicians and staff, as well as for other specialists at the ED.

The presented Sepsis Alert studies add to the mounting evidence that the additional support from an ID physician at the ED, is associated with improved outcomes, and needs to be considered in addition to sepsis bundles (96, 151, 201, 245-247). By working with tailored implementation, adjusting in collaboration with local sepsis care teams and management in the different EDs, the Sepsis Alert can be rewardingly adapted, even in settings where bedside evaluation by an ID physician is not feasible.

Comment on inclusion

Sepsis studies use various definitions of infection, and often the inclusion "blood culture taken and antibiotic treatment for four days" is applied (26). However, to enable evaluation of missed patients or patients with viral sepsis in the unselected ED patient cohort, these inclusion criteria may be less relevant (27). By evaluating all patients within one acuity segment, in contrast to most previous sepsis studies, the Sepsis Alert studies allowed for inclusion of a broad spectrum of patients, including for example unconscious patients, patients with limitation of care, and patients receiving palliative care.

Hence, when considering criteria for triggering the Sepsis Alert, great effort was put into including as many severe sepsis patients as possible, while at the same time avoiding alert fatigue and displacement effects. To enable this, we decided to use the highest priority group (red RETTS), which was already an alert group, and to add a fever criterion to this group (214). In the early stages of developing the Sepsis Alert, a more complicated trigger for Sepsis Alert was evaluated. In one of the pre-pilots in Malmö, we applied the inclusion "signs of infection", including for example fever/history of fever, hypothermia, catarrhalia, influenza symptoms, cough, urinary tract symptoms, flank pain, vomiting, diarrhoea, new severe pain, arthritis, severe headache, cerebral

dysfunction, exanthema, and cellulitis. When applying this detailed inclusion criteria, we learned that multiple triggers for Sepsis Alert were less easily implemented and risked diminishing the alert frequency. In addition, it is important to identify history of fever since sepsis symptoms may fluctuate. Also, supportive measures, analgesics, and antipyretics administrated prehospitally or at the ED may normalise symptoms and vital signs, rendering a "false" positive measurable effect in the patients.

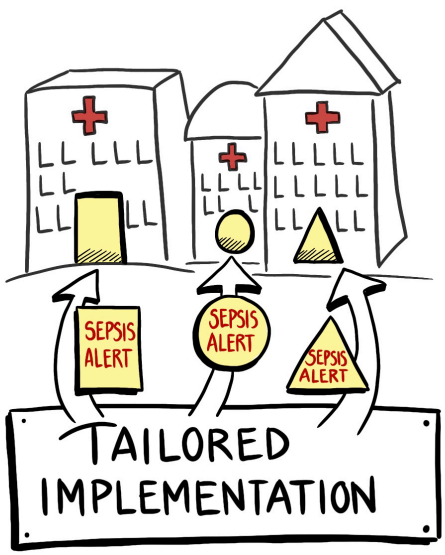
With these aspects in mind, we chose to apply a low cut-off for fever, ≥38°C, and the additional instructions to trigger Sepsis Alert if information of history of fever/chills were present. In Study I, hypothermia <35°C was used as a trigger for Sepsis Alert, but in Study IV this inclusion criterion was omitted in accordance with the Regional Sepsis Care Guidelines. However, to apply a fever criterion as a trigger for Sepsis Alert has obvious limitations, since several sepsis patients do not exhibit fever, including patients with extremes of age, chronic liver or renal dysfunction, or patients on immunosuppressive treatment (127, 128, 167, 190, 191). Also, a linear association between increased body temperature at ED and survival has been shown, a finding that targets the complex presentation of severe sepsis (123). To try improving the Sepsis Alert model, such additional triggers as hypothermia or suspicion of infection may need to be considered. This may lead to better sensitivity, however the subsequent consequences on specificity may be untenable.

Comment on implementation

Previous studies have evaluated the importance of ID support in handling patients with severe infections/sepsis (96, 151), however to the best of our knowledge, there are no previous studies corresponding to the regional implementation of Sepsis Alert.

When implementing the Sepsis Alert, we aimed at working in a fashion contrary to a 'top-down' approach and placed considerable responsibility on the competence of local sepsis care teams, while, at same time, the regional coordinator was continuously available for support and educational efforts. The ED management and local sepsis care teams decided on "how" and "when" to implement the Regional Sepsis Care Guidelines, while the Regional Sepsis Care Guidelines provided "what" was to be implemented. Several innovative solutions to achieve the set goals of sepsis care emerged during the implementation process, perhaps due to the free rein given the local sepsis care teams. An example of this ingenuity was the "sepsis kit" (containing material for relevant cultures, referral documents, fluids for resuscitation, and care guidelines in print), that a local sepsis nurse at one of the community hospitals prepared. Since the community hospitals handled sepsis patients less frequently, this was a brilliant way to always be prepared for the next sepsis patient.

To adjust to each ED´s prerequisite, and achieve tailored implementation, the coordinators focused on implementing Sepsis Alert at one ED at a time, enabling close collaboration with the local sepsis care team and the ED management during a limited time period. The coordinators customized the implementation according to the significant differences between a tertiary academic care centre and a community hospital, and carefully analysed the current ED´s strengths and weaknesses before start-up. The coordinators attentively supported the local sepsis care teams during educational sessions and in preparing cases, etc. However, the aim was for the local sepsis care teams to be as autonomous as possible, while receiving support from the regional coordinating team as necessary. An unforeseen plethora of events were handled by the regional coordinators, e.g., when members of the local sepsis care team resigned in the middle of the implementation process, and when a member of the local sepsis care team got sick just before lecturing. Hence, the regional coordinators were available for all EDs during and after the implementation and had an ambitious and vital policy of answering all questions (by e-mail or telephone) within 24 hours. Now, five years later, the coordinators still support the local sepsis care teams, but at a lower intensity.



While implementing and coordinating Sepsis Alert since 2011, one important lesson learned was to "keep it simple". When considering criteria for triggering Sepsis Alert in Study I, several pre-pilots and discussions with ID colleagues were conducted. We investigated, i.a., the possibility of applying the trigger "suspected infection", including the forementioned list of infectious disease symptoms, as an inclusion criterion. However, the more detailed inclusion criteria risked containing measures of subjectivity and would

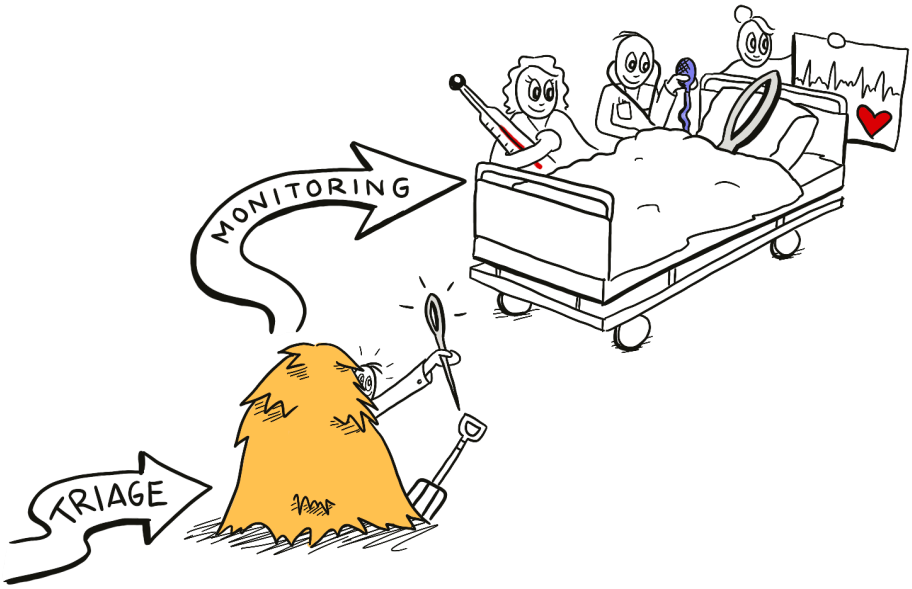
also risk making the evaluation less stringent, hence the fever criterion ≥38°C or history of fever/chills within the past 24 hours was chosen henceforth, to facilitate the algorithm and to enable evaluation of the process.

Another important lesson was the importance of engaging all personal categories when implementing new ED processes. As previously stated in the Methods section, the medical secretaries were not engaged in the local sepsis care teams at start-up in Study I. When the medical secretaries were included in the process, the team became more complete, and the handling of data more accurate, and subsequently compliance improved. There may be several explanations for this, however, as the role of the medical secretaries indicate, reflecting the importance of the complete chain.

The medical secretaries also assisted in documenting vital signs, lactate levels, time to antibiotics, etc., in a novel electronic application, enabling real-time measurement of key performance indicators to facilitate adequate, and continuous feed-back. This system was not fully adopted during the implementation in Study IV, but it has greatly simplified concurrent self-evaluation for the EDs, which is probably one important factor in the encouraging and sustainable goal fulfilment of quality markers of sepsis care five years after the implementation.

By simultaneously improving patient care and workflow with knowledge of the unique situation of each ED, and with the support of local opinion leaders, the ED personnel swiftly adopted the new model. "We have been wating for this kind of model", was an opinion expressed at several of the case-seminars. Perhaps due to the ED personnel's persistent concern about this highly diverse patient group, compliance for Sepsis Alert soon rose to about 82%, a rather high compliance compared to previous studies on implementation of sepsis improvement programs (220).

Also, applying a simple algorithm that harmonised with the current ED triage system, as opposed to applying a parallel triage line, is probably advantageous to achieve continuous compliance and sustainable results in the unique ED setting. Also, the coordinators adjusted the time of implementation to the request of each hospital, a fact that may have contributed to the compliance. Further, the importance of endurance when implementing new models and/or guidelines in health care, also needs to be properly addressed. The implementation strategies applied in current Sepsis Alert studies have been used advantageously, and are thoroughly described in previous studies (194-198, 201, 203, 204). For further reading regarding the Sepsis Alert implementation process, please see the implementation report in accordance with CReDECI provided in the Supplementary material in Study IV.



Comment on NEWS/NEWS2

NEWS was initially constructed in 2012 by Royal College of Physicians (RCP) to standardise different early warning scores (EWS) systems in the UK, and hereby provide consistency in assessment of illness severity (215, 227). With the aim of applying the same model and nomenclature for sepsis identification throughout the care chain, in the updated RCP guidelines from 2017, the NEWS2 has been suggested as a triage tool for sepsis at the ED.

However, to date, research evaluating the ability of NEWS/NEWS2 as a triage tool for sepsis at the ED is insufficient (219). Current studies are conducted in non-representative, often small patient cohorts, and often combined with some form of triage system. In some studies, NEWS has shown appropriate sensitivity at cut-off of 3–5 points, however the specificity is very low at this level, which will risk leading to alert fatigue in the ED. Hence, an appropriate cut-off for NEWS/NEWS2 in sepsis triage at the ED is yet to be established (11, 228-231).

In addition to the stated shortcomings, it is rather concerning that in the Royal College of Physicians NEWS2 document, one of the highlighted studies has been falsely cited, rendering an overestimation of the risk of ICU care and 28-day mortality. In the NEWS spans 5–6 and 7–8, the risk of ICU care and 28-day mortality in this document

is almost twice as high as the risk presented in the original manuscript (215, page 25 Table 3, 230).

Although applying the same system and nomenclature for evaluating sepsis throughout the care chain may be appealing, it may risk neglecting the important and fundamental differences between a screening tool, identifying a certain disease within a larger pool of patients, and the monitoring and risk-stratifying of a patient with a certain (or suspected) disease. Further, to abandon one system in favour of another, without the needed prospective validation, seems rash. Hence, we patiently await ongoing studies that may clarify the role of NEWS2 in sepsis triage at the ED, but in the meantime, active expectance is probably the most appropriate way forward.

Limitations

Deeper analysis of the sub-group of patients with hypotension at admittance, and patients admitted to the ICU, has yet to be accomplished. In addition, the importance of consultation by phone versus bedside has not been evaluated so far. Another interesting aspect that needs to be addressed is whether and how the prescribing patterns of empirical antibiotics differed in between the study years. Further limitations of the Sepsis Alert studies include the before-after design, hence unmeasured confounding factors as outbreaks and personnel turnover cannot be ruled out. Also, sepsis patients presenting with less severe vital signs may not be identified by Sepsis Alert. However, a study evaluating the patients in the second highest RETTS (orange) priority group is currently taking form (214). Also, due to, i.a., carry-over effects, three of the eight centres had some form of sepsis triage system at start-up. Interestingly, when these three centres were excluded from the analysis, the outcomes became more distinct. Another limitation in the Sepsis Alert studies is the lack of assessment of severity, however, consecutive patients for both the 2015 and the 2017 cohorts were selected according to the RETTS registration by staff not engaged in the study. This should diminish the risk for selection bias. Further, the cohorts were similar in terms of patient characteristics and comorbidity, including presence of severe sepsis and limitation of care orders. They also showed similar vital signs and laboratory values at admission, including lactate and CRP.

The Biomarker studies - Papers II & III

With the objective to create broad knowledge, and to develop clinically applicable biomarkers for early identification and risk stratification of common acute conditions, in 2013 Prof. Melander and colleagues started a biobank for patients with dyspnoea, arrhythmia, diabetes, and sepsis at the ED in Malmö. About 3 000 patients have been enrolled in this biobank, of which more than 800 patients are included in the sepsis biobank. The aim of the sepsis biobank has been to identify biomarkers for early identification of sepsis, sepsis-related organ dysfunction, and risk stratification of sepsis patients at the earliest time point at the ED with a single assessment of biomarker(s).

In previous studies, MR-proADM's ability as a prognostic marker stratifying mortality and degrees of organ failure has been identified (292-297). MR-proADM may also identify patients at risk of treatment failure in need of alternative therapeutic interventions despite ongoing antibiotics (295). Study II was based on a previous multicentre study involving about 2 000 patients included at nine EDs across Europe and the US. In this study, the ability of PCT, CRP, lactate, and MR-proADM to assess disease progression, and hospitalisation in patients with suspected infection at the ED, was evaluated. Here, MR-proADM was shown to accurately assess disease severity in patients with suspected infectious disease at the ED. Further, levels of MR-proADM assisted in identifying subgroups of patients with risk of disease progression (Saeed K et al 2019, related paper I, not included in this thesis).

In a subset of patients from this study, consisting of 213 patients attending the ED at Skåne University Hospital Malmö with sepsis in accordance with Sepsis-2, a post-hoc analysis was conducted to evaluate MR-proADM's ability to guide the need of antibiotic therapy. Also, the ability of MR-proADM to assess low risk of ICU care and/or 28-day mortality was studied. Here, we found that MR-proADM had the strongest association with the requirement for antibiotic administration at the ED, compared to the other biomarkers PCT, CRP, and lactate. Also, ICU care and 28-day mortality were zero in patients with low MR-proADM, irrespective of PCT levels. Hence, our results suggest that reduced levels of MR-proADM may identify a group of sepsis patients with low-risk of poor prognosis. Although MR-proADM may be considered a promising biomarker for early risk-stratification in sepsis, systematic randomised multicentre trials are needed to confirm these findings. Also, to enable clinical use, available diagnostic platforms are needed, as is point of care diagnostic testing.

Sepsis frequently leads to organ failure, and the kidney is an organ that is often affected, as more than half of patients with septic shock develop AKI, leading to substantially

increased risk of death (130, 133). The current definition of AKI, Kidney Disease Improving Global Outcomes (KDIGO) and Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease (RIFLE), is based on SCr and urine output (317). However, in clinical daily practice, ED physicians in general solely rely on SCr to assess renal function, since urine output often is inaccessible. A fact that is clearly illustrated in Study III, where the definition of AKI is reliant on SCr in plasma, since evaluation of urine output in most cases was not present at the ED. One needs to consider that SCr-based definitions may involve confounders such as muscle mass, hydration status, diet, rhabdomyolysis, and use of nephrotoxic agents. Also, the SCr increase is delayed, and repeated values are required to evaluate the extent of kidney damage (317).

In previous studies, penKid has been shown to be a specific marker for renal function and associated with AKI in the ICU setting. Also, penKid has been shown to be highly specific for renal function, despite the dysregulated immunological response that is present in sepsis (309, 310, 313). In contrast to other biomarkers for AKI prediction, concentrations of penKid remain low in the absence of renal dysfunction in septic patients (309).

In Study III, we investigated penKid's ability to predict AKI, MOF, and 28-day mortality in unselected sepsis patients at the ED at Skåne University Hospital Malmö. In this study, we found that penKid predicted AKI, however, these findings were attenuated when adjusting for eGFR. However, in unselected sepsis patients with subclinical AKI at the ED, penKid predicted progression from renal-SOFA ≤ 1 to higher renal-SOFA scores, which may provide relevant clinical information to the ED physician. Also, penKid predicted MOF and 28-day mortality at the ED.

Although the primary outcomes were traditional in present biomarker studies and chosen in accordance with international guidelines, these outcomes in sepsis care may be considered hard, albeit a bit rough. Conceivably, more granularity in this regard may be of benefit to patients, focusing on deteriorations upstream of MOF, ICU care, and 28-day mortality (despite treatment) to avoid these endpoints. Study III illustrates this ambition, since levels of penKid may raise awareness of septic patients with subclinical AKI and identifying these patients early on may prevent further renal deterioration, RRT, and serious sequelae such as chronic kidney disease (CKD). Hence, we believe that penKid may provide valuable insights when monitoring sepsis patients, which may enable early nephroprotective strategies as discontinuing or dose-adjusting potentially harmful drugs as renin-angiotensin blockers and aminoglycosides, and to enable adequate intravenous fluid treatment.

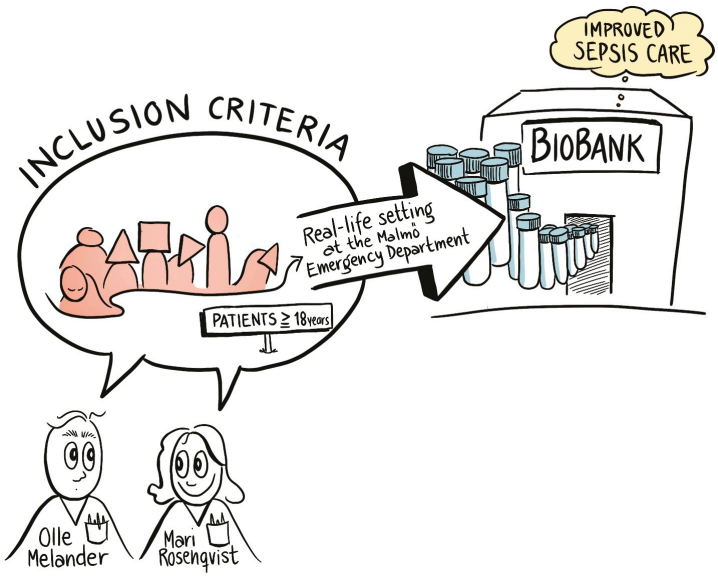
Despite the encouraging results of our two biomarker studies, Pierrakos and colleagues add an interesting, although a bit discouraging, temporal aspect to the search for useful sepsis biomarkers. In 2010, they published a review of 178 biomarkers, and at that time, as well as a decade later, they conclude that progress in identifying biomarkers with clinical significance in sepsis has been limited. The same authors also adequately highlighted the methodological insufficiencies in several available biomarker studies: few biomarker studies include more than 300 patients, sepsis biomarkers rarely exceed AUROC above 70, and many of the biomarkers have been evaluated in a limited number of clinical studies, and one-third in just a single study (274, 275).

Sepsis may, as previously stated, be considered an entity of its own, due to its lack of pathognomonic symptoms and the complex, varied, and multifaceted host response to infection that is dependent on the type of pathogen, site of infection, host-related factors, and treatments, which altogether render a unique situation. Finding biomarkers that adequately manage to identify the full spectrum of sepsis patients, from an 18-year-old patient with meningococcal sepsis to a multimorbid 90-year-old patient with pneumonia, although a paramount objective, may not be possible due to different pathophysiological processes (41). Hence, a more personalised approach guided by one or a combination of several biomarkers may be beneficial (279). Focusing on early identification of subgroups of patients, such as patients with increased risk of developing septic shock, may prevent further deterioration and in the best-case lead to none or less organ dysfunction. Also, a more accurate identification of patients with uncomplicated infections with low risk of deterioration, i.e., rule-out, may increase the number of out-patient treatments with subsequent positive consequences for patients and health care.

Comment on inclusion

The intention of the present biomarker studies was to apply as broad inclusion of patients with suspected or established infectious diagnose as possible, preferably "suspected infection". However, patients attending with "suspected infection" in the ED, often presented with tropical infections, enteroviruses, and Borrelia, hence a highly selected patient group which inevitably should have led to selection bias. As previously stated, patients with sepsis often attend with non-specific symptoms such as general weakness, nausea, vomiting, abdominal pain, and, in the majority of cases, patients are triaged to the internal medicine line. After weighing the pros and cons of different inclusion criteria, we decided to apply the current Sepsis-2 guidelines, 2 SIRS criteria plus suspected infection, and to include sepsis patients in the medicine and infectious flow at the ED (2). A huge effort was made to include patient groups that are frequently

excluded from research studies, such as patients with limitations of care, pregnant women, patients with ongoing substance abuse, or with a need for interpreters. Here, the engagement and the continuity of the three ED research nurses collecting data ensured broad inclusion and the data quality.



Limitations

In these biomarker studies, applying a single assessment biomarker approach was a conscious choice. The objective for this setting was to support the ED physician in assessing the sepsis patients at presentation, and before therapy would be initiated. However, additional serial assessment of biomarkers would probably be beneficial, since only assumptions may be made concerning disease progression and sepsis development and association with biomarker level. In addition, the non-consecutive setting (6 am–6 pm) may have contributed to selection bias. Another difficulty was that sepsis criteria were changed during the study period. However, we decided to apply the Sepsis-2 criteria throughout the study, and for compatibility with the updated Sepsis-3 criteria, the renal Sequential Organ Failure Assessment (rSOFA) sub-score within 48 h was calculated. Finally, sepsis is defined as an infection leading to dysregulated host response including organ dysfunction, however whether the organ dysfunction is due to the infection or caused by dehydration, comorbid condition or pharmacological effects may be uncertain. This difficulty remains in most sepsis studies, and consequently also in the studies included in this thesis.

Conclusions

I. The implementation of the novel triage algorithm Sepsis Alert at the ED at Skåne University Hospital in Malmö resulted in a larger proportion of sepsis patients receiving antibiotic treatment within one hour, more blood cultures and lactate measurements being taken, and the length of hospital stay being decreased. Mortality was not affected.

II. The establishment of the triage algorithm Sepsis Alert at eight EDs in Skåne Region resulted in a larger proportion of sepsis patients receiving timely and appropriate antibiotics and supportive care. Also, fulfilment of the Surviving Sepsis Campaigns' process measures of sepsis care improved significantly. In a subgroup of 5/8 EDs, the proportion of patients in need of ICU care decreased. A trend towards decreased length of hospital stay was noted. Mortality was not affected.

III. Low concentration of the biomarker MR-proadrenomedullin, on arrival at the ED, was associated with significantly reduced use of, and longer time to antibiotic therapy. Also, irrespective of PCT concentrations, in patients with low levels of MR-proadrenomedullin, ICU care and 28-day mortality was zero.

IV. High concentration of the biomarker penKid on arrival at the ED predicts acute kidney injury. However, the association decreases after adjustment of eGFR. Also, penKid predicts progression from rSOFA = 0 and ≤ 1 to higher rSOFA score, multi-organ failure, and mortality, independently of eGFR.

Final reflections & future perspectives

This thesis explores aspects of early identification and risk-stratification of patients with sepsis at the ED by investigating the role of vital signs and biomarkers. Inspired by cardiologists and neurologists, we created and implemented a novel triage model, Sepsis Alert, which includes early identification and evaluation by an infectious disease physician, to raise the minimum level of care and improve process quality. In return, we gained valuable insights about implementation of new models and guidelines in healthcare which may be valuable for other (urgent) conditions. Additionally, a biobank for future research was created and the risk stratification impact of the biomarkers MR-proADM and penKid was studied. The intention of this thesis has been to conduct sepsis research in unselected ED cohorts, applying as few exclusion criteria as possible. By applying this setting, we hope that the research findings may benefit as many patients as possible, regardless of gender, age, ethnicity, multi-morbidity, treatment limitations, economic conditions, etc.

The research work associated with the sepsis biobank has just begun. The biobank now contains samples from over 800 sepsis patients and may hopefully continue to contribute to identifying biomarkers for early identification and risk-stratification of sepsis patients for a long time. It may also assist in achieving greater understanding of early immunological or other predisposing factors and assist in early identification of sepsis patients with increased risk of long-term consequences of sepsis. Also, point of care measurements of biomarkers (as MR-proADM and penKid) may in the future add valuable support to enable risk stratification of sepsis patients in different settings outside the ED, such as in ambulances, home settings and virtual care.

During a decade of working with early identification of sepsis at the ED, several lessons have been learned. Improving health care requires broad anchoring, and the courage to implement and adjust models, in addition to sufficient research supporting the interventions. The focus and ingenuity of the local sepsis care teams has greatly benefited the implementation process. The engagement and knowledge of the members of these teams provides a solid ground for further improvement of sepsis care in the region. Also, in bridging ambulatory and hospital care, the ED offers a unique

opportunity to apply, for example, measures preventing health associated infections early in the care chain.

The triage model Sepsis Alert has been shown to improve quality markers of sepsis care, decrease length of stay, and, in 5/8 EDs with no prior sepsis triage, the need for ICU care was significantly reduced. By applying inclusion criteria already qualifying for generating an alert, the risk of alert fatigue and displacement effects have been minimised. Sepsis Alert is today an integrated part of the daily routine at the EDs in the Skåne Region, and it is gratifying that the experiences and knowledge from the Sepsis Alert studies has fortified the national work on "Personcentrerat och sammanhållet vårdförlopp för sepsis". These national guidelines have recently been established, and a national implementation plan is currently taking form.

In the more resource-rich parts of the world, the focus may well be on introducing standardised care chains for early identification and treatment of sepsis at the ED, as suggested by SSC and IDSA. Unfortunately, sepsis care guidelines developed for emergency care in high-income countries may, due to the discrepancies in health care systems, not be applicable in low- or middle-income countries, where most of the sepsis burden lies. As WHO states, approximately 85% of sepsis cases and sepsis-related mortality occur in low- or middle-income countries, hence guidelines must be regionally and locally modified to be applicable and beneficial in the unique emergency setting.

In anticipation of more personalised sepsis treatments and pharmacological agents, early recognition of sepsis and preventive measures remain the most important aspects requiring research focus. Also, the research community must put effort into studying not only sepsis patients in the ICU setting, but rather the entire sepsis population, including the multimorbid elderly, patients with limitation of care, and other patient groups often excluded from sepsis research. Since early identification is imperative to enable early and appropriate antibiotic treatment, source control, and supportive care, we need to reconsider and adjust the present triage models to achieve the best possible outcomes for sepsis patients.

If you want to go fast, go alone – if you want to go far, go together.

Frequently Asked Questions (FAQ)

Q: When implementing a Sepsis Alert, isn't there a risk for alert fatigue and displacement effects?

Certainly, these are very important aspects when implementing the Sepsis Alert at EDs. In the present studies, we applied the Sepsis Alert in the highest priority group (red RETTS) that was already generating a medical alert. Consequently, the same number of alerts were triggered before and after the implementation. However, if one would choose to apply another trigger for Sepsis, not currently generating an alert, the risk of alert fatigue is evident. Further, a physician must always prioritise which patients to attend first, and the ID physician may have to prioritise attending the Sepsis Alerts at the expense of other tasks, with a risk that displacements effects may appear. To prevent this, resources need to be allocated to compensate for the additional workload of the ID physicians.

Q: Isn't there a risk of increased unnecessary antimicrobial treatments when applying the Sepsis Alert?

I would claim the contrary. When applying the Sepsis Alert, an ID physician is involved in the initial evaluation of patients with severe infections. The ID physician contributes knowledge regarding appropriate decisions about diagnostic procedures, surveillance, antibiotic, and supportive treatment. The early evaluation by an ID physician ensures that appropriate antibiotics are initiated when needed, and the ID physician simultaneously prevents unnecessary antibiotic treatment. In this study, the proportion of patients receiving correct empirical antibiotics at the ED, compared to subsequent blood culture results, increased significantly after the implementation, from 78.6% to 90.2%. Since the antibiotic treatment initiated at the ED is often continued after admission, the initial decisions on diagnostics and treatment have major impact throughout the care chain. However, an interesting study remains to be concluded after finalising this thesis, namely evaluating prescribing patterns of antibiotics before and after the implementation of Sepsis Alert.

Q: Why were patients with primarily surgical conditions excluded from Sepsis Alert?

We agree that it would be preferred to include all sepsis patients that present to the ED, including those with surgical conditions. However, the EDs in our region have to date been divided into medical and surgical lines, and including the surgical lines was not considered feasible at start-up. In the pilot study, conducted at the ED at Skåne University Hospital Malmö, we reasoned that it was more efficient to focus on the non-surgical line, in order to attain satisfactory compliance with the algorithm, and that we could thereafter consider broadening the inclusion criteria to include patients with predominating surgical conditions. Today, the Swedish Government and Sweden´s Municipalities and Regions (SKR) has launched national sepsis guidelines "Personcentrerat och sammanhållet vårdförlopp för sepsis" that also includes patients with predominating surgical conditions in the guidelines, a positive and welcome development that creates an opportunity to allocate resources for education, and to improve sepsis care for these patients.

The link to "Personcentrerat och sammanhållet vårdförlopp för sepsis" in Swedish:

https://d2flujgsl7escs.cloudfront.net/external/Personcentrerat_och_sammanhallet_vardforlopp_Sepsis.pdf

Q: Was mortality reduced after implementation of Sepsis Alert?

Previous studies have shown that reducing time to antibiotics have resulted in reduced mortality. In our studies, the early engagement of ID physicians either bedside at the ED, or by phone, led to improved compliance to the SSC bundles including prompt and appropriate antibiotics, rendering higher quality in sepsis care, shortened length of stay, and decreased need for ICU care (at 5/8 EDs with no prior sepsis triage). However, mortality was not significantly reduced after the implementation, 17.7% and 15.2%, respectively. The reasons for this may include insufficient power in the study, or the high proportion of limitation of care, amounting to 40.4% of the patients during hospital stay. This issue is further discussed in the thesis, please see page 92

Q: Wasn't lactate ≥3.5 mmol/L included as an additional trigger for the Sepsis Alert?

Yes. Patients with ≥38°C or history of fever/chills within the past 24 hours and lactate level ≥3.5 mmol/L would be appointed to the designated sepsis line for immediate evaluation of ED and ID physician, regardless of RETTS colour. However, when evaluating the Sepsis Alert project overall, this particular aspect was difficult to evaluate, since we were not able to identify all patients with lactate levels ≥3.5 mmol/L. The

patients with elevated lactate levels are distributed across all RETTS priority groups, and we decided early in the pilot-study (Study I) to only evaluate patients in accordance with vital signs. While we unfortunately cannot present the exact number of patients who fulfilled this lactate criteria, however, they were few. Importantly, patients with elevated lactate levels constitute a high-risk group of sepsis patients that deserves extra attention. Hopefully, this aspect can be further evaluated in the future.

Q: Is it reasonable for a busy ID physician to prioritise attending a Sepsis Alert in very old multimorbid patients?

As clinicians we always need to prioritise which patients to attend first, and the Sepsis Alert is no exception. The ID patient in most need of ID expertise should be prioritised. Old and multimorbid patients often have several risk factors for sepsis, and research has shown that patients with limitation of care benefit from early evaluation and treatment. Also, attendance by ID physicians should always be adapted to the demands of the specific situation. Hence, some consultations may take a few minutes only, while others take hours. Also, since the patients triggering Sepsis Alert are already evaluated by an ED physician, the patient is still prioritised. If the ID physician needs to prioritise another task, ID consultation by phone may be conducted.

Q: Is NEWS/NEWS2 superior to RETTS in triaging sepsis patients?

NEWS/NEWS2 has mostly been evaluated in its ability to monitor patients with a (suspected) disease, and relevant research supporting NEWS/NEWS2 as a triage tool for sepsis patients at the ED is to date insufficient. To identify one patient in a large population is quite different from monitoring a patient with a known or suspected disease. This issue has been discussed in greater detail in this thesis, please see page 59 and 97.

Q: Were all personnel categories at all EDs receptive to implementation of the Sepsis Alert?

Barriers to implementing the Sepsis Alert were few. As stated previously, sentiments of "We have been waiting for this" were expressed several times during the case-seminars at implementation. However, when work processes are changed, there is often some reluctance, especially if the changes are associated with increased workload. However, with the encouraging results from Study I, the limited initial resistance was gradually resolved.

Q: Do sepsis teams need to include all professions? Our hospital is so small.

My answer is a definite yes, sepsis teams must include all the involved professions. We believe that the conscious choice to include all personnel categories is an important factor contributing to the positive and sustainable outcomes of Sepsis Alert. In smaller hospitals, the amount of time needed to be engaged in the local sepsis care team may be limited, and consequently the cost and efforts will be less. But our experience is that the advantages of creating a complete sepsis team at each hospital, regardless of size, are considerable.

Q: What are the costs for implementing the Sepsis Alert, are the associated costs motivated?

The Centre for Health Economics, Informatics, and Healthcare Research (CHIS) at Region Stockholm, Sweden, has recently conducted an analysis that highlights the health economic aspects of implementing Sepsis Alert, based on, i.a., the studies from Skåne. Encouragingly, they conclude that the costs for coordination were shown to be relatively small in relation to the estimated cost savings. They also concluded that previous follow-up studies of similar initiatives indicate that the effects on length of stay that would be required to recoup costs for the intervention Sepsis Alert are achievable. As limitations, they note that the two Sepsis Alert studies were conducted from the same research groups, and that the studies had a before-after design.

The link to ”Konsekvensbeskrivning för personcentrerat och sammanhållet vårdförlopp - Sepsis” in Swedish:

https://kunskapsstyrningvard.se/download/18.5ab5d19617988faf97273f85/1622200963008/Vardforlopp-sepsis-konsekvensbeskrivning.pdf

Q: How long will regional sepsis coordinators be needed?

Having worked with the Sepsis Alert since 2012, monitoring a process like this to achieve long-term sustainable results is of great importance. The project was initially regionally financed. However, the cost of the last few years of financing, including ID physician (25%), regional sepsis nurse (25%), and medical secretary (4 weeks) annually, has been attributed to the three heads of administration in Skåne Region. Our experience is that a continuous monitoring of Sepsis Alert frequency and quality markers of sepsis care is needed. Since the alert is a prerequisite to enable timely identification and treatment, the coordinators monitor the Sepsis Alert frequency to ensure that it is adequate and stable. When (or if) the Sepsis Alert frequency declines,

the coordinators may for example assist in supporting the local sepsis care teams to address the reasons for the decline and participate in educational efforts as needed. When considering previously suggested cost savings, the cost of these coordinators may be considered well-motivated.

Tack

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Errata

In the original manuscript of **Study III**, there is an error in the Abstract. The number of patients included in the study was 647, not 644, and the number of patients excluded were 59 not 56, as erroneously stated in the Abstract.

Further, AKI in **Study III** is defined by an increase in SCr of > 44 µmol/L (> 0.5 mg/dL) between any two measurements, or need for acute RRT, or an increase in creatinine corresponding to 1.5-fold of baseline with an initial value of > 160 µmol/L (> 2.0 mg/dL), not according to AKIN stage 3, as stated.

Also, there is an error in Table 3 in **Study III**. When evaluating AKI within 7 days, the wrong denominator has been used in the analysis. The correct percentages of N events (% of total)[b] is 6,8% in quartile 1, 5,4% in quartile 2, 11,6 % in quartile 3, and 40,1% in quartile 4. Further in the body text of Table 4, the number of organs affected to define multi-organ-failure (MOF) should be ≥4, not >4 as incorrectly stated.

In the Supplementary material in the original manuscript of **Study IV**, there is a typo in Table 3. The correct numbers of lactate measurements were 21 in 2015, and 17 in 2017.