

Appendix 1. Sequential Organ Failure Assessment (SOFA) Score^{1,2}.

System	Score				
	0	1	2	3	4
Respiration					
PaO ₂ /FiO ₂ , mmHg (kPa)	≥400 (53.3)	<400 (53.3)	<300 (40)	<200 (26.7) with respiratory support	<100 (13.3) with respiratory support
Coagulation					
Platelets, ×10 ³	≥150	<150	<100	<50	<20
Liver					
Bilirubin, mg/dL (μmol/L)	<1.2 (20)	1.2-1.9 (20-32)	2.0-5.9 (33-101)	6.0-11.9 (102-204)	>12.0 (204)
Cardiovascular					
	MAP ≥70 mmHg	MAP <70 mmHg	Dopamine <5 or dobutamine (any dose) ^a	Dopamine 5.1-15 or epinephrine ≤0.1 or norepinephrine ≤0.1 ^a	Dopamine >15 or epinephrine >0.1 or norepinephrine >0.1 ^a
CNS					
GCS	15	13-14	10-12	6-9	<6
Renal					
-Creatinine, mg/dL (μmol/L)	<1.2 (110)	1.2-1.9 (110-170)	2.0-3.4 (171-299)	3.5-4.9 (300-440)	>5.0 (440)
-Urine output, mL/d				<500	<200

PaO₂= partial pressure of oxygen, FiO₂= fraction of inspired oxygen, CNS= Central nervous system, GCS= Glasgow coma scale, MAP= mean arterial pressure.

^aCatecholamine doses are given as μg/kg/min for at least 1 hour.

1. Vincent JL, Moreno R, Takala J, et al. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. On behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine.
2. Singer M, Deutschman CS, Seymour CW, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *Jama* 2016;315:801-10.

Appendix 2. The SSC updated 1-hour sepsis bundle 2018³.

Surviving Sepsis Campaign Hour-1 Bundle of Care Elements:

- Measure **lactate** level*
- Obtain **blood cultures** before administering antibiotics.
- Administer broad-spectrum **antibiotics**.
- Begin rapid administration of 30mL/kg **crystalloid** for hypotension or lactate level ≥ 4 mmol/L.
- Apply **vasopressors if hypotensive** during or after fluid resuscitation to maintain MAP ≥ 65 mm Hg.

* Remeasure lactate if initial lactate is elevated (> 2 mmol/L).

“Starting time” for the Hour-1 bundle is defined as the recognition of sepsis.

Ideally these interventions would all begin in the first hour from sepsis recognition but may not necessarily be completed in the first hour.

3. Surviving Sepsis Campaign. Hour-1 Bundle. Surviving Sepsis Campaign; 2018.

Appendix 3. The “Sepsis six”^{4, 5}.

-within 1 hour:

- 1. Administer high-flow oxygen.**
- 2. Take blood cultures.**
- 3. Administer empiric intravenous antibiotics.**
- 4. Measure serum lactate and check complete blood status.**
- 5. Initiate intravenous fluid administration.**
- 6. Initiate adequate monitoring of diuresis.**

4. Daniels R, Nutbeam T, McNamara G, Galvin C. The sepsis six and the severe sepsis resuscitation bundle: a prospective observational cohort study. *Emerg Med J.* 2010.

5. Robson WP, Daniel R. The Sepsis Six: helping patients to survive sepsis. *British journal of nursing* (Mark Allen Publishing). 2008;17(1):16-21.

Appendix 4. Discharge diagnoses; ICD-10-codes applied in Study I-III.

A02.1 Sepsis caused by Salmonella
A22.7 Anthrax sepsis
A26.7 Sepsis caused by Erysipelothrix
A32.7 Sepsis caused by Listeria
A39.2 Acute meningococemia
A39.4 Meningococemia, unspecified
A40.0-A40.2 Sepsis caused by Streptococci group A, B, D
A40.3 Sepsis caused by Streptococcus pneumoniae
A40.8-40.9 Other/unspecified streptococcal sepsis
A41.0 Sepsis caused by Staphylococcus aureus
A41.1-41.2 Sepsis caused by other specified/nonspecified staphylococci
A41.3 Sepsis caused by Hemophilus influenzae
A41.4 Sepsis caused by anaerobic bacteria
A41.5 Sepsis caused by other gram-negative organisms
A41.8 Other specified forms of sepsis
A41.9 Sepsis, unspecified
B37.7 Candida sepsis
R57.2 Septic shock
R65.0 Systemic Inflammatory Response syndrome (SIRS) of infectious origin with organ
R65.1 Systemic Inflammatory Response syndrome (SIRS) of infectious origin without organ
*M00.0B-M.00.2X Septic arthritis

ICD-10= International Classification of Diseases, Tenth Revision

*Septic arthritis was added in Study III.

Appendix 5. Definition of suspected infection applied in the current thesis.

-Ordering blood cultures and antibiotics were added in Study II.

-C-reactive protein $>100^{10}$ was added in Study III.

-White blood cell count $>12 \times 10^9$ was not included in study IV due to the redefined Sepsis-3 definition.

Appendix 5. Definition of suspected infection. One or more of the following criteria:	
Fever/ Chills	fever/chills as reported by patient or related persons/ED documentation that the patient feels hot / feels feverish / has hot skin/ temperature $>38.0^{\circ}\text{C}$ measured at arrival to the ED.
Diarrhoea	in combination with other signs consistent with infection*.
Vomiting	vomiting in combination with other signs consistent with infection*. Without other obvious reasons such as cerebrovascular lesion, new medication known to cause vomiting, benign postural vertigo, myocardial infarction or after trauma of the head.
Pneumonia	current treatment for pneumonia <i>or</i> cough/chest pain /increased sputum/breathing difficulties in combination with other signs consistent with infection* <i>or</i> a low oxygen saturation without explaining predisposing conditions. If the patient suffered from isolated respiratory distress and had other, more likely causes, the patient was not considered to have a suspected pneumonia. Neither was Cheyne-Stokes respiration in combination with unconsciousness considered as pneumonia.
Abdominal pain/ distension	abdominal pain/ tenderness during physical examination <i>or</i> a tense, distended <i>or</i> bloated abdomen in combination with other signs consistent with infection*.
Urinary tract infection	current treatment for urinary tract infection <i>or</i> cloudy urine/foul-smelling urine/new-onset hematuria without trauma <i>or</i> dysuria/new difficulties to empty bladder <i>or</i> tenderness over the kidneys <i>or</i> urinary bladder on physical examination, in combination with other signs consistent with infection*.
Wound infection	bad smelling/purulent/black/deteriorated/exuding wounds. Patients with chronic wounds without statement of deterioration were not considered to have a wound infection.
Septic arthritis	red/ swollen/ warm/ painful joint without trauma <i>or</i> other, more likely, causes (such as, for instance known metastasis/fracture)

Meningitis	headache in combination with neck stiffness / photophobia/ a reduced level of consciousness and fever.
Cellulitis/ Soft tissue infection	red/ swollen/ warm/ painful soft tissue without trauma including ongoing ab treatment for erysipelas
Infected indwelling device	redness/purulent secretions or pain at site of venous catheters or signs consistent with infection* after catheterization within the last days.
Otitis	new-onset ear pain, without trauma, in combination with other signs consistent with infection*.
Tonsillitis/ Epiglottitis	new-onset throat pain, without trauma, in combination with other signs consistent with infection*.
Documentation of fever/ infection	Documentation of fever/ infection (infection, urinary tract infection, pneumonia, meningitis, flu, gastroenteritis. Also, cholangitis with antibiotic treatment/ peritonitis with antibiotics were included) / sepsis (sepsis, septic, urosepsis, septicaemia, blood poisoning)
Drawn blood cultures	Blood cultures ordered by ED doctor**
Antibiotics ordered	Antibiotics ordered by ED doctor**
Increased C-reactive protein	CRP>100 mg/L¹⁰ without explaining predisposing conditions, and in combination with other signs consistent with infection*

*fever/chills, new-onset weakness/ malaise/ nausea/vomiting/ altered mental status/ hypotension.

** Added in Study II.

°C=degrees Celsius.

10. Svenska Infektionsläkarföreningen. Vårdprogram Sepsis och septisk chock – tidig identifiering och initial handläggning 2018. June 2018 ed. Infektion.net: Swedish Society of Infectious Medicine; 2018.

Appendix 6. Definition of severe sepsis in Study I and III

Severe sepsis was defined as fulfilment of one or more of the following criteria during EMS transport; systolic blood pressure <90 mmHg¹ or an EMS statement of a non-measurable blood pressure, oxygen saturation of ≤86% if the lung was not the focus of infection or oxygen saturation ≤78% if the lung was focus of infection², acute altered mental status², mottling¹ or cardiopulmonary arrest due to sepsis (but admitted alive to in-hospital care).

1. Levy MM, Fink MP, Marshall JC, et al. 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. *Critical care medicine* 2003;31:1250-6.
2. Infektionsläkarföreningen S. Vårdprogram Svår sepsis och septisk chock -tidig identifiering och initial handläggning. 2012.